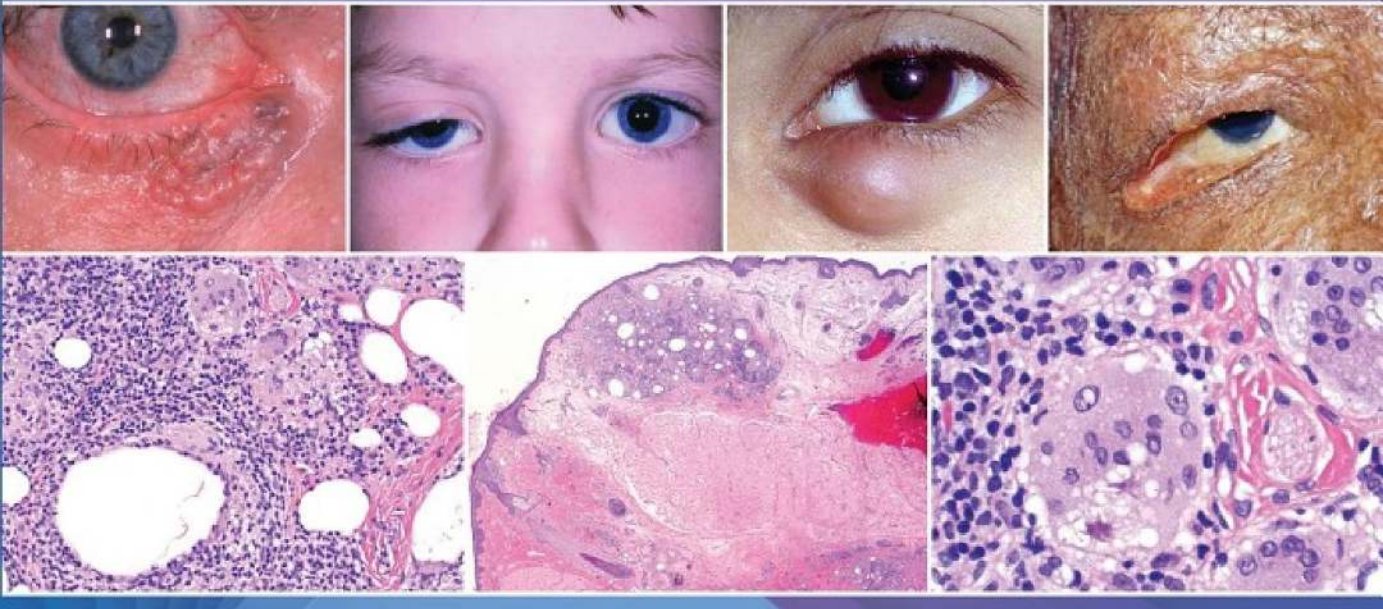
COMPREHENSIVE TEXTBOOK OF
Eyelid Disorders and Diseases



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COMPREHENSIVE TEXTBOOK OF Eyelid Disorders and Diseases

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PREFACE

This work is intended as a clinical reference tool for anyone interested in or concerned with evaluating and managing disorders and diseases of the eyelids. The concept arose from the near-total lack of any single volume dedicated to the clinical disorders and pathology of the eyelids and brows. Although many comprehensive books on ophthalmology include sections on the eyelids, the coverage is typically very limited in scope and significantly restricted in depth. This book was designed to serve as a single, comprehensive source of clinical and histopathological information for clinicians and pathologists dealing with anomalies of the eyelids, eyebrows, and upper face.

The book represents the most up-to-date summary currently available on congenital and acquired disorders and diseases of the eyelids. It is divided into four sections: Eyelid Malpositions; Anomalies, Movement Disorders, and Aging Phenomena; Benign Lesions and Disorders of the Eyelids; and Malignant Tumors of the Eyelids. Several introductory chapters discuss the origin and evolution, embryology, and anatomy of the vertebrate eyelids; tissues of origin for eyelid lesions; common histopathology terminology and microscopic features; and techniques for history taking and clinical examination for eyelid malpositions and lesions. In the main body of the book, disorders and diseases are arranged alphabetically within each section, with the discussion arranged under uniform headings including Introduction, Etiology and Pathogenesis, Clinical Presentation, Differential Diagnosis, Treatment, Prognosis, Histopathology, and References.

The book encompasses 147 chapters covering a large number of

eyelid disorders, with 1585 clinical and histopathologic color photographs arranged in 667 figures. We have tried to illustrate the range of clinical presentations and the most important histologic features for each eyelid condition using photographs, either from our clinical practices or through the generosity of numerous colleagues. The text summarizes the current literature, including state-of-the-art treatment options. More than 8700 references are included so that the reader can dive deeper into the primary literature for more detailed research.

Knowledge is cumulative, but certainly not static. It continues to expand, often exponentially, through the combined efforts of a vast number of individual clinical experiences and research studies. As factual knowledge increases, our ability to understand and solve clinical problems is constantly enhanced. We hope that this book helps to contribute to our knowledge base, and we look forward to future editions as the literature continues to expand.

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Our debt of gratitude also goes to those individuals whose efforts generally contributed to the production of this book, including our secretaries, staff assistants, and our families.

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    1. **FIGURE 8.1** A-D, Typical presentations of involutional aponeurotic ptosis with reduced MRD1 and narrow palpebral fissure.
    2. **FIGURE 8.2** A and B, Upper eyelid aponeurotic ptosis with an elevated eyelid crease.
    3. **FIGURE 8.3** A and B, Severe aponeurotic ptosis with thinning of the upper eyelids, absent eyelid crease, and deep superior sulcus.
    4. **FIGURE 8.4** Right upper eyelid ptosis with a compensatory elevation of the brow.
    5. **FIGURE 8.5** A and B, Left upper eyelid ptosis with pseudoretraction of the right upper eyelid.
    6. **FIGURE 8.6** A-D, Hering phenomenon. A, Bilateral asymmetric ptosis with elevation of the right lesser ptotic eyelid from the Hering phenomenon. B, With manual elevation of the more ptotic left upper eyelid, there is a lowering of the right eyelid. C, Pseudoptosis of the right upper eyelid from retraction of the left upper eyelid due to the Hering phenomenon. D, When the retracted left eyelid is mechanically lowered, the ptotic right eyelid elevates to a normal position.
2. Chapter 9: Blepharoptosis: Mechanical and Pseudoptosis
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 9.1** Examples of mechanical ptosis. A, Depressed eyelid from a medial solitary fibrous tumor. (Courtesy of Dr Robert Goldberg.) B, Ptosis due to frontoethmoidal mucocele. C, Mechanical ptosis from metastatic breast carcinoma. D, Mechanical ptosis due to chalazion.
        2. **FIGURE 9.2** A, Mechanical ptosis from intraocular silicone oil migration into the eyelid. B, At surgery transparent cysts filled with silicone oil are observed infiltrating the levator muscle and the preaponeurotic fat (arrowheads). C, Mechanical ptosis due to periorbital filler injection. D, During surgery, filler granulomas are seen infiltrating the preaponeurotic fat and levator muscle (asterisks).
        3. **FIGURE 9.3** Left eyelid pseudoptosis due to the contralateral right upper eyelid retraction in thyroid eye disease.

4. **FIGURE 9.4** A, Apparent ptosis due to severe brow ptosis with excess upper eyelid skin overhanging the eyelid margin in facial nerve palsy. B, Apparent ptosis from excessive upper eyelid skin in dermatochalasis.
3. Chapter 10: Blepharoptosis: Myopathic, Dysgenetic
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 10.1** Spectrum of involvement of the upper eyelid in unilateral myopathic dysgenetic ptosis. A, Moderate ptosis. B, Severe ptosis.
        2. **FIGURE 10.2** Spectrum of involvement of the upper eyelid in bilateral myopathic dysgenetic ptosis. A, Severe dysgenetic ptosis which is symmetrical in both sides. B, Severe dysgenetic ptosis which is only minimally asymmetric (the pupillary light reflex can be observed in the OS only). C, Bilateral myopathic dysgenetic ptosis with marked asymmetry. Frontalis muscle recruitment with compensatory eyebrow elevation may mask the ptosis in the less ptotic side.
        3. **FIGURE 10.3** Complications of synthetic suspensory materials. A, Extrusion of the silicone sling through the skin. B, Extrusion of the silicone sling through the conjunctiva. C, Granuloma and abscess formation following the use of Gore-Tex (expanded polytetrafluoroethylene, or ePTFE) as a sling material. D, Extrusion of Gore-Tex suspensory material through the skin (asterisk).
    10. Tables
        1. **TABLE 10.1Pathophysiologic Classification of Ptosis**
4. Chapter 11: Blepharoptosis: Myopathic, Dystrophic, and Mitochondrial
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 11.1** Progressive symmetrical ptosis over 20 years in a case of presumptive oculopharyngeal muscle dystrophy with mild limitation of upgaze, dysphagia, and proximal limb weakness.

2. **FIGURE 11.2** Myotonic dystrophy. A, Bilateral ptosis with severe restriction of ocular motility, bilateral polychromatic cataracts, frontal baldness, and limb-girdle weakness. B, Incomplete eyelid closure with poor Bell phenomenon on attempted forceful eyelid closure due to orbicularis muscle weakness.
3. **FIGURE 11.3** Chronic progressive external ophthalmoplegia. A, Moderate, bilateral, symmetric slowly progressive ptosis with early onset in the fourth decade. B, More severe bilateral progressive symmetric ptosis with marked limitation of motility.
4. **FIGURE 11.4** This levator palpebrae superioris muscle biopsy from an elderly individual with chronic progressive external ophthalmoplegia exhibits changes typical of chronic muscular dystrophies. A, There are atrophic fibers (arrows), fibers with internal nuclei (arrowheads), and a split fiber (double arrows) in a background of fibrosis and fatty replacement. B, Endomysial fibrosis surrounds atrophic muscle fibers with prominent internal nuclei.
5. **FIGURE 11.5** The inferior oblique muscle from a child with Pompe disease (infantile-onset glycogen storage disease type II) shows prominent vacuolar myopathy due to glycogen accumulation within muscle fibers.

5. Chapter 12: Blepharoptosis, Neurogenic
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 12.1** The spectrum of eyelid involvement in patients with myasthenia gravis. A, Moderate unilateral ptosis. B, Severe unilateral ptosis. C, Bilateral asymmetric ptosis. D, Bilateral symmetric ptosis.
        2. **FIGURE 12.2** The spectrum of eyelid involvement in patients with oculomotor nerve palsy. A and B, Complete ptosis, extraocular motility disturbance, and pupillary abnormalities in a patient with an internal carotid-posterior communicating artery dissecting aneurysm. C and D, Pupil-sparing oculomotor nerve palsy due to an ischemic etiology (diabetes).
        3. **FIGURE 12.3** Horner syndrome with moderate ptosis and myosis.
        4. **FIGURE 12.4** Drooping of the left upper eyelid following botulinum toxin injection.

5. **FIGURE 12.5** Taping of the eyelid to clear the visual axis as an alternative to surgery in a patient with neurogenic blepharoptosis.

10. Tables
    1. **TABLE 12.1Summary of Tests Used to Help in the Diagnosis of MG/OMG**

6. Chapter 13: Brow Ptosis
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 13.1** Temporal brow hooding due to age-related descent of the brow.
        2. **FIGURE 13.2** Severe brow ptosis causing a significant loss of the superior visual field.
        3. **FIGURE 13.3** Facial nerve palsy causing significant unilateral brow ptosis with brow asymmetry and lower eyelid ectropion. (Courtesy of Dr. Ilya Leyngold.)
7. Chapter 14: Congenital Tarsal Kink
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Characteristics
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 14.1** Spectrum of involvement of the upper eyelid in patients with congenital horizontal tarsal kink. A, Moderate entropion trichiasis. B, Severe entropion trichiasis with complete obliteration of the upper eyelid crease.
8. Chapter 15: Dermatochalasis
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 15.1** A-D, Upper lid dermatochalasis of varying degrees with significant lateral hooding.

2. **FIGURE 15.2** Dermatochalasis with prolapse of the upper eyelid medial fat pad.
3. **FIGURE 15.3** Upper eyelid dermatochalasis with eyelid margin entropion and secondary eyelash ptosis.
4. **FIGURE 15.4** Lower eyelid dermatochalasis with mild (A) and marked (B) prolapse of fat pads and dewlap skin redundancy (C and D).
5. **FIGURE 15.5** Premature aging and dermatochalasis in a patient with cutis laxa.

9. Chapter 16: Ectropion, Cicatricial
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 16.1** A, Cicatricial ectropion of the lower eyelid from a contracted scar. B, Upper eyelid cicatricial ectropion due to penetrating trauma. C, Cicatricial ectropion of the lower eyelid due to burn injury. D, Upper eyelid cicatricial ectropion due to excessive radiotherapy as a child.
        2. **FIGURE 16.2** A, Severe lower eyelid ectropion from a contracted cutaneous malignant neoplasm. B, Cicatricial ectropion of the lower eyelid due to excision of skin neoplasm left to heal by granulation. C, Mild and (D) moderate lateral lower eyelid cicatricial ectropion from sun-exposed skin contracture.
10. Chapter 17: Ectropion, Congenital
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 17.1** Congenital upper eyelid eversion with severe conjunctival chemosis. The eyelid margin is completely everted (arrowhead), and the meibomian glands are clearly visible (asterisk). (Courtesy of Dr. Elshaimaa Taher.)
        2. **FIGURE 17.2** A, Congenital upper eyelid eversion without conjunctival chemosis 1 week after birth. B, Complete spontaneous resolution at 4 weeks of age.

3. **FIGURE 17.3** Congenital ectropion involving the upper and lower eyelids in Down syndrome.
4. **FIGURE 17.4** Chronic conjunctivitis and corneal scarring in an 18-year-old female patient with Down syndrome and neglected upper eyelid ectropion.

11. Chapter 18: Ectropion, Involutional
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 18.1** A, Medial ectropion with punctal eversion. B, Ectropion involving the lateral part of the lower eyelid. C, Generalized ectropion involving all parts of the lower eyelid. D, Tarsal ectropion with complete 180° eversion of the lower eyelid.
        2. **FIGURE 18.2** Snap back or distraction test. A, The eyelid is pulled away the globe centrally; a distance of 8 mm or more is a positive test for eyelid laxity. B, When released, the eyelid does not immediately retract to its normal position, but slowly drifts back.
12. Chapter 19: Entropion, Cicatricial
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 19.1** Cicatricial entropion. A, Mild entropion with secondary trichiasis from Stevens-Johnson syndrome. B, Lateral upper eyelid entropion in a case of trachoma. C, Cicatricial entropion with retraction of the upper eyelid from severe conjunctival scarring. D, Severe entropion of upper and lower eyelids from ocular cicatricial pemphigoid.
        2. **FIGURE 19.2** Segmental cicatricial entropion. A, Medial lower eyelid entropion following trauma. B, Medial upper eyelid entropion and corneal scarring resulting from an alkali burn.
        3. **FIGURE 19.3** Conjunctival scarring associated with cicatricial entropion. A, Mild scarring of the upper eyelid conjunctiva. B, Symblepharon and shortening of the fornix of the lower eyelid. C, Medial symblepharon

of the lower eyelid. D, Marked loss of the conjunctiva from ocular cicatricial pemphigoid.
13. Chapter 20: Entropion, Involutional
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 20.1** Spectrum of involvement of the lower eyelid in involutional entropion. A, Mild entropion with eyelashes anterior to the corneal surface. B, Moderate entropion where the eyelashes approach the globe with intermittent corneal touch. C, Advanced involutional entropion with most of the eyelashes directed toward the ocular surface. D, Severe involutional entropion with inversion of the tarsal plate and the entire mucocutaneous border of the eyelid, together with the eyelashes, is directed against the globe. A prominent preseptal orbicularis oculi muscle completely overrides its pretarsal counterpart.
14. Chapter 21: Epiblepharon
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 21.1** Congenital epiblepharon with the absence of the lid crease and a fold of skin overriding the eyelid margin.
        2. **FIGURE 21.2** A and B, Epiblepharon in an older child with accentuated eyelid margin inturning during downgaze.
        3. **FIGURE 21.3** I-IV, Morphological classification of the lower lid epiblepharon according to the height of the lower lid skin fold. **Class I**. The fold is below the lower eyelid margin. **Class II**. The fold is at the level of the lower eyelid margin without concealing it. **Class III**. The fold is above the level of the lower lid margin but conceals <one-third of the lid margin medially. **Class IV**. The fold is above the level of the lower lid margin and conceals >one-third of the lid margin.

4. **FIGURE 21.4** Acquired secondary epiblepharon from an oversized ocular prosthesis.
5. **FIGURE 21.5** A, A young child with epiblepharon and an inturned eyelid margin. B, The eyelid margin is repositioned into a normal orientation following crease reformation with full-thickness Quickert-Rathbun sutures.
6. **FIGURE 21.6** A-C, Surgical excision of a strip of skin and orbicularis muscle for correction of epiblepharon in an older child.
7. **FIGURE 21.7** Recurrence of epiblepharon restricted to the medial side of the eyelid as a complication of the modified Hotz procedure.

15. Chapter 22: Eyelid Retraction
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 22.1** A and B, Eyelid retraction in thyroid eye disease with equal retraction of both the upper and lower eyelids.
        2. **FIGURE 22.2** Variations in the pattern of eyelid retraction in thyroid eye disease. A and B, Upper eyelid retraction. C and D, Lower eyelid retraction.
        3. **FIGURE 22.3** Left eyelid retraction in a patient with marked left upper eyelid aponeurosis from orbital septum fibrosis and contraction following multiple failed ptosis procedures.
16. Chapter 23: Facial Nerve Paralysis
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 23.1** Degrees of facial paralysis. A, Mild paralysis (House-Brackmann grade II) with minimal weakness of facial muscles. B, Severe facial paralysis (House-Brackmann grade IV) with loss of all tone in facial muscles and disfiguring asymmetry. (Courtesy of Dr. Allen Putterman.)

2. **FIGURE 23.2** A and B, Ophthalmic manifestations of facial nerve palsy with brow ptosis, secondary dermatochalasis, and lower eyelid laxity.
3. **FIGURE 23.3** Facial paralysis. A, Left facial muscle weakness and mouth droop. B, Marked lagophthalmos and corneal exposure on attempted eyelid closure. (Courtesy of Dr. Kyle Godfrey.)

3. III: Anomalies, Movement Disorders, and Aging Phenomena
    1. Chapter 24: Ablepharon
        1. Key Points
        2. Etiology and Pathogenesis
        3. Clinical Presentation
        4. Differential Diagnosis
        5. Treatment
        6. Prognosis
        7. Histopathology
        8. References
        9. Figures
            1. **FIGURE 24.1** Ablepharon. Severe anterior lamellar shortening is seen, and the upper eyelid margin is very close to the eyebrows. (Courtesy of Dr. Antonio Augusto Cruz.)
            2. **FIGURE 24.2** Ablepharon-macrostomia syndrome. In addition to the severe anterior lamellar lid shortening, these patients exhibit a wide fishlike mouth (macrostomia).
    2. Chapter 25: Ankyloblepharon
        1. Key Points
        2. Etiology and Pathogenesis
        3. Clinical Presentation
        4. Differential Diagnosis
        5. Treatment
        6. Prognosis
        7. Histopathology
        8. References
        9. Figures
            1. **FIGURE 25.1** Two female siblings with classic congenital ankyloblepharon involving the medial canthal region. A, A milder form of medial ankyloblepharon. The lacrimal passages are patent. B, Severe medial ankyloblepharon. The plica semilunaris and caruncle are absent, and the lacrimal passages are rudimentary.
            2. **FIGURE 25.2** Ankyloblepharon filiforme adnatum (AFA). A, Type I or isolated nonsyndromic ankyloblepharon. A single central thin band can be observed. B, Another example of type I ankyloblepharon. Multiple broader bands can be seen. C, Type IV AFA. Multiple ankyloblepharon bands associated with cleft lip/palate. (Courtesy of Dr. Alan McNab.)

3. **FIGURE 25.3** Acquired ankyloblepharon. A, Traumatic ankyloblepharon involving the medial canthus. B, Ankyloblepharon due to ocular cicatricial pemphigoid. C, Ankyloblepharon following bicanalicular lacrimal system intubation.

10. Tables
    1. **TABLE 25.1Classification of AFA According to Systemic Associations**

3. Chapter 26: Apraxia of Eyelid Opening
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Characteristics
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 26.1** A-D, Apraxia of eyelid opening; there is involuntary eyelid closure without forceful orbicularis muscle contraction and with elevation of the brows.
4. Chapter 27: Blepharochalasis
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 27.1** Hypertrophic changes in blepharochalasis. A, Asymmetrical fat bulge with predominant protrusion of the nasal pad of fat. B, Bilateral hypertrophic changes with a generalized fat bulge. C, An unusual case of persistence of hypertrophic eyelid changes through old age with asymmetrical generalized fat bulging.
        2. **FIGURE 27.2** Atrophic changes in blepharochalasis. A, Blepharochalasis patients show signs of premature aging with marked thinning of the skin, acquiring the landmark sign, “wrinkled cigarette paper skin.” B, There is partial atrophy of orbital fat, and the skin is thin, stretched, atrophic, and redundant. C, In severe cases, a pseudoepicanthal fold can be observed due to marked atrophy of the nasal pad of fat. Again, the skin is loose, and discolored with abundant fine wrinkles.
        3. **FIGURE 27.3** Ptosis in patients with blepharochalasis. A, Severe ptosis which is more marked in the OD can be seen. This is associated with severe wrinkling of the skin

as well as a pseudoepicanthal fold. B, Another patient with more advanced ptosis completely occluding the visual axis. (Courtesy of Dr. Alan McNab.)

5. Chapter 28: Blepharophimosis Syndrome
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 28.1** Typical findings of blepharophimosis syndrome. A, Blepharophimosis. B, Ptosis. C, Epicanthus inversus. D, Telecanthus.
        2. **FIGURE 28.2** Variable degrees of ptosis in blepharophimosis syndrome. A, Moderate ptosis without obstruction of the visual axis. B, Moderate ptosis with bisection of the visual axis. C, Severe ptosis obstructing the visual axis. D, Severe profound ptosis completely obliterating the visual axis with the typical chin-up head position.
        3. **FIGURE 28.3** Variable degrees of lower eyelid ectropion in blepharophimosis syndrome. A, Mild ectropion. B, Moderate-severe ectropion. Anterior lamellar shortening is obvious particularly laterally.
        4. **FIGURE 28.4** Schwartz-Jampel syndrome (SJS). A, The fixed facial features of Schwartz-Jampel syndrome (ptosis, blepharophimosis, and a puckered mouth) are related to the chronic contracture of the periocular as well as the perioral muscles. (Courtesy of Dr. Antonio Augusto Cruz.) B, A more severe example of SJS with more marked puckering of the mouth. Blepharophimosis is also more pronounced.
        5. **FIGURE 28.5** Three different surgical approaches for blepharophimosis syndrome. A, The traditional or *epicanthus-first* approach starts with the repair of the epicanthus and telecanthus first followed by repair of ptosis 3-6 months later. B, In the *ptosis-first* approach, the sequence may be reversed. Ptosis is corrected first and canthal surgery is deferred for later. C, The *one-stage* approach. Ptosis together with epicanthus and telecanthus are repaired simultaneously in the same setting, which may result in a temporary medial undercorrection.
        6. **FIGURE 28.6** The natural history of untreated blepharophimosis syndrome according to the age of the patient. A, In infants and children, the full spectrum of the disorder can be observed. B, In older individuals

presenting with untreated blepharophimosis, there may be a slight or moderate improvement in epicanthus and telecanthus, but the ptosis persists and dominates the picture. (Courtesy of Dr. Allen Putterman.)
6. Chapter 29: Congenital Upper and Lower Eyelid Coloboma
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
        1. *Classification of Colobomas*
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 29.1** Clinical spectrum of complete cryptophthalmos. A, Bilateral cryptophthalmos. The lateral two-thirds of the eyebrows is absent and an abnormal tongue of hair is seen extending from the scalp hairline to the brows. B, Unilateral cryptophthalmos. A tuft of eyelashes can be seen at the presumed junction between the undeveloped upper and lower eyelids. C, Unilateral cryptophthalmos. No rudimentary lashes can be seen but a tongue of hair extending from the hairline to the brow can be observed. (A, Courtesy of Dr. Alan McNab.)
        2. **FIGURE 29.2** Incomplete cryptophthalmos. A, The patient has a deceptively insignificant upper eyelid coloboma because the colobomatous part of the eyelid is largely replaced by the oversized skin fold. The lateral eyelid structures are normal, and the medial lip of the upper eyelid including the lacrimal system is also preserved. The concealed part of the cornea is mostly keratinized, and the prognosis for functional reconstruction/visual development is dismal. B, The lateral eyelid structures are also preserved but the lacrimal system is absent because the abnormal skin fold in this patient also involves the medial part of the upper eyelid.
        3. **FIGURE 29.3** Spectrum of involvement of the upper eyelid in congenital symblepharon variant (CSV), which is usually bilateral. A, Bilateral moderately sized coloboma with mild corneal involvement. The cornea is relatively spared. B, A 2-week-old infant presenting with a bilateral corneal abscess. The moderately sized eyelid defect is associated with significant corneal adhesions that are responsible for extensive corneal morbidity. C, Asymmetrical presentation with a near-total eyelid colobomatous defect (OD) and a moderately sized defect in the OS. D, Close-up view of

corneopalpebral adhesions, which are a universal finding in CSV but is minimal to moderate in this particular case. E, Close-up of extensive corneo-palpebral adhesions (CPA) involving the entire colobomatous defect.

4. **FIGURE 29.4** Simple colobomas involving the upper eyelid are usually unilateral and may assume a triangular or quadrangular shape. A, Simple coloboma associated with Goldenhar syndrome. B, Simple isolated coloboma without a syndromic association. C, Close-up view of a triangular coloboma. D, Close-up view of a quadrangular coloboma.
5. **FIGURE 29.5** Lower eyelid colobomata. A, Simple isolated lower eyelid coloboma with tissue maldevelopment in the medial canthal region. Neither a syndromic association nor a craniofacial cleft could be demonstrated. B, Patients with Treacher Collins syndrome show the characteristic downward and lateral (antimongoloid) slanting of the palpebral fissure, which is almost pathognomonic of the condition and gives these patients the characteristic “sad-looking eyes.” Mid-facial hypoplasia can be seen.
6. **FIGURE 29.6** Spectrum of involvement of the eyelids in patients with Tessier clefts (oblique facial clefts). A, Tessier cleft #9 with a paramedian coloboma and frontal encephalocele. The lateral two-thirds of the ipsilateral eyebrow is absent. B, TC #10 with a frontal encephalocele, and an eccentric coloboma of the upper eyelid that was inadequately repaired. The orbital roof is absent as well as the entire ipsilateral eyebrow. C, Unilateral TC #3 with an extensive medial lower eyelid defect but without an associated cleft lip. D, A rare case of bilateral TC #3 with bilateral cleft lip and palate, and a predominantly unilateral extensive medial lower eyelid defect. (C, Courtesy of Dr. Amir Elbarbary.)
7. **FIGURE 29.7** Spectrum of involvement of the eyelids in lateral canthal clefts or lateral canthal colobomata (the so-called Tessier cleft #8). All patients have Goldenhar syndrome, but none of the patients had an associated bony defect. A and B, True lateral commissure colobomata with a maldeveloped (absent) lateral canthus and an associated dermolipoma. The rest of the upper and lower eyelids are normal. C, An extensive dermolipoma is associated with a strip of skin that disrupts the normal anatomy of the lateral canthus. Another coloboma in the medial part of the upper eyelid can be seen. D, A lateral canthal coloboma in the lateral half of the upper eyelid. An extensive dermolipoma can be seen.

8. **FIGURE 29.8** A rare case of group I proboscis lateralis arising exclusively from the lower eyelid. A, Frontal view. B, Lateral view.
9. **FIGURE 29.9** This left upper eyelid coloboma was removed at the age of 3 years. It was part of a facial deformity incompletely repaired at 2 days of age. A, A mixture of epidermis and conjunctival epithelium lines the coloboma. B, At the edge of the coloboma, the eyelid has pseudoepitheliomatous hyperplasia of the epidermis, only a focus of atrophic orbicularis oculi muscle, and lacks tarsus.

7. Chapter 30: Distichiasis
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 30.1** Distichiasis. A, Congenital distichiasis of the upper and lower eyelids. B, Acquired distichiasis of the upper eyelid. C, Acquired distichiasis of the lower eyelid.
        2. **FIGURE 30.2** A, Cilium incarnatum externum. A single lash is seen buried beneath the skin (black arrow). B, High magnification view (slit lamp photomicrograph) of another patient with cilium incarnatum externum showing the buried lash. C and D, Cilium incarnatum internum. An eyelash can be observed extending into the undersurface of the eyelid beyond the eyelid margin (white arrow). (A and C, Courtesy of Drs. Bhupendra Patel and Raman Malhotra.)
        3. **FIGURE 30.3** A, Ectopic cilia. B, Eyelashes arising from a conjunctival lipodermoid. Both conditions are away from the eyelid margin and should not be confused with distichiasis.
8. Chapter 31: Epicanthal Folds
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 31.1** Epicanthal folds obscuring part of the medial upper eyelid and medial canthus.

        2. **FIGURE 31.2** Types of epicanthal folds. A, Epicanthus supraciliaris. B, Epicanthus palpebralis. C, Epicanthus tarsalis. D, Epicanthus inversus.
9. Chapter 32: Essential Blepharospasm
    1. Key Points
    2. Etiology and Pathophysiology
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 32.1** A-D, Essential blepharospasm as a focal dystonia involving the eyelids. Note contraction of the orbicularis muscle and downward traction on the eyebrows.
        2. **FIGURE 32.2** A, Segmental dystonia of EB and midfacial dystonia (Meige syndrome). B, Regional dystonia with EB, midfacial dystonia, and torticollis.
        3. **FIGURE 32.3** Various mechanisms used by patients to maintain some visual function with EB. A and B, Manual elevation of the eyelids with fingers. C, Eyelid taped to the forehead. D, Ptosis crutches fixed to eyeglasses.
        4. **FIGURE 32.4** Secondary reflex blepharospasm from severe blepharitis simulating essential blepharospasm.
10. Chapter 33: Euryblepharon
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
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    9. Figures
        1. **FIGURE 33.1** Isolated euryblepharon. (Courtesy of Dr. Alan McNab.)
        2. **FIGURE 33.2** Cardinal features of the blepharocheilodontic syndrome (BCD syndrome). A, Euryblepharon. B, Cleft lip. C, Hypodontia and conical teeth.
        3. **FIGURE 33.3** Marked cheek and lower eyelid hypoplasia with the typical antimongoloid slant but not euryblepharon in a patient with Treacher Collins syndrome.
11. Chapter 34: Floppy Eyelid Syndrome
    1. Key Points
    2. Etiology and Pathogenesis

3. Clinical Presentation
4. Differential Diagnosis
5. Treatment
6. Prognosis
7. Histopathology
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9. Figures
    1. **FIGURE 34.1** Spectrum of involvement of the upper eyelid in patients with floppy eyelid syndrome. A, Grade 1 (mild FES): One-third of the tarsal conjunctiva is exposed upon eyelid eversion. B, Grade 2 (moderate FES): Between one-third and half of the tarsal conjunctiva is exposed with eyelid eversion. C, Grade 3 (severe FES): More than half of the tarsal conjunctiva is exposed. D, Grade 3 with severe conjunctivitis.
    2. **FIGURE 34.2** Additional palpebral features of floppy eyelid syndrome. A, Involvement of the lower eyelid in floppy eyelid syndrome. B, Blepharoptosis C, Eyelash ptosis and loss of eyelash alignment. D, Eyelid imbrication (overhanging of the upper eyelid over the lower eyelid).
    3. **FIGURE 34.3** Features of pachydermoperiostosis. A, Severe ptosis and massive eyelid thickening. B, Floppy eyelids. C, Digital clubbing.
    4. **FIGURE 34.4** This left upper eyelid resection was from the 43-year-old man with pachydermoperiostosis reported by Neufeld and coworkers.[37] A, Full-thickness photomicrographic section of the eyelid with marked thickening of the dermis (bracket) due to sclerosis and hyperplasia of hair follicles, sebaceous glands, eccrine glands, and apocrine glands. Meibomian gland hyperplasia thickens the tarsal plate (). B, Higher magnification of the dermis showing hyperplasia of hair follicles, apocrine glands, and eccrine glands. C, Sebaceous glands were focally hyperplastic within the dermis. D, The conjunctival epithelium is markedly thickened and has superficial keratinization with a paucity of goblet cells, the substantia propria is thickened by dense collagenous tissue with areas of hyalinization, and there is slight chronic inflammation.
12. Chapter 35: Hemifacial Spasm
    1. Key Points
    2. Etiology and Pathophysiology
    3. Clinical Presentation
    4. Differential Diagnoses
    5. Treatment
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1. **FIGURE 35.1** A-D, Clinical features of hemifacial spasm.

13. Chapter 36: Horner Syndrome
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Lesion Localization
    5. Differential Diagnosis
    6. Treatment
    7. Prognosis
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    10. Figures
        1. **FIGURE 36.1** Spectrum of ocular and periocular involvement in patients with Horner syndrome. A, Isolated ptosis of the right eyelid. B, Right eyelid with ipsilateral miosis. C, Ptosis with ipsilateral miosis and pseudoenophthalmos due to subtle upside-down ptosis of the lower eyelid.
14. Chapter 37: Madarosis
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
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        1. **FIGURE 37.1** A and B, Madarosis associated with chronic blepharitis.
        2. **FIGURE 37.2** Chronic eyelid rubbing with breakage of eyelashes at their base.
        3. **FIGURE 37.3** Sebaceous carcinoma along the lower eyelid margin with loss of eyelashes.
        4. **FIGURE 37.4** Recurrent lower eyelid chalazion with madarosis.
        5. **FIGURE 37.5** Marginal eyelid arteriovenous malformation associated with loss of eyelashes.
        6. **FIGURE 37.6** Reconstructed upper eyelid following Cutler-Beard procedure with absence of eyelashes.
        7. **FIGURE 37.7** Congenital coloboma of the upper eyelid with absence of the eyelid margin and eyelashes.
15. Chapter 38: Marcus Gunn Jaw Wink Ptosis
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis

7. Histopathology
8. References
9. Figures
    1. **FIGURE 38.1** A-D, Type 1 MGJWP or external pterygoid-levator synkinesis with synkinetic eyelid elevation when the jaw is moved to the contralateral side.
    2. **FIGURE 38.2** A-D, Type 1 synkinesis with eyelid elevation when the jaw is opened widely. (A, Courtesy of Dr. Allen Putterman.)
    3. **FIGURE 38.3** A and B, Jaw wink synkinesis with smiling.
    4. **FIGURE 38.4** A, Inverse Marcus Gunn jaw winking with no ptosis at rest. B, The eyelid droops on opening the mouth and MRD-1 is reduced. C, Marin-Amat syndrome 5 years following facial nerve palsy in the right side with no ptosis at rest. D, The eyelid droops on attempted chewing and in contrast to inverse Marcus Gunn both MRD-1 and MRD-2 are reduced.
    5. **FIGURE 38.5** Rare synkinetic eyelid movements. A and B, Right-sided levator-medial rectus muscle synkinesis. The eyelid retracts and the ptosis disappears on attempted adduction. C and D, Trochlear-oculomotor synkinesis. The eyelid retracts with depression of the eye in adduction.

16. Chapter 39: Microblepharon
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 39.1** A, Mild microblepharon of the upper eyelid. B, A mild case of lower eyelid microblepharon.
        2. **FIGURE 39.2** In mild cases of microblepharon, the diagnosis may be elicited by asking the child to look down.
        3. **FIGURE 39.3** Severe upper and lower eyelid microblepharon.

17. Chapter 40: Myokymia
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology

8. References
18. Chapter 41: Telecanthus
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 41.1** A-D, Congenital telecanthus associated with blepharophimosis syndrome. D, (Courtesy of Dr. Allen Putterman.)
        2. **FIGURE 41.2** A and B, Pseudoesotropia due to telecanthus.
        3. **FIGURE 41.3** Traumatic telecanthus. (Reprinted with permission from Elbarbary AS, Ahmed AL. Medial canthopexy of old unrepaired Naso-orbital-ethmoid (NOE) traumatic telecanthus. *J Cranio-Maxillofacial Surg.* 2014; 42:106-112.)
19. Chapter 42: Trichiasis
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 42.1** A and B, Minor trichiasis with fewer than six eyelashes touching the globe.
        2. **FIGURE 42.2** A and B, Minimal major trichiasis with six or more aberrant eyelashes. A, Six poliotic eyelashes on the upper eyelid contacting the cornea. The posterior eyelid margin is sharp and there is no entropion. B, Seven trichiatic eyelashes along the central lower eyelid.
        3. **FIGURE 42.3** Major trichiasis with numerous aberrant eyelashes contacting the corneal surface. A, Lower eyelid trichiasis with Stevens-Johnson syndrome. B-D, Trichiasis from conjunctival scarring in a case of trachoma.
        4. **FIGURE 42.4** Management of trichiasis. A, Manual epilation. B, Electroepilation. C, Cryosurgery. D, Laser ablation.
        5. **FIGURE 42.5** A, Lid splitting procedure with advancement of the anterior lamella. B, Direct internal eyelash bulb resection.
20. Chapter 43: Trichomegaly

1. Key Points
2. Etiology and Pathogenesis
3. Clinical Presentation
4. Differential Diagnosis
5. Treatment
6. Prognosis
7. Histopathology
8. References
9. Figures
    1. **FIGURE 43.1** Excessive elongation of eyelashes in trichomegaly. (Reprinted with permission from Wolters Kluwer: Kosal UI, Pilanci KN, Ordu C, et al. Trichomegaly induced by cetuximab; case series and review of the literature. *Am J Therapeut*. 2016;23:e1226-e1229.)
    2. **FIGURE 43.2** Trichomegaly with dark, thick elongated lashes in the lateral half of the upper eyelid.
    3. **FIGURE 43.3** A, Trichomegaly associated with topical prostaglandin F2α analog use, resulting in increase in number, thickness, and pigmentation of the eyelashes. B, Long eyelashes in trichomegaly adherent to the tear film and in contact with the eye.

4. IV: Benign Lesions and Disorders of the Eyelids
    1. Chapter 44: Abscess and Preseptal Cellulitis
        1. Key Points
        2. Etiology and Pathogenesis
        3. Clinical Presentation
        4. Differential Diagnosis
        5. Treatment
        6. Prognosis
        7. Histopathology
        8. References
        9. Figures
            1. **FIGURE 44.1** Eyelid abscess. A, Upper eyelid with surrounding cellulitis. B, Large upper eyelid and brow abscess. C, Abscess formation in the medial canthal region following minor trauma. D, Surgical drainage of a large upper eyelid and brow abscess with copious purulent material.
            2. **FIGURE 44.2** Preseptal cellulitis. A, Preseptal cellulitis following brow epilation involving the upper eyelid. B, Mild preseptal cellulitis involving the lower eyelid. C and D, Diffuse preseptal cellulitis involving the entire upper eyelid with secondary mechanical ptosis.
            3. **FIGURE 44.3** A, Suppurative granulomatous inflammation, with granulomatous inflammation surrounding a small abscess, is a feature of unusual skin infections such as this case resulting from *Purpureocillium lilacinum* (formerly termed *Paecilomyces lilacinus*) infection after a laceration

contaminated by soil (hematoxylin and eosin). B, Staining with Grocott methenamine silver technique highlights septate hypha in the center of the suppurative granuloma. The morphology of the fungus is compatible with the culture growing *Purpureocillium lilacinum*, but *Aspergillus* spp., *Fusarium* spp., *Scedosporium* spp., *Trichoderma* spp., and other hyaline molds may appear similar.[66]
4. **FIGURE 44.4** Acute cellulitis has neutrophils infiltrating the deep dermis and often the subcutaneous tissue (hematoxylin and eosin).

2. Chapter 45: Acrochordon
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 45.1** A-D, Sessile acrochordons on the eyelids.
        2. **FIGURE 45.2** A and B, Pedunculated and filiform acrochordons. (B, Courtesy of Dr. Charles Soparkar.)
        3. **FIGURE 45.3** A and B, Eyelid acrochordons usually feature acanthotic epidermis forming interdigitating cords resembling those in seborrheic keratoses. The epidermis covers a fibrovascular core () that may have loose or dense connective tissue. Several hyperkeratotic areas are evident (arrows).
3. Chapter 46: Actinic Keratosis
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 46.1** Actinic keratosis (AK) of the eyelids and brow. A and B, AK at the lateral lower eyelid. (Courtesy of Dr. Robert Goldberg). C, AK on the inferior brow with superficial scales. D, Erythematous macular AK on the medial lower eyelid.
        2. **FIGURE 46.2** A, Large hyperkeratotic actinic keratosis (AK) on the central lower eyelid. B, Small AK on the lateral upper eyelid with a cutaneous horn.

3. **FIGURE 46.3** A and B, An area of hypertrophic actinic keratosis (AK) arises abruptly at the eyelid margin (arrow). At higher magnification (B), the hypertrophic AK has acanthosis with dysplastic disorganized keratinocytes in the lower half of the epidermis. Normal eyelid epidermis is at the right of the photomicrograph (). C and D, This eyelid hypertrophic AK has mild to moderate acanthosis and profound hyperkeratosis. The patient had a cutaneous horn clinically, but the superficial portion of the hyperkeratosis dislodged during specimen handling. Dysplastic keratinocytes are evident in the basal epidermis when viewed at higher magnification (D). E, This eyelid lichenoid AK has dysplastic keratinocytes in the basal half of the epidermis, irregular acanthosis, vacuolar change of occasional basal cells, an apoptotic keratinocyte with bright pink cytoplasm near the surface of the epidermis (arrow), parakeratosis, and a band-like infiltrate of mononuclear leukocytes in the superficial dermis. F, Melanin accumulation in the dysplastic basal keratinocytes distinguishes pigmented AK.

4. Chapter 47: Amyloidosis
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 47.1** A-D, Periorbital amyloidosis cases with chronic eyelid edema and mechanical ptosis.
        2. **FIGURE 47.2** A, Racoon eyes from spontaneous hemorrhage in bilateral periorbital amyloidosis. B, Upper and lower eyelid amyloidosis with numerous small confluent papulonodular masses.
        3. **FIGURE 47.3** A-D, Conjunctival amyloid with salmon patch infiltrations, subconjunctival masses, erythema, madarosis, and mechanical ectropion. (A, Courtesy of Dr. Bita Esmaili.)
        4. **FIGURE 47.4** A, Amyloidosis of the tarsal conjunctiva usually has irregularly shaped, amorphous, eosinophilic deposits in the substantia propria with clefts and scattered intervening fibroblasts. Amyloid is also within the walls of blood vessels (arrows; hematoxylin and eosin). B, In the eyelid dermis, amyloid often forms small nodules that may become confluent (hematoxylin and eosin). C, On rare occasions, the eyelid may have amyloid confined to the papillary dermis () without

vascular involvement, similar to lichen amyloidosis and macular amyloidosis elsewhere in the body. Actinic elastosis is below the band of amyloid that abuts the epidermis (hematoxylin and eosin). D, Lymphocytes, plasma cells, and foreign body-type multinucleated giant cells (arrows) may infiltrate the amyloid deposits (hematoxylin and eosin). E, Amyloid stains various shades of red, when viewed with unpolarized light in sections stained with Congo red at an alkaline pH. The intensity of staining and color are influenced by pH, length of fixation in formaldehyde-containing solutions, the thickness of the cut sections, and length of storage of cut paraffin sections (Congo red). This is the same case of conjunctival amyloid as shown in Figure 47.4A. F, In sections stained with Congo red, amyloid appears bright red against a less intense red background when viewed using fluorescence microscopy with a tetramethylrhodamine isothiocyanate or Texas Red filter set. The use of fluorescence microscopy is beneficial for confirming the diagnosis of amyloid in cases that are equivocal using polarization microscopy and those with only small amounts of amyloid. This is the same case of eyelid dermal amyloid shown in Figure 47.4C.

5. **FIGURE 47.5** Ptosis developed in a man with an orbital amyloidoma associated with a localized plasma cell dyscrasia. A, This biopsy of Müller muscle shows envelopment of the spindle-shaped smooth muscle fibers by amorphous eosinophilic amyloid. B, The amyloid stained red using Congo red. It was birefringent and dichroic using polarization microscopy, confirming its identity as amyloid.

5. Chapter 48: Angioedema
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 48.1** A-D, Clinical presentations of eyelid angioedema.
        2. **FIGURE 48.2** A, Angioedema of the eyelid has pallor of the deep dermis due to the accumulation of extracellular edema fluid with separation of collagen bundles. A dilated venule is present (arrow) (hematoxylin and eosin). B, The collagen bundles are spaced widely apart due to the accumulation of edema fluid. Mast cells (arrows) and a plump reactive fibroblast

() are evident at higher magnification. Enlarged fibroblasts are more prominent in chronic than acute angioedema.

6. Chapter 49: Angiofibroma
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 49.1** A, Solitary nonhereditary angiofibroma near the eyelid margin. (Courtesy of Dr. Norman Charles.) B, Angiofibroma involving the upper eyelid. C, Angiofibromas of the upper and lower eyelids. (Courtesy of Dr. Richard Anderson.) D, Massive pedunculated angiofibromas involving upper and lower eyelids. (Courtesy of Dr. David Jordan.)
        2. **FIGURE 49.2** A, Angiofibroma with a papillomatous appearance from the lateral left upper eyelid of a teenager with tuberous sclerosis complex. The dermis is fibrotic with prominent dilated blood vessels. Concentric fibrosis surrounds hair follicles, and sebaceous glands are absent. B, A common feature in angiofibromas is concentric lamella of hyalinized fibrous tissue surrounding hair follicles. Many dilated vessels are evident in the fibrotic dermis.
7. Chapter 50: Arteriovenous Malformations
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 50.1** A and B, Arteriovenous malformations involving the eyelids and face. (B, Courtesy of Dr. Jeffrey Nerad.)
        2. **FIGURE 50.2** A, Progression of an arteriovenous malformation of the left orbit and eyelid from Schöbinger stage I in 2013. B, Brain CT-angiography (December 2013) with an arterial feeder from the external carotid artery and a feeder from the ophthalmic artery. C and D, The same patient (August 2021) with progression to Schöbinger stage III following multiple procedures.

3. **FIGURE 50.3** A, Arteriovenous malformation of the left upper eyelid composed of thick-walled arteries (on right) and thin-walled veins (on left). The proportion of arteries and veins varies from one region of a malformation to another (hematoxylin and eosin). B, Lesion extending through the orbicularis muscle (hematoxylin and eosin).

8. Chapter 51: Arthropod Bites and Stings
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Characteristics
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 51.1** A and B, Nonspecific insect bites with local erythema and edema of the lower eyelids. A, (Courtesy of Dr. Robert A. Goldberg.)
        2. **FIGURE 51.2** A conjunctival granuloma (ophthalmia nodosa) resulted from the hair of a woolly bear caterpillar, the larval form of the isabella tiger moth (*Pyrrharctia isabella*).
        3. **FIGURE 51.3** Caterpillar hair in a meibomian gland orifice. (Reprinted with license from Wolters Kluwer: Rajagopalan J, Joy A, Yadalla D. A rare hideout for caterpillar hairs. *Ophthalmic Plast Reconstr Surg.* 2020;36(4):e93-e94; Figure 2.)
        4. **FIGURE 51.4** A woolly bear caterpillar hair penetrated into the cornea; this is the same patient shown in Figure 51.3.
        5. **FIGURE 51.5** A and B, Spider bite lesions with edema, erythema, and focal tissue necrosis. (Courtesy of Dr. Charles Soparkar.)
        6. **FIGURE 51.6** Scanning electron micrograph of a pubic louse (*Pthirus pubis*) attached to a plucked eyelash.
        7. **FIGURE 51.7** A, This biopsy 1.5 weeks following a tick bite shows a prominent perivascular inflammatory infiltrate. The epidermis has spongiosis with an overlying serum crust. B, At higher magnification, the 1.5-week-old tick bite has eosinophils mixed with macrophages and lymphocytes. C, The perivascular inflammation may persist for a long time, as shown in this biopsy several months following an insect bite. These vessels in the deep dermis have a mild perivascular infiltrate of macrophages, lymphocytes, and eosinophils.
        8. **FIGURE 51.8** Ophthalmia nodosa features granulomas surrounding caterpillar hairs, as shown in this nodule

removed from the anterior episclera of the patient shown in Figure 51.2.
9. Chapter 52: Atopic Dermatitis
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 52.1** A, Spongiotic dermatitis with a small medial patch of an inflammatory rash with cracked skin and fluid. B, Atopic dermatitis with eyelid edema and erythema.
        2. **FIGURE 52.2** Eyelid thickening with violaceous coloration.
        3. **FIGURE 52.3** A and B, Medial eyelid thickening and lichenification.
        4. **FIGURE 52.4** This eyelid biopsy was from a 5-year-old boy with an approximately 1-year history of photosensitivity and atopic dermatitis. His arms and legs had eczematous, scaly, erythematous patches, and thin plaques, and his upper and lower eyelids were thickened and erythematous. A, There are focal parakeratosis adjacent to a follicular orifice (arrow), acanthosis with occasional fusion of elongated rete ridges to form plates, perivascular mononuclear leukocytes, and lymphangiectasia. The papillary dermis appears more dense than usual (fibrotic), though this is subjective. B, Scattered mononuclear cells (cells with darker nuclei and a surrounding clear zone) infiltrated the epidermis. Mononuclear leukocytes (lymphocytes and macrophages) surround blood vessels in the superficial dermis. C, The infiltrate around blood vessels in the papillary and superficial reticular dermis was occasionally prominent. The small vessels have prominent endothelial cells. D, An immunohistochemical stain using antibodies to CD3 highlights T lymphocytes around dermal blood vessels and infiltrating the epidermis. Macrophages accounted for the other perivascular mononuclear cells, as evidenced using staining with antibodies to CD68 (image not shown). Only rare B lymphocytes were seen using antibodies to CD20 (image not shown).
10. Chapter 53: Blepharitis
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation

4. Differential Diagnosis
5. Treatment
6. Prognosis
7. Histopathology
8. References
9. Figures
    1. **FIGURE 53.1** A and B, Blepharitis of the lower eyelids manifest as erythema and madarosis.
    2. **FIGURE 53.2** A, Severe chronic blepharitis with thickening of the eyelid margins. B, Secondary blepharospasm from severe blepharitis and corneal irritation.
    3. **FIGURE 53.3** A, Marginal blepharitis with meibomian gland plugging. B, Thickened and ropy meibomian gland secretions from blepharitis. (A and B, reprinted with license from Wolters Kluwer, Duncan K, Jeng B. Medical management of blepharitis. *Curr Opin Ophthalmol*. 2015;26:289-294; Figure 1.)
    4. **FIGURE 53.4** This left medial canthus eyelid margin biopsy with subacute spongiotic dermatitis was performed because of thickening and induration for the prior 18 months, refractory to topical antibiotic and corticosteroid steroid therapy. A, The epidermis is acanthotic with a thin layer of parakeratosis. The papillary dermis is focally edematous and has an infiltrate of lymphocytes, macrophages, and occasional eosinophils. B, In this area, the papillary dermal inflammation is mostly macrophages with fewer lymphocytes and eosinophils. C, There were a few areas with prominent spongiosis. There are lymphocytes and eosinophils within the spongiotic epidermis (exocytosis).
    5. **FIGURE 53.5** A man in his early 60s had bilateral thickening of his eyelid skin with erythema and pruritus. The eyelid abnormalities developed over 6 years, during which he was using various types of eye drops for treating glaucoma. A, The left lower eyelid has psoriasiform dermatitis with acanthosis, parakeratosis, and chronic dermal inflammation. The surface has focal excoriation. B, A biopsy of the right lateral canthus has psoriasiform dermatitis similar to that in the left lower eyelid. Subsequent patch testing indicated that his blepharitis was most compatible with chronic allergic contact dermatitis.
    6. **FIGURE 53.6** This example of lichen planus-like keratosis was from the left upper eyelid of a man in his late 40s who developed a white lesion that was clinically suspicious for malignancy. A, A dense band of chronic inflammatory cells (lichenoid infiltrate) is in the dermis abutting the epidermis. B, The epidermis is atrophic

with hyperkeratosis and hypergranulosis. C, The lichenoid dermal inflammatory infiltrate contains lymphocytes and macrophages without many plasma cells. The keratinocytes lack cytological atypia. D, The epidermis had scattered necrotic keratinocytes (colloid bodies) in the basal epidermis and adjacent papillary dermis (arrows). Lichen planus-like keratosis is a common benign skin condition that is most often biopsied to exclude a cutaneous malignancy.[85,86]

11. Chapter 54: Cavernous Venous Malformations
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 54.1** Cavernous venous malformation of the eyelid. (Courtesy of Dr Mohsen Kashkouli.)
        2. **FIGURE 54.2** Cavernous venous malformation of the conjunctiva. (Reprinted with permission from Yazici B, Ucan G, Adim SB. Cavernous hemangioma of the conjunctiva: case report. *Ophthalmic Plast Reconstr Surg*. 2011;27:e27-e28.)
        3. **FIGURE 54.3** A, An anteriorly located orbital cavernous venous malformation that protrudes through the eyelid skin. B, Axial CT scan of the right orbit showing the anteromedial CVM. (A and B, Courtesy of Dr Daniel Rootman.)
        4. **FIGURE 54.4** This cavernous venous and lymphatic malformation, excised at the age of 3 years, was noted at birth and involved the left anterior orbit and left upper eyelid. A, The orbital component of the malformation is a venous malformation with vessels having marked variability in caliber. B, The orbital venous malformation has marked variability in vessel wall thickness, with some having mural smooth muscle. C, The vascular malformation infiltrated into the eyelid beneath the conjunctiva and had numerous irregularly-shaped dilated vascular channels. D, The vessels vary in size and wall thickness, with only some having smooth muscle in their wall. Two lymphatics have thin walls and lumens with lightly eosinophilic material devoid of erythrocytes.
        5. **FIGURE 54.5** This cavernous venous malformation of the lateral right upper eyelid was present for 15 years before excision in the patient's middle 40s due to enlargement over 3 years. A, Large malformed venous

channels are in the dermis. Thrombus is within a large vessel and two smaller vessels beneath it. The black ink at the specimen base was for orienting the tissue during embedding in paraffin. B, The thrombus is organizing, as reflected by the ingrowth of spindle cells and capillaries.
6. **FIGURE 54.6** A and B, This involuting capillary hemangioma involved the left upper eyelid and anterior orbit of a young boy. It was present since birth and excised at age 6 years due to thickened eyelid with reduced mobility. A, At low magnification, there are lobules of dilated vascular spaces. Meibomian glands are at the bottom of the photomicrograph. B, At high magnification, the involuting capillary hemangioma has dilated and normal caliber capillaries, which help distinguish this lesion from a cavernous malformation. C and D, This cherry angioma was removed from the left upper eyelid of a woman in her early 60s. C, It consists of a circumscribed collection of dilated vessels in the superficial dermis. D, At higher magnification, the thin-walled vessels are compatible with dilated capillaries and postcapillary venules. E and F, This cavernous vascular lesion was removed from the right upper eyelid of a woman in her late 40s. The lesion felt cystic, was blue, and had been present for 1.5 years with a slow increase in size. E, The lesion was well circumscribed and completely excised. Orbicularis oculi muscle is at the base of the lesion composed of markedly distended blood vessels separated by fibrous septa. F, At high magnification, the vessels are lined by flat endothelium and lack mural smooth muscle. Dense fibrous tissue separates the vascular channels. This lesion has a histological appearance identical to orbital cavernous hemangiomas/malformations.

12. Chapter 55: Chalazion and Hordeolum
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
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        1. **FIGURE 55.1** A-D, Acute hordeolum of the eyelid pointing to the skin.
        2. **FIGURE 55.2** A-D, Chronic chalazion forming an anterior subcutaneous bulge or pointing posteriorly.
        3. **FIGURE 55.3** A, Deep chalazion featuring a lipogranuloma with many large vacuoles of dissolved

lipid in the connective tissue adjacent to the tarsal meibomian glands. B, In a histological section adjacent to that in (A), the lipogranulomatous inflammation is in continuity with a meibomian duct, and lipogranulomatous inflammation has replaced the glands that would normally be present in this area. The inflammatory infiltrate contains many epithelioid cells, a few multinucleated giant cells, and lymphocytes and plasma cells. C, Foreign body giant cells, such as those in this photomicrograph, are the most common multinucleated giant cells seen in chalazia. Giant cells engulf the lipid droplets.
4. **FIGURE 55.4** This full-thickness left upper eyelid resection was from an older woman with multiple recurrences of chalazia. A, The eyelid had both a superficial chalazion arising from glands of Zeiss () and a deep chalazion arising from meibomian glands (arrow). B, The superficial chalazion has abundant variably-sized vacuoles of dissolved lipid surrounded by lipogranulomatous inflammation. C, The lipogranulomatous response features epithelioid cells with light pink cytoplasm, Langhans (arrow), and foreign body () giant cells, dissolved lipid droplets, and interspersed lymphocytes, plasma cells, and macrophages. D, This multinucleated foreign body giant cell contains dissolved lipid droplets and a prominent asteroid body (arrow). Asteroid bodies are stellate or star-shaped eosinophilic cytoplasmic inclusions within multinucleated giant cells. In our experience, they are seen uncommonly in chalazia.
5. **FIGURE 55.5** This chronic chalazion has ill-defined granulomas with prominent fibrosis and absent giant cells.

13. Chapter 56: Comedones
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        1. **FIGURE 56.1** Favre-Racouchot syndrome. A, Large comedones involving the medial and lateral canthal regions. B and C, Medial canthal comedones. D, Dark comedones in the lateral canthal region.
        2. **FIGURE 56.2** Nevus comedonicus with unilateral comedones arranged in linear streaks which follow Blaschko lines (asterisk). (Reprinted from Pavithra S, et

al. Nevus comedonicus syndrome. *Indian J Dermatol*. 2011; 56(2):771-772. © Indian Journal of Dermatology. CC BY-SA 3.0.)
3. **FIGURE 56.3** A solitary giant or macrocomedo (dilated pore of Winer) presenting as a single white, markedly dilated giant comedo, with sharply defined margins and a central black core (blackhead).
4. **FIGURE 56.4** A, This open comedone shows a follicular infundibulum distended by keratin, which protrudes from the orifice. Green ink was used for orientation and is present on the epidermal surface. B, The comedone is lined by stratified squamous epithelium having an inconspicuous granular cell layer. Colonies of *Cutibacterium acnes* are present among the keratin and appear as basophilic particles ().
5. **FIGURE 56.5** A, A dilated pore of Winer histologically appears as a keratin-plugged, cystically dilated hair follicle. Acanthotic stratified squamous epithelium lines the dilated pore and forms irregular projections into the adjacent dermis. B, Lamellae of keratin occupy the cystically dilated hair follicle. Irregular budding of the epithelium into the adjacent dermis is characteristic of dilated pores.

14. Chapter 57: Cutaneous Horn
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        1. **FIGURE 57.1** Various shapes of eyelid cutaneous horns. A, Conical horn. B, Nodular shape overlying the lacrimal punctum. C, Multiple lobular cutaneous horns. D, Filiform horn. (Courtesy of Dr. Charles Soparkar.)
        2. **FIGURE 57.2** The spectrum of surface characteristics of eyelid cutaneous horns. A, Rugose surface. B, Crusted surface. (Courtesy of Dr. Robert Goldberg.) C, Pigmented horn. (Courtesy of Dr. Charles Soparkar.) D, Irregular keratinous horn. (Courtesy of Dr. Robert Goldberg.)
        3. **FIGURE 57.3** This cutaneous horn shows a layer of amorphous or lamellated keratin arising over an actinic keratosis.
        4. **FIGURE 57.4** Cutaneous horn formed over a hyperkeratotic seborrheic keratosis on the right upper eyelid.
    10. Tables

1. **TABLE 57.1Histopathology of Epidermal Abnormalities Associated With Cutaneous Horns**

15. Chapter 58: Dermoid Cyst
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        1. **FIGURE 58.1** Major locations of periorbital dermoid cysts. A, Superomedial dermoid. B, Axial magnetic resonance scan of a medial orbital and eyelid dermoid cyst. C, Superotemporal dermoid cyst. D, Axial CT scan of a superotemporal dermoid cyst.
        2. **FIGURE 58.2** A-D, Superotemporal periorbital dermoid cysts.
        3. **FIGURE 58.3** A, Superotemporal periocular dermoid cyst with a keratinized, stratified squamous epithelium with sebaceous glands and hair follicles. The cyst cavity contains keratin and hair shafts. B, Close-up of the cyst wall showing the keratinized, stratified squamous epithelium, keratin debris in the lumen, and multiple hair follicles, one of which (arrow) has a hair projecting through the lining epithelium.
        4. **FIGURE 58.4** A, This periocular dermoid cyst had ruptured, resulting in a focal granulomatous response with lymphocytes, macrophages, and fibrosis adjacent to the granuloma. The granuloma has large foreign body giant cells, several containing eosinophilic keratin debris surrounded by a halo. B, This lesion removed from the superotemporal periocular region lacked a cyst and showed only keratin debris, hair fragments (arrow), and a granulomatous reaction.

16. Chapter 59: Dermatofibroma
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        1. **FIGURE 59.1** A-D, Dermatofibroma of the eyelid. (A, Courtesy of Dr. Robert Goldberg; B, Courtesy of Dr. Suzanne Freitag; C, Courtesy of Dr. Frederick Jakobiec.)

2. **FIGURE 59.2** A and B, Dermatofibroma of the neck illustrating a hypercellular proliferation of plump spindle-shaped cells with scant cytoplasm, a prominent storiform pattern, and collagen trapping (arrows).
3. **FIGURE 59.3** Dermatofibroma of the right upper eyelid in a man in his middle 50s. A-C, The tumor is composed of lightly eosinophilic cells with scant cytoplasm and oval vesicular nuclei between bundles of brightly eosinophilic collagen. The tumor is separated from irregularly, mildly acanthotic epidermis by normal papillary dermis (in A). The tumor cells were immunoreactive using antibodies to factor XIIIa (D) but negative for CD34 expression.

17. Chapter 60: Distensible Venous Malformations (Varices)
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        1. **FIGURE 60.1** The spectrum of presentations of eyelid varices. A, Small varix of the upper eyelid skin. B, Multifocal varix of the lower eyelid. C, Serpentine varix of the upper eyelid and lateral canthus. D, Extensive varix involving the lower eyelid and conjunctiva.
        2. **FIGURE 60.2** Medial upper eyelid varix before (A and C) and during (B and D) a Valsalva maneuver.
        3. **FIGURE 60.3** Medial conjunctival varix.
        4. **FIGURE 60.4** A, This varix from the left upper eyelid was present for several years. At low magnification, a dilated vein filled with acute thrombus is in the dermis. B, The varix wall has an endothelial lining and a thin layer of smooth muscle cells and fibrous connective tissue, features characteristic of a small muscular venule.[39]
18. Chapter 61: Erysipelas
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        1. **FIGURE 61.1** Mild erysipelas with areas of erythema and vesicles.

2. **FIGURE 61.2** Severe erysipelas with black skin, ruptured bullae, and areas of raw skin. (Courtesy of Dr. John Holds.)
3. **FIGURE 61.3** A, The dermis in erysipelas is edematous with a diffuse and heavy infiltrate of neutrophils, which may be accentuated around dilated blood vessels (arrows). B, Neutrophils predominate in the edematous dermis of acute erysipelas.

19. Chapter 62: Erythema Multiforme
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        1. **FIGURE 62.1** Diffuse macules of erythema multiforme involving the upper and lower eyelids. (Courtesy of Dr. Robert Goldberg.)
        2. **FIGURE 62.2** Persistent inflammatory erythema multiforme with areas of bullae and necrosis. (Courtesy of Dr. Charles Soparkar.)
        3. **FIGURE 62.3** A, This erythema multiforme target lesion shows prominent vacuolar degeneration of basal keratinocytes (), a small intraepidermal blister (vesicle) containing necrotic keratinocytes (arrow), and the edge of a larger intraepidermal blister (arrowhead). B, The target lesion has numerous brightly eosinophilic necrotic keratinocytes, along with an area of vacuolar degeneration occupying almost the full thickness of the epidermis. Macrophages and lymphocytes are in the papillary dermis with extension into the basal epidermis. C, Close-up view of the necrotic keratinocytes having brightly eosinophilic cytoplasm and pyknotic or absent nuclei. Melanin is in many of the necrotic cells of this black patient.
20. Chapter 63: Fibrous Histiocytoma
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        1. **FIGURE 63.1** A-C, Nodular lesions of benign fibrous histiocytoma in the medial eyelid and medial canthus.

(A, Courtesy of Dr. Robert Goldberg; B and C, Courtesy of Dr. Ramon Malhotra.)
2. **FIGURE 63.2** Malignant fibrous histiocytoma of the upper eyelid following radiation therapy for retinoblastoma as a young child.
3. **FIGURE 63.3** A, This fibrous histiocytoma arose in the left upper eyelid connective tissue between the orbicularis oculi muscle () and the tarsus. The tumor is circumscribed and has several large vessels (arrows) resembling those in solitary fibrous tumors. B, The plump spindle cells have a storiform configuration, which is typical in deep fibrous histiocytomas.
4. **FIGURE 63.4** A, This fibrous histiocytoma arose approximately 30 years after radiation therapy for retinoblastoma as a young child. The tumor was well-circumscribed and located between the conjunctiva and the tarsus. B, The tumor cells are elongated spindle cells with pale eosinophilic cytoplasm. Though the tumor cells resemble those in solitary fibrous tumors and neurofibromas, they did not stain for either CD34 or S100 protein, thus ruling out those possibilities.

21. Chapter 64: Glomuvenous Malformation (Glomus Tumor)
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        1. **FIGURE 64.1** Solitary subcutaneous glomuvenous malformation in the lateral brow (arrow). (Courtesy of Dr. Kyle Godfrey.)
        2. **FIGURE 64.2** Surgical excision of the lesion in Figure 64.1. (Courtesy of Dr. Kyle Godfrey.)
        3. **FIGURE 64.3** This glomuvenous malformation (GVM) of the eyelid was part of a larger lesion involving the face. A, At low magnification, the GVM resembles a cavernous hemangioma with interlacing, contorted, dilated blood vessels. B and C, A variably thick layer of glomus cells ensheaths the blood vessels. D, The glomus cells are uniform, large, round or cuboidal cells with a round nucleus, a rim of pale, lightly eosinophilic cytoplasm, and a distinct cell membrane that is slightly more eosinophilic than the cytoplasm. E, Immunohistochemical staining using antibodies to CD31 highlights the endothelial cells but not the glomus cells. F, The glomus cells are immunoreactive using antibodies to α-smooth muscle actin.

22. Chapter 65: Granuloma Annulare
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        1. **FIGURE 65.1** Granuloma annulare (GA) involving the eyelids. A, Nodular subcutaneous lesion in the lateral upper eyelid. B, GA nodule in the upper medial canthus. C and D, Small nodules of GA in the upper and lower eyelids. Arrows indicated the subcutaneous lesions.
        2. **FIGURE 65.2** Granuloma annulare of the eyelid. A, A large zone of altered (necrobiotic) collagen () has fragmented collagen bundles, hyalinization, and basophilia. B, Palisading histiocytes and lymphocytes surround the necrobiotic collagen. The long axes of the histiocytes are perpendicular to the necrotic zone creating the palisading. C, Alcian blue stain highlights abundant mucin (glycosaminoglycan) accompanying the necrobiosis.
23. Chapter 66: Granulomatosis With Polyangiitis
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        1. **FIGURE 66.1** A-C, Granulomatosis with polyangiitis with eyelid erythema, edema, entropion, and periocular cellulitis. D, Nasocutaneous fistula in the medial canthus. (A-C, Courtesy of Dr. Charles Soparkar; D, Courtesy of Dr. Alan McNab.)
        2. **FIGURE 66.2** “Bumps” in the upper eyelid were the first manifestation of granulomatosis with polyangiitis (GPA) in this young woman. An increase in size and number of the nodules prompted this punch biopsy. A, At scanning magnification, the epidermis is normal while the superficial through deep dermis is inflamed. The most intense inflammation surrounds zones of necrosis (*). B, Palisading histiocytes (*) surround a zone of necrosis containing a small artery and vein with leukocytoclastic vasculitis (arrows). The small basophilic particles around the vessels are nuclear debris

due to the disintegration of leukocytes. C, Palisading granulomatous inflammation surrounds a broad zone of collagen necrosis with several thrombosed small vessels (arrows). D, The palisading granulomatous inflammation consisted mostly of histiocytes, a lesser number of lymphocytes, and occasional multinucleated giant cells (arrows). E, This small artery has chronic lymphocytic vasculitis with lymphocytes infiltrating the tunica media and tunica intima. Lymphocytes and neovascularization expand the intima. The intimal neovascularization is indictive of chronicity. F, This small vein has lymphocytic vasculitis with fibrinoid necrosis (arrow). G, Granulomatous vasculitis is a rare finding in cutaneous GPA but is shown here involving a small artery (arrow). Lymphocytes and histiocytes disrupt the arterial wall and occlude the lumen. H, The wall of this small artery is effaced by granulomatous inflammation.

24. Chapter 67: Herpes Simplex Blepharitis
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        1. **FIGURE 67.1** Early classic presentation of herpes simplex. A, Eyelid erythema and edema of the lower eyelid. B, Upper and lower eyelid swelling and erythema and blepharoconjunctivitis. (Courtesy of Dr. Robert Goldberg.)
        2. **FIGURE 67.2** A-C, Herpes simplex eyelid vesicles and erosions. D, Herpetic dendritic keratitis. (A and B, Courtesy of Dr. Kenneth Cohen.)
        3. **FIGURE 67.3** Herpes simplex vegetans in a patient with congenital T-cell immunodeficiency. (Reprinted with permission from Blieden LS, Chévez-Barrios P, Yen MT. Herpes simplex vegetans presenting as an eyelid mass. *Ophthalmic Plast Reconstr Surg*. 2011; 27:e58-e59.)
        4. **FIGURE 67.4** A, This herpes simplex virus (HSV) skin lesion preceded conjunctival and medial canthus HSV infection in a patient with HIV infection. The epidermis is ulcerated and acanthotic, and there are intraepidermal and subepidermal vesicles. The dermis has a marked infiltrate of lymphocytes, plasma cells, macrophages, and scattered eosinophils. B, The area of epidermal ulceration has infected keratinocytes mixed among

numerous neutrophils. The infected cells are larger than the normal keratinocytes and have lost their cohesion with each other. C, Two enlarged, multinucleate, infected keratinocytes have eosinophilic nuclear inclusions (arrows). D, Immunohistochemical staining using antibodies specific for HSV antigen confirms the diagnosis. The infected cells are brown, while adjacent keratinocytes and inflammatory cells do not stain.

25. Chapter 68: Herpes Zoster Ophthalmicus
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        1. **FIGURE 68.1** A-D, Early acute eruptive phase of *herpes zoster* ophthalmicus with scattered papulovesicular lesions and rash on the nose, forehead, and eyelids.
        2. **FIGURE 68.2** A and B, Late acute eruptive phase with bullous eruptions, eyelid erythema, edema, and ptosis.
        3. **FIGURE 68.3** A and B, Chronic posteruptive phase with skin necrosis, ectropion, and depigmentation.
        4. **FIGURE 68.4** A, Varicella-zoster virus (VZV) infection has resulted in an intradermal vesicle (). B, The vesicle contains infected cells, some of which are multinucleate (arrow). There are neutrophils among the infected keratinocytes. C, Close-up of multinucleated cells in the epidermis adjacent to the vesicle (short arrows). Eosinophilic intranuclear inclusions are in a multinucleated cell and a mononuclear keratinocyte (long arrows). D, Immunohistochemical staining using antibodies to VZV antigen confirms the diagnosis. Infected cells stain brown using diaminobenzidine as the chromogenic detection agent.
26. Chapter 69: Hidradenoma
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        1. **FIGURE 69.1** A-D, Hidradenoma. A (Courtesy of Dr. Bettina Meekins). B (Courtesy of Dr. David Jordan).

2. **FIGURE 69.2** This hidradenoma of the right upper eyelid is typical of that we have encountered most often in the periocular region. A, The tumor is based in the dermis, is well circumscribed, and has a lobular pattern. B, The tumor is predominantly solid with a few small cystic areas. C, Polygonal cells with pale eosinophilic cytoplasm form sheets or tubules.
3. **FIGURE 69.3** A and B, This hidradenoma of the left lower eyelid has a prominent population of clear cells containing glycogen. Much of the glycogen dissolves from the tissue during processing, leaving clear cytoplasm. Clear cells are often abundant in hidradenomas of other body sites, but they are uncommon in eyelid hidradenomas in our experience.
4. **FIGURE 69.4** A, This hidradenoma of the right lower eyelid is well circumscribed with a solid and cystic pattern. B, There are scattered small pools of mucin among the sheets of polygonal cells. C, A majority of the cells are round or polygonal with lightly eosinophilic cytoplasm and round nuclei. Small pools of mucin are among the tumor cells. D, A mucicarmine stain highlights mucin pools and scattered small intracellular mucin globules.

27. Chapter 70: Hidrocystoma
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        1. **FIGURE 70.1** A-D, Apocrine hidrocystoma on the eyelid margins with a layered precipitate.
        2. **FIGURE 70.2** A-D, Eccrine hidrocystoma containing a clear watery secretion.
        3. **FIGURE 70.3** A, This left lower eyelid apocrine hidrocystoma is multiloculated. B, It is lined by two layers of cells. Columnar cells with eosinophilic cytoplasm and decapitation secretion form the inner layer. Flat to low cuboidal myoepithelial cells compose the outer layer. Lightly eosinophilic proteinaceous material is in the lumen. C and D, Apocrine cystadenomas have papillae with fibrous cores or an adenomatous appearance, as in this example from the right lower eyelid. Decapitation secretion is evident in some of the adenomatous glands ().
        4. **FIGURE 70.4** A, This cyst from the right lower eyelid was classified as an eccrine hidrocystoma since it was

unilocular and lacked evidence of decapitation secretion by the inner lining of cells. At low magnification, the cyst has a convoluted profile due to collapse during surgical removal. B, The cyst is lined by two layers of epithelium: an inner layer of cuboidal cells and an outer layer of low cuboidal to flat cells.

5. **FIGURE 70.5** The epithelium of hidrocystomas and apocrine cystadenomas may be pigmented, as seen in this left medial canthus hidrocystoma. A, The cyst is unilocular with convolutions due to its collapse during removal. B, The cyst lining is two-layer thick, and the inner layer lacks features of decapitation secretion. The cells are less eosinophilic than a typical hidrocystoma and have a tan tinge. C, The intracytoplasmic pigment is more readily apparent in the section stained using the Fontana-Masson method for demonstrating melanin. The pigment has remained tan and brown, indicating that it is not melanin, which turns black utilizing this procedure.

28. Chapter 71: Ichthyosis
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    3. Syndromic Ichthyoses
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        1. **FIGURE 71.1** A, Bilateral cicatricial ectropion on the lower eyelids in ichthyosis. B, Bilateral severe cicatricial ectropion of the lower eyelid and mild ectropion of the upper eyelids.
        2. **FIGURE 71.2** Corneal exposure secondary to cicatricial ectropion in ichthyosis. A, Inferior corneal haze with epithelial irregularities. B, Severe exposure with dense corneal opacification from upper and lower eyelid cicatricial ectropion.
        3. **FIGURE 71.3** Severe lower eyelid retraction and ectropion from skin contraction in a case of ichthyosis.
        4. **FIGURE 71.4** A, This example of ichthyosis vulgaris has an atrophic epidermis with a moderately thick layer of orthohyperkeratosis and a stratum granulosum reduced to one cell in thickness. B, This ichthyosis vulgaris biopsy has an acanthotic epidermis, an absent stratum granulosum, and a moderately to markedly thickened stratum corneum with a mixture of orthohyperkeratosis and parakeratosis.

29. Chapter 72: Impetigo
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        1. **FIGURE 72.1** Eyelid impetigo. A, As maculopapular pustules. B, Ruptured bullae, exuding purulent exudate on an erythematous base. (A, Courtesy of Dr. Roman Shinder.)
        2. **FIGURE 72.2** A, This example of bullous impetigo has a subcorneal blister containing neutrophils, debris, and bacteria. There is acute hemorrhage in the papillary dermis but no inflammation. B, Common impetigo has subcorneal accumulation of neutrophils and bacteria. In this example, there is parakeratosis, a feature of older lesions.
30. Chapter 73: Infantile Hemangioma
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        1. **FIGURE 73.1** Early minimally elevated infantile hemangiomas on the eyelids and periorbital region.
        2. **FIGURE 73.2** Late proliferative phase hemangiomas causing significant functional limitation of the eyelids or severe aesthetic disability.
        3. **FIGURE 73.3** A and B, Deep subcutaneous infantile hemangiomas in the eyelid may extend into the anterior orbit.
        4. **FIGURE 73.4** A, This infantile hemangioma of the glabella is a well-defined unencapsulated dermal mass of closely apposed capillaries. B, The capillaries form lobules separated by thin fibrous septa. C, The capillaries have small lumina and are lined by plump endothelial cells rimmed by plump pericytes. D, The endothelial cells highly express glucose transporter 1, while the pericytes are negative for this protein.
31. Chapter 74: Intravascular Papillary Endothelial Hyperplasia
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    2. Etiology and Pathogenesis

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    1. **FIGURE 74.1** Intravascular papillary endothelial hyperplasia (IPEH). A, Vascular lesion in the medial lower eyelid (arrow). B, Medial brow and upper eyelid IPEH (arrow). C, Surgical excision of the lesion in Figure B. (B and C, Courtesy of Dr. Tamara Fountain.)
    2. **FIGURE 74.2** A, This example of intravascular papillary endothelial hyperplasia arose within a partially thrombosed varix of the right lower eyelid. B, The IPEH is present overlying thrombus (arrow). C, Small, eosinophilic papillae covered by a layer of endothelial cells overlie thrombus. D, The endothelial cells in this lesion are flat, but they may be plump or multilayered in other cases.

32. Chapter 75: Inverted Follicular Keratosis
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        1. **FIGURE 75.1** A and B, Inverted follicular keratosis as a mild swelling on the mucocutaneous eyelid margin.
        2. **FIGURE 75.2** A and B, Nodular inverted follicular keratosis.
        3. **FIGURE 75.3** A, Large inverted follicular keratosis (IFK) with a rugose scaly surface. B, Small pigmented IFK. (Courtesy of Dr. Gregg Gayre.)
        4. **FIGURE 75.4** A, This nodular inverted follicular keratosis has a thick layer of hyperkeratosis and parakeratosis overlying a tumor composed of a large and small lobule and a fingerlike projection into the actinically damaged dermis. The tumor cells around the periphery of the lobules are basaloid, resulting in the darker blue staining. B, Squamous eddies with concentric layers of flattened squamous cells in a whorled pattern are usually most frequent at the junction of the basaloid cells and squamous cells.
        5. **FIGURE 75.5** A, This nodular inverted follicular keratosis has lobules and broad interdigitating cords of tumor cells within the dermis. The basaloid layer around

the periphery of the lobules and cords is prominent. B, The basaloid layer has a cuff of mononuclear inflammatory cells, and scattered lymphocytes infiltrate the basaloid layer. A small keratinous cyst is in the squamous portion of the tumor.

33. Chapter 76: Keratoacanthoma
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        1. **FIGURE 76.1** Early-stage keratoacanthoma on the eyelid margin with an incipient central crater.
        2. **FIGURE 76.2** A and B, Mature phase domed keratoacanthoma with a central keratinous crater. A, (Courtesy of Dr. Suzanne Freitag). B, (Courtesy of Dr. Alan McNab).
        3. **FIGURE 76.3** A and B, Late-stage hyperkeratotic keratoacanthomas with surface necrosis.
        4. **FIGURE 76.4** This right upper eyelid keratoacanthoma arose over several months and appeared clinically to be a cutaneous horn. The lesion has features characteristic of a fully developed exoendophytic lesion with a proliferation of well-differentiated, keratinizing squamous epithelium forming lobules at the sides and bottom of the lesion, a central keratin-filled crater, and a lip of epidermis (collarette) overlapping the central crater. The dermis has a moderately intense infiltrate of lymphocytes, plasma cells, and macrophages.
        5. **FIGURE 76.5** A, This medial right upper eyelid lesion appeared over 1 month. There is a lobular proliferation of well-differentiated squamous epithelium with keratin filling the central crater. B, The lobules are predominantly composed of epithelial cells with lightly eosinophilic (pale pink) glassy cytoplasm surrounding laminated keratinization. C, The periphery of lobules had basophilic cells, and the borders were minimally infiltrative. The dermis has a dense infiltrate of mononuclear leukocytes without fibrosis.
34. Chapter 77: Keratinous Cysts, Cutaneous
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9. Figures
    1. **FIGURE 77.1** A-D, The spectrum of clinical appearance of intradermal cutaneous keratinous cysts. A (Courtesy of Dr. Charles Soparkar).
    2. **FIGURE 77.2** Deeper, subcutaneous cutaneous keratinous cysts.
    3. **FIGURE 77.3** A, Epidermoid cyst of the outer canthus lined by keratinized, stratified squamous epithelium identical to the interfollicular epidermis and filled with laminated keratin. B and C, Darkly basophilic keratohyaline granules are prominent in the granular cell layer keratinocytes as one approaches the cyst lumen.
    4. **FIGURE 77.4** A and B, Trichilemmal cyst of the left lower eyelid showing a fibrous capsule on which rests a layer of darkly staining basal cells resembling the external root sheath of the hair follicle. C, The basal cells merge with stratified squamous epithelium whose cells increase in size and vertical diameter and become more eosinophilic as they mature. The innermost cells are often anucleate and abruptly change into the eosinophilic-staining keratin within the lumen.
    5. **FIGURE 77.5** This proliferating trichilemmal cyst arose in the right upper eyelid of a young girl. A, The cyst wall is much thicker and more irregular than a regular trichilemmal cyst. The cyst wall proliferation extended both toward the outside and inside of the cyst, resulting in irregular inner and outer borders. B and C, The proliferating epithelium lacks keratohyaline granules and has features similar to that in a routine trichilemmal cyst. The cyst lumen contained keratin and necrotic debris, clusters of neutrophils, and patchy calcification resembling that in a pilomatrixoma.

35. Chapter 78: Keratinous Cyst, Intratarsal
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        1. **FIGURE 78.1** A-D, Anterior nodules of intratarsal keratinous cysts of the eyelids. A and B (Courtesy of Dr. Reza Vagefi). C (Courtesy of Dr. Suzanne Freitag). D (Courtesy of Dr. Robert Kersten).
        2. **FIGURE 78.2** A and B, Posterior intratarsal keratinous cysts pointing on the conjunctival surface. A (Courtesy

of Dr. Reza Vagefi). B (Courtesy of Dr. Robert Kersten).
3. **FIGURE 78.3** A and B, Intratarsal keratinous cyst located within the dense collagenous tissue of the tarsus. C and D, The cyst is lined by stratified squamous epithelium with an inner layer that may be undulating or corrugated and lacks keratohyalin granules, goblet cells, or sebaceous cells. The lumen contains loose, eosinophilic keratin (C).
4. **FIGURE 78.4** This intratarsal (A) cyst has the typical epithelial lining (B and C) of an intratarsal keratinous cyst but only minimal luminal contents (B). It is not possible to determine if the minimal luminal content is due to this being an early cyst lacking time for the keratin to accumulate or if the contents drained before or during surgery.

36. Chapter 79: Leiomyoma
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        1. **FIGURE 79.1** A, Leiomyoma on the conjunctival surface at the medial lower eyelid. B, Piloleiomyoma nodular mass of the right upper eyelid in a 13-day old infant. (A, Courtesy of Dr. Roman Shinder. B, Reprinted with permission from Alam S, Banerjee P, Subramanian K. A rare case of congenital piloleiomyoma of the eyelid. *Orbit*. 2020 Aug 26, Online ahead of print.)
        2. **FIGURE 79.2** A, This piloleiomyoma has acanthotic epidermis separated from intersecting bundles of palely eosinophilic smooth muscle cells with entrapped brightly eosinophilic collagen bundles. A thin layer of normal dermis (grenz zone) separates the epidermis from the dermal tumor. B, The well-differentiated neoplastic smooth muscle cells have palely eosinophilic cytoplasm, perinuclear vacuoles, and fibrillary cytoplasm. The intersecting smooth muscle bundles have entrapped brightly eosinophilic collagen bundles.
        3. **FIGURE 79.3** A, This angioleiomyoma has the typical sharp circumscription of these neoplasms. B, Cytologically bland smooth muscle cells form fascicles arrayed around blood vessels.
        4. **FIGURE 79.4** A, This dermal atypical smooth muscle tumor is separated from the epidermis by a thin layer of normal dermis. B, Brightly eosinophilic collagen

bundles are entrapped by fascicles of well-differentiated smooth muscle cells with more lightly eosinophilic cytoplasm. C, Tumor cells have elongated nuclei with blunt ends. Atypical smooth muscle neoplasms differ from piloleiomyomas by nuclear atypia (arrowhead) and more frequent mitotic figures (arrow).

37. Chapter 80: Lipoblastoma and Lipoblastomatosis
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    9. Figures
        1. **FIGURE 80.1** Lipoblastomatosis of the left upper and lower eyelids with erythema, crusting, and mechanical ptosis.
        2. **FIGURE 80.2** A, A well-differentiated lipoblastoma in the subcutis (arrows). B, Fibrovascular septa separate the adipocytes into lobules. C, The tumor cells have a variable appearance ranging from primitive stellate or spindled mesenchymal cells (preadipocytes) to mature adipocytes. D, The number of lipoblasts (arrow) is variable, and they may be rare in mature lipoblastomas.
38. Chapter 81: Lipoid Proteinosis
    1. Key Points
    2. Etiology and Pathophysiology
    3. Clinical Presentation
    4. Differential Diagnosis
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    7. Histopathology
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    9. Figures
        1. **FIGURE 81.1** Moniliform blepharosis of the eyelid margins in lipoid proteinosis. A, Tiny beaded papules along the upper and lower eyelid margins. (Courtesy of Dr. Alan McNab.) B, Small papules on the medial upper eyelid margin. (Courtesy of Dr. Mohammad Javed Ali.)
        2. **FIGURE 81.2** A, This lipoid proteinosis example shows lamellae of hyaline eosinophilic material adjacent to a hair follicle seabceous gland (arrowhead) and concentrically surrounding dermal capillaries (arrows). B, Hyaline eosinophilic deposits surround an eccrine sweat gland (arrowhead) and nerve (arrow). C, Hyaline eosinophilic material encompasses all of the dermal capillaries, several of which have occluded lumens.
39. Chapter 82: Lipoma

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    1. **FIGURE 82.1** Lipomas of the brow and eyelid. A (Courtesy of Dr. Alan McNAb). C (Courtesy of Dr. Philip Custer).
    2. **FIGURE 82.2** A, Massive lipoma involving the right upper eyelid and brow. B, Surgical excision of the lipoma in A through an upper eyelid crease incision.
    3. **FIGURE 82.3** A, This conventional lipoma is sharply circumscribed and composed of mature adipocytes with thin, incomplete fibrous septa containing blood vessels. B, The adipocyte nuclei are uniform and without atypia.
    4. **FIGURE 82.4** Dermal lipomas feature scattered groups of mature adipocytes between collagen bundles and are less circumscribed than conventional lipomas.

40. Chapter 83: Lupus Erythematosus
    1. Key Points
    2. *Acute Cutaneous Lupus Erythematosus*
    3. *Subacute Cutaneous Lupus Erythematosus*
    4. *Chronic Cutaneous Lupus Erythematosus*
    5. Etiology and Pathophysiology
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    7. Differential Diagnosis
    8. Treatment
    9. Prognosis
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    11. References
    12. Figures
        1. **FIGURE 83.1** A and B, Eyelid lupus erythematosus manifesting as erythema and edema. A, (Courtesy of Dr. Robert Goldberg). B, (Courtesy of Dr. Charles Soparkar).
        2. **FIGURE 83.2** Advanced systemic lupus erythematosus (SLE) of the eyelids. A, Scaly plaque on the lower eyelid. B, Central lower eyelid SLE with depigmentation, madarosis, and ulceration. A, (Courtesy of Dr. Charles Soparakar). B, (Courtesy of Dr. Gordon Klintworth).
        3. **FIGURE 83.3** These eyelid biopsies were all diagnosed as discoid lupus erythematosus (DLE) based on correlating the histopathological and clinical findings. A, Interface dermatitis with superficial and deep perivascular and periadnexal chronic inflammation. The

epidermis is atrophic, and the hair follicle on the right has keratotic plugging. B, The epidermis has parakeratosis and acanthosis, and there is superficial perivascular and periadnexal chronic inflammation. C, Interface dermatitis extends down the hair follicle with keratinocyte cell death. D, The epidermis is infiltrated with lymphocytes, and there are two cells undergoing apoptosis with brightly eosinophilic cytoplasm in the basal epidermis. The epidermal basement membrane is eosinophilic, markedly thickened, and undulating. Lymphocytes and macrophages infiltrate the papillary dermis. E, Pseudoepitheliomatous (pseudocarcinomatous) epidermal hyperplasia. The angulated nuclei, thickened basement membrane, and Civatte bodies are clues to DLE diagnosis and are not features expected in squamous cell carcinoma, which this lesion mimicked clinically. F, Alcian blue stain highlights prominent derma mucin accumulation. Alcian blue stains normal skin only faintly, if at all.

41. Chapter 84: Lymphatic Malformation
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    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
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        1. **FIGURE 84.1** Deep lymphatic malformations lesion in eyelids and orbit.
        2. **FIGURE 84.2** Eyelid lymphatic malformations with upper eyelid ptosis.
        3. **FIGURE 84.3** Infiltrative lymphatic malformations involving the eyelids, conjunctiva, and orbit with massive proptosis. (Courtesy of Dr. Michael Hawes.)
        4. **FIGURE 84.4** Lymphatic malformations of the conjunctiva.
        5. **FIGURE 84.5** A, This biopsy is from the left upper eyelid of a child with a congenital lymphatic malformation (LM) involving the eyelid and preseptal orbit. At low magnification, dilated, irregularly shaped lymphatics dissect between the eyelid stroma. B, Lymphatics lacking an adventitial coat extend through the orbicularis muscle. C, An immunohistochemical stain using antibodies to podoplanin highlights variability in the size and shape of lymphatic channels in this LM involving the right eyelid and anterior orbit.
        6. **FIGURE 84.6** A, This conjunctival lymphangioma was a discrete lesion in the inferolateral quadrant of the left

eye just inside the palpebral fissure of a middle-aged woman. Minimal stroma separates widely dilated lymphatics containing eosinophilic lymph. B, The lymphatics have thin walls, and focal hemorrhage is manifest as erythrocytes mixed with the lymph. C, The lymphatics have widely spaced endothelial cells, no adventitial coat, and sparse, loose stroma between them.

42. Chapter 85: Lymphedema
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 85.1** Lymphedema associated with Melkerson-Rosenthal syndrome.
        2. **FIGURE 85.2** The spectrum of manifestations of lymphedema involving the eyelids.
        3. **FIGURE 85.3** This right upper eyelid biopsy is from a man in his late 40s with edema for 4 months. There is lymphangiectasia, dermal edema with increased spacing between collagen bundles, and perivascular inflammatory infiltrates of lymphocytes, macrophages, and mast cells.
        4. **FIGURE 85.4** This woman in her middle 60s with orofacial granulomatosis had unilateral swelling of the right upper eyelid for 1.5 years. A, Lymphangiectasia and dermal edema, manifest as pallor, are prominent at low magnification. B, Perilymphatic noncaseating granulomas (arrows) and intralymphatic histiocytes (arrowheads) were frequent in this case, but they are sparse in some cases. C, High magnification photomicrograph showing a perilymphatic noncaseating granuloma and a cluster of histiocytes and multinucleated giant cells within the lymphatic lumen. D, An immunohistochemical stain using D2-40 antibodies to podoplanin highlights the lymphatic endothelial cells. Histiocytes are in all of the lymphatics, with the large lymphatic on the left distended by histiocytes.
43. Chapter 86: Melanocytic Nevus
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Characteristics
    4. Differential Diagnosis
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9. Figures
    1. **FIGURE 86.1** Marginal nevi along the cutaneous/conjunctival border.
    2. **FIGURE 86.2** A and B, Compound melanocytic nevi. C and D, Intradermal melanocytic nevi.
    3. **FIGURE 86.3** A-C, Elevated, rugose melanocytic nevi with hair. D, Flat diffuse nevus of the lower eyelid and face. A, (Courtesy of Dr, Richard Anderson).
    4. **FIGURE 86.4** Divided (Kissing) nevus involving the medial upper and lower eyelids.
    5. **FIGURE 86.5** A-D, Congenital blue nevus of the eyelids. C and D, (Courtesy of Dr. Robert Goldberg).
    6. **FIGURE 86.6** Common melanocytic (nevocellular) nevi are classified according to the location of nevus cells. A and B, Intradermal nevi are the most frequent nevus in the eyelid and feature nests and cords of nevus cells in the dermis separated from the overlying epidermis by an intact zone of dermal collagen. C, Junctional nevi have discrete nests of nevus cells at the junction of the epidermis and dermis, usually on the rete ridges, which often exhibit some elongation. Junctional nevi are very uncommon in the eyelid skin. D, Compound nevi have junctional (arrow) and intradermal nests of nevus cells.
    7. **FIGURE 86.7** This common blue nevus was in the right lower eyelid of a man in his early 30s. A, The blue nevus has only scattered heavily melanin-laden spindle cells. There is a zone of normal dermis separating the blue nevus from the overlying epidermis. B, The melanin-laden spindle cells are intermixed with nonpigmented or minimally pigmented oval to spindle melanocytes. There is no cytological atypia or mitotic figures. C, An immunohistochemical stain using antibodies to MART-1 (Melan-A) highlights the spindle melanocytes comprising the common blue nevus. The presence of melanin-containing dermal melanocytes interspersed with the nonpigmented cells aids in differentiating lightly pigmented blue nevi from other spindle cell tumors such as dermatofibroma. Immunohistochemical stains using antibodies to melanocytic markers, such as MART-1, may be helpful to confirm the identity of lightly pigmented blue nevi.
    8. **FIGURE 86.8** A and B, This combined nevus was in the central left lower eyelid of a man in his early 70s. The melanin-laden spindle blue nevus cells and nests of round to oval nevocellular nevus cells are easiest to discern at high magnification (B). C and D, This combined nevus arose in the right caruncle and plica

semilunaris of a woman in her late 20s. The melanin-laden spindle melanocytes tended to be around the periphery of the round to oval nevocellular nevus cell nests.
9. **FIGURE 86.9** This congenital compound nevus from the right lower eyelid of a 3-year-old girl also involved the upper cheek. It was visible at birth and grew slowly larger and darker over the next 3 years. A, The compound nevus has small nests of nevus cells at the epidermal-dermal junction, in the papillary and superficial reticular dermis, and in the deep reticular dermis. In the deeper aspect of the lesion, the nevus cells percolate between collagen bundles as individual cells or in a single file. B, A section stained using antibodies to MART-1 shows the nevus cells extending into the deep reticular dermis. The superficially located nevus cells are nested, while those in the deep dermis form single files or occur individually. C, Nevus cells form single files between collagen bundles, insinuate into an eccrine lobule, and infiltrate an arrector pili muscle. D, Nevus cells form single files between collagen bundles in the deep reticular dermis.
10. **FIGURE 86.10** A, This compound combined conjunctival nevus is composed of a mixture of nevocellular nevus cells and spindle blue nevus cells. The nevus was present around the punctum of the right upper eyelid for 35 years before being biopsied due to a change in color over 8 months. The tissue was sectioned parallel to the epithelial surface resulting in epithelium on both sides of the substantia propria. B, This compound nevus involved the medial right lower eyelid conjunctiva in a child who had other nevi in the right caruncle and the right lower eyelid skin. The numerous goblet cells in the conjunctival epithelium result from the biopsy being from the medial lower eyelid.[150]

44. Chapter 87: Milia
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        1. **FIGURE 87.1** Milia involving the upper and lower eyelids.
        2. **FIGURE 87.2** A, This eyelid milium was an incidental finding in an excision of a right lower eyelid seborrheic keratosis. The milium resembles a miniature epidermoid

cyst in the superficial dermis. B, The epithelial lining is thin and resembles that of an epidermoid cyst with keratinized, stratified squamous epithelium and prominent keratohyaline granules in the cells nearer the cyst lumen. Laminated keratin fills the cyst lumen.

45. Chapter 88: Molluscum Contagiosum
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Characteristics
    4. Differential Diagnosis
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        1. **FIGURE 88.1** A-D, Solitary, dome-shaped, umbilicated molluscum lesions of the eyelid. (B, Courtesy of Dr. Mohammad Javed Ali; D, Courtesy of Dr. Alan McNab.)
        2. **FIGURE 88.2** A and B, Multiple molluscum lesions. (A, Courtesy of Dr. Mohammad Javed Ali.)
        3. **FIGURE 88.3** Giant molluscum on the upper eyelid. (Courtesy of Dr. Gary Lelli.)
        4. **FIGURE 88.4** A, This eyelid molluscum contagiosum shows the characteristic lobules of hyperplastic squamous cells expanding into the underlying dermis with fine septa of dermis between lobules. Keratinized debris and viral inclusion bodies are being discharged onto the skin surface through a dilated ostium. B, Close-up of the ostium showing the keratin debris and molluscum bodies being discharged. Molluscum bodies are eosinophilic but may become basophilic near the skin surface, as seen in this case. C, Molluscum bodies may occupy almost the entire cell with compression of the nucleus toward the periphery of the cell.
46. Chapter 89: Mucormycosis
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Characteristics
    4. Differential Diagnosis
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    9. Figures
        1. **FIGURE 89.1** A, Sinus and orbital mucormycosis with proptosis and ophthalmoplegia. B, Orbital-cutaneous mucormycosis with progressive facial and eyelid induration, edema, and cellulitis.

2. **FIGURE 89.2** Cutaneous mucomycosis with necrosis of the lateral nose and eyelid in a patient with lymphocytic leukemia. (Reprinted with permission from Bonifaz A, Tirado-Sánchez A, Hernández-Medel ML, et al. Mucormycosis with cutaneous involvement. A retrospective study of 115 cases at a tertiary care hospital in Mexico. *Autralas J Dermatol*. 2021;62:162-167, Figure 2C.)
3. **FIGURE 89.3** A, The hyphae of mucormycosis are basophilic in sections stained with hematoxylin and eosin. The hyphae are broad (5-20 μm), thin walled, irregularly contoured, pleomorphic, and typically branch from 45° to 90°. The hyphae are pauciseptate (arrow) and are in infarcted adipose tissue in this patient with cerebro-rhino-orbital mucormycosis. B, The hyphae are often twisted (arrows), folded, and collapsed due to their thin walls. Many hyphae have absent cytoplasm and appear clear. C, Vascular invasion and thrombosis are ubiquitous with mucormycosis. D, Mucormycosis may stimulate a granulomatous reaction, as seen in this case with basophilic fungal hyphae (arrows) enveloped in a granuloma.

47. Chapter 90: Myasthenia Gravis
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    4. Differential Diagnosis
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    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 90.1** Myasthenia gravis presenting with asymmetric blepharoptosis of the right eyelid. (Courtesy of Dr. Kyle Godfrey.)
        2. **FIGURE 90.2** A patient with myasthenia gravis showing asymmetric blepharoptosis and pupil-sparing adduction weakness on the right side.
        3. **FIGURE 90.3** The ice test. A, Left eyelid ptosis before the ice is applied. B, Immediately after the ice pack is applied to the left eyelid for 5 minutes, the patient is asked to open the eyelids. The rest test should provide similar results.
        4. **FIGURE 90.4** The eyelid fatigability test. A, Before the start of levator muscle contraction. B, Sustained upgaze for 2 to 5 minutes. C, Immediately following the test, the ptosis is increased. (Courtesy of Dr. Robert Kersten.)
48. Chapter 91: Necrotizing Fasciitis
    1. Key Points
    2. Etiology and Pathogenesis

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    1. **FIGURE 91.1** Necrotizing fasciitis involving the eyelids. A, Upper and lower eyelid edema, erythema, and early devitalization of eyelid skin. B, Bilateral skin necrosis and crusting. C, Bilateral involvement with necrosis of the left eyelids. D, Severe necrosis of upper and lower eyelids with extensive loss of tissue. (A, Courtesy of Dr. Charles Soparkar; B, Courtesy of Dr. Grant Gilliland; C, Courtesy of Dr. James Gigantelli; D, Courtesy of Dr. John Holds.)
    2. **FIGURE 91.2** Clostridial myonecrosis (gas gangrene). A, Clinically, clostridial myonecrosis looks remarkably similar to necrotizing fasciitis. B, On closer examination, gas bubbles can be seen coming out of necrotic eyelid tissue. C, Noncontrast CT scan of the orbit shows the presence of an extensive amount of air along fascial planes and muscles of the periorbital region.
    3. **FIGURE 91.3** A 12-month-old boy developed necrotizing fasciitis of the left lower eyelid after blunt trauma.[36] Skeletal muscle (A) and fascial connective tissue (B) were infiltrated by neutrophils and macrophages, accompanied by extensive necrosis. C, Areas with numerous bacterial cocci caused a stippled appearance in the hematoxylin- and eosin-stained sections D, Rare vessels (arrow) contained fibrin thrombi.

49. Chapter 92: Neurofibroma, Solitary
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    2. Etiology and Pathogenesis
    3. Clinical Characteristics
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
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    9. Figures
        1. **FIGURE 92.1** A and B, Solitary neurofibroma of the eyelids.
        2. **FIGURE 92.2** Neurofibromas in the setting of neurofibromatosis type 1. Hundreds of small lesions on the face, forehead, and eyelids.
        3. **FIGURE 92.3** Nodular neurofibromas on the eyelid skin and conjunctival surfaces.

4. **FIGURE 92.4** A, This solitary (sporadic) neurofibroma arose in the medial right upper eyelid of a woman in her early 60s without a history or clinical manifestations of neurofibromatosis type 1. The dermal tumor is nonencapsulated, well circumscribed, and more palely eosinophilic than the surrounding dermis. B, A band of the normal dermis (grenz zone) separates the tumor from the overlying epidermis. C, This solitary neurofibroma is composed of spindle-shaped cells with scant palely eosinophilic cytoplasm and indistinct cytoplasmic borders. D, The tumor cells have oval and curved nuclei.
5. **FIGURE 92.5** A, This isolated neurofibroma developed in the right upper eyelid of a woman in her early 50s with a history of neurofibromatosis type 1. The tumor is indistinguishable from a sporadic solitary neurofibroma. The lightly eosinophilic neurofibroma was centered between the orbicularis oculi muscle and the tarsal plate. B, A band of normal dermis separates the tumor from the overlying epidermis. Tumor surrounds hair follicles and sebaceous glands without altering their structure. C, The tumor is composed of spindle cells in a vascularized fibrillary stroma. D, The tumor cells have oval and occasionally wavy nuclei. A mast cell is present among the tumor cells (arrow).

50. Chapter 93: Neurofibroma, Plexiform
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
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    8. References
    9. Figures
        1. **FIGURE 93.1** Plexiform neurofibroma. A, Involvement of the tarsus (asterisk). B, Involvement of the conjunctiva (asterisks). The lateral canthal tendon has become disinserted allowing the ease of eyelid eversion.
        2. **FIGURE 93.2** Variations in upper eyelid plexiform neurofibroma. A, Mild ptosis. B, Moderate eyelid infiltration with an S-shaped contour. C, More extensive disease with irregular eyelid infiltration extending beyond the lateral canthus. D, Heavily infiltrated bulky eyelid with complete ptosis and poor apposition of both eyelids.
        3. **FIGURE 93.3** A and B, Rare plexiform neurofibroma involvement of the lower eyelids.
        4. **FIGURE 93.4** A and B, Combined involvement of both upper and lower eyelids with plexiform neurofibroma. (B, Courtesy of Dr. Charles Soparkar.)

5. **FIGURE 93.5** A, This child with neurofibromatosis type 1 had a plexiform neurofibroma in the right upper eyelid dermis forming a nodule near the eyelid margin (arrows). B, A close-up view shows large segments of enlarged convoluted peripheral nerve fascicles that correspond to a “bag of worms” texture on palpation. C, The dermis has expanded nerve fascicles, each surrounded by a thickened perineurium. The expanded fascicles have a patchy pale appearance due to glycosaminoglycan accumulation in the endoneurium. Dense fibrous tissue is between the nerve fascicles and appears as an extension of the thickened perineurium. D, Expanded fascicles contain wavy nerve fibers, spindle-shaped Schwann cells, fibroblasts, mast cells, small blood vessels, and glycosaminoglycan-rich endoneurium.
6. **FIGURE 93.6** This teenager with neurofibromatosis type 1 had a plexiform and diffuse neurofibroma involving the right orbit and entire upper eyelid. A, The tumor's plexiform component () is very pale due to marked endoneurial accumulation of glycosaminoglycans. B, The diffuse component of the tumor (), composed of spindle-shaped cells with eosinophilic cytoplasm and indistinct cell borders, surrounds the plexiform fascicle.

51. Chapter 94: Neurothekeoma
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    2. Etiology and Pathogenesis
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    4. Differential Diagnosis
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    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 94.1** A-D, Neurothekeoma of the eyelids and conjunctiva. (C, Reprinted with permission from Gray ME, Palileo CM, Sheridan RM. Cellular neurothekeoma of the eyelid in a 6-year-old boy. *JAAPOS*. 2016;20:374-376; D, Courtesy of Drs. Daniel Lefebvre and Michael Migliori.)
        2. **FIGURE 94.2** This cellular neurothekeoma (CNTK) presented as a 5.5 mm tumor of the left upper eyelid in a 4-year-old girl. A, Tumor cells form variably sized and shaped nodules within the dermis with sclerotic areas of brightly eosinophilic collagen. B, Tumor cells are spindle shaped or epithelioid with lightly eosinophilic cytoplasm and mostly indistinct cell borders. C, The matrix between cells and between nodules stains palely indicative of myxoid change (glycosaminoglycan

accumulation). An atypical tripolar mitotic figure is present (arrow) but is not indicative of malignancy in CNTKs.[10] D, Some areas of the tumor feature large multinucleated cells. E, Myxoid matrix in and between tumor nodules is highlighted blue using Alcian blue stain. F, Tumor cells and stromal fibroblasts between nodules are uniformly immunoreactive using antibodies to vimentin. G, All of the tumor cells stain intensely using antibodies to NKI/C3 (CD63). H, The tumor cells express CD68, with the most intense staining being in the large multinucleated cells.
3. **FIGURE 94.3** This cellular neurothekeoma (CNTK) was a 6 mm nodule in the medial left upper eyelid of a 13-year-old girl. A, The tumor features coalescent nodules, many with a whorled configuration. Numerous large multinucleated tumor cells are seen even at this low magnification. Orbicularis oculi muscle is at the bottom of the picture. The bright vertical streaks are sectioning artifacts. B, The islands of spindle-shaped and epithelioid cells have pale myxoid stroma, and thin dermal collagen bands separate them. C, Marked nuclear pleomorphism, such as seen in this photomicrograph, does not indicate malignancy in CNTKs. D, Tumor cells infiltrate between orbicularis oculi muscle fibers, but this does not signify malignancy in CNTKs.

52. Chapter 95: Nevus Flammeus
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    2. Etiology and Pathogenesis
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    4. Differential Diagnosis
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    9. Figures
        1. **FIGURE 95.1** A child with numerous unilateral patchy port-wine stains primarily in the distribution of the maxillary division of the trigeminal nerve.
        2. **FIGURE 95.2** An older individual with a well-defined nevus flammeus of the medial lower eyelid. (Courtesy of Dr. Alan McNab.)
        3. **FIGURE 95.3** A, Port-wine stain with numerous capillaries of varying caliber within the dermis. B, Higher magnification of the varying caliber capillaries lined by endothelial cells and lacking a muscle layer.
53. Chapter 96: Nevus Sebaceous of Jadassohn
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
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9. Figures
    1. **FIGURE 96.1** Lateral canthal and facial lesions in nevus sebaceous of Jadassohn. (Courtesy of Dr. Mohammad Javed Ali.)
    2. **FIGURE 96.2** Warty nevus sebaceous of Jadassohn of the upper eyelid. (Courtesy of Dr. Alan McNab.)
    3. **FIGURE 96.3** This nevus sebaceous of Jadassohn (NSJ) of the left occipital scalp was excised at age 12 years after a new papule developed. A, Papillary epidermal hyperplasia with hyperkeratosis, sebaceous gland hyperplasia, and apocrine gland hyperplasia is prominent at scanning magnification. B, Epidermal acanthosis and hyperkeratosis, hyperplasia of sebaceous and apocrine glands, and dermal fibrosis are common features of NSJ after 11 years. The hair follicle is maldeveloped with an absent hair shaft.
    4. **FIGURE 96.4** This scalp nevus sebaceous of Jadassohn was noted at birth and excised at 10 years of age due to increasing size and itchiness. A, The epidermis is acanthotic, and pilosebaceous units and apocrine glands are absent. B, The acanthosis is due to thickened stratum spinosum, and the papillary dermis is fibrotic.
    5. **FIGURE 96.5** This nevus sebaceous of Jadassohn of the right medial canthus was noted at birth and excised at the age of 1 year. A, There are an increased number of sebaceous glands and no normal hair follicles at scanning magnification. B, The superficial dermis has many abnormally developed hair follicles with cords of undifferentiated cells and rudimentary follicles. C, Small lobules of sebaceous glands connect to incompletely formed hair follicles.

54. Chapter 97: Nodular Fasciitis
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Characteristics
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 97.1** Large subcutaneous lesion of nodular fasciitis at the lateral brow. (Courtesy of Dr. Gordon Klintworth.)
        2. **FIGURE 97.2** Nodular fasciitis beneath the superior episcleral conjunctiva.

3. **FIGURE 97.3** This NF arose at the right lateral canthus in a woman in her late 20s. The NF was painless, nontender, and erythematous and grew continuously over 7 months to 1.5 cm in diameter. A, The NF extends from the papillary dermis through the reticular dermis. In this area, the NF has a fascicular pattern, with many of the fascicles having a loose appearance. The epidermis has an artifactual fold. B, The fascicular appearance is prominent in this area, and there is a focus of extravasated erythrocytes in the stroma. C, There were scattered multinucleated giant cells throughout the tumor. D, Some areas of the NF had a more compact appearance with sheets of spindle cells and intervening capillaries. E, Immunohistochemical staining with antibodies to smooth muscle actin is positive in >95% of cases of NF. F, Immunohistochemical expression of CD68, a marker of macrophages (histiocytes), was present in this case of NF, but the proportion of cases expressing CD68 has varied widely in published series of NF.
4. **FIGURE 97.4** A septuagenarian woman developed a round, firm, mobile mass of her right upper eyelid that increased to a diameter of 5 to 6 mm over 6 months. A, Excisional biopsy disclosed a bilobed mass with intravascular fasciitis (IF) of a small artery on the right, and a larger adjacent extravascular nodule of fasciitis. B, The IF had cells with oval nuclei and indistinct cell borders embedded in a predominantly myxoid stroma. C, Movat pentachrome stain highlights the arterial smooth muscle light red, the internal elastic lamina black, and the myxoid IF stroma blue. D, Immunohistochemical staining with antibodies to smooth muscle actin showed intense staining of the arterial wall smooth muscle and slightly less intense staining of the IF cells.

55. Chapter 98: Ocular Cicatricial Pemphigoid
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 98.1** A and B, Oral mucous membrane involvement with cicatricial pemphigoid. A, (Courtesy of Dr. Charles Soparkar.)
        2. **FIGURE 98.2** A and B, Early OCP with conjunctivitis, fornix shortening, and symblepharon formation.

3. **FIGURE 98.3** OCP with (A) entropion and trichiasis and (B) ankyloblepharon.
4. **FIGURE 98.4** Late-stage OCP with (A) corneal opacification and symblepharon and (B) complete obliteration of upper and lower fornices.
5. **FIGURE 98.5** A, This conjunctival biopsy frozen section has normal epithelium, a mild diffuse infiltrate of lymphocytes and macrophages in the substantia propria, and focal perivascular accentuation of the mononuclear inflammation. B, The same biopsy had a continuous linear band of IgA deposited along the basement membrane zone.

56. Chapter 99: Oculodermal Melanocytosis
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 99.1** Cutaneous pigmentation in oculodermal melanocytosis. A, Pigmentation involving the periocular upper and lower eyelids. B, Scattered pigmentation on the forehead. This patient also had pigmentation of the choroid, orbital fat, orbital bones, and intracranial dura.
        2. **FIGURE 99.2** Ocular pigmentation with ODM. A, Conjunctiva. B, Sclera.
        3. **FIGURE 99.3** A, Heavily pigmented melanocytes are in the upper and mid-dermis in ODM. B, The melanocytes are spindle shaped and oriented parallel to the skin surface except around epidermal appendages. C, High magnification to show the characteristic abundant melanin within the spindle-shaped melanocytes. The dispersed melanocytes are separated by intervening collagen bundles. The dispersion of melanocytes distinguishes ODM from a blue nevus.
57. Chapter 100: Pemphigus Vulgaris
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Characteristics
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures

1. **FIGURE 100.1** Bilateral hyperemic conjunctivitis in a case of pemphigus vulgaris. (Courtesy of Dr. Mohsen Kashkouli.)
2. **FIGURE 100.2** Pemphigus vulgaris with erosion of the eyelid margin and madarosis. (Courtesy of Dr. Gordon Klintworth.)
3. **FIGURE 100.3** This biopsy from the left lower eyelid is from the patient shown in Figure 100.2. A, There is acantholysis with cleft formation between the basal cells and the overlying prickle cells. B, A suprabasal bulla with tapering at the periphery causing the edge to have an acute angle. C, Direct immunofluorescence demonstrating IgG in the intercellular regions of the epidermis.

58. Chapter 101: Phakomatous Choristoma
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Characteristics
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 101.1** Phakomatous choristoma. (A, Courtesy of Dr. Stefan Seregaard. C, Reprinted with permission from Harris BF, Harris JP, Ducey PJ, et al. Phakomatous choristoma of the orbit with involvement of the inferior oblique muscle. *Ophthalmic Plast Reconstr Surg*. 2019;35:e9-e12.)
        2. **FIGURE 101.2** This phakomatous choristoma of the medial right lower eyelid of a baby boy was present from birth and excised at 3 months. A, Irregularly shaped islands of eosinophilic tumor cells are within dense collagenous tissue. B, The island of epithelial cells on the left surrounds a central zone of eosinophilic material, while the island on the right has entrapped basement membrane surrounding two small cysts. C, Higher magnification of the island on the right in (B) showing hyaline basement membrane surrounding two small cysts containing eosinophilic material with cells having pyknotic nuclei. D, Periodic acid-Schiff stain highlights a thick layer of basement membrane around the epithelial islands.
        3. **FIGURE 101.3** This phakomatous choristoma, present since birth, was removed from the preseptal medial right orbit at age 13 months due to anisometropia and eyelid deformity. A, Irregularly shaped, palely eosinophilic islands of epithelial cells are within dense, brightly eosinophilic collagenous tissue. B, Epithelial cells

surround acellular eosinophilic material at the top right, while the island at the lower left has a bladder (Wedl) cell (arrow). C, Periodic acid-Schiff stain demonstrates thick ribbons of basement membrane among epithelial cells.

59. Chapter 102: Pilomatrixoma
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Characteristics
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 102.1** A-D, Solitary pilomatrixoma of the eyelids. A, (Courtesy of Dr. Charles Soparkar.) B, (Courtesy of Dr. Alan McNab.) C, (Courtesy of Dr. Nahyoung Grace Lee). D, (Courtesy of Dr. Peter Rubin.)
        2. **FIGURE 102.2** Pilomatrixoma of the medial lower eyelid with crusting and areas of superficial ulceration.
        3. **FIGURE 102.3** A and B, Pilomatrixoma of the lateral brow. B, (Courtesy of Dr. Robert Kersten.)
        4. **FIGURE 102.4** This pilomatrixoma developed in the left medial eyebrow of a middle-aged man. It arose over 3 months and was firm, mobile, and erythematous. The tumor fragmented during removal. A, At low magnification, the pilomatrixoma has a mixture of basophilic cells and eosinophilic shadow cells. B, Basophilic cells surround eosinophilic shadow cells. Both islands of tumor cells have an intermediate zone of transitional cells between the basophilic cells and the shadow cells. C, Transitional zone cells have progressively more eosinophilic cytoplasm and increasingly pyknotic nuclei as they move toward the center of the islands and become shadow cells. D, Pilomatrixomas often have foreign-body multinucleated giant cells, most often around the areas of shadow cells.
60. Chapter 103: Pleomorphic Adenoma (Mixed Tumor)
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Characteristics
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures

1. **FIGURE 103.1** Pleomorphic adenoma of the medial canthus and side of the nose. (Courtesy of Dr. Alan McNab.)
2. **FIGURE 103.2** Benign cutaneous apocrine mixed tumor of the lateral left lower eyelid of a man in his early 40s. It was a freely movable 1.5 × 0.9 cm tumor that had been slowly growing for about 5 years and was associated with episodic eyelid swelling.
3. **FIGURE 103.3** Benign cutaneous apocrine mixed tumor from the patient in Figure 103.2. A, Cords and tubules of epithelial cells are in a stroma having adipose (top) and chondroid (bottom) metaplasia. The stroma on the right is hyalinized and brightly eosinophilic. B, The epithelial cells formed solid cords, as well as ductlike structures. C, Chondroid metaplasia of the stroma was a prominent feature of this neoplasm.
4. **FIGURE 103.4** This malignant mixed tumor in a woman in her mid-70s involved most of the left lower eyelid and inferior anterior orbit and extended into the lateral left upper eyelid and superior anterior orbit. The tumor did not involve the lacrimal gland. A, The tumor is contiguous with the epidermis. Much of the epidermis is ulcerated, as seen on the right side of the photomicrograph. B, Nests of tumor cells were embedded in a faintly basophilic chondroid matrix focally. C, In most areas, the tumor cells formed cords, rudimentary tubules, and nests within a lightly basophilic, myxoid fibrous stroma. D, Alcian blue stain for glycosaminoglycans is strongly positive, confirming the stroma's myxoid nature. E, A rudimentary tubule is at the arrowhead. There were frequent mitoses; a tripolar mitotic figure is at the arrow. F, Perineural invasion (*arrow*) by tumor was common. G, Some tumor cells were immunoreactive using antibodies to S100 protein. The expression of S100 protein by the tumor cells varied widely from one area to another within the tumor. H, CAM5.2 antibodies, immunoreactive principally to cytokeratin 8 (Becton Dickinson Biosciences), highlighted some tumor cells. The normal epidermis lacked immunoreactivity. I, All of the tumor cells were immunoreactive using antibodies to vimentin, which also highlighted the stromal cells.

61. Chapter 104: Poliosis
    1. Key Points
    2. Etiology and Pathogenesis
        1. *Poliosis and Genetic Syndromes*
        2. *Poliosis and Acquired Conditions*
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment

6. Prognosis
7. Histopathology
8. References
9. Figures
    1. **FIGURE 104.1** Poliosis associated with vitiligo. (Courtesy of Dr. Alan McNab.)
    2. **FIGURE 104.2** Poliosis associated with trichiasis. To the best of our knowledge, this association is hitherto unknown and could be accidental.

62. Chapter 105: Pseudoepitheliomatous Hyperplasia
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Characteristics
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 105.1** A, Subcutaneous nodule of pseudoepitheliomatous hyperplasia (PEH) in the medial lower eyelid. B, PEH around the superior punctum. (A, Courtesy of Dr. Suzanne Freitag. B, Reprinted with permission from Bothra N and Ali JM. Punctal pseudoepitheliomatous hyperplasia mimicking a mass lesion. *Orbit*. 2021;40(1):73-74.)
        2. **FIGURE 105.2** Cutaneous pseudoepitheliomatous hyperplasia at the site of newly formed scar from recent melanoma surgery. A, The epidermis has extensive irregular hyperplasia with anastomosing downward projections into the dermis with jagged borders and rounded or pointed bases. B, The epidermis has hyperkeratosis, and keratin pearls are in the anastomosing epidermal masses projecting into the dermis. C, There is minimal cytological atypia and foci of keratinization with brightly eosinophilic cytoplasm.
        3. **FIGURE 105.3** Pseudoepitheliomatous hyperplasia of the right upper eyelid in a man with ulcerative sarcoidosis. There is a thick layer of parakeratosis and pseudoepitheliomatous hyperplasia of the epidermis. The dermis has non-necrotizing granulomatous inflammation with a sparse lymphocytic infiltrate around discrete and coalescing granulomas. The focal hemorrhage at the base of the lesion is from the biopsy.
        4. **FIGURE 105.4** Pseudoepitheliomatous hyperplasia of the conjunctiva in a middle-aged man with herpes simplex virus conjunctivitis secondary to immunosuppression. There is an irregular thickening of the conjunctival epithelium with extension into markedly inflamed substantia propria. There are

discrete, isolated nests of epithelium in the substantia propria (arrows).
63. Chapter 106: Punctal Stenosis and Agenesis
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Characteristics
    4. Differential Diagnosis
    5. Treatment
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    8. References
    9. Figures
        1. **FIGURE 106.1** Lower eyelid punctal stenosis showing its small size. (Courtesy of Dr. Javed Mohammad Ali.)
        2. **FIGURE 106.2** Punctal agenesis. (Courtesy of Dr. Javed Mohammad Ali.)
64. Chapter 107: Pyogenic Granuloma
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
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    8. References
    9. Figures
        1. **FIGURE 107.1** Pyogenic granuloma. A, Central lower eyelid palpebral conjunctiva. B, Medial lower eyelid conjunctiva.
        2. **FIGURE 107.2** A, PG of the lower eyelid palpebral conjunctiva. B, Lateral upper eyelid PG from the conjunctiva associated with a traumatic defect. A, (Courtesy of Dr. Robert A. Goldberg.)
        3. **FIGURE 107.3** A, A small PG arising from the inferior punctum. B, An extensive PG in the medial canthal palpebral conjunctiva and the medial bulbar conjunctiva. B, (Courtesy of Dr. Robert A. Goldberg.)
        4. **FIGURE 107.4** This conjunctival PG arose following surgery for a pterygium removal. A, At low magnification, proliferating capillaries within an edematous stroma radiate from a narrowed base toward the surface. The overlying epithelium is ulcerated, and there is focal hyperplastic epithelium creating a collarette at the lesion's base. B, Capillaries of varying caliber are within edematous stroma containing numerous leukocytes. C, The leukocytic infiltrate has a mixture of neutrophils, lymphocytes, plasma cells, and macrophages.
        5. **FIGURE 107.5** A, Epidermis covers this cutaneous PG, a collarette of hyperplastic epidermis surrounds the base,

stromal edema is minimal, and inflammation is sparse. B, Lobules of capillaries are enmeshed in loose fibrous stroma and separated by dense fibrocollagenous septa.
6. **FIGURE 107.6** A, This intravenous PG arose in a vein at the left upper eyelid's lateral edge and was manifest clinically as a freely mobile subcutaneous mass. It was present clinically for 6 months before excision. B, The polypoid lesion is formed of lobules of capillaries enmeshed in fibromyxoid stroma with few chronic inflammatory cells. C, Immunohistochemical staining using antibodies to CD31 highlights the capillary endothelial cells.

65. Chapter 108: Rhabdomyoma
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Characteristics
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 108.1** Submucosal rhabdomyoma of the medial canthus.
        2. **FIGURE 108.2** Surgical excision of the lesions in Figure 108.1.
        3. **FIGURE 108.3** This adult rhabdomyoma developed in the base of the tongue of a man in his early 60s. A, Well-circumscribed lobules of tumor cells are in the submucosa. B, The tumor cells are large and round to polygonal and have eosinophilic and vacuolated cytoplasm. Round nuclei with distinct nucleoli are in the center or periphery of the cells. One cell has cytoplasmic strands between vacuoles creating a “spider web appearance” (*arrow*). There is scant stroma with blood vessels between tumor cells. C, The cells have variable vacuolation and focal cross-striations (*arrow*).
        4. **FIGURE 108.4** Intermediate fetal rhabdomyoma from the orbit of a 3-year-old boy. A, Eosinophilic tumor cells form fascicles with some sectioned longitudinally, others in cross-section. B, The tumor is a mixture of cells with scant cytoplasm and many strap cells with abundant eosinophilic cytoplasm and occasional cross-striations. There were no mitotic figures identified in the tumor.
        5. **FIGURE 108.5** This skeletal muscle hamartoma (rhabdomyomatous mesenchymal hamartoma) was excised from the medial left lower eyelid of a 57-year-old woman.[57] A, Multiple striated muscle fiber bundles () are in the superficial to deep reticular dermis. B,

Irregularly thickened collagen bundles are between and among the bundles of skeletal muscle fibers. C, Most of the myocytes have a splayed appearance with retained cross-striations.

66. Chapter 109: Rosacea
    1. Key Points
    2. Etiology and Pathophysiology
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 109.1** Rosacea primarily involving the central face with little or no simultaneous eyelid involvement. A, Facial rosacea with telangiectasis and mild erythema of the eyelids. B, Diffuse facial rosacea. A, (Courtesy of Dr. Morris Hartstein.)
        2. **FIGURE 109.2** A, Facial and eyelid rosacea with sebaceous pustules. B and C, Facial and eyelid rosacea acne. D, Rosacea involving the face, eyelid, and forehead, with rhinophyma. C, (Courtesy of Dr. Charles Soparkar.) D, (Courtesy of Dr. Peter Rubin.)
        3. **FIGURE 109.3** Eyelid rosacea with recurrent chalazia of the lower eyelids. B, (Courtesy of Dr. Peter Rubin.)
        4. **FIGURE 109.4** A man in his mid-70s with clinical rosacea had an incisional biopsy of an erythematous plaque of his right upper eyelid that was clinically suspicious for basal cell carcinoma. A, The papillary and superficial reticular dermis have telangiectatic vessels with marked edema of the papillary dermis (). A granuloma is in the superficial reticular dermis (*arrow*). B, Markedly dilated vessels have irregular shapes, and some have a discontinuous endothelial cell lining (). The papillary dermis is markedly edematous with separation of the collagen fibers and fibroblasts by clear edema fluid. C, Lymphohistiocytic infiltrate around a dermal blood vessel with swollen endothelial cells.
        5. **FIGURE 109.5** This man in his early 70s with chronic blepharitis had a biopsy of a hyperkeratotic area associated with madarosis. A, The epidermis is acanthotic with hyperkeratosis and parakeratosis. B, The dermis is diffusely infiltrated by lymphocytes and granulomas composed of loose aggregates of epithelioid cells with occasional multinucleated giant cells. The dermis between granulomas has a dense infiltrate of lymphocytes. C, The granulomas contain mostly epithelioid cells with a few giant cells. No fungi or acid-fast microorganisms were identified using histochemical

stains. The histological findings in the biopsy are nonspecific, but the predilection for hair follicles favors granulomatous rosacea.

67. Chapter 110: Rosai-Dorfman Disease
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Characteristics
    4. Differential Diagnosis
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    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 110.1** Rosai-Dorfman disease with bilateral upper eyelid swelling.
        2. **FIGURE 110.2** A, Bilateral lower eyelid thickening with telangiectatic vessels and mechanical ptosis. B, Massive edema of the eyelids with ptosis in a patient with Rosai-Dorfman disease. A, (Courtesy of Dr. Roman Shinder.) B, (Courtesy of Dr. David Jordan.)
        3. **FIGURE 110.3** A-D, Rosai-Dorfman disease of the upper eyelid with predominantly pale staining, foamy histiocytes having indistinct cytoplasmic borders. There are scattered small aggregates of lymphocytes and plasma cells, as well as individual cells percolating among the histiocytes. A large histiocyte with a binucleate plasma cell and a neutrophil in its cytoplasm (emperipolesis) is in C (*arrow*). The histiocytes were all immunohistochemically positive for expression of CD68 (E) and S100 protein (F).
        4. **FIGURE 110.4** A and B, Rosai-Dorfman disease of the lower eyelid with histiocytes having eosinophilic, finely vacuolated cytoplasm and indistinct cytoplasmic borders. Lymphoid follicles with germinal centers are present, as seen in A (*arrow*). There is a diffuse infiltrate of lymphocytes and plasma cells among the predominating histiocytes.
        5. **FIGURE 110.5** A and B, Rosai-Dorfman disease of the orbit featuring large, polygonal, histiocytes with eosinophilic cytoplasm and distinct cytoplasmic borders. There are numerous lymphocytes and plasma cells and scattered eosinophils among the histiocytes.
68. Chapter 111: Sarcoidosis
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Characteristics
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology

8. References
9. Figures
    1. **FIGURE 111.1** Lacrimal gland involvement with sarcoidosis.
    2. **FIGURE 111.2** Sarcoid granulomatous inflammation of the upper eyelid palpebral conjunctiva.
    3. **FIGURE 111.3** Papular and nodular sarcoid lesions on the eyelids.
    4. **FIGURE 111.4** Necrotizing sarcoidosis with extensive tissue destruction of upper and lower eyelids.
    5. **FIGURE 111.5** Scar sarcoidosis. A, Sarcoid arising in an old basal cell carcinoma scar. B, Subcutaneous sarcoidosis adjacent to an old traumatic lateral canthal scar.
    6. **FIGURE 111.6** In his mid-20s, a man with iritis in his left eye developed an elevated, soft, mobile irregularity under the skin of the right lateral canthus with epidermal hypopigmentation. He was diagnosed with eyelid, lacrimal gland, intraocular, and pulmonary sarcoidosis. A, Numerous granulomas extend from the superficial to the deep dermis with areas of coalescence. B, Some areas have loose aggregates of epithelioid cells (top half of photomicrograph) with adjacent circumscribed, compact granulomas (bottom left and right). Epithelioid cells far outnumber lymphocytes in the granulomas. C, Coalescent epithelioid granulomas with admixed lymphocytes and two Langhans giant cells. D, Epithelioid cells and interspersed lymphocytes surround two Langhans giant cells. A basophilic Schaumann body is in the cytoplasm of one of the Langhans giant cells (right).
    7. **FIGURE 111.7** This conjunctival biopsy was from a woman in her late 70s with bilateral, chronic, severe conjunctivitis with minimal cicatrization. The conjunctival substantia propria contains multiple well-circumscribed granulomas (*arrows*) with focal scarring (). The granulomas are composed of epithelioid cells, multinucleated giant cells, and a thin rim of lymphocytes (inset). Epithelium is only on the right side of the photomicrograph; most of the epithelium is artifactually detached.
    8. **FIGURE 111.8** A man in his 30s with pulmonary and cutaneous sarcoidosis developed progressive right upper eyelid irritation, mild pain, and a 12-mm-diameter ulcer. A, The right upper eyelid lesion has healing ulceration with a thick layer of parakeratosis and pseudoepitheliomatous hyperplasia of the epidermis. B, The dermis contains nonnecrotizing granulomatous inflammation with discrete and coalescing granulomas composed of epithelioid cells and occasional

multinucleated giant cells surrounded by a sparse lymphocytic infiltrate.
10. Tables
    1. **TABLE 111.1Histopathological Features of Cutaneous Sarcoidosis**
69. Chapter 112: Schwannoma
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    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 112.1** Smooth, solid nodular schwannomas of the eyelid. A and B, (Courtesy of Dr. David Jordan.)
        2. **FIGURE 112.2** A rare case of malignant schwannoma of the eyelid and conjunctiva.
        3. **FIGURE 112.3** A, Cutaneous schwannomas are encapsulated well-circumscribed nodules usually located in the subcutaneous fat. B, This schwannoma of the left thigh is composed of interlacing fascicles of spindle-shaped Schwann cells. C, The neoplastic cells have elongated, twisting, tapering nuclei and eosinophilic cytoplasm with indiscernible cell borders. An indistinct Verocay body, formed by palisaded tumor cell nuclei with intervening eosinophilic cell processes, is in the center of the image. D, The tumor cells stain intensely and uniformly positive using antibodies to S100 protein.
        4. **FIGURE 112.4** This schwannoma of the lateral left upper eyelid dermis presented as a 2-mm-diameter dome-shaped papule near the ciliary margin in a middle-aged woman. A, The schwannoma was encapsulated and well circumscribed. B, Interlacing fascicles of spindle-shaped Schwann cells with long, tapering, often wavy nuclei. C, Close-up photomicrograph showing tapering nuclei, lack of cytological atypia, and cytoplasmic nuclear inclusions in some of the neoplastic Schwann cells. Cell borders are not discernible. D, All of the tumor cells strongly expressed S100 protein. E, Expression of calretinin by tumor cells supports the diagnosis of schwannoma. Axons were sparse in a section stained using antibodies to neurofilament protein (not shown). F, Perineurial cells in the capsule are immunoreactive using antibodies to epithelial membrane antigen (MUC1).
70. Chapter 113: Sebaceous Adenoma
    1. Key Points
    2. Etiology and Pathogenesis

3. Clinical Characteristics
4. Differential Diagnosis
5. Treatment
6. Prognosis
7. Histopathology
8. References
9. Figures
    1. **FIGURE 113.1** Sebaceous adenoma. B, (Courtesy of Dr. Suzanne Freitag.)
    2. **FIGURE 113.2** A, Sebaceous adenoma with fine telangiectasias. B. Sebaceous adenoma with fine filiform projections. A, (Courtesy of Dr. Bettina Meekins.)
    3. **FIGURE 113.3** Large sebaceous adenoma in Muir-Torre syndrome. (Courtesy of Drs. Josiah To and Paul Phelps.)
    4. **FIGURE 113.4** This sebaceous adenoma presented as a cutaneous horn of the right lower eyelid of a 60-year-old man who was subsequently diagnosed with Muir-Tore syndrome. A, The adenoma forms lobules contiguous with the epidermis and is surrounded by an epithelial collarette creating a keratoacanthoma-like appearance. The lesion's surface has sebaceous material, foci of hemorrhage, and parakeratosis, creating the horn noted clinically. B, Mature sebaceous cells outnumber germinative cells. The overlying horn contains abundant sebaceous material released by holocrine secretion and areas of parakeratosis. C, The tumor lobules contain germinative basaloid cells, transitional cells with lightly eosinophilic cytoplasm, and mature sebaceous cells in the center of the lobules. D, The amount of cytoplasm increases and becoxmes reticulated as the germinative cells mature.
    5. **FIGURE 113.5** This sebaceous adenoma in a 67-year-old man was manifest clinically as a 5 × 5 mm pedunculated mass of the right caruncle that did not involve the right lower eyelid. A, The caruncular sebaceous adenoma has numerous lobules forming a mass that is not contiguous with the surface epithelium. B, The lobules have a one-to two-cell thick layer of germinative cells, a predominance of transitional cells with pink cytoplasm, and centrally located mature sebaceous cells with clear cytoplasm.
    6. **FIGURE 113.6** This sebaceoma arose in the right upper eyelid of a man in his early 50s. A, The tumor is a well-circumscribed nodule in the dermis contiguous with the epidermis. The overall predominance of basaloid (germinative) cells distinguishes sebaceoma from sebaceous adenoma. B, This tumor lobule shows continuity with the epidermis, more germinative than mature sebaceous cells, and the sharp border of the

tumor and adjacent dermis. C, Maturation of germinative cells is similar to that in sebaceous adenoma.
7. **FIGURE 113.7** This meibomian gland sebaceous adenoma developed in the lateral left lower eyelid of a woman in her late 20s. It had been present for approximately 9 years, fluctuated in size, was intermittently erythematous, and itched continuously. A, The sebaceous adenoma is a nodular mass of sebaceous lobules (acini) extending anteriorly from the tarsus at the eyelid margin. The meibomian duct is dilated distal to the tumor. B, Lobules of tumor surround and compress the meibomian duct. C, The tumor lobules vary in size. The germinative layer is thicker than normal. D, The adenomatous lobules have a prominent peripheral germinative layer and abundant transitional cells with pink cytoplasm. A normal meibomian gland is at the bottom right corner of the image and has a flattened germinative cell layer surrounding mature sebaceous cells with clear reticulated cytoplasm.

71. Chapter 114: Sebaceous Duct Cyst
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 114.1** Sebaceous duct cyst on the medial canthus and nasal bridge. (Courtesy of Dr. Roman Shinder.)
        2. **FIGURE 114.2** Small medial upper eyelid sebaceous duct cyst.
        3. **FIGURE 114.3** Steatocystoma simplex of the lateral left upper eyelid from the patient whose histopathology is in Figure 114.4.
        4. **FIGURE 114.4** This steatocystoma simplex of the lateral left upper eyelid was a 7- to 8-mm-diameter cystic lesion in a man in his late 40s. It was present for 5 years, had no associated discharge or pain, and was a dark cystic lesion on slit-lamp examination. A, The cyst collapsed during sectioning causing evaginations that appear as multiple small cysts and pilosebaceous units. Sebaceous cells are in and adjacent to the cyst wall. B, The largest area of the cyst has a wavy wall, absent granular cell layer, and laminated and amorphous keratinous debris in the lumen. C, The cyst lining lacks a granular cell layer and has an eosinophilic crenulated

luminal surface. Both laminated and amorphous keratinous debris is in the lumen. D, The luminal surface of the epithelial cyst lining is eosinophilic and crenulated.
5. **FIGURE 114.5** A vellus hair cyst developed in the right lower eyelid of a woman in her late 60s. She noted a whitish bump that increased in size over 2 to 3 months with no change in color, discharge, or pain. A, The unilocular cyst is in the dermis, is lined by stratified squamous epithelium, and is filled with laminated keratin and vellus hairs. B, The epithelial lining lacks a granular cell layer. Both laminated keratin and vellus hairs cut in cross-section are present in the lumen.

72. Chapter 115: Seborrheic Keratosis
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 115.1** A-D. Sharply demarcated hyperkeratotic seborrheic keratosis. B and C, (Courtesy of Dr. Alan McNab.)
        2. **FIGURE 115.2** A, Multiple small seborrheic keratosis (SK) of the eyelids and face. B, Pigmented SK on the upper eyelid margin. C, Hyperkeratotic SK with a "stuck-on" appearance. D, Hyperkeratotic SK on the lateral brow. B, (Courtesy of Dr. Robert Kersten.) C, (Courtesy of Dr. Charles Soparkar.)
        3. **FIGURE 115.3** A and B, Acanthotic (regular) seborrheic keratosis (SK) of the left lower eyelid with broad interdigitating columns of hyperplastic epidermis and many horn cysts. C, Reticulated (adenoid) type of SK of the left lower eyelid with thin, mostly double-rows, of anastomosing basaloid cells with horn cysts. D, Keratotic (papillomatous) SK with a hyperkeratotic and saw-tooth appearing epidermal surface creating a church-spire appearance. E, This keratotic SK of the right upper eyelid had massive hyperkeratosis creating a cutaneous horn. F, Pigmented type of SK of the left lower eyelid with increased melanin pigmentation of keratinocytes. G and H, This irritated SK of the right upper eyelid had numerous aggregates of eosinophilic squamous cells (squamous eddies). The dermis, not seen in this image, had prominent chronic inflammation.
73. Chapter 116: Solitary Fibrous Tumor
    1. Key Points

2. Etiology and Pathophysiology
3. Clinical Presentation
4. Differential Diagnosis
5. Treatment
6. Prognosis
7. Histopathology
8. References
9. Figures
    1. **FIGURE 116.1** Solitary fibrous tumor (SFT) of the lower eyelid and conjunctiva.
    2. **FIGURE 116.2** Solitary fibrous tumor (SFT) of the upper eyelid causing mechanical ptosis. (Courtesy of Dr. Robert A. Goldberg.)
    3. **FIGURE 116.3** Solitary fibrous tumor (SFT) metastatic to the eyelid and orbit.
    4. **FIGURE 116.4** A man in his middle 30s developed tearing due to a solitary fibrous tumor (SFT) involving the left medial canthus and left lacrimal sac. A, SFT is present in the lacrimal sac subepithelium and extends into the adjacent connective tissue. The lacrimal sac epithelium has goblet cells individually and forming mucous glands.[87] B, The cellularity of SFTs is variable. This area of the tumor has low cellularity and abundant collagen. C, This area of the tumor has high cellularity and sparse stroma. D, The SFT has areas of prominent vascularization with large thin-walled vessels. (Reprinted with permission from Paulsen F. *The Human Nasolacrimal Ducts*. Springer; 2003:19.)
    5. **FIGURE 116.5** This solitary fibrous tumor (SFT) of the right lower eyelid mucocutaneous junction lateral to the punctum was from a woman in her late 60s. The lesion was raised, had a diameter of about 1 mm, and there was telangiectasia but no madarosis. It was present for about 1 to 2 years before biopsy during ectropion repair. A, The SFT is in the conjunctival substantia propria with a thin zone of normal connective tissue between the tumor and thickened conjunctival epithelium. B, The SFT is cellular, with spindle cells forming fascicles with interspersed stromal collagen. Some areas had many blood vessels. C, The spindle cells are cytologically bland, mitotic figures and necrosis are absent, and abundant eosinophilic collagen is present among the fascicles of spindle cells. The tumor cells exhibit cytoplasmic staining using antibodies to CD34 (D) and CD99 (E). The tumor cells did not express smooth muscle actin, S100 protein, or glial fibrillary acidic protein (not shown). F, Approximately 95% of superficial SFTs exhibit nuclear expression of STAT6.

74. Chapter 117: Stevens-Johnson Syndrome
    1. Key Points

2. Etiology and Pathogenesis
3. Clinical Presentation
4. Differential Diagnosis
5. Treatment
6. Prognosis
7. Histopathology
8. References
9. Figures
    1. **FIGURE 117.1** Hyperemia and scarring of the upper eyelid tarsal conjunctiva in SJS.
    2. **FIGURE 117.2** SJS with eyelid blisters and skin sloughing. (Courtesy of Dr. Charles Soparkar.)
    3. **FIGURE 117.3** A, This SJS biopsy has full-thickness epidermal necrosis, a subepidermal blister, and a scant dermal inflammatory infiltrate. B, Individual hypereosinophilic necrotic keratinocytes are in this SJS biopsy, along with a subepidermal bulla and a sparse perivascular dermal inflammatory infiltrate of lymphocytes and macrophages. C, The epidermal necrosis in this SJS biopsy varies from full thickness () to partial thickness (*arrow*). There are subepidermal blisters and minimal dermal inflammation.

75. Chapter 118: Subepidermal Calcinosis
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Characteristics
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 118.1** Calcinosis cutis. A, Papillomatous nodule on the upper eyelid. B, Small lower eyelid lesion. C, Nodular calcinosis lesion around the lower eyelid punctum. D, Calcinosis lesion on the lower eyelid margin. B and C, (Courtesy of Dr. Javed Mohammad Ali.) D, (Courtesy of Dr. Norman Charles.)
        2. **FIGURE 118.2** This subepidermal calcified nodule arose on a young girl's medial left upper eyelid (shown in Figure 118.1A). The nodule was diagnosed clinically as a pilar (trichilemmal) cyst, and it was treated with hot compresses and massage three times per day. It went entirely away after 1 week of treatment, but it then recurred at the same site with intermittent drainage and swelling. It was excised 8 months after its appearance. A, The SCN is well circumscribed in the dermis and abuts the acanthotic epidermis. Numerous clefts are present in the nodule, at least partially reflecting artifacts from the extensive calcification. B, The epidermis has

prominent hyperkeratosis. There are innumerable calcific deposits, some directly in contact with the basal epidermis. C, The calcific deposits vary widely in size from punctate particles to small, irregular, but primarily round to oval deposits. Larger deposits tend to be more basophilic than the minute particles.
3. **FIGURE 118.3** Subepidermal calcinosis (calcinosis cutis) developed in the medial left upper eyelid near the medial canthus of a man in his early 30s. The lesion started as a 2 × 3 mm keratotic papule thought to be a verruca vulgaris. There was no response to two cryotherapy applications, and the lesion was excised about 4 months later. Deposits of basophilic calcification in clear lacunae are in the superficial dermis and are typical of idiopathic calcinosis cutis. The empty spaces around the calcific deposits result from fragmentation and loss of deposits during histological sectioning.

76. Chapter 119: Syringocystadenoma Papilliferum
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 119.1** Syringocystadenoma papilliferum of the upper eyelid with trichiasis and madarosis. (Courtesy of Dr. Philip Custer.)
        2. **FIGURE 119.2** SCAP of the medial left lower eyelid with a rugose surface surrounding the punctum.
        3. **FIGURE 119.3** An elevated, yellow/tan multilobulated SCAP on the left lateral upper eyelid margin. (Courtesy of Dr. Anne Barmettler.)
        4. **FIGURE 119.4** A, This SCAP of the neck has large irregular papillary projections covered with acanthotic stratified squamous epithelium with hyperkeratosis. A duct extends from the lesion's surface to an underlying dilated duct containing papillae. A cystically dilated eccrine duct resembling a hidrocystoma is in the dermis to the right of the SCAP. B, Numerous papillae having plasma cell-rich connective tissue cores are within the dilated duct. C, Two layers of epithelium line the papillae. The outer layer of cells is cuboidal, while the inner layer is columnar. The papillae have a dense infiltrate of plasma cells in their connective tissue cores.
        5. **FIGURE 119.5** This SCAP from the right upper eyelid of a woman in her early 30s was present since

childhood. The recent onset of irritation and bleeding prompted its removal. A, Sectioning parallel to the epidermis has resulted in epidermis surrounding the SCAP. A dilated duct connects focally to the epidermis at the top left of the photomicrograph. The dermis contains dilated ducts with many papillae. B, Dilated ducts with papillae are easily seen at higher magnification. Stratified squamous epithelium transitions to a two-layered epithelium in the dilated duct at the bottom left. C, Close-up of the transition zone between stratified squamous epithelium and the two-layered epithelium characteristic of SCAP. The fibrovascular cores of papillae are laden with plasma cells. D, The inner columnar epithelial layer of epithelium had areas of decapitation secretion typical of apocrine differentiation.

77. Chapter 120: Syringoma
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 120.1** Syringomas of the eyelids as soft, skin-colored papules. A, (Courtesy of Dr. Robert Goldberg.)
        2. **FIGURE 120.2** This conventional syringoma was one of many involving all four eyelids in a woman in her middle 50s. A, The syringoma is well circumscribed and in the mid and upper dermis without connecting to the overlying epidermis. B, The tumor is composed of small nests and ducts (tubules) embedded in a collagenous eosinophilic stroma. An epithelial strand at the end of the ductule at the bottom right creates a tadpole appearance. C, Two layers of flattened to low cuboidal cells form the ducts. The ductal lumens contain homogeneous material. Tumor cells are cytologically bland with small nuclei and eosinophilic cytoplasm.
        3. **FIGURE 120.3** This clear-cell syringoma was from the right lower eyelid of a woman in her early 50s with well-controlled diabetes mellitus. She had multiple tumors of both lower eyelids. A, The syringoma is well circumscribed and mainly in the mid-dermis. The epidermis and superficial dermis near the center of the biopsy are artifactually disrupted. The tumor is difficult to see at low magnification due to the clear cytoplasm in the tumor cells. B, The tumor is composed mostly of small nests and cords with a few ducts (tubules)

embedded in a collagenous eosinophilic stroma. C, Almost all of the cells have clear cytoplasm due to glycogen accumulation. Eosinophilic material is in duct lumens.

78. Chapter 121: Trachoma
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Characteristics
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 121.1** A, Conjunctival scarring from repeated or persistent ocular infection with *Chlamydia trachomatis*. B, Late-stage trachomatous scarring with linear von Arlt line on the superior tarsal conjunctiva and follicular conjunctivitis. A and B, (Courtesy of Dr. Antonio Augusto Cruz.)
        2. **FIGURE 121.2** Herbert pits within a pannus along the superior corneal limbus. (Courtesy of Dr. Antonio Augusto Cruz.)
        3. **FIGURE 121.3** Upper eyelid cicatricial entropion in late-stage trachoma. A, (Courtesy of Dr. Antonio Augusto Cruz.) B, (Courtesy of Dr. Roman Shinder.)
        4. **FIGURE 121.4** Secondary trichiasis of the upper eyelid in late-stage trachoma. A, (Courtesy of Dr. Alan McNab.) B, (Courtesy of Dr. Roman Shinder.)
        5. **FIGURE 121.5** Corneal opacification from trachomatous entropion and trichiasis.
        6. **FIGURE 121.6** This biopsy was from the right inferior fornix of a young woman with bilateral chronic follicular conjunctivitis, confirmed as *Chlamydia trachomatis* infection using the cobas CT/NG v2.0 Test (Roche Diagnostics). A, A band of chronic (mononuclear) inflammatory cells is beneath the epithelium, and a follicle is present in the deeper substantia propria (*arrow*). The follicle center cells are large, pale, activated B lymphocytes with admixed macrophages and some T cells.[54] B, In this biopsy area, there is a band of dense subepithelial mononuclear inflammation with a vague follicle (*arrow*). A band of fibrosis is beneath the inflammation (). C, The epithelium is superficially keratinized, and there is a marked reduction in the number of goblet cells customarily found at this location.[56] The inflammatory infiltrate contains numerous plasma cells along with lymphocytes and macrophages. D, Giemsa stain highlights the numerous plasma cells, including several

in the epidermis (*arrows*). A few eosinophils are also present (*arrowheads*).
79. Chapter 122: Verruca Vulgaris
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 122.1** Verruca vulgaris. A, Pedunculated filiform lesion on the upper eyelid. B, Broad-based sessile verruca wart in the medial lower eyelid.
        2. **FIGURE 122.2** A, Flesh-colored, finger-like projections of verruca vulgaris. B, Multiple small filiform and lobular verruca warts.
        3. **FIGURE 122.3** Soft rugose conjunctival verrucae.
        4. **FIGURE 122.4** A, This verruca vulgaris was one of many warts involving the eyelids of a child. There is papillomatosis, marked hyperkeratosis, acanthosis, and parakeratosis. At the edge of the lesion, elongated rete ridges bow inward, a process termed arborization (*arrow*). Near the center, the rete ridges are confluent (). B, Parakeratosis, arranged as a vertical column, overlies a papillomatous projection (*arrow*). C, The granular cell layer is prominent due to coarse intracellular clumps of basophilic keratohyaline granules (). Other keratinocytes in the granular cell layer have vacuolar change with small hyperchromatic nuclei surrounded by a halo of clear cytoplasm with absent keratohyaline granules (*arrow*).
80. Chapter 123: Xanthelasma Palpebrarum
    1. Key Points
    2. Etiology and Pathophysiology
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Histopathology
    7. References
    8. Figures
        1. **FIGURE 123.1** A-D, Xanthelasma palpebrarum involving the upper and lower eyelids and medial canthus.
        2. **FIGURE 123.2** A, Xanthelasma appearing as bilateral brown firm lesions. B, Periorbital xanthelasma with a nodular mass on the medial canthus in a patient with hypercholesterolemia.

3. **FIGURE 123.3** A and B, Large upper eyelid xanthelasma causing mechanical ptosis.
4. **FIGURE 123.4** A, Typical xanthelasma with clusters of vacuolated, lipid-laden macrophages (foam cells) in the papillary and upper reticular dermis forming nodules separated by dermal connective tissue with scattered individual foam cells. B, Foam cells have a perivascular predilection, although they are usually present as individual cells and small clusters between the larger aggregates of perivascular foam cells. Lymphocytes and nonxanthomatous macrophages are common but often inconspicuous. C, Lipid vacuoles within the macrophages create a finely reticular, pale-staining cytoplasm. D, Xanthelasma may have occasional multinucleated foam cells (arrow), but Touton giant cells are rare.

81. Chapter 124: Xanthogranuloma and Histiocytoses
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 124.1** A and B, Juvenile xanthogranuloma nodules on the eyelids. A, (Courtesy of Dr. Brian Brazzo.) B, (Courtesy of Dr. David Lyon.)
        2. **FIGURE 124.2** A-D, Adult-onset xanthogranuloma. C, (Courtesy of Dr. Charles Soparkar.)
        3. **FIGURE 124.3** A-D, Adult-onset xanthogranuloma. A, (Courtesy of Dr. Robert Goldberg.) B, (Courtesy of Dr. Robert Machemer.) C, (Courtesy of Dr. Charles Soparkar.)
        4. **FIGURE 124.4** Necrobiotic xanthogranuloma. A, Bilateral granulomas with orbital involvement and secondary ptosis of the right eye. B, Close-up view of the right eye of the patient in 1A.
        5. **FIGURE 124.5** A, Juvenile xanthogranuloma with lipid-laden macrophages (foam cells), Touton giant cells, and numerous interspersed lymphocytes. B, Touton giant cells have a ring of nuclei surrounding eosinophilic nonvacuolated cytoplasm centrally and lipid-filled foamy cytoplasm peripherally.
        6. **FIGURE 124.6** A, This adult-onset xanthogranuloma presented as a left lower eyelid dome-shaped nodule. B, A thin band of collagen separates the epidermis from the dermal infiltrate containing foam cells, numerous giant cells, and occasional lymphocytes. C, Both Touton ()

and foreign-body (arrow) giant cells were present in the dermal infiltrate. D, All of the mononuclear and multinuclear foam cells expressed CD68.
7. **FIGURE 124.7** A and B, Necrobiotic xanthogranuloma with macrophages, foam cells, Touton giant cells, and lymphocytes surrounding necrobiotic tissue having numerous cholesterol clefts. C and D, Necrobiotic xanthogranuloma with macrophages, foam cells, Touton and foreign-body giant cells, and lymphocytes surrounding bands of necrobiotic collagen without cholesterol clefts.
8. **FIGURE 124.8** A, Orbital Erdheim-Chester disease showing islands of pale-staining foam cells separated by whorls of dense fibrosis. Several lymphoid aggregates are also evident. B, The foam cells are histologically similar to those in juvenile and adult xanthogranuloma and xanthelasma. C, High magnification showing Touton giant cells separated from foam cells by dense fibrous tissue.

82. Chapter 125: Xeroderma Pigmentosum
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Characteristics
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 125.1** A-D, Xeroderma pigmentosum involving the eyelids and face. (Courtesy of Dr. Maria Claudia Schellini.)
        2. **FIGURE 125.2** Invasive squamous cell carcinoma of the conjunctiva in a child with XP. The tumor is histologically the same as invasive squamous cell carcinoma of the conjunctiva in individuals without XP. (Photomicrograph prepared from a histological slide distributed by Dr. Fausto Rodriguez at the 2012 meeting of the Eastern Ophthalmic Pathology Society.)

5. V: Malignant Tumors of the Eyelids
    1. Chapter 126: Adenoid Cystic Carcinoma
        1. Key Points
        2. Etiology and Pathogenesis
        3. Clinical Presentation
        4. Differential Diagnosis
        5. Treatment
        6. Prognosis
        7. Histopathology
        8. References
        9. Figures

1. **FIGURE 126.1** A and B, Indurated, nodular adenoid cystic carcinoma of the lower eyelids with madarosis.
2. **FIGURE 126.2** This adenoid cystic carcinoma arose in the left upper eyelid of a man in his mid-30s. A, Tumor infiltrated the dermis and orbicularis oculi. B, The tumor cells formed tubules (bottom of image) or a cribriform pattern with pseudocysts containing lightly eosinophilic mucin. C, Higher magnification showing tumor cells with hyperchromatic nuclei and scant eosinophilic cytoplasm having a cribriform pattern with pseudocysts. D, In another area of the tumor (bottom right of Figure 126.2A), the tumor cells are multilayered and form pseudocysts or solid islands. (Photomicrographs were prepared from a slide distributed by Dr. Ahmed Hidayat at the 1994 meeting of the Eastern Ophthalmic Pathology Society.)
3. **FIGURE 126.3** A, This lacrimal gland adenoid cystic carcinoma infiltrated adjacent connective tissues and surrounded and infiltrated a nerve (B) located in the center of this photomicrograph.

2. Chapter 127: Angiosarcoma
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 127.1** Extensive angiosarcoma of the forehead and upper eyelid. (Courtesy of Dr. Robert Goldberg.)
        2. **FIGURE 127.2** A, Tumor of the nasal bridge, left lower eyelid, and cheek. B, Angiosarcoma in the lower eyelid with hemorrhage and ulceration. A, (Courtesy of Dr. Antonio Augusto Cruz.) B, (Courtesy of Dr. Philip Custer.)
        3. **FIGURE 127.3** This angiosarcoma arose in the left lower eyelid of a woman in her middle 50s. There were multiple tumor recurrences, followed by tumor metastatic to cervical lymph nodes. A, Irregular vascular channels, some lined with plump endothelial cells, dissect through the eyelid dermis (hematoxylin and eosin). B, Plump, pleomorphic endothelial cells are evident at higher magnification. Some of the endothelial cells line slit-like spaces, while others line spaces containing erythrocytes (hematoxylin and eosin). C, Vascular channels are hard to identify in poorly differentiated angiosarcoma. D, Immunohistochemical staining using antibodies to CD31 is useful for

confirming a diagnosis of angiosarcoma, especially in poorly differentiated tumors. (D, Reprinted with permission from Dutton JJ, Gayre GS, Proia AD. Diagnostic atlas of common eyelid diseases. *Inform Healthcare*; 2007.)

3. Chapter 128: Basal Cell Carcinoma
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Predisposing Genetic Syndromes
        1. *Nevoid Basal Cell Carcinoma Syndrome*
        2. *Bazex-Dupre-Christol Syndrome*
        3. *Xeroderma Pigmentosum*
        4. *Nevus Sebaceous of Jadassohn*
    8. Histopathology
    9. References
    10. Figures
        1. **FIGURE 128.1** Nodular basal cell carcinoma.
        2. **FIGURE 128.2** Pigmented basal cell carcinoma.
        3. **FIGURE 128.3** Flat superficial basal cell carcinoma with erythema, fine scales, and a small area of ulceration.
        4. **FIGURE 128.4** Infiltrative morpheaform basal cell carcinoma.
        5. **FIGURE 128.5** Medial canthal basal cell carcinoma with orbital invasion.
        6. **FIGURE 128.6** Nevoid basal cell carcinoma (Gorlin-Goltz) syndrome.
        7. **FIGURE 128.7** Histopathology of low-risk basal cell carcinoma subtypes. A, *Nodular BCC* of the left lower eyelid with discrete and interconnecting, variably shaped, large and smaller nests of basaloid cells (basophilic tumor cells with hyperchromatic nuclei and little cytoplasm) in the papillary and reticular dermis. B, Same *nodular BCC* as in A, showing peripheral radially arranged cells with their long axes parallel to each other, creating so-called peripheral palisading. The stroma surrounding the tumor lobule is mildly myxoid and artifactually shrank away from the tumor island during histological processing, creating a narrow cleft (retraction artifact). C, *Adenoid variant of nodular BCC* of the medial left lower eyelid. This tumor area has peripheral cribriform nests; other areas had solid islands of basaloid tumor cells typical of nodular BCC. D, *Superficial BCC* with basaloid tumor cells projecting from the epidermis forming lobules in the papillary dermis with an axis parallel to the epidermal surface. E,

Pigmented BCC of the left lower eyelid with prominent melanin pigmentation. The architecture is otherwise typical of nodular BCC. F, This *infundibulocystic BCC* of the left upper eyelid was one of many 1-to 2-mm-diameter lesions involving all four eyelids in a young child with nevoid basal cell carcinoma (Gorlin-Goltz) syndrome. The tumor is sharply circumscribed, has a single infundibular cyst-like structure, central squamoid (eosinophilic) cells, and peripheral palisading. The large gap in the tumor is an artifact from sectioning the small tumor.

8. **FIGURE 128.8** Histopathology of high-risk basal cell carcinoma subtypes. A, *Micronodular BCC* of the right upper eyelid with small nests of tumor in the deep reticular dermis and infiltrating the orbicularis oculi muscle (*arrows*). The larger tumor micronodule surrounded by orbicularis oculi muscle fibers is 0.05 mm in diameter. The anterior eyelid dermis contained typical nodular BCC with the micronodular subtype at the lateral and deep edges of the tumor. B, *Infiltrating BCC* with variably sized and shaped nests of basaloid tumor cells in the dermis surrounded by myxoid fibrotic stroma. Many of the tumor islands are angulated, and most are >5 to 8 cells thick. C, *Sclerosing/morpheic BCC* of the right medial canthus demonstrating thin cords of basaloid tumor cells surrounded by dense collagenous stroma. The tumor cords are 1 to 3 cells thick in this tumor. BCC also involved the glabella, and there was extensive perineural invasion. D, *Basosquamous carcinoma* involving the right lower eyelid and face with extension into the orbit. This area is a mixture of adenoid BCC and squamous cell carcinoma (SCC; cells with pink cytoplasm). Other areas of the tumor had a mixture of nodular BCC and SCC with areas of transition.

4. Chapter 129: Cutaneous T-Cell Lymphoma
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 129.1** A, Early manifestation of mycosis fungoides as erythematous induration of the eyelids. B, Late-stage tumorous mycosis fungoides. A, (Courtesy of Dr. Bita Esmaeli.)

2. **FIGURE 129.2** T-cell cutaneous lymphoma in Sézary syndrome. (Courtesy of Dr. Timothy Sullivan.)
3. **FIGURE 129.3** A man in his late 50s, clinically in remission from CTCL, developed an itchy, faint erythematous patch under his left eyelid. A, The epidermis is acanthotic, and there is a papillary and reticular dermal perivascular infiltrate of lymphocytes and macrophages in this patch-stage MF. B, The papillary dermis has a perifollicular and perivascular infiltrate of macrophages and lymphocytes and one collection of atypical lymphocytes in the epidermis (Pautrier microabscess). The black at the bottom right is ink used for orienting the biopsy. C, Atypical lymphocytes with pleomorphic convoluted (cerebriform) nuclei form the Pautrier microabscess. D, The dermal infiltrate contains scattered atypical lymphocytes with irregular nuclear configurations.
4. **FIGURE 129.4** A woman in her upper 30s with a 1-year history of CTCL developed an erythematous, scaly plaque on her left upper eyelid. This plaque-stage MF has a dense papillary dermal infiltrate of atypical lymphocytes with extensive epidermotropism and numerous Pautrier microabscesses. Many of the individual lymphocytes in the basal epidermis have clear cytoplasmic rims (halo cells). The lymphocytes were CD3+, CD4+, and CD5+.
5. **FIGURE 129.5** This biopsy is from the lower eyelid of the MF tumor shown in Figure 129.1B. A, Atypical lymphocytes extensively infiltrate the epidermis and efface the dermis. B, Only a few bands of collagen are present in the dermis among the diffuse infiltrate of atypical lymphocytes. C, Sheets of atypical lymphocytes extensively replace the subcutaneous adipose tissue. Some of the atypical lymphocytes feature cerebriform nuclei, others have prominent nucleoli, and a mitotic figure is near the center of the photomicrograph.
6. **FIGURE 129.6** A, A man in his middle 30s developed an ulcerated 2-cm-diameter lesion of his left upper eyelid over 2 months. B, The dermis has a diffuse infiltrate of mostly large lymphocytes with fewer intermixed small lymphocytes and neutrophils. C, The large lymphocytes are anaplastic with irregularly shaped nuclei, large nucleoli, and a moderate amount of amphophilic cytoplasm. There are neutrophils between the lymphoma cells. D, The large anaplastic lymphocytes express CD30 on their cell membrane. The CD30+ anaplastic lymphocytes also expressed CD4 (T helper lymphocyte marker). They were negative for the expression of B-lymphocyte markers CD19 and CD22. There was no evidence of systemic lymphoma, and he

received chemotherapy and radiotherapy and had resolution of his eyelid disease with no recurrence after 10 years.

5. Chapter 130: Dermatofibrosarcoma Protuberans
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 130.1** Subcutaneous nodule of dermatofibrosarcoma in the medial lower eyelid and medial canthus. (Courtesy of Drs. John Holds and Scott Fosko.)
        2. **FIGURE 130.2** DFS of the medial brow. (Courtesy of Dr. Jurij Bilyk.)
        3. **FIGURE 130.3** Surgical excision of the lesion in Figure 130.1 showing the subcutaneous location. (Courtesy of Drs. John Holds and Scott Fosko.)
        4. **FIGURE 130.4** This classic dermatofibrosarcoma protuberans involved the left forehead and eyebrow of a child. A, The dermis has a proliferation of spindle-shaped tumor cells resulting in a blue hue compared with the underlying eosinophilic frontalis muscle. B, The tumor cells have a storiform (cartwheel) architecture typical of DFSP. The individual tumor cells have a uniform appearance without mitotic figures. C, Tumor cells infiltrate the frontalis muscle. D, The tumor cells are diffusely and strongly positive for CD34 expression. Tumor cells surround but do not infiltrate the eccrine glands near the bottom of the photomicrograph.
6. Chapter 131: Fibrosarcoma
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 131.1** Infant with a 5-cm nonpulsatile congenital fibrosarcoma of the glabella. (Reprinted with permission from Elsevier; Nicholas RG, Brennan TE. Congenital infantile fibrosarcoma of the glabella: Nuances of achieving surgical cure without cosmetic or

functional deformity. Int J Pediatr Otolaryngol 2019;117:110-114.)
2. **FIGURE 131.2** A massive fibrosarcoma of the eyelids, glabella, and forehead in an infant. (Courtesy of Dr. Peter Dolman.)
3. **FIGURE 131.3** This fibrosarcoma arose in the right orbit of a 7-year-old boy and recurred 8 years following excision. The recurrent tumor was 25 × 28 × 17 mm and extended into the lower eyelid. A, At scanning magnification, the tumor extends anterior to the orbital septum. B, The tumor is composed of interlacing fascicles of spindle-shaped cells, creating a herringbone pattern. C, The tumor cells are spindle shaped and have oval nuclei, minimal cytoplasm, and indistinct cytoplasmic borders. There are scattered hyperchromatic nuclei. (Photomicrographs were prepared from a slide distributed by Dr. Ahmed A. Hidayat at the 1984 meeting of the Eastern Ophthalmic Pathology Society.)

7. Chapter 132: Kaposi Sarcoma
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Characteristics
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 132.1** A-D, Kaposi sarcoma involving the eyelid skin. (A and C, Courtesy of Dr. Timothy Sullivan; D, Courtesy of Dr. Thomas Johnson.)
        2. **FIGURE 132.2** A-C, Kaposi sarcoma involving the conjunctiva. (B, Courtesy of Dr. Roman Shinder; C, Courtesy of Dr. Timothy Sullivan.)
        3. **FIGURE 132.3** A man in his middle 40s developed Kaposi sarcoma due to chronic immunosuppression following orthotopic solid organ transplantation. The chest and abdominal skin had many KS nodules, with the largest being 2.1 cm in diameter. Innumerable nodules of Kaposi sarcoma were in both lungs and in the stomach and jejunum walls. A, Interlacing fascicles of spindle cells with slit-like vascular channels form the plaques and nodules of Kaposi sarcoma. B, Erythrocytes are present in the slit-like vessels, and there are a few macrophages with intracellular hemosiderin granules (arrows). C, Tumor cells uniformly express factor VIII-related antigen (von Willebrand factor). D, Most tumor cells express human herpesvirus-8 (HHV-8) latent nuclear antigen.
8. Chapter 133: Leukemia Cutis

1. Key Points
2. Etiology and Pathogenesis
3. Clinical Presentation
4. Differential Diagnosis
5. Treatment
6. Prognosis
7. Histopathology
8. References
9. Figures
    1. **FIGURE 133.1** Leukemia cutis involving the eyelids. (A, B, & C, Courtesy of Dr. Charles Soparkar.)
    2. **FIGURE 133.2** A man in his late 30s with acute myeloid leukemia, probable M5a (acute monoblastic leukemia) by cytogenetic analysis, developed numerous papules on his legs and papules and nodules on his abdomen. This biopsy is from an abdominal skin nodule. A, The leukemic cells form a sheet in the dermis with only a few in the zone immediately beneath the epidermis. B, The leukemic cells have mostly oval nuclei with irregular borders, fine chromatin, an occasional prominent nucleolus and scant to small amounts of faintly basophilic cytoplasm.

9. Chapter 134: Liposarcoma
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 134.1** A large, lobular subcutaneous liposarcoma of the lower eyelid. (Courtesy of Dr. Santha Amrith.)
        2. **FIGURE 134.2** A, This punch biopsy of the back shows a liposarcoma in the subcutaneous tissue that arose at the site of prior radiation therapy. B, Lobules of tumor cells have a lightly basophilic myxoid stroma. C, The tumor cells are pleomorphic adipocytes with admixed lipoblasts. In a subsequent wide local excision, liposarcoma extended from the superficial dermis to the deep subcutis and had predominantly myxoid features.

10. Chapter 135: Lymphoma
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis

7. Histopathology
8. References
9. Figures
    1. **FIGURE 135.1** Superficial cutaneous lymphoma of the eyelids. B, (Courtesy of Dr. Jurij Bilyk.)
    2. **FIGURE 135.2** Lymphoma involving the conjunctiva.
    3. **FIGURE 135.3** Cutaneous lymphoma manifesting as eyelid edema and palpable mass.
    4. **FIGURE 135.4** A woman in her early 70s developed a nodule in her right upper eyelid. Following the biopsy diagnosis of lymphoplasmacytic lymphoma (immunocytoma), radiotherapy resulted in the complete resolution of her eyelid tumor. A, The dermis has a diffuse infiltrate of small and medium-sized lymphocytes, plasmacytoid lymphocytes, and a few plasma cells. B, A majority of the cells are plasmacytoid lymphocytes resembling a plasmacytoma. Lymphoplasmacytoid lymphocyte cells expressed CD20 and kappa light chains. Uniform expression of CD20 helps differentiate lymphoplasmacytic lymphomas from plasmacytomas, which are usually negative for CD20 or have expression by only a small subset of the cells.[88] (Reprinted with permission from McKenna RW, Kyle RA, Kuehl WM, et al. Plasma cell neoplasms. In, Swerdlow SH, Campo E, Harris NL, et al, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Revised*. 4th ed. International Agency for Research on Cancer; 2017:241-258.)
    5. **FIGURE 135.5** A man in his middle 70s with a history of follicular lymphoma developed firm periocular swelling around his left eye. A, This biopsy of the left lower eyelid has a dense lymphoid infiltrate in the dermis with a vaguely follicular appearance manifest as the central area of lymphocytes being paler than the surrounding lymphocytes. B, The vaguely defined follicle center is composed of small cleaved cells with occasional larger centroblast-like cells. The immunophenotype was characteristic of follicular lymphoma,[89] and a monoclonal B-cell population was detected by immunoglobulin heavy chain polymerase chain reaction analysis. (Reprinted with permission from Jaffe ES, Harris NL, Swerdlow SH, et al. Follicular lymphoma. In, Swerdlow SH, Campo E, Harris NL, et al, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Revised*. 4th ed. International Agency for Research on Cancer; 2017:266-277.)

11. Chapter 136: Malignant Melanoma
    1. Key Points
    2. Etiology and Pathogenesis

3. Clinical Presentation
4. Differential Diagnosis
5. Treatment
6. Prognosis
7. Histopathology
8. References
9. Figures
    1. **FIGURE 136.1** Lentigo maligna. A, Flat, irregular pigmented lesion along the lateral eyelid mucocutaneous border. B, Irregular, variably pigmented conjunctival lentigo maligna on the eyelid margin and palpebral conjunctiva. C, Lightly pigmented, multicentric macules and small nodules at the lateral canthus and lateral cheek. D, Very diffuse, variably pigmented flat lesion on the medial canthus, lower eyelid, and nasal bridge. (A, Courtesy of Dr. Robert Kersten.)
    2. **FIGURE 136.2** Spectrum of presentations of eyelid and conjunctival melanoma. A, Desmoplastic melanoma arising in a melanocytic nevus. B, Amelanotic melanoma of the lateral canthus. C, Multiple nodules of melanoma in the caruncle and palpebral conjunctiva arising in areas of PAM. D, Deeply pigmented melanoma involving the upper and lower eyelids and medial canthus. (B, Courtesy of Dr. Bita Esmaeli.)
    3. **FIGURE 136.3** Melanoma involving the eyelid and adjacent areas of the face. A, Diffuse melanoma on the nose and lower eyelid. B, Multicentric melanoma at the lateral canthus and adjacent cheek. C, Widespread diffuse lightly pigmented melanoma of the lower eyelid and cheek. D, Multiple nodules of metastatic cutaneous melanoma in the eyelids, forehead, and face. (C, Courtesy of Dr. Bita Esmaeli.)
    4. **FIGURE 136.4** Conjunctival melanoma. A, Nodular melanoma of the lower eyelid palpebral conjunctiva. B, Deeply pigmented melanoma in the upper eyelid palpebral conjunctiva. C, Small nodular melanoma arising in the caruncle with surrounding vascular congestion. D, Extensive amelanotic melanoma arising in the caruncle and adjacent lower eyelid. (B, Courtesy of Dr. Bita Esmaeli.)
    5. **FIGURE 136.5** A, This example of lentigo maligna, the in situ precursor lesion of lentigo maligna melanoma, has the classic pattern with a broad, contiguous proliferation of atypical epithelioid melanocytes along the dermoepidermal junction with a few nests of atypical melanocytes hanging down from the dermoepidermal junction in a drop-like pattern. B, Antibodies to the melanocyte marker MART-1 highlight the contiguous atypical melanocytes along the dermoepidermal junction in the lentigo maligna. C, This invasive superficial

spreading melanoma has scant melanin pigmentation. The epidermis over the invasive tumor has intraepidermal melanoma with tumor nests and areas of confluent melanoma cells along the dermoepidermal junction with pagetoid spread into the more superficial epidermis. D, This superficial spreading melanoma is heavily pigmented, making the pagetoid spread in the epidermis readily apparent. E, This desmoplastic melanoma of the right lower eyelid shows a paucicellular dermal tumor composed of spindle-shaped cells with intervening collagen bundles and occasional lymphocytes and macrophages. The epidermis over the tumor has a lentigo maligna melanocytic proliferation. F, The desmoplastic melanoma cells stain strongly using antibodies to S100 protein.

6. **FIGURE 136.6** A, Conjunctival melanoma in situ features cytologically atypical melanocytes extending through >75% of the epithelial thickness. B, This invasive melanoma of the right superior fornix has two nests of invasive melanoma in the stroma beneath epithelium replaced by in situ melanoma. The invasive melanoma cells are predominantly spindle-shaped, and the nest on the right is cystic. C, This invasive melanoma of the left lower eyelid conjunctiva arose in association with in situ melanoma. The sheet of epithelioid melanoma cells is amelanotic.

12. Chapter 137: Merkel Cell Carcinoma
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 137.1** Nodular Merkel cell carcinoma involving the eyelid margins. (A, Courtesy of Dr. Robert Kersten. B and C, Courtesy of Dr. Bita Esmaeli. D, Courtesy of Dr. Robert Goldberg.)
        2. **FIGURE 137.2** A, Ulcerated Merkel cell carcinoma on the eyelid margin. B, Diffuse infiltration of the lower eyelid and conjunctiva. C, Upper eyelid marginal Merkel cell carcinoma. D, Subcutaneous lower eyelid Merkel cell carcinoma. (A, Courtesy of Dr. Charles Soparkar. B, Courtesy of Dr. Robert Goldberg. C, Courtesy of Dr. Bita Esmaeli. D, Courtesy of Dr. Charles Soparkar.)
        3. **FIGURE 137.3** This Merkel cell carcinoma of the left cheek was located in the dermis of a man in his middle

70s. A, A narrow zone of normal dermis separates the anastomosing nodules of tumor from the overlying epidermis. B, Sheets of tumor cells form the nodules. The edges of the tumor are infiltrative into the adjacent dermis. C, The tumor cells are discohesive, intermediate size, and mostly round to oval. The chromatin is finely granular, and nucleoli are not apparent. The tumor cells are immunoreactive using broad-spectrum antibodies to cytokeratins (AE1/AE3; D), CK20 (E), and synaptophysin (F).
4. **FIGURE 137.4** Merkel cell carcinomas (MCCs) commonly have lymphovascular invasion (LVI). Identifying LVI is aided using immunohistochemical stains for blood vessel (A; anti-CD31 antibodies) and lymphatic endothelium (B; D2-40 anti-podoplanin antibody). Endothelial cells (brown) surround tumor cells in the lumen of a vein (A, arrow) and two lymphatics (B, arrows). C, Small MCC lymph node metastases (arrows) are often difficult to distinguish from large lymphocytes. D, Small subcapsular metastases and individual tumor cells are highlighted brown using antibodies to synaptophysin.

13. Chapter 138: Metastatic Tumors to the Eyelids
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 138.1** A and B, Metastatic breast carcinoma to the eyelids in patients with a previous history of breast cancer and systemic metastases.
        2. **FIGURE 138.2** A, Multiple metastatic cutaneous melanoma nodules to the bilateral eyelids and face. B, Nasopharyngeal metastasis to the eyelid.
        3. **FIGURE 138.3** A, Metastatic leiomyosarcoma to the upper eyelid. B, Small cell carcinoma to the eyelid margin. (A and B, Courtesy of Dr. Bita Esmaeli.)
        4. **FIGURE 138.4** A woman in her late 50s presented with eyelid swelling and ptosis. Following a biopsy of her right upper eyelid, she was found to have a lobular carcinoma of the breast metastatic to the eyelid and orbit. A, The papillary dermis and superficial reticular dermis are edematous. The metastatic tumor is in the deeper reticular dermis, orbicularis oculi muscle, and the subcutis crating the more cellular appearance evident at low magnification. B, Tumor cells surround and

infiltrate between orbicularis oculi muscle fibers. C, Tumor cells are found individually, as small clusters, and in one to two cell-wide columns. D, Many of the tumor cells have a histiocytoid appearance, while others have a signet ring character due to large cytoplasmic vacuoles displacing the nucleus peripherally (arrows).
5. **FIGURE 138.5** This primary signet ring cell/histiocytoid arose in the left upper eyelid of a man in his early 60s. The diagnosis was based on the histological and immunohistochemical appearance of the tumor and the lack of a primary tumor detectable elsewhere in the body by clinical and radiological examination. A, Histiocytoid and signet ring tumor cells dissect individually and in small clusters between the dermal collagen fibers. B, The tumor cells have finely vacuolated pink-brown cytoplasm using mucicarmine stain. The rim of large cytoplasmic vacuoles (arrows) stains red. The tumor cells were immunoreactive using a cocktail of antibodies to low-and high molecular weight cytokeratins, CK7 (C), E-cadherin (D), gross cystic disease fluid protein-15 (E), carcinoembryonic antigen (F), epithelial membrane antigen, and p63. The tumor cells were negative using antibodies to CK20, CD68, mammaglobin, epithelial cell adhesion molecule (BerEP4), thyroid transcription factor 1, CDX-2, podoplanin, S100 protein, and prostate-specific antigen.

14. Chapter 139: Microcystic Adnexal Carcinoma
    1. Key Points
    2. Etiology and Pathophysiology
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 139.1** A, MAC presenting as lower eyelid swelling with ecchymoses. B, Reddish MAC nodule on the medial upper eyelid. C, Eyelid margin ulceration with diffuse eyelid and lateral canthal infiltration of tumor. D, Indistinct tumor margins infiltrating the medial lower eyelid, with madarosis. B, (Courtesy of Dr. David Jordan) D, (Courtesy of Dr. Alan McNab.)
        2. **FIGURE 139.2** A man in his early 60s developed a MAC in his left lower eyelid margin. A, Cords and nests of cytologically uniform squamous cells and horn cysts within a desmoplastic stroma form the tumor. The superficial tumor islands have palisaded tumor peripherally. B, A horn cyst filled with keratin is at the bottom left. Other tumor nests are solid or have ductal

differentiation with empty lumens or intraluminal amphophilic to lightly eosinophilic amorphous material. C, A small horn cyst is on the left. The tumor nest at the top right has ductal differentiation and a tail of tumor cells. The collagenous tumor stroma is partially hyalinized (top left corner). D, The deep aspect of the tumor is composed of small tumor nests, with lumens indicating ductal differentiation. Two layers of cells line the ducts.

3. **FIGURE 139.3** This MAC arose in the left eyebrow of a man in his early 50s. A, This tumor has a stratified appearance with tumor islands, cornifying cysts, and tumor strands in a sclerotic dermis. The midzone has mostly strands of tumor cells, while the deeper tumor (not seen in this photomicrograph) was smaller nests and strands of cells, often with two layers of small cuboidal cells. B, This tumor area in the superficial dermis shows the characteristic cornifying cysts along with small tumor islands, strands, and a small duct-like structure. C, The middle and deeper dermis had two-cell thick cords of tumor cells embedded in densely sclerotic, hyalinized stroma. D, Tumor widely infiltrates the frontalis muscle. E, Small tumor nests and cords are in sclerotic stroma around a nerve and invade the perineurium. F, Tumor within the subcutaneous adipose tissue forms nodules surrounded by dense sclerotic stroma.

15. Chapter 140: Mucoepidermoid Carcinoma
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 140.1** A, Mucoepidermoid carcinoma (MEC) of the central upper eyelid margin. B, Medial upper eyelid MEC with scaling and madarosis. C, Extensive MEC of the lateral canthal conjunctiva and eyelid margin. D, Nodular MEC on the upper eyelid margin. (A and B, Courtesy of Dr. Charles Soparkar; C, Courtesy of Dr. Seymour Brownstein; D, Courtesy of Dr. Rachel Sobel.)
        2. **FIGURE 140.2** This tumor arose from the tarsal conjunctiva of the left upper eyelid and invaded the orbit. It was originally classified as mucoepidermoid carcinoma but is better classified as squamous cell carcinoma with mucinous differentiation using the terminology proposed by Mudhar et al.[67] A, The tumor

features neoplastic conjunctival epithelium and extensive substantia propria invasion. B, Alcian blue stain highlights areas of mucinous differentiation. C, Most of the tumor is nonkeratinizing squamous cell carcinoma with areas of acantholysis. D, Alcian blue stain shows the intracellular location of the mucin.
3. **FIGURE 140.3** This "mucoepidermoid carcinoma" arose in the limbal conjunctiva of the left eye. It is better classified as an adenosquamous carcinoma using the terminology proposed by Mudhar et al.[67] A, The tumor has areas of glandular differentiation with intracellular and intraluminal mucin. B, This area stained with mucicarmine shows nests of nonkeratinizing squamous epithelium, cells with intracellular mucin, and glands with intraluminal mucin.

16. Chapter 141: Plasmacytoma
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Characteristics
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 141.1** Plasmacytoma of the eyelids. A, Circumscribed nodular mass on the medial eyelid margin. B, Diffuse eyelid swelling from lateral eyelid plasmacytoma. (A, Courtesy of Dr. Henry D. Perry.)
        2. **FIGURE 141.2** Large plasmacytoma of the posterior eyelid lamella. (Courtesy of Dr. Jurij Bilyk.)
        3. **FIGURE 141.3** Recurrent plasmacytoma involving the lower eyelid conjunctiva. (Courtesy of Dr. Philip Custer.)
        4. **FIGURE 141.4** A sheet of normal-appearing plasma cells forms this plasmacytoma. The cells are oval with an eccentrically placed round to slightly oval nucleus and abundant amphophilic cytoplasm. The nuclear chromatin is clumped, and some cells have chromatin arranged around the periphery of the nucleus in a radial pattern.
        5. **FIGURE 141.5** A woman in her middle 30s developed a nodule in her lateral left upper eyelid. The tumor was located in the eyelid posterior to the orbicularis oculi, extended into the superolateral orbit, and involved the lacrimal gland palpebral lobe. The lesion was resected in its entirety and has not recurred after more than 10 years. A, The plasmacytoma features sheets of lymphoid cells and abundant pink amyloid. B, The plasma cells have a variable appearance. Some resemble normal

plasma cells, but many have enlarged nuclei with irregular nuclear borders, diffuse chromatin, and decreased cytoplasm. C, The plasma cells uniformly express CD138 (syndecan-1). D, Immunohistochemical staining showed a vast majority of the plasma cells strongly expressed kappa light chains (left panel) while only rare cells expressed lambda light chains.
6. **FIGURE 141.6** This octogenarian developed ptosis with a mass in the temporal fossa. A, The plasmacytoma is composed of sheets of cytologically atypical plasma cells with irregular nuclear contours, diffuse chromatin, diminished cytoplasm, and frequent mitoses. B, The tumor cells strongly and uniformly express CD138. C, Chromogenic in situ hybridization shows that 100% of the plasma cells are positive for lambda light chain mRNA (left panel), while none of the cells has kappa light chain mRNA (right panel).

17. Chapter 142: Primary Cutaneous Mucinous Carcinoma
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 142.1** A, Nodular PCMC on the lateral lower eyelid. B, Small lightly pigmented eccrine carcinoma on the upper eyelid margin. C, Mulitinodular MCMC on the medial lower eyelid. D, Large nodular eccrine tumor on the medial upper eyelid. (B and C, Courtesy of Dr. Roman Shinder.)
        2. **FIGURE 142.2** A, Small nodule of PCMC in the eyelid margin. B, A large protruding PCMC in the lateral lower eyelid. (A, Courtesy of Dr. John Holds; B, Courtesy of Dr. Philip Custer.)
        3. **FIGURE 142.3** This PCMC arose in the left lower eyelid of a woman in her late 50s. A, The dermal tumor is well circumscribed with islands of tumor suspended in mucin and separated by delicate fibrovascular septa. B, Some of the tumor islands are solid, and others have a cribriform architecture. The mucin appears clear at this magnification. C, The tumor cells have a basaloid appearance with round to slightly oval nuclei and small amounts of lightly eosinophilic cytoplasm. The mucin is faintly basophilic. D, This tumor has foci of tumor cells surrounded by p63+ myoepithelial cells indicating an in situ tumor component, supporting a PCMC.

4. **FIGURE 142.4** This endocrine mucin-producing sweat gland carcinoma was in the medial right lower eyelid of a woman in her early 60s. A, The tumor is well circumscribed and multinodular with thin fibrous bands between tumor nodules. Only the nodule on the right has obvious mucin creating the light areas surrounded by tumor cells. B, The small foci of mucin are lightly basophilic. The tumor cells have mostly round nuclei with minimal eosinophilic cytoplasm. C, Colloidal iron stain highlights extracellular and focal intracellular mucin. D, The neuroendocrine marker chromogranin was expressed by scattered tumor cells. E-I, The tumor cells diffusely expressed nuclear estrogen (E) and progesterone (F) receptors, WT1 (G), and GATA3 (H). I, Areas of the tumor had mammaglobin expression by a majority of the tumor cells.

18. Chapter 143: Rhabdomyosarcoma
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 143.1** A, Child with a rhabdomyosarcoma of the left upper eyelid presenting as eyelid swelling and ecchymoses. B, Rhabdomyosarcoma of the medial canthus and upper eyelid. (A, Courtesy of Dr. Ilya Leingold. B, Courtesy of Dr. Antonio Augusto Cruz.)
        2. **FIGURE 143.2** This embryonal rhabdomyosarcoma was from the right orbit of a 9-year-old girl. A, The tumor is a patternless sheet of small tumor cells. B, Most tumor cells have variable amounts of eosinophilic cytoplasm, while a minority have clear cytoplasm. Some cells, often termed “strap cells,” have elongated eosinophilic cytoplasm and their nucleus displaced to one end of the cell. C, All of the tumor cells are immunoreactive using antibodies to muscle-specific actin.
        3. **FIGURE 143.3** This embryonal rhabdomyosarcoma arose in the left lower eyelid conjunctiva of a 4-year-old girl. Computed tomography showed 1 cm of preseptal thickening without postseptal involvement. The tumor had two distinct histological features. There were sheets of small basophilic cells with oval nuclei (A and B) and interlacing fascicles of pleomorphic spindle cells (C and D). The tumor cells were immunoreactive using antibodies to desmin, myogenin, and muscle-specific

actin. (Photomicrographs are from a microscopic slide distributed by Dr. Norman C. Charles at the 2012 meeting of the Eastern Ophthalmic Pathology Society.)
19. Chapter 144: Sebaceous Carcinoma
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Histopathology
    8. References
    9. Figures
        1. **FIGURE 144.1** A-D, Sebaceous carcinoma mimicking benign lesions such as chalazion.
        2. **FIGURE 144.2** A-D, Sebaceous carcinoma mimicking inflammatory lesions and blepharitis.
        3. **FIGURE 144.3** A-D, Sebaceous carcinoma with features similar to other eyelid malignancies. (D, Courtesy of Dr. Bita Esmaeli.)
        4. **FIGURE 144.4** This well-differentiated (histologic grade 1) sebaceous carcinoma arose in the right lower eyelid meibomian glands of a man in his late 60s. A, Lobules of neoplastic cells are adjacent to a meibomian duct. The neoplastic lobules infiltrate among benign meibomian glands (arrows). B, The tumor lobules have sharp borders, with most cells having sebaceous differentiation. C, Cytoplasmic lipid vacuoles reflect the sebaceous differentiation of the neoplastic cells.
        5. **FIGURE 144.5** This well-to moderately differentiated sebaceous carcinoma developed from the right lower eyelid meibomian glands of a man in his early 50s. A, At low magnification, the tumor is in the tarsus around residual meibomian ducts. B, Intraepithelial sebaceous carcinoma extensively involves the eyelid margin. C and D, Tumor in the tarsus is a mixture of cells with sebaceous differentiation and others with minimal or no vacuolation. E, Intraepithelial carcinoma is a mixture of small nests and more superficial individual tumor cells (pagetoid spread). F, This area of the tumor has prominent conjunctival intraepithelial spread over poorly differentiated, moderately infiltrative sebaceous carcinoma that extended into the anterior orbit.
        6. **FIGURE 144.6** A man in his late 60s had poorly differentiated sebaceous carcinoma involving the left upper and lower eyelid epidermis and conjunctiva and the bulbar conjunctiva multifocally, with invasive tumor in both eyelids. A, Neoplastic cells replace the conjunctival epithelium and form lobules in the substantia propria. The lobule of invasive tumor at the

top left (arrow) has central necrosis with calcification (comedocarcinoma). B, Poorly differentiated neoplastic cells replace the full thickness of the eyelid conjunctival epithelium and push into the substantia propria in several areas. The epithelial basement membrane is intact, indicating that the tumor is not invasive in this area. C, This lobule of invasive tumor has scant sebaceous differentiation and an abnormal mitotic figure (arrow). D, The tumor cells have small vacuoles and granules of staining using antibodies to adipophilin.

10. Tables
    1. **TABLE 144.1Immunohistochemical Analysis of Sebaceous Carcinomas Showing Percentages of Tumors Positive for Various Antibodies**

20. Chapter 145: Squamous Cell Carcinoma
    1. Key Points
    2. Etiology and Pathogenesis
    3. Clinical Presentation
    4. Differential Diagnosis
    5. Treatment
    6. Prognosis
    7. Predisposing Genetic Syndromes
        1. *Xeroderma Pigmentosum*
        2. *Dyskeratosis Congenita*
        3. *Epidermolysis Bullosa*
    8. Histopathology
    9. References
    10. Figures
        1. **FIGURE 145.1** Early squamous cell carcinoma of the eyelid. A, Localized area of inflammation on the lateral lower eyelid margin. B, Thickening of upper and lower eyelids with complete madarosis.
        2. **FIGURE 145.2** Advanced squamous cell carcinoma (SCC). A, Deeply invasive, ulcerated lesion involving the upper and lower eyelids and lateral canthus. B, Ulcerated SCC of the conjunctiva and eyelids. C, SCC completely replacing the conjunctiva and eyelids. D, Multinodular SCC of the lower eyelid extending to the palpebral and bulbar conjunctiva.
        3. **FIGURE 145.3** Conjunctival squamous cell carcinoma (SCC). A, Conjunctival intraepithelial squamous neoplasia (Bowen disease) of the upper eyelid tarsal surface. B, Sessile, minimally elevated SCC arising in the superior bulbar conjunctiva. C, Papillomatous SCC of the superior conjunctiva. D, Extensive conjunctival SCC replacing the globe and invading deeply into the orbit.
        4. **FIGURE 145.4** Unusual presentations of squamous cell carcinoma (SCC) on the eyelids. A, A nodular lesion with a central ulcer crater simulating a basal cell

carcinoma. B, Flat erosive plaques of the upper and lower eyelids with crusting and scales. C, SCC with eyelid thickening, madarosis, and crusted exudate. D, Extensive SCC presenting with massive hyperkeratosis and orbital invasion.
5. **FIGURE 145.5** In situ squamous cell carcinoma arose in a background of actinic keratosis in the right upper eyelid of a man in his early 70s. Cytologically atypical keratinocytes extend through the entire thickened epidermis. The neoplastic cells lack their normal polarity. The surface of the tumor has a layer of parakeratosis.
6. **FIGURE 145.6** A, This well-differentiated squamous cell carcinoma (SCC) involved the full thickness of the right lower eyelid in a man who was immunosuppressed following solid organ transplantation. B, The tumor arose along the eyelid margin in an area of in situ SCC. Numerous keratin pearls are evident. C, Squamous cell carcinoma invaded the tarsus with tumor nests adjacent to meibomian glands. D, The tumor cells are pleomorphic with brightly eosinophilic cytoplasm and form keratin pearls, solid nests, and irregular islands. The tumor stroma has an infiltrate of macrophages, lymphocytes, and eosinophils. E, Intercellular bridges are prominent in this tumor island. F, Tumor invades the perineurium and parenchyma of a nerve.
7. **FIGURE 145.6** Continued
8. **FIGURE 145.7** A, Well-differentiated squamous cell carcinoma developed in a woman's medial left lower eyelid palpebral conjunctiva. B, Tumor cells occupy the entire thickness of the epithelium. The black ink at the base of the tissue was for orienting the specimen. C, At the base of the lesion, a few small tumor nests are in the superficial substantia propria (superficially microinvasive squamous cell carcinoma).
9. **FIGURE 145.8** Superficially microinvasive, moderately differentiated squamous cell carcinoma of the right inferior forniceal conjunctiva from a man in his 80s.

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2. **FIGURE 146.2** A, Trichilemmal carcinoma of the scalp showing an abrupt transition from the normal epidermis to an ulcerated, hemorrhagic, invasive tumor composed of lobules and interconnecting cords. B, The interdigitating tumor cords are in a desmoplastic and hemorrhagic stroma. Tumor cells with pale eosinophilic or clear cytoplasm due to abundant cytoplasmic glycogen predominate. The tumor cords have areas of keratinization. C, Tumor cells with clear cytoplasm are evident at higher magnification. Trichilemmal keratinization features an abrupt transition from neoplastic cells to keratin without a granular layer.

22. Chapter 147: Undifferentiated Pleomorphic Sarcoma (Malignant Fibrous Histiocytoma)
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        1. **FIGURE 147.1** Large nodular undifferentiated pleomorphic sarcoma on the lower eyelid mucocutaneous border. (Courtesy of Dr. Timothy Sullivan.)
        2. **FIGURE 147.2** Undifferentiated pleomorphic sarcoma arising in the palpebral conjunctiva. (Reprinted with permission from Gounder P, Lamb M, Vinciullo C, de Sousad JL. Malignant fibrous histiocytoma masquerading as pyogenic granuloma. *Orbit*. 2017;36:122-123.)
        3. **FIGURE 147.3** This undifferentiated pleomorphic sarcoma (UPS) formed a 1-cm diameter, mobile, subcutaneous nodule in the lateral right upper eyelid beneath the eyebrow of a woman in her middle 50s. Following the biopsy, the nodule was completely excised by Mohs micrographic surgery; there has been no recurrence after 10 years. A, The UPS is centered in the subcutaneous tissue on the right side of the photomicrograph. B, The tumor cells form fascicles with a storiform pattern. C, Pleomorphic plump fibroblasts form the fascicles. The tumor cells lacked any immunohistochemical markers for differentiation leading to the diagnosis of UPS.
        4. **FIGURE 147.4** This undifferentiated pleomorphic sarcoma arose in the right superomedial orbit and

recurred following biopsy and Mohs micrographic surgery. Orbitotomy with attempted resection had positive surgical margins, and orbital exenteration was subsequently performed. The tumor recurred following orbital exenteration, and the patient died with metastatic disease. A, The orbital tumor has a storiform pattern with numerous multinucleated giant tumor cells. B, Plump spindle cells with multinucleated giant cells having brightly eosinophilic cytoplasm compose the tumor. The tumor cells lacked immunophenotypic evidence of differentiation.

5. **FIGURE 147.5** This atypical fibroxanthoma/dermal pleomorphic sarcoma (superficial undifferentiated pleomorphic sarcoma) arose on the frontal scalp of an octogenarian man. A, Plump spindle tumor cells are in the superficial reticular dermis, replace the papillary dermis, and abut the epidermis. B, The tumor has many multinucleated giant tumor cells. An atypical mitotic figure is at the right of a multinucleated giant cell.

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CHAPTER 1

Origin and Evolution of the Vertebrate Eyelids and Adnexa

In humans, the eyelids form a flexible soft-tissue structure that serves important functions of protecting the cornea from direct injury, adding elements to the precorneal tear film, and helping to distribute these layers evenly over the surface of the eye. Together with the lacrimal drainage apparatus, the eyelids collect and propel tears to the medial canthus where they drain into the nose. The eyelashes on the eyelid margins sweep air-borne particles from in front of the eye, and the constant voluntary and reflex movements of the eyelids help modulate the amount of light that enters the pupil and protect the eye from excessive glare.

When closed, the eyelids cover the cornea and close the anterior entrance to the orbit. The periorbital fascia extends into the eyelids as the orbital septum and separates the orbit from the eyelid. All structures anterior to the orbital septum are technically in the eyelid so that the orbicularis oculi muscle and palpebral skin are usually considered to be part of the eyelid. However, anatomically this distinction is difficult to completely support since the orbital septum does not extend the full length of the eyelid and does not extend over the tarsus. In the medial canthal region, the septum divides into several separate layers, so that it cannot be used as a convenient division between the orbit and eyelid in this location.[1] While it may be useful to think about the septum as anatomically separating the orbit and eyelid, physiologically the eyelid, with all of its layers from the skin to the conjunctiva, forms a single functional complex. Many of its structures, such as the levator aponeurosis in the upper eyelid and Müller supratarsal sympathetic muscle, bridge the boundary between orbit and eyelid. Therefore, any topographic division between these two compartments becomes somewhat arbitrary.

Like so many anatomical structures, it is easy and rather anthropocentric to assume that common structures in the human body are the same in other familiar animals. This was a long-held belief in antiquity that led to many erroneous descriptions of the heart and its circulation, the renal system, and the eye and orbit. Since the advent of the scientific revolution, increased biological and medical inquiry, and the lifting of prohibitions against human dissection, it has become clear that many aspects of human anatomy, not least the eye and its adnexa, are rather unique among different vertebrate groups.

The explosion of anatomic studies on animals and humans during the 19th and 20th centuries has shown a vast variety of visual adaptations of the eyes and adnexal structures subserving them. With respect to the eyelids, very basic primordial structures arose in some of the earliest vertebrate classes more than 400 million years ago and evolved in many different directions influenced by spatial partitioning of genetic diversity from population migration, reproductive isolation, differential reproductive success, and natural selection.

Within the subphylum Vertebrata, there are nine classes grouped into two superclasses, vertebrates without jaws (Agnatha) and those with jaws (Gnathostomata). Five of these classes are fishes including the extant hagfish and lamprey (Agnatha), Chondrichthyes, and Osteichthyes, and the extinct Placodermi. The others are Amphibia, Reptilia, Aves, and Mammalia. It is important to remember that all of the extant members of these groups have the same long evolutionary history and do not strictly represent a straight line lineage. Rather, they represent the current anatomical and physiological stages of each group that diverged from common ancestors in the distant past and which evolved at different rates, with some groups retaining more primitive features admixed with more recent adaptive changes.

The Eyelids and Adnexa in Fishes

The Jawless Fishes

The earliest stem vertebrates and fishes arose in the late Ordovician Period about 500 million years ago. Of the five classes of fishes, the hagfish and lamprey (superclass Agnatha) are jawless, have a cartilaginous skeleton with a persistent notochord, and have a completely open orbit. They lack scales, paired fins, a swim bladder, and a stomach. In the hagfish, the eyes are undifferentiated with no cornea, lens, or iris and they are covered by translucent skin with no eyelids. In the orbit, there are no extraocular muscles or motor nerves. It is still debated whether the hagfish visual system is a primitive vertebrate stage or if it is a derived, degenerate condition.

The lamprey passes through three stages during its life cycle. In the larval stage, the visual system is very simple with a nondirectional light-detecting eye spot, no extraocular muscles, and simple pretectal central neural connections. The larva enters a metamorphic stage with the gradual stepwise development of a well-developed image-forming camera eye without intraocular

muscles[2] and the development of more complex central visual control.[3] In the adult, the orbit is an incomplete spherical connective tissue capsule *(Print pagebreak 4)* with only cartilaginous otic capsules.[4] There are six extraocular muscles arising from three cephalic mesodermal myotomes to form three functionally complementary pairs (vertical, horizontal, and oblique). It has been proposed that these metamorphic stages in the lamprey visual system mirror the sequence of evolution in the early vertebrate visual system. Even though the adult lamprey extraocular muscles may resemble the primordial pattern in vertebrates, the specific arrangement differs from those of cartilaginous and bony fishes and homologies are not entirely clear.[3,5] The dorsal (superior) and anterior (medial) rectus muscles and the caudal (inferior) oblique muscles are innervated by the oculomotor nerve. The caudal (lateral) rectus and vertical (inferior) rectus muscles are innervated by the abducens nerve, and the anterior (superior) oblique muscle is innervated by the trochlear nerve.[4,6] The anterior (superior) and caudal (inferior) oblique muscles originate close together in the medial anterior orbit and rotate the globe axially. The anterior (medial) rectus muscle also originates anteriorly in the orbit. There is no retractor bulbi muscle. A unique extraocular muscle in the lamprey, the cornealis muscle, inserts by a tendon onto the cornea and aids in accommodation.[2] The lamprey lacks true eyelids and the cornea is covered by a translucent cutaneous spectacle. The eyeball is separated from the surrounding skin by a shallow circumferential depression between the corneal epithelium and the skin, and the slightly raised outer ridge may represent the beginning of a rudimentary proto-eyelid (Figure 1.1).

FIGURE 1.1 In the lamprey, the eye is small, without eyelids, and covered with transparent skin. (Image used under license from Shutterstock.com.)

The Cartilaginous Fishes

The Chondrichthyes include the cartilaginous sharks, skates, and rays, and they arose about 400 million years ago. The orbit is formed in cartilage and is incomplete, and the eye is cushioned by loose connective tissue. As in the lamprey, there are six extraocular muscles: four recti and two obliques. The two oblique muscles still originate anteriorly and insert onto the globe in common with the vertical rectus muscles. But unlike the lamprey, the medial rectus now originates posteriorly in common with the other rectus muscles.[4] Neural innervation to the extraocular muscles is similar to that of higher vertebrates with the inferior rectus muscle now innervated by the oculomotor nerve. A unique orbital feature is a cartilaginous optic pedicle that forms a proplike structure extending from the cranium to the eye where it forms a cup-shaped synovial articulation with the posterior sclera, providing firm support to the globe while allowing full ocular motility.[7] In some sharks and rays, this cartilaginous prop is thin and flexed so that when the rectus muscles relax, it pushes the eye forward aiding in passively opening the eyelids.[4] In some deep benthic species, two additional orbital muscles arise from the cranium and insert onto the pedicle cup, and they may help to guide eye movements along a specific visual axis. These muscles are absent in bony fishes and higher vertebrates.

FIGURE 1.2 Coral shark eye with short thick fatty eyelids. (Image used under license from Shutterstock.com.)

Most sharks have short limited mobile flaps of skin and fatty tissue that can function as eyelids (Figure 1.2).[8] Several species have a conjunctival fold forming a nictitating membrane or third eyelid, which is unusual in the eyes of fishes. The upper and lower eyelids are simple structures of skin folds containing diffuse muscle fibers forming a superficial palpebral retractor muscle and a deep palpebral depressor muscle, with the fibers of both being more or less blended.[9] These palpebral muscles are derived from facial muscles and are supplied by the seventh cranial nerve.

A nictitating membrane (nictitans) is a form of protective eyelid that is found almost universally in terrestrial vertebrates as a mechanism to protect the eye from desiccation. While it is not needed in aquatic vertebrates, an analogous structure evolved from the lower eyelid is found in several families of sharks. In these sharks, the nictitans closes passively as the jaw opens during feeding, presumably to protect the eye,[7] and it may be anatomically equivalent to the nictitating membrane in amphibians, birds, and mammals.[7]

(Print pagebreak 5)

FIGURE 1.3 Eye in a teleost bony fish with a circumocular groove but no true eyelids. (Image used under license from Shutterstock. com.)

The Bony Fishes

The Osteichthyes include the teleost bony or ray-finned fishes that account for the vast majority of living fish species and the lobe-finned fishes. The orbit is usually closed around the anterior rim, surrounded by circumorbital thin bones including some of the bones seen in higher vertebrates as well as a variable number of accessory bones of the head that can number more than 100 separate elements. The orbit is open posteriorly with no septum between the two sides and communicates with the nasopharynx. The orbital space is filled with loose connective tissue containing venous sinuses that cushion the globe. There are six extraocular muscles with configuration and innervation similar to sharks and higher vertebrates.[10] The eye is separated from the surrounding skin by a shallow circumferential depression between the corneal epithelium and the skin (Figure 1.3). The slightly elevated outer rim of this sulcus anatomically represents a small lid fold and can be considered an early analogy of a proto-eyelid.[9] In some swift-swimming species, the eye is partially covered by what has been referred to as adipose lids, horizontally opposed thin folds of skin arising from the outer lip of the circumferential sulcus and containing fatty tissue.[4] Rarely they are lined by epithelium and fused over the cornea forming a closed conjunctival sac and a transparent spectacle. Some bottom-dwelling species that agitate dirt and sand also have small immobile upper “eyelid” flaps of fleshy tissue or skin that allow debris to roll off to avoid injuring the eye.[8]

The Eyelids and Adnexa of Amphibia

Amphibians are cold-blooded, tetrapod vertebrates that inhabit a wide variety of terrestrial, arboreal, and freshwater aquatic habitats. The earliest amphibians evolved in the Devonian Period about 350 million years ago from a group of bony lobed-finned teleostean fishes with lungs (Dipnoans). Almost all species of frogs and salamanders begin as larvae with gills, confined to water. These larvae or tadpoles lack eyelids and orbital glands. They later undergo metamorphosis into adult air-breathing forms with lungs. During early amphibian evolution, intermittent terrestrial life demanded numerous adaptations to protect the skin and the eyes. As a result, the ocular adnexa in amphibians differs very significantly from those of fishes. Complicated adaptations evolved to protect and lubricate the eye that was now exposed to air. Eyelids remain absent in those adult frog and salamander species that live their adult life in the water. In most terrestrial species, however, upper and lower eyelids develop during metamorphosis. When the eye is open, the eyelids are completely retracted (Figure 1.4). During a blink, the upper eyelid is immobile, and the longer lower eyelid does most of the job in covering the cornea (Figure 1.5). The blink is largely passive, with the eyelid closing as the globe is pulled into the orbit by specialized orbital muscles.

FIGURE 1.4 Anuran amphibian (frog) eye wide open with retraction of the eyelids. (Image used under license from Shutterstock.com.)

Although ancestral amphibians had a relatively closed orbit with bones similar to higher vertebrates, in modern frogs and salamanders, the orbit is much simplified, mostly membranous, and widely open with no bony separation between the two orbits or between the orbits and the nasopharynx.

The normal vertebrate pattern of six extraocular muscles and their innervations are present in amphibians, except that both the superior and inferior oblique muscles still originate close to each other in the anterior medial orbit (Figure 1.6). Two new muscles appear for the first time. The retractor bulbi muscle, innervated by the abducens nerve, is possibly derived from the lateral rectus muscle.[4] It arises in the posterior orbit around the optic nerve and inserts by several fascicles onto the sclera posterior to and between the rectus muscles (Figure 1.6). Contraction of this muscle pulls the globe posteriorly into the orbit, allowing the lower eyelid *(Print pagebreak 6)* to close passively. The second muscle, the levator bulbi, is a large muscle complex with many slips derived from jaw-musculature innervated by the maxillary division of the trigeminal nerve. It separates the orbital floor from the mouth and anatomically it is analogous to the smooth orbital muscle of Müller in mammals that lies between the orbital floor and the pterygopalatine fossa (Figure 1.6). It not only can elevate the globe but may also act as an accessory respiratory muscle by changing the size of the mouth cavity.[12] When the eye is pulled into the head by the retractor bulbi muscle, the levator bulbi bulges downward into the roof of the mouth and helps to propel food down the throat.[13] It may also help return the lower eyelid to its opened position when the retractor bulbi relaxes.

FIGURE 1.5 Anuran eye with elevation of the lower eyelid and closure of the nictitating membrane. (Image used under license from Shutterstock.com.)

The third group of amphibians, Gymnophiona (Caecilians), are limbless, fossorial, snakelike animals that have small, somewhat simplified eyes, covered with transparent skin that is not fused to the cornea. The orbit contains the usual six extraocular muscles as seen in frogs and salamanders. The retractor bulbi muscle is present; however, it does not insert onto the sclera as in other vertebrates, but onto the tentacle sac, an epithelial-lined sac homologous to the conjunctival sac, and unique to caecilians.[14] A lubricating organ, the harderian gland, secretes into the tentacle, which is associated with the vomeronasal organ and serves as a chemosensory organ.[15]

In frogs and salamanders, a translucent conjunctival fold forms a false nictitating membrane that arises in the lower eyelid and extends upward (Figure 1.5), but it is not homologous with the horizontally oriented nictitating membrane of reptiles, birds, and mammals. It is rudimentary in salamanders but better developed in frogs and toads. In the latter group, the membrane is stiffened by a cartilaginous plate. A tissue cord from this fold extends back into the orbit around the posterior part of the globe to the retractor bulbi muscle so that when this muscle contracts and the eye is pulled into the orbit, this cord passively draws the nictitating membrane upward over the cornea. At the end of the blink cycle, the levator bulbi muscle in the floor of the orbit pushes the globe upward and forward, and the nictitating membrane returns to its normal position behind the lower eyelid.

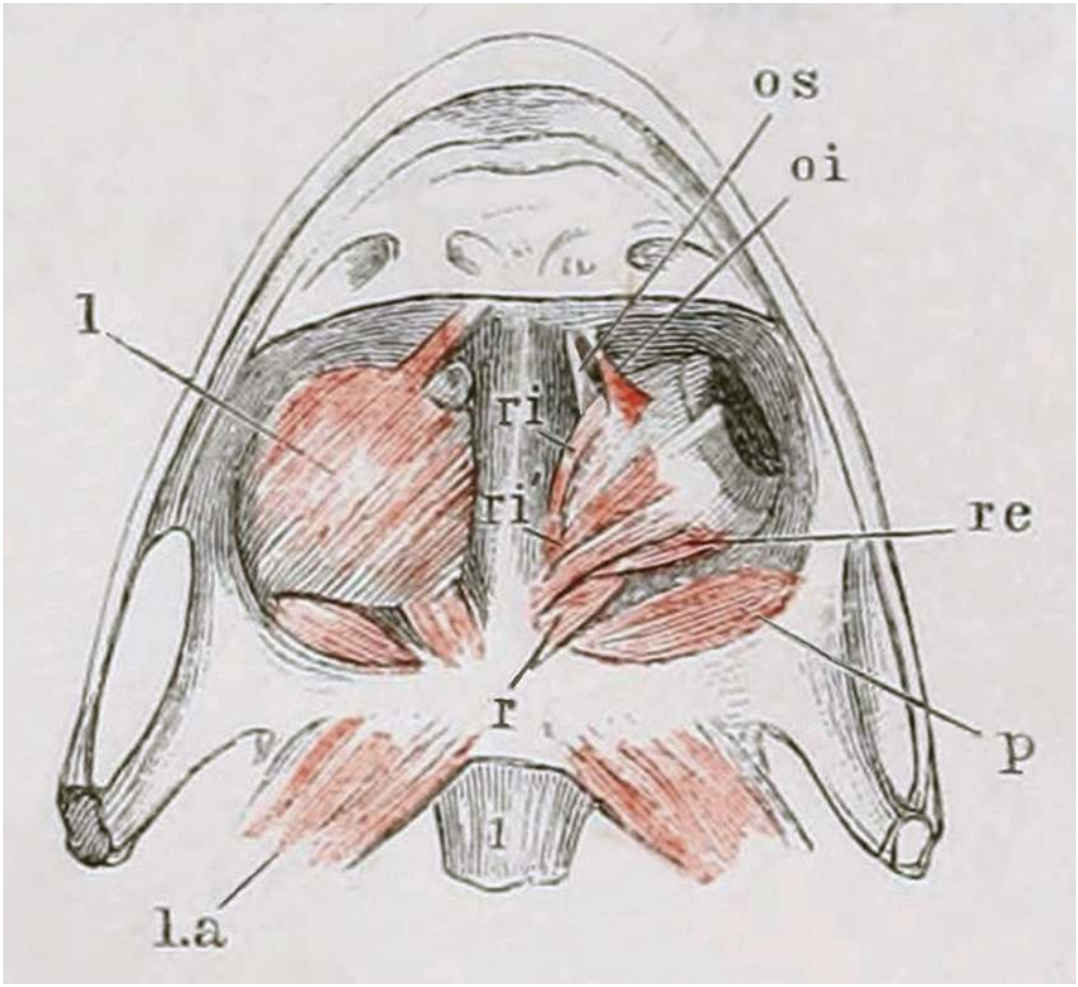

FIGURE 1.6 Woodcut drawing showing the anterior origins of the superior and inferior oblique, and the retrobulbar retractor bulbi muscles in the frog, seen from below. I, levator bulbi muscle; I.a, levator anguli scapulae; oi, inferior oblique; os, superior oblique; p, pterygoid muscle; r, retractor bulbi; re, lateral rectus; ri, medial rectus, ri′, inferior rectus. (Image from Ecker A, Wiedersheim R. *Die anatomie des frosches; ein handbuch für physiologen, ärzte und studirende*. Erste Abtheilung Knocken und Muskellehre. Braunshweig, F. Vieweg und Sohn; 1864:66.)[11]

During metamorphosis, glands develop in the upper eyelid margin and provide lubrication to the eye. Some glands on the medial side develop into the large harderian glands that nearly fill the orbit, and those on the lateral side may be a precursor of the lacrimal gland,[9] but a true lacrimal gland is absent in frogs.[4] A lacrimal punctum is present on the marginal border of the lower eyelid, and a subcutaneous canaliculus carries lubricating fluids to a nasolacrimal duct extending into the nasal cavity.[16] In frogs, studies have suggested that secretions from the harderian gland are carried through the nasolacrimal duct to the external naris where they bind chemical stimuli that are then actively transported into the auxiliary olfactory vomeronasal sensory organ of Jacobson.[17]

The Eyelids and Adnexa in Reptiles

Living reptiles represent a diverse group of vertebrates that includes lizards and snakes, crocodilians, turtles and tortoises, and the tuatara of New Zealand. The oldest group is *(Print pagebreak 7)* the Squamata encompassing the living and fossil lizards and snakes, which emerged in the late Permian Period, about 250 million years ago.

The orbit of most lizards is open and highly fenestrated with no interorbital septum. A small lacrimal gland is present in the superotemporal orbit and a large harderian gland inferonasally.[18] Among the lizards, the harderian gland exhibits a great deal of morphological variation and several different relationships with other structures such as the lacrimal duct and the vomeronasal organ. Its most likely function in these groups seems to facilitate vomerolfaction as a source of enzymes for sensory transduction, or as a source of lubricant, or both.[19]

The usual four rectus and two oblique muscles are present as is a well-developed retractor bulbi muscle that pulls the globe into the orbit facilitating passive closure of the eyelids. A transparent nictitating membrane, formed from a fold of conjunctiva at the medial canthus, moves across the cornea horizontally from nasal to temporal as in higher vertebrates. An additional orbital muscle, the bursalis muscle, is innervated by both the oculomotor and abducens nerves and inserts into the posterior sclera near the optic nerve.

[20] A tendon from the nictitating membrane extends back into the orbit and loops around the bursalis muscle so that with contraction of this muscle the membrane extends passively across the eye. In crocodilians, this tendon becomes muscular, named the pyramidalis muscle, so that the nictitating membrane can extend over the eye under direct muscle control independent of eyelid closure.[8] In turtles, the pyramidalis muscle is also present and extends to both the nictitating membrane and the lower eyelid so that when the retractor bulbi muscle contracts and the globe is retracted, the nictitating membrane covers the cornea, and the lower eyelid moves upward to meet the immobile upper eyelid.[8]

Most lizards have two eyelids covered with small scales (Figure 1.7). Like amphibians, the smaller upper eyelid remains relatively stationary and it is the larger lower eyelid that is mobile and contains a fibrous tarsal plate (Figure 1.8). The eyelid closes passively with contraction of the retractor bulbi muscle, and retraction is mediated by a specialized retractor (levator) muscle attached to the border of the tarsus in the lower eyelid. A nictitating membrane is well developed, except in burrowing species where it is usually absent. Lacrimal puncta and canaliculi are present on the medial eyelids and drain into the mouth through a narrow nasolacrimal duct. In most geckos the eyelids are absent and these species lick their eyes to clean and lubricate them.

FIGURE 1.7 Reptilian (lizard) eye with small circumocular scales on the eyelids. (Image used under license from Shutterstock.com.)

In the chameleon, the very large eyes are markedly proptosed and lie outside of the bony orbit. The organization of extraocular muscles in chameleons is similar to other reptiles except for the absence of the retractor bulbi muscle. The eyelids are fused into a single cone-shaped lid that covers the entire eye except for a small opening over the pupil, and the eyelid and the globe move together as a unit (Figure 1.9). *(Print pagebreak 8)* This arrangement of extraocular muscles and eyelid structure allows for fast saccadic eye movements with a range approaching 180° horizontally and independent movement of each eye.[21]

FIGURE 1.8 Lizard eyelids closed by elevation of the lower eyelid. (Image used under license from Shutterstock.com.)

FIGURE 1.9 Massively proptosed chameleon eye with fixed and fused conical eyelid and a small central opening. (Image used under license from Shutterstock.com.)

Some lizard species that live in a desert or rocky environment have a transparent window in the lower eyelid where the scales are reduced or absent providing corneal protection while allowing vision when the eyelids are closed. In burrowing species, the transparent lower eyelid is fused with the upper eyelid forming a spectacle over the globe that is separated from the cornea by a closed conjunctival sac.[22] In squamates with a spectacle, the nictitating membrane is not needed and is reduced or absent.[19]

During the evolutionary transition from lizard to snake, terrestrial forms went through a fossorial or burrowing stage with a simplification of the prototypical eye and adnexal anatomy.[23] The eyelids became fused over the eye to form a transparent spectacle lined by epithelium (Figure 1.10) and separated from the cornea by a closed conjunctival sac, beneath which the eye is freely moveable. The outer layers of the spectacle are shed when the skin is shed during growth. The nictitating membrane, the retractor bulbi and bursalis muscles, and the lacrimal gland are all absent. However, a very large harderian gland is present, producing an oily secretion that flows into the closed conjunctival sac to lubricate the cornea.[9] Secretions drain through a single nasolacrimal duct to the vomeronasal organ of Jacobson and then into the mouth where they provide additional saliva to aid in swallowing.

Turtles have a closed orbit behind but anteriorly have lost the nasal and lacrimal bones. The pyramidalis muscle sends slips to both the nictitating membrane and the lower eyelid so that both close when the retractor bulbi contracts.[8] The nasolacrimal duct is absent and ocular lubrication is from a large harderian gland. The lower eyelid is large and mobile, and there is a nictitating membrane.

FIGURE 1.10 Eye of a snake with the eyelids fused to form a transparent spectacle over the cornea. (Image used under license from Shutterstock.com.)

The Eyelids and Adnexa in Birds

In birds, the orbits are large and open laterally and inferiorly and are separated by a thin interorbital septum. The eyes are very large, nearly filling the orbital space. The orbits have large spaces separating the bones, similar to the pattern seen in most reptiles. The eyes are cushioned by orbital fat and protected by a ring of scleral ossicles that encircle the eye immediately behind the corneal limbus. Because of the large size of the eyes, the extraocular muscles are small and thin providing minimal ocular mobility in most species. The usual vertebrate pattern of four rectus and two oblique muscles is preserved. However, the extraocular muscles exhibit significant physiological differences from one group to another related to behavioral variations in ocular movements and closure of the eyelids.[24] In the owl, there is little or no ocular movement so that the extraocular muscles serve only to stabilize the position of the large, tubular eyes held within a sclerotic ring projecting out of the orbit. In diurnal raptors like the hawk, the eyes are more globose within the orbit, and larger extraocular muscles facilitate rapid eye movement for tracking prey.[24] The lacrimal gland is located in the inferotemporal orbit and a small harderian gland is in the medial orbit. A single lacrimal punctum is located medially in each eyelid and drains into a nasolacrimal duct.

In birds, there are well-developed eyelids (Figure 1.11), and contrary to amphibians and reptiles, both upper and lower eyelids are

mobile and participate in eyelid closure, although the lower eyelid is more mobile and moves further to meet the upper lid (Figure 1.12). Some species have a fibrous tarsal plate in the eyelids, but meibomian glands are absent. A striated circumocular orbicularis muscle is present, which closes *(Print pagebreak 9)* the eyelids. Opening of the eyelids is aided by a very small levator palpebrae superioris muscle in the upper eyelid and an analogous depressor palpebrae ventralis in the lower eyelid.[25] There are no eyelashes in birds, but some species have short modified feathers along the edges of the eyelids that may serve a similar function (Figure 1.11).

FIGURE 1.11 Eagle eye with eyelids open and fine feathers along the margins. (Images used under license from Shutterstock.com.)

FIGURE 1.12 Eagle with eyelids closed; the lower lid is more mobile. (Images used under license from Shutterstock.com.)

FIGURE 1.13 Owl with the nictitating membrane closed on the right side. (Images used under license from Shutterstock.com.)

A thin transparent nictitating membrane (nictitans) is present and extends horizontally from medial to lateral (Figure 1.13). As in reptiles, its function is controlled by pyramidalis and bursalis (quadratus) muscles. The pyramidalis tendon originates from the sclera medially and wraps around the globe temporally to insert into the nictitating membrane affecting its closure. The quadratus muscle keeps the tendon from impacting the optic nerve but may also aid in closure of the nictitans.[26] These muscles also retract the globe into the orbit replacing the absent retractor bulbi muscle. A distinct muscle, the depressor palpebrae inferioris, innervated by the oculomotor nerve, stabilizes the lower eyelid so that it does not move laterally when the nictitans closes.[26] Unlike mammals, in birds the nictitating membrane can close independent of eyelid closure.[25] This serves a protective function during rapid flight without loss of vision, but it has been proposed that this membrane may also serve to reduce glaring ambient sunlight during flight.[25] In diving birds the nictitating membrane has a central clear refractive window that acts as a form of goggles.

The Eyelids and Adenexa in Mammals

Mammals arose from a group of therapsid mammal-like reptiles about 210 million years ago and lived in the shadow of the dinosaurs for 150 million years with little evolutionary change. At least seven different mammalian groups evolved, of which only three survive today, the Montremata, Marsupialia, and Placentalia.

Monotremata

The Montremata includes only five species, the platypus, and four species of echidna, all indigenous to Australia and New Guinea. These are egg-laying, warm-blooded animals with hair, mammary glands, a single jaw bone, and three middle ear ossicles, all of which define mammals. In the semiaquatic platypus, the skull bones are similar to their reptilian ancestors, except for the absence of the lacrimal bone. There is no postorbital bridge and the orbit is open to the temporalis fossa as in most other mammals. The orbit is a shallow depression that has only superior and medial bony walls. There is a thin interorbital septum between the orbits and the floor is separated from the mouth only by a well-developed sheet of connective tissue and striated muscle. Paranasal sinuses are absent.[27] There is a large lacrimal gland inferotemporally and a harderian gland medially.

The usual six vertebrate extraocular muscles are present and insert into the sclera that is cartilaginous in its posterior two-thirds.[28] Unlike all lower vertebrates from fishes to reptiles, the superior oblique muscle now takes its origin from the orbital apex close to the origin of the rectus muscles and passes through a trochlea on the superomedial orbital wall. In the echidna, in addition to the posteriorly originating superior oblique muscle and tendon reflected through the trochlea, a separate muscular slip from the superior anterior orbital wall runs directly to the globe,[4] which may be an atavistic relic of the reptilian pattern. A retractor bulbi muscle is also present in all monotremes. In the platypus, striated muscle fibers run above the superior rectus muscle from the posterior orbit to the upper eyelid and represent the levator palpebrae superioris muscle.

The eyes of monotremes are small and in the platypus, they lie in a groove in the skin that closes when diving (Figure 1.14). The eyelids are well-developed and thick with a *(Print pagebreak 10)* small circular palpebral fissure. There are no eyelashes and the hair on the skin extends to the eyelid margins. Sebaceous glands are associated with hair follicles along the eyelid margin and may serve the same function as meibomian glands in placental mammals. An orbicularis oculi muscle is present and sparse smooth muscle fibers are present just beneath the conjunctiva, similar to the Müller supratarsal muscle in placental mammals. The platypus has a weak, opaque nictitating membrane, but this structure is absent in the echidna. Walls[4] mentions that the platypus has tarsal plates in both upper and lower eyelids, but Newell[28] did not find any in a specimen he dissected. The echidna has a tarsus only in the lower eyelid.

FIGURE 1.14 Monotreme mammal (platypus) with small eyes and thick eyelids lying in a groove of skin. (Image used under license from Shutterstock.com.)

Marsupialia

Marsupials are a group of mammals that give birth to relatively undeveloped young that are suckled in a pouch located on their mother's abdomen for a period of time. About 70% of extant species occur in Australia, New Guinea, and nearby islands, and about 30% are found in North and South America.

The orbit of marsupials is partially open with the lateral wall and part of the ventral wall formed only by connective tissue fascia. A small lacrimal gland is situated in the superior lateral orbit, and a large harderian gland is present medially draining into the conjunctival sac between the cornea and the nictitating membrane. There are seven extraocular muscles including the four recti, two obliques, and a well-developed retractor bulbi. The superior oblique originates posteriorly as in all mammals and is reflected through a cartilaginous trochlea on the superomedial orbital wall. The inferior oblique muscle still originates anteriorly, but its insertion is low on the inferomedial wall in a depression just behind the maxillary orbital rim. A retractor bulbi muscle innervated by both the abducens and oculomotor nerves inserts onto the sclera posterior to the insertions of the four rectus muscles as it does in almost all mammals except for higher primates. However, in the opossum, it is a continuous muscle without separate fascicles.[29]

FIGURE 1.15 Marsupial (koala) eyes with short upper and lower eyelids and medial upper eyelid vibrissae. (Image used under license from Shutterstock.com.)

The eyelids are small but otherwise similar to the anatomy of placental mammals (Figure 1.15), and there is a well-developed orbicularis oculi muscle. A levator palpebrae superioris muscle is present, sharing a common tendon of origin with the superior rectus muscle, and is innervated by a branch of the superior division of the oculomotor nerve.[29,30] The muscle runs forward superior and medial to the superior rectus muscle and then fans out into an aponeurosis as it inserts into the upper eyelid.

The upper eyelid is longer than the lower with long, coarse eyelashes. There is one lacrimal punctum in the medial margin of each eyelid that drains into canaliculi and then directly into a nasolacrimal duct without a lacrimal sac. A poorly developed nictitating membrane lined by conjunctival epithelium on both sides and containing a plate of hyaline cartilage conforming to the globe surface is located in the medial canthus and closes laterally. On closure, it only covers the medial one-third of the cornea.[30]

Placentalia

The Placentalia is the largest group of mammals, characterized by the presence of an advanced placenta, which facilitates the exchange of oxygen, nutrients, and waste between the blood of the mother and the fetus. This group includes all living mammals except for monotremes and marsupials. Young are born alive and in a more advanced stage of development than in marsupials. Based on fossil evidence and geomolecular dating, *(Print pagebreak 11)* stem placental mammals arose during the Late Cretaceous Period, about 85 to 90 million years ago.[31] They then underwent a remarkable adaptive radiation into 17 orders beginning about 66 million years ago at the Cetaceous-Paleogene extinction event that ended the age of dinosaurs.

The various orders of placental mammals are extremely diverse and adapted to a wide range of habitats from aquatic, to terrestrial and arboreal, and from desert to forest and arctic. As a result, almost every anatomic feature that distinguishes placental mammals from other vertebrates and from lower mammals has become highly variable among the different orders.

The orbit in almost all placental mammals is open laterally where it broadly communicates with the temporalis fossa. In many groups such as primates and carnivores, the evolution of increasing degrees of stereopsis conferred a high selective advantage resulting in progressive orbital convergence to a more frontal orientation. In higher primates, especially in the Homininae (great apes and humans), expansion of the frontal lobes of the brain was associated with an anterior progression of the forehead, associated

with a simultaneous regression of the midface and jaw. This was manifest as a clockwise rotation of the skull around the orbit as viewed from the right.[32,33] This resulted in a forward migration of the temporalis fossa and temporalis muscle, encroaching upon the open posterolateral orbit so that with chewing the eyes were vulnerable to movement and disruption of visual fixation. In anthropoid apes (orangutan, gorilla, and chimpanzee) and humans, a gradual closure of the lateral orbital wall by a growth of the greater sphenoid wing separated the temporalis muscle from the orbital contents. This complete closure of the orbit except anteriorly is a unique feature of the anthropoid and human orbits.

Three eyelids are present in most placental mammals: an upper and lower (Figure 1.16), and a nictitating membrane (Figure 1.17). The upper eyelid is larger and more highly mobile compared with the lower, unlike the situation in lower vertebrates where the lower eyelid is the more mobile. The orbicularis oculi is well developed and in primates, the corrugator, depressor supercilii, and procerus muscles are differentiated from it. There is a well-developed frontalis muscle in most placentals.[34,35] A tarsal plate of dense fibrous tissue is present in the upper eyelid, but its presence in the lower eyelid is more variable. Except in aquatic mammals, meibomian glands providing an oily secretion are present in the tarsal plates and open onto the eyelid margins, evolved from the sebaceous glands associated with cutaneous hair follicles. Glands of Moll are present in many different orders such as ungulates, carnivores, and primates. Well-developed eyelashes are present as are eyebrows, which are sometimes specialized as long tactile vibrissse (Figure 1.16). All placental mammals have a well-developed levator palpebrae superioris muscle to retract the upper eyelid as well as a sympathetic smooth supratarsal muscle. In cetaceans (whales, dolphins, and porpoises) the rectus muscles have two insertions, a small tendon inserting onto the eye and a much larger one inserting into the eyelids that may function to help retract the eyelids.[36] They also have two accessory eyelid muscles, the retractor anguli oculi medialis and lateralis, which probably serve to increase the horizontal length of the palpebral fissure.[36] They also have two additional muscles that encircle the anterior orbit, the internal (ICM) and external (ECM) circular muscles. The ICM lies between the insertions of the retractor bulbi muscle and the rectus muscles and its function is unknown. The ECM lies external and is firmly adherent to the rectus muscle insertions and blends with their fibers. It has been proposed that the ECM functions to protrude the eye from the orbit as an antagonist to the retractor bulbi muscle, to support and protect the orbital contents during mandibular movements, and possibly also to regulate blood flow or pressure in the vascular plexi associated with the retractor bulbi.[37]

FIGURE 1.16 Placental carnivore (dog) with mobile upper and lower eyelids similar to humans. (Image used under license from Shutterstock.com.)

FIGURE 1.17 Dog eye with partial extension of the nictitating membrane in the medial canthus. (Image used under license from Shutterstock.com.)

(Print pagebreak 12)

Most placental orders possess a lacrimal gland secreting a watery fluid that has moved to a superolateral position in the orbit. A large harderian gland is present in the nasal orbit of most orders and may function in lubricating the nictitating membrane, except in higher primates where this gland and the nictitans are vestigial or absent. Tears drain into one punctum on the inner eyelid surface at the medial corner of each eyelid, except in higher primates (including humans) where they are on the eyelid margin. There is a variable development of a lacrimal sac and a well-developed lacrimal duct opening into the nose. In cetaceans (whales, dolphins, and porpoises), ocular glands consist of a highly integrated system of multifunctional secretory cells arranged as discrete orbital glandular masses or as diffuse tissue in the eyelids that produce a continuous stream of a complex, heterogeneous orbital fluid that covers the entire eye and presumably provide a protective function.[38] The lacrimal gland is variably present in different cetacean species. The harderian gland is a large semicontinuous mass in the anterior orbit between the eye and the eyelid around the conjunctival fornix. A palpebral gland mass is present in one or both eyelids, homologous to the glands of Wolfring and Krauss. An encircling ring of diffuse small glands lies along the eyelid margins which are not sweat glands or sebaceous glands and do not represent Moll glands or meibomian glands.[37]

The nictitating membrane in placental mammals is still present but generally is poorly developed (Figure 1.17). It is frequently supported by a plate of hyaline cartilage but without any intrinsic musculature. Unlike lower vertebrates, the orbital muscles (bursalis [quadratus] and pyramidalis) that facilitate closure of the nictitans are either absent or highly vestigial. The nictitating membrane extends over the cornea passively only when the globe is retracted into the orbit by the retractor bulbi muscle. However, in primates, a functional nictitans is present only in lemurs and lorises. In monkeys, apes, and humans, it is reduced to a vestigial plica semilunaris (Figure 1.18) that may have persisted as a fold of redundant conjunctiva to allow a greater degree of abduction, or lateral rotation, of the globe. Very rarely, a partial nictitans may be seen in humans as an atavistic structure.[39]

Except for higher primates, the extraocular muscles of most placental mammals comprise four rectus and two oblique muscles, and a retractor bulbi muscle, which is the common pattern for mammals in general. As in marsupials, the superior oblique muscle originates near the orbital apex and its tendon is reflected through a trochlea before turning posterolaterally to insert onto the posterior sclera. In humans and their closest relatives the chimpanzees, the superior oblique tendon passes superior to the superior rectus muscle, whereas in most other mammals it passes beneath this muscle. In some carnivores, the tendon pierces through the superior rectus muscle on its way to the globe. The retractor bulbi muscle persists in most placentals and as in lower vertebrates, it arises in the orbital apex and runs within the muscle cone around the optic nerve to insert into the sclera behind the rectus muscle insertions (Figure 1.19). On contraction, it retracts the eye into the orbit and simultaneously and passively extends the nictitating membrane across the cornea. It is principally innervated by the abducens nerve as it is mainly derived from the common anlage of the abducens musculature. But the muscle origin occasionally includes the muscle anlage innervated by the inferior division of the oculomotor nerve forming a complex muscle innervated by both the oculomotor and abducens nerves.[40]

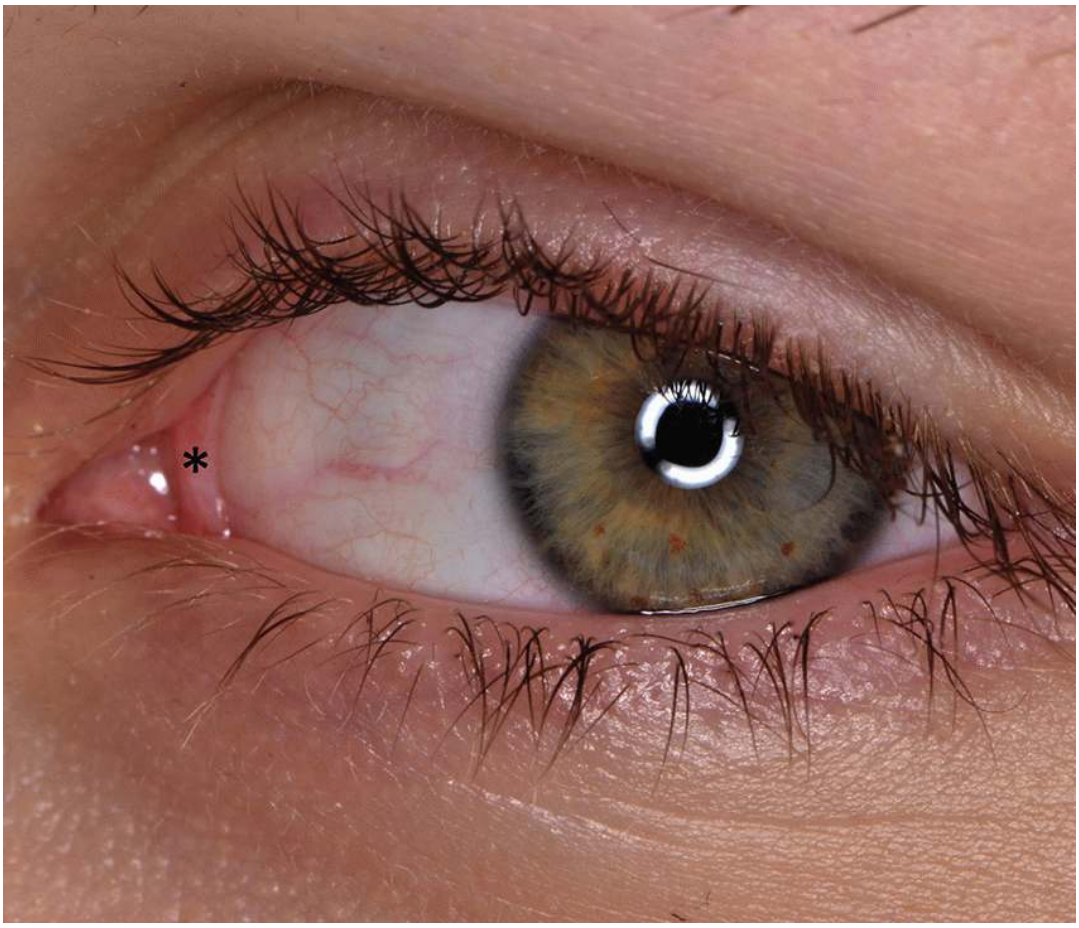

FIGURE 1.18 Human eye with the nictitating membrane reduced to a nonfunctional plica semilunaris (asterisk). (Image used under license from Shutterstock.com.)

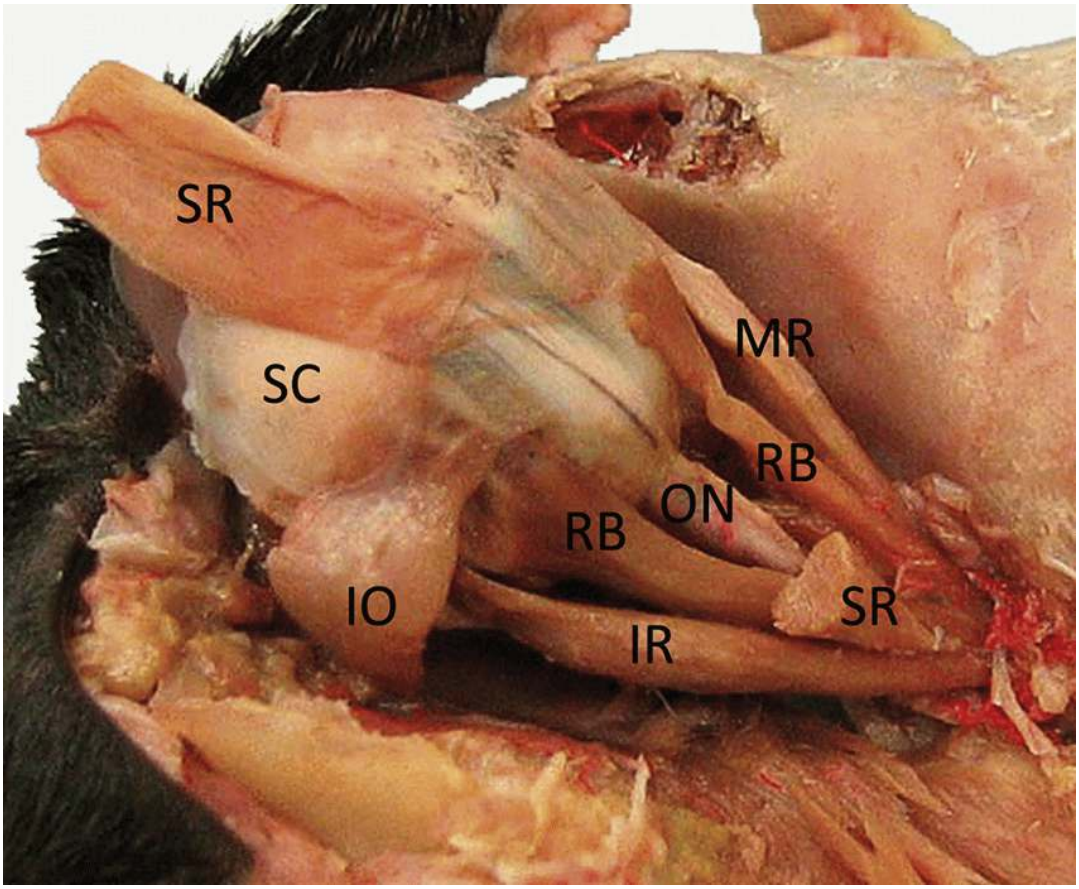

FIGURE 1.19 Orbital dissection of a dog orbit showing retractor bulbi muscle fascicles within the rectus muscle cone. IO, inferior oblique; IR, inferior rectus, MR, medial rectus, ON, optic nerve, RB, retractor bulbi, SC, sclera, SR, superior rectus. (Courtesy of Dr. C. Clarkson. From the University of Minnesota College of Veterinary Medicine, Guide to Dissection of the Dog, 8th ed., Lab 24, Image 5, 2019.)

(Print pagebreak 13)

In some monkeys the retractor bulbi muscle is vestigial and in apes and humans, it is absent. This developed along with the evolution of orbital convergence, increasing bifoveal fixation and stereoscopic vision since globe retraction with each blink would otherwise disrupt visual fixation and blur vision. In the evolution of higher primates, stable stereoscopic foveal fixation and sharp vision were important selective adaptations favoring reduction and finally loss of the retractor bulbi system. However, the globe in apes and humans is still able to retract somewhat during the blink and this function has been taken over by co-contraction of the rectus muscles.[41]

A well-developed smooth muscle (Müller orbital muscle) is present in placental mammals and separates the inferior orbit from the pterygopalatine fossa. As the lateral orbital wall closed with expansion of the greater sphenoid wing, this inferior opening was reduced to a narrow slit, the inferior orbital fissure, bridged over by connective tissue and remaining smooth muscle fibers.[1]

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(Print pagebreak 14)

CHAPTER 2

Embryology of the Eyelid

Key Points

- Prenatal development in humans is divided into two periods: embryonic and fetal
- During the embryonic period, eyelid morphogenesis is a dynamic process involving complex interactions between the developing epidermis and dermis
- Intra-epithelial and epithelial-mesenchymal interactions are integral for normal eyelid formation
- Surface ectoderm gives rise to the conjunctiva, skin epithelium, hair follicles, Zeis glands, glands of Moll, and meibomian glands
- The tarsal plate, levator muscle, orbicularis muscle, orbital septum, and tarsal muscle of Müller develop from the mesenchyme
- Mesenchymal contributions to the developing eyelid primarily originate from the cranial neural crest cells
- Development of definitive eyelid structures begins following eyelid fusion in the ninth week in the fetal period

Prenatal development in humans is divided into two arbitrary periods: embryonic and fetal.[1] The embryonic period begins with fertilization of the egg and ends 8 weeks later. The fetal period begins at week 9 and continues until delivery. During this embryonic period, eyelid morphogenesis is a dynamic process that involves complex interactions between the developing epidermis and dermis.[1,2,3] A large number of signaling molecules and pathways coordinate two major tissue interactions during early eyelid development; these are intra-epithelial and epithelial-mesenchymal interactions. Both types of interactions are critical for normal eyelid development.[4] In general, the eyelids develop from secondary mesenchyme that is invaded by cranial neural crest cells, as well as from surface ectoderm.[5,6,7] The surface ectoderm gives rise to the conjunctiva, epithelium of the skin, hair follicles, Zeis glands, glands of Moll, and meibomian glands. The tarsal plate, levator muscle, orbicularis muscle, orbital septum, and tarsal muscle of Müller develop from the mesenchyme.[8,9] Mesenchymal contribution to the developing eyelid primarily originates from cranial neural crest cells. The mesodermal contribution is limited to the endothelium of blood vessels and striated muscles in the eyelids and orbit.[7]

The Embryonic Stage

At the 31- to 35-day (5-7 mm) embryonic stage, the lens pit starts to invaginate from the surface ectoderm, but there is as yet no indication of an eyelid fold.[10] The first indication of the embryonic eyelid occurs around the beginning of week 6 (37-42 days, 8-11 mm stage) where small grooves develop in the surface ectoderm immediately above and below the developing eye. These rapidly deepen to form the eyelid folds.[7,10] By the end of week 6 (42-44 days, 11-14 mm stage), the upper eyelid fold is barely visible and is less distinct than the lower eyelid fold,[7,10,11] but distinct upper and lower eyelid folds are well defined by week 7 (48-51 days, 16-18 mm stage). At this stage, the upper eyelid starts to assume its dominant role compared with the lower eyelid.[12] Both folds are covered by epithelium on their anterior and posterior surfaces.[10] Also at this stage, a solid cord of epithelial cells invaginates into the thickened mesenchyme in the medial 1/6th of the eyelid and bifurcates forming the precursors of puncti and canaliculi.[11,13,14,15]

At the beginning of week 8 (54-56 days, 23-28 mm), there is a persistent gap between the upper and lower eyelid folds, exposing the cornea. The surface ectoderm cells start to migrate toward each other from the rim of both eyelids, beginning the process of eyelid fusion.[4,7,16] When a connection is established between both sides, the surface cells flatten again and form a continuous sheet, ultimately covering the cornea (Figures 2.1 and 2.2).

The epidermal layer is involved in eyelid fusion, but the eyelid mesenchyme remains distinct and unfused (Figures 2.3 and 2.4).[17]

By the end of week 8 (56-60 days, 27-31 mm), the process of eyelid fusion is complete, and this coincides with the conclusion of the embryonic stage and the beginning of the fetal stage.[10,11]

The Fetal Stage

The development of definitive eyelid structures begins in the ninth week immediately following eyelid fusion.[13] Mesenchymal cell condensations and ingrowth of surface epithelium into the underlying mesenchyme both contribute to the formation of some eyelid structures (Figure 2.5).[11,13] The first to appear is the orbital portion of the orbicularis oculi muscle. The canaliculi start to canalize around week 10 (76 ± 7 mm).[15]

The primordial tarsal plate, followed by the eyelash follicle anlages, and the primordial orbital septum appear by the *(Print pagebreak 15)* 11th week (87 ± 8 mm).[11,18] The meibomian gland anlages also first appear around week 11. After a series of signaling processes between the dermis and the overlying epidermis, the epithelial placodes of the meibomian anlagen invaginate into the underlying mesenchymal condensation to form solid cords of cells that later form lateral outgrowths. These differentiate into connecting ductules and secretory holocrine sebaceous acini. The central epithelial cylinder of the meibomian anlage forms a central canal that subsequently develops into the central duct.[11,12,19]

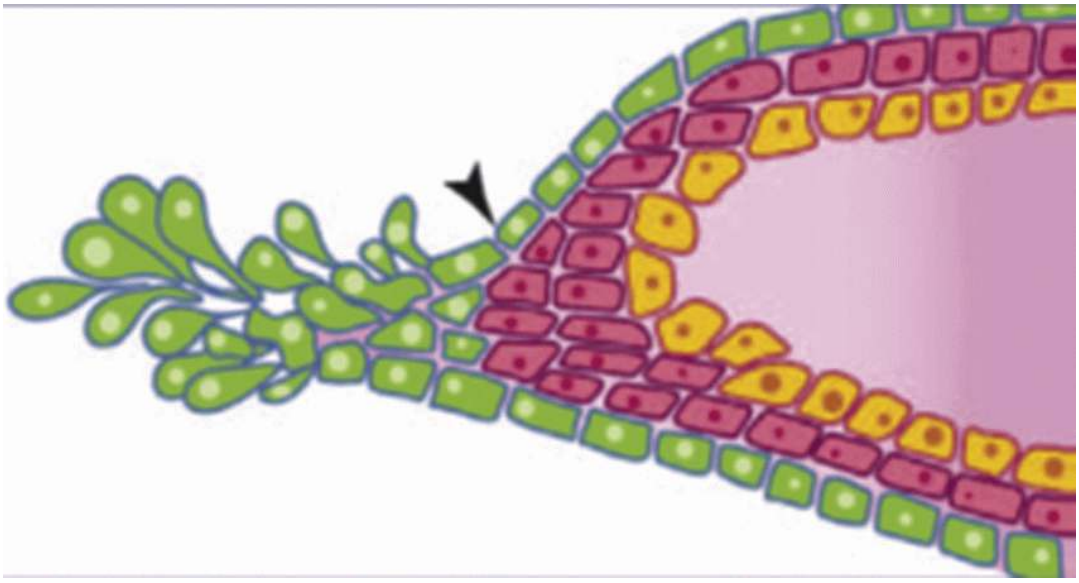

FIGURE 2.1 Beginning in embryonic week 8, the flattened periderm cells (*arrowhead*) undergo a morphogenetic and proliferative change into rounded or cuboidal periderm cells.

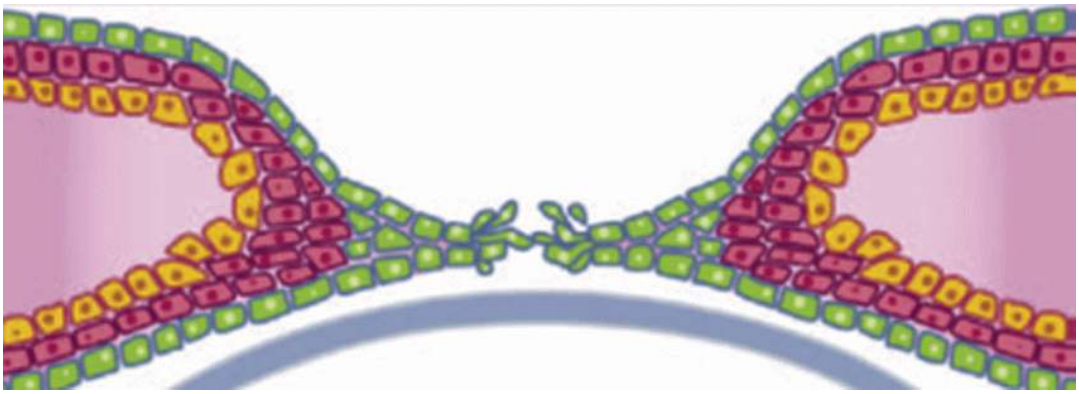

FIGURE 2.2 The leading edge of these proliferating cells helps make contact with the advancing edge of the opposing eyelid periderm cells until a connection is established.

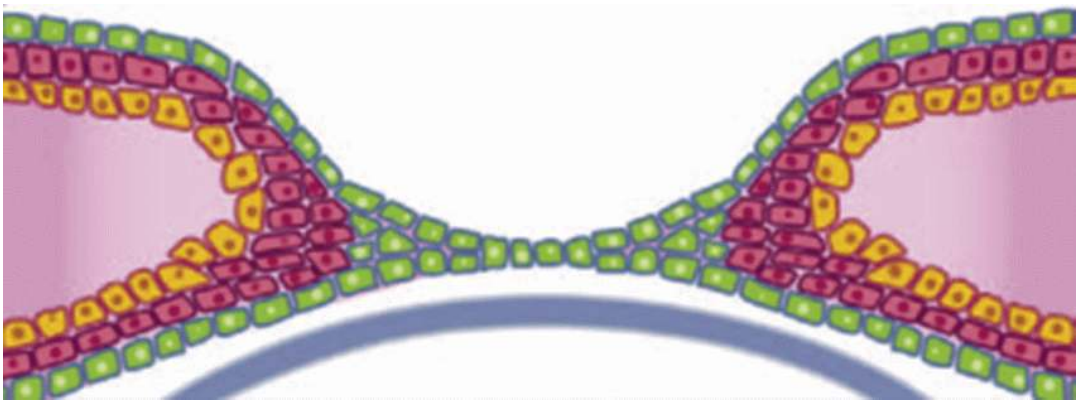

FIGURE 2.3 When a connection is established between both sides, these periderm cells flatten again and form a continuous sheet ultimately covering the cornea.

By week 12 (98 ± 9 mm), several eyelashes can be seen. The orbital part of the orbicularis oculi muscle is well developed, and the levator muscle and its aponeurosis start to appear.[6,13,20] Throughout the embryonic and most of the fetal periods, the levator muscle shares a common epimysium with the superior rectus muscle.[6,20] During the 12th week, the levator aponeurosis is observed running downward close to the primordium of the orbital septum.[11] Müller sympathetic smooth muscle is not yet seen.[11,13]

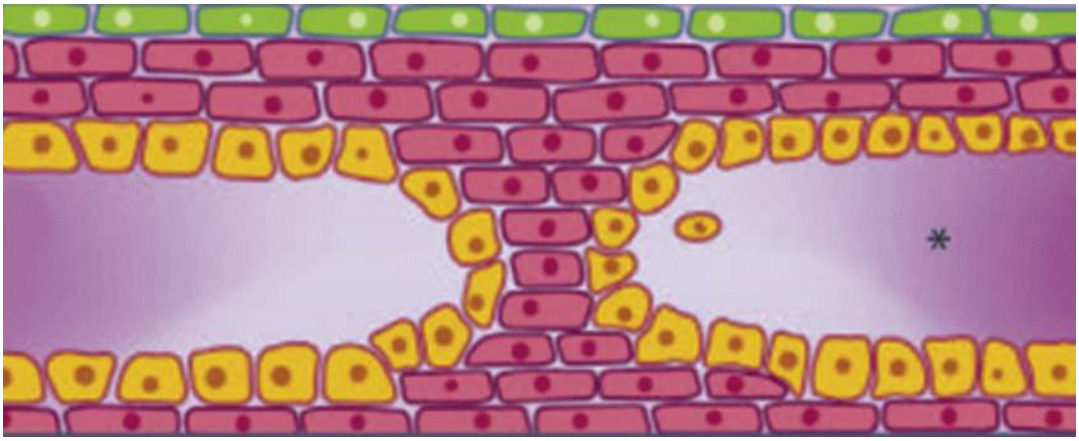

FIGURE 2.4 Only the periderm and epidermal layers are involved in eyelid fusion while eyelid mesenchyme (*) remains distinct. (Modified with permission from Yu et al, 2008.)

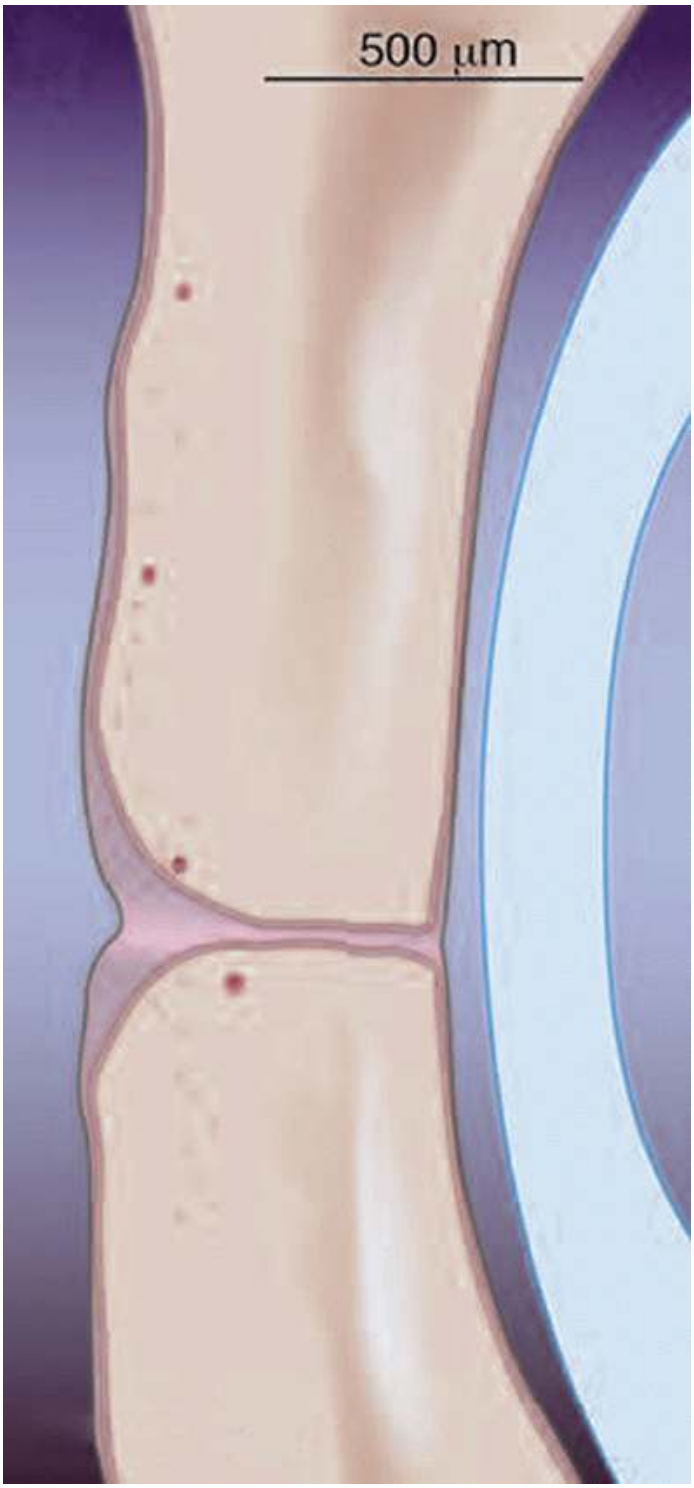

FIGURE 2.5 During fetal week 9, the development of eyelid structures begins immediately following eyelid fusion with mesenchymal cell condensations and an occasional ingrowth of surface epithelium into the underlying mesenchyme. Together, these contribute to the formation of several eyelid structures, the first being the orbital part of the orbicularis oculi muscle.

During the 13th week (109 ± 10 mm), the eyelash anlagen develops lateral outgrowths,[21] which differentiate into the holocrine sebaceous glands of Zeis and modified sweat *(Print pagebreak 16)* glands of Moll.[19,21] By week 14 (121 ± 11 mm), the eyelid is divided into separate layers. Sweat and sebaceous glands appear, the orbital septum is well defined, and Müller muscle makes its first appearance (Figure 2.6). The orbital fat is seen as a definite structure by week 16 (145 ± 12 mm), and its extraconal components are seen posterior to the orbital septum.[11] Also by week 16, the canaliculi are patent, but the puncti will remain closed until after the eyelids separate.[15,22]

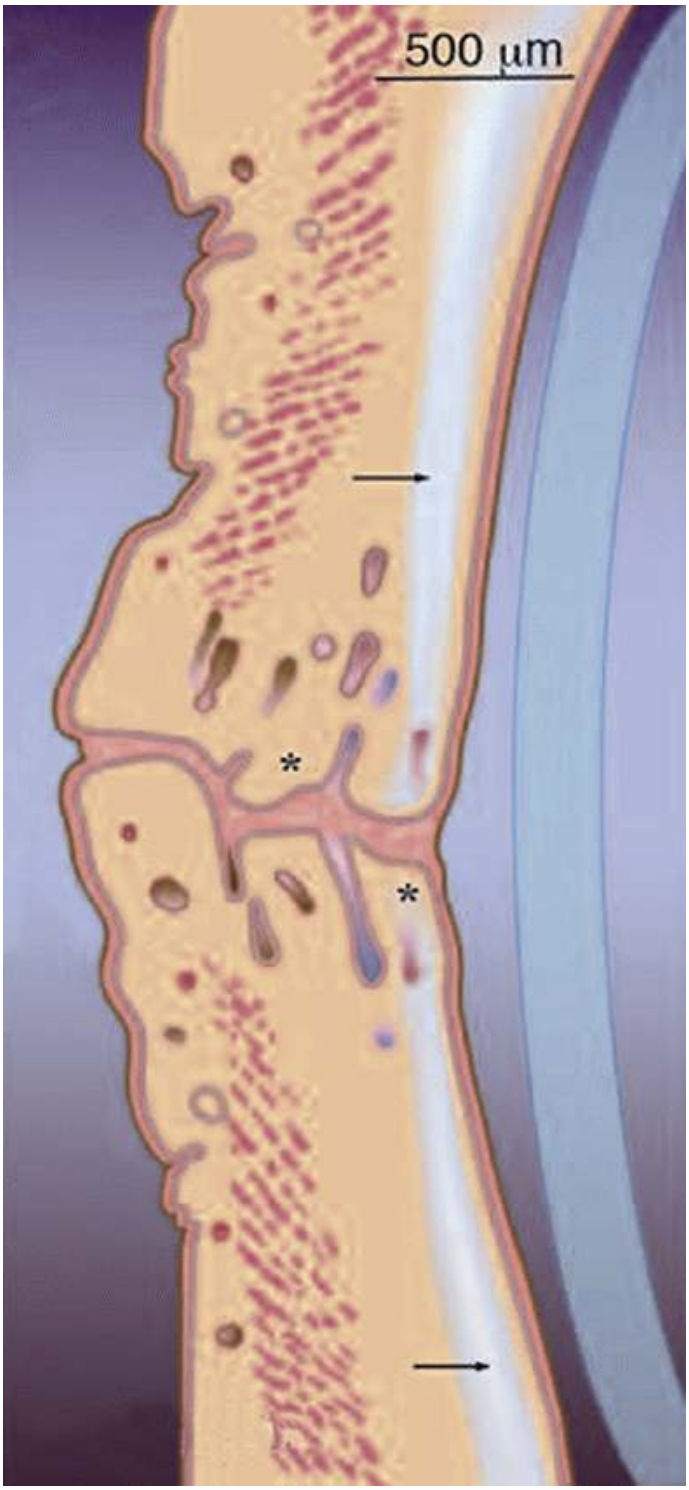

FIGURE 2.6 In fetal week 14, the eyelid is divided into separate layers. Rudimentary eyelashes, sebaceous glands, and sweat glands (*) are seen near the eyelid margin, and a primordial tarsal plate has formed (small arrow).

By week 18 (171 ± 14 mm), the tarsal plates and the vascular arcades are well defined, and the meibomian gland anlages are observed.[11] By week 20 (195 ± 15 mm), the lateral horn of the levator aponeurosis has expanded above the globe and divides the lacrimal gland into its orbital and palpebral lobes.[7,8,11]

Eyelid separation begins around the 20th week (195 ± 15 mm) (Figure 2.7). Although the exact mechanism remains a matter of controversy, keratinization of the epidermal surface,[21,23] holocrine production of lipids from the developing meibomian glands,[7,23] and apoptosis-induced reduction in the size of the junctional area have been proposed as key elements in eyelid separation.

By week 24 (232 ± 18 mm), after eyelid separation, the eyelids begin to take their nearly developed shape.[11,13,18] The orbicularis oculi muscle extends medially and laterally to be attached to the medial and lateral palpebral ligaments, respectively[13]; the tarsal plate has lengthened and increased in width; the levator palpebrae superioris muscle, aponeurosis, and the orbital septum are all

visible; and the Müller muscle is visibly attached to the superior border of the tarsus and is posterior to the levator aponeurosis.[11] By week 28 (267 ± 27 mm), the differentiation of the orbicularis oculi muscle is almost complete, and the pretarsal, preseptal, and orbital components are discerned.[7] Opening of the puncti onto the lid margin is also observed around the 28th week after the eyelids separate.[15]

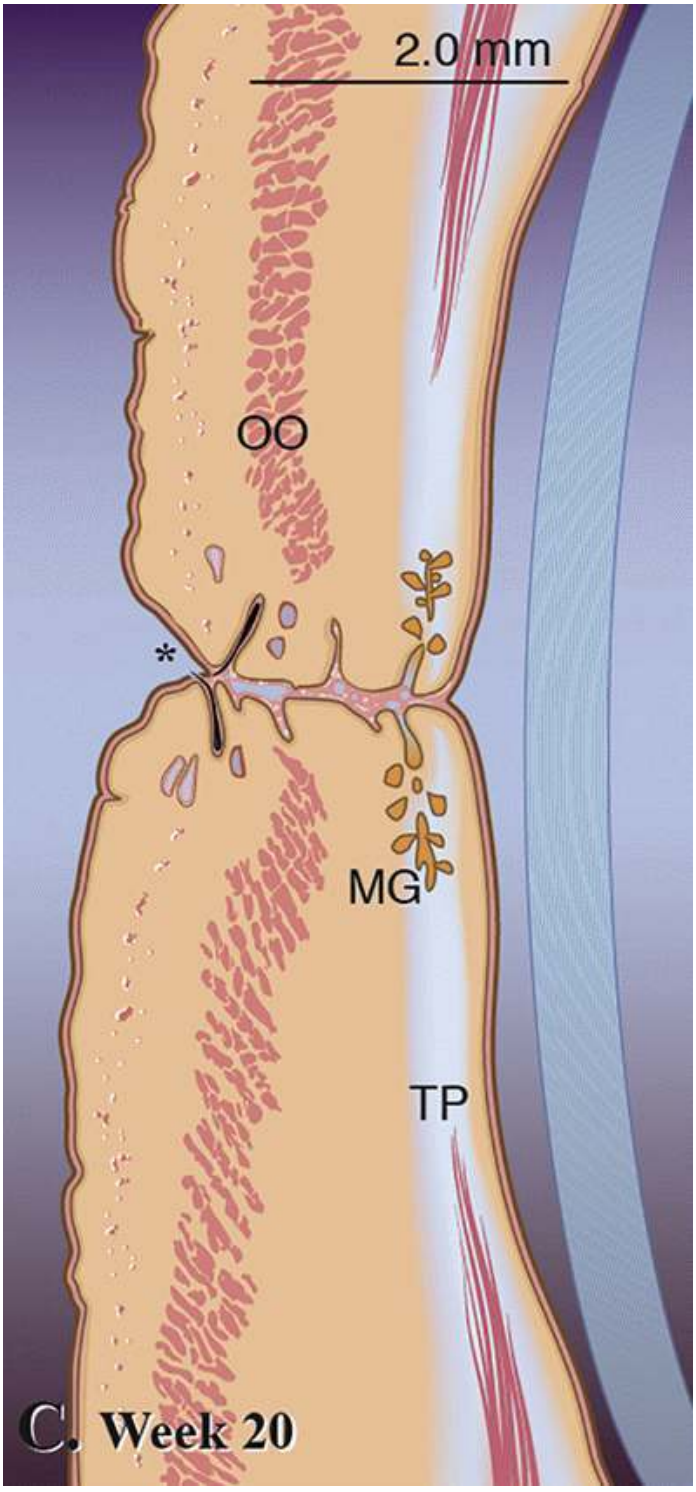

FIGURE 2.7 At week 20, the eyelids are still visibly fused, but separation has already started anteriorly (*) and is visible in the middle microscopically. Meibomian gland branching is observed, the tarsal plate has lengthened, and the orbicularis oculi muscle is more fully developed. Nearly mature eyelash follicles are also evident. mg, meibomian glands; oo, *orbicularis oculi muscle;* tp, *tarsal plate*.

By week 32 (301 ± 33 mm), the eyelids are separated and attain nearly their final development (Figure 2.8). The upper eyelid central fat pad and the preseptal fat are well defined.[11] Meibomian glands increase in length and are present in two-thirds of the length of the tarsal plate.[13]

By week 36 (336 ± 32 mm), the eyelid is almost fully formed with smooth lid margins (Figure 2.9).[7] The tarsal glands now occupy almost the entire length of the tarsal plate, the orbicularis oculi is located directly subcutaneously, and the levator muscle is connected to the Müller muscle.[11]

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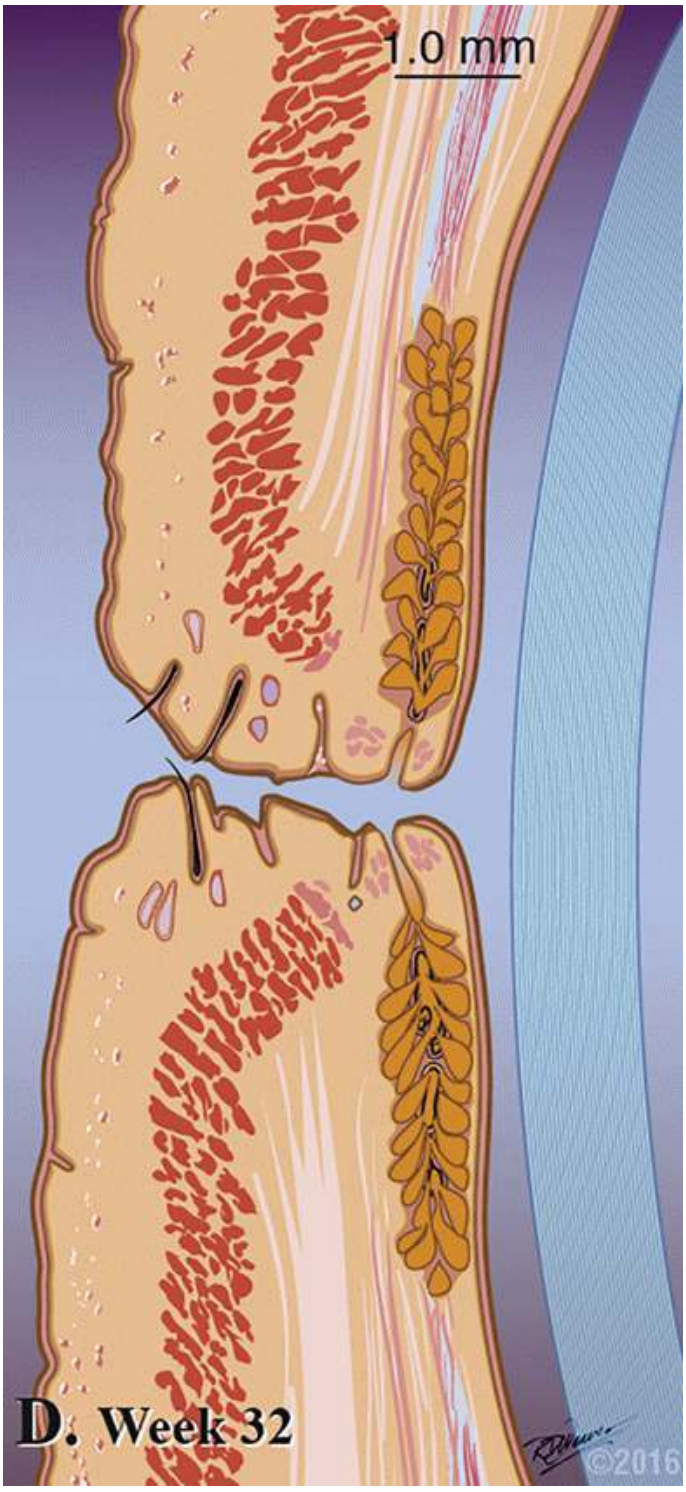

FIGURE 2.8 During week 32, the eyelid is nearly fully developed. Meibomian glands increase in length and the eyelids are fully separated.

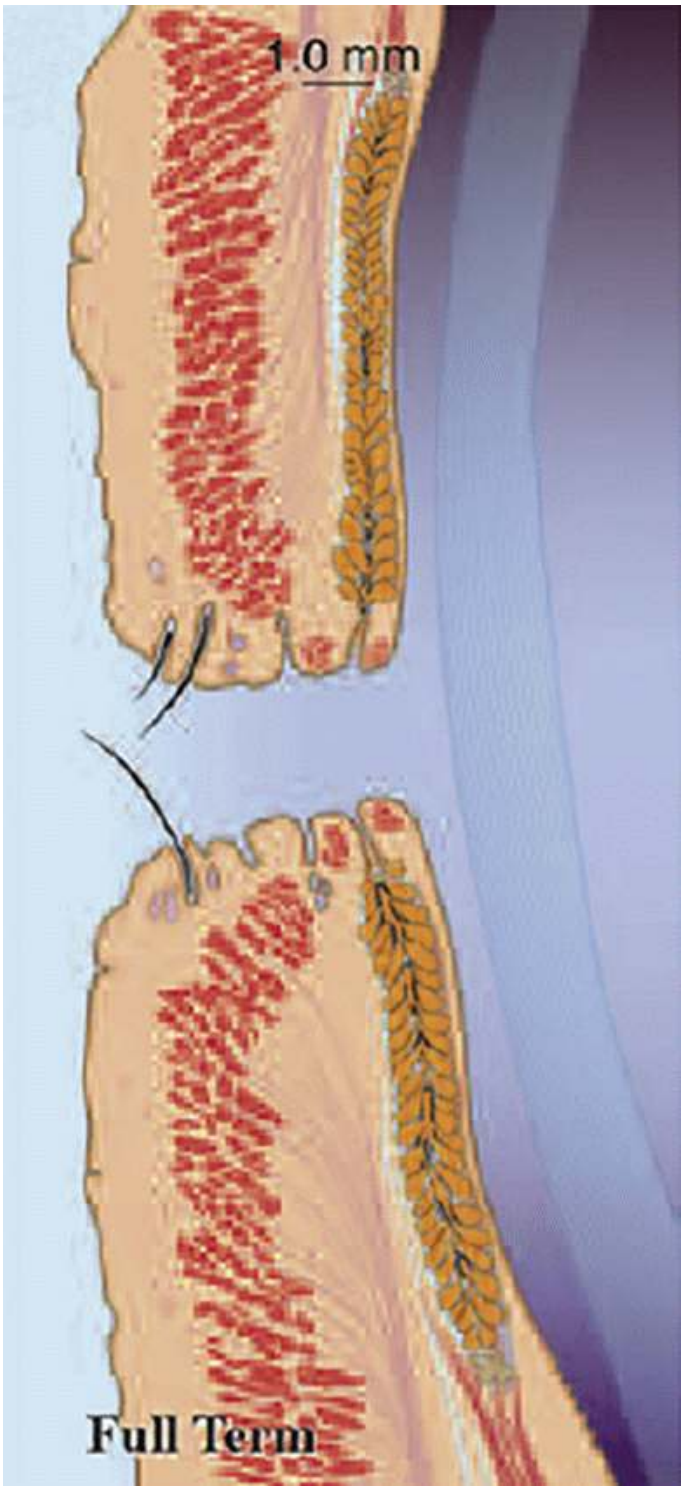

FIGURE 2.9 At term, the eyelids are similar to their adult counterparts.

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CHAPTER 3

Anatomy of the Eyelids

Key Points

- In adults, the interpalpebral fissure measures 8 to 10 mm and the horizontal length of the fissure is 30 to 31 mm
- The eyelid margin is about 2 mm thick, covered posteriorly by conjunctival epithelium interrupted by meibomian gland orifices, and anteriorly by cutaneous epidermis
- The anterior lamella of the eyelid consists of skin and orbicularis muscle that is divided anatomically into three contiguous parts—the orbital, preseptal, and pretarsal portions
- The posterior lamella consists of the tarsus, levator aponeurosis, Müller muscle, and conjunctiva
- The orbital septum is a fibrous layer separating the anterior and posterior lamellae
- An extension of extraconal orbital fat separates the septum from the aponeurosis and is a key landmark for identifying the aponeurosis during ptosis surgery
- The aponeurosis and Müller muscle are the major retractors of the upper eyelid
- The arterial supply to the eyelids includes anastomoses between the internal and external carotid systems
- Lymphatic drainage from the eyelids is anterior into the preauricular, submandibular, and cervical nodes

The eyelids serve several important functions. Along with the iris, they help mediate light exposure by adjusting the palpebral fissure size. They provide important elements of the precorneal tear film, add essential mucin and lipid layers, and help distribute these evenly over the surface of the eye. With each blink, the eyelids propel tears toward the medial canthus where they enter the lacrimal drainage system. The eyelashes sweep air-borne particles from in front of the eye, and the constant voluntary and reflex movements of the eyelids protect the cornea from injury and glare.

In the young adult, the interpalpebral fissure measures 10 to 11 mm in vertical height. With advancing age it is reduced to only about 8 to 10 mm.[1,2] The horizontal length of the fissure is 30 to 31 mm. The upper and lower eyelids meet at an angle of approximately 60° medially and laterally. In the primary position, the upper eyelid margin lies at the superior corneal limbus in children and 1.5 to 2.0 mm below it in the adult. The lower eyelid margin rests at the inferior corneal limbus (Figure 3.1).

The margin of each eyelid is about 2 mm thick. Posteriorly the marginal tarsal surface is covered with conjunctival epithelium, interrupted by the meibomian gland orifices.[2] Anteriorly the margin is covered with cutaneous epidermis from which emerge the eyelashes. The gray line is a faint linear zone separating these two regions (Figure 3.2).

Skin

The eyelid skin is the thinnest in the body, averaging about 0.5 mm in thickness. It consists of the same basic layers as in other parts of the body. The epidermis is composed of four layers. The outermost layer, the stratum corneum, is a thin layer of dead cells filled with keratin that flake off the surface (Figure 3.3). The stratum granulosum is the first layer of living cells with a granular appearance and produce keratin. The stratum spinosum is a thick layer with a spiny appearance from fine filaments that join the cells together. The stratum basalis is the lowermost layer of the epidermis where cell production occurs and is characterized by mitoses.

Beneath the epidermis is the dermis composed of a papillary and reticular layer.[2] The dermis contains dense connective tissue, collagen, and elastic fibers, melanocytes, nerves, and blood vessels. Several dermal appendages lined with epithelium lie within the dermis. These include hair follicles associated with an arrector pili muscle attached to the dermal-epidermal junction. Apocrine sweat glands of Moll are coiled glands in the deep dermis that empty via a long ductule into the uppermost portion of the hair

follicle. Apocrine glands secrete by cellular decapitation with the apical portion of the secretory cell mixed with sialomucin producing a more viscous secretion with cellular debris. They are concentrated along the eyelid margins. Eccrine sweat glands are also present in the dermis but they are not associated with the hair follicle. They open directly onto the epidermal surface via a long straight ductule. Eccrine glands secrete a clear fluid composed of water, salts, glycogen, and sialomucin.

Sebaceous glands contain epithelium that is an outgrowth of the external root sheath of the hair follicle. These are holocrine glands that shed the entire epithelial cell along with secretory products of complex oils, fatty acids, wax, and cholesterol esters called sebum. Usually two sebaceous glands, termed glands of Zeis, are associated with each follicle and empty their secretions directly into the follicle through short ducts. The hair follicle along with the sebaceous and Moll glands forms the pilosebaceous unit.

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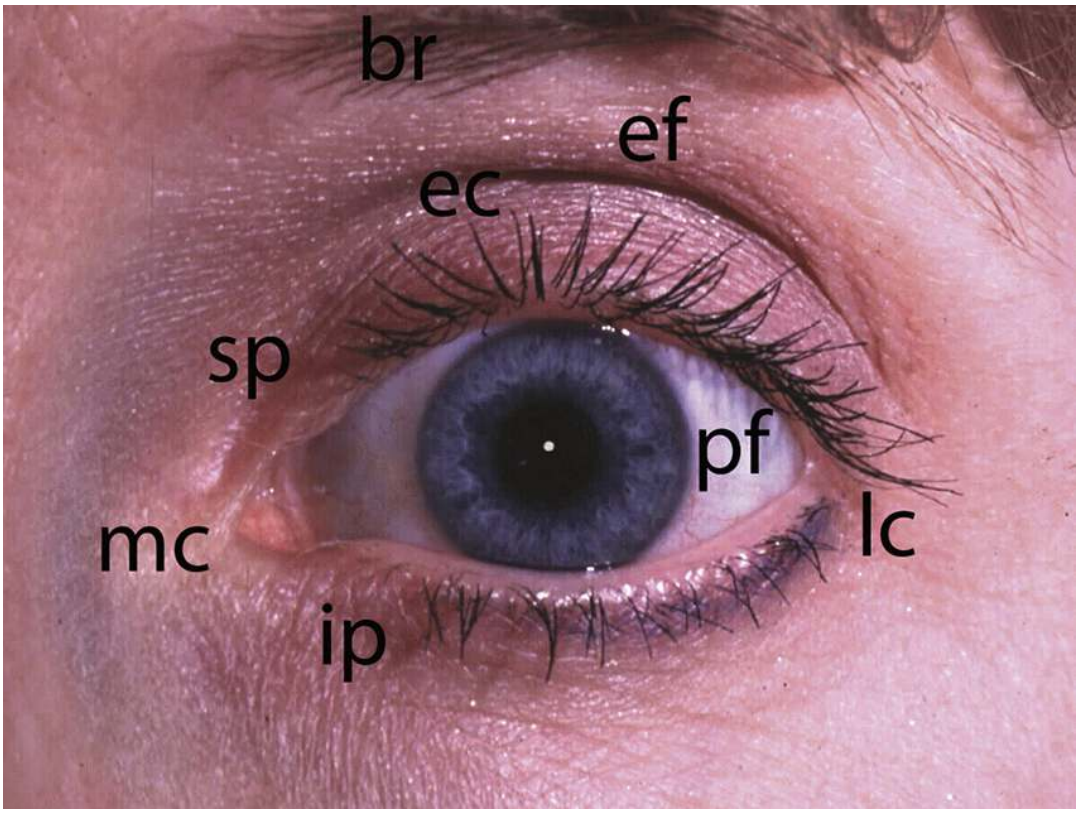

FIGURE 3.1 External eyelid. br, brow; ec, eyelid crease; ef, eyelid fold; ip, inferior punctum; lc, lateral canthus; mc, medial canthus; pf, palpebral fissure; sp, superior punctum.

Beneath the dermis is a subcutaneous layer of fat and connective tissue. Subcutaneous fat is very sparse beneath the preseptal portion of the eyelid skin, and absent from the more distal pretarsal portions. In the skin of the eyelid are also found other structures that can be the focus of disease processes. On the subconjunctival side of the eyelid, these structures include the accessory lacrimal glands of Krause and Wolfring beneath the conjunctiva (Figure 3.4) and the meibomian glands which are modified sebaceous glands within the tarsal plates (Figure 3.5).[2]

Eyelashes

The eyelashes protect the eye from particulate matter and wind from impacting the corneal surface. In the adult, there are about 70 to 80 lashes on the lower eyelid margin and 90 to 160 in the upper eyelid. The growth phase is short so that they fall and are replaced without attaining a length greater than 10 to 12 mm. Unlike hairs on the body, eyelashes are not associated with arrector pili muscles.[2] Many disorders can affect the eyelashes, including trichiasis, distichiasis, hypertrichosis, and poliosis, as well as several neoplastic diseases such as trichoepithelioma and trichofolliculoma.

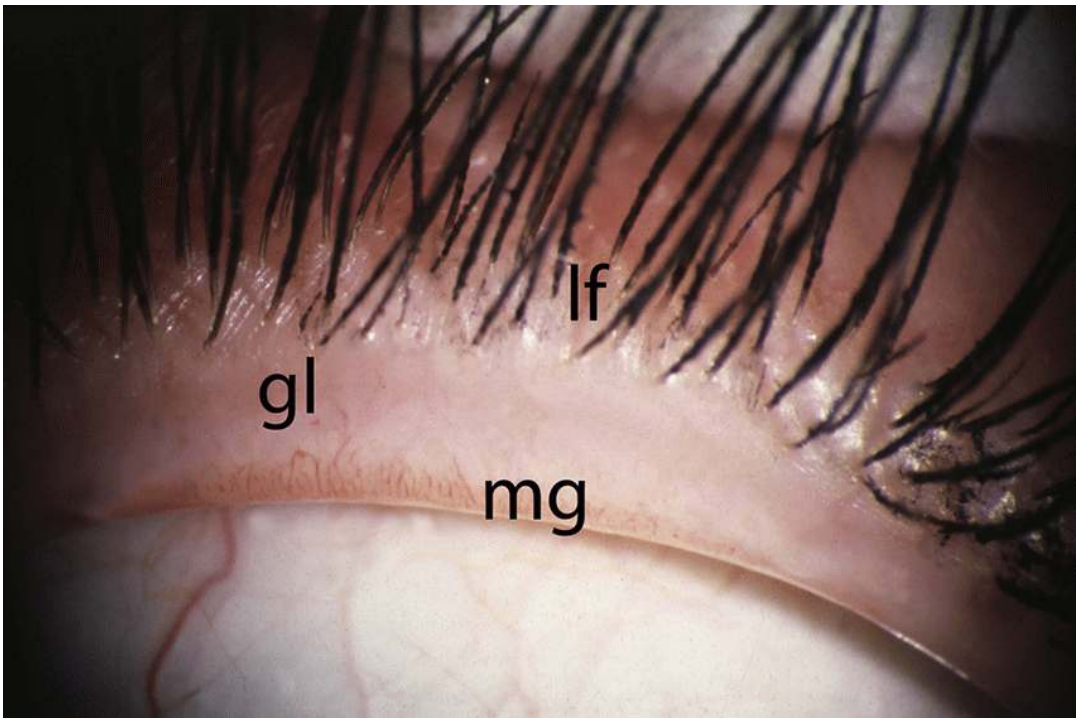

FIGURE 3.2 Eyelid margin. gl, gray line; lf, eyelash follicles; mg, meibomian gland orifices.

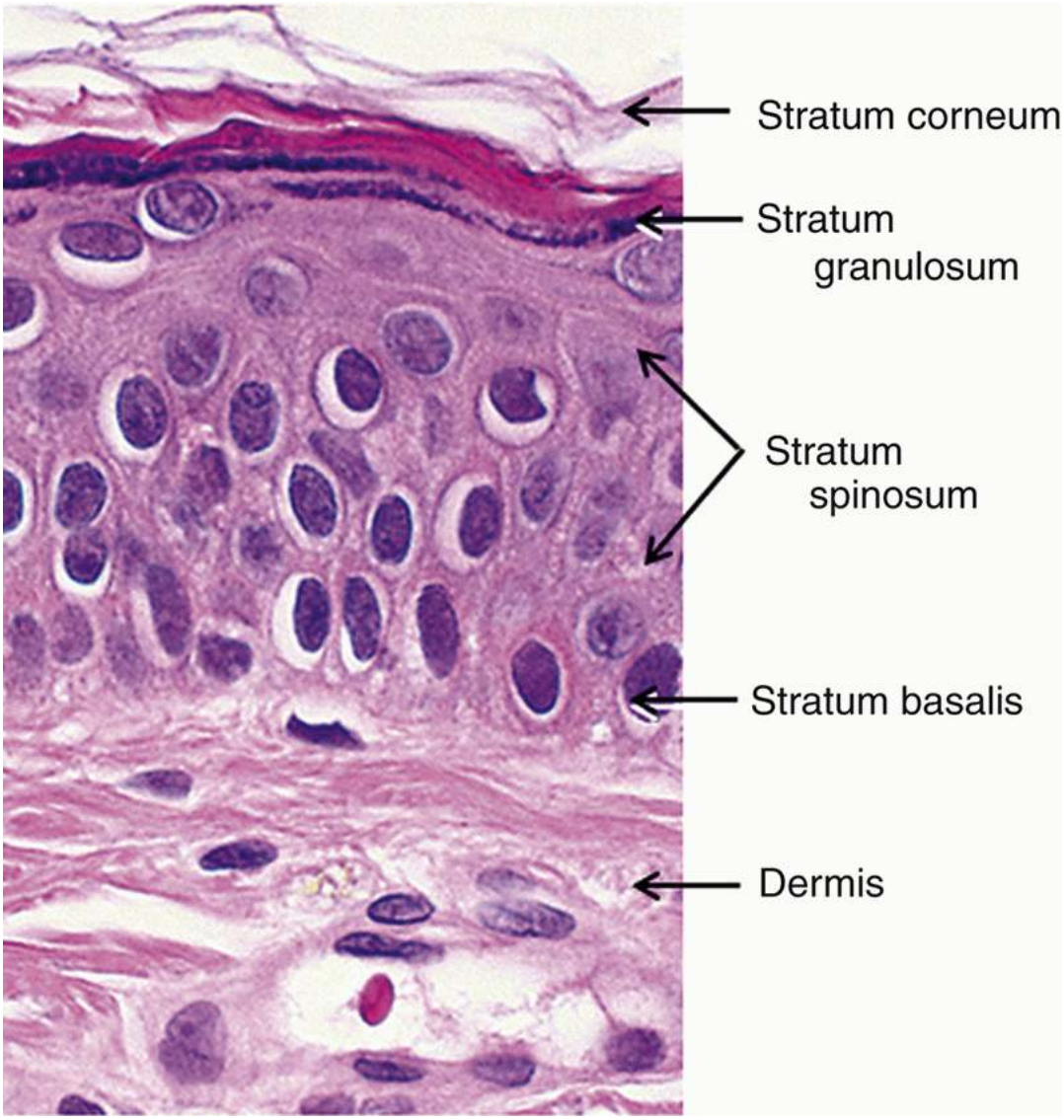

FIGURE 3.3 Histologic section showing layers of the skin.

Orbicularis Muscle

The orbicularis oculi is a complex striated muscle sheet that lies just below the skin (Figures 3.5, 3.6, 3.7). It is divided anatomically into three contiguous parts—the orbital, preseptal, and pretarsal portions (Figure 3.8). The orbital portion overlies the bony orbital rims. It arises from insertions on the frontal process of the maxillary bone, the orbital process of the frontal bone, and the common medial canthal tendon. Its fibers pass around the orbital rim to form a continuous ellipse without *(Print pagebreak 20)* interruption at the lateral palpebral commissure and insert just below their points of origin.

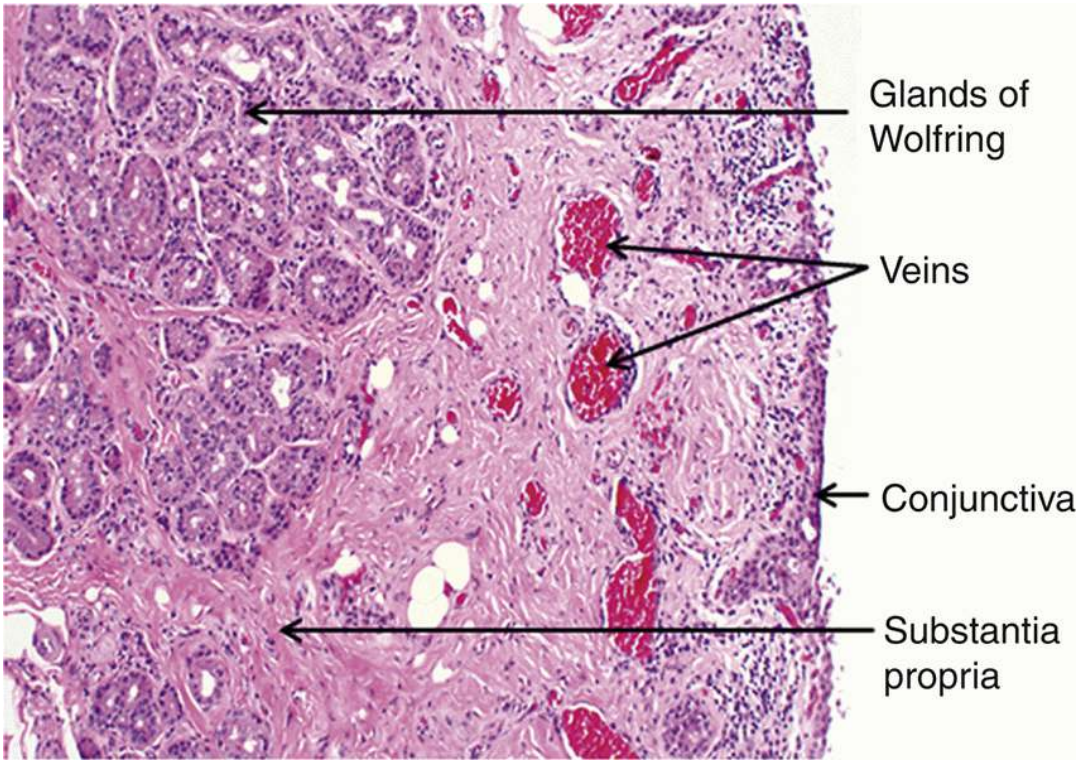

FIGURE 3.4 Histologic section of the posterior lamella of the eyelid showing the conjunctiva with numerous glands of Krause.

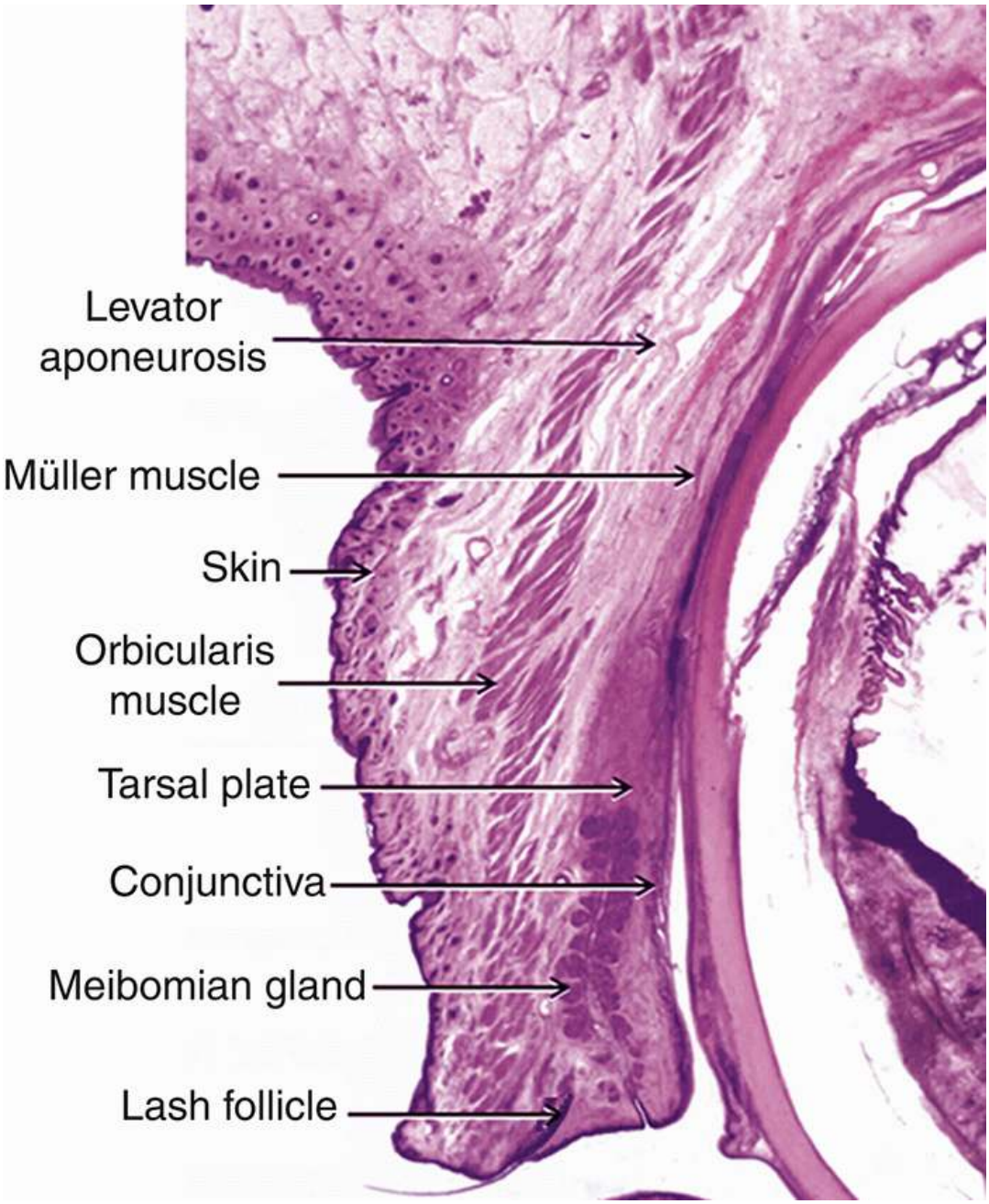

FIGURE 3.5 Full-thickness sagittal section through the upper eyelid.

The palpebral portion of the orbicularis muscle overlies the mobile eyelid from the orbital rims to the eyelid margins. The muscle fibers sweep circumferentially around each lid as a half ellipse, fixed medially and laterally at the canthal tendons. Although this portion forms a single anatomic unit in each eyelid, it is customarily further divided topographically into two parts, the preseptal and pretarsal orbicularis.[2]

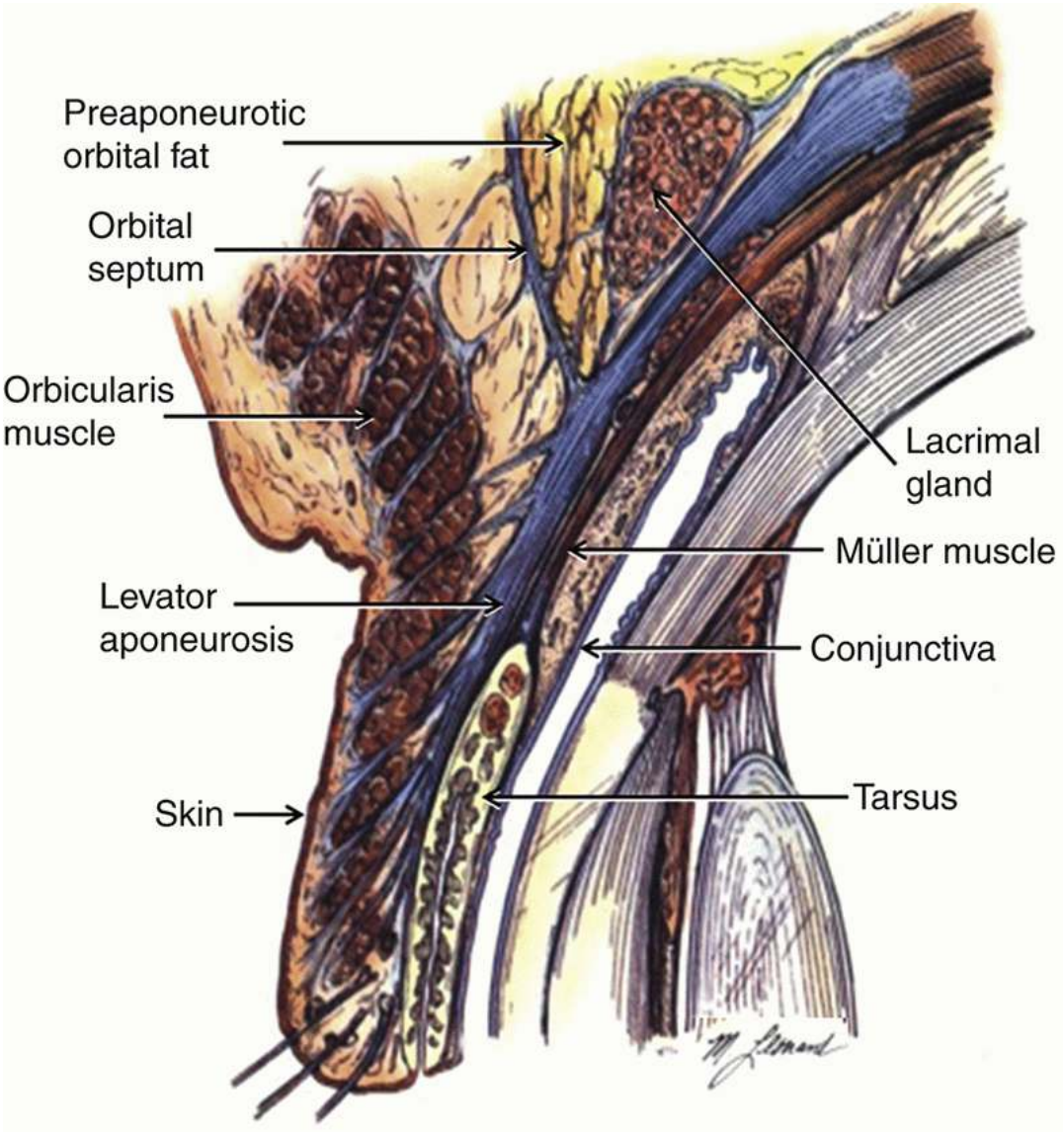

FIGURE 3.6 Drawing of the upper eyelid in cross-section.

The preseptal portion of the muscle is positioned over the orbital septum in both upper and lower eyelids, and its fibers originate perpendicularly along the upper and lower borders of the medial canthal tendon. Fibers arc around the eyelids and insert along the lateral horizontal raphé. The pretarsal portion of the muscle overlies the tarsal plates. Its fibers originate from the medial canthal tendon via separate superficial and deep heads, arch around the lids, and insert onto the lateral canthal tendon and raphé. Contraction of these fibers aids in the lacrimal pump mechanism.[2] Medially the deep heads of the pretarsal fibers fuse to form a prominent bundle of fibers, Horner muscle, that runs just behind the posterior limb of the canthal tendon. It inserts onto the posterior lacrimal crest. Horner muscle helps maintain the posterior position of the canthal angle, tightens the eyelids against the globe during eyelid closure, and may aid in the lacrimal pump mechanism.[3]

Orbital Septum

The orbital septum is a thin fibrous multilayered membrane anatomically beginning at the arcus marginalis along the orbital rim and represents a continuation of the orbital fascial system (Figure 3.9). The orbital septum originates from the arcus marginalis of the frontal bone and consists of two layers. The outer (superficial) layer descends just posterior to the orbicularis muscle to interdigitate with the levator aponeurosis via loose connective tissue. The inner (deep) layer follows the superficial one initially, but at the levator aponeurosis, it changes direction and continues posteriorly with the levator sheath.[4,5] The point of insertion is usually about 3 to 5 mm above the tarsal plate but can be as much as 10 to 15 mm.[6] In the lower eyelid the septum fuses with the capsulopalpebral fascia several millimeters below tarsus, and the common fascial sheet inserts onto the inferior tarsal edge.[7,8]

The septum can always be identified at surgery by pulling it distally and noting firm resistance against its bony attachments. Immediately behind the septum are yellow fat pockets that lie immediately anterior to the levator aponeurosis in the upper lid and the capsulopalpebral fascia in the lower lid. This anatomical relationship is important to note since identification of the levator

aponeurosis or capsulopalpebral is critical in many eyelid surgical procedures.

Preaponeurotic Fat Pockets

The preaponeurotic fat pockets in the upper eyelid and the precapsulopalpebral fat pockets in the lower eyelid are anterior extensions of extraconal orbital fat. These eyelid fat pockets are surgically important landmarks and help identify a plane immediately anterior to the major eyelid retractors. In the upper eyelid, there are typically two *(Print pagebreak 21)* fat pockets: a medial pocket and a central one. Laterally, the lacrimal gland may be mistaken for a third fat pocket (Figure 3.10). In the lower eyelid, there are three pockets: medial, central, and lateral.

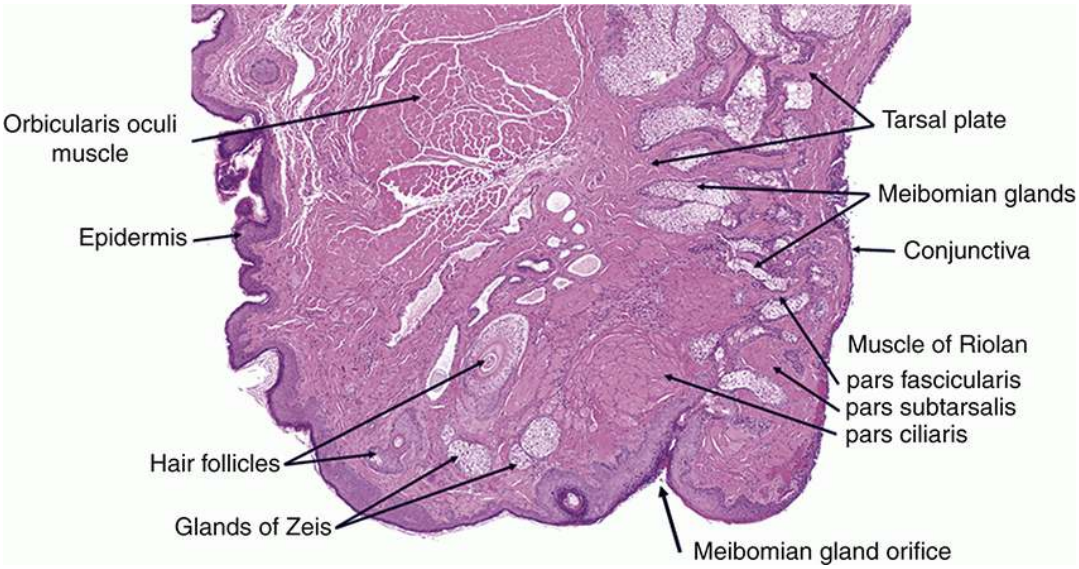

FIGURE 3.7 Sagittal section through the upper eyelid margin.

Major Eyelid Retractors

The retractors of the upper eyelid consist of the levator palpebrae and Müller muscles. The levator palpebrae superioris muscle arises from the lesser sphenoid wing just above the annulus of Zinn. The muscle runs forward in the superior orbit just above the superior rectus muscle. Near the superior orbital rim, a condensation is seen along the muscle sheath, that attaches medially and laterally to the orbital walls and soft tissues. This is the superior transverse orbital ligament of Whitnall.[9] Its exact role remains a matter of controversy, but it appears to provide some support for the fascial system that maintains spatial relationships between a variety of anatomic structures in the superior orbit.

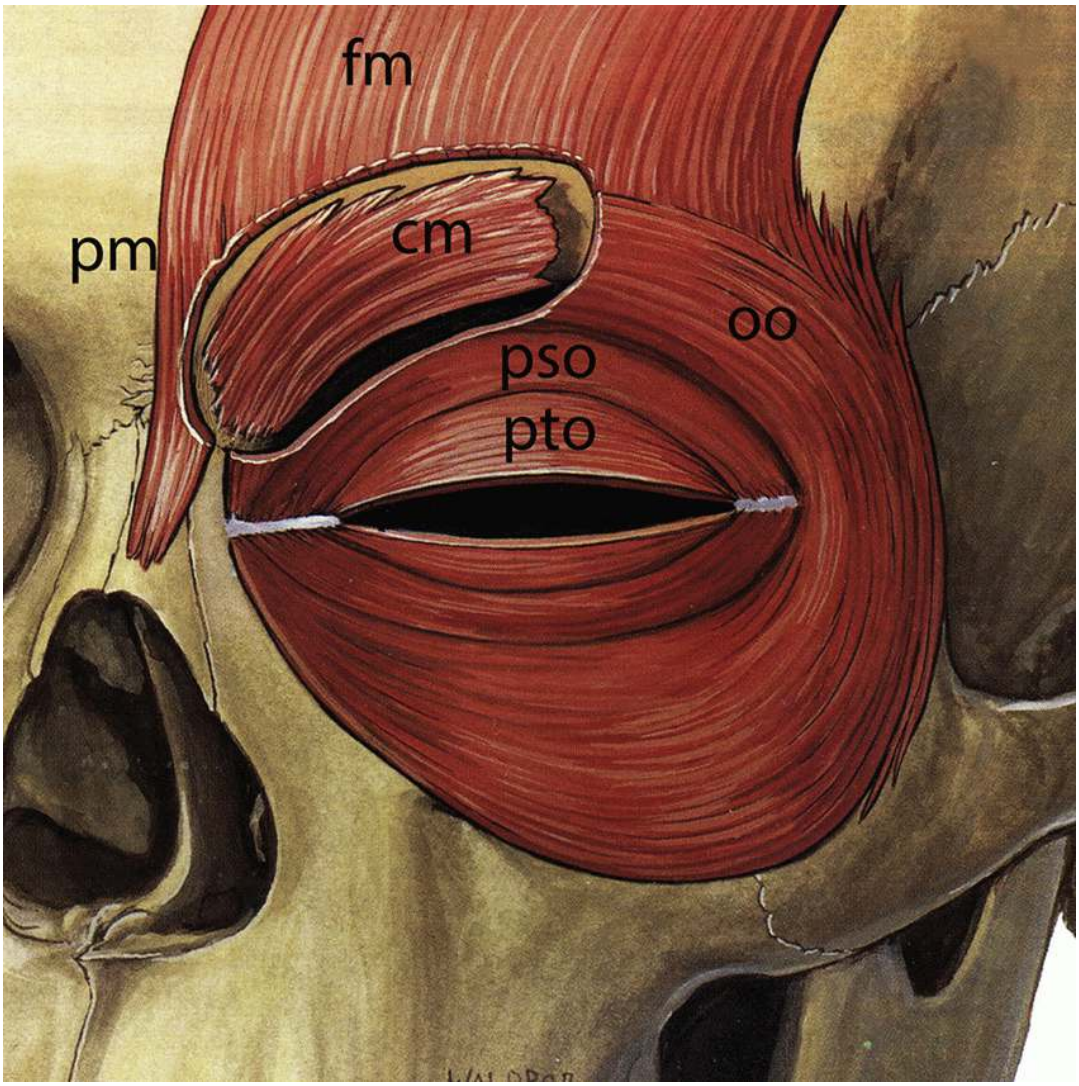

FIGURE 3.8 Muscles of eyelid closure and brow depression. cm, corrugator muscle; fm, frontalis muscle; oo, orbital portion of orbicularis muscle; pm, procerus muscle; pso, preseptal orbicularis portion of orbicularis muscles; pto, pretarsal portion of the orbicularis muscle.

From Whitnall ligament the muscle passes into its aponeurosis (Figure 3.11). This sheet continues downward 14 to 20 mm to its insertion near the marginal tarsal border. The aponeurotic fibers are most firmly attached at about 3 to 4 mm above the eyelid margin.[10,11] Beginning near the *(Print pagebreak 22)* upper edge of the tarsus, the aponeurosis also sends numerous delicate interconnecting slips forward and downward to insert onto the interfascicular septa of the pretarsal orbicularis muscle and subcutaneous tissue. These multilayered slips maintain the close approximation of the skin, muscle, aponeurosis, and tarsal lamellae, thus integrating the distal eyelid as a single functional unit. This relationship defines the upper eyelid crease of the western eyelid.

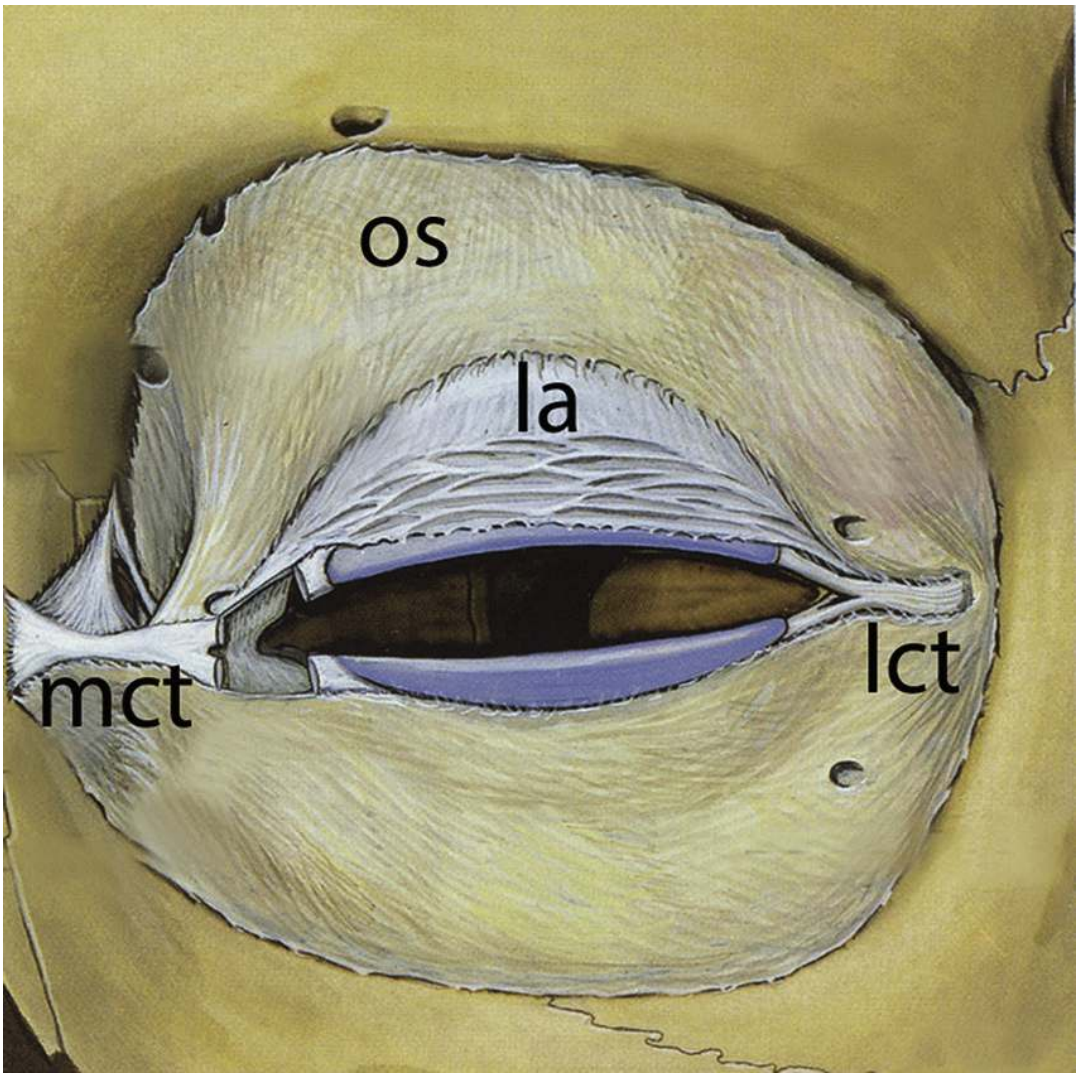

FIGURE 3.9 Orbital septum. la, levator aponeurosis; lct, lateral canthal tendon; mct, medial canthal tendon; os, orbital septum.

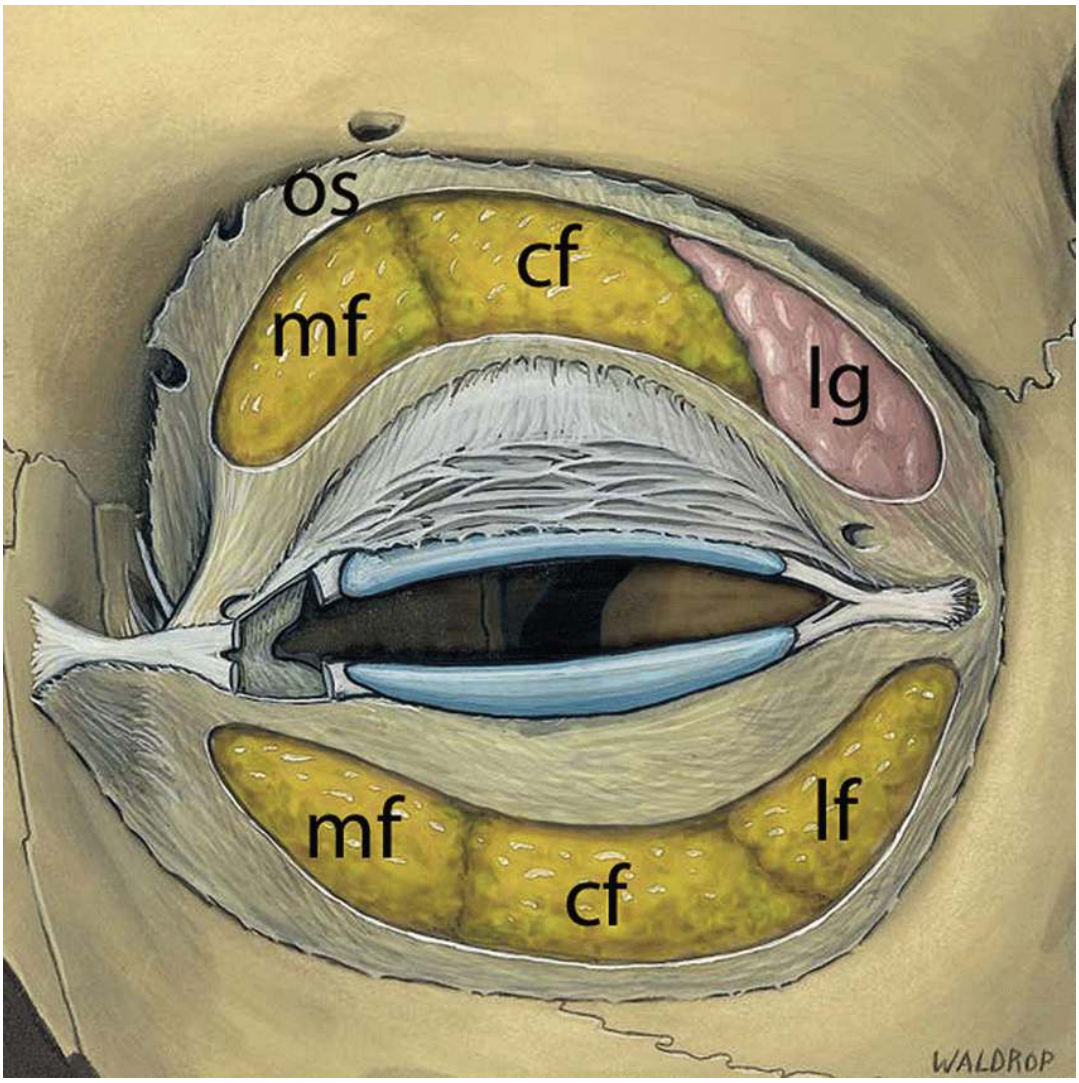

FIGURE 3.10 Anterior orbital fat pockets. cf, central fat pockets; lf, lateral fat pocket in lower eyelid; lg, lacrimal gland; mf, medial fat pockets; os, orbital septum.

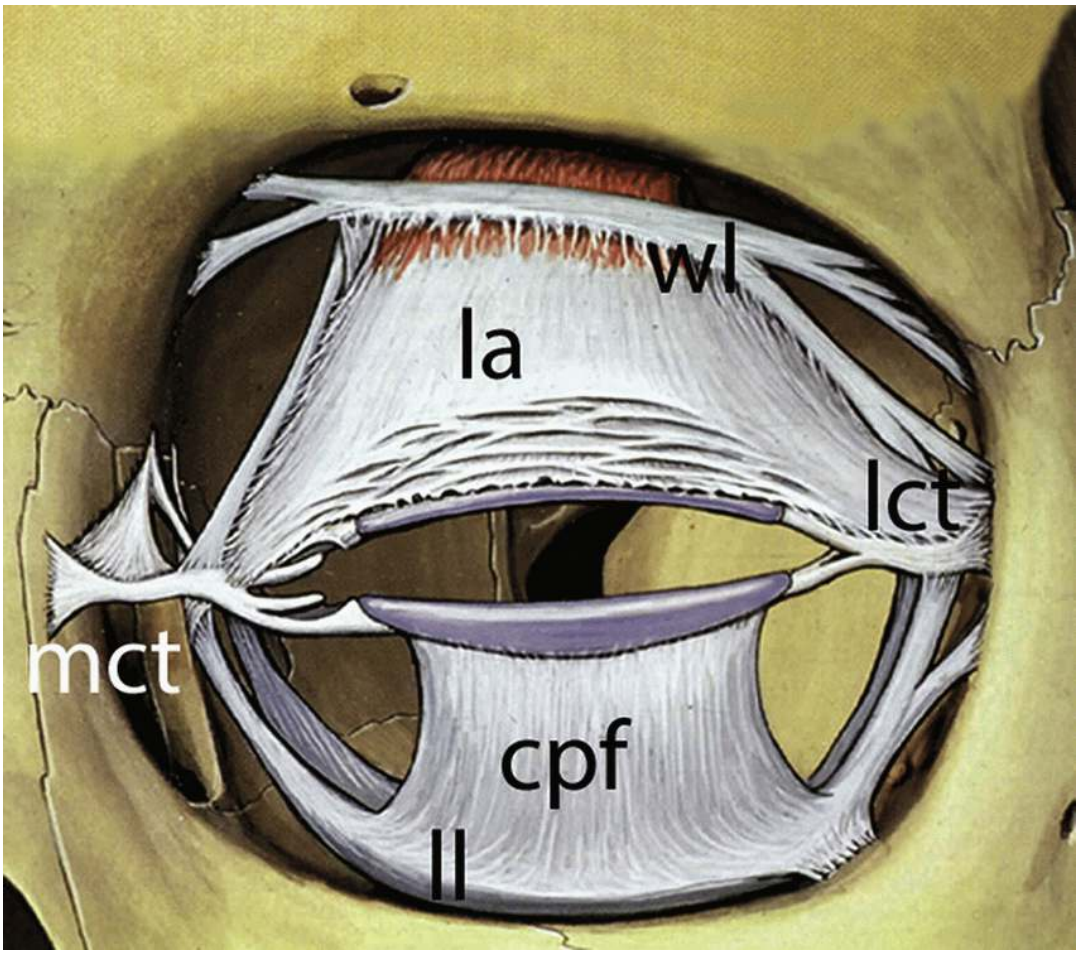

FIGURE 3.11 Anterior orbital fascial system. cpf, capsulopalpebral fascia; la, levator aponeurosis; lct, lateral canthal tendon; ll, Lockwood ligament; mct, medial canthal tendon; wl, Whitnall ligament.

As the levator aponeurosis passes into the eyelid from Whitnall ligament, it broadens to form the medial and lateral "horns." The lateral horn forms a prominent fibrous sheet that indents the posterior aspect of the lacrimal gland, defining its orbital and palpebral lobes. It inserts through numerous slips onto the lateral orbital tubercle of the zygomatic bone, at the lateral retinaculum.[2] The medial horn is less well-developed. It blends with the intermediate layer of the orbital septum and inserts onto the posterior crus of the medial canthal tendon and the posterior lacrimal crest. Together, the two horns serve to distribute the forces of the levator muscle along the aponeurosis and the tarsal plate.

In the lower eyelid, the capsulopalpebral fascia is a fibrous sheet arising from Lockwood ligament and the sheaths around the inferior rectus and inferior oblique muscles. It passes upward and generally fuses with fibers of the orbital septum about 4 to 5 mm below the tarsal plate. From this junction, a common fascial sheet continues upward and inserts onto the lower border of the tarsus. Fine fibrous slips pass forward from this fascial sheet to the orbicularis intermuscular septae and subcutaneous tissue, forming the lower eyelid crease and uniting the anterior and posterior lamellae into a single functional unit.

Sympathetic Accessory Retractors

Smooth muscles innervated by the sympathetic nervous system are present in both upper and lower eyelids and serve as accessory retractors.[12] In the upper eyelid, the supratarsal muscle of Müller originates abruptly from the undersurface of the levator muscle just anterior to Whitnall ligament (Figure 3.6).[13] It runs downward, posterior to the levator aponeurosis to which it is adherent and inserts onto the anterior edge of the superior tarsal border. In the lower eyelid, the sympathetic muscle is less well defined. Fibers run behind the capsulopalpebral fascia to insert onto the lower border of the tarsus, although they may end 2 to 5 mm below the tarsus.[14]

Disruption of sympathetic innervation to these muscles results in Horner syndrome. This is characterized by the classic triad of ptosis, miosis, and ipsilateral anhidrosis of the face. Specific clinical findings vary according to the location of the lesion along the polysynaptic pathway. The upper eyelid ptosis and elevation of the lower eyelid result from loss of sympathetic smooth muscle tone and accessory retraction.

Tarsus

The tarsal plates consist of dense fibrous tissue approximately 1 to 1.5 mm thick that gives structural integrity to the eyelids (Figures 3.5 and 3.6). Each measures about 25 mm in horizontal length and is gently curved to conform to the anterior contour of the globe. The central vertical height of the tarsal plate is 8 to 12 mm in the upper eyelid and 3.5 to 4.0 mm in the lower.[2] Medially and laterally they taper to 2 mm in height as they pass into the canthal tendon (Figure 3.12). As these *(Print pagebreak 23)* tarsal plates approach the canthal tendons, they broaden slightly toward the margin and narrow toward the proximal surface, thus assuming a more triangular cross-section. Within each tarsus are the meibomian glands, approximately 25 in the upper lid, and 20 in the lower lid (Figure 3.13). These are holocrine-secreting sebaceous glands not associated with lash follicles. Each gland is multilobulated and empties into a central ductule that opens onto the posterior eyelid margin behind the gray line (Figure 3.14). They produce the lipid layer of the precorneal tear film.

Canthal Tendons

Medially the tarsal plates pass into fibrous bands that form the crura of the medial canthal tendon. These lie between the orbicularis muscle anteriorly and the conjunctiva posteriorly. The superior and inferior crura fuse to form a stout common tendon that inserts via three limbs.[2] The anterior limb inserts onto the orbital process of the maxillary bone in front of and above the anterior lacrimal crest (Figures 3.12 and 3.15). It provides the major support for the medial canthal angle. The posterior limb arises from the common tendon near the junction of the superior and inferior crura and passes between the canaliculi. It inserts onto the posterior lacrimal crest just in front of Horner muscle. The posterior limb directs the vector forces of the canthal angle backward to maintain close approximation with the globe. The superior limb of the medial canthal tendon arises as a broad arc of fibers from both the anterior and posterior limbs. It passes upward to insert onto the orbital process of the frontal bone. The posterior head of the preseptal orbicularis muscle inserts onto this limb and the unit forms the soft-tissue roof of the lacrimal sac fossa. This tendinous extension may function to provide vertical support to the canthal angle,[15] but also appears to play a significant role in the lacrimal pump mechanism.

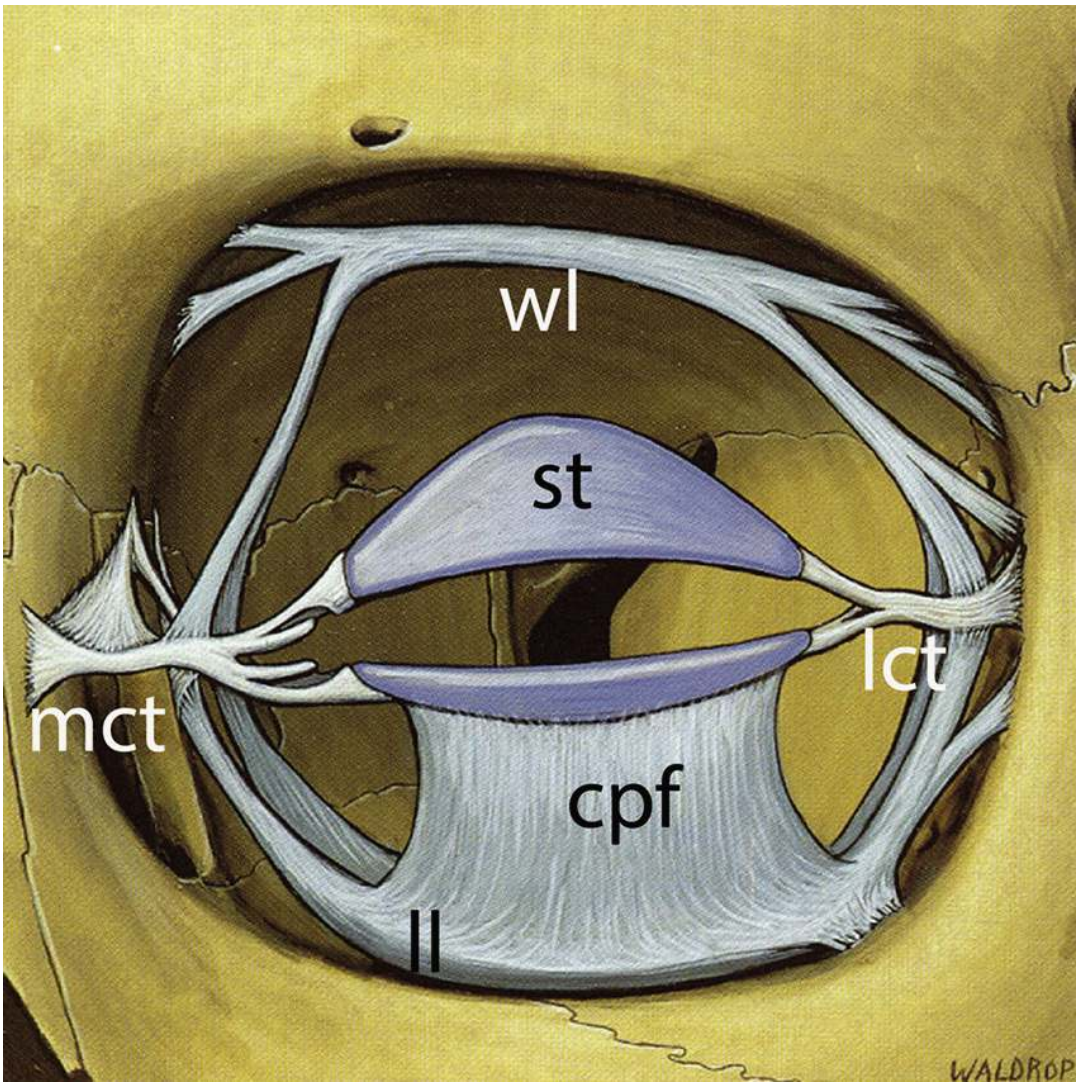

FIGURE 3.12 Canthal tendons and anterior orbital suspensory system. cpf, capsulopalpebral fascia; lct, lateral canthal tendon; ll, Lockwood ligament; mct, medial canthal tendon; st, superior tarsus; wl, Whitnall ligament.

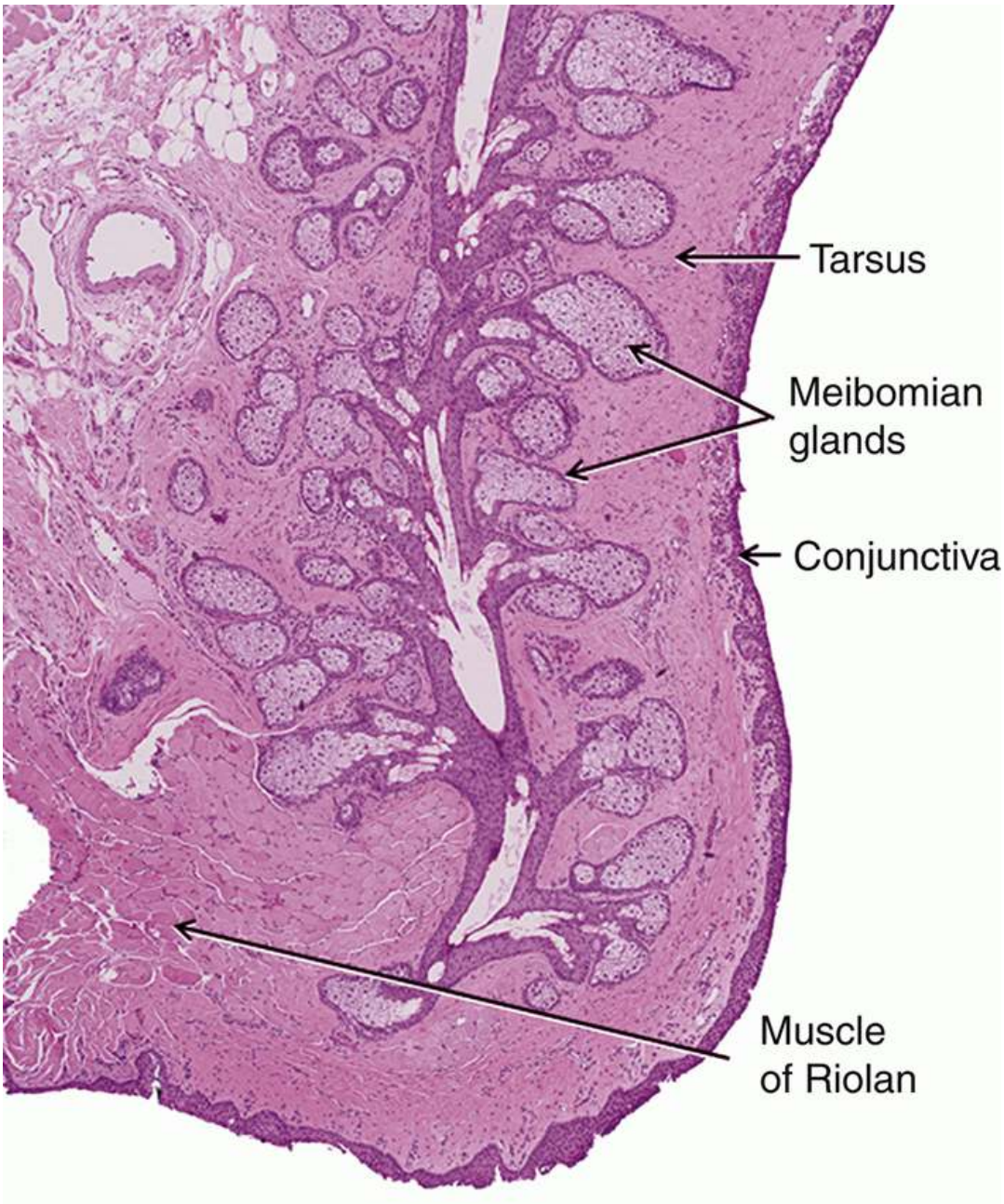

FIGURE 3.13 Marginal section of the upper eyelid showing the tarsal plate and meibomian glands.

Laterally the tarsal plates pass into less well-developed fibrous strands that become the crura of the lateral canthal tendon. The lateral canthal tendon is a distinct entity separate from the orbicularis muscle and measures about 1 mm *(Print pagebreak 24)* in thickness, 3 mm in vertical width, and approximately 5 to 7 mm in length.[16] Insertion of these fibers extends posteriorly along the lateral orbital wall where it blends with strands of the lateral check ligament from the sheath of the lateral rectus muscle.

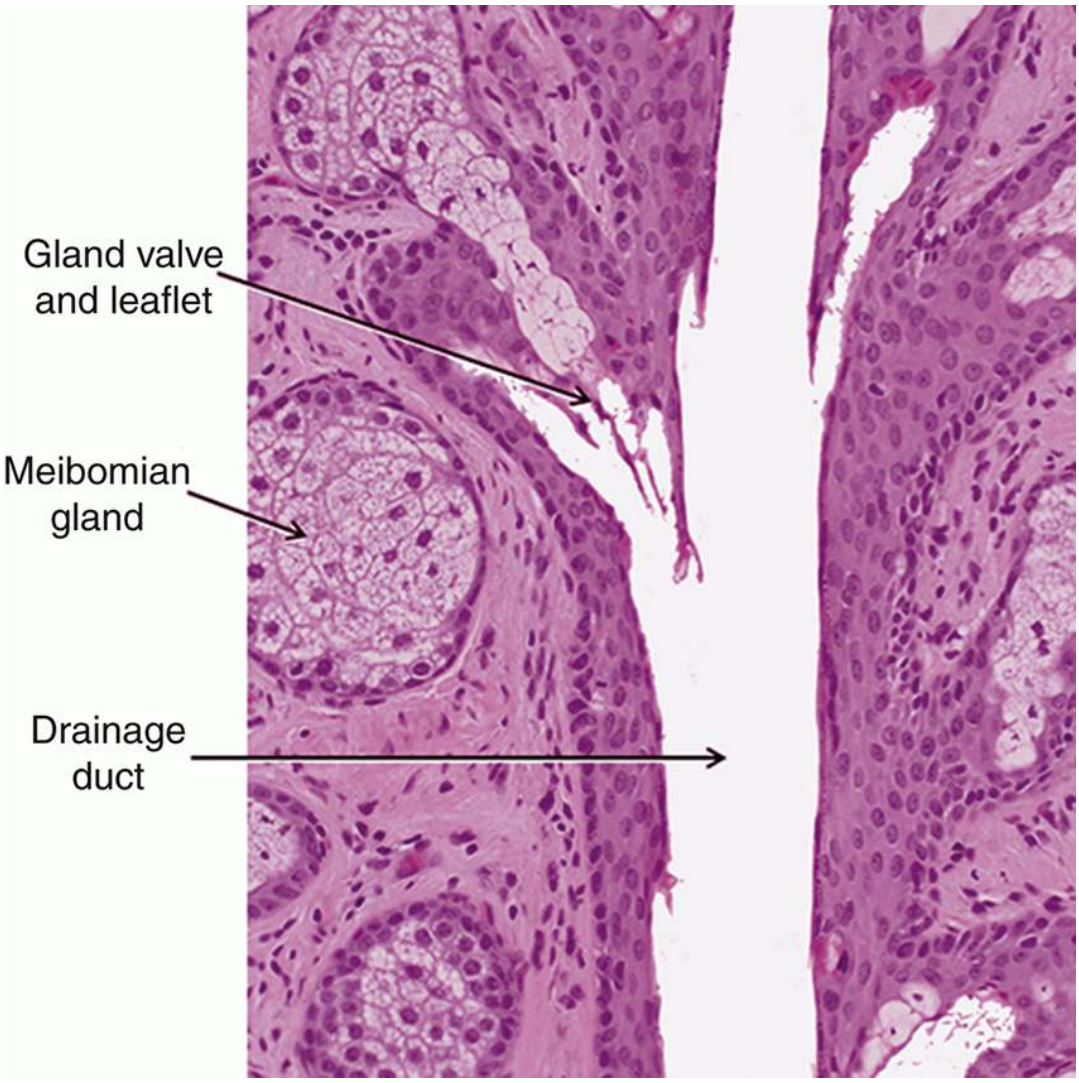

FIGURE 3.14 Detailed section through a meibomian gland ductile.

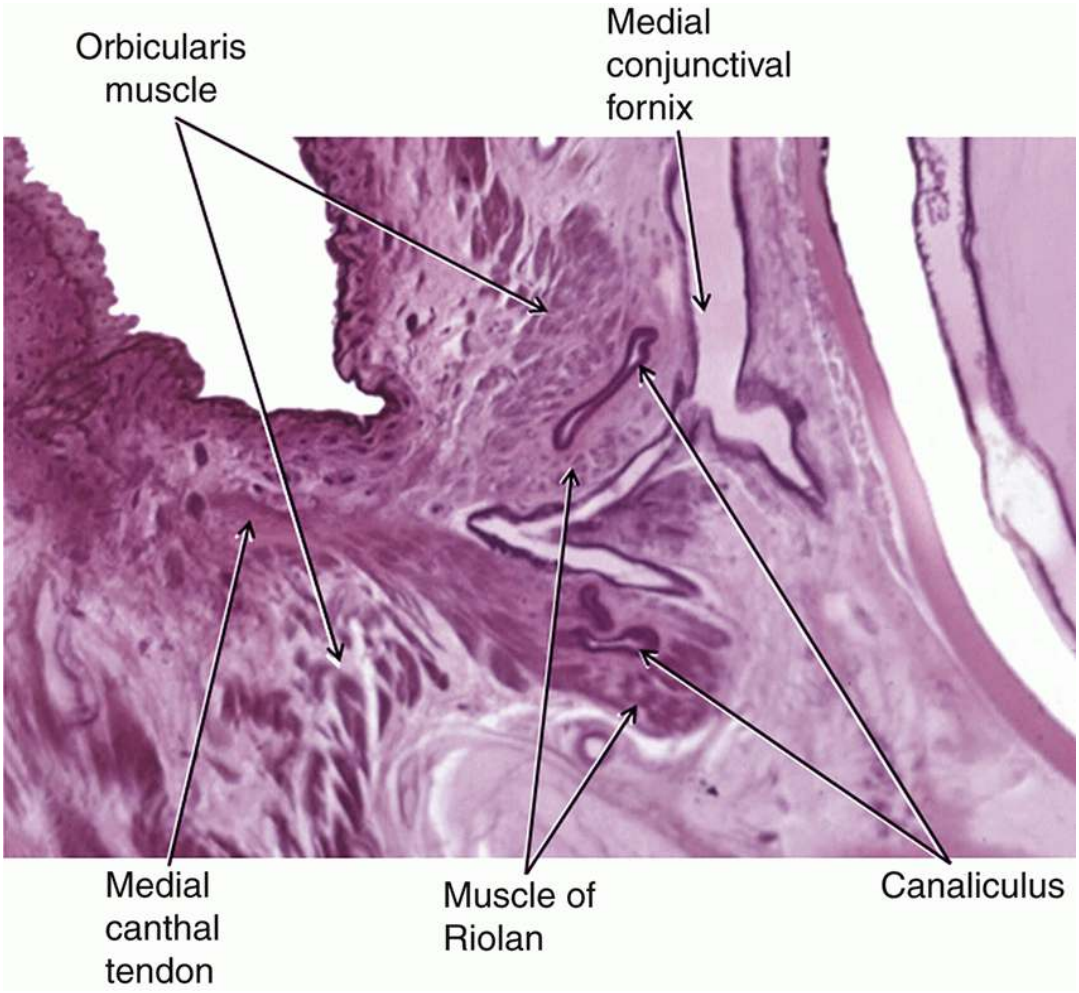

FIGURE 3.15 Histologic section through the medial canthus at the level of the anterior crus of the medial canthal tendon and lacrimal canaliculi.

Conjunctiva

The conjunctiva is a mucous membrane that covers the posterior surface of the eyelids and the anterior pericorneal surface of the globe. The palpebral portion is closely applied to the posterior surface of the tarsal plate and the sympathetic tarsal muscle of Müller. It is continuous around the fornices above and below where it joins the bulbar conjunctiva. Small accessory lacrimal glands are located within the submucosal connective tissue (Figure 3.4).

At the medial canthal angle is a small mound of tissue, the caruncle. This consists of modified skin containing fine hairs, sebaceous glands, and sweat glands. Just lateral to the caruncle is a vertical fold of conjunctiva, the plica semilunaris. The submucosa contains adipose cells and smooth muscle fibers resembling the nictitating membrane of lower vertebrates. This likely represents a vestigial structure that has been modified to allow enough horizontal slack at the shallow medial fornix for rotation of the globe.

Nerves to the Eyelids

The motor nerves to the orbicularis muscle derive from the facial nerve (N. VII) through its temporal and zygomatic branches (Figure 3.16). The facial nerve divides into two divisions: an upper temporofacial division and a lower cervicofacial division.[17] The upper division further subdivides into the temporal and zygomatic branches that innervate the frontalis and orbicularis muscles. The lower cervicofacial division gives rise to the buccal, mandibular, and cervical branches, innervating muscles of the lower face and neck. There is variation in branching patterns, and in some individuals, extensive anastomoses interconnect all these peripheral branches.

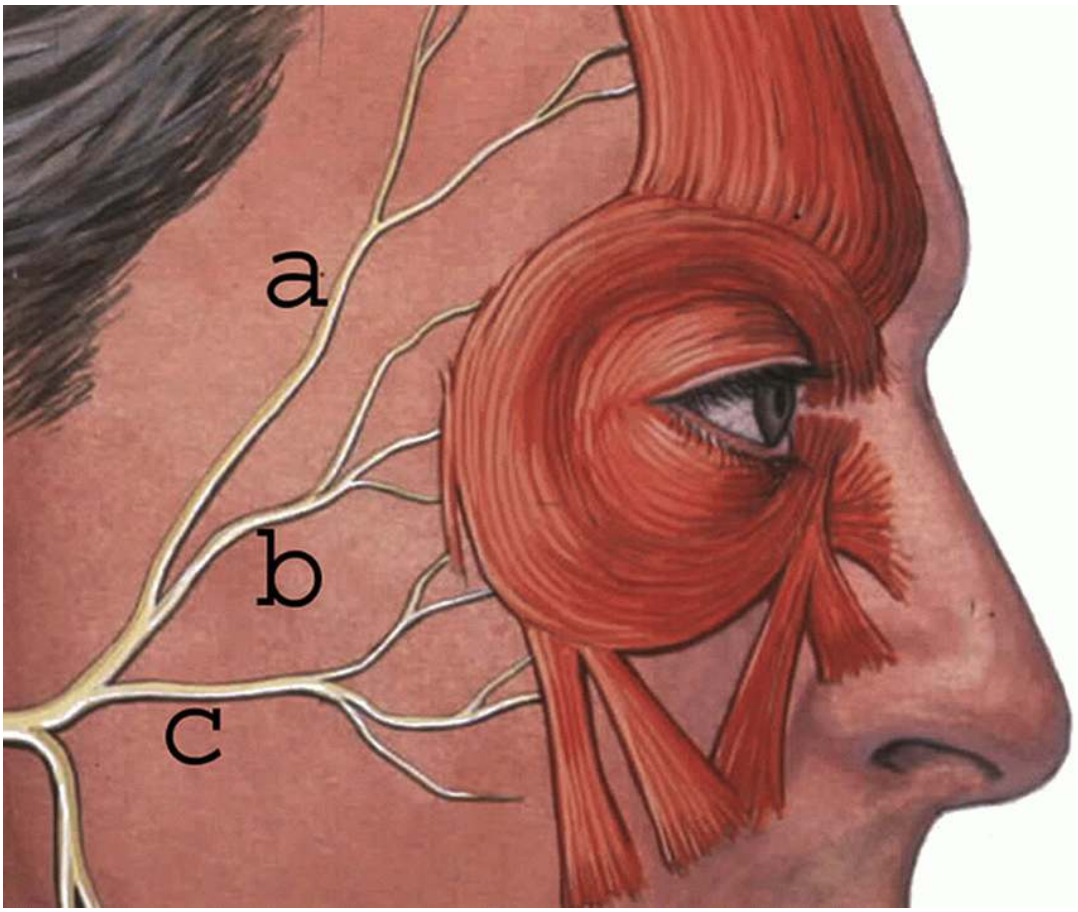

FIGURE 3.16 Motor branches of the facial nerve (CN VII) to the eyelid and brow muscles. a, Frontal branch. b, Zygomatic branch. c, Buccal branch.

The sensory nerves to the eyelids derive from the ophthalmic and maxillary divisions of the trigeminal nerve. Sensory input from the upper lid passes to the ophthalmic division primarily through its main terminal branches, the supraorbital, supratrochlear, and lacrimal nerves. The infratrochlear nerve receives sensory information from the extreme medial portion of both upper and lower eyelids. The zygomaticotemporal branch of the lacrimal nerve innervates the lateral portion of the upper eyelid and temple. These branches also innervate portions of the adjacent brow, forehead, and nasal bridge. The lower eyelid sends sensory impulses to the maxillary division via the infraorbital nerve. The zygomaticofacial branch from the lacrimal nerve innervates the lateral portion of the lower lid, and part of the infratrochlear branch receives input from the medial lower lid.

Vascular Supply to the Eyelids

Vascular supply to the eyelids is extensive. The posterior eyelid lamellae receive blood through the vascular arcades. In the upper eyelid, a marginal arcade runs about 2 mm from the eyelid margin, and a peripheral arcade extends along the upper border of the tarsus between the levator aponeurosis and Müller muscle (Figure 3.17). These are supplied medially by the superior medial palpebral vessel from the terminal ophthalmic artery and laterally by the superior lateral palpebral vessel from the lacrimal artery. The lower lid arcade *(Print pagebreak 25)* receives blood from the medial and lateral inferior palpebral vessels.

The venous drainage system is less well-defined than the arterial system. Drainage is largely into several large vessels of the facial system (Figure 3.18). Lymphatic drainage from the eyelids is restricted to the region anterior to the orbital septum. Drainage from the lateral two-thirds of the upper eyelid and the lateral one-third of the lower eyelid is inferior and lateral into the deep and superficial parotid and submandibular nodes. Drainage from the medial one-third of the upper eyelid and the medial two-thirds of the lower eyelid is medially and inferiorly into the anterior cervical nodes. Extensive excision of subcutaneous eyelid tissues or deep incisions in the inferolateral eyelid area may result in persistent lymphedema due to disruption of these vessels.

Lymphatics from the eyelids drain into two groups of vessels. Traditionally, it has been thought that the lateral two-thirds of the upper eyelid and the lateral one-third of the lower eyelid drain into the superficial and deep preauricular and submandibular nodes and then into the deep cervical nodes. The medial one-third of the upper eyelid and medial two-thirds of the lower eyelid drain into the submaxillary lymph nodes and then into the anterior cervical nodes (Figure 3.19). More recent studies have suggested that this classic concept may not be accurate, and drainage may be less precisely defined. Using lymphoscintigraphy, it has been shown that

in 72% of patients drainage was into the preauricular nodes, regardless of where around the eyelids the injection was given, and 90% of study patients did not follow the classic drainage pattern.[18]

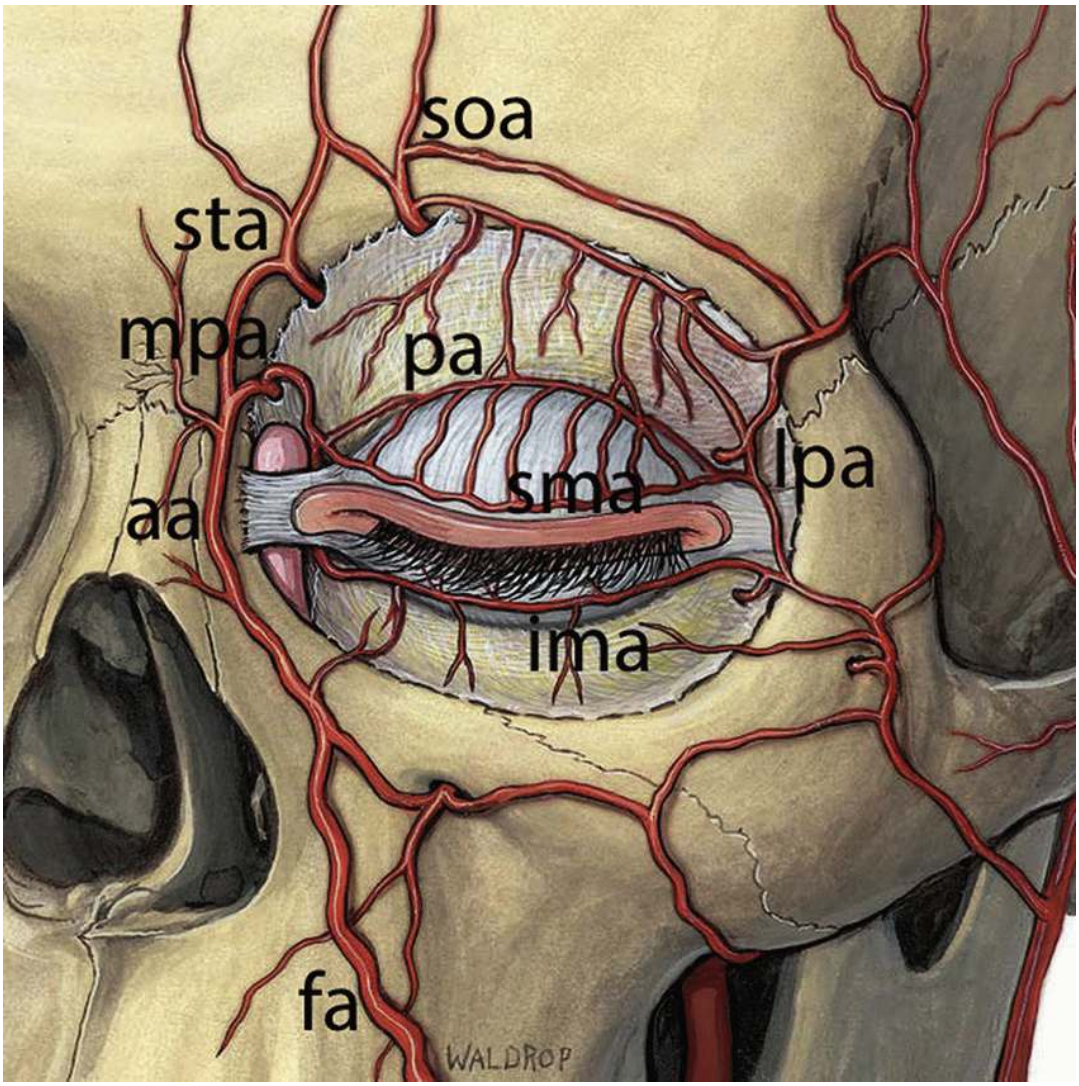

FIGURE 3.17 Arterial supply to the eyelids. aa, angular artery; fa, facial artery; ima, inferior marginal arcade; lpa, lateral palpebral artery; mpa, medial palpebral artery; pa, superior peripheral arcade; sma, superior marginal arcade; soa, supraorbital artery; sta, supratrochlear artery.

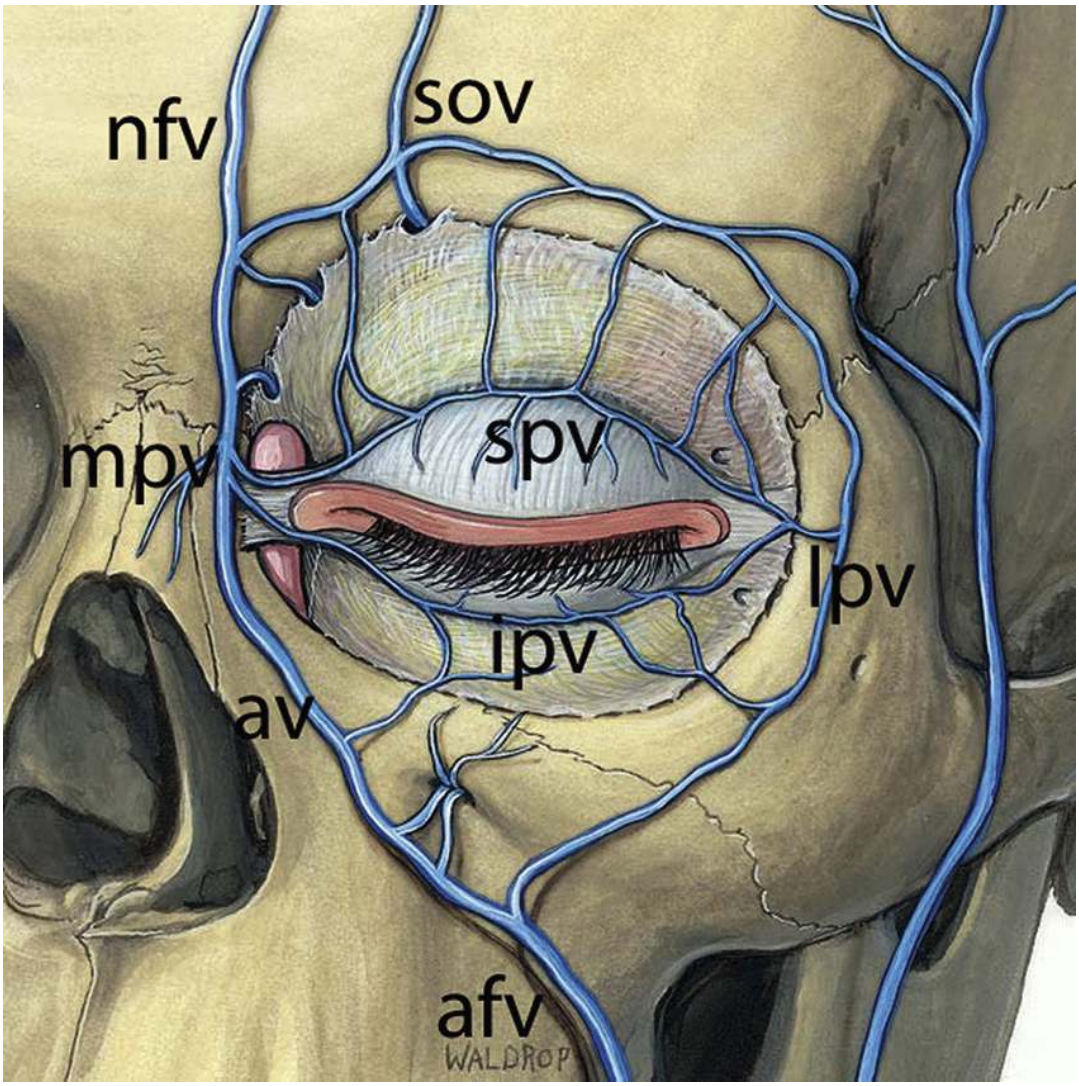

FIGURE 3.18 Venous supply from the eyelids. afv, anterior facial vein; av, angular vein; ipv, inferior peripheral venous arcade; lpv, lateral palpebral vein; mpv, medial palpebral vein; nfv, nasofacial vein; sov, supraorbital vein; spv, superior peripheral venous arcade.

Lacrimal Drainage Apparatus

The lacrimal drainage system is a complex structure that spans the distance from the medial eyelids to the inferior nasal meatus. Tears enter the system at the puncta, propelled by a pump mechanism that involves the orbicularis muscle *(Print pagebreak 26)* and the blink cycle, as well as aerodynamic pressure changes in the lacrimal sac, duct, and nose.

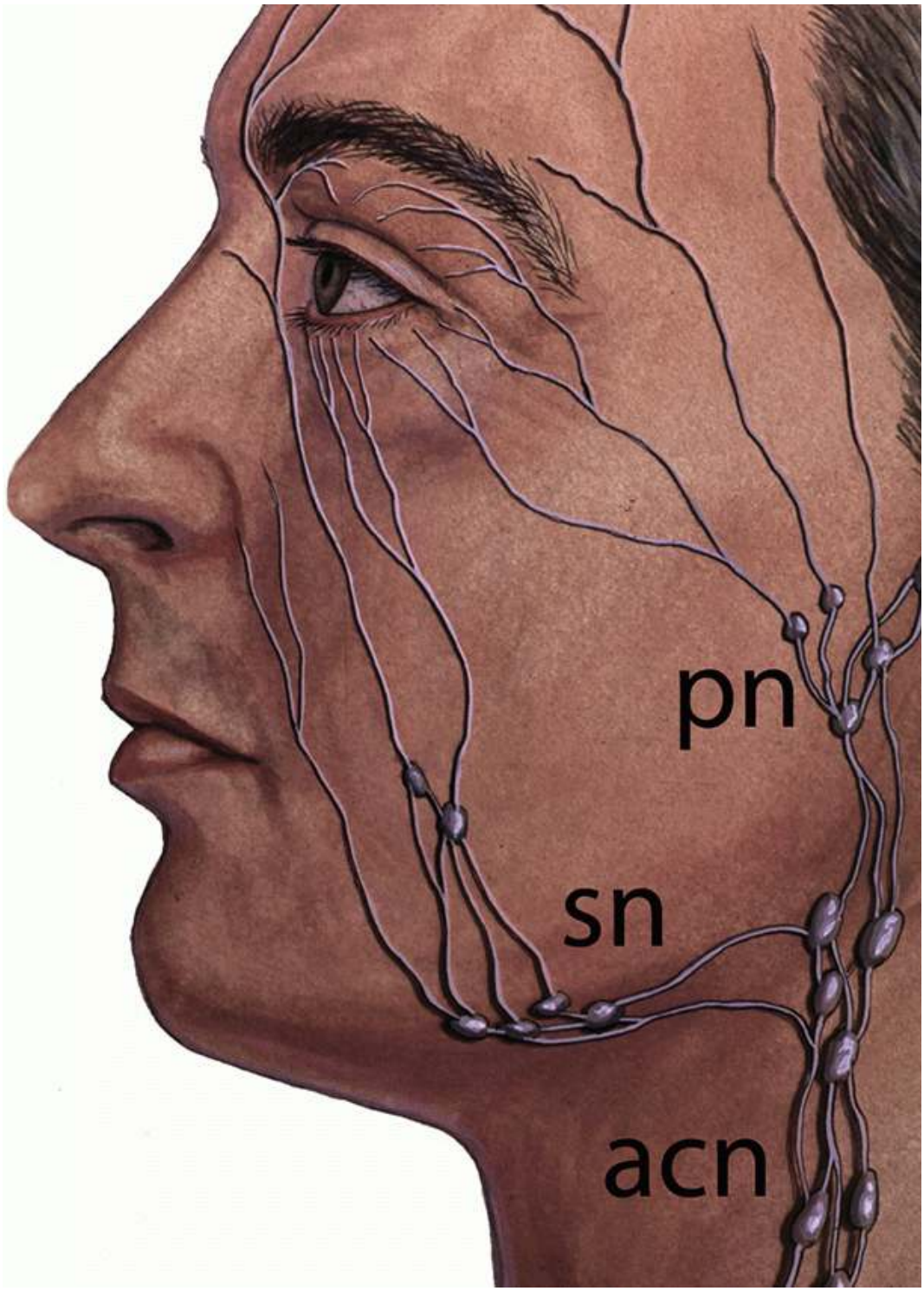

FIGURE 3.19 Lymphatic drainage from the eyelids. acn, anterior cervical nodes; pn, parotid (preauricular) nodes; sn, submandibular nodes.

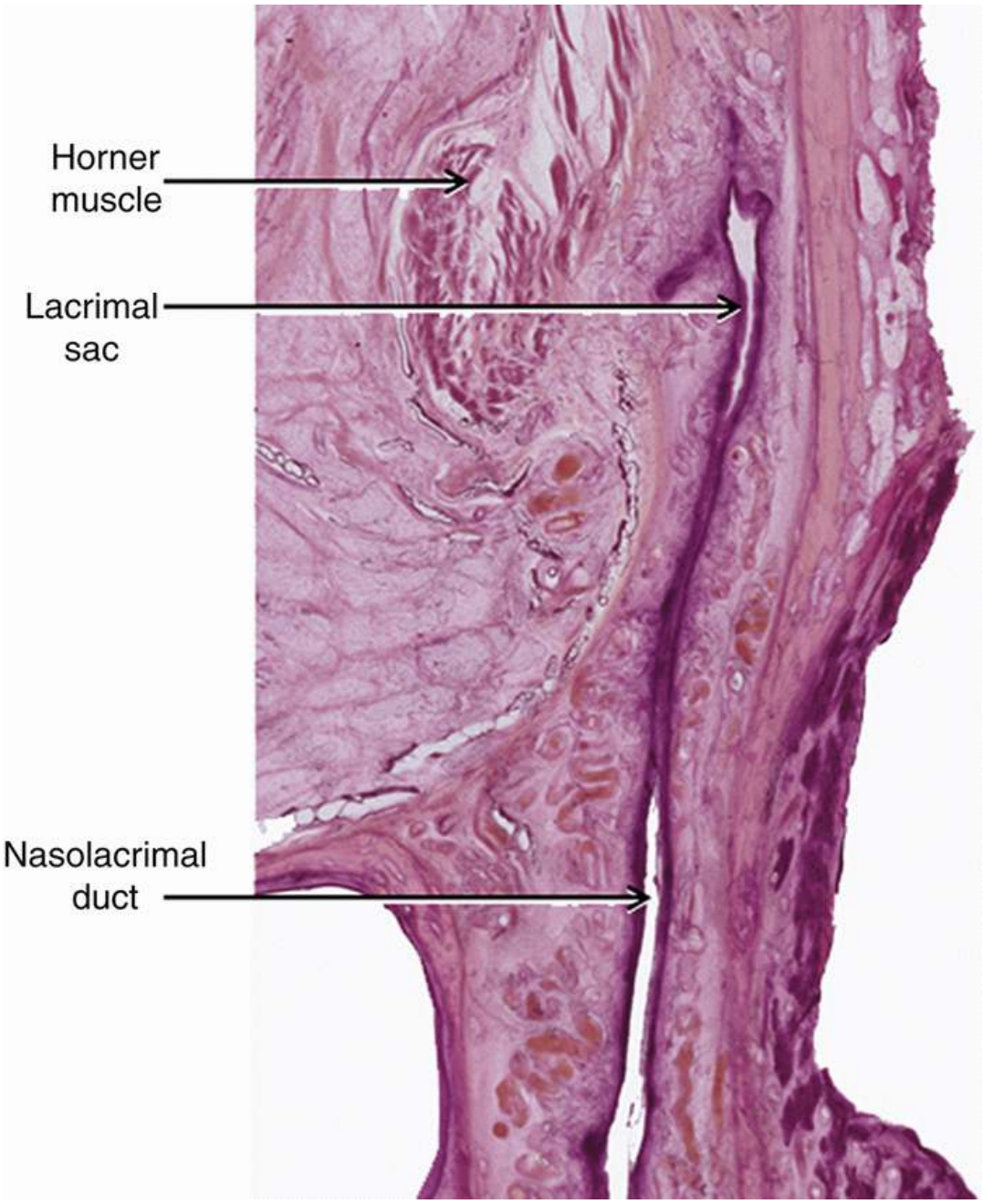

FIGURE 3.20 Longitudinal histologic section through the medial canthus and lacrimal sac and duct with Horner muscle.

The lacrimal puncta are situated on the upper and lower eyelid mucocutaneous margins 5 to 6 mm from the medial canthal angle (Figure 3.1). They measure 0.2 to 0.3 mm in diameter and open into a 2 mm vertical canalicular segment called the ampulla. The canaliculi then make a 90° turn medially, and run about 8 to 9 mm where they join as a common canalicular duct in about 90% of normal individuals.[2] In the other 10%, the upper and lower canaliculi enter the lacrimal sac independently. Along this horizontal path, the canaliculi are partially invested by a specialized portion of the orbicularis muscle, the muscle of Riolan (Figure 3.15), that merge to form Horner muscle (more appropriately Horner-Duverney muscle)[19,20] as it passes posteriorly to the posterior lacrimal crest (Figure 3.20). These muscles aid in the lacrimal pump mechanism with each eyelid blink.

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CHAPTER 4

Eyelid Lesions and Their Origin in Eyelid Tissues

There are a great many different types of lesions that occur in the eyelids. Numerous, sometimes confusing names have been applied to different tumors that often offer little help for identification or management. Placing such lesions into a more or less organized system based on anatomical tissues of origin can help the clinician understand the etiology of these diseases.[1]

Lesions arising in the eyelids can be thought of as originating from two sources. Those that grow in the eyelids but derive from remote sources in the body are *exogenous* lesions and include metastatic tumors from sites such as the breast, lung, or prostate. Infiltrative lesions also are exogenous to the eyelid and only secondarily involve eyelid structures. Included here are diseases such as amyloidosis, sarcoidosis, infectious inflammations such as herpes and cellulitis, xanthelasmas, acute atopic dermatitis, erythema multiforme, granuloma annulare, and lymphoid and myeloid infiltrates. All exogenous lesions disturb the normal eyelid architecture to varying degrees and may be generalized throughout the eyelid or be confined to specific locations of eyelid tissues.

The majority of lesions seen on the eyelids are *endogenous*, derived from normal eyelid tissues and structures. The epidermis is the source of a large number of lesions that characteristically disturb the fine wrinkles and pores that are normally seen on the skin surface (Figure 4.1). These include many common cutaneous malignancies. Basal cell carcinoma arises from the basal cells in the deep epidermis. Squamous cell carcinoma is derived from stratified squamous cells of the epidermis. Malignant melanoma develops from melanocytes that normally reside in the basal epidermis, but some may arise from dermal nevoid cells.

Of the benign lesions that arise from the epidermis, many clinically look similar. Some may remain within the epidermis, whereas others may extend deeply into the underlying dermis. Epidermal lesions include papilloma, actinic keratosis, seborrheic keratosis, inverted follicular keratosis, ichthyosis, keratoacanthoma, lentigo, molluscum contagiosum, and acquired melanosis.[1] When epidermal cells become buried beneath the surface, keratin can accumulate to form an epidermoid cyst.

The dermis is composed largely of collagen with a small number of elastin fibers. Few lesions arise directly from these two materials, but the dermis is frequently involved with infiltrative and other processes (Figure 4.2). In angioedema, the dermis is edematous with an inflammatory cell infiltrate. White blood cell infiltration also predominates in blepharitis, cellulitis, and insect bite and sting reactions. Leukemic infiltrates also accumulate within the dermal stroma.

Although melanocytes usually migrate to the epidermis during embryogenesis, they can arrest in the dermis where they can form pigmented dermal lesions. These include the junctional and compound nevi located at the epidermal/dermal junction and dermis respectively, common blue nevus and cellular blue nevus within the dermis, and oculodermal melanocytosis. Lymphatic malformations arise from lymphatic endothelium within the dermis. Several lesions occur in the dermis but are of uncertain cellular etiology. Among these, the cylindroma may have eccrine relationships but also involves the dermal collagen to a large extent. Dermatofibroma demonstrates some relationship to fibroblasts, but its specific etiology remains uncertain. The origin of Merkel cell tumors remains controversial, but they appear to have neuroendocrine relationships. Myxomas have an association with dermal fibroblasts that secrete the surrounding matrix, but their cellular etiology remains unclear. Microcystic adnexal carcinoma is derived from dermal ductal elements but also includes epidermal relationships.

The dermis also contains epithelial appendage structures that are a source of many eyelid lesions. The pilosebaceous unit consists of the hair follicle and associated holocrine sebaceous glands and apocrine sweat glands of Moll. All of these structures can be the site of origin for eyelid lesions. The diverse cellular components of this apparatus can give rise to many different lesions that can look similar clinically. Lesions can be grouped into four categories depending upon their differentiation toward sebaceous, hair follicle, apocrine, or eccrine tissues. Within these groups, lesions are further subdivided into hyperplasias, hamartomas, adenomas, and carcinomas.

The hair follicle is a tubule with root cells at the base around the papilla and bulb (Figure 4.3). Higher up, follicular epithelium lines the follicle, and finally cortical cells lay down the outer keratin layers to the hair shaft. Tumors arising from proliferations of cortical cells are termed pilomatrixomas. Solid proliferations of follicular cells manifest as trichofolliculomas, whereas obstruction of the follicle results in a cystic lesion called trichilemmal cyst. Solid tumors arising from the basal epithelial bulb are trichoepitheliomas.

Large sebaceous glands empty into the hair follicle (Figure 4.4) and proliferation of the secretory epithelium produces solid dermal tumors called sebaceous adenomas. Occasionally *(Print pagebreak 28)* the excretory duct becomes blocked with accumulation of sebum, producing a sebaceous duct cyst. More commonly, however, the obstruction is higher up in the follicle, in which case the

cyst still contains some sebum but the epithelial lining adds keratin and leads to an epidermoid (infundibular) or trichilemmal (pilar) cyst. Apocrine sweat glands of Moll normally produce a somewhat viscous secretion that empties into the hair follicle (Figure 4.5). Solid tumors arising from the secretory epithelium give rise to apocrine adenomas. If the duct becomes obstructed, a cyst results that can have a layered precipitate of cellular debris. These are apocrine hidrocystomas.

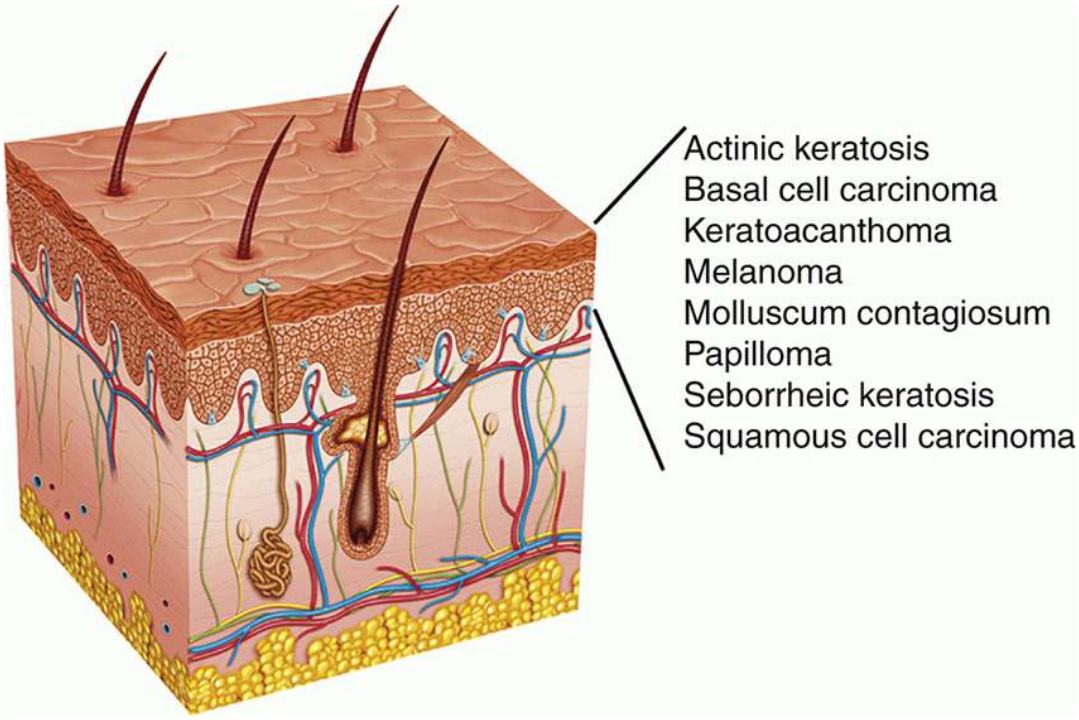

FIGURE 4.1 Cutaneous lesions arising from the epidermis.

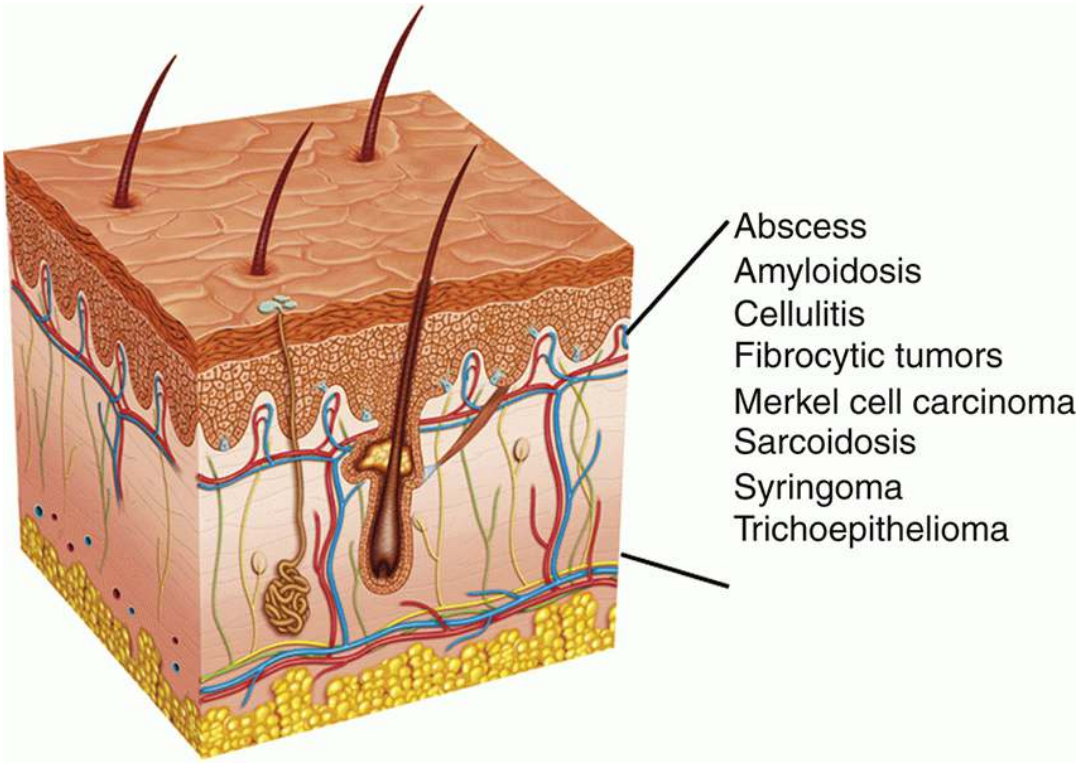

FIGURE 4.2 Lesions arising in the dermis.

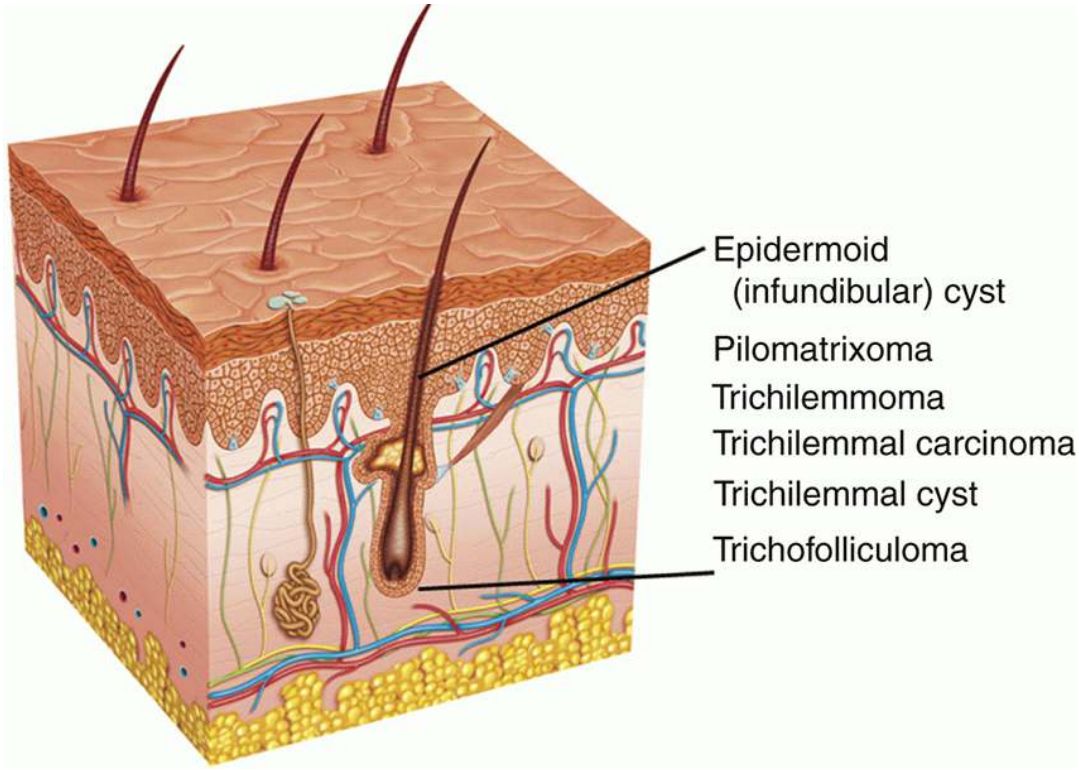

FIGURE 4.3 Tumors and cysts arising from the hair follicle.

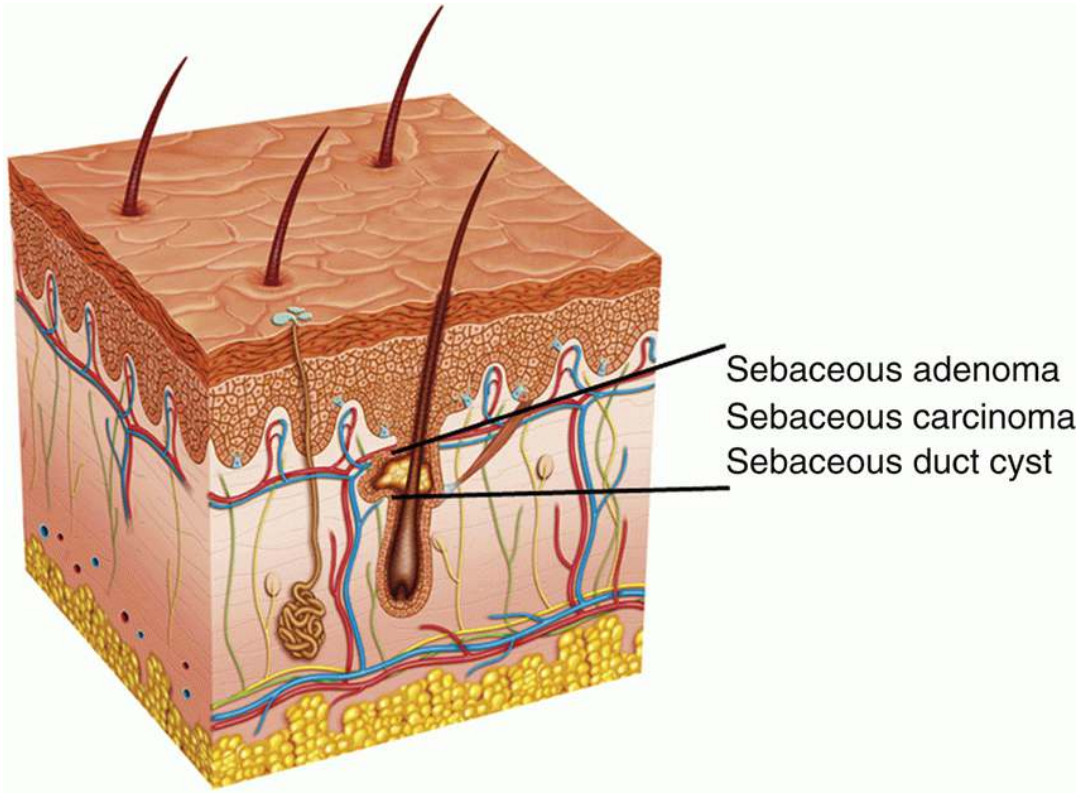

FIGURE 4.4 Lesions arising within sebaceous glands.

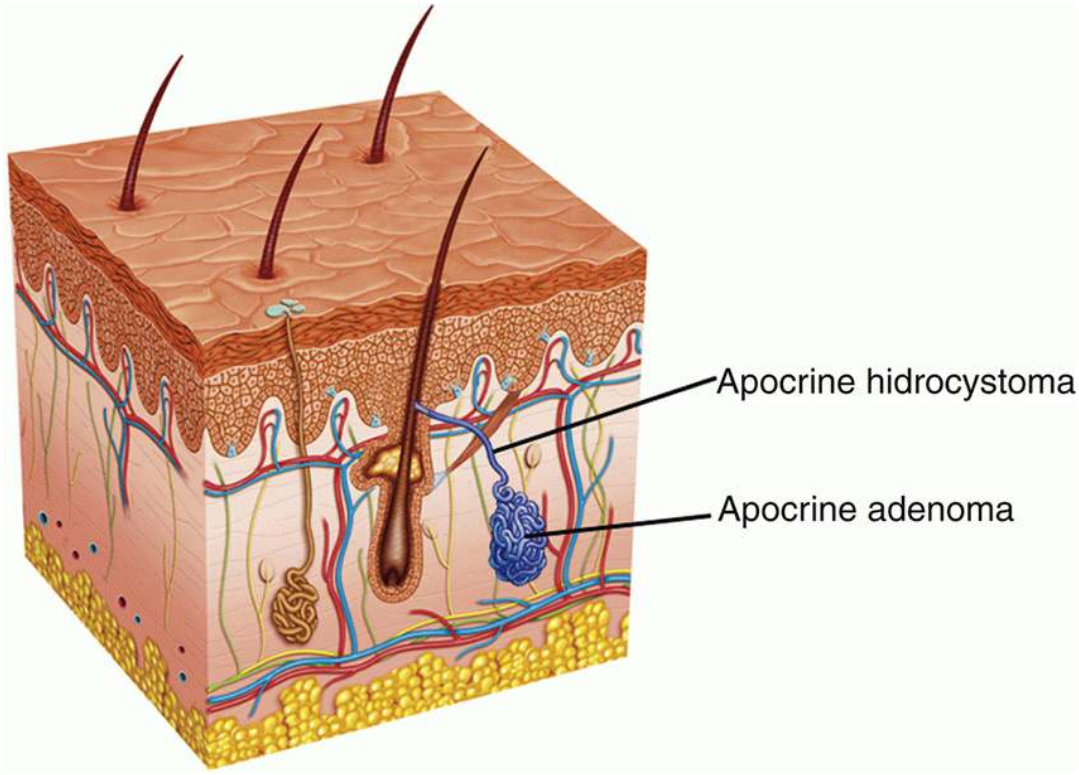

FIGURE 4.5 Lesions arising from the apocrine glands of Moll within the reticular dermis.

Eccrine sweat glands empty directly to the skin surface (Figure 4.6). Like the apocrine sweat glands, these can form solid or cystic lesions. Tumors arising from the ductal epithelium are called syringomas, whereas those from the tubular secretory epithelium are nodular hidradenomas. Obstruction of the secretory duct will result in an eccrine hidrocystoma filled with a clear fluid. Clinically, the eccrine and apocrine cysts may not always be distinguishable although apocrine cysts often contain a layered precipitate of cell fragments.

Vascular elements are present in the dermis and can give rise to a number of important eyelid lesions (Figure 4.7). These include arteriovenous malformations, cavernous venous malformations, and angiosarcomas derived from endothelial *(Print pagebreak 29)* cells, and solitary fibrous tumors arising from the endothelial pericyte. Nerves are another component of the dermis and are the tissues of origin for neural tumors such as neurofibromas and schwannomas (Figure 4.7).

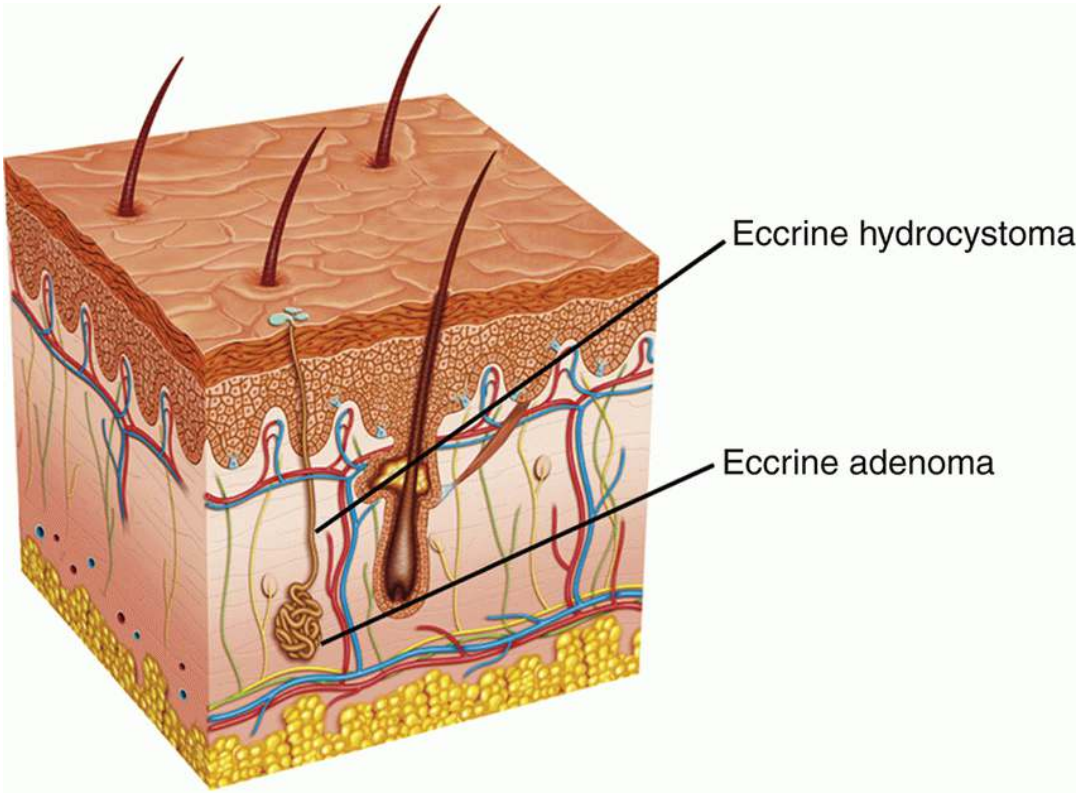

FIGURE 4.6 Tumors and cysts arising from eccrine sweat glands.

In addition to cutaneous layers and their adnexal appendages, eyelid lesions can arise from other eyelid structures. Most important in this group are the tarsal plate meibomian glands. These are modified holocrine sebaceous glands arranged as tubules, with about 25 to 30 in the upper eyelid and 20 in the lower lid. They are not associated with the eyelashes or a pilosebaceous unit, although they can occasionally revert to such a structure where they can be related to the development of abnormal hairs called distichiasis. Obstruction of the meibomian duct can result in an infected cyst called a chalazion. A similar infection involving small isolated sebaceous glands (glands of Zeis) or those associated with the skin pilosebaceous units causes a more acute and superficial process called a hordeolum. Any of these sebaceous glands can also give rise to a malignant tumor, the sebaceous cell carcinoma.

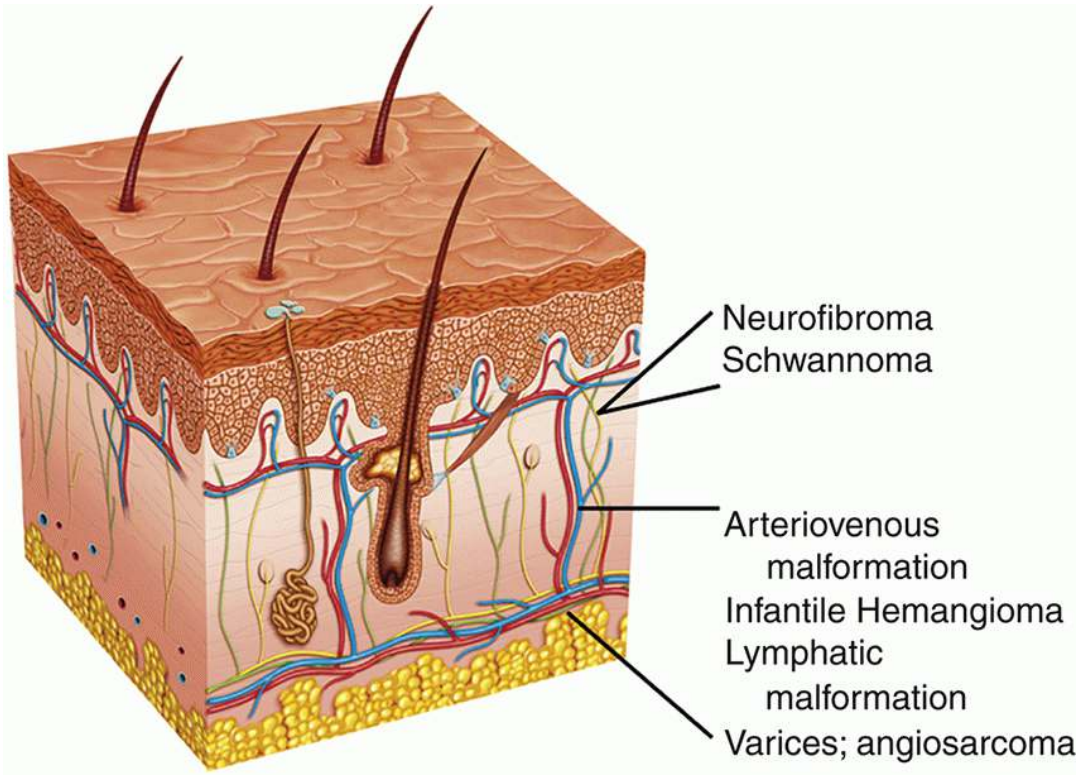

FIGURE 4.7 Dermal and subcutaneous lesions arising from neural and vascular structures.

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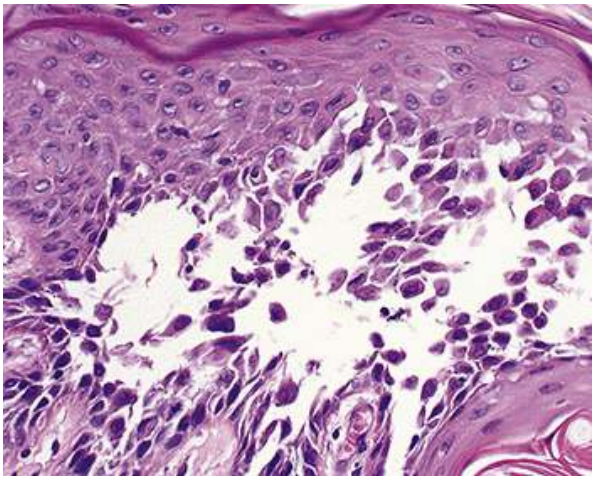
CHAPTER 5

Histopathologic Terminology

The use of descriptive terms in histopathology is a valuable method for standard communication that allows both the pathologist and the clinician to understand specific histologic characteristics of biological materials. One or more of these characteristics may be specific for certain lesions allowing a more precise diagnosis. In some cases, knowledge of such characteristics can also help the clinician make a provisional diagnosis that might allow therapeutic decisions such as biopsy or not, or to treat medically or observe.

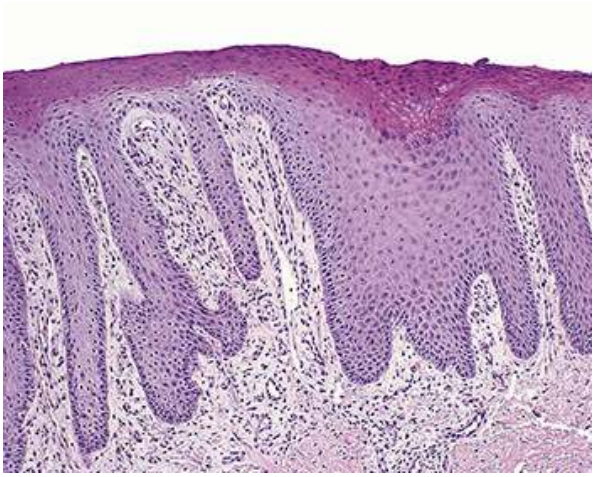
In the following pages, we describe and illustrate the more common descriptive terms in the histopathologic diagnosis of skin diseases, and which are used throughout this book.

Acantholysis



Acantholysis is the loss of cohesion between epidermal (or epithelial) cells leading to the formation of intraepidermal clefts, vesicles, or bullae. Primary acantholysis results from the dissolution or separation of the desmosomes between unaltered cells. Secondary acantholysis occurs between damaged cells such as during a viral infection. An example of primary acantholysis in pemphigus vulgaris is shown.

Acanthosis



Acanthosis is an increase in the thickness of the prickle cell layer (stratum spinosum) of the epidermis. Acanthosis often results in elongated projections of the epidermis into the dermis, as shown in this example.

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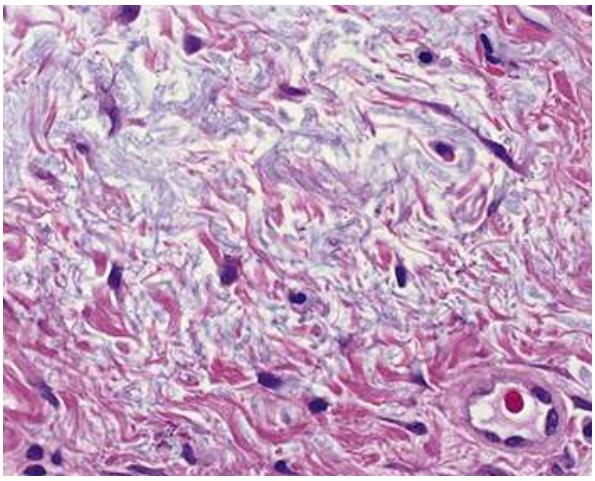
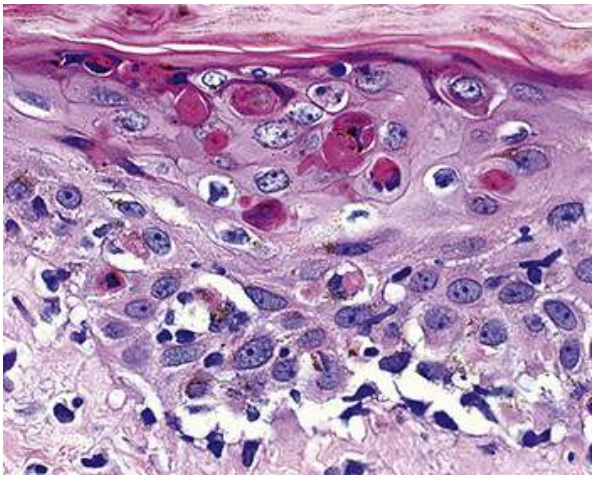
Actinic Elastosis



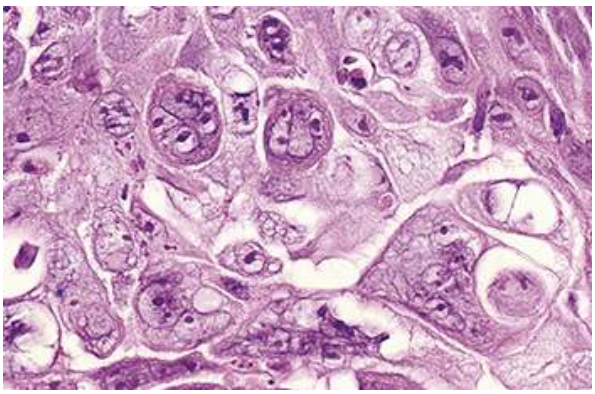
Actinic elastosis, also referred to as solar elastosis, is characterized by lightly basophilic, irregular, thickened elastic fibers in the dermis. Individual fibers are sometimes not evident, and there may be only an amorphous mass of lightly basophilic material in the dermis. Elastic tissue stains may be used to highlight actinic elastosis.

Apoptosis



Apoptosis is programmed cell death recognizable morphologically by chromatin condensation, cell shrinkage, and hypereosinophilia. Apoptotic cells with no remaining nucleus appear as homogenous, eosinophilic, round structures termed colloid bodies or cytoid bodies. Apoptosis requires energy, transcription of new genes, and protein synthesis.

Ballooning Degeneration of the Epidermis



In ballooning degeneration of the epidermis, marked intracellular edema leads to acantholysis and subsequent intraepidermal vesicle or bulla formation. Ballooning degeneration is characteristic of cutaneous viral infections.

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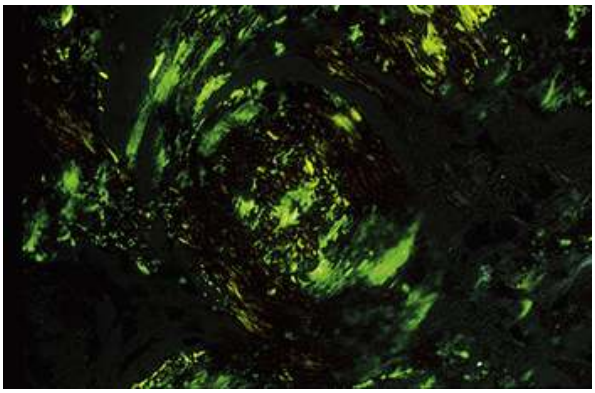
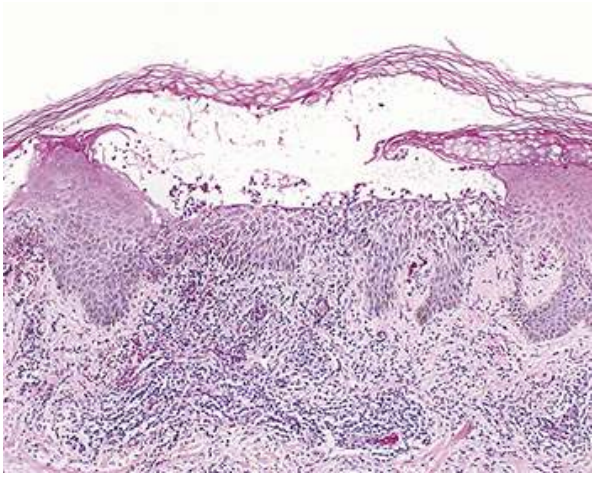
Birefringence

Birefringence is the splitting of a light wave into two waves that



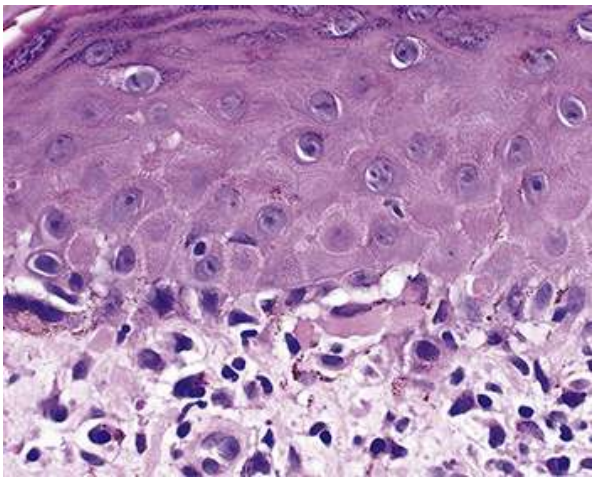
have perpendicular polarizations and speed of travel.[1],[2],[3] Birefringence results from a substance having different indexes of refraction and is thus also referred to as double refraction. Birefringent objects appear as shining bodies on a dark background when viewed with polarized light. Birefringent objects are usually white or yellow in sections stained with hematoxylin and eosin. Collagen and hair are normal structures in the skin that are birefringent, while foreign bodies are the most frequent extraneous birefringent materials.[1] Amyloid is birefringent when stained with Congo red, as shown in the photomicrograph taken using polarized light.

Bulla



A bulla is a fluid-filled blister greater than 0.5 or 1 cm. in diameter, depending on the author. Bullae may be subcorneal (illustrated), intraepidermal, suprabasilar, or subepidermal.

Colloid Body



Colloid bodies are also known as cytoid bodies, Civatte bodies, hyaline bodies, and apoptotic bodies. They are apoptotic epidermal cells (keratinocytes) lacking nuclei and appear as homogeneous, eosinophilic, and round structures. Colloid bodies are not specific for any disease, but they are commonly seen in lupus erythematosus, lichen planus, and graft-versus-host disease.

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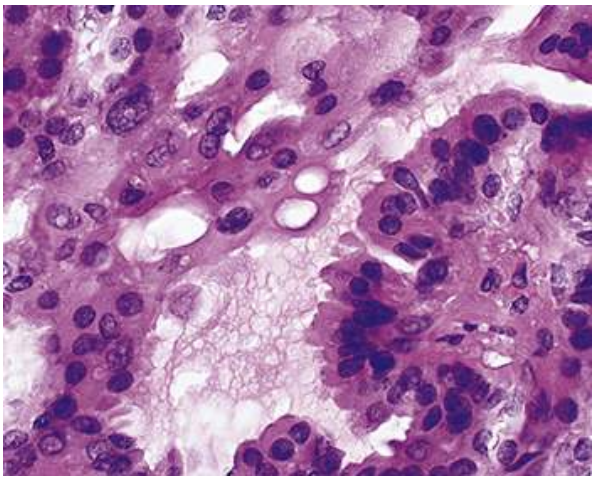
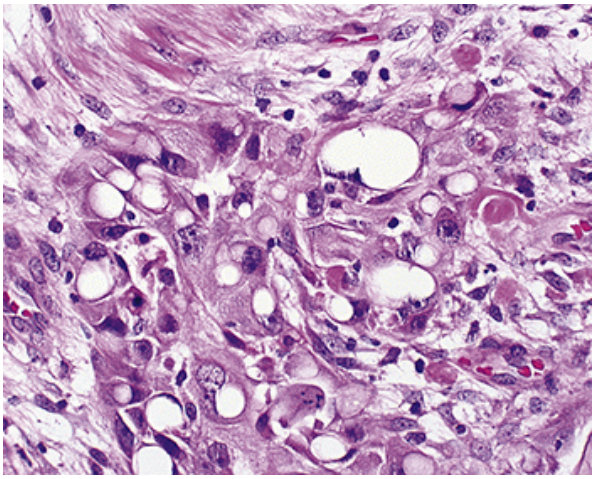
Decapitation Secretion



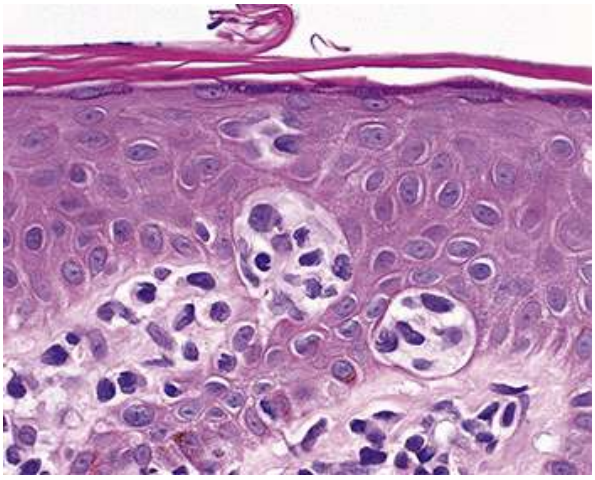
Decapitation secretion is characteristic of apocrine cells. During decapitation secretion, portions of the apical eosinophilic cytoplasm of the cells are pinched off into the lumina lined by the apocrine cells.

Dyskeratosis



The meaning of the term “dyskeratosis” varies depending on the disease. In acute graft-versus-host disease, lichen planus, and lupus erythematosus, dyskeratotic cells are cells undergoing apoptosis, are smaller than adjacent epidermal keratinocytes, and have brightly eosinophilic cytoplasm and shrunken hyperbasophilic nuclei (see photo under “apoptosis”). In acantholytic dermatosis, the dyskeratotic cells are also termed “corps ronds” and have a central, basophilic, pyknotic nucleus surrounded by a clear halo and enveloped within a basophilic or eosinophilic rim. Neoplastic dyskeratosis is manifest as brightly eosinophilic bodies, sometimes with remnants of nuclei, within a tumor (shown at left). These bodies represent neoplastic cells undergoing apoptosis.

Epidermotropism



Epidermotropism is the presence of atypical lymphocytes in the epidermis *without spongiosis* and is characteristic of mycosis fungoides. The atypical lymphocytes in the epidermis may occur singly surrounded by a clear halo, or they may form small clusters referred to as Pautrier microabscesses.

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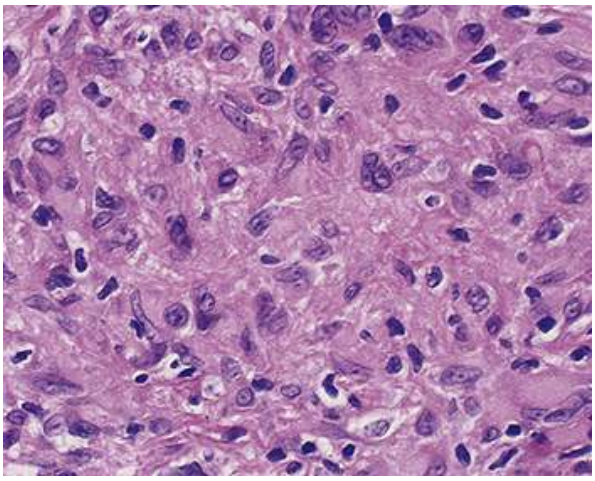
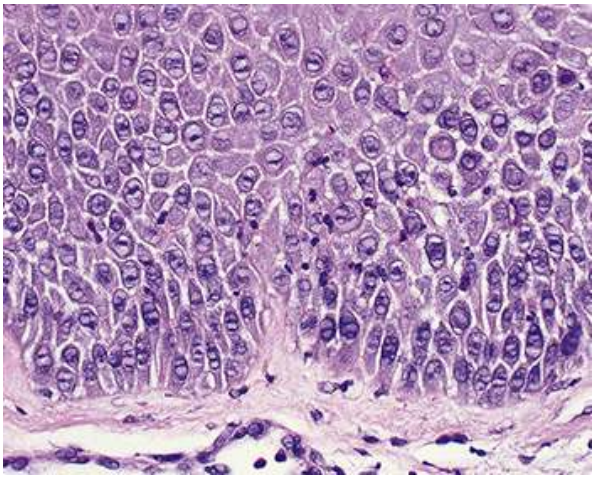
Epithelioid Cells



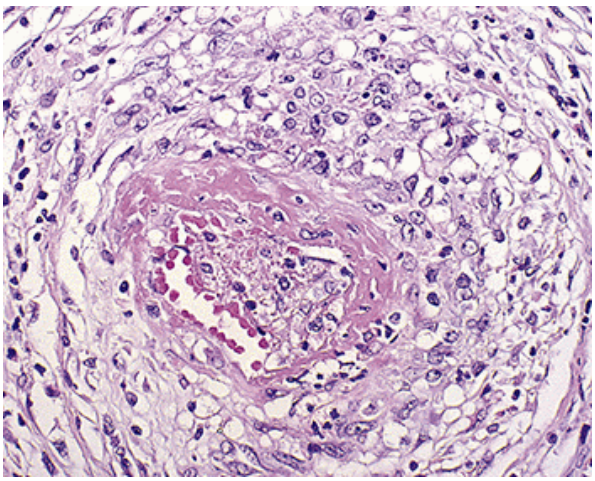
Epithelioid cells are activated macrophages that have an epithelial-like appearance. They are large cells with oval to elongated nuclei, eosinophilic cytoplasm, and indistinct cell borders. They occur singly or may form groups termed granulomas.

Exocytosis



Exocytosis refers to the presence of inflammatory cells within the epidermis in conjunction with spongiosis. Exocytosis is characteristic of inflammatory dermatoses.

Fibrinoid Degeneration (Necrosis)



Fibrinoid degeneration, also referred to as fibrinoid necrosis, manifests by the deposition of fibrin within vessel walls or dermal collagen. Fibrin is homogeneous and eosinophilic in sections stained with hematoxylin and eosin. In the skin, fibrinoid necrosis of vessel walls is seen in leukocytoclastic vasculitis, while fibrin deposition in dermal collagen is seen in rheumatoid nodules and sometimes in lupus erythematosus, especially the systemic variant. The example illustrated is an orbital vessel in a patient with granulomatosis with polyangiitis (Wegener granulomatosis).

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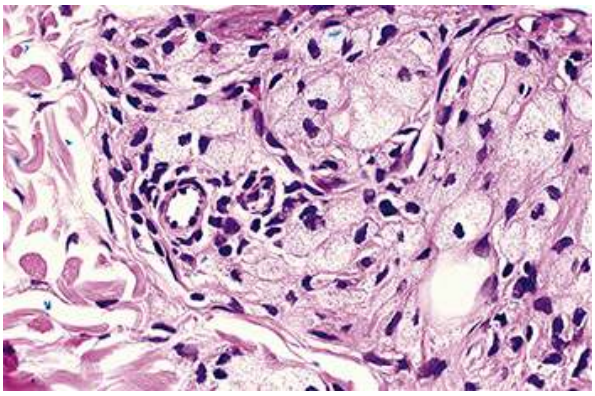
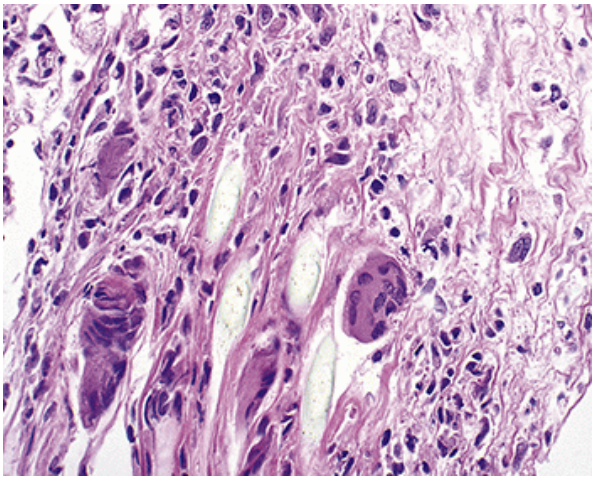
Foam Cells



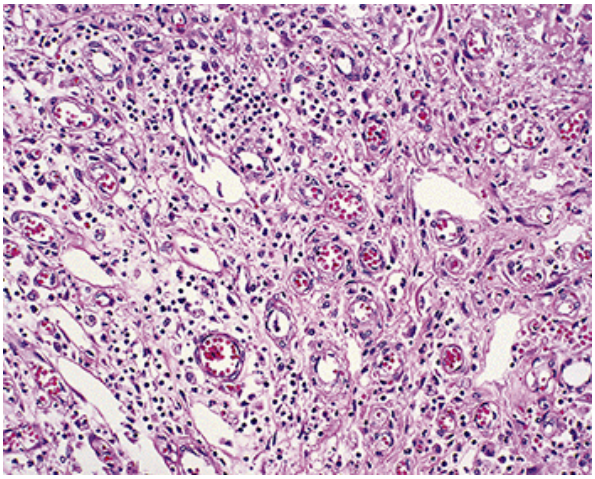
A foam cell is a macrophage laden with lipid, causing it to have vacuolated, bubbly-appearing cytoplasm.

Foreign Body Giant Cell



A foreign body giant cell is a multinucleated giant cell derived from a fusion of epithelioid cells (activated macrophages). Foreign body giant cells are characterized by their large size and haphazardly arrayed nuclei.

Granulation Tissue



Granulation tissue is the hallmark of wound healing, and the term comes from the soft, pink, granular appearance when viewed from the surface of a wound. Histologically, granulation tissue consists of a proliferation of small blood vessels and fibroblasts, often accompanied by edema.

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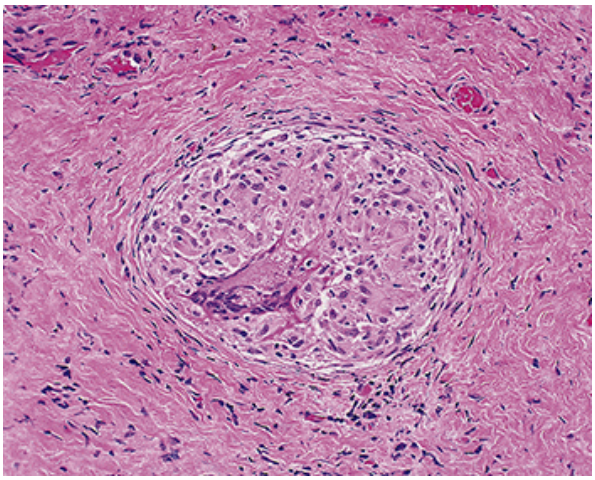
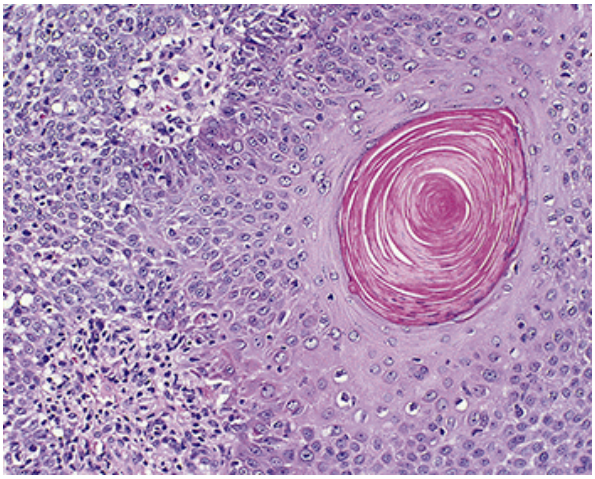
Granuloma

A granuloma is a microscopic aggregate containing varying proportions of activated macrophages (epithelioid cells), multinucleated giant cells resulting from the fusion of epithelioid cells, and other mononuclear leukocytes (lymphocytes, plasma cells, monocytes, and macrophages).[4],[5],[6]*Foreign body granulomas* are reactions to relatively inert particles and typically



have multinucleated giant cells, macrophages, and usually only small numbers of epithelioid cells. *Immune or allergic granulomas* are a response to insoluble particles that can induce a cell-mediated immune response; they may result from foreign substances such as zirconium, beryllium, or dyes used for tattoos, or microbes such as *Mycobacterium tuberculosis* and fungi. Immune/allergic granulomas typically contain abundant epithelioid cells and variable numbers of multinucleated giant cells. Other descriptors used for granulomas are *sarcoidal*, *tuberculoid*, and *palisading*. *Sarcoidal granulomas*, also termed *naked granulomas*, have epithelioid cells and multinucleated giant cells with only a spare periphery of lymphocytes (shown at left). Sarcoidal granulomas are characteristic not only of sarcoidosis, but they also are seen in some infections, granulomatous rosacea, orofacial granulomatosis (including the Melkersson-Rosenthal syndrome), and as a response to some foreign materials. *Tuberculoid granulomas* have epithelioid cells, multinucleated giant cells (especially Langhans giant cells), and a moderate to dense periphery of lymphocytes. Central necrosis ("caseation necrosis") may or may not be present. Tuberculoid granulomas are characteristic not only of *Mycobacterium tuberculosis* infection but are also seen in other infectious diseases. *Palisading granulomas* in the skin have a central zone of degenerated collagen (termed "necrobiosis") surrounded by macrophages, palisading epithelioid cells, lymphocytes, and variable numbers of multinucleated giant cells. Palisading granulomas are characteristic of granuloma annulare, necrobiosis lipoidica, rheumatoid nodules, and necrobiotic xanthogranuloma.

Horn Cyst



A horn cyst is a circumscribed, round, intraepidermal accumulation of keratin. Keratin-filled invaginations of the epidermis are referred to as "pseudohorn cysts." Both horn cysts and pseudohorn cysts are characteristic of seborrheic keratoses, though they may also be seen in other neoplasms of the skin.

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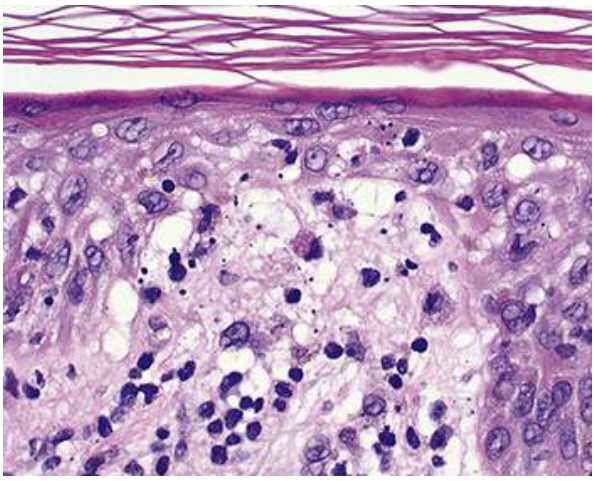
Hydropic Degeneration of Basal Layer

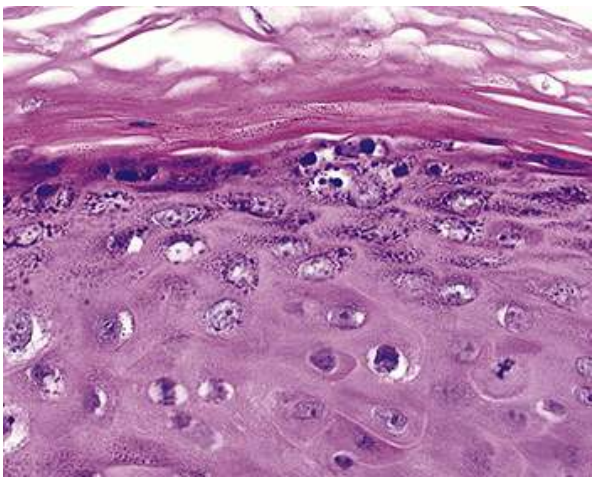


Hydropic degeneration of the basal layer, also termed vacuolar degeneration and liquefactive degeneration, refers to degeneration of the basal cell layer characterized by the formation of clear spaces (vacuoles) beneath the basal layer. It is a histological feature prominent in lupus erythematosus, erythema multiforme, graft-versus-host disease, as well as other dermatological diseases not common to the eyelids.

Hyperkeratosis

Hyperkeratosis is increased thickness of the stratum corneum (horny layer) of the epidermis. Hyperkeratosis may result from orthokeratosis, parakeratosis, or a combination of these two. Please refer to descriptions of orthokeratosis and parakeratosis below.

Keratohyalin



Keratohyalin is seen as darkly basophilic granules found in keratinocytes of the granular layer (stratum granulosum) of the epidermis. Keratohyalin granules form a matrix that cements cytokeratin tonofibrils together, resulting in increased strength and stability.

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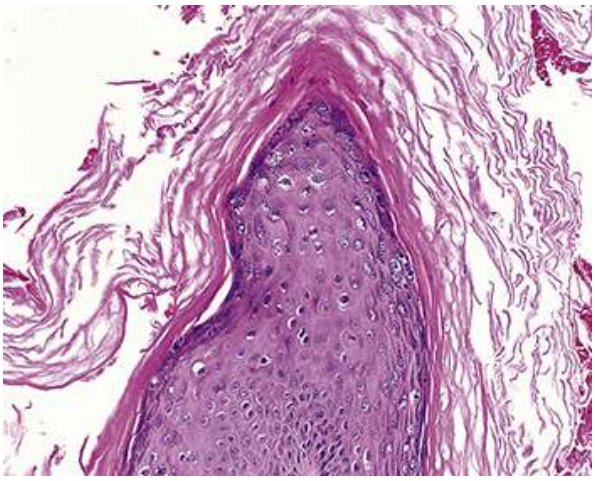
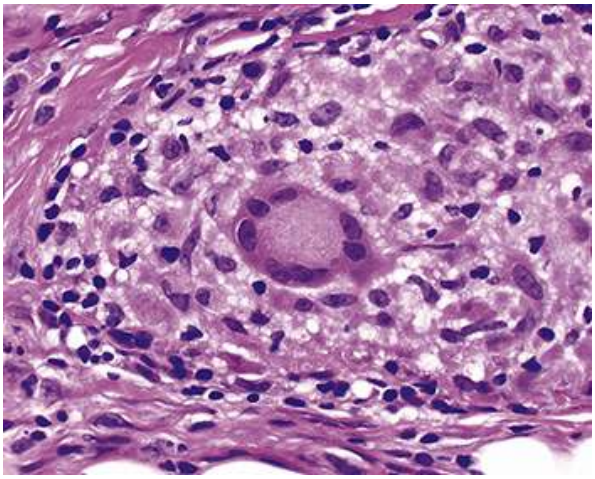
Koilocyte



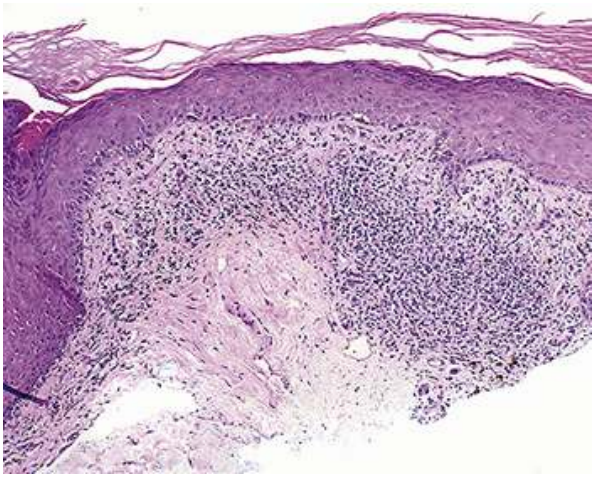
Koilocytes are vacuolated keratinocytes with eccentrically placed, basophilic, shrunken nuclei surrounded by clear halos. They are found in the upper spinous and granular cell layers of the epidermis in human papillomavirus infections (verruca vulgaris, in the eyelid).

Langhans Giant Cell



Langhans giant cells are multinucleated giant cells derived from the fusion of epithelioid cells (activated macrophages). They are large cells with their nuclei arranged along the periphery of the cell, forming an arc. Langhans giant cells are nonspecific, and they may be seen in both immune-type granulomas (such as sarcoidosis and tuberculosis) and foreign body granulomas.

Lichenoid Inflammation



Lichenoid inflammation or lichenoid reaction pattern refers to a dense band of lymphocytes clustered around the interface between the epidermis and dermis, often causing it to be obscured. Lichenoid inflammation is common to many dermatological conditions, though only a few, such as erythema multiforme and graft-versus-host disease, are seen in the eyelids.

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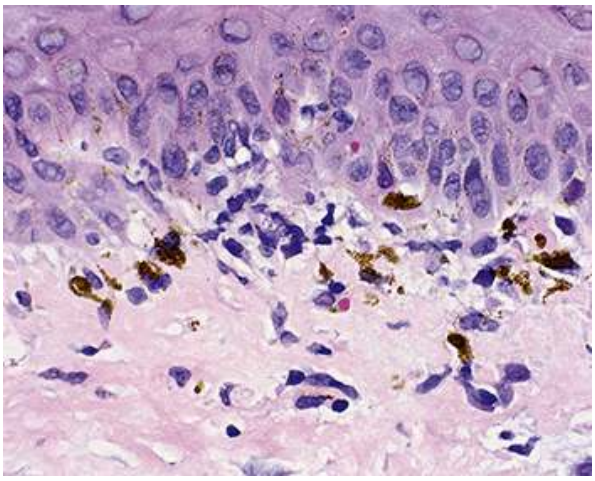
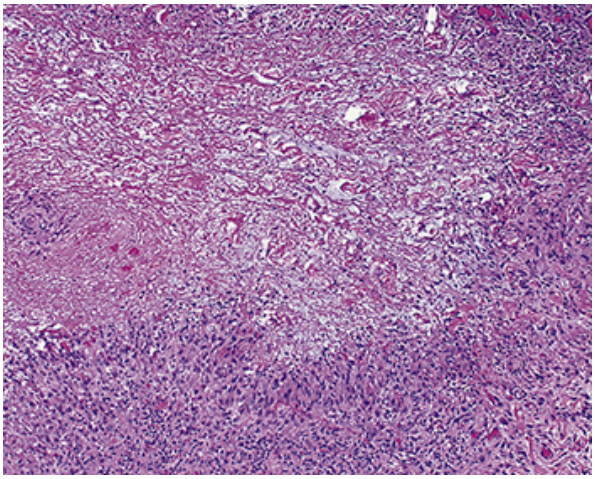
Melanophage



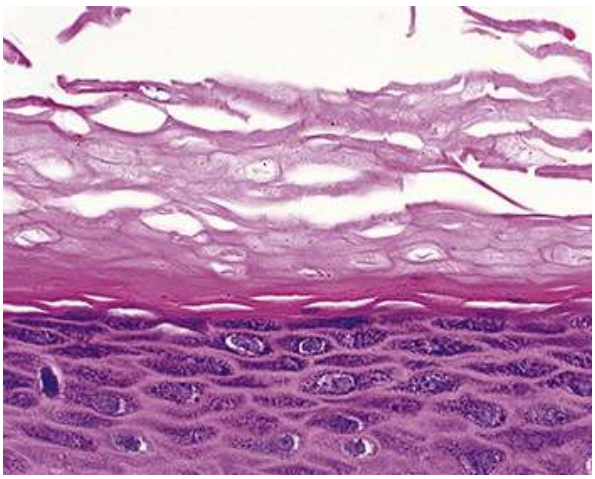
A macrophage containing phagocytized melanin is referred to as a melanophage. Melanin granules are dark brown and nonrefractile in sections stained with hematoxylin and eosin. Melanophages are seen in the dermis in inflammatory conditions affecting the epidermis, as well as in neoplasms such as seborrheic keratosis, blue nevus, and melanomas.

Necrobiosis



Necrobiosis refers to the death of cells or tissue due to aging or overuse. Zones of smudged or homogenized dermal collagen characterize it histologically. Necrobiosis is often seen as the center of a palisading granuloma. In granuloma annulare, the necrobiotic zone contains mucin, while in rheumatoid nodules there is usually fibrin within the necrobiotic area. The photomicrograph shows a zone of necrobiosis at the top left, surrounded by palisading epithelioid cells in a case of granuloma annulare involving the eyelid.

Orthokeratosis



Orthokeratosis is an increased thickness of the horny layer (stratum corneum) by normal-appearing squamous cells lacking nuclei. Orthokeratosis may be compact, laminated, or have a basket-weave configuration.

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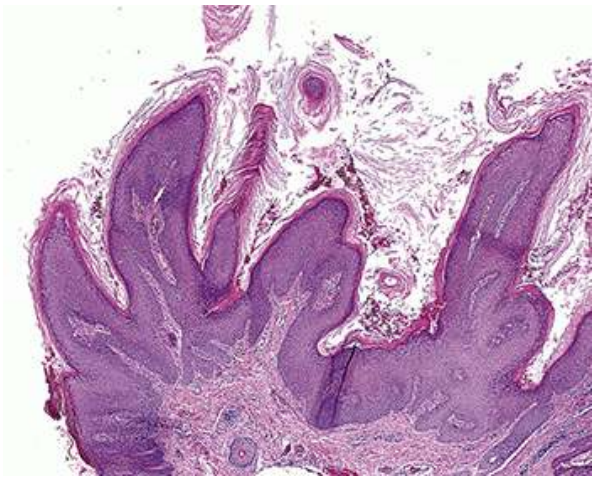
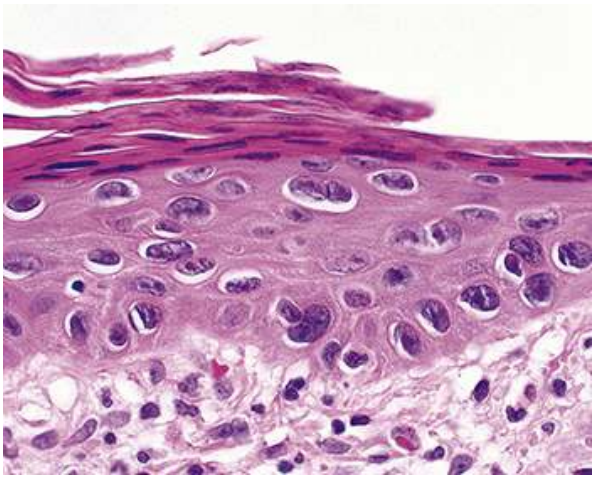
Papillomatosis



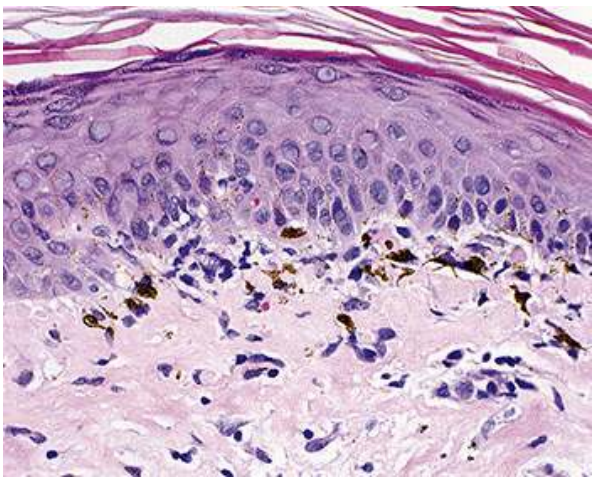
Papillomatosis is characterized histologically by the abnormally elongated epidermis and papillary dermis resulting in irregular undulation of the epidermal surface. Papillomatosis is seen most commonly in seborrheic keratosis and verruca vulgaris (shown at left).

Parakeratosis



Parakeratosis is an increased thickness of the horny layer (stratum corneum) by nucleated cells. Parakeratosis represents a defect in cellular differentiation and is usually associated with a thinned or absent granular layer. An example of parakeratosis in a specimen with actinic keratosis is shown here.

Pigment Incontinence



Pigment incontinence refers to the release of melanin granules from the epidermis and its resulting deposition in the upper dermis either free or within macrophages (melanophages).

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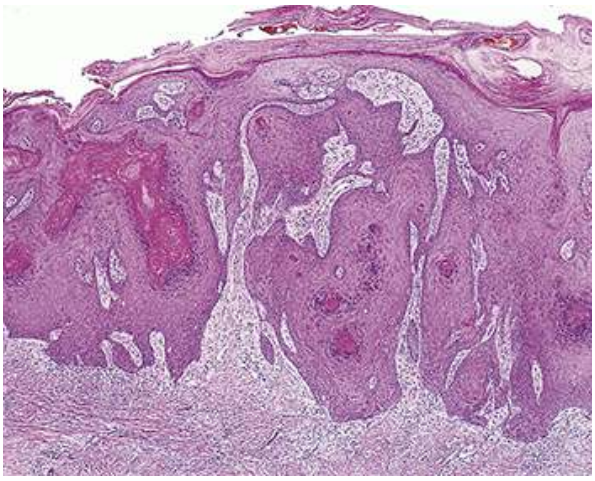
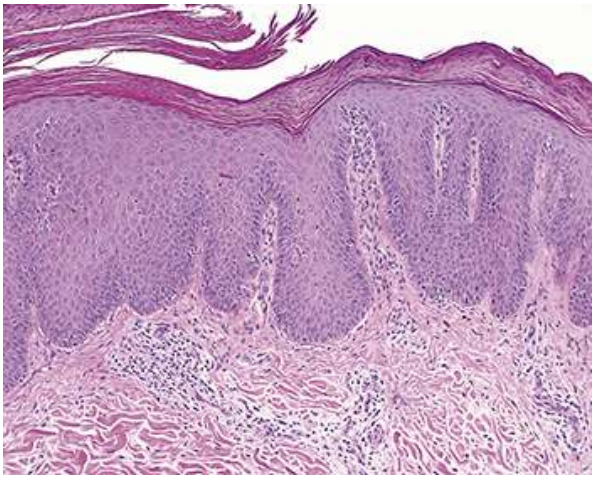
Pseudocarcinomatous (Pseudoepitheliomatous) Hyperplasia



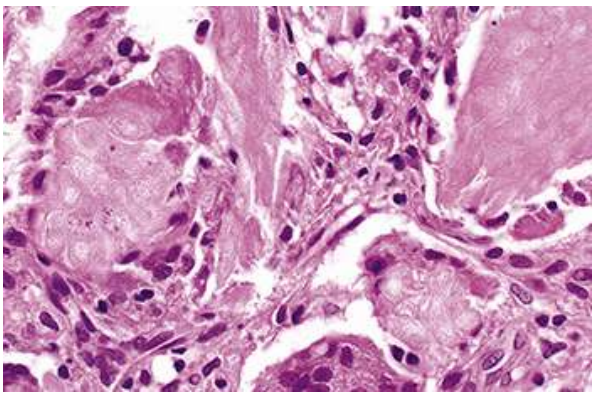
Pseudocarcinomatous hyperplasia is a histopathological reaction pattern manifest as irregular hyperplasia of the epidermis with prominent acanthotic down-growth of the epidermis. The epidermal proliferation occurs in response to a wide range of stimuli including chronic irritation, trauma, and dermal fungal infections. Pseudocarcinomatous hyperplasia differs from squamous cell carcinoma by having minimal cytological atypia and fewer mitoses.

Psoriasiform Dermatitis



Psoriasiform dermatitis, also known as superficial dermatitis with psoriasiform proliferation, refers to a form of epidermal thickening with uniform elongation of rete ridges that extend downward into the dermis. Parakeratosis is common. The nature of the inflammatory cells in the dermis, the presence and the degree of spongiosis, and the presence of exocytosis are features that aid in rendering a more specific diagnosis.

Shadow Cell



Shadow cells, also known as ghost cells, are characteristic of pilomatrixomas. They are pale, eosinophilic cells with a clear area in place of the nucleus.

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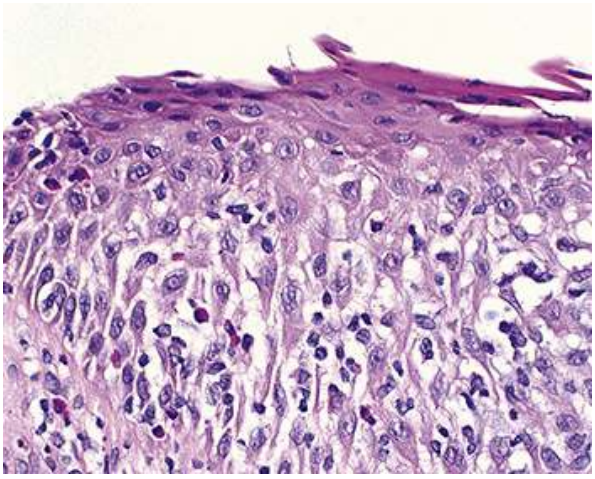
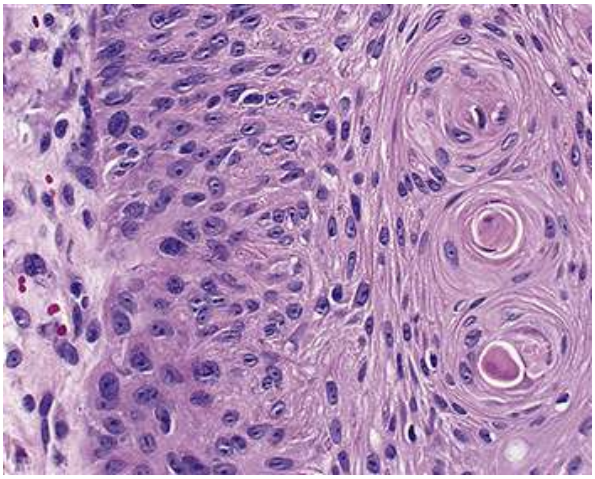
Spongiosis



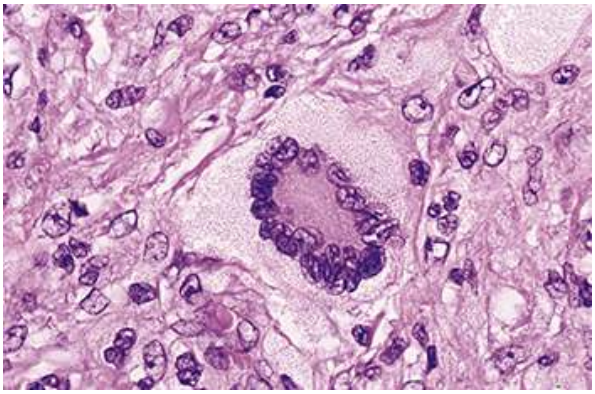
Spongiosis is intercellular edema between squamous cells of the epidermis. It is characteristic of acute dermatitis and may lead to micro- and macrovesicles (spongiotic blisters). Intracellular edema may accompany severe spongiosis, resulting in the bursting of epidermal cells and the formation of multilocular bulla.

Squamous Eddies



Squamous eddies are whorled onion skin-like foci of brightly eosinophilic keratinocytes. They are a typical feature of irritated seborrheic keratoses.

Touton Giant Cell



Touton giant cells are multinucleated giant cells derived from the fusion of epithelioid cells (activated macrophages). They have a ring of nuclei surrounding eosinophilic nonvacuolated cytoplasm centrally and lipid-filled foamy cytoplasm peripherally.[7] They are characteristic of xanthogranulomas.

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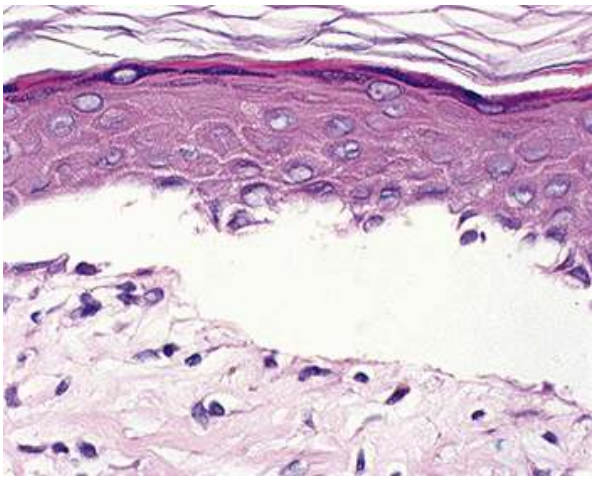
Vesicle



A vesicle is a small blister, generally less than 0.5 cm. in diameter. A subepidermal blister is shown.

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CHAPTER 6

Evaluation of Eyelid Malpositions

Key Points

- The ability to obtain a proper medical history is of paramount importance
- The time of onset may help discern congenital from acquired cases
- A positive family history of a similar condition may indicate a more serious genetic syndrome
- The tempo of onset should be evaluated in all patients. An acute onset may be the result of trauma, hemorrhage, metabolic disturbance, or a compressive orbital lesion. A gradual onset of an eyelid malposition is more typically indicative of an involutional disease
- A past or present history of a thyroid disease should be elicited from the patient
- The whole face should be observed for any associated asymmetry or facial deformity
- A complete ophthalmic examination including slit lamp examination, assessment of vision, evaluation of the pupil, dry eye evaluation, palpation of the eyelid and anterior orbit, Hertel exophthalmometry measurement, as well as the assessment of extraocular motility should be carried out
- Eyelid evaluation should exclude the presence of entropion or ectropion of the eyelid margins, excessive eyelid skin (dermatochalasis), and fat herniation (steatoblepharon), and the interpalpebral fissures should be measured vertically with a millimeter ruler
- Levator muscle function should be properly assessed, Hering's phenomenon should be tested, and the patient should be asked to gently close the eyes to rule out preexisting lagophthalmos
- Appropriate photographic documentation of all eyelid malpositions is mandatory

When a patient presents with an eyelid malposition, a thorough eyelid examination and history must be included in the initial encounter and recorded documentation. Before consideration of any surgical or nonsurgical intervention, an accurate diagnosis of the specific malposition should be made along with some determination of its etiology.

History

An adequate history will typically provide important clues to the cause of the eyelid malposition and may also suggest the need for further evaluation before any surgery. In some cases, the history may make immediate surgical intervention unwise.

The time of onset of the eyelid abnormality may be congenital,[1] or acquired later in life. In the case of blepharoptosis, a careful birth history will uncover the possible use of forceps during delivery or the occurrence of other birth trauma. Similar abnormal eyelids in other family members should alert the observer to the possibility of a familial disorder, such as blepharophimosis syndrome or craniosynostosis syndrome. The presence of other congenital anatomical deformities or especially neurologic deficiencies may indicate a more serious genetic syndrome, congenital oculomotor nerve palsy, or a central mechanism for the eyelid disorder.

The time course of onset should be evaluated in all patients. Acute-onset ptosis in an adult may be the result of a metabolic disturbance or a compressive orbital lesion. Hemorrhage into a preexisting, unsuspected eyelid or orbital mass can result in sudden-onset ptosis, especially in children, often associated with some degree of proptosis or ocular motility disturbance. A

history of recent trauma with new-onset eyelid malposition should raise suspicion not only of scarring or levator transection but also for a retained foreign body. Blunt trauma without eyelid laceration is more likely to result in a contusive injury to the levator muscle or the oculomotor nerve. These types of injuries have a high probability of spontaneous recovery over time. Unsuspected orbital fractures can be associated with eyelid malpositions. Ptosis that evolves over several days following eyelid trauma may indicate an enlarging hematoma or abscess.

Gradual onset of an eyelid malposition is more typically indicative of involutional disease but may also occur with a paralytic or cicatricial process. Eyelid changes occurring with other extraocular muscle dysfunction or loss of vision demands immediate imaging investigation of the orbital apex and cavernous sinus. History of decreased facial movement with associated ocular surface irritation, tearing, or blurred vision may accompany lagophthalmos or paralytic ectropion. A history of changes in the eyelid skin might suggest a chronic inflammatory process, infection, or dermatosis that has led to cicatricial changes in the anterior eyelid lamella. Chronic ocular surface *(Print pagebreak 45)* disease may result in tarsus or conjunctiva scarring, shortening of the conjunctival fornices, or symblepharon formation.

A history of slow progression is not uncommon with most involutional eyelid changes, but this usually occurs over several years.[2] Almost all patients with ptosis or dermatochalasis will report variable fissure height, with some increase in droopiness late in the day or when tired. This does not usually indicate myasthenia gravis. The occurrence of an eyelid malposition with orbital pain is always worrisome and demands an investigation to rule out neoplasm or inflamation. Any such association requires radiographic study.

A history of previous eye, eyelid, or sinus surgery is important. Eyelid malpositions are not uncommon sequelae of retinal detachment surgery, strabismus surgery, or cataract extraction.[3,4] Ptosis is reported to occur following cataract surgery in 7% to 8% of cases. Other surgery, especially intracranial or thoracic procedures, may result in central third nerve palsy or Horner syndrome, respectively.[5]

The patient should be questioned carefully about previous episodes of eyelid edema, as with allergic angioneurotic edema or blepharochalasis syndrome, which can affect eyelid position.[6] This is particularly true in younger patients. A past or present history of systemic diseases that commonly affect the eyelid and orbit, such as thyroid ophthalmopathy, should be noted. Symptoms of thyroid hormone imbalance should be reviewed since the eyelid manifestations of Graves disease may precede the diagnosis of systemic thyroid dysfunction.

A thorough ocular history should be obtained to attempt to uncover the presence of chronic conjunctivitis or uveitis, or a past or present history of cicatricial diseases, such as ocular pemphigoid or Stevens-Johnson syndrome. A history of morning ocular irritation and spontaneous eyelid eversion during sleep, particularly in an obese male, should lead to careful examination of the conjunctiva for papillary conjunctivitis, and of the tarsus for possible floppy eyelid syndrome.

Any prior malignancy should raise the possibility of a mechanical etiology for a malpositioned eyelid from metastatic disease. The previous excision of an eyelid or periocular tumor should alert the observer to the possibility of deep orbital recurrence resulting in distortion of eyelid position.

Observation

While taking the history, the surgeon should observe the patient's eyes and face. It should be noted whether the eyelid malposition is unilateral or bilateral and whether there is any associated disorder affecting the brows and midface. The position of the eyelids, canthal angles, and eyelash orientation should be noted (Figure 6.1). The presence of concurrent anatomical deformities, such as brow ptosis, facial paralysis, skeletal abnormalities, clefting disorders, or stigmata of Down syndrome or other genetic syndromes, should be recorded. Any abnormal eyelid movements with extraocular muscle contraction or with jaw movement should be documented. A head turn or tilt should lead to careful evaluation of ocular motility to rule out the presence of associated strabismus.

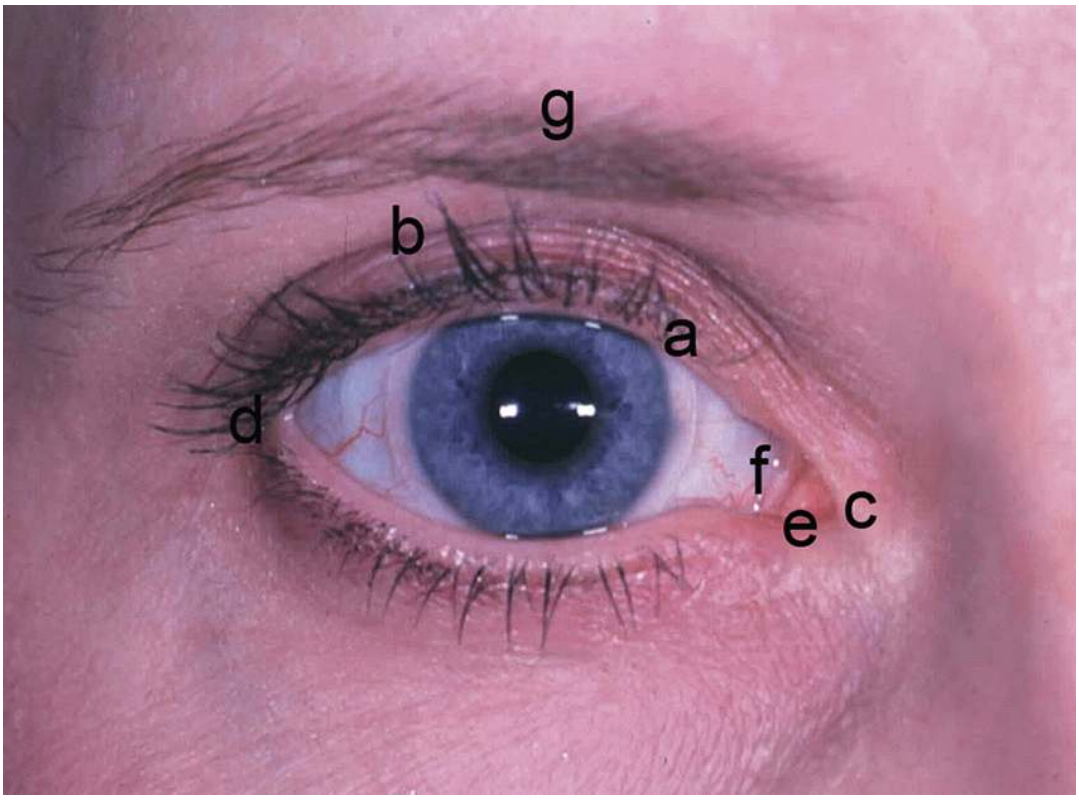

FIGURE 6.1 Major features of the normal eyelid. a, Eyelid margin with cilia. b, Upper eyelid crease. c, Medial canthus. d, Lateral canthus. e, Caruncle. f, Plica. g, Brow.

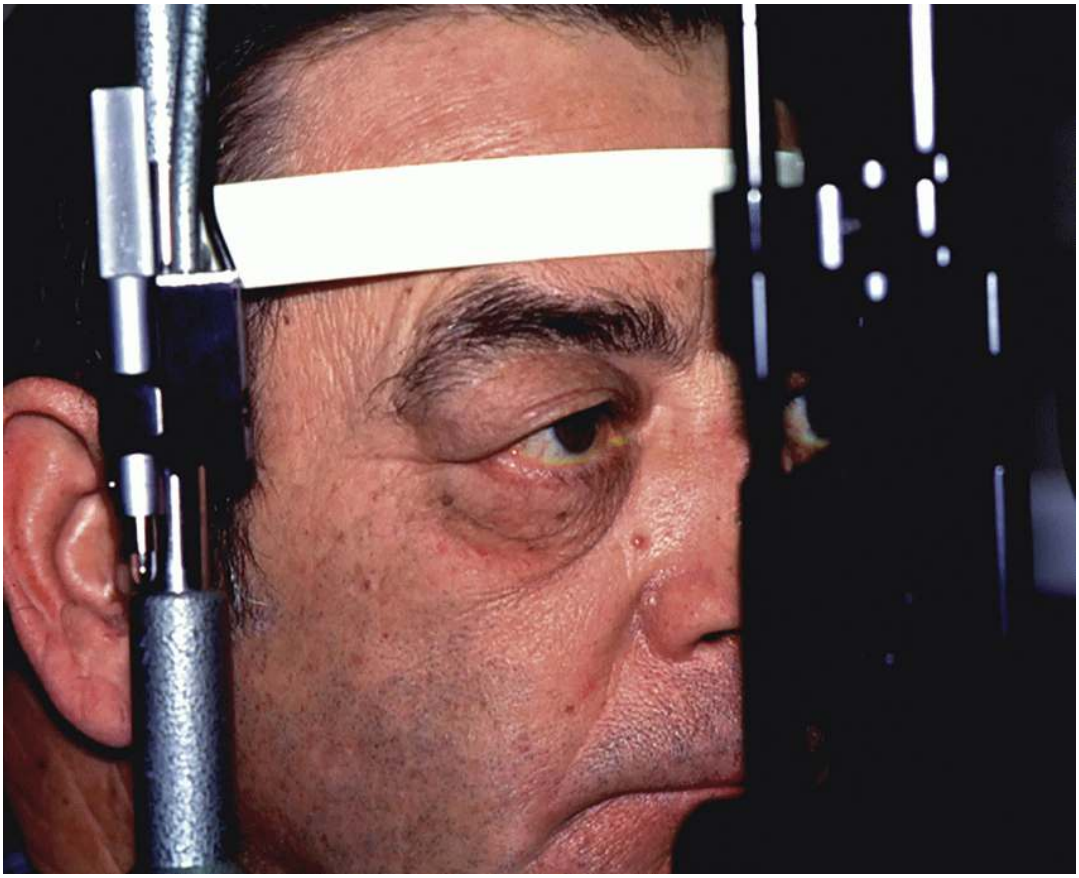

FIGURE 6.2 Slit lamp examination of the anterior segment of the eye and the eyelid margins.

Examination

For all patients with eyelid malpositions, a complete ophthalmic examination is important. Visual acuity with a current refraction is recorded, and especially in children presenting with upper eyelid ptosis, the presence of amblyopia must be ruled out. In any patient, unexplained decreased visual acuity requires a comprehensive investigation. Pupil size and reactivity to light should be measured, and any asymmetry noted. The corneal examination must evaluate the presence of keratopathy secondary to corneal exposure as a result of the malpositioned eyelid, or any deficit in corneal sensation.

A slit lamp examination should include a magnified evaluation of the conjunctiva and eyelid margin (Figure 6.2). Thickening of the lid margin or injection of the conjunctiva may represent inflammation or an infiltrating neoplasm. Malpositions or misalignments of the eyelashes should be noted.

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A Schirmer's test is essential in all older adults to establish the adequacy of tear production[7] (Figure 6.3). Ptosis repair or blepharoplasty in patients over 40 to 50 years of age with borderline tear function can push them into a symptomatic dry eye syndrome. Some inflammatory diseases or those that involve the lacrimal gland can also be associated with dry eye syndrome.

Extraocular motility is examined in all patients and the presence of an adequate Bell's phenomenon should be noted.[8] The absence of Bell's phenomenon should lead the surgeon to be more cautious in consideration of elevating the eyelid in patients where lagophthalmos and corneal exposure might result. Hypotropia may be responsible for pseudoptosis, and strabismus surgery rather than ptosis repair may be more appropriate. The lack of spontaneous eye or eyelid movements may suggest chronic progressive external ophthalmoplegia.

A pupillary examination should be recorded. The presence of anisocoria should raise the possibility of Horner syndrome, third nerve palsy, or ocular trauma.

Palpation of the eyelid and anterior orbit may reveal a mass lesion or deep scar responsible for a mechanical eyelid malposition. The upper eyelid should be everted to examine the tarsal plate and palpebral conjunctiva for any irritative lesions or symblepharon formation that could influence the eyelid position. The bulbar conjunctiva should also be examined up to the superior fornix using an eyelid retractor if necessary.

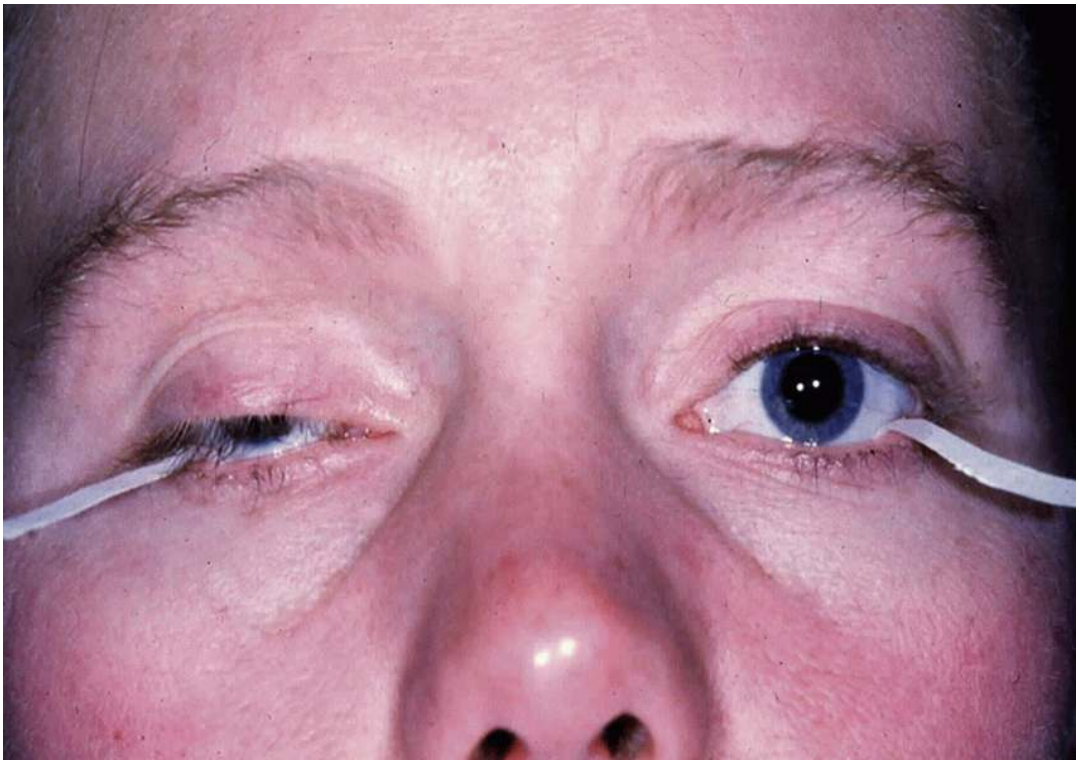

FIGURE 6.3 Shirmer's test for tear secretion.

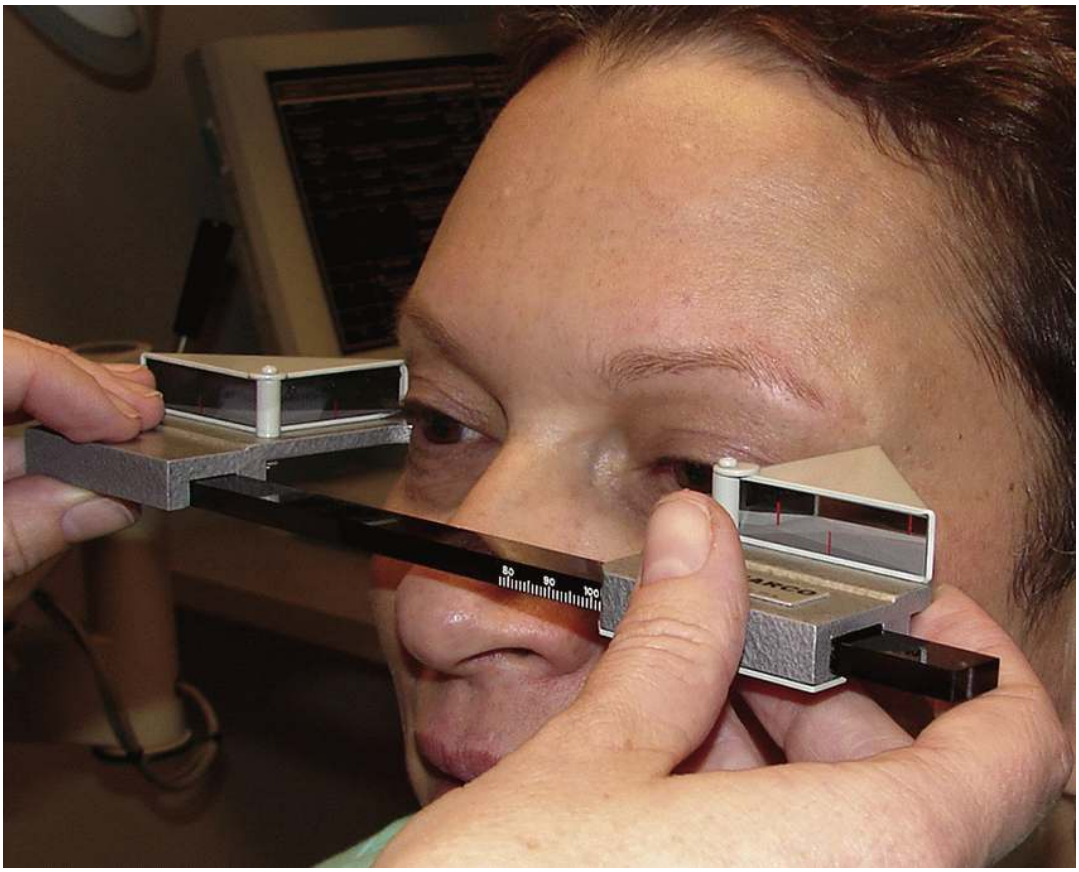

FIGURE 6.4 Hertel exophthalmometer for the measurement of proptosis.

FIGURE 6.5 Plexiform neurofibroma. A, Lesion of the left eyelids and brow. B, Axial CT scan with neurofibroma infiltrating the left eyelids, brow, and temple.

A thorough orbital examination should be recorded, and actual or relative proptosis evaluated by Hertel exophthalmometry (Figure 6.4). A relatively proptotic globe may give the illusion of eyelid retraction while an enophthalmic globe may give the impression of ptosis. Some eyelid diseases can extend posterior to the orbital septum to involve the orbit. If there are any orbital signs such as proptosis, motility disturbance, palpable masses beneath the orbital rims, or vascular congestion, orbital imaging with CT or MRI should be ordered (Figure 6.5).

Simple observation will reveal the presence of entropion or ectropion of the eyelid margins.[9,10] If not immediately *(Print pagebreak 47)* obvious, asking the patient to squeeze the eyelids closed may trigger spontaneous entropion formation. The snap-back test (pulling outward on the eyelid and observing for spontaneous re-apposition to the globe) will often demonstrate excessive eyelid laxity or subtle ectropion (Figure 6.6). The eyelids normally maintain enough elasticity to re-appose the globe in less than 2 seconds.

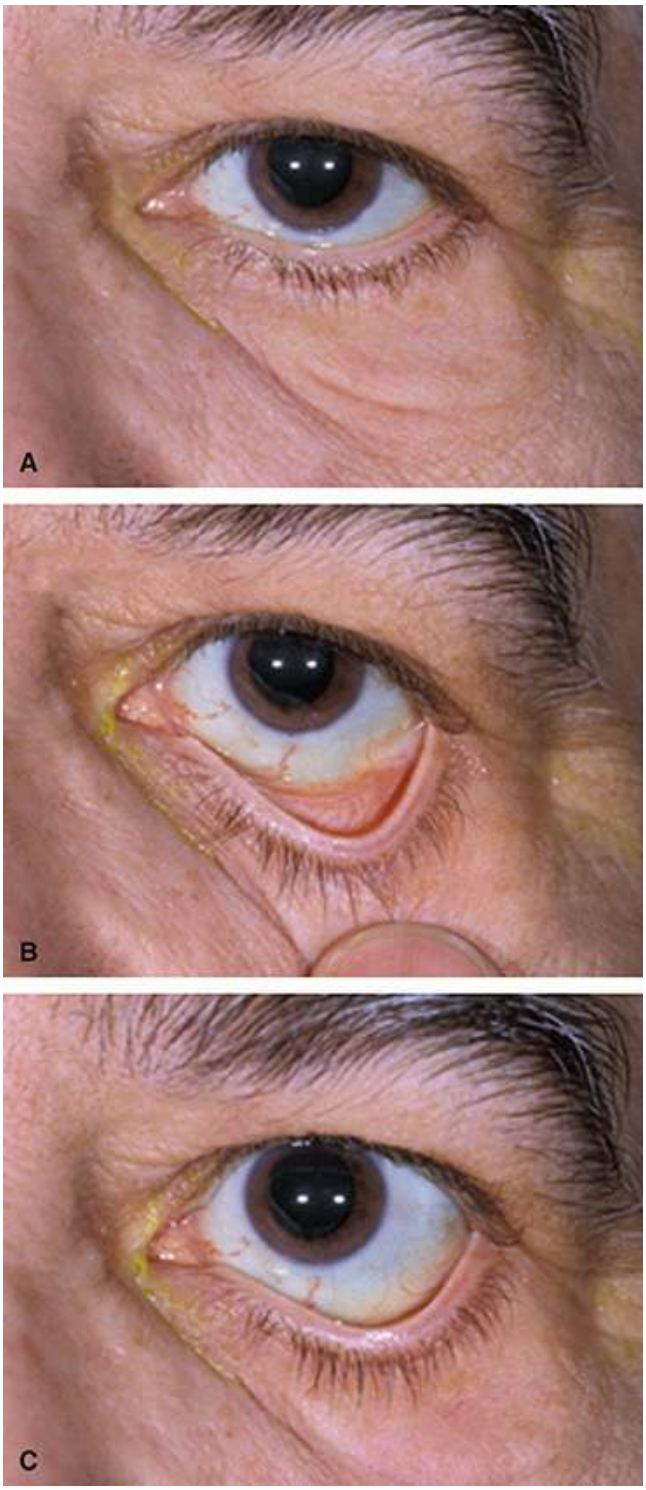

FIGURE 6.6 Lower eyelid laxity determined with the snap-back test. A, The lid in normal position after a blink. B, The lid is pulled forward away from the eye. C, Before another blink, the lax lid fails to snap back against the eye indicating significant laxity.

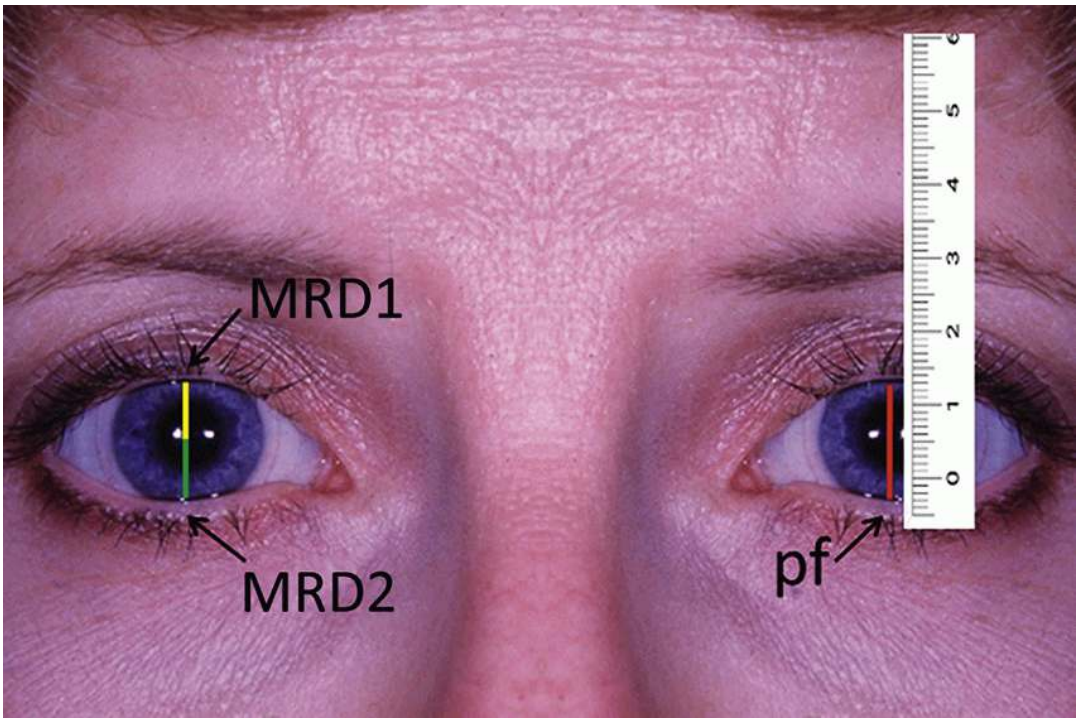

FIGURE 6.7 Margin-to-reflex distance (MRD1 and MRD2) and measurement of vertical palpebral fissure (pf).

Excessive upper or lower eyelid skin (dermatochalasis) and fat herniation (steatoblepharon) should be noted. Hooding of skin over the eyelashes should be noted and any associated upper eyelid ptosis is observed. This redundant tissue should carefully be lifted to evaluate the position of the upper eyelid margin relative to the pupil.

The interpalpebral fissures are measured vertically with a millimeter ruler at the level of the pupil with eyes in the primary position (Figure 6.7). The degree to which the eyelid margin covers the superior corneal limbus is also recorded. Additionally, the distance between the upper eyelid margin and the central pupillary reflex, known as the margin-to-reflex distance (MRD1) is a useful measurement, since total vertical fissure distance may be unreliable in the presence of lower eyelid retraction. The distance between the lower eyelid margin and the central pupillary reflex is sometimes recorded as the MRD2.

Next, the patient is asked to gently close the eyes. Any residual lagophthalmos is measured and recorded. The presence or absence of an eyelid crease gives some indication of the status of the levator aponeurosis and its position above the eyelid margin should be measured. Care must be taken to measure the true crease which may be covered by redundant skin. The absence of a definitive eyelid crease, or a very high position (more than 10 mm), suggests redundancy or disinsertion of the levator aponeurosis but is also seen in poor to absent-function myopathic ptosis.

Levator muscle function is perhaps the single most important measurement made during the preoperative evaluation and is most predictive of the surgical outcome for ptosis repair following any particular surgical procedure. It must be performed with great care. Function is recorded as maximum eyelid excursion from extreme downgaze (without closing the eyes) to extreme upgaze position. A millimeter ruler is placed in front of the eyelids with the patient looking down as far as possible, and the position of the upper eyelid margin noted against the scale. The patient is asked to look up as far as possible and the eyelid margin position on the scale is again noted (Figure 6.8). The difference between *(Print pagebreak 48)* the two readings is the total excursion and is recorded as the levator function. Contraction of the frontalis muscle can elevate the eyelid by up to 3 to 4 mm so that the examiner must be certain to eliminate any possible contribution from this source. This is done properly by placing a thumb firmly over the brow to immobilize it against the supraorbital rim during measurement. This procedure is critical in patients with poor levator function, since a difference of only 1 or 2 mm in function may influence the choice of a surgical procedure.

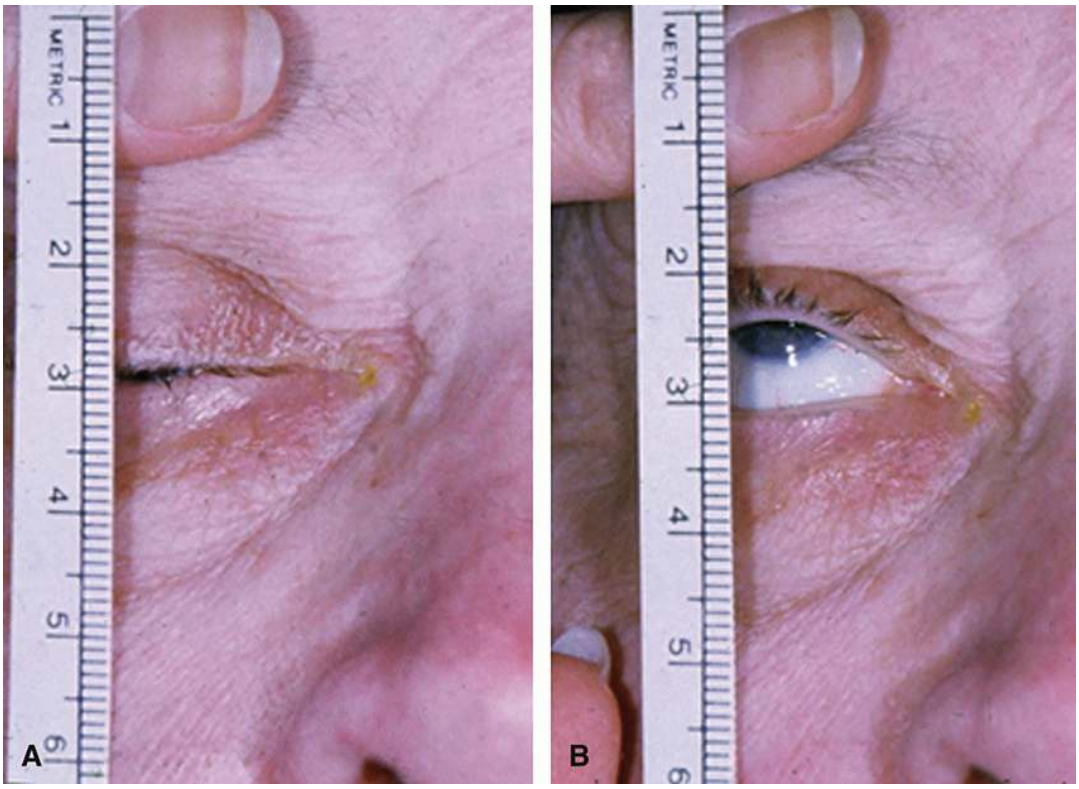

FIGURE 6.8 Measurement of levator muscle function. A, Extreme downgaze. B, Extreme upgaze.

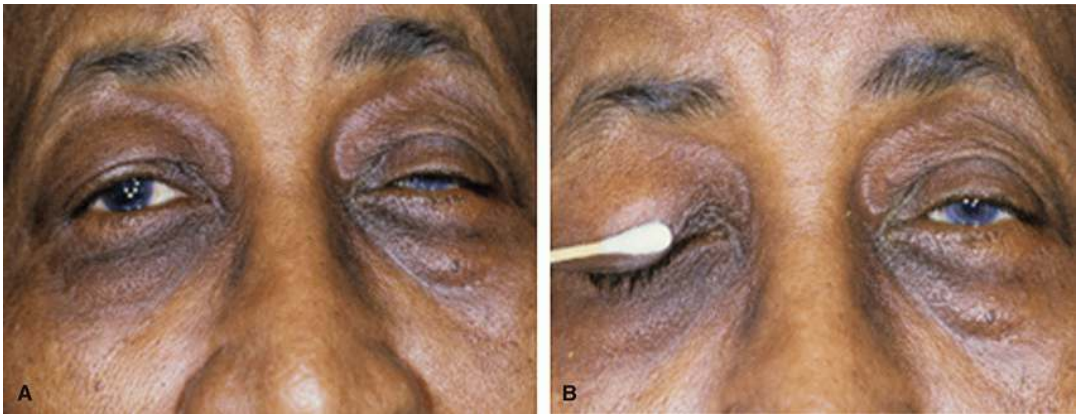

FIGURE 6.9 A and B, Positive Hering's phenomenon. When the apparent normal eyelid is manually depressed, the ptotic eyelid elevates suggesting that both eyelids may be ptotic but one appears normal because of the Hering's phenomenon.

All cases of ptosis or eyelid retraction should be tested for a Hering's phenomenon.[11] Because central innervation of the levator muscles is bilaterally equal, an asymmetry in eyelid height may result in a central compensatory increase or decrease in motor output to the levator muscles, thus masking an abnormal position of the contralateral eyelid. For example, a patient with bilateral but asymmetric ptosis may have a centrally mediated unconscious increased eyelid height to improve the visual field. The more ptotic lid still appears ptotic, but the less ptotic lid may appear normal. Surgical correction of the apparent ptotic eyelid could uncover ptosis in the opposite eyelid which may require additional surgery. In some patients, this can be uncovered preoperatively by manually elevating the ptotic lid and seeing the "normal" lid drop (Figure 6.9). Conversely, the "normal" *(Print pagebreak 49)* lid might actually be retracted, and a decrease in central output might result in both lids being lower, with the contralateral lid now appearing ptotic. In this case, depressing the "normal" lid downward could result in the ptotic lid coming up. This so-called Hering's phenomenon is sometimes useful in predicting the results of surgery. However, the results of this test are not always reliable in predicting the behavior of the eyelids after surgical correction.

In congenital myopathic ptosis, levator function is usually reduced because of levator fibrosis, with deficient stretching as well as impaired contraction. Typically, the eyelid is ptotic in primary gaze, more ptotic in upgaze, but less ptotic or even relatively retracted in downgaze (Figure 6.10). This contrasts with acquired ptosis where the eyelid characteristically shows the same degree of ptosis in all positions of gaze.

Any patient with a history of significant worsening of ptosis late in the day or when tired should be suspected of having myasthenia gravis.[12] This is especially true if the eyelid appears near normal in the morning, or the condition is associated with difficulty in swallowing, generalized weakness, or diplopia. A levator fatigue test can be performed easily without risk. The patient is asked to look upward for several minutes without blinking. The position of the eyelid is measured before and immediately after the test. Any increase in ptosis with fatigue of the muscle is suggestive of myasthenia gravis. The definitive diagnostic procedure is the Tensilon test, which should be performed on all patients with a high suspicion of the disease.

Appropriate documentation of all eyelid malpositions with photographs and formal perimetry showing the relative impact of the eyelid on vision have become mandatory by third-party payers before approval of any surgical intervention for an eyelid malady. A current refraction should be documented since any change in the height or tone of the eyelid can result in a postoperative change in corneal astigmatism. Finally, the patient's expectations for both visual and cosmetic improvement should be carefully elicited as this may impact the technique of surgical repair selected.

Once the nature and etiology of the eyelid malposition have been determined, the appropriate therapy must be selected. When the cause is determined to result from mechanical obstruction to eyelid movement, orbital disease, or ocular irritation, initial therapy must be directed toward the source of the pathology. Frequently the malposition may resolve upon treatment of the inciting factor. Surgical correction of eyelid malpositions ranges from simple to quite complex and may require specialized reconstructive techniques. A description of individual surgical techniques for various eyelid malpositions is beyond the scope of this text, but several generalities are true.

The success of ptosis repair depends a great deal on selecting the most appropriate procedure for each particular patient. In many cases, this will be rather easy. All eyelid procedures can be performed on an outpatient basis under minimal intravenous sedation and local infiltrative anesthesia. Extensive reconstructive techniques requiring flaps and grafts may require a greater level of anesthetic control. When surgery is performed while the patient is conscious, it better enables the surgeon to predict the position of the eyelids postoperatively and minimize the risk of postsurgical complications such as eyelid retraction, lagophthalmos, residual eyelid laxity, and excessive eyelid skin removal.

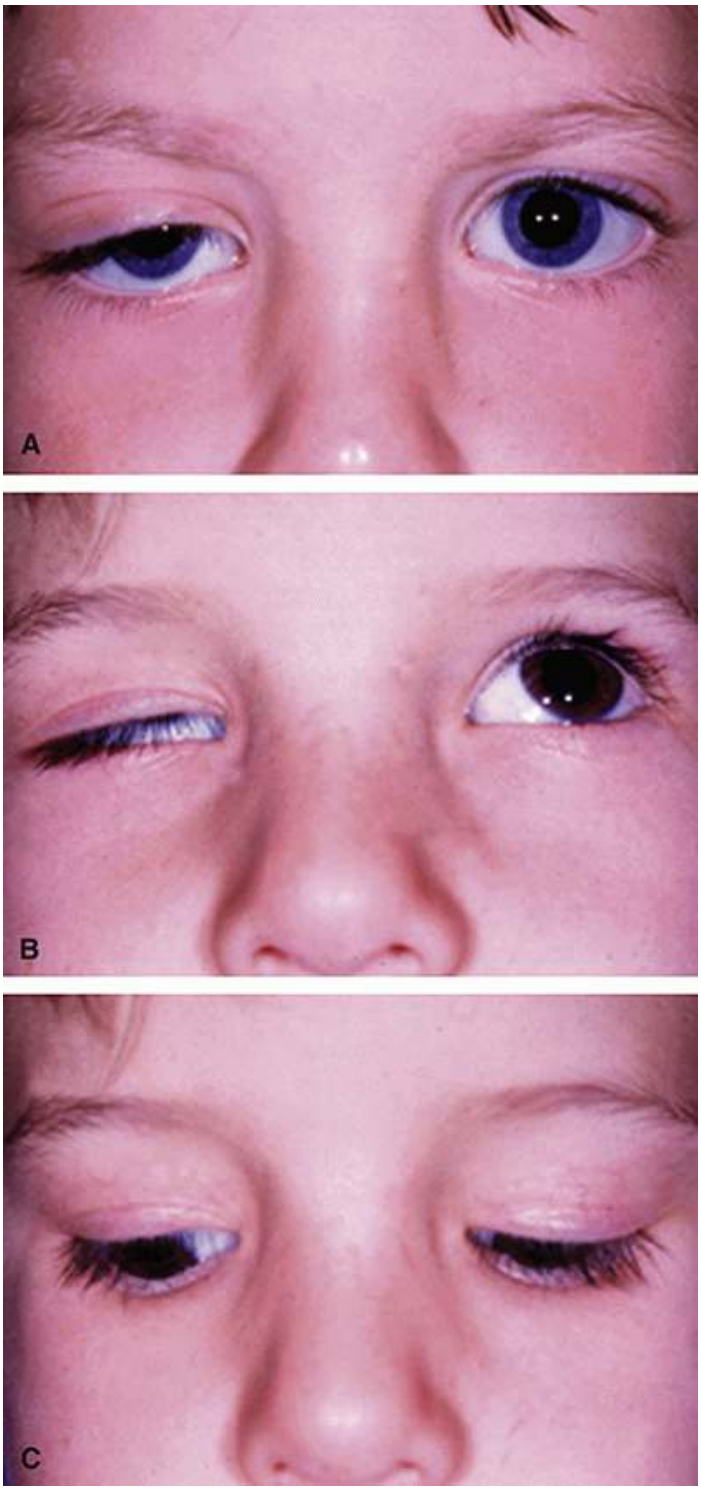

FIGURE 6.10 Congenital myogenic ptosis showing fibrosis of the levator muscle. A, In primary position the lid shows moderate ptosis. B, In upgaze the ptosis increases. C, In downgaze the ptosis decreases or even reverses.

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Perhaps the most dreaded complication of eyelid surgery is vision loss. With proper surgical technique, this is an unlikely event. Unrecognized intraoperative or postoperative orbital hemorrhage can lead to compressive optic neuropathy. This risk is minimized by having the patient refrain from any medication that may inhibit the clotting mechanism and determining in advance any patient with a coagulation disorder. The cornea and sclera are at risk for laceration, particularly when laser, electrical, or radiofrequency devices are used by inexperienced surgeons. Postoperative infection is rare, but severe infection of the orbit or ocular surface may lead to permanent vision loss.

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CHAPTER 7

Evaluation of Eyelid Lesions

Key Points

- Obtaining a proper medical history is of paramount importance. Current and past illnesses should be reviewed. Rash-like symptoms or past allergic reactions should be noted
- Family history should be reviewed because some neoplasms such as neurofibromatosis may be heritable
- Examination of the eyelids should include observation of the skin, conjunctiva, eyelid margin, and eyelashes
- Proper evaluation of an eyelid lesion begins with visual recognition of characteristics including size, color, consistency, shape, or surface modifications (acanthosis, hyperkeratosis, excessive keratin deposition)
- Signs of malignancy should be sought including an irregular shape, rolled “pearly” borders, associated induration, a “hardened” feel on palpation, fixation to deeper tissues or bone, regional lymphadenopathy, as well as restriction of ocular motility and/or proptosis
- If malignancy is suspected, except for basal cell carcinoma, systemic evaluation for metastases should be undertaken
- Appropriate photographic documentation of all eyelid lesions is mandatory

Alarge variety of benign and malignant lesions can affect the eyelids.[1] Many are common elsewhere on the body, but some are seen predominantly on the eyelids. Although accurate diagnosis in many cases may require histopathologic examination, a clinical diagnosis can be made in about 80% of cases based on the gross appearance, texture, color, and behavior of lesions and on the unique characteristics of eyelid skin.[2]

Some cutaneous and systemic disorders may be associated with eyelid lesions. In many cases, the eyelid findings are specific for a particular disorder, but at other times they may be nonspecific. These ocular findings, in combination with other cutaneous and systemic abnormalities, can often allow the clinician to make the correct diagnosis, even before the biopsy. Localized unilateral eyelid lesions may represent benign or malignant neoplasms, infections, or inflammations. Bilateral lesions more frequently represent disseminated systemic conditions such as collagen vascular diseases, metabolic disorders, vesico-bullous disease, dermatoses, or hypersensitivity reactions.

Eyelid lesions can be classified according to the anatomic structures from which they arise. These include the epidermis, dermis, subcutaneous fat, as well as various cells and adnexal structures within these layers.[3] Eyelid inflammations may present as a localized or diffuse erythematous area. They can be associated with loss of eyelashes, eyelid edema, induration, eczematous changes, tissue necrosis, and ulceration. If skin contraction occurs, the eyelid margins may become malpositioned manifesting as entropion, ectropion, or canthal angle dystopia. Inflammatory lesions may be painful and at times can be associated with lymphadenopathy. Infectious conditions of the eyelid result from viral, bacterial, fungal, or parasitic processes and may be primary or secondary. The latter can result from extensions of head and neck foci such as the sinuses or lacrimal sac, or from hematogenous spread from distant sites. The cause of the infection on the eyelid is often evident, such as in a site of trauma or recent surgery. However, when the infection is either atypical or recurrent, a biopsy, smear, or culture may help to exclude the presence of occult malignancy or uncover an unusual infectious organism. A systemic evaluation would be valuable for particularly aggressive infections and those caused by fungi and parasites.

From several recent large series looking at the frequency of eyelid lesions, benign processes account for approximately 40% to 85%, and malignant neoplasms for 15% to 60%. Among the benign lesions, the most frequent diagnoses are squamous papilloma, nevus, cysts, seborrheic keratosis, vascular lesions, and neural lesions. In the United States, South America, and Western Europe, the most common malignant tumor on the eyelid is the basal cell carcinoma (70%-90%) followed in rapidly descending order by squamous cell carcinoma (5%-15%), sebaceous carcinoma (2%-7%), and malignant melanoma (1%). Other rare tumors such as Kaposi sarcoma, adnexal carcinomas, and Merkel cell tumors are occasionally seen, as are metastatic cancers. Several series of malignant

eyelid tumors from Asia and India reported sebaceous carcinoma to be the second most frequent periorbital cutaneous malignancy at between 20% and 40% and in some cases equal to or more frequent than basal cell carcinoma.[4,5,6,7] Interestingly, studies from Taiwan, Hong Kong, and Singapore report a lower incidence of sebaceous carcinoma in the range of 10% to 20%.[8,9,10,11] But both basal cell and squamous cell tumors are significantly less common in non-Caucasian populations, which is likely responsible for this frequency disparity.

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History

As with diseases elsewhere in the body, a detailed medical history is very important in establishing the identification of eyelid diseases and should precede the ophthalmic examination. Some congenital eyelid lesions are associated with developmental anomalies, and these systemic conditions require pediatric consultation, including possible genetic counseling. In the adult, acquired malpositions and involutional changes usually precipitate or accompany the development of cutaneous lesions. Inflammatory conditions have characteristic clinical findings, but these often overlap with more serious diseases, such as malignant tumors. A careful history that focuses on the onset of the eyelid disorder, the time course, presence of concomitant changes or symptoms, travel history, and prior therapy helps narrow the examination and making a decision on any specific ancillary studies.

Current and past illnesses should be reviewed. Of importance in patients presenting with rash-like symptoms is the recognition of atopy (as manifest by hay fever or asthma) since this history may be suggestive of atopic dermatitis. Inquiry regarding past allergic reactions to food or medications is essential. Any systemic condition that may suppress the immune system, and thus predispose the patient to cutaneous infections or neoplasia (such as HIV and diabetes), should be questioned.

The family history should also be reviewed since the presence of eczema or atopy may be important in pruritic lesions. Many neoplasms, such as neurofibromatosis, occur as part of a heritable illness. Social and travel history is also critical. An occupational history is important as a considerable number of skin reactions are caused by or are worsened by exposure to various chemicals and environmental pollutants in the work environment.

Eyelid Examination

Examination of the eyelids should include observation of the skin, conjunctiva, eyelid margin, and eyelashes. Lesions localized to any one or several of these structures may offer important diagnostic information. The distribution of lesions on the skin itself is also important. One should first determine whether the distribution is random or whether certain areas are preferentially involved. Finally, certain distributions that suggest the participation of underlying nerves or vessels (dermatomal and segmental distributions) may point to diagnoses such as *Herpes* infection or oculodermal melanocytosis. Proper evaluation of an eyelid lesion begins with visual recognition of characteristics and recording an appropriate description. Appropriate terminology is important in making a diagnosis and allowing the physician to better document the examination.

Types of Lesions

Macule

A macule represents a small area of color change but is otherwise flat and not palpable (Figure 7.1). They are not raised or depressed and are less than 10 mm in diameter. Macules do involve changes in the thickness or texture of the skin. Examples include moles, freckles, inflammation, and postinflammatory hyper- or hypopigmentation.

Patch

A patch is an extension of a macule in both length and width. By definition, a patch is an area of color change that is 15 mm or larger in diameter. An example is a port-wine stain.

Papule

A papule is a small palpable elevated lesion less than 10 mm in diameter (Figure 7.2). Papules may be of any color and the surface may be smooth or rough. They come in a variety of shapes such as sessile, pedunculated, filiform, and verrucous. Examples include

nevi, some skin cancers, and verrucae.

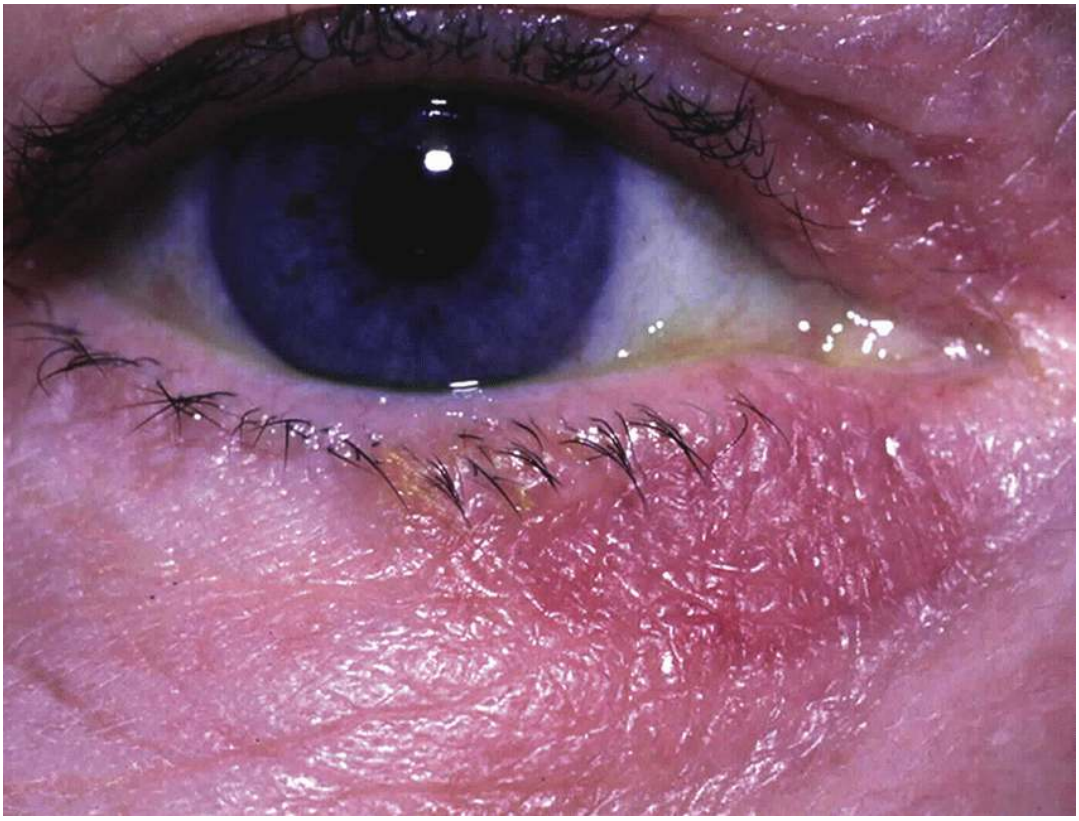

FIGURE 7.1 Macule showing a nonpalpable flat area of color change.

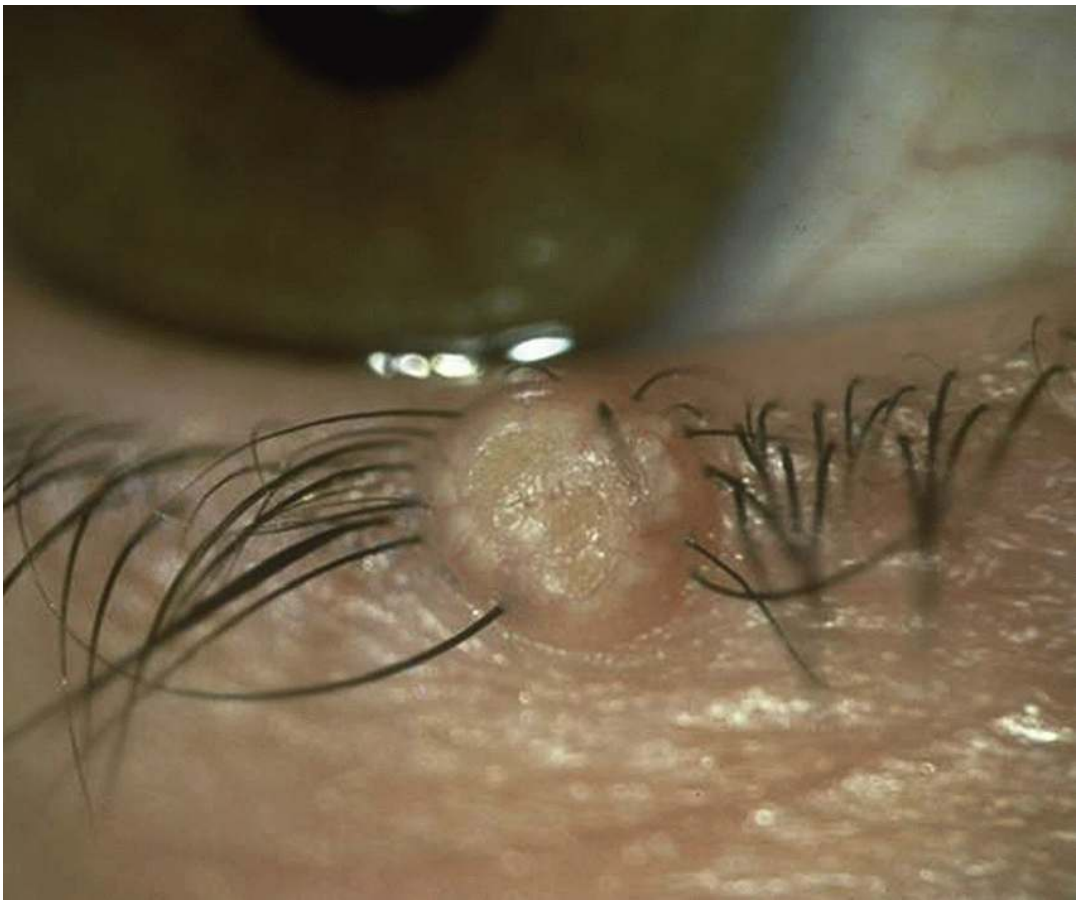

FIGURE 7.2 A slightly elevated palpable papule.

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Wheal

A wheal is an edematous papule in which the substance of the lesion is made up of nonloculated, interstitial fluid.

Plaque

A plaque is an enlargement of a papule in both length and width. Most plaques are elevated (Figure 7.3) and may be flat-topped or rounded. Examples include seborrheic keratosis, xanthelasma, and hemangioma.

Nodule

Nodules are firm, solid, elevated lesions that may be epithelial, dermal, subcutaneous, or at the myocutaneous junction of the skin (Figure 7.4). Examples include some malignancies, lipomas, and fibromas.

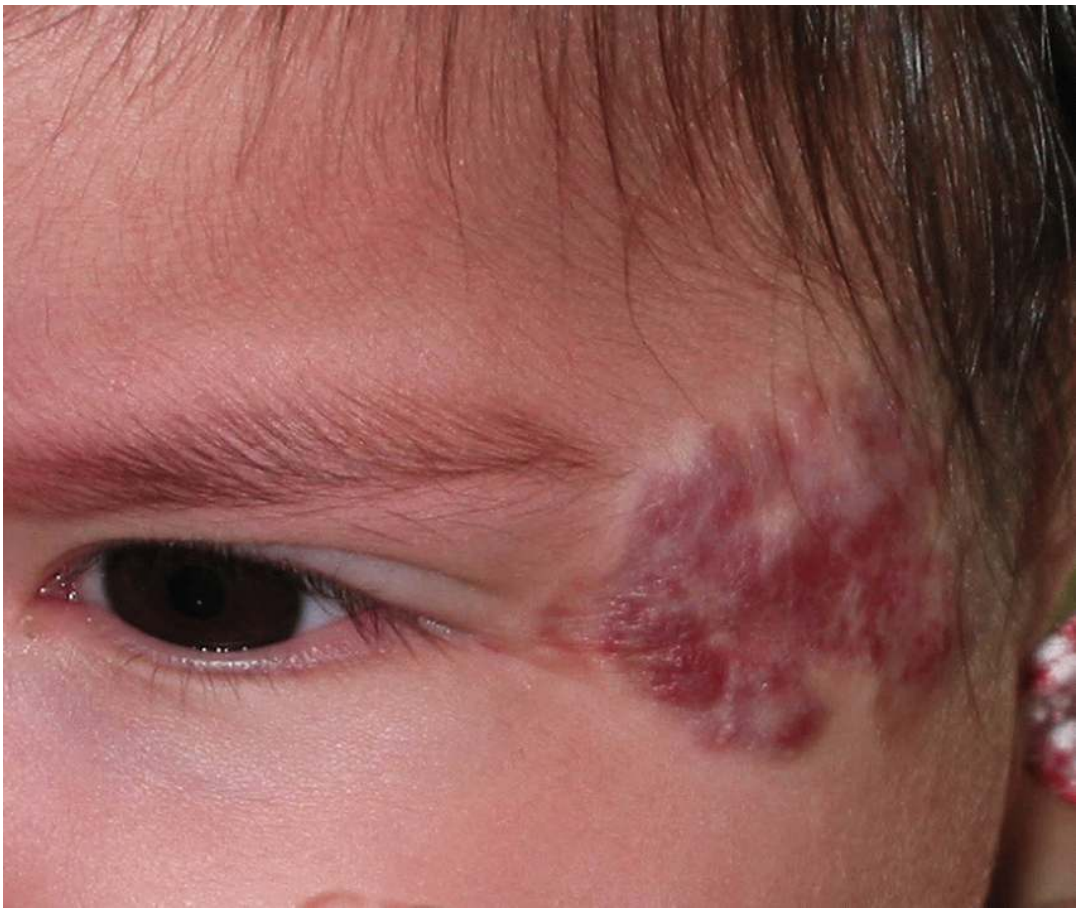

FIGURE 7.3 Infantile hemangioma forming an irregular plaque at the lateral canthus.

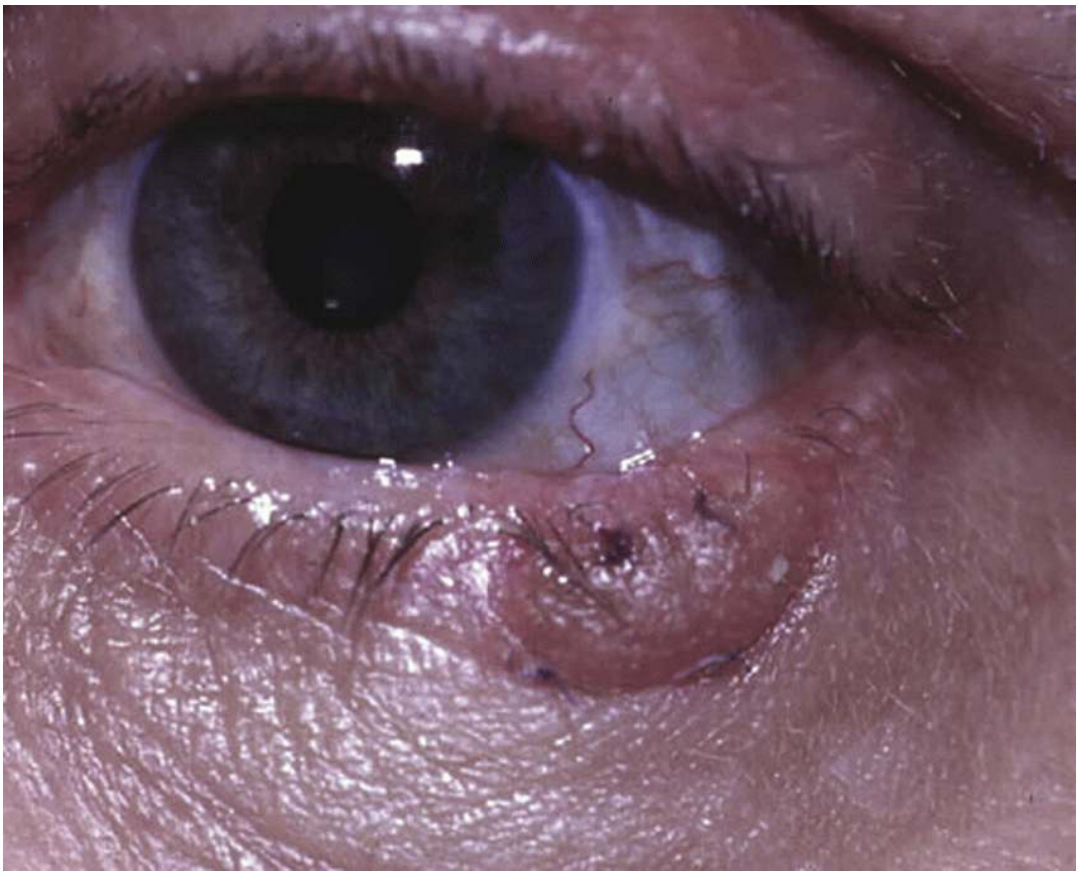

FIGURE 7.4 Lower eyelid nodule from a basal cell carcinoma.

Cyst

A cyst is a cavity with a cellular lining derived from glandular, ductal, or epidermal elements (Figure 7.5). It is filled with fluid or more consolidated material secreted by these cells. An example is a hidrocystoma.

Vesicle

A vesicle is a small clear fluid-filled blister less than 10 mm in diameter. When the roof of a vesicle is incised, the fluid runs out and the compartment collapses in contrast to a wheal which when incised produces a drop of fluid on the surface, but the lesion does not change in size or shape. Examples include allergic dermatitis and herpes simplex.

Pustule

A pustule is a vesicle that is filled with neutrophils (Figure 7.6). For this reason, it is white, or yellow-white in color. Examples are folliculitis and bacterial infections.

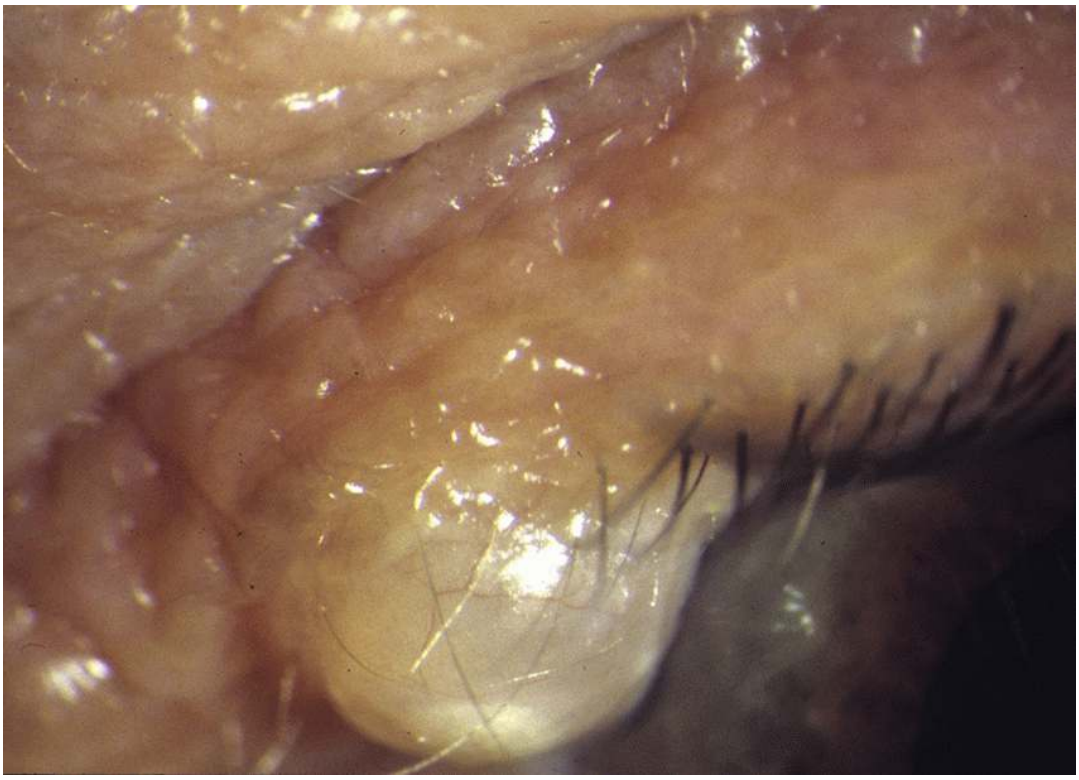

FIGURE 7.5 Clear sweat gland cyst, representing a fluid-filled cavity.

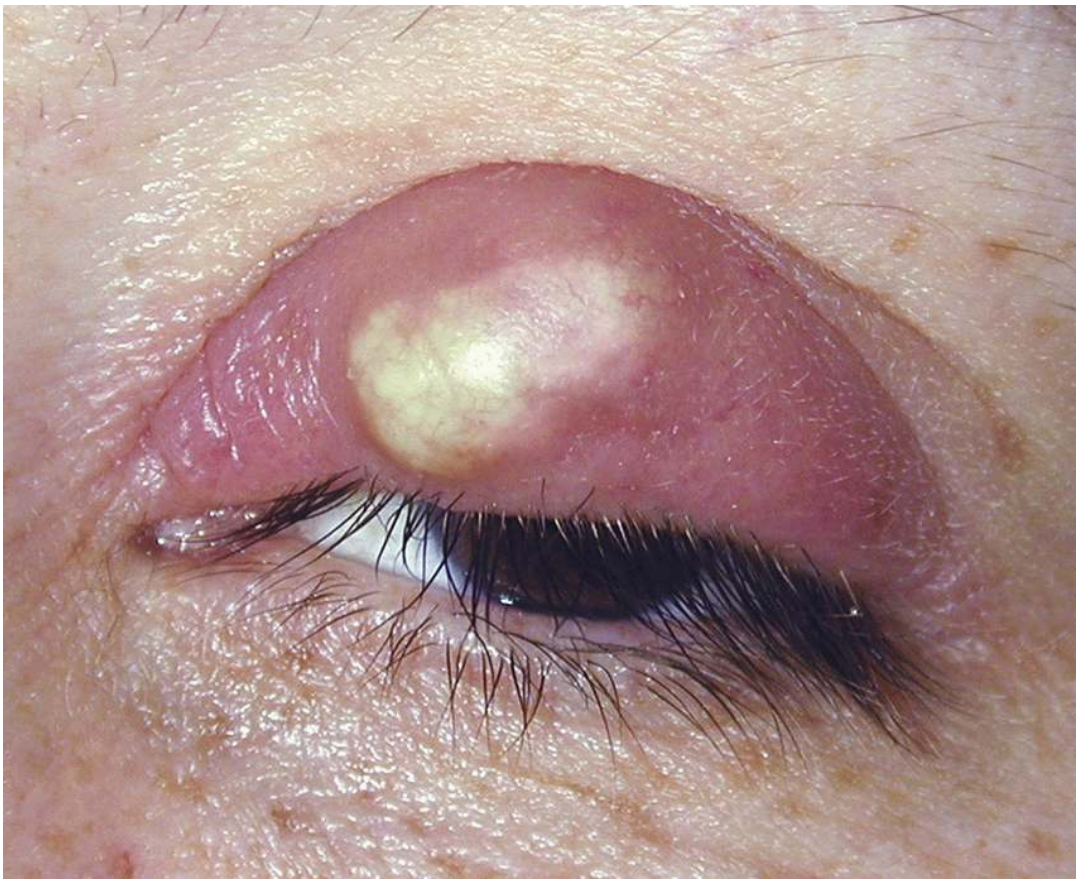

FIGURE 7.6 A chalazion pustule filled with purulent material of neutrophils.

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Bulla

A bulla is a vesicle that is 15 mm or larger in diameter. It is otherwise entirely similar to a vesicle. The fluid in a bulla is usually contained in a single compartment, but occasionally multiple compartments can be present.

Modifications of Lesions

Many lesions, regardless of their etiology, can show surface modifications involving their epidermal component. These can sometimes make identification more difficult and in some cases can mask the underlying pathologic process. The epidermis may be thickened (acanthotic) or its surface can be scaling (hyperkeratotic). Excessive keratin deposition can be seen on the surface of many different types of lesions leading to a “cutaneous horn.” However, this is a descriptive term only and can be seen with numerous benign and malignant lesions. The epidermis may be damaged causing weeping and crusting, or areas of missing epidermis result in areas of erosion or ulceration.

Scale

Scale occurs when there is an abnormal increase in the outermost layer of the epidermis, which is the stratum corneum. A scale is thus made up of flattened keratinized cells that, for one reason or another, are accumulating on the surface of the lesion. This process may be due either to faster than normal creation or to slower than normal exfoliation of these cells. Several types of scale are recognized: pityriasis-type scale and lichen-type scale.

Pityriasis-Type Scale

Pityriasis-type scale consists of flakes too small to be individually visualized. For this reason, the pityriasis-type scale cannot ordinarily be seen unless the surface of the lesion is scraped. Scraping the surface in this situation results in a small pile of fine white powder. Because of this characteristic, pityriasis-type scales are just barely palpable as a slight roughness on the surface of the lesion.

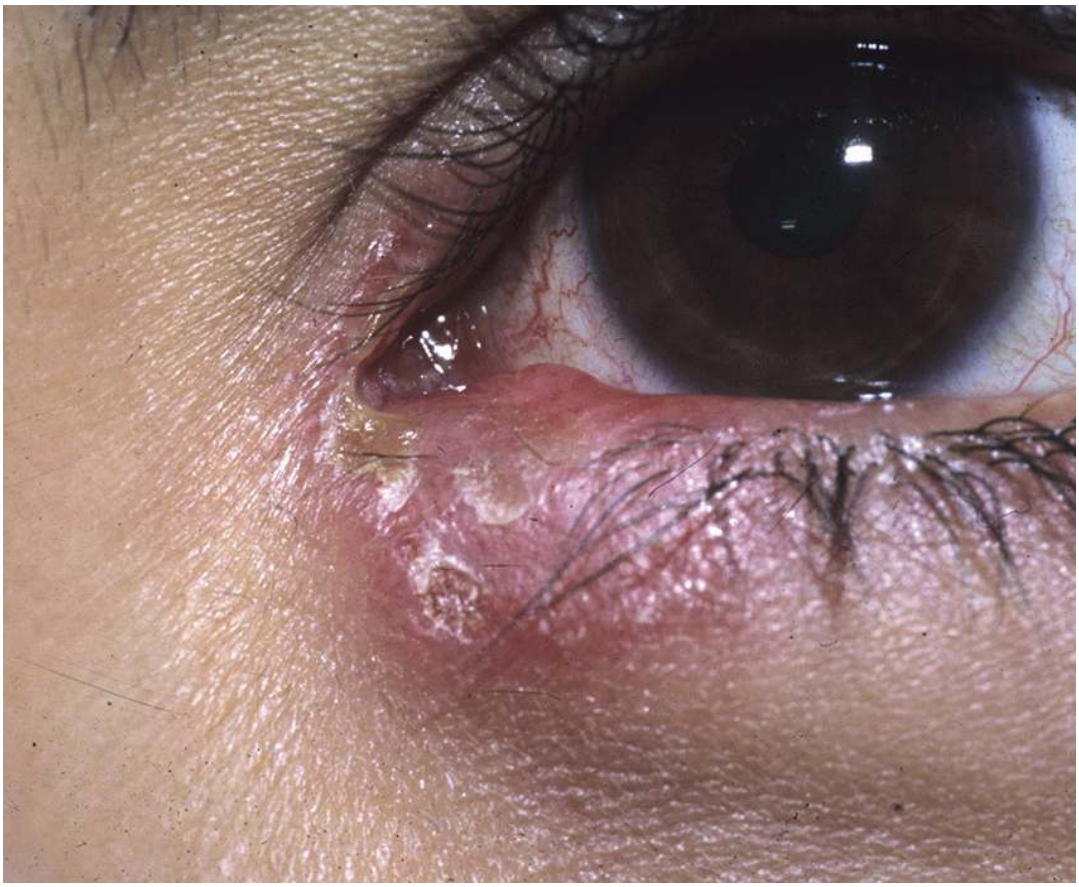

FIGURE 7.7 Lichen-type scale with a shiny, reflective surface.

Lichen-Type Scale

The lichen-type scale is tightly adherent to the surface of the lesion. It is palpable as a slight roughness and, because of reflected

light, is visible as a shiny surface (Figure 7.7). To appreciate this shininess, it is often necessary to move the light back and forth over the lesion until just the right angle for reflection is obtained.

Crust

Crusts occur when plasma exudes through a damaged or absent epidermis. It represents the dried serum proteins after the water has evaporated. A crust is rough on palpation and is visible as amorphous material that is yellow to brown (Figure 7.8). Where damage to the skin occurs more deeply than the level of the epidermis, blood vessels will be disrupted and there may be a component of dried blood mixed in with the crust. In such situations, the color of the crust will be red, violet, or black depending on the amount and freshness of the blood present.

Erosion

Erosion occurs when the epithelial surface of a lesion is absent (Figure 7.9). This may occur either because of the breakdown (or removal) of an overlying blister roof or as the result of trauma, especially that of scratching. Erosions formed as a secondary change to blisters are generally round in configuration. They often have an encircling collarette of *(Print pagebreak 55)* scale representing the peripheral remnants of the blister roof. On the other hand, erosions formed as a result of external trauma generally are angular or linear in configuration and lack the collarette of scale. The visible depth of an erosion is quite shallow since, by definition, no dermal damage is present. The surface of an erosion may be moist (weeping) or may be covered with crust. A fissure is a special type of erosion that forms as a thin crack between adjacent islands of intact epithelium; these fissures form when epithelial cells shrink as a consequence of excessive dryness. They can be conceptualized as similar to the cracks that form in a dry lakebed.

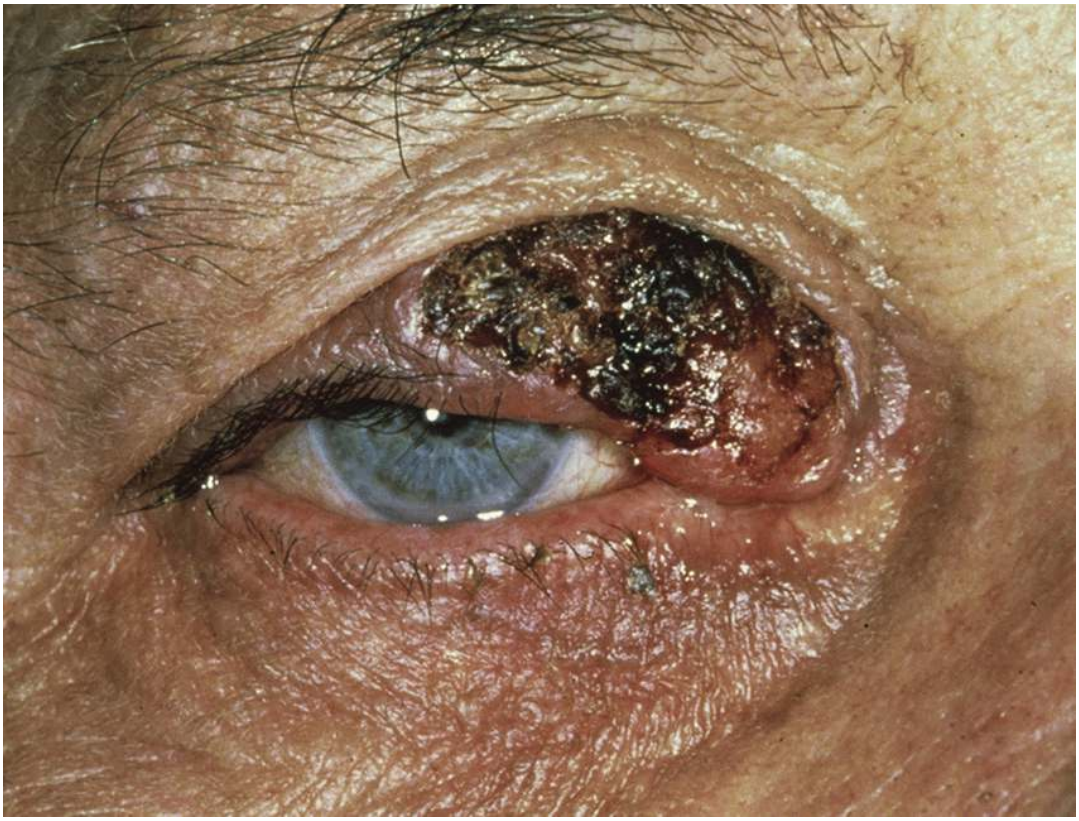

FIGURE 7.8 A surface crust formed from dried blood and exudate on a basal cell carcinoma.

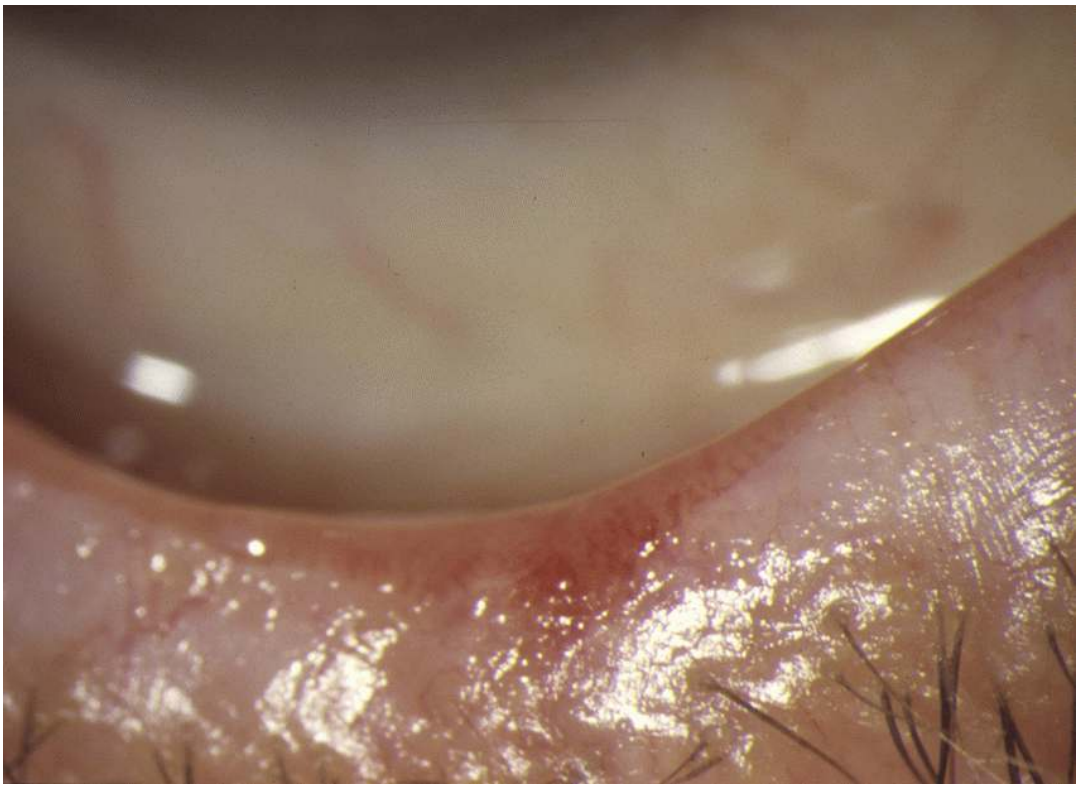

FIGURE 7.9 A superficial erosion with missing epithelium from a small eyelid malignancy.

Ulcer

An ulcer is similar to an erosion in that the overlying epithelium is absent. However, dermal damage is present, and the resultant defect is visible deeper than that of an erosion (Figure 7.10). This dermal damage is almost always accompanied by vessel disruption and bleeding. Hence, the crusts that form within ulcers have red, violet, or blue-black hues, which accompany the presence of blood. The blood also adds fibrin which in turn adds "toughness" and adherence to the curst. This difficult-to-remove dark-colored crust is known as *eschar*.

Lichenification

The epidermis responds to chronic trauma with increased cell proliferation and increased keratin production (Figure 7.11). The characteristic morphologic features of lichenification include (1) palpable thickness of the skin compared to nearby normal skin; (2) accentuation of the normal cross-hatched skin markings; and (3) the presence of lichen-type scale. Lichenification is especially characteristic in the chronic lesions of atopic dermatitis and neurodermatitis. It is particularly marked in the variant of these two diseases known as *lichen simplex chronicus.*

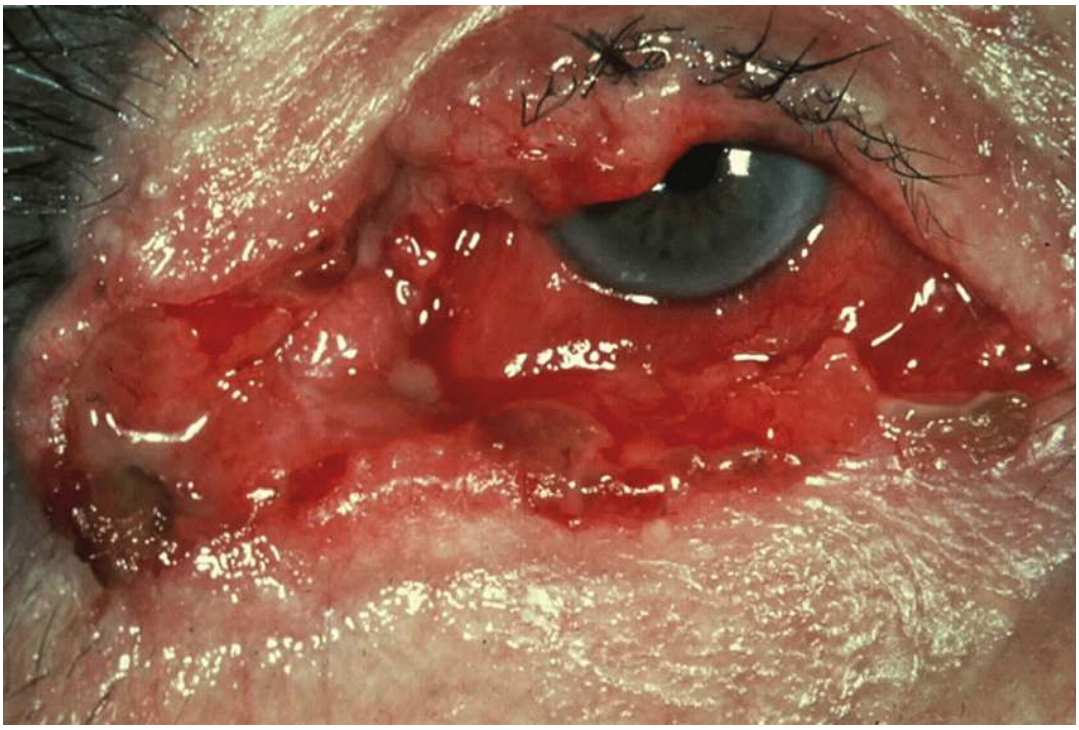

FIGURE 7.10 Deep ulcer involving the epidermis and dermis in a morpheaform basal cell carcinoma.

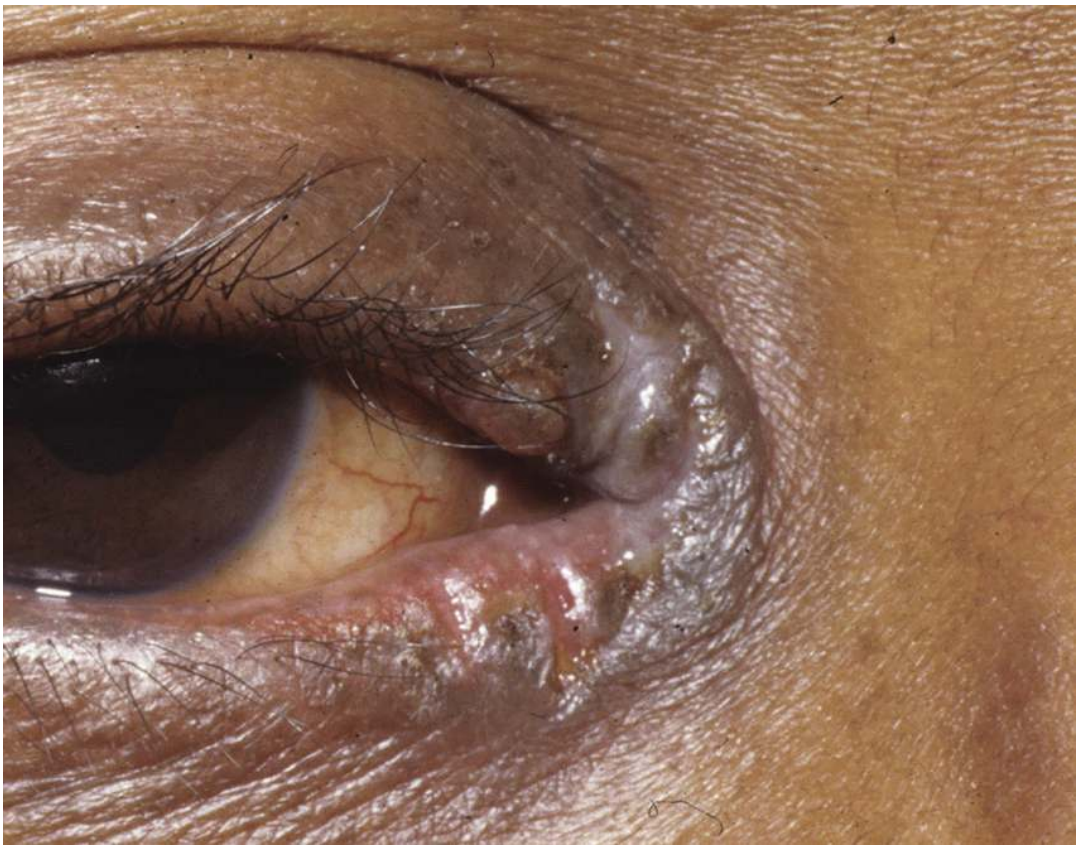

FIGURE 7.11 Lichenification with thickening of the epidermis and superficial scales.

Atrophy

Atrophy refers to a thinning and wrinkling of the skin due to aging, sun exposure, and some inflammatory or neoplastic diseases.

Arrangement

The arrangement of lesions refers to the pattern or relationship of nearby, nonconfluent, lesions. Typical arrangement patterns include *clustering* (a grouping of lesions), *beading* (closely set, but not confluent papules in a linear or circular arrangement), *satellitosis* (small peripheral lesions around a central larger lesion), *reticular* (lattice or net-like arrangements), and *linear*.

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Morphology

Size

A rough estimation of size is indicated by the term chosen for the basic lesion: vesicle versus bulla, macule versus patch, and papule versus plaque. In each of these pairs, the point of separation occurs at about 10 mm in diameter. However, in most instances, an actual measurement of the diameter should be given. Where a lesion is other than round, the shortest and the longest diameter should be stated. Where multiple lesions are present, one can determine the size of the most representative lesion and then give the range of sizes.

Color

Color is surprisingly hard to describe accurately. This is partly due to the lack of absolute color standards and partly due to the confounding effect that the patient's normal skin color has on lesional color. One must also discount the color contributed by "*secondary*" characteristics such as scale or crust. This can usually be accomplished by looking at the peripheral edge of a lesion since both scale and crust are often less prominent in this location. The basic hues found in skin lesions are red, white, blue, brown, black, yellow, and "*skin*" color. Each of these colors often gives a clue to the nature of the lesion (Figure 7.12A-F). A pink or red color suggests a vascular or inflammatory etiology. Blue color can represent blood or pigment deep within the skin layers or subcutaneously. A dark brown or black color is usually associated with melanin-bearing cells or with old blood, whereas a yellow lesion suggests lipid or fat. Lesions that are gray or white are often associated with an accelerated turnover of keratin.

Consistency

The consistency of a lesion is stated as being soft, medium, firm, or fluctuant. Soft lesions are easily compressible (lipomas, neurofibromas), medium lesions are slightly compressible (most inflammatory lesions), and firm lesions cannot be compressed at all (fibromas). The consistency of cysts is somewhat of an exception to this grading cyst. A cyst may be somewhat compressible as you first start to squeeze it, but the limits of elasticity of the wall are quickly reached and the lesion then begins to feel quite firm.

Configuration

Configuration represents the shape of the lesion as it is seen from above. Common types of configurations include *nummular* (coin-sized and coin-shaped), *gyrate*, *annular* (ring-like border with some degree of clearing in the center), and *linear* lesions. Most lesions have a circular configuration. A few lesions are oval, notably, those of pityriasis rosea and many others are irregular in shape. Examples of irregular shapes include gyrate and serpiginous lesions, which generally occur due to the melding of adjacent lesions that are enlarging in a centrifugal manner until they reach the point of confluence. Such lesions are frequently found, for example in psoriasis and urticaria. On the other hand, irregular lesions with angular or linear shapes generally occur as a result of external trauma such as scratching or are due to the direct inoculation of antigen (ocular medications) or virus (linear warts). Linear lesions (the shape, not the arrangement of a group of lesions) are special types that occur as part of the *Koebner phenomenon*. Here, external trauma is followed sometime later by the appearance of lesions in the traumatized site. This phenomenon, also known as the isomorphic response, is a characteristic feature of psoriasis, lichen planus, and a few other less common diseases.

Margination

Margination describes the nature of the transition between the lesion and normal skin. In general, margination is said to be either sharp (distinct) or diffuse (Figure 7.13). Lesions are considered to be sharply marginated or well-circumscribed when the transition from normal to abnormal skin occurs in the space of a millimeter or less, and when this degree of sharpness is maintained around the whole periphery of the lesion. In many cases, the further description of the transitional zone is helpful. Thus a lesion can have square borders or shoulders (verruca vulgaris, seborrheic keratosis), rolled borders (basal cell carcinoma), or sloped or domed borders (dermatofibroma). In a general way, the shape of the shoulder reflects the depth of the pathology; very superficial lesions tend to be square-shouldered and deep lesions tend to have sloped shoulders. Diffuse margination refers to a blending of the lesion into the surrounding skin over several millimeters such that the edges cannot be precisely defined.

Surface Characteristics

The surface of a lesion provides clues as to its location within the eyelid skin. Lesions arising from the epidermis tend to have more sharply marginated edges. The lesion itself is usually irregular with loss of normal epithelial fine markings and topography. In contrast, dermal lesions tend to elevate and stretch the overlying epidermis which usually retains normal topography, although with large lesions the epithelium may be thin, smooth, and shiny. The edges of dermal lesions are sloped and blend gently into the surrounding tissue.

In general, the surface of a lesion is often described as smooth or rough (Figure 7.14). Roughness occurs when either scale or crust is present. Differentiation between these two changes is important since the scale is usually associated with epithelial hyperplasia, and crust is associated with epithelial damage. The crust is always visible, whereas scale may or may not be visible. Thus, roughness in the absence of visible change is always due to the presence of scale. The crust may be of the superficial type (yellow or yellow-brown color) or of the hemorrhagic type (red, violaceous, or black color). The former overlies erosions, and the latter overlies ulcers.

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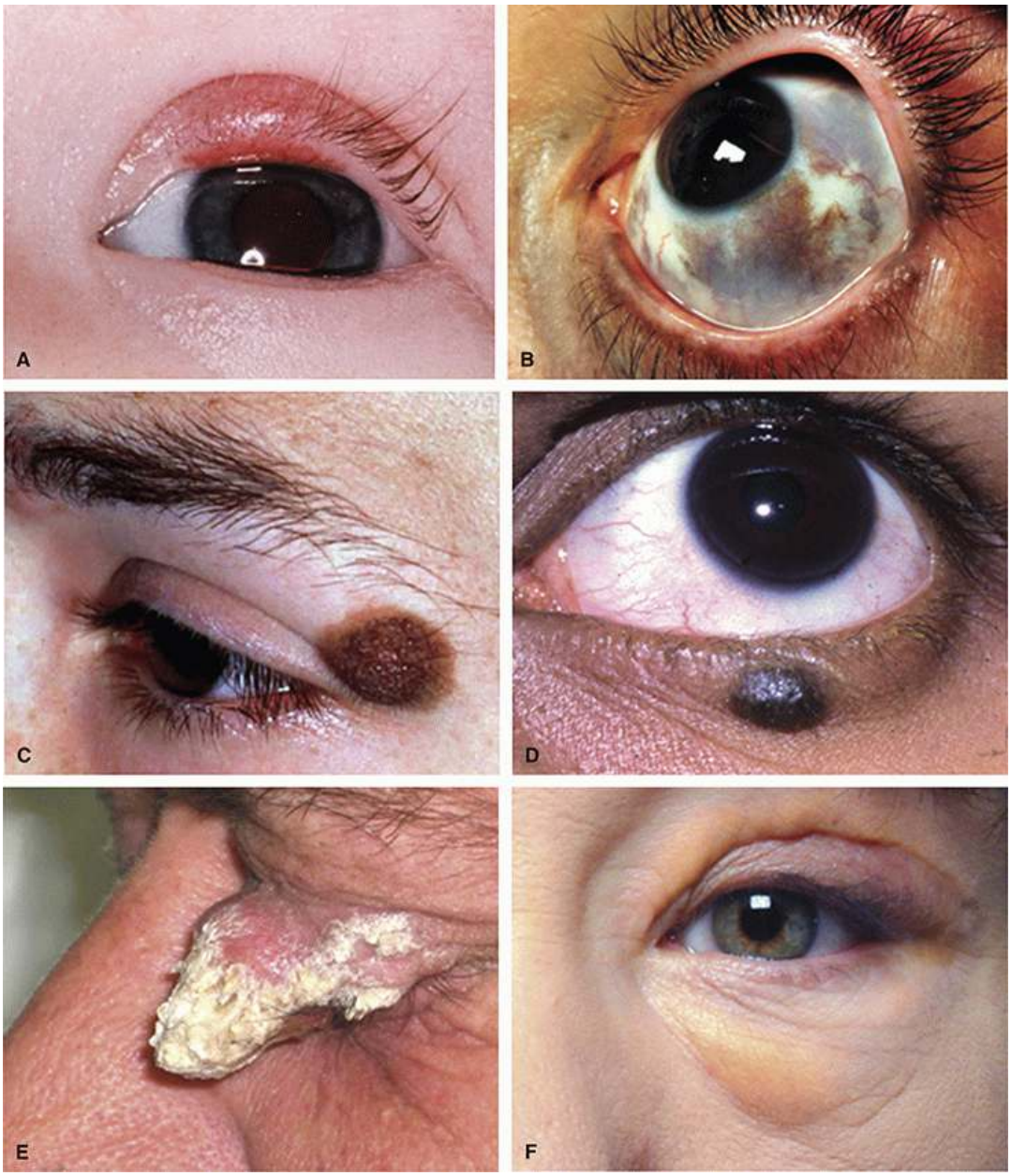

FIGURE 7.12 Color variations of eyelid lesions. A, Red (hemangioma). B, Blue (ectatic sclera). C, Brown (junctional nevus). D, Black (melanoma). E, White/gray (cutaneous horn). F, Yellow (xanthogranuloma).

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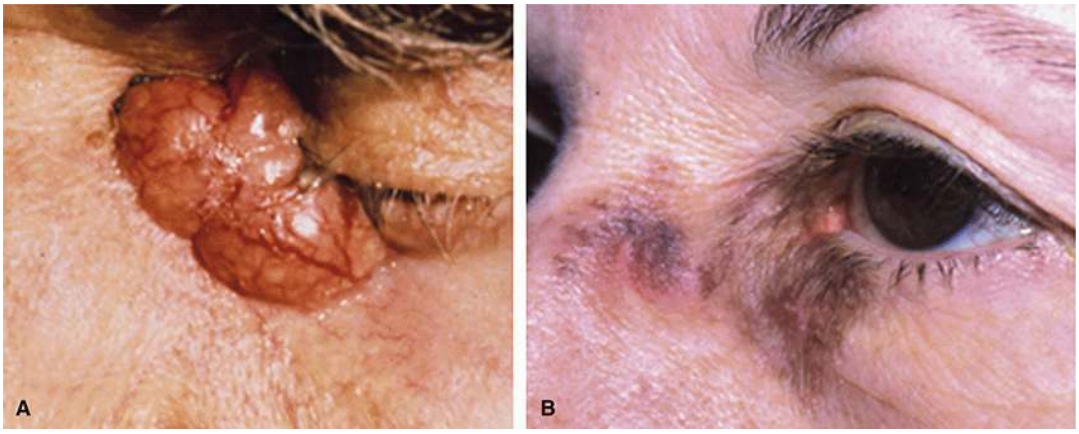

FIGURE 7.13 Margin characteristics of eyelid lesions. A, Sharply defined borders. B, Diffuse margins.

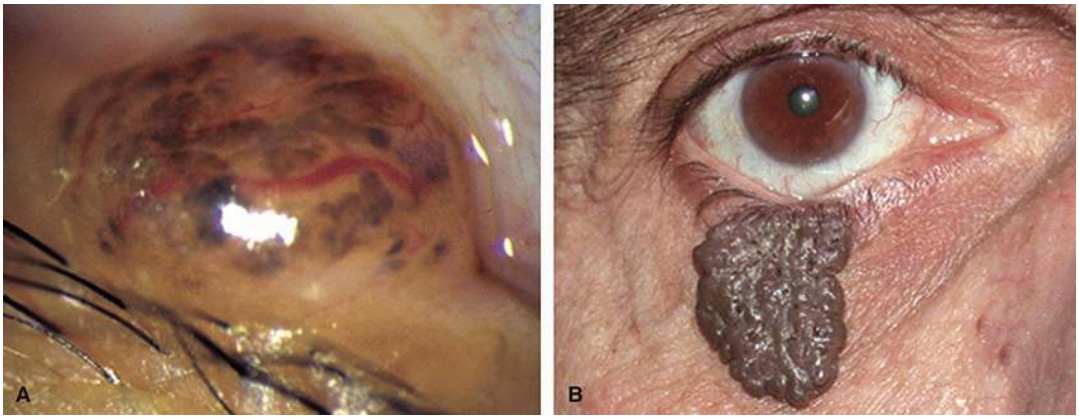

FIGURE 7.14 Surface characteristics of eyelid lesions. A, Smooth surface. B, Rough surface.

Signs of Malignancy

In the evaluation of any eyelid lesion, one of the major goals is to rule out malignancy. Most malignant neoplasms arising on the eyelid skin can mimic benign lesions and therefore can easily be missed. Although the large majority of eyelid lesions will be benign, the consequences of misdiagnosis are significant enough that any undiagnosed lesion or one that does not respond to medical therapy should be biopsied for histopathologic examination.

Information gained from the clinical history may also suggest malignancy. Most important here is progressive growth which may be slow or rapid. Other suggestive findings are irritation, intermittent drainage, bleeding, crusting, and changes in pigmentation.

Certain clinical characteristics often suggest malignancy. These include irregular shapes, rolled "*pearly*" borders, and associated induration (Figure 7.15). Malignant lesions often have a "*hardened*" feel on palpation when compared to the surrounding skin. Erosion is common as is ulceration leading to hemorrhage, exudation, and crust formation. Telangiectasias, or fine new vessels, are particularly suggestive of malignancy (Figure 7.16). Alterations of normal architecture including the obliteration of epithelial folds and lines, loss of lashes (Figure 7.17), and absence of meibomian gland orifices are particularly characteristic; benign lesions generally do not invade or distort normal eyelid structures. Malignant lesions frequently are not painful or tender.

Another important warning sign is fixation to deeper tissues or bone. This often suggests infiltration. Regional lymphadenopathy can be seen with infectious lesions, but should also raise suspicion for squamous cell, and especially sebaceous carcinoma. Restriction of ocular motility *(Print pagebreak 59)* and proptosis suggest deep orbital extension and require evaluation using CT or MRI scanning. If malignancy is suspected, except for basal cell carcinoma, systemic evaluation for metastases should be undertaken.

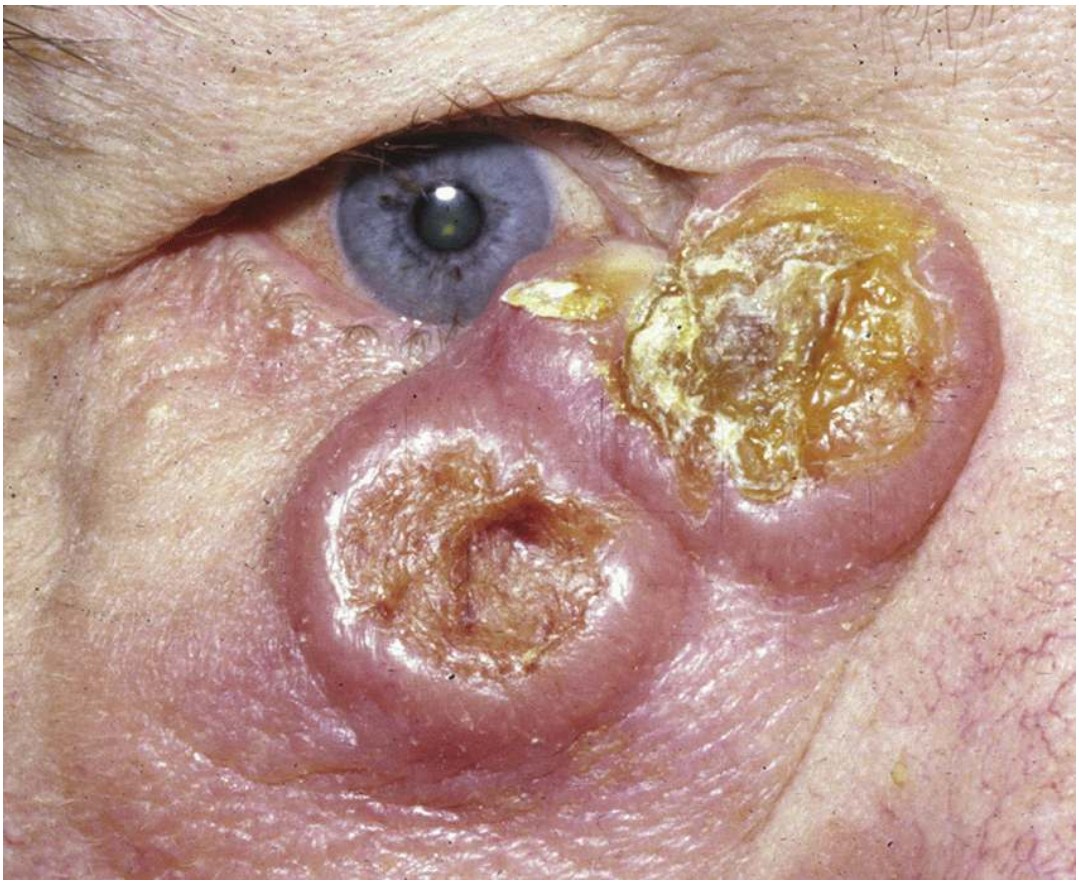

FIGURE 7.15 Rolled pearly borders suggestive of malignancy.

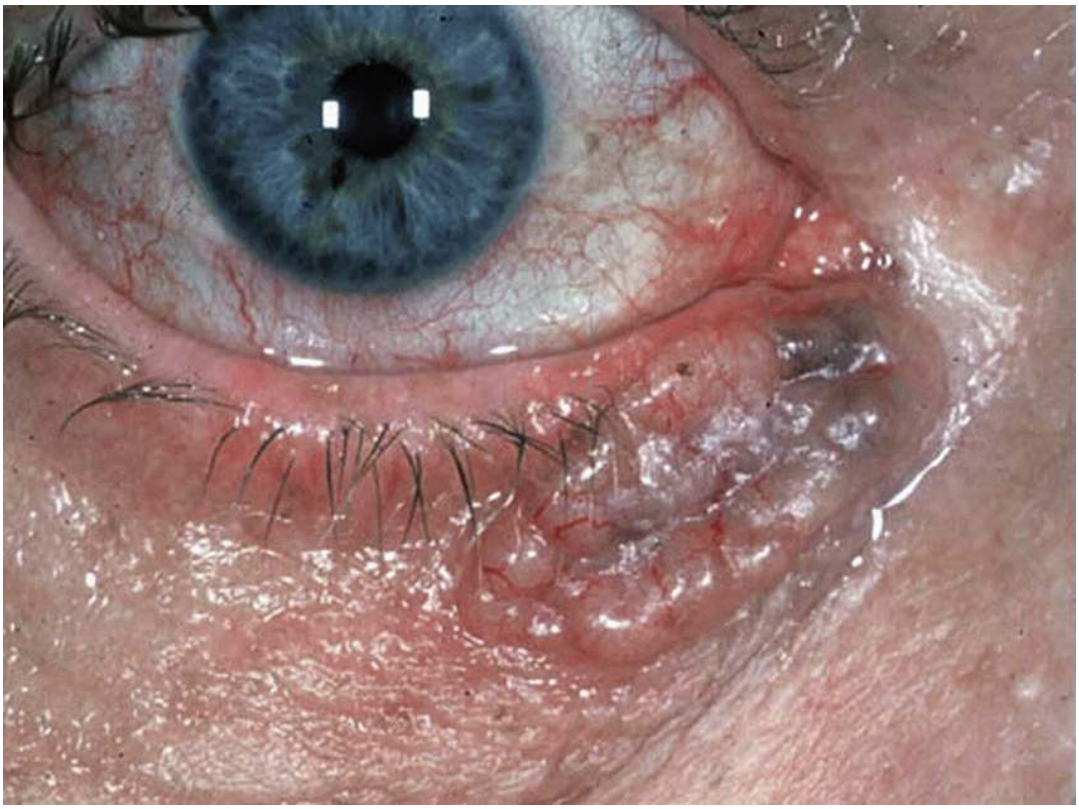

FIGURE 7.16 Fine dilated telangiectatic blood vessels on the surface of a basal cell carcinoma.

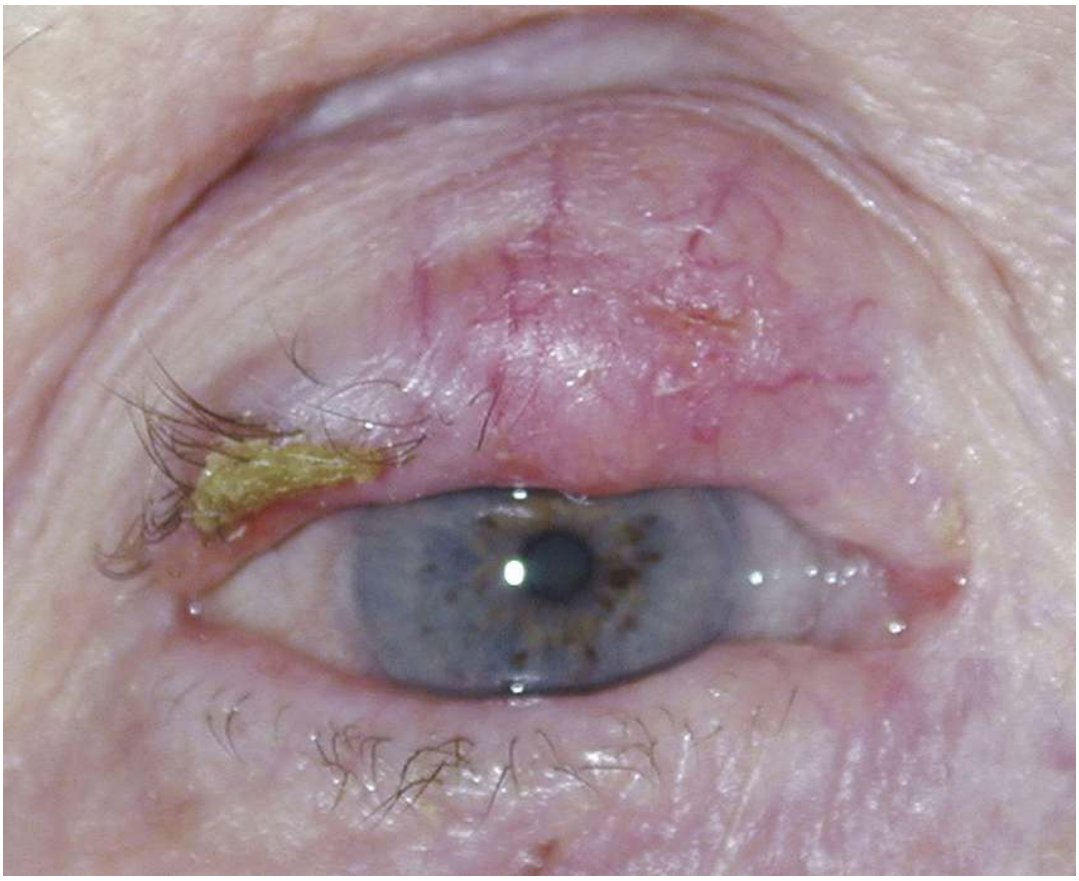

FIGURE 7.17 Loss of eyelashes (madarosis) associated with carcinoma of the eyelid.

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CHAPTER 8

Blepharoptosis, Aponeurotic (Involutional)

Key Points

- Aponeurotic, or involutional ptosis, is caused by levator aponeurosis disinsertion or redundancy with normal levator muscle function, and without any identifiable myopathic or neurogenic cause
- It results from a localized or generalized disinsertion of the levator aponeurosis or to weakening and attenuation of the distal aponeurosis fibers without frank disinsertion
- The condition is usually involutional, but can also result from trauma, repeated eyelid edema, or contact lens use
- Clinical findings are a reduced vertical palpebral fissure and MRD1, with normal levator muscle function
- Treatment is surgical, via either an anterior transcutaneous approach with reattachment or tucking of the aponeurosis, or with a posterior conjunctival Müller muscle resection procedure
- With either procedure, the prognosis is excellent with a very high success rate in achieving a symmetric elevation of the palpebral fissure

Aponeurotic, also referred to as involutional ptosis, accounts for the majority of acquired ptosis encountered in clinical practice[1,2] and is defined as ptosis caused by levator aponeurosis disinsertion or redundancy but with normal levator muscle function, without any identifiable myopathic or neurogenic cause.[1]

Etiology and Pathogenesis

Aponeurotic ptosis is a condition that results from a localized or generalized true disinsertion of the levator aponeurosis. Alternatively, it may be due to a weakening and attenuation of the distal levator aponeurosis fibers without frank disinsertion.[3] It may be age-related (involutional) or may occur due to a variety of factors, including trauma, repeated eyelid edema (blepharochalasis), long-term contact lens wear, chronic eyelid rubbing, postsurgical changes, or floppy eyelid syndrome.[1,3,4,5,6,7] In the young population, trauma-related aponeurotic ptosis is the most common cause.[1] Contact lens use with or without associated giant papillary conjunctivitis is another frequent cause of aponeurotic disinsertion.[1] Postsurgical or postoperative ptosis is an acquired ptosis that occurs after intraocular surgery, which was a significant issue in the past. However, its frequency has been decreasing as cataract surgery and anesthetic techniques have evolved, a fact which is reflected by the sharp decline in the number of publications discussing the subject since the advent of phacoemulsification.[5,7] The etiology of postcataract ptosis is poorly understood but is probably multifactorial. Postoperative levator muscle/aponeurotic injury could occur due to mechanical forces, myotoxicity, and/or neurotoxicity.[7] Mechanisms proposed in the past to cause this complication include eyelid edema, bridle suture placement, superior rectus grasping, size and location of the surgical incision, peribulbar or retrobulbar anesthesia, prolonged patching, and ocular massage, but most of these are no longer performed with modern phacoemulsification techniques. However, other factors such as a preexisting narrower vertical palpebral aperture, eyelid speculum placement, previous intraocular surgery, and most importantly, a reduced preoperative levator function may still play a role.[7]

Cadaveric and histologic studies show direct as well as indirect evidence of attenuation of the aponeurosis as the etiopathogenetic mechanism behind aponeurotic ptosis.[6,7,8,9] Direct evidence includes thinning, stretching, and disinsertion of the levator from its attachments to the tarsus and pretarsal orbicularis muscle.[6,7,8,9,10] When the distal end of the aponeurosis is missing in histologic specimens, this is considered indirect evidence of an aponeurotic event.[8] Another anatomic change in aponeurotic ptosis which is seldom referred to in the literature despite its surgical relevance is an age-related thinning and dehiscence of the medial limb of Whitnall ligament and the medial horn of the levator, resulting in a lateral or anterolateral displacement of the tarsus.[10,11] In a recent study on senile Asian cadavers, the average width of the medial horn of the levator was 6.0 mm while that of the lateral horn was 12.3 mm making it more vulnerable to age-related redundancy. If not specifically addressed, these changes may subsequently cause medial undercorrection after ptosis surgery.[10,11] Of note is that a recent clinicopathologic study showed evidence of muscle

damage and decreased muscle fiber bulk in patients with aponeurotic ptosis.[5] These findings suggest that even though it is believed that the levator muscle is preserved in aponeurotic ptosis on a macroscopic level, there is an ongoing process of muscle damage on the microscopic level, and further research is necessary to fully understand its role in the pathogenesis of aponeurotic ptosis.[5]

Intuitively, aponeurotic changes should be the only expected histopathologic findings in patients with aponeurotic ptosis, and indeed some studies do show a normal levator *(Print pagebreak 64)* muscle. However, other histologic studies have documented atrophy, and fibrosis, as well as fatty infiltration of the levator muscle, suggesting a possible age-related myopathic process as a component in the pathogenesis of this condition.[6,9] Whether these changes do play a role in the pathogenesis of aponeurotic ptosis is controversial, and two alternative explanations exist for those degenerative levator muscle abnormalities, and both are entirely plausible. Sarcopenia or loss of muscle mass and strength as a consequence of aging is a universal finding throughout the body, and there is no reason to believe the levator should be an exception. Alternatively, this fatty infiltration of the levator muscle could be a degenerative response to long-standing aponeurotic disinsertion.[6,10,12] Atrophic changes are also observed in the Müller muscle itself, which becomes thinner and more elongated, shows significant fatty infiltration with advancing age, and may even migrate from the superior tarsal border. As we shall see later, these changes have implications for interpreting the results of phenylephrine testing.[12,13,14,15,16]

Clinical Presentation

Aponeurotic ptosis is by far the commonest type of ptosis, and although frequently termed “senile” or “involutional” blepharoptosis in the literature, the former is a clear misnomer, and in general, the use of both terms may be confusing since aponeurotic ptosis may occur at any age including neonates.[17,18] Important measurements and definitions have to be clarified before describing the clinical picture of aponeurotic ptosis which is crucial for surgical planning. The palpebral fissure height (PFH) is defined as the distance between the upper and lower lid margins while the patient is looking in primary gaze (normal range can vary from 7 to 12 mm).[4,19,20,21,22] The amount of ptosis in mm is calculated by subtracting the PFH value on the normal side from that on the ptotic side in unilateral cases and from a reference value of 10 in bilateral cases. The problem with such measurements is that it is assumed that the lower eyelid is normal in position, which is not always the case. Therefore, the superior margin to reflex distance (MRD1) is more accurate.[19,20] MRD1 is defined as the distance between the upper eyelid margin and the corneal light reflex or the pupillary center; the normal value is 3.5 to 5 mm. MRD1 is assigned a negative value if the eyelid margin lies below the corneal light reflex. MRD2 is the distance from the margin of the lower lid to the central corneal reflex; normal is 4 to 5 mm.[4,19,20,21,22] The normal position of the upper eyelid crease is 7 to 10 mm above the eyelid margin.[3] The most important measurement to make during the examination of a ptosis patient is the levator muscle function or the range of excursion of the eyelid margin from extreme down-gaze to extreme up-gaze. The normal function ranges from about 13 to 16 mm.[2] Except in patients with Horner syndrome where the MRD2 may be reduced, MRD2 is of little clinical significance in actual clinical practice, and physicians rely more on the MRD1 and PFH, the former being the more clinically accurate.[3] To obtain accurate measurements of the levator muscle function, PFH, and MRD1, it is important to assure that the frontalis muscle is completely neutralized by pressing the brow firmly against the superior orbital rim.[2,21,23]

Although the clinical diagnosis of ptosis is relatively simple and can be made from a routine clinical examination, to plan appropriate management proper identification of the cause of the ptosis is important, and often requires a thorough history taking, not just from the patient but from family members as well even if the patient was an adult.[1] History taking should retrieve the following information: age of onset, family history, prior intraocular or eyelid surgery, predisposing factors such as contact lens wear or trauma, recurring episodes of eyelid swelling, whether the ptosis worsens throughout the day, the presence of any aberrant eyelid positions with facial movements, and if there is double vision. Past medical history as well as a list of current medications, including the use of blood-thinning products, is also important.[24]

Patients with aponeurotic ptosis present with an upper eyelid that is lower in position than normal (Figure 8.1), with an elevated or absent eyelid crease (Figure 8.2).[6] By definition, the levator muscle function is usually ≥10 mm and generally exceeds 12 mm, but in contrast to myopathic dysgenetic ptosis (Chapter 10), there is no correlation between PFH and levator muscle function.[5,25] The ptosis is constant in all positions of gaze including downgaze, and it may become more noticeable by the end of the day when the patient is tired. Thinning of the eyelid with a deep upper eyelid sulcus (Figure 8.3) can also be observed in more severe cases.[4] This is often associated with a compensatory brow elevation due to the unconscious recruitment of the ipsilateral frontalis muscle to help raise the eyelid from its lower resting position and increase the superior visual field (Figure 8.4).[26,27] In unilateral cases, compensatory contralateral pseudoretraction may be observed due to the Hering law (Figure 8.5), and for the same reason, contralateral ptosis might develop postoperatively.[28,29] Therefore, Hering law dependency should be tested in every patient as it has been demonstrated in ≥50% of aponeurotic ptosis patients (Figure 8.6).[30] The test for the Hering phenomenon can be performed by manually elevating the ptotic eyelid to a normal position,[30] or by pharmacologic elevation of the ptotic eyelid with 2.5% or 10% phenylephrine.[29,31]

When aponeurotic ptosis is suspected, the phenylephrine test is often performed. Phenylephrine is an alpha-1 adrenergic agonist that

contracts the sympathetically innervated Müller muscle, a secondary eyelid retractor, and elevates the eyelid.[23] The first step in this test involves measuring the MRD1, preferably with photographic documentation, followed by instillation of 1 drop of 2.5% or less commonly 10% phenylephrine in the superior conjunctival fornix or on the superior limbus of the ptotic eye, with the eye looking down.[23] After a waiting period of 3 to 5 minutes, the MRD1 is measured again.[23] If phenylephrine results in an improvement in eyelid height of >2 mm, this is considered a positive *(Print pagebreak 65) (Print pagebreak 66)* response, but if the eyelid lift is <2 mm this is considered a negative or poor response.[15] The 2.5% is preferred by many oculoplastic surgeons because it has nearly the same efficacy as 10%, without the side effects.[15,32,33] Adrenergic side effects can include cardiac arrhythmias, myocardial infarction, severe hypertension, pulmonary edema, and even cardiac arrest or subarachnoid hemorrhage.[15] The difference in eyelid lift between the 2.5% and 10% concentrations is within the range of 0.2 mm, which is clinically irrelevant and therefore does not justify the use of the higher concentration.[15,33] Patients with mild ptosis have the greatest response rate and the highest degree of eyelid elevation, while patients with severe ptosis may not respond well to the test and are therefore considered poor candidates for Müller muscle conjunctival resection surgery (MMCR).[3,23] The phenylephrine test may also be important in deciding whether to operate on one or both sides, as patients with unilateral ptosis who manifest Hering dependency in the contralateral eyelid after phenylephrine testing may be considered for bilateral surgery.[34]

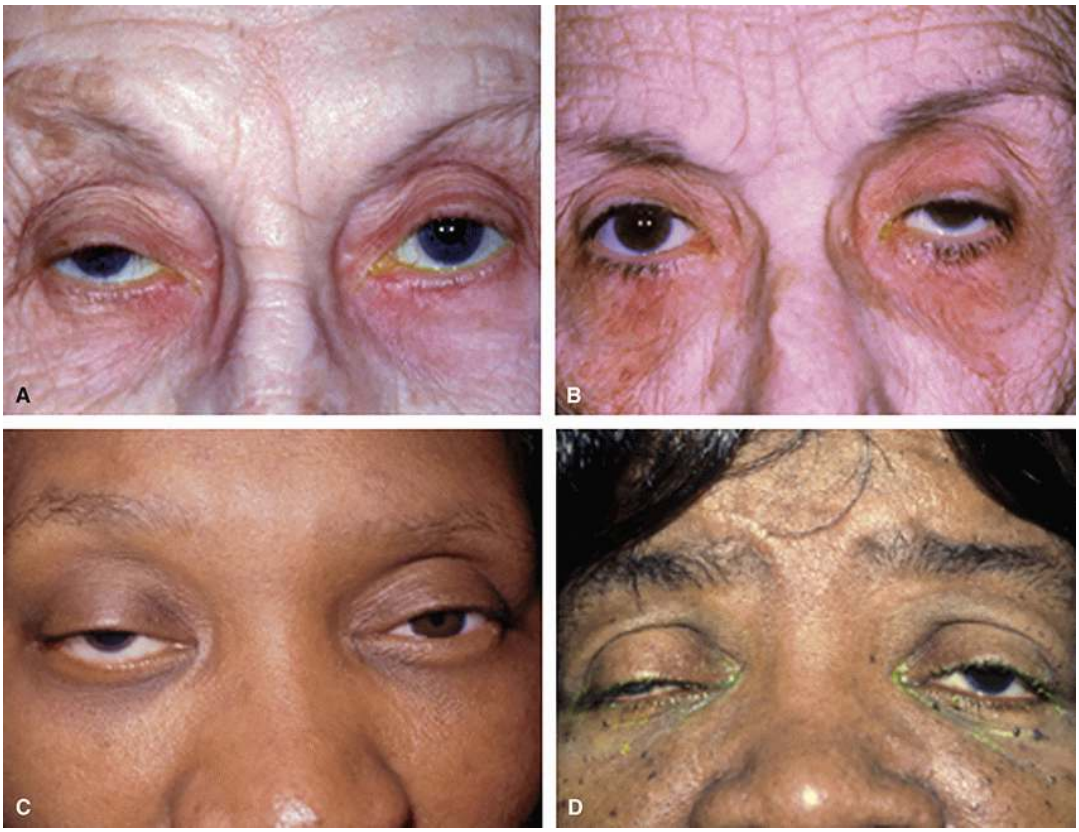

FIGURE 8.1 A-D, Typical presentations of involutional aponeurotic ptosis with reduced MRD1 and narrow palpebral fissure.

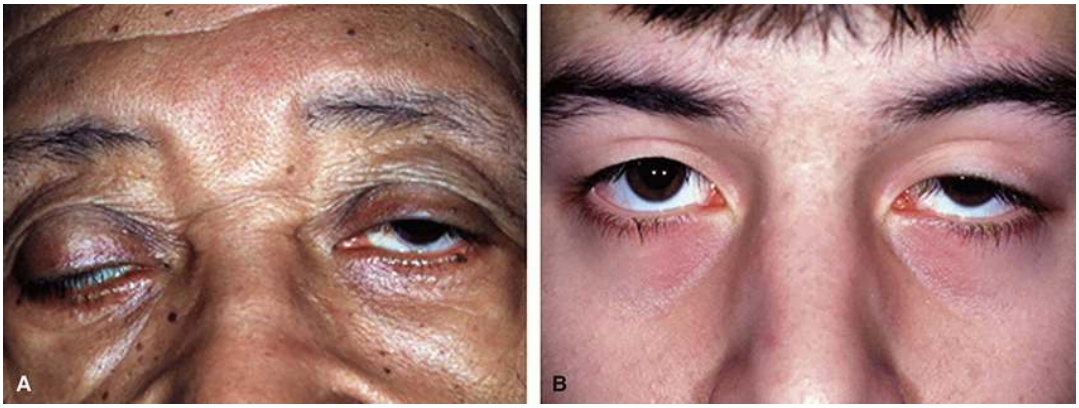

FIGURE 8.2 A and B, Upper eyelid aponeurotic ptosis with an elevated eyelid crease.

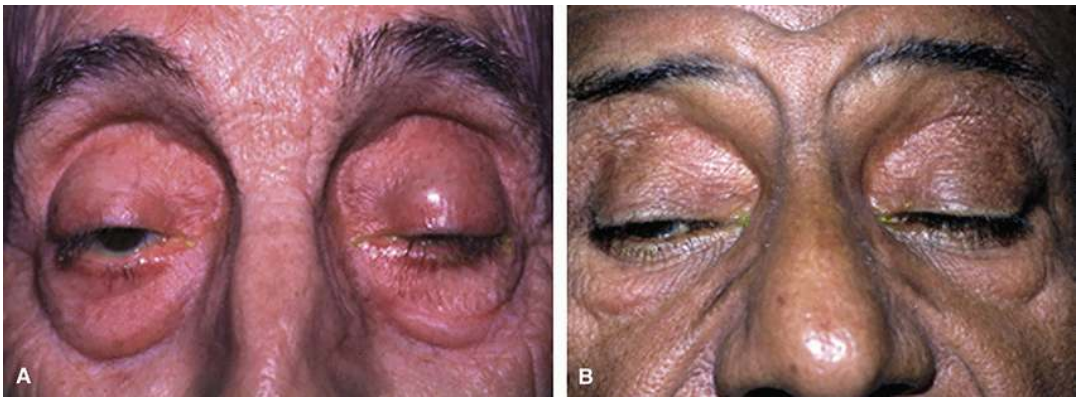

FIGURE 8.3 A and B, Severe aponeurotic ptosis with thinning of the upper eyelids, absent eyelid crease, and deep superior sulcus.

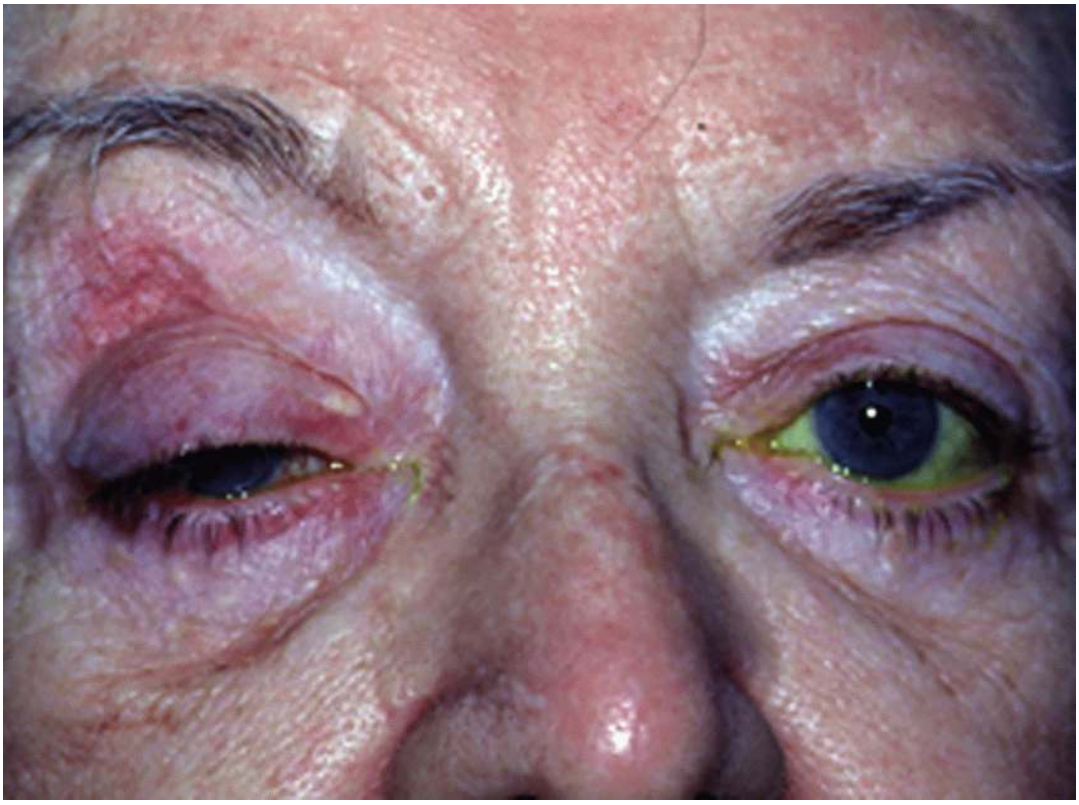

FIGURE 8.4 Right upper eyelid ptosis with a compensatory elevation of the brow.

Although a good response to the phenylephrine test is useful and is a necessary prerequisite MMCR,[22,23,35] there are certain reservations regarding the role of this test as a true predictor of MMCR success.[36] Although the majority of receptors in the Müller muscle are alpha-2 receptors,[14,36,37] phenylephrine is a direct alpha-1 selective adrenergic agonist and not alpha-2 (the levator muscle predominantly shows β1 receptors).[37] Therefore, it seems plausible to suggest that the phenylephrine test is not as sensitive an indicator of the role of Müller muscle function as was previously thought, and a search for an alternative drug that more accurately and fully depicts muscle function is required.[14,36] Some patients with a negative response to the test may still benefit from MMCR. This is more commonly observed in older patients with long-standing ptosis and is attributed to degenerative changes in the Müller muscle which may cause atrophy of adrenergic receptors.[12,13,14] Additionally, although MMCR is indicated primarily for mild to moderate ptosis, a certain percentage of patients with severely ptotic eyelids do respond well to phenylephrine testing and may benefit from MMCR. Therefore, the use of the test in clinical practice should not be restricted to milder cases and may be performed even in cases of severe aponeurotic ptosis.[23]

An ocular motility examination should routinely be performed to exclude an underlying neurogenic etiology.[38] However, some elderly patients with aponeurotic ptosis will have slightly decreased eye movements on up-gaze, which could confuse the clinician into suspecting myopathic ptosis, while in fact, it may be due to disuse because patients with severe aponeurotic ptosis may chronically be reluctant to look-up.[25] This behavior may also be responsible for the infrequent clinical observation of patients with long-standing aponeurotic ptosis whose levator function is *(Print pagebreak 67) (Print pagebreak 68)* less than the cut-off point of

10 mm, again misdirecting the clinician toward a myopathic etiology, even though at surgery a simple aponeurotic advancement corrects the ptosis and no corneal problems are encountered.[25] Pupil assessment is also important to rule out the existence of Horner syndrome or oculomotor palsy.[38] Slit lamp examination is necessary to rule out active corneal disease, corneal dryness, or corneal anesthesia.[38] Although rare, corneal anesthesia should be ruled out in aponeurotic ptosis patients, particularly when it develops after vitrectomy surgery, predominantly in diabetics undergoing 20-gauge surgery.[39] Even though a Bell phenomenon is usually intact in patients with aponeurotic ptosis, it still should be evaluated. An additional factor that is more relevant but may be more of a concern in the elderly is the quality of the tear film.[40]

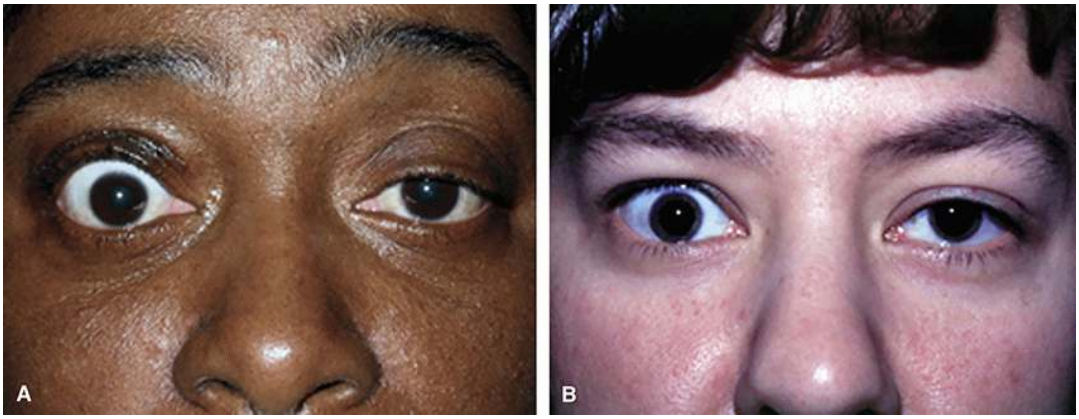

FIGURE 8.5 A and B, Left upper eyelid ptosis with pseudoretraction of the right upper eyelid.

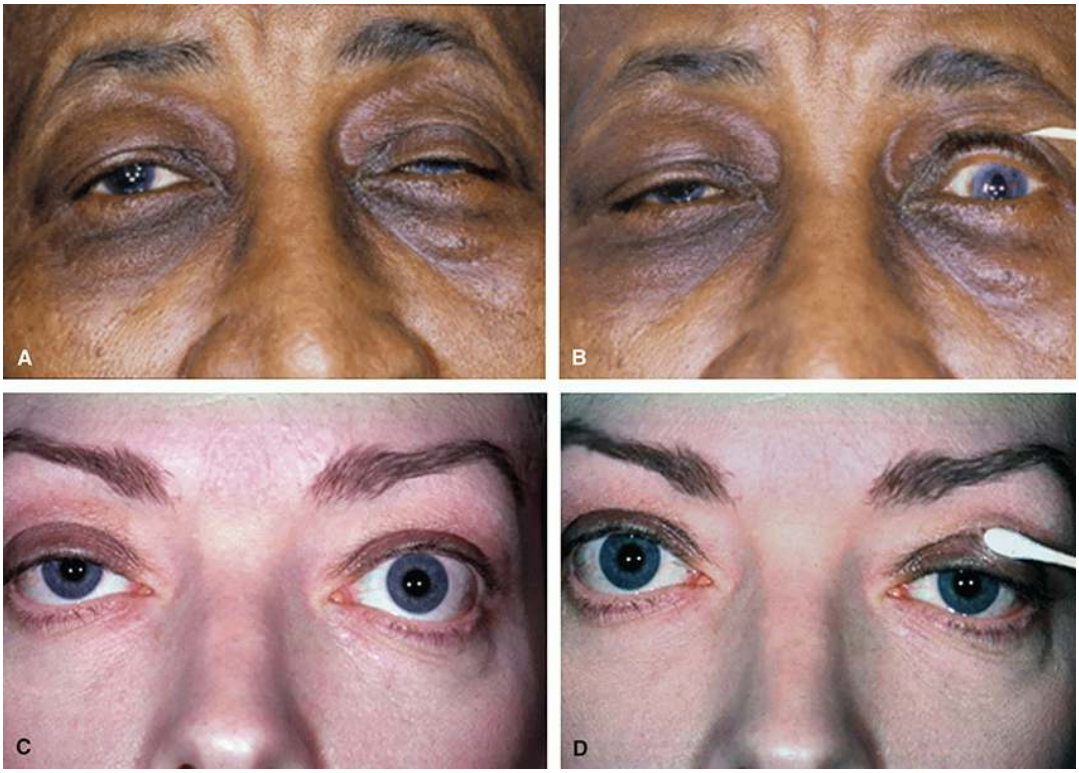

FIGURE 8.6 A-D, Hering phenomenon. A, Bilateral asymmetric ptosis with elevation of the right lesser ptotic eyelid from the Hering phenomenon. B, With manual elevation of the more ptotic left upper eyelid, there is a lowering of the right eyelid. C, Pseudoptosis of the right upper eyelid from retraction of the left upper eyelid due to the Hering phenomenon. D, When the retracted left eyelid is mechanically lowered, the ptotic right eyelid elevates to a normal position.

Differential Diagnosis

True aponeurotic ptosis may be easy to differentiate from dysgenetic ptosis on an age basis alone, although aponeurotic disinsertion has been observed in children.[41] Noting the eyelid position on downgaze may help confirm the diagnosis because in aponeurotic ptosis, the ptotic eyelid follows the globe and ptosis persists unchanged in downgaze. In dysgenetic myopathic ptosis, the eyelid lags behind the globe and the normal contralateral upper eyelid so that the apparent ptosis increases on downgaze.[24]

Although the majority of patients presenting with an acquired drooping of the eyelid will probably have age-related aponeurotic ptosis, it is important to remember that the diagnosis of aponeurotic ptosis is occasionally difficult to make and other types of acquired ptosis may confuse the clinician.[42] An alert physician should exclude other causes first before proceeding to surgery. The list of simulating conditions is long and includes neurogenic, myogenic, pseudo, and mechanical etiologies. While a mechanical etiology would be hard to miss, the examination of ocular motility and pupillary examination could help exclude a myopathic or neurogenic cause. Although the hallmark of myasthenic ptosis is variability, this is not a pathognomonic sign as virtually any type of ptosis including the aponeurotic type can worsen by the end of the day due to frontalis fatigue.[2,4] Aponeurotic ptosis should also be differentiated from pseudoptosis as several scenarios are encountered in clinical practice where both conditions may be confused. A pseudoptosis may be associated with eyelid retraction of the contralateral side due to thyroid eye disease. An atrophic eye or a small prosthetic shell may also give the upper lid a lower than normal position despite normally functioning levator and Müller muscles.[42] The causes of pseudoptosis are discussed separately in Chapter 9. Statin-induced myositis is an important cause of ptosis so that all adult/elderly patients with cardiovascular disease presenting with involutional ptosis should be queried about the use of anticholesterol therapy, and they specifically be asked about the presence of systemic symptoms of myopathy or myositis (dysphagia, difficulty walking, etc.). Although some patients may also complain of diplopia which is in agreement with a myopathic cause, levator function is usually within the normal range. The issue of anti-cholesterol-associated ptosis is underappreciated in the literature, and it is critical to bear it in mind to avoid unnecessary surgery because this type of ptosis is reversible with the cessation of the drug.[43]

Treatment

Treatment options for aponeurotic ptosis are strictly surgical, the basic tenets of which have changed little over the past 3 decades,[44,45] and they involve either the transcutaneous (aponeurotic advancement) or the transconjunctival (MMCR) approach. However, in certain situations, the precise timing of surgery is also an important factor to consider. According to the results of a recent study that discussed postsurgical ptosis, surgery for postoperative ptosis following phacoemulsification should be deferred for 6 months because even if ptosis were significant enough at 1 month, it rapidly resolves in the majority of patients.[7]

The ptosis surgeon should familiarize themselves with both approaches to choose the best possible and most suitable option for each patient.[45] Ptosis surgery is based on a thorough and precise knowledge of the anatomy of the upper eyelid, and in this context, external aponeurotic advancement may be the more intuitive surgical approach to choose because it is the aponeurosis that anatomically is responsible for ptosis in the majority of cases, not the conjunctiva or the Müller muscle.[16,32,46] However, there is a definite recent trend toward approaching mild to moderate aponeurotic ptosis cases with the posterior approach.[32] Anterior approach advocates argue that the transcutaneous approach more accurately addresses the underlying pathologic process, is suitable for all degrees of aponeurotic ptosis, leaves the conjunctiva intact, is intraoperatively titratable, and avoids excision of goblet cell and accessory lacrimal glands of Wolfring.[26,46,47,48]

Proponents of MMCR argue that Müller muscle resection transmits the contraction force of the levator muscle directly to the tarsal plate and not through its aponeurotic attachment.[49] Also, they believe that MMCR provides a better cosmetic appearance because a skin incision is avoided and the outcome is maintained over time.[50] Posterior approach ptosis procedures may also provide a better eyelid contour because the septum is not violated.[26,50] Furthermore, there is no need for intraoperative adjustment, and patient cooperation is not required. Therefore, the need for general anesthesia is not a relative contraindication as is the case with anterior aponeurotic advancement.[26,49,50,51] Moreover, several authors who have investigated the effect of MMCR on dry eye found no effect of the procedure on tear production.[52,53] Two unique situations where the external levator advancement may be safer are in patients with anophthalmia and patients who have undergone prior glaucoma filtering surgery where *(Print pagebreak 69)* conjunctival fornix shallowing or conjunctival manipulation may be of concern.[26,49,54]

The surgical details of both techniques are beyond the scope of this chapter, but several specifics deserve to be mentioned. For severe degrees of ptosis, and those patients with a poor response to the phenylephrine test, external aponeurotic advancement is the preferred surgical approach. This can also be combined with an upper eyelid blepharoplasty in patients with excess upper eyelid skin.[4,45] Whenever possible, anterior aponeurotic ptosis surgery should be performed under local anesthesia which allows better estimation of the postoperative eyelid height and a more predictable outcome.[4,46,55] In anxious patients requiring intravenous sedation during injection of the local anesthetic, the anesthesiologist should be instructed to use short-term agents to ensure that the patients are fully awake throughout a procedure that is typically short.[4,55] Operating on a fully conscious patient is important so that intraoperative adjustment can be performed as needed, and they can be seated upright to ensure that an appropriate eyelid height has been achieved.[45] It has been demonstrated that MRD1 measurements in the seated position are more accurate than those taken in the supine position, possibly due to the elimination of the effect of

gravity in the supine position.[56,57]

For external surgery, the use of a small skin incision (8-10 mm) instead of the standard 20 to 22 mm has been advocated.[58] However, this usually does not provide enough exposure and limits surgical access.[59] After the levator is exposed, if there is an actual disinsertion of the levator, Müller muscle and the peripheral vascular arcade will be seen running horizontally just above the superior tarsal border beneath the lower edge of the aponeurosis which is observed to be retracted a few millimeters in a cephalad direction.[55] Not infrequently, however, no actual disinsertion is observed at all and the ptosis may simply result from an attenuation or thinning of the distal aponeurotic insertion. Reattaching or retightening the distal aponeurotic attachment to the tarsal plate restores the eyelid to its normal position regardless of the original position of the aponeurosis.[55] Any rarefaction of the medial portion of the Whitnall ligament or dehiscence of the medial horn of the levator should be identified and repaired immediately.[60] It is frequently recommended that the surgeon uses a broad-based central suture, which should run through the tarsus horizontally for a width of about 5 mm.[55] A wider base may result in a flat contour while a narrower base may cause notching.[55] When placing sutures in the aponeurosis, some authors discourage suturing the temporal part of the aponeurosis because it allegedly can lead to a temporal flare.[46] Slight overcorrection after surgery, particularly before suturing the eyelid skin, is considered necessary.[61] This intentional overcorrection ranges from 1.5 to 3 mm and is essential because of the anesthetic effect on the orbicularis muscle and the stimulatory effect of epinephrine on the Müller muscle. An important tip to remember is to judge the eyelid level or height intraoperatively before tightening the aponeurosis sutures. If the ptosis appears to have corrected itself without any sutures, the surgeon may opt for a higher value of overcorrection (3 mm) to nullify the stimulatory effect of epinephrine on Müller muscle.[60,61] It is important to attain a higher level of overcorrection before and not after suturing the skin because once the skin is sutured and the orbicularis edges are reapproximated, the eyelid height usually drops a little.[56,57]

MMCR may be the preferred method in patients with mild to moderate degrees of ptosis (1-2 mm), good response to phenylephrine, and good levator function.[4] The exact mechanism of action of MMCR is not yet fully understood, but in general MMCR surgery is probably mechanistically concerned with shortening of the posterior lamella which is achieved through excision of Müller muscle, conjunctiva, and quite possibly some levator aponeurosis fibers, and advancement or plication of the levator aponeurosis itself.[14,26,33,62,63,64] Regardless of the exact mechanism, it appears that the procedure is independent of Müller muscle function as evidenced by the fact that the technique works in Horner syndrome where the muscle is denervated.[35]

MMCR requires careful preoperative planning to determine the exact amount of Müller muscle and conjunctiva to be excised. The amount of resection depends on two factors: (1) the absolute value of the preoperative MRD1 and (2) response to the phenylephrine test.[14,26,44] Insofar as MRD1 is concerned, nomograms like the classic 4:1 algorithm are used. The 4:1 rule states that for every 1 mm of the required increase in MRD1, 4 mm of the conjunctiva and Müller muscle should be resected.[35,44] Current teaching also dictates that the eyelid height attained with the phenylephrine test can be achieved with resection of 8.25 mm provided that phenylephrine increases MRD1 by 2 mm, or raises the eyelid to a level roughly equal to the contralateral normal side.[35,55,65] If phenylephrine raises the eyelid above the normal one, the amount of resection is decreased to as low as 6.5 mm. Up to 9.5 mm of tissue resection can be performed if the results of the phenylephrine test are subnormal.[55] Because neither approach is accurate, countless modifications have been attempted to fine-tune both rules to determine the appropriate amount of tissue resection and to provide a more predictable outcome.[15,44] This underlies the fact that there is a certain degree of unpredictability with any ptosis surgery and MMCR is no exception.[44] Because patient cooperation is not required, the choice of the anesthetic route is irrelevant.[26]

Regardless of the surgical approach used, patients should be told that after unilateral surgery, the overall incidence of ptosis developing in the contralateral eye ranges between 10% and 17%.[66,67] This is at least partly attributed to the fact that the Hering law plays a far more significant role in aponeurotic ptosis than in dysgenetic ptosis. This should be taken into account in the decision making because patients are usually more concerned preoperatively with the more ptotic eyelid and disregard the less ptotic one.[60,68] In addition, in patients where Hering dependency is demonstrated before surgery, simultaneous bilateral surgery provides better symmetry than sequential surgery,[30] and this may be preferable to *(Print pagebreak 70)* reduce the rate of reoperations.[30] If, however, Hering dependency is not demonstrated preoperatively, simultaneous surgery is not expected to provide superior results to sequential surgery.[30] Not unexpectedly, ocular dominance seems to be correlated positively with Hering dependency if the ptosis involves the dominant eye.[29]

Alternatives to the two traditional routes for correction of aponeurotic ptosis include tucking of the aponeurosis instead of advancement and combining MMCR with a tarsectomy. Tucking of the aponeurosis, a technique that remerges every few years should be avoided since there are no raw surfaces for primary intention healing to occur.[61] Tarsectomy has also been proposed as an adjunctive procedure to MMCR[44,64,69]; however, tarsal procedures blur the line between MMCR and the Fasanella Servat procedure, although both techniques are conceptually and anatomically distinct.[44] More importantly, the tarsus plays no role in the induction of ptosis whether aponeurotic or otherwise; therefore, it may not be pathophysiologically appropriate to resect it.[46] Numerous other modifications have been suggested over the years for MMCR including open sky

total or subtotal resection of the Müller muscle, and white line advancement.[50] A full discussion of these modifications is beyond the scope of this chapter.

Tear film dynamics and composition may temporarily be altered after either aponeurotic or MMCR surgery resulting in symptoms of photophobia and dryness, but these changes usually improve after the eyelid level stabilizes.[52] Overcorrection with eyelid retraction and mild lagophthalmos is generally more common than undercorrections because the levator function in these patients is good.[60] Although some authors recommend early intervention for overcorrection 1 to 3 weeks after surgery, there is a general tendency for a progressive decline in eyelid level over time when the ptosis is corrected through the anterior approach.[49,70] Therefore, it may be more prudent to wait a little more than 3 weeks and recommend eyelid massage, unless there is severe overcorrection (≥2.5 mm) causing corneal complications. This watchful approach is recommended because when a decline in lid height does occur, it is usually observed between 2 and 4 months following surgery or even years after the original surgery.[70,71] This late decline in eyelid level may be attributed to a failure of the absorbable polyglactin sutures to form sufficient scar tissue to firmly anchor the edge of the aponeurosis to the tarsus, which prompted some authors to recommend using nonabsorbable sutures.[60,70] However, the pattern of lid descent is often not sudden coinciding with the suture resorption time but is frequently more gradual in the first few weeks following surgery which suggests continued stretch or dehiscence of the aponeurosis following surgery.[70] It is highly unlikely that late recurrences occurring years after ptosis surgery represent true surgical failures. Instead, they likely represent a progression of the same involutional changes that resulted in ptosis in the first place.[71] Those late "recurrences" lend support to the intraoperative observation where no true disinsertion is observed at surgery.

If bilateral surgery is undertaken, the asymmetry between both eyelids is just as important as the actual eyelid height. If a slight asymmetry is observed in the immediate postoperative period, it is often due to asymmetrical edema and typically resolves spontaneously within a few weeks. In moderate degrees of asymmetry, massage of the slightly overcorrected side may be attempted. If there is marked asymmetry, surgical intervention will be required, and in this scenario, the patients' preference should be taken into account as to which side they prefer.[60]

Prognosis

The criterion for the success of ptosis surgery has to be strictly defined before discussing the prognosis. Success is usually defined as ≤1 mm of residual ptosis or ≤1 mm of MRD1 difference between the two sides at a 1-year follow-up.[46,72] The overall success rate for both the anterior and posterior procedures is comparable and ranges between 75% and 98%.[46,49,70,71,72] Comparing the outcome of both procedures is difficult because, to the best of the authors' knowledge, only five studies in the literature have attempted a direct comparison between both procedures.[26,34,48,62,73] These studies suggest that both procedures are almost equally effective across different etiologies of aponeurotic ptosis, but the rate of undercorrections may be slightly higher in the MMCR, while overcorrections and contour abnormalities may be more common in the external advancement group.[73] Anterior approach patients may also have a slightly higher reoperation rate.[34,48,73] Unfortunately all five studies except one[48] are retrospective, and they suffer from selection bias as the cohort of patients undergoing external levator advancement had more severe ptosis and lower MRD1 values than the MMCR group. This obvious weakness underlies the fact that aponeurotic advancement is a potentially far more powerful tool for elevation of the upper eyelid than MMCR.[26,49]

What the surgeon considers a successful surgery does not automatically translate to a happy patient. Patient satisfaction is of paramount importance and it is an issue that should be addressed in the examination room before surgery. One important cause for patient dissatisfaction is Hering law, the consequences of which should specifically be explained to the patient before surgery. Failure to do so might prompt the patient to blame the procedure for a "new-onset" ptosis in the unoperated eye. Patients should also be informed that while both techniques are excellent, the time taken for each technique to achieve the final eyelid height is different. MMCR patients can experience an initial undercorrection but the eyelid tends to rise later. The reverse is true for patients undergoing aponeurotic advancement where an initial overcorrection tends to subside over the ensuing weeks.[48,62]

Histopathology

Eyelid tissue from patients with age-related (involutional) aponeurotic ptosis may demonstrate disinsertion of the levator aponeurosis from the tarsus,[8,74] aponeurosis attenuation,[8] *(Print pagebreak 71)* levator palpebrae superioris muscle bundle splitting,[5] thinning or discontinuous fibrosis of Müller muscle,[75] or variable degrees of fatty infiltration of the aponeurosis and Müller muscle.[75] Müller muscle fibrosis characterizes hard contact wear-induced aponeurotic ptosis.[75]

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CHAPTER 9

Blepharoptosis: Mechanical and Pseudoptosis

Key Points

- Mechanical ptosis is caused by a physical obstruction to eyelid elevation in the presence of normal levator muscle function
- Causes include conjunctival, eyelid, or orbital masses; eyelid infections; benign and malignant tumors; or scars
- Pseudoptosis is a drooping of the eyelid with normal eyelid retractors, induced by the Hering effect in cases of contralateral upper lid retraction or by ipsilateral enophthalmos
- Apparent ptosis is not a true ptosis, but a visual narrowing of the vertical palpebral fissure in the face of normal eyelid retractors, caused by conditions such as excessive dermatochalasis or severe brow ptosis
- Clinically, in mechanical ptosis the palpebral fissure is narrowed with reduction in the MRD1 and the inciting mass or other eyelid condition is usually obvious on examination
- Treatment of mechanical ptosis or pseudoptosis is directed at the inciting pathology which may be managed medically or surgically
- Following management of the eyelid mass, additional surgery to elevate the eyelid may be necessary
- The prognosis is generally good following treatment of the eyelid mass or other inciting pathology
- Treatment of apparent ptosis is typically surgical with a blepharoplasty or brow ptosis repair

Mechanical ptosis is a true ptosis caused by an increased weight or obstruction to elevation of the upper eyelid due to an eyelid mass, scar, or an inflammatory episode.[1] Despite the ptotic position of the eyelid, the eyelid retractors and nerve supply are typically normal. In pseudoptosis, there also is a decrease in the margin-to-reflex distance (MRD1) in the face of normal eyelid structures and neural innervation, but without a mechanical obstruction to eyelid opening. Apparent ptosis can be considered a special form or subset of pseudoptosis where upper eyelid structures and neural innervation are normal and the MRD1 is also normal, but the vertical palpebral fissure is reduced due to excessive dermatochalasis or severe brow ptosis. In all cases of mechanical ptosis and pseudoptosis, the anatomy and function of the levator muscle and aponeurosis, as well as the Müller muscle, are anatomically and physiologically normal.[2,3]

Etiology and Pathogenesis

Causes of mechanical ptosis include conjunctival, eyelid, or orbital masses; eyelid infections such as chalazia or cellulitis; eyelid hematomas; hemangiomas; or orbital roof fractures with inferior displacement of bony fragments.[2,4,5] Although a true structural ptosis and dermatochalasis may coexist in the elderly, long-standing skin redundancy is an important cause of mechanical ptosis due to the relative extra weight of the excess skin.[6] Traumatic cicatrization of the eyelid skin can also mechanically restrict the eyelid in a ptotic position although the levator muscle is essentially normal.[7] Any of the aforementioned morbidities causing mechanical disturbance of the upper eyelid can result in an anatomic ptosis because they limit the ability of the levator muscle to elevate the eyelid due to the sheer weight or obstruction of a mass.

The most common causes of pseudoptosis are contralateral upper lid retraction and posterior globe dystopia.[8,9] Contralateral eyelid retraction due to thyroid eye disease is by far the most common cause.[2] Enophthalmos or posterior displacement of the globe relative to the orbital rim can also cause a droopy eyelid due to lack of support from the retrodisplaced globe.[8] This can be seen with structural abnormalities of the orbit causing orbital volume expansion (orbital fractures, absence of the sphenoidal wing in neurofibromatosis [NF-1], or silent sinus syndrome). Fibrotic orbital processes such as scirrhous carcinoma of the breast can cause posterior traction on the globe and enophthalmos with pseudoptosis. Enophthalmos can also be seen with conditions such as age-

related lipoatrophy, trauma, or drug-induced prostaglandin-associated periorbitopathy[2,10,11] that can result in orbital fat atrophy allowing the globe to move posteriorly within the orbit. Posterosuperior migration or recession of the preaponeurotic fat into the orbit in the elderly population may also cause pseudoptosis.[12] Pseudoptosis can also be observed after aggressive upper eyelid blepharoplasty with excessive resection of the orbicularis muscle or the preaponeurotic fat.[13] This sunken pseudoptotic appearance may take years to evolve after the original surgery. Globe size asymmetry from conditions such as microphthalmia or phthisis bulbi can present with a pseudoptosis.[5,8] Other causes of pseudoptosis include essential blepharospasm, so-called apraxia of eyelid opening, hemifacial spasm, and even psychogenic eyelid closure,[14] all of which cause a narrowing of the vertical palpebral fissure from spasm of the orbicularis muscle.

Apparent ptosis, on the other hand, is only the visual impression of a narrow palpebral fissure without a true *(Print pagebreak 74)* decrease in the MRD1. It can be caused by marked upper eyelid dermatochalasis, excessive brow ptosis with overhanging skin, or vertical strabismus so that the cornea is displaced upward beneath the eyelid margin.[2,8] The illusion of ptosis can also be seen if the contralateral upper eyelid is relatively elevated in patients with unilateral axial myopia because the myopic eye is longer and more prominent. Upward globe dystopia (hyperglobus) due to an inferior orbital mass or a tumor extending from the maxillary sinus into the orbit may displace the eye upward so that the upper eyelid margin appears lower with respect to the cornea, resulting in a reduced MRD1[2,8] even though the vertical palpebral fissure may be normal.

Clinical Presentation

It is important to obtain a thorough and focused history to distinguish patients who require surgery for a true ptosis from those who need an alternative management route.[8] The clinician should inquire about past or present thyroid status, history of cancer, and a prior history of trauma or recent intraocular surgery which may have caused minimal or evolving phthisis that has not yet fully manifested. A history of use of topical prostaglandin analog antiglaucoma medications is also important to exclude the possibility of prostaglandin-associated periorbitopathy which can lead to periorbital fat atrophy, enophthalmos, and consequently pseudoptosis.[11]

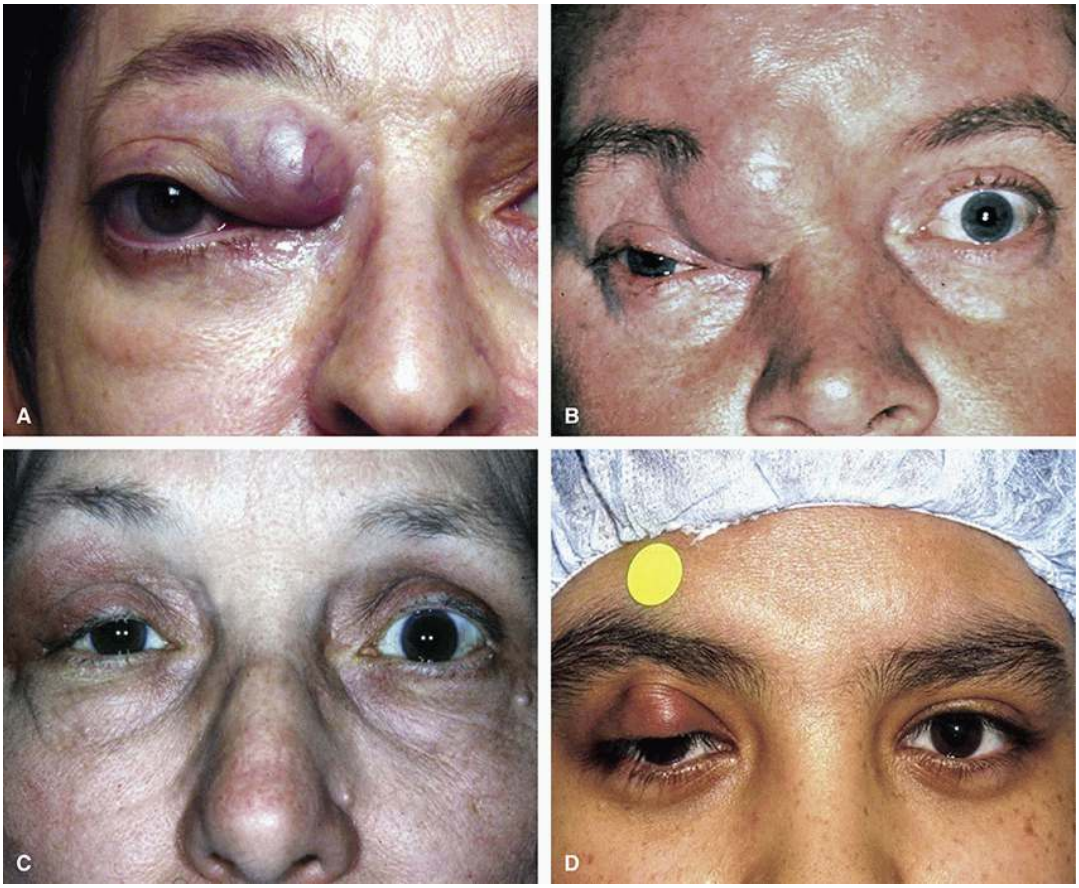

FIGURE 9.1 Examples of mechanical ptosis. A, Depressed eyelid from a medial solitary fibrous tumor. (Courtesy of Dr Robert Goldberg.) B, Ptosis due to frontoethmoidal mucocele. C, Mechanical ptosis from metastatic breast carcinoma. D, Mechanical ptosis due to chalazion.

Examination of the eyelids should focus on any eyelid mass lesion such as infection, cyst, or malignancy (Figure 9.1). The examiner should also look for evidence of old trauma like eyelid scars or orbital rim displacement. The upper eyelid should routinely be everted to exclude the presence of a conjunctival cystic or solid mass, or conditions such as giant papillary conjunctivitis.[5] This is

especially important in older individuals to rule out an ocular adnexal lymphoproliferative disorder in the superior fornix masquerading as simple *(Print pagebreak 75)* ptosis.[2] When a patient presents with extreme redundancy of the upper eyelid skin, the clinician should gently lift the excess skin to determine the true position of the eyelid margin. The patient should also be questioned about any previous ocular surgery such as vitrectomy with silicone oil, or eyelid cosmetic procedures such as filler injections (Figure 9.2).

Attention should be directed to the height and depth of the eyelid crease. The crease height is measured to help rule out an aponeurotic disinsertion even if a mechanical cause has been confirmed. In contrast to pseudoptosis where the levator muscle, its aponeurosis, and Müller muscle are anatomically normal, in long-standing mechanical ptosis disinsertion of the levator aponeurosis may also occur.[1] A faint or absent upper eyelid crease should alert the clinician to the possibility of an infiltrative mass. The contralateral upper eyelid should be examined both in the primary position and in downgaze to rule out contralateral eyelid retraction due to thyroid eye disease (Figure 9.3).

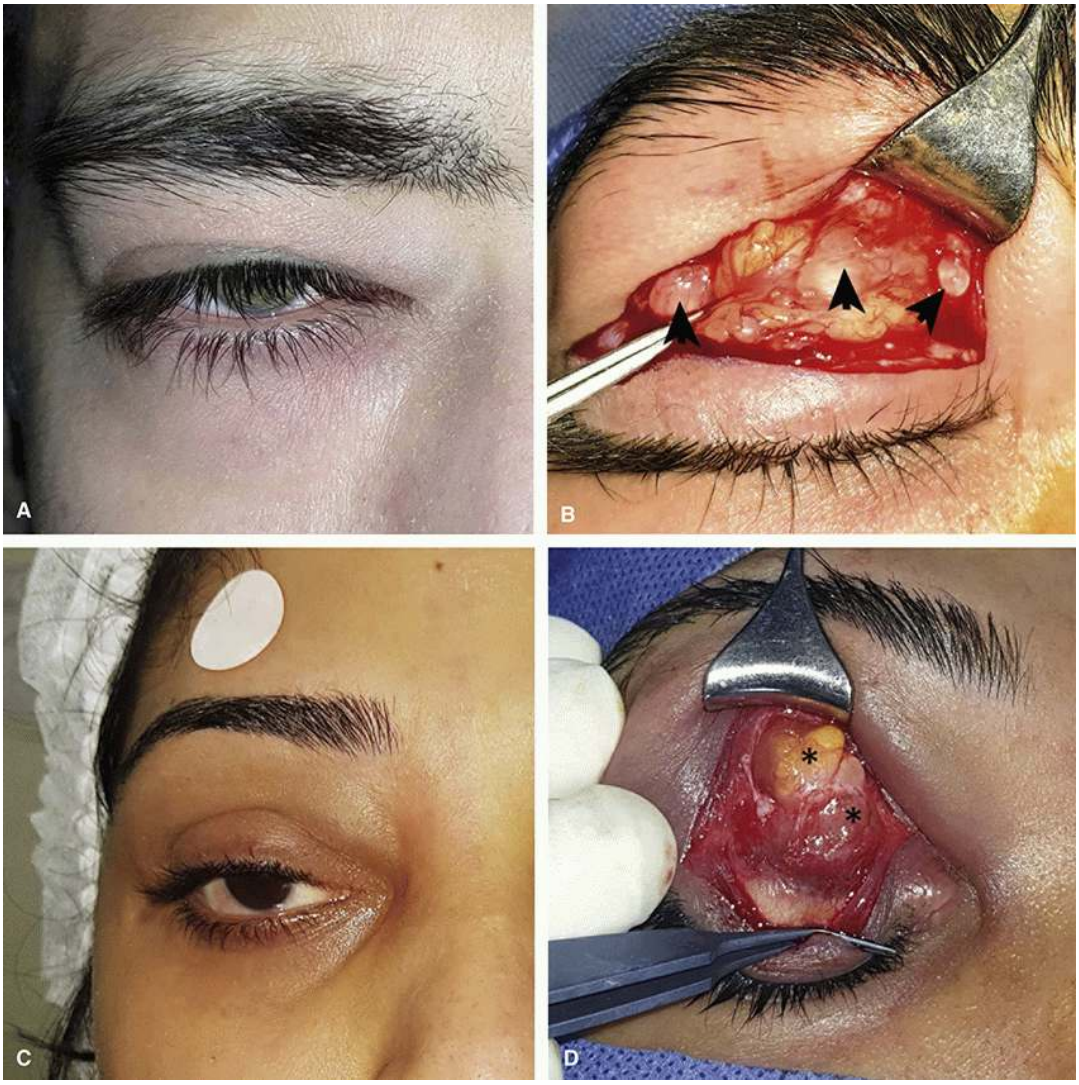

FIGURE 9.2 A, Mechanical ptosis from intraocular silicone oil migration into the eyelid. B, At surgery transparent cysts filled with silicone oil are observed infiltrating the levator muscle and the preaponeurotic fat (arrowheads). C, Mechanical ptosis due to periorbital filler injection. D, During surgery, filler granulomas are seen infiltrating the preaponeurotic fat and levator muscle (asterisks).

Brow position also should be assessed, because severe brow ptosis with excess skin overhanging the eyelid margin *(Print pagebreak 76)* is an important cause of apparent eyelid ptosis (Figure 9.4).[9] Compensatory or pseudo-brow elevation can also be observed in patients with apparent ptosis associated with dermatochalasis, even in the absence of true ptosis.[15] Excision of this redundant skin allows the brows to fall back into normal position.[15]

It is important to assess the size and position of the globe to rule out any orbital/globe process manifesting as a pseudoptosis. The orbital margin is palpated to look for old trauma or an orbital mass extending into the upper eyelid or beneath the globe in the lower eyelid. Although globe size disparity is usually clinically apparent, changes in the size of the globe can be subtle clinically and may

occasionally be missed on cursory examination.[2,8]

Visual assessment is important especially in the pediatric population because mechanical ptosis in children, which may occur due to infantile hemangiomas or plexiform neurofibromas, may cause occlusion amblyopia and astigmatic/anisometropic amblyopia.[7] Examination of ocular motility is important because patients with metastatic scirrhous carcinoma of the breast may present with unilateral restrictive external ophthalmoplegia, in addition to the usual history of progressive ptosis and enophthalmos that typically evolve over several months.[2] Patients with previous orbital trauma also may present with restrictive strabismus. If hypotropia is suspected as the cause of apparent ptosis, it is important to allow the hypotropic eye to fixate separately on a distant target with cross-cover testing to unmask the ptosis and evaluate the eyelid level which should elevate to a normal position.[2,8,16] This is especially important to remember before embarking on ptosis surgery in patients with Marcus-Gunn jaw wink because the ptosis may be associated with hypotropia. Therefore, it is possible that ptosis and pseudoptosis can coexist.[17]

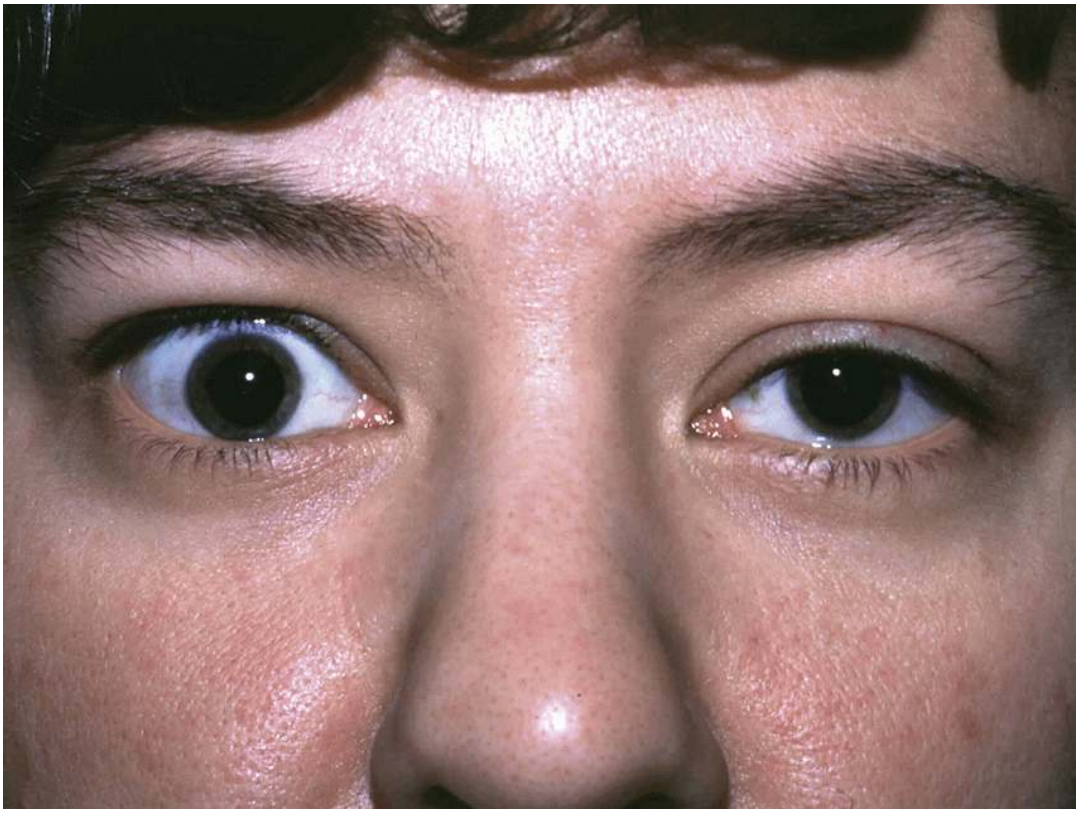

FIGURE 9.3 Left eyelid pseudoptosis due to the contralateral right upper eyelid retraction in thyroid eye disease.

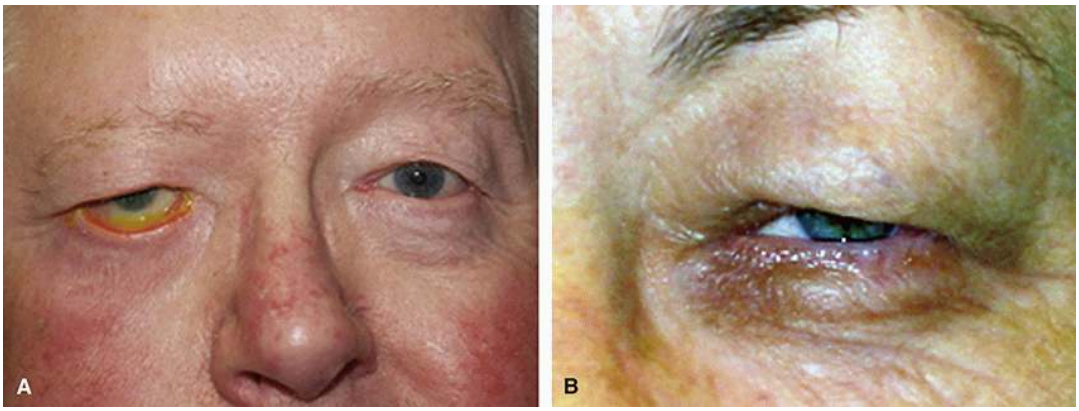

FIGURE 9.4 A, Apparent ptosis due to severe brow ptosis with excess upper eyelid skin overhanging the eyelid margin in facial nerve palsy. B, Apparent ptosis from excessive upper eyelid skin in dermatochalasis.

In cases of pseudoptosis with concomitant enophthalmos, a radiologic examination should be ordered. While the majority of orbital lesions would instantly be identified with a standard CT, the radiologic signs of metastatic carcinoma of the breast may be subtle and may require an MRI.[2,4] In the majority of patients with metastatic breast cancer to the orbit, a poorly circumscribed retro-orbital lesion is usually observed on CT or MRI.[18] However, in the early course of the disease, an increase in the reticular pattern of the intraconal fat is often all that is observed. It is therefore important to have a high index of suspicion in older females with a

history of breast cancer and to alert the radiologist to the possibility.

Visual field testing may be required in patients with dermatochalasis presenting with pseudoptosis because these patients may suffer from a significant superior visual field defect secondary to the redundant upper eyelid tissue,[19] a situation that is not dissimilar to the visual field changes in patients with aponeurotic ptosis. Patients with dermatochalasis represent one of the true functional indications for upper eyelid blepharoplasty.[19]

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Differential Diagnosis

Ptosis surgeons should realize that eyelid asymmetry does not automatically mean a true ptosis.[8] Although the etiologic cause in most cases of mechanical ptosis and pseudoptosis can be determined at the time of initial diagnosis, it is important not to miss subtleties of globe malposition or eyelid pathology before proceeding to correct the ptosis while missing a potentially life-threatening diagnosis.[8] On the other hand, even when an alternative diagnosis other than true ptosis is obvious, it should be kept in mind that in some cases of pseudoptosis the underlying etiology may also cause true ptosis as an additional comorbidity.[8] Infantile hemangiomas and neurofibromatosis type 1 are prime examples of such a scenario.[7] Likewise, an infiltrating orbital mass may involve the levator muscle, causing the reduction of levator function and myopathic true ptosis.[2] Furthermore, the same traumatic events that instigate phthisis bulbi can also disinsert the levator aponeurosis causing true ptosis.

One non-life-threatening situation which indeed presents a diagnostic challenge is the patient with ptosis on one side and eyelid retraction on the other. Both levator muscles are subserved by one midline subnucleus located on the superior surface of the oculomotor nuclei. This presents a unique problem attributable to the Hering law of equal innervation. Unilateral eyelid retraction can cause contralateral ptosis and unilateral ptosis can cause a pseudorotation of the opposite side. Determining the side with the actual pathology can be confusing, particularly if the thyroid workup is negative. Even so, one should not recommend ptosis surgery immediately because some of these patients may progress later to frank thyroid eye disease.[2] If in doubt, a waiting period of at least 6 months or even more may be necessary to rule out thyroid eye disease with repeat laboratory workup.

Treatment

Two main strategies dominate the management of mechanical ptosis and pseudoptosis. The first obvious step is the treatment of the cause which in the majority of cases will lead to resolution of the apparent ptosis. Such treatment may be medical or surgical depending upon the specific diagnosis and the nature of the obstruction to eyelid elevation. After the specific cause has been addressed, if the ptosis persists or fails to improve sufficiently, the original condition may have infiltrated the levator muscle or may have induced a traumatic disinsertion of the levator aponeurosis. In such cases, reinsertion of the aponeurosis may be required later.[1] In cases of apparent ptosis, the excess eyelid skin is removed with a blepharoplasty or the ptotic brow can be elevated.

Prognosis

The prognosis of mechanical ptosis and pseudoptosis depends on the cause. In many cases, such as eyelid edema, abscess, or uncomplicated mass, the prognosis can be very good, and the eyelid can be returned to a normal position following medical or surgical treatment. In other cases where there may be extensive scarring associated with the initial pathology, surgical repair may be more problematic. For apparent ptosis, the prognosis is excellent and easily corrected with appropriate surgery.

Histopathology

There is no specific histopathology related to mechanical ptosis in general. The pathology depends upon each peculiar lesion restricting eyelid elevation. Each entity is discussed in its appropriate chapter in this book.

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CHAPTER 10

Blepharoptosis: Myopathic, Dysgenetic

Key Points

- Myopathic dysgenetic ptosis results from developmental anomalies during embryogenesis
- This is the major cause of simple congenital ptosis
- Dysgenetic congenital ptosis is idiopathic, persistent, and nonprogressive in which the levator muscle is partially replaced with fibrous tissue
- Clinically it presents most frequently as a congenital unilateral ptosis with reduced levator muscle function
- Deprivation amblyopia may be a major complication with unilateral ptosis obstructing the visual axis
- Treatment is surgical to elevate the eyelid enough to clear the pupil
- The exact surgical procedure will depend upon the levator muscle function and varies from aponeurosis tuck to frontalis suspension
- The prognosis is generally excellent in achieving symmetrical eyelid elevation

Blepharoptosis, often abbreviated in the literature as "ptosis," is defined as an upper eyelid that is lower than its normal anatomic position, essentially narrowing the vertical dimension of the palpebral fissure. This condition may affect individuals of any age, from neonates to the elderly.[1,2,3,4,5,6,7,8,9,10,11] There are numerous causes of blepharoptosis that include pathologies of the levator muscle, its innervation by the oculomotor nerve, and acquired involutional changes in the mechanical linkage of the levator muscle to the upper eyelid. Pathologies involving the levator muscle include genetic and developmental dysgenetic anomalies, progressive dystrophic degenerations, and mitochondrial myopathies. In this chapter, the authors discuss ptosis resulting from developmental muscle dysgenesis. When present at birth due to idiopathic developmental dysgenesis of the levator muscle, it is usually referred to in the literature as simple congenital ptosis.[1,3] If not treated, ptosis will persist and might have a profound functional and psychological impact on the child.[3]

Etiology and Pathogenesis

A working classification of ptosis is critical because subdividing the disorders can optimize patient management, distinguish progressive from static myopathy, and help in deciding when interdisciplinary care is needed (Table 10.1). It also helps the clinician decide when genetic testing or laboratory investigations may be required, factors that could ultimately maximize patient surgical outcomes.[5] More than 30 years ago, Beard warned that the terms congenital and acquired ptosis should be abandoned.[4] The temporal classification of ptosis into congenital and acquired provides little clinically useful information and is not helpful for management purposes. Nevertheless, unfortunately, it is still commonly used today, long after it has lost true clinical relevance.[6,7,8,9] This textbook uses a modification of a mechanistic or etiologic classification that was originally proposed by Frueh in 1980.[10] That etiological approach classified ptosis into myogenic, aponeurotic, mechanical, and neurogenic subtypes, as well as simulating conditions causing pseudoptosis or apparent ptosis.[10,11] In this system, simple or dysgenetic congenital ptosis is classified under the rubric of myopathic ptosis because it is of myogenic origin. However, it shares little if any clinical features with other types of myogenic ptosis that are discussed in a separate chapter (Chapter 11). An alternative classification has recently been proposed,[5] which is also a modification of the mechanistic classification system and has a particular emphasis on myopathic ptosis. These authors further subclassified myogenic ptosis into two categories (static vs progressive) according to the disease tempo. The first category, which they dubbed static myopathic ptosis, includes the classic congenital myopathic ptosis (discussed in this chapter), in addition to Duane retraction syndrome, Marcus Gunn jaw-winking ptosis (Chapter 38), congenital fibrosis of the extraocular muscles (CFEOM 1, 2, 3A-C), monocular elevation deficiency (formerly double elevator palsy), as well as blepharophimosis-ptosis-epicanthus inversus syndrome (Chapter 28). The progressive variety consists of oculopharyngeal dystrophy, chronic progressive

external ophthalmoplegia, and myotonic dystrophy, which are discussed separately in Chapter 11.[5]

Simple or dysgenetic myopathic blepharoptosis is an idiopathic, persistent, nonprogressive type of ptosis, which results from a primary developmental defect in the levator muscle and replacement of muscle tissue by fibrous and fatty tissue.[12,13,14,15,16,17,18,19,20] Currently, the consensus is that it is of a muscular dysgenetic etiology (nonprogressive developmental defect) and should not be classified as a dystrophy (inherited, progressive muscle weakness) as was previously thought.[21,22,23,24,25] Indeed, histologic studies have shown the destruction of muscle fibers and their replacement with fibrous tissue, changes that are usually proportional to the severity of the ptosis.[12,13,14,15,16,17,18,19,20] The lack of subsequent regeneration of muscle *(Print pagebreak 79)* fibers, as well as the lack of inflammatory cells, lends further support to the theory of dysgenesis of the levator muscle rather than progressive dystrophy.[13,14,15,16,17,18,19,20] Fatty infiltration of the muscle has also been observed in some studies, but this is probably a degenerative response.[14,17] Of note is that a recent study has demonstrated fatty infiltration with or without fibrotic changes (fibrous bands or sheets) in the levator aponeurosis. Whether these findings represent a true developmental abnormality of the aponeurosis and its surrounding fibrous frame that may be partially involved in the genesis of ptosis, or whether these changes are simply a secondary degenerative or inflammatory response, is unknown at present.[15]

TABLE 10.1 Pathophysiologic Classification of Ptosis

I. Myopathic Ptosis

1. A. Myopathic Ptosis: Dysgenesis
    1. 1. Simple congenital ptosis
    2. 2. Congenital fibrosis of the extraocular muscles
    3. 3. Blepharophimosis syndrome
2. B. Myopathic Ptosis: Dystrophy
    1. 1. Oculopharyngeal muscular dystrophy (OPMD)
    2. 2. Oculopharyngodistal myopathy (ODM)
    3. 3. Myotonic dystrophy (MD)
3. C. Myopathic Ptosis: Mitochondrial myopathy
    1. 1. Chronic progressive external ophthalmoplegia (CPEO)
    2. 2. Kearns-Sayre syndrome (KSS)
    3. 3. Mitochondrial myopathy, encephalopathy, lactic acidosis, stroke-like episodes (MELAS)
    4. 4. Mitochondrial encephalopathy with ragged red fibers (MERRF)

II. Aponeurotic Ptosis

- Involutional
- Late-onset hereditary ptosis
- Trauma to the levator
- Blepharochalasis

III. Neurogenic Ptosis

- Myasthenia gravis
- Oculomotor nerve palsy
- Horner syndrome
- Marcus Gunn Jaw-winking

IV. Mechanical Ptosis

- Tumor mass
    - Eyelid
    - Conjunctiva
    - Superior orbit
- Brow ptosis

V. Pseudoptosis	Dermatochalasis	
	Fracture roof with inferior displacement	
	Contralateral eyelid retraction	
	Orbital volume loss	
		Enophthalmos
		Anophthalmia
		Phthisis bulbi
	Essential blepharospasm/apraxia of eyelid opening	
	Psychogenic eyelid closure	

Data compiled from[4],[5],[6],[7],[8]

Although most cases are sporadic, Mendelian autosomal dominant (AD) or x-linked dominant (XD) inheritance periodically have been suggested.[26],[27],[28] However, it is highly unlikely that there is a single genetic defect responsible for simple congenital ptosis, and despite a heritability index of 0.75 in identical twins, local in utero environmental factors cannot be excluded.[12],[28] Possible candidate genes are the 1p32 (PTOS1), Xq24 (PTOS2), 12q24.3, 14q22.3, 8q21.1 (ZFH-4 gene), and 4q25 (COL25A1 gene).[29],[30],[31],[32],[33],[34]

Clinical Presentation

The incidence rate of simple myopathic dysgenetic ptosis is difficult to establish because of the scarcity of population-based studies in the literature.[35],[36],[37],[38],[39],[40] Unfortunately, most of these studies discuss the prevalence of pediatric ptosis in general and make no reference to dysgenetic congenital ptosis in particular, except one study which estimated the prevalence to be 1 in 842 live births.[35] Another population-based study from China, which was conducted on 247,000 live births, showed a slightly higher prevalence of 1:552, or 0.18%.[40] In general, unilateral poor function simple dysgenetic myopathic ptosis is the most common form of ptosis, and for unknown reasons, it more frequently involves the left side (Figure 10.1).[35],[41],[42] Bilateral cases are less frequently observed (Figure 10.2).

Thorough history taking is of paramount importance in all forms of ptosis, especially dysgenetic myopathic ptosis. Parents should specifically be questioned if the ptosis was immediately noticed at birth or shortly afterward, and whether it was stable since birth or improved.[43] Occasionally, *(Print pagebreak 80)* parents may comment that ptosis has slightly improved by the end of the first year of life and later stabilized. This variability in eyelid level or palpebral fissure height in the first year of life is a normal physiologic phenomenon.[44] If parents cannot recall these details, photographic documentation should be sought.[43] Acquiring the details of the child's delivery is important in assessing the possibility of a traumatic injury during the birth process.[43] Infants and toddlers may be unwilling to be examined and the physician must start observing the inattentive child from a nonthreatening distance while taking history long before a formal examination has started.[43] Several characteristics such as the degree of the ptosis, recruitment of the frontalis muscle, the adoption of a chin-up head position, and the presence of strabismus can all be assessed without even touching the patient.[43] When formal examination later begins, the child is usually more at ease with the examiner.

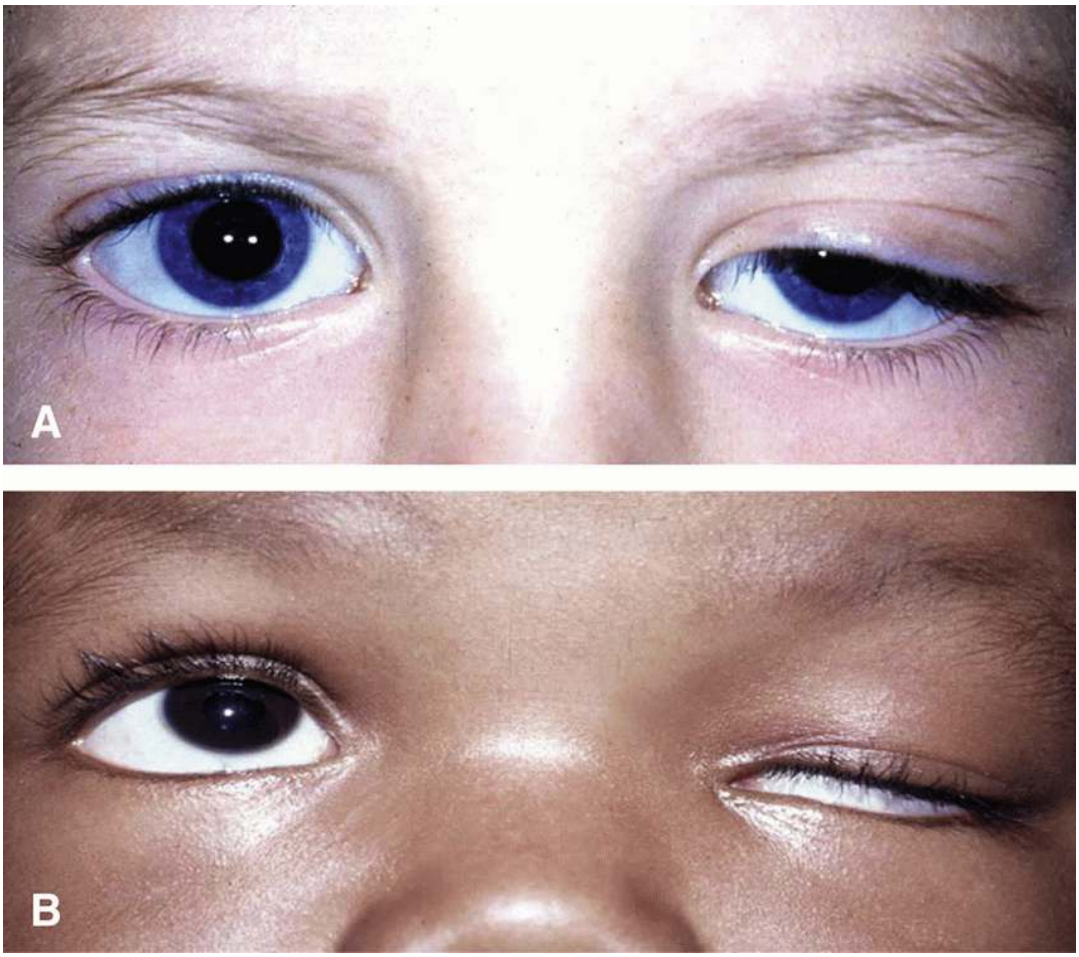

FIGURE 10.1 Spectrum of involvement of the upper eyelid in unilateral myopathic dysgenetic ptosis. A, Moderate ptosis. B, Severe ptosis.

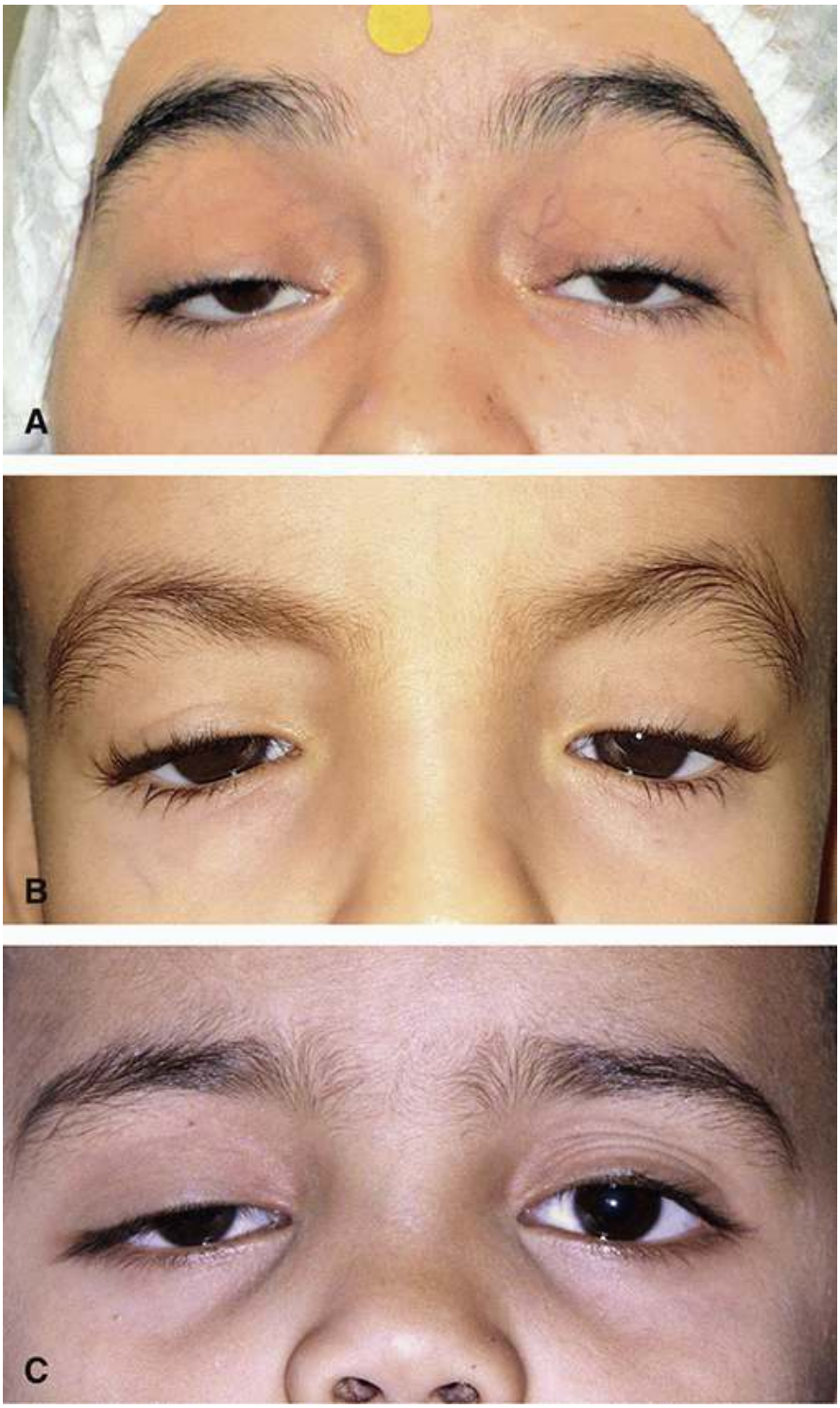

FIGURE 10.2 Spectrum of involvement of the upper eyelid in bilateral myopathic dysgenetic ptosis. A, Severe dysgenetic ptosis which is symmetrical in both sides. B, Severe dysgenetic ptosis which is only minimally asymmetric (the pupillary light reflex can be observed in the OS only). C, Bilateral myopathic dysgenetic ptosis with marked asymmetry. Frontalis muscle recruitment with compensatory eyebrow elevation may mask the ptosis in the less ptotic side.

It usually is not easy to obtain adequate ptosis measurements in pediatric patients, but if possible, the most important parameters to measure are the levator excursion and the margin reflex distance 1 (MRD 1). When assessing the severity of ptosis it is the MRD 1 and not the vertical palpebral fissure height that is relevant because this measurement is not confounded by the position of the lower eyelid.[43] MRD 1 measures the distance between the upper eyelid margin and the center of the pupil. A value of zero indicates a ptotic eyelid that bisects the pupil. Positive and negative numbers are given if the eyelid position is above or below that level, respectively.[43] Levator function is the most important single measure to retrieve, although it may be difficult to assess in young infants. Ideally, the brow should be fixed firmly with the thumb; the child is instructed to look downward in extreme downgaze and then to raise their eyelids slowly toward the ceiling. The amount of lid lift or “levator excursion” is measured with a millimeter

ruler.[45]

The position of the upper eyelid crease is noted. It may be absent if levator function is poor, but still may be observed at its normal position in patients with good to moderate levator function.[45] The position of the brows should also be marked. Compensatory frontalis muscle overaction may raise a ptotic eyelid to a deceptively normal position. This may be encountered in the less ptotic eyelid in patients with bilateral asymmetric ptosis and could give the impression that the contralateral upper eyelid is normal and that the ptosis is unilateral (Figure 10.2C).[43] Another factor that may confuse inexperienced clinicians is that overstimulation of the levator muscle in the ptotic eyelid rarely may translate into overstimulation of the contralateral "normal" levator with subsequent pseudoretraction.[43,46,47] Both factors are variations of the Hering law of equal innervation, which admittedly plays a far less significant role in simple dysgenetic myopathic ptosis than in aponeurotic ptosis because in the congenital variety the levator is fibrotic.[43,46,47]

Because amblyopia is a devastating complication of ptosis in young children, ophthalmic and eyelid examinations should both go hand in hand.[11,43] Visual acuity and refraction should be a routine part of the assessment, and amblyopia, as well as anisometropia, should be ruled out.[11,43,45] Amblyopia in children with ptosis is multifactorial. It could be deprivational from occlusion of the visual axis, anisometropic, or strabismic.[48,49] Estimates vary from as low as 14.8% to as high as 71%,[35,48,49,50,51,52] but even with the lowest estimates, the incidence of amblyopia is still several times higher than among the general population (3%).[51] As expected, amblyopia mostly develops in unilateral or in bilateral but asymmetric ptosis.[50] Why stimulus deprivation amblyopia develops in some and not all children with moderate to severe ptosis remains an enigma, but a compensatory head posture may nullify the effect of ptosis through clearing the *(Print pagebreak 81)* visual axis.[53] Refractive errors in the form of anisometropia or astigmatism are also quite prevalent both before[47,54,55] and after ptosis surgery.[56,57] More than 70% ptosis cases show a transient change toward with-the-rule astigmatism after ptosis surgery. This effect appears to regress gradually during the first postoperative year.[56]

Ocular motility examination is also important to exclude preexisting strabismus, especially a superior rectus weakness or vertical ocular deviation.[11] Contrary to popular belief, horizontal deviations are more common in simple congenital ptosis[48,52,55] than is an ipsilateral weakness of the superior rectus muscle. Also, an adequate Bell phenomenon should be documented. Occasionally, it may not be impossible to test adequately; therefore the ability to raise the globe should be demonstrated by observing the child from a higher position while they are sitting on the parents' lap. Another challenging situation when evaluating infants or toddlers is that they may sleep due to a prolonged period of rest in the waiting area, and an important tip to wake them up is to dim the lights in the clinic to elicit the eye-popping reflex.[43,58,59] The eye-popping reflex is defined as a sudden transient and forceful opening of the palpebral fissure when the lights are suddenly dimmed.[43,58,59]

Differential Diagnosis

The list of conditions causing or simulating ptosis in any age group is a very long one.[4,60] Although adult-onset ptosis is usually subjected to a more thorough search for alternative etiologies, it is still important to realize that not every child with ptosis is a child with simple myopathic dysgenetic ptosis.[2] Rarely, ptosis may be associated with blepharophimosis epicanthus inversus syndrome (see Chapter 28), or Marcus Gunn jaw-winking (see Chapter 38).[14] In addition, some cases of congenital cranial dysinnervation disorders (CCDDs) may have associated ptosis. CCDDs can include aberrant innervation of the ocular musculature resulting from abnormal development of individual or multiple cranial nerve nuclei or their axonal connections. CCDDs with associated ptosis include CFEOM and Duane retraction syndrome.[61,62]

Failure to identify alternative conditions like CFEOM could lead to a potentially blinding outcome after ptosis surgery. All patients with CFEOM manifest with eye movement disorders caused by nonprogressive restrictive strabismus as well as bilateral congenital ptosis.[62] Three subtypes exist: CFEOM1, CFEOM2, and CFEOM3. CFEOM1 manifests with bilateral ophthalmoplegia with the eyes fixed in an infraducted position below the horizontal midline along with bilateral ptosis. CFEOM2 is characterized by bilateral ptosis with eyes fixed in an exotropic position, while type 3 is phenotypically heterogenous and manifests with ptosis, ophthalmoplegia, facial dysmorphia, digital anomalies, and/or cognitive impairment.[1,43]

Even if the parents do not volunteer the information, an astute clinician should rule out Marcus Gunn jaw-winking both through specific questioning during history taking and while examining the child, as the movement may occasionally be subtle. Failure to identify a jaw wink may exacerbate the aberrant movement after levator resection (LR) surgery (see Chapter 38). A monocular elevation deficiency (double elevator palsy) may or may not be associated with a jaw wink, and it is important to realize when examining a patient with double elevator palsy that the condition may be associated with either true ptosis, or pseudoptosis (due to hypotropia), and occasionally elements of both true and pseudoptosis may coexist together.[63,64] The diagnosis of Duane retraction syndrome can easily be clinched by abduction (type 1), or adduction paresis (type 2), or both (type 3). Other congenital conditions that should not be missed include congenital myasthenia or congenital facial paralysis, but it is usually difficult to miss the ancillary clinical findings in these conditions.[2] A detailed discussion of systemic syndromes associated with simple congenital ptosis is

beyond the scope of this chapter, but the list includes Turner syndrome, Noonan syndrome, Smith-Lemli-Opitz syndrome, and Rubinstein-Taybi syndrome.[2]

A higher than normal upper eyelid crease should alert the clinician to rule out aponeurotic ptosis even in children. Another diagnostic dilemma not infrequently encountered in clinical practice is a child who presents with presumed simple myopathic dysgenetic ptosis on one side and unilateral congenital eyelid retraction or pseudoretraction on the other side. To settle this dilemma, Collin and associates set two strict criteria for a definition of congenital upper eyelid retraction: (1) The retracted upper eyelid should lie above the limbus on the affected side with a difference of at least 1.5 mm between the upper eyelid levels on the two sides, and (2) the contralateral upper eyelid has to cover the limbus by no more than 1.5 to 2 mm.[65]

Treatment

Ptosis correction is one of the most common yet challenging and controversial eyelid procedures in oculoplastic surgery. Traditionally, the proper surgical procedure is usually determined according to ptosis severity, and levator muscle function with 4 mm of levator function as a decisive cut-off point for the choice between several surgical procedures. To a large extent, this approach is particularly true.[43,66,67] Procedures described for the management of congenital dysgenetic ptosis fall into two mechanistic categories: (1) those that utilize tissue from within the eyelid such as levator muscle resection, and (2) those that utilize tissues that originally lie outside the eyelids.[43] Frontalis suspension (FS) with synthetic material or autogenous fascia lata, together with the frontalis flap technique, falls in this category.[43] Mild to moderate ptosis with good to moderate levator function (≥5 mm) is usually treated with LR, whereas severe ptosis with poor levator function (≤4 mm) is usually treated using FS.[35,67,68,69,70,71] However, uni- vs bi-laterality, as well as the age of the patient, also plays a role in the decision-making process.

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Unilateral surgery for simple dysgenetic myopathic ptosis generally is considered more challenging than its bilateral counterpart.[72,73] In these patients, bilateral FS is often rejected leaving LR as the most logical option even in patients with poor levator function.[72]

Another important controversy is the age at which the ptosis should be corrected.[47] Some authors take a radical approach and operate on all patients with simple congenital ptosis at the age of 1 year or even earlier if there is a major threat of deprivation amblyopia.[43] The most valid argument for early surgery is to prevent deprivation amblyopia.[67] Proponents of this early surgical approach also argue that sufficient clinical information can be obtained from very young children and that surgery at this young age, where the tissues are smaller, does not compromise the outcome. They also argue that toddlers are more manageable by the parents postoperatively, and most importantly that early surgery eliminates the emotional trauma suffered by the child if the operation is performed at a later date.[43] Opponents of early surgery argue that the palpebral fissure does not fully mature until the age of 2 years.[74] In one study, early surgery (≤2 years) was associated with a higher failure rate (30%) than late surgery (≥2 years) where the failure rate was only 7.5%.[75] The authors attributed this failure to incomplete maturation of the palpebral fissure.[75] Quaranta-Leoni et al[41] chose a middle-of-the-road approach by recommending surgery between the ages of 2 and 3, noting that the highest rate of complications occurs in older children, particularly those operated upon after the age of 8 years.

The details of LR surgery are outlined elsewhere.[72] However, several clinical points deserve to be mentioned. Even today, the exact amount of levator muscle to be excised is a controversial issue. Historically, there have been two major approaches for LR surgery, the qualitative approach advocated by Berke[76] versus the quantitative approach adopted by Beard.[77] Berke et al [76] simply placed the eyelid at the superior border of the corneal limbus or slightly lower or higher after surgery according to the degree of preoperative levator excursion,[72,78] while Beard[77] and others[5,25,69,78] preferred a quantitative approach designing algorithms and tables to calculate on a millimeter-per-millimeter basis, the exact amount of levator muscle to be resected. Neither approach is perfect, and there is a certain element of unpredictability with LR regardless of the approach used. Beard rejected Berke's qualitative approach arguing that the action of the levator may vary according to the depth of anesthesia used, and thus the final height attained when the child awakes may be different from the intraoperative height.[5] Berke's proponents counter that the elasticity of the dysgenetic muscle varies from one patient to the other, thus it is difficult to calculate the exact amount of levator to be resected in each patient.[72,78]

Another important surgical tip to remember is that although the skin crease should be marked at a position equal to the contralateral side, a subtle lowering of the crease marking below the level of the normal side may be required in cases where undercorrection is expected postoperatively because a smaller tarsal platform on the operated side may mask ptosis undercorrection.[79] During dissection of the levator muscle, care should be taken to avoid injury to the superior oblique tendon

medially and the lacrimal gland laterally.[72,80] A certain degree of overcorrection is probably required in all patients undergoing LR surgery, and Anderson and Doxanas overcorrected by 3 mm whenever possible.[81] It is also recommended that a Frost suture be placed from the lower eyelid and taped to the brow, and left in place for a period of up to 1 week to protect the cornea during sleep,[72] and possibly help reduce the impact of dependent eyelid edema which if excessive, may break the levator sutures. Expected immediate complications include overcorrection, an immobile lid, a diminished blink reflex, and corneal punctate erosions.[72] These tend to improve in the first week or two, but intermediate or long-term complications start to emerge later as the edema subsides. These include undercorrections or less commonly overcorrections, contour abnormalities such as nasal, central, or temporal peaking (30%), temporal droop, lash ptosis, or frank entropion (30%).[72,82]

The management of patients with severe unilateral dysgenetic ptosis and poor levator function (0-4 mm) is particularly challenging and deserves a discussion of its own.[72] For decades, authors have warned against maximal or supramaximal LR because of the usual requirement of cutting the Whitnall ligament.[11,83] However, more recent anatomical studies have underplayed the actual physiologic role of the Whitnall ligament as a levator pulley-like structure.[72] Consequently, maximal and supramaximal LR surgery have remerged in the literature.[72,84] Technically, maximal/supramaximal LR is a form of sling and therefore suffers from complications that are not dissimilar to FS procedures. These include loss of the dynamic elasticity of the eyelid, lagophthalmos, lid lag on downgaze, diminished spontaneous blinking, and a more frequent occurrence of corneal erosions or ulcerations.[72] For reasons that remain unknown, it seems that over time, the cornea adapts to the new eyelid dynamics and it rarely poses any problem afterward.[72]

Tissue recruitment from areas outside the confines of the upper eyelid represents the second paradigm of ptosis surgery. Patients with unilateral or bilateral poor or absent levator function (≤4 mm) ptosis may benefit from an FS procedure using synthetic materials or autogenous fascia lata, or from a frontalis flap procedure.[41,85] Regardless of the sling material chosen, the aim of surgery is to establish and maintain a good linkage between the frontalis muscle and the upper eyelid postoperatively.[86]

Cable suspensory sutures like prolene, nylon, or supramid are generally not recommended and have been associated with a high rate of ptosis recurrence, ranging between 29% and 43%.[42,87,88] A silicone rod may produce a somewhat better outcome than cable slings with a recurrence rate of 29% after 3 years.[89] First described in 1966,[90] silicone has the advantage that the surgeon can tighten, loosen, or remove the sling easily at a later date,[91] but silicone slings have their own set of *(Print pagebreak 83)* complications which may eventually require removal of the sling material.[42,91,92,93,94,95] These include infection or inflammation around the sling material, sling extrusion, and fistula or granuloma formation around the incision sites (Figure 10.3A and B).[42,91,92,93,94,95] Another synthetic suspensory material is Gore-Tex (expanded polytetrafluoroethylene, or ePTFE) which has an excellent success rate, reportedly even better than fascia lata (85%-100%).[86,96,97,98] Unfortunately, it has a very high infection rate (up to 45% of patients) which is four times higher than the infection rate of any other material, eventually requiring explantation (Figure 10.3C and D).[42,85] Interestingly, banked fascia lata is considered the worst material to use for FS with a recurrence rate of around 50%.[85,99]

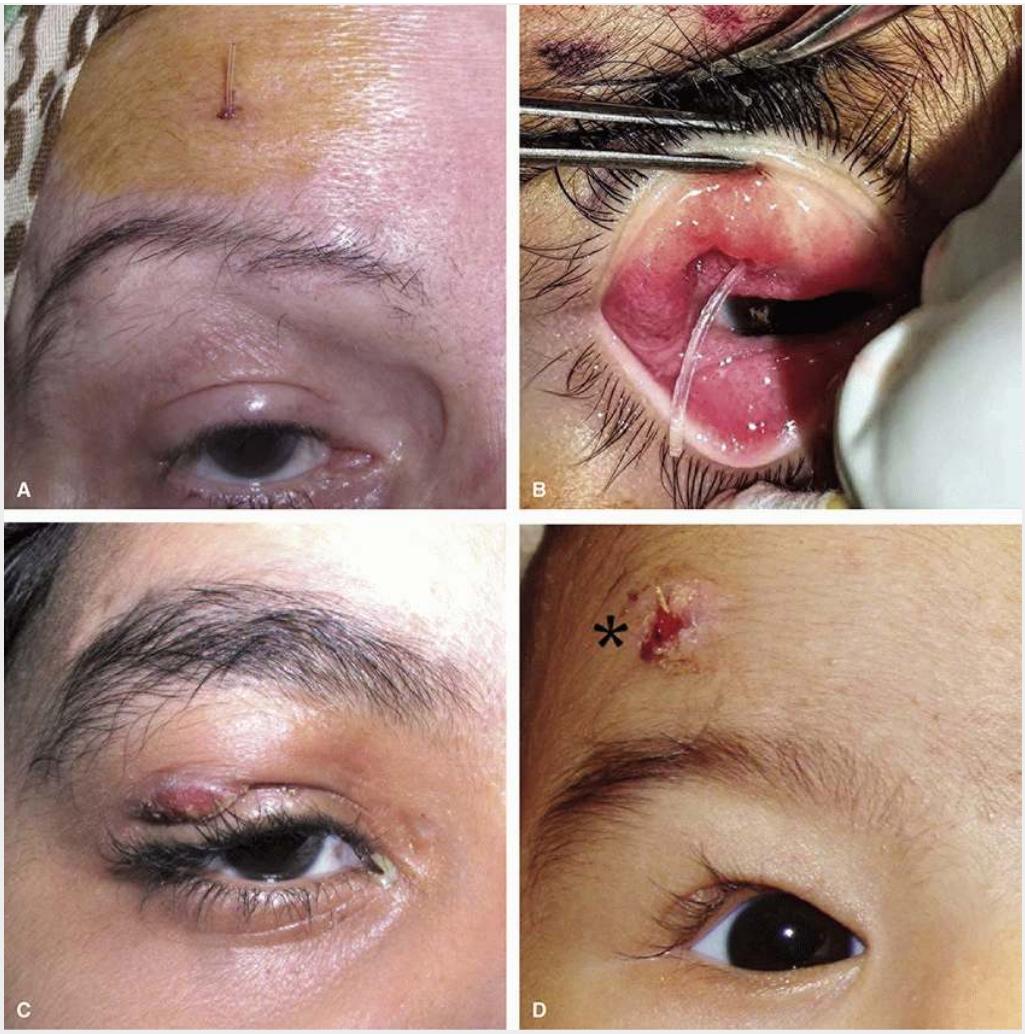

FIGURE 10.3 Complications of synthetic suspensory materials. A, Extrusion of the silicone sling through the skin. B, Extrusion of the silicone sling through the conjunctiva. C, Granuloma and abscess formation following the use of Gore-Tex (expanded polytetrafluoroethylene, or ePTFE) as a sling material. D, Extrusion of Gore-Tex suspensory material through the skin (asterisk).

For over a 100 years, autogenous fascia lata has endured as the material of choice for FS. However, this requires a separate procedure to harvest the fascia with additional anesthesia time and it can be associated with donor site complications. Autogenous fascia lata has the dual advantage of a *(Print pagebreak 84)* high success rate (92%-100%) and a low infection rate.[42,85,100] Although most patients may complain of pain or difficulty walking that usually only lasts a few days, long-term donor site complications are infrequent. These include an unsightly muscle bulge along the incision line, as well as wound-related problems especially an unsightly scar, or a wound hematoma which may be troublesome and may require evacuation.[42,101] A layered closure of the cutaneous incision together with the use of high leg incision fascia lata harvesting technique, or the so-called "high-thigh" technique[102,103,104,105] may help reduce the incidence of these complications compared to the traditional lower incision described in 1956.[106] One caveat with using fascia lata is that it rapidly integrates with tissues making revision surgery difficult, even within just a few weeks after the original procedure. It is therefore important that the eyelid position and contour are set correctly during the initial procedure.[42]

Several geometric designs for suspensory material placement have been described over the years including a single loop, pentagon, single rhomboid, double rhomboid, Crawford double triangular configuration, or even a single base-down triangle.[86,107] To the best of our knowledge, no specific benefit of any single design over the others has been demonstrated so far.[86]

Regardless of the suspensory material or the geometric pattern used, FS does have some unique complications. These include exposure keratopathy, acute or chronic eyelid infections, focal notching, contour abnormalities, entropion, under- or overcorrections, together with tenting of the pretarsal and preseptal skin with subsequent obliteration of the eyelid crease, which may be problematic especially in unilateral patients. Pulling the upper eyelid away from the globe when the brow elevates is another problem that is seen infrequently. This problem is usually related to the superficial placement of the suspensory material over the superior orbital rim and is not indicative of overcorrection.[42,86,107,108]

An alternative to the traditional approaches of LR or FS includes the Whitnall sling procedure in which the levator aponeurosis is excised and the tarsus is sutured directly to the Whitnall transverse ligament with or without a partial tarsal resection.[73] The Fasanella-Servat procedure is no longer in vogue,[109] and is not appropriate for poorer function ptosis cases. The frontalis flap (FF) technique is based on the same concept as FS where the lifting force of the frontalis muscle is transferred to the tarsal plate.[109] The difference is that with FF techniques this transmission is a direct one in contrast to FS where this is achieved indirectly through the use of suspensory material. FF techniques were introduced in the 1980s and after a period of popularity fell out of favor. But interest in the technique has rekindled recently.[110,111,112,113,114,115] The procedure was originally described with the use of two incisions, a lid crease incision, and an infrabrow incision to advance a flap from the frontalis muscle and secure it to the tarsus. Since then, the technique underwent several modifications regarding flap design, incision placement, and incorporation of the orbicularis muscle in the flap. Most authors currently use only a lid crease incision to carry out the entire procedure.[109] A homogenous distribution of the force of the flap along the width of the tarsus is critical in achieving a good contour postoperatively; however, lateral dissection of the flap carries a risk of injury to the frontotemporal branch of the facial nerve with loss of motor supply to the muscle.[109] In a recent meta-analysis, the median recurrence rate was 12.2%.[109] Another complication of the procedure, which is not unexpected due to the rich blood supply of the region, is hematoma formation postoperatively which may be severe enough that some authors routinely place a drain and compressive dressings in the immediate postoperative period.[116]

Prognosis

Although surgery for dysgenetic myopathic ptosis may be less rewarding than for aponeurotic ptosis surgery,[81] it is still highly successful. Previously, success was defined as an elevation of the ptotic eyelid by 2 to 2.5 mm, and even with this modest criterion, success rates were frequently lower than 50%.[117] In general, the surgical outcome is defined as optimal, suboptimal, or poor.[68] An optimal or good outcome is achieved if the two upper eyelids are within 1 mm height of each other with an acceptable contour and symmetric creases and no corneal exposure.[89,109] A suboptimal outcome is identified if there is more than a 1 mm difference in lid height, and an asymmetric skin crease or contour.[89] The surgical result is considered poor if reoperation is required.

The results of LR surgery in the early postoperative period may be acceptable (70%-82%),[72,82,118,119] and there is a definite observable improvement of levator function after LR surgery. While this may provide an additive effect on the surgical outcome,[119] if the surgeon does not aim for an initial overcorrection, there is a tendency for a progressive decline in lid level in the few months following surgery, particularly in the 2 to 4 month time frame.[72,81,118] Late failures occurring years after surgery are still observed, especially in patients with poor levator function, ultimately making undercorrections up to 2 to 3 times more common than overcorrections.[81,82,119,120] Although an initial undercorrection may be less risky on the cornea[121] and may be even more cosmetically acceptable, a better final long-term outcome may be achieved if the surgeon is willing to overcorrect at least initially. This may require more attention and frequent follow-ups to monitor the cornea and watch out for postoperative lagophthalmos, as well as giving repeated reassurances to the parents that the eyelid will eventually go down.[81,118,121]

Histopathology

Baldwin and Manners reviewed the histopathological features of normal levator palpebrae superioris and congenital blepharoptosis.[12] In their thorough review, they separated published studies into those supporting muscular dystrophy and those favoring dysgenesis.[12] Histopathological features favoring muscular dystrophy are muscle fiber atrophy, *(Print pagebreak 85)* degenerative changes in muscle fibers, and endomysial fibrosis and fatty infiltration.[12,16] Studies supporting dysgenesis noted a decreasing number of skeletal muscle fibers as the degree of ptosis increases and a lack of muscle fiber atrophy, degeneration, or regeneration.[12,18] The recent study by Surve and coworkers noted that the number of muscle fibers correlated inversely with the severity of ptosis and absence of degenerating or regenerating muscle fibers, both features supporting dysgenesis.[14] Internalization of muscle fiber nuclei favored muscular dystrophy.[14] To reconcile the divergent studies, we postulate primary dysgenesis with secondary, possibly aberrant, myopathic changes from prolonged disuse atrophy.[122,123]

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(Print pagebreak 88)

CHAPTER 11

Blepharoptosis: Myopathic, Dystrophic, and Mitochondrial

Key Points

- Myopathic ptosis refers to any abnormality in the levator muscle causing a reduction or absence of levator muscle function
- The group of diseases causing dystrophic myopathic ptosis are generally inherited, progressive degenerative processes leading to muscle atrophy, dysfunction, and weakness
- These include oculopharyngeal muscular dystrophy and myotonic dystrophy
- Mitochondrial myopathies are genetic diseases characterized by a primary dysfunction in the mitochondrial respiratory chain
- Those causing ptosis include chronic progressive external ophthalmoplegia; Kearns-Sayre syndrome; mitochondrial myopathy, encephalopathy, lactic acidosis, stroke-like episodes; mitochondrial encephalopathy with ragged red fibers; and neurogastrointestinal encephalopathy
- Clinically, these conditions present as acquired ptosis with reduced levator function, limitation of ocular motility, with or without muscle weakness involving the face or the body
- Extreme caution should be exercised in performing ptosis surgery with the main objective being only to clear the pupillary axis while minimizing the risk of corneal exposure
- The prognosis for the disease is poor and is usually progressive, but visual improvement can usually be achieved with judicious surgery

Myopathic ptosis is a term that is used when ptosis is acquired due to any abnormality in the levator muscle itself, causing a reduction or elimination of levator muscle function.[1,2,3] Excluding the dysgenetic variety of myopathic ptosis discussed in Chapter 10, patients with dystrophic myopathic ptosis usually present with progressive ptosis due to reduced levator muscle action, along with restricted ocular motility, abnormal facial expression, and a myriad of systemic features.[1,2,3]

Etiology and Pathogenesis

The causes of nondysgenetic myopathic ptosis fall into two categories: dystrophic myopathic ptosis and mitochondrial myopathies (MMs). Dystrophic myopathic ptosis is characterized by progressive weakness and breakdown of skeletal muscles and includes oculopharyngeal muscular dystrophy (OPMD), oculopharyngodistal myopathy (ODM), and myotonic dystrophy (MD).[3,4] OPMD is an autosomal dominant disease with 100% penetrance and pronounced expressivity.[5,6] More than 20 mutations have been found in the *PABPN1* gene, which is the gene responsible for OPMD and maps to the long arm of chromosome 14 at 14q11. Gross examination of the levator muscle and the Müller muscle shows heavy infiltration with fat, while the levator aponeurosis appears intact.[7] Light microscopy shows the characteristic rimmed vacuoles within muscle fibers which point to a dystrophic process, while electron microscopy shows intranuclear tubulofilamentous inclusions.[5] Both of these findings are highly suggestive of OPMD.[5] Other histological changes that lend further support to a dystrophic process include loss of muscle fibers, abnormal variation in fiber size, increase in the number of nuclei, and expanded interstitial fibrous and fatty connective tissue.[5]

MD type 1 is an autosomal dominant disorder caused by abnormalities in the dystrophia myotonica protein kinase (DMPK) gene mapped to chromosome 19 at 19q13. MD is considered one of the trinucleotide repeat disorders, which is a kind of genetic mutation whereby the number of trinucleotide repeats exceeds the normal threshold. The number of CTG nucleotide repeats in the DMPK gene increases with each successive generation and results in a phenomenon called “anticipation,” whereby the phenotype is characterized by an increase in generational severity and earlier onset.[8,9] More than 1000 CTG repeats result in congenital onset

and severe disease. Maternal inheritance also results in a more severe phenotype than paternal inheritance.[9] Histopathology shows that both atrophic and swollen muscle fibers may be observed grossly, as well as with light microscopy.[10,11]

MMs are a group of genetic diseases characterized by a primary dysfunction in the mitochondrial respiratory chain, which causes a deficit in adenosine triphosphate energy production, particularly in skeletal muscle, but other metabolically active tissues such as the nervous system are also involved.[12] Mitochondrial function is controlled both by mitochondrial and nuclear DNA; therefore hereditary transmission of MM can occur either maternally or in a traditional Mendelian fashion. Several mutations in mitochondrial DNA (mtDNA) and at least seven genes have been demonstrated to cause MM.[8] MMs with ocular involvement include chronic progressive external ophthalmoplegia (CPEO); Kearns-Sayre syndrome (KSS); mitochondrial myopathy, encephalopathy, lactic acidosis, stroke-like episodes; mitochondrial *(Print pagebreak 89)* encephalopathy with ragged red fibers; and neurogastrointestinal encephalopathy.[12,13,14] Because all MMs with extraocular involvement share the same ophthalmic manifestations (a pupil-sparing progressive external ophthalmoplegia with ptosis), in a sense CPEO may be considered both a disease of its own and a symptom of several other MMs.[12] Some authorities even reject CPEO as a separate disease entity, suggesting it is merely a symptom in a disease spectrum that may occur alone at the milder end of the spectrum (isolated CPEO), or may be associated with other systemic manifestations (CPEO-plus).[13]

The histopathology of the extraocular muscles in MM patients is indeed consistent with a primary myopathy.[13] When MM is suspected, the orbicularis oculi and not the levator muscle is usually recommended as a better site for muscle biopsy because of the ease of harvesting, and because the levator muscle proper is nestled within the orbit where it may be difficult to obtain enough tissue for histologic, histochemical, and genetic analyses.[15,16] On light microscopy, patients usually show red-staining granules (abnormal mitochondria) within the subsarcolemmal zones of muscle fibers on Gomori trichrome stain, or the so-called “ragged red fibers,” which are morphologically correlated to impaired protein synthesis.[13] Patients may also show decreased cytochrome C oxidase (COX), reduced nicotinamide adenine dinucleotide, and succinate dehydrogenase staining of muscle fibers.[16,17] Electron microscopy may show a mix of normal and abnormal “ghost” or irregularly shaped mitochondria (heteroplasmy),[13,16,17] while genetic studies may show a single large deletion in mtDNA, or other mitochondrial abnormalities.[16,17,18] The recognition of ragged-red fibers was traditionally hailed as the morphological hallmark of MM; however, this assumption predates the molecular/genetic era.[18] The presence of ragged-red fibers in the orbicularis oculi muscle may be a normal aging finding. It may be related to oxidative stress, coupled with the fact that mitochondrial mutations increase as age advances. Therefore, the demonstration of ragged-red fibers alone may not be sufficient to establish the diagnosis,[15,17] and supplementary electron microscopic/genetic studies are recommended by some authors.[15]

Clinical Presentation

Several shared clinical features characterize dystrophic myopathic ptosis. Any new-onset or acquired ptosis with reduced levator function and limitation of ocular motility with or without muscle weakness involving the face or the whole body should alert the clinician to the possibility of dystrophic myopathic ptosis.[3] The levator function is usually poor, the Bell phenomenon may be absent, and lagophthalmos and occasionally ectropion may be present if the orbicularis muscle is weak.[19] This disease is a frequent cause of significant visual disability as the visual axis gradually becomes occluded by the upper eyelid.[20] Patients also frequently present with a posterior head tilt and deep eyebrow furrows because of chronic contraction of the frontalis muscle.[19]

OPMD is an adult-onset disease that usually starts in the fifth or sixth decade of life. There is no sex predilection, and the condition is characterized by progressive ptosis, swallowing difficulties (dysphagia), and proximal limb weakness. Although initially described in a French-Canadian family in 1915, it does have a worldwide distribution and has been reported in more than 30 countries. However, the largest clusters are still observed among Bukhara Jews in Israel and the French-Canadian population, with an estimated prevalence of 1:600 and 1:1000, respectively. Without these two populations, the prevalence is calculated to be 1:100,000.[5] Ptosis is always bilateral but may be asymmetrical. Extraocular motility usually remains intact, although supraduction may be affected. Saccades are usually reduced in speed even when the extraocular motility appears normal, but complete external ophthalmoplegia is extremely rare (Figure 11.1).[5,8,21] Initially, patients complain of dysphagia for solid foods only; then as the disease progresses, liquids become difficult to swallow and the tongue muscles may become weak as well.[5] Other systemic symptoms in the form of voice/speech impairment (dysarthrophonia), facial weakness, and proximal muscle weakness occur later. Permanent disability in the form of severe malnutrition or immobility requiring a wheelchair rarely occurs.[5] Although the family history, the typical clinical symptoms, and the characteristic histopathologic findings may help, the diagnosis of OPMD requires molecular genetic testing to confirm the presence of abnormalities in the PABPN1 gene.[22]

MD is a rare disease with a prevalence of 1:8000 in the general population. It is a slowly progressive multisystem disorder with onset usually in the second or the third decades of life. It may be associated with significant systemic disability as the disease advances.[8,9,10,23] MD has a clinical picture almost identical to CPEO, with ptosis (59%), extraocular muscle abnormalities (82%), and orbicularis weakness (Figure 11.2).[10] Ptosis is usually severe and the levator function rarely exceeds 3 mm.[23] The orbicularis muscle weakness is also much more pronounced in MD and usually results *(Print pagebreak 90)* in severe meibomian gland

dysfunction, a situation not unlike patients with facial nerve paralysis.[8,23] According to some authors, the presence of a myopathic form of ptosis combined with meibomian gland dysfunction is virtually pathognomonic of MD.[8] Patients may also experience hypotonia of the face with difficulty raising the eyebrows, as well as generalized hypotonia that may be more commonly distal.[10] Other findings include myotonia (delayed muscle relaxation after contraction), cardiac conduction abnormalities, polychromatic cataracts, hypogonadism, and frontal balding. The overall clinical picture of MD simulates the appearance of "accelerated aging."[9]

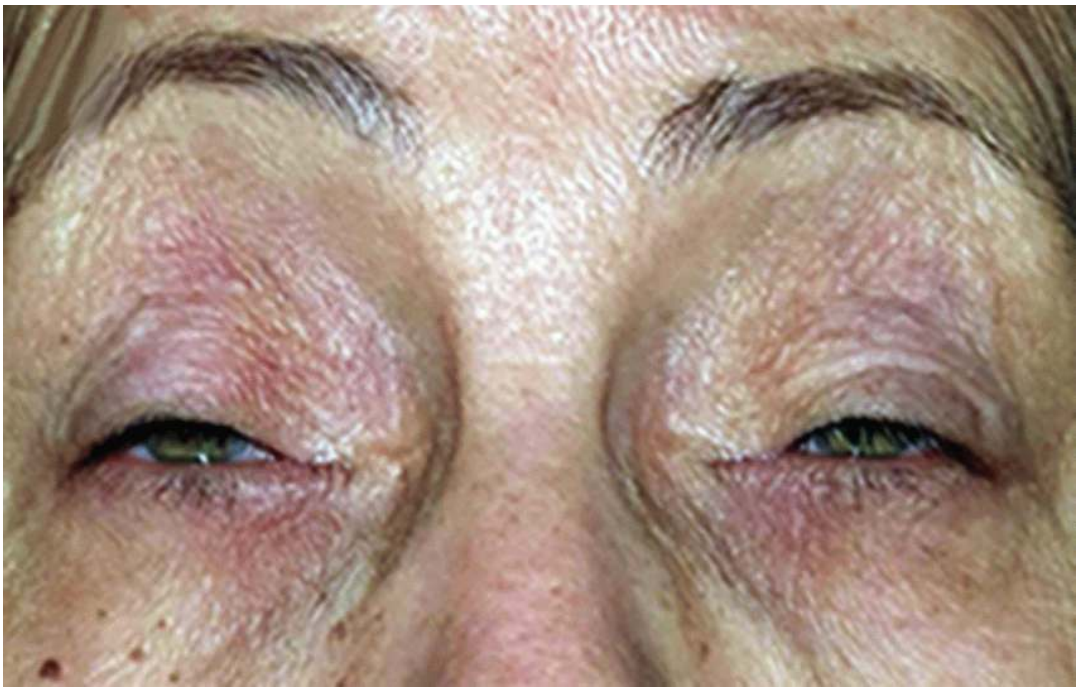

FIGURE 11.1 Progressive symmetrical ptosis over 20 years in a case of presumptive oculopharyngeal muscle dystrophy with mild limitation of upgaze, dysphagia, and proximal limb weakness.

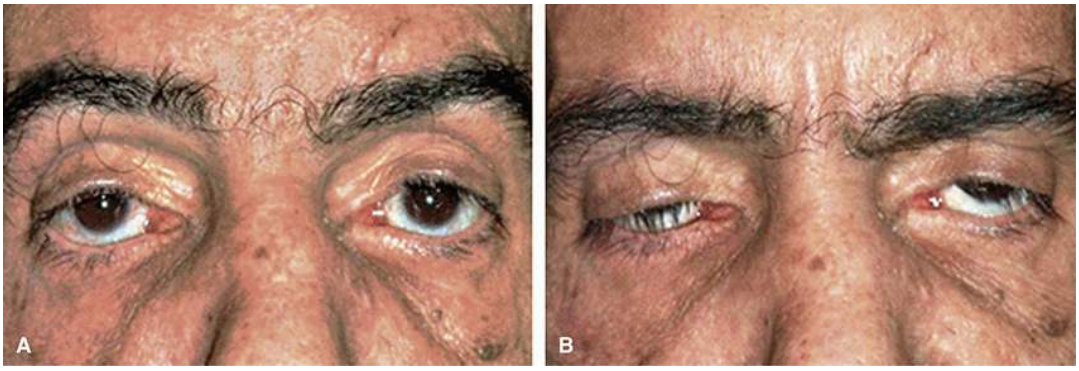

FIGURE 11.2 Myotonic dystrophy. A, Bilateral ptosis with severe restriction of ocular motility, bilateral polychromatic cataracts, frontal baldness, and limb-girdle weakness. B, Incomplete eyelid closure with poor Bell phenomenon on attempted forceful eyelid closure due to orbicularis muscle weakness.

The prevalence of mitochondrial disorders as a whole averages approximately 1 in 10,000, although the carrier rate of mtDNA mutations in the general population is about 1 in 200.[12] The onset of MM with extraocular involvement is variable, but the more severe phenotypes present earlier in life, while the milder phenotypes present later.[12] The course is usually progressive and can produce significant systemic disability and occasionally death, which may occur due to nonmuscle involvement such as cardiac conduction defects or seizures.[12] The clinical picture is highly variable involving any tissue with high energy consumption, such as the nervous system, muscle system, cardiac and endocrine systems.

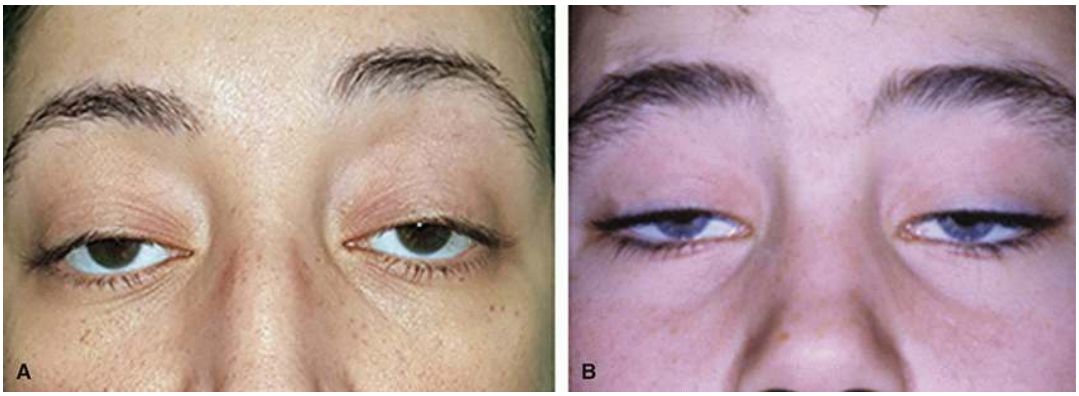

FIGURE 11.3 Chronic progressive external ophthalmoplegia. A, Moderate, bilateral, symmetric slowly progressive ptosis with early onset in the fourth decade. B, More severe bilateral progressive symmetric ptosis with marked limitation of motility.

CPEO is the mildest form of MM.[12] The disease may manifest at any age from the first until the ninth decades; however, a typical presentation occurs during the sixth and seventh decades, advancing slowly over years or even decades.[12,16] CPEO is characterized by progressive bilateral, usually asymmetric ptosis, orbicularis muscle weakness, and extraocular muscle weakness. The ptosis usually precedes ophthalmoplegia by many years (Figure 11.3). Limitation of motility is observed in all directions of gaze, but with relative sparing of downgaze.[16] All other MMs with extraocular *(Print pagebreak 91)* involvement share the same clinical ophthalmic features (progressive external ophthalmoplegia).[12] Additional ocular features may be found in the form of pigmentary retinopathy in KSS. The differentiating clinical features that distinguish each type of MM are beyond the scope of this chapter and are discussed elsewhere in the literature,[12,13,14] but in general, all MM patients are liable to cardiomyopathy, epilepsy, or stroke-like episodes.[14]

Differential Diagnosis

Although myopathic ptosis is uncommon, it should be differentiated from other types of acquired progressive ptosis like aponeurotic or neurogenic ptosis.[3] The most common type that may be confused with myogenic ptosis is aponeurotic ptosis. A normal levator excursion would point to an aponeurotic cause, while a diminished levator function in an adult patient should alert the clinician to a myopathic or a neurogenic etiology.

Genetic testing is usually required to differentiate one form of myopathic ptosis from another, and to exclude myasthenia gravis; however, some clinical points may help.[22] The orbicularis muscle is exceptionally weak in MD, much more than in patients with MM, whereas in OPMD it may be normal.[8] The presence of meibomian gland dysfunction could suggest MD,[8] while a relative sparing of the extraocular muscles and a good Bell phenomenon may point to OPMD.

Excluding myasthenia gravis may occasionally be challenging because some myasthenia patients may not present with the typical variability or the muscle-use-dependent fatiguability, the so-called “chronic and fixed myasthenia,”[13] and some myasthenic patients may test negative for anti-acetylcholine receptor antibodies.[22] In these situations, the presence of marked asymmetrical eyelid findings, systemic fatiguability, electromyography (EMG) with single fiber EMG or repetitive stimulation, a chest CT to rule out the presence of a mediastinal mass, as well as additional laboratory investigations with newer antibody tests (MUSK and Lrp4) may help clinch the diagnosis,[9,24] although the association with MuSK positivity and ocular symptoms is extremely rare.

An important entity to exclude which may simulate myopathic or neurogenic ptosis is statin-induced ptosis. Statins (3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors) are lipid-lowering drugs that reduce cardiovascular disease-associated mortality. However, one of the significant side effects of this class of medications is generalized myopathy, reported in 0.1% to 0.2% of patients.[25] Diplopia is observed in 4.4% of patients taking statins or herbal alternatives and ptosis may or may not be associated with it. When anticholesterol-induced myopathic ptosis is suspected, laboratory confirmation with serum levels of creatinine kinase and myoglobulin should be obtained to document muscle fiber damage. Of note is that ptosis is reversible with the cessation of the drug.[25]

Treatment

Extreme caution has to be exercised before recommending ptosis surgery in these patients.[23] It should be explained to the patient or parent that the main goal of surgery is to clear the pupillary axis while minimizing the risk of corneal exposure.[26,27]

The surgeon should not be driven by the patient's desire to "look better and see better," a path that may turn out with a catastrophic outcome on both vision and esthetics.

As with dysgenetic congenital ptosis, either levator muscle resection or frontalis suspension can be used for ptosis repair. The levator muscle function is the decisive factor in selecting the most appropriate procedure, but with a lower threshold for using slings.[20] In contrast to dysgenetic ptosis where the cut-off point in deciding between these two approaches is generally 4 mm of levator excursion, the dividing line for myopathic ptosis more often is arbitrarily put at 8 mm,[3,28] or even 10 mm.[29] Although some authorities favor levator resection and insist on the traditional approach using 4 mm as the cut-off point and not 8 mm,[7,20,30] proponents of frontalis suspension argue that ptosis in these conditions is associated with a progressively increasing weakness in levator function,[8,29] and therefore a lower threshold for frontalis suspension could, at least in theory, spare the patients further surgeries down the road. Due to its inherent elasticity and reversibility, silicone may be the material of choice for frontalis suspension in patients with myopathic ptosis.[26,27] This is in contrast to congenital dysgenetic ptosis where a more robust material like fascia lata has been advocated as the material of choice.[26,27] There are still caveats with the use of silicone. The orbicularis muscle should be strong enough to overcome the tensile strength of the silicone sling for the palpebral fissure to close, and the frontalis muscle should not be excessively weak because frontalis suspension depends on the frontalis tone.[31] If the surgeon elects to operate on the levator, it may be safer and even more efficacious to advance the levator aponeurosis together with the Müller muscle and avoid resecting the levator muscle itself, which is usually grossly infiltrated with fat.[7]

Alternatively, reorientation of the palpebral fissure may allow more aggressive lifting of the upper eyelid. This is achieved with prophylactic lower eyelid elevation with a spacer graft, performed concomitant with, or prior to, ptosis surgery. This repositions the narrow palpebral fissure centered over the pupil with significant improvement in the overall visual field.[20,32] Another alternative approach is to perform a conservative upper eyelid blepharoplasty to clear the visual axis and relieve the risk on the cornea[33]; however, an aggressive blepharoplasty is still risky and should be avoided because it reduces the blink reflex.[34]

Prognosis

Surgeons are usually reluctant to undertake surgery in patients with myopathic ptosis, owing to the possibility of postoperative corneal exposure.[20,35] The risk of corneal *(Print pagebreak 92)* exposure is not only attributed to abnormal ocular motility and a poor Bell phenomenon, but orbicularis muscle weakness plays a crucial role as well. The levator muscle shares phenotypic similarities with the orbicularis muscle, even more than it shares with the extraocular muscles. Therefore, both may significantly be affected, further compromising the eye-protective mechanisms after surgery.[10,16] Provided that patients' expectations are set to the proper level, the subjective improvement reported by patients is usually overwhelming, even for a modest objective improvement in lid level of 1 mm.[20] Patients should also be informed that the recurrence of ptosis may vary between 10% and 30% because all varieties of myopathic ptosis have a progressive course.[7,26,29,36] That said, it should be noted that patients with OPMD, in particular, have a better prognosis with less frequent corneal exposure problems because they retain good orbicularis muscle strength and Bell phenomenon.[29,37] In contrast, patients with MD have the worst prognosis, with a very high rate of corneal problems necessitating the frequent release of the frontalis suspension in the immediate postoperative period.[23]

Histopathology

Chronic muscular dystrophies have similar histopathological features that do not always correlate with clinical severity[38] and result from skeletal muscle fiber necrosis and regeneration.[38,39,40,41] Muscle necrosis occurs segmentally in individual or clusters of muscle fibers.[41] It begins as coagulative necrosis with pale uneven cytoplasm followed by macrophage infiltration and ingestion of necrotic sarcoplasm ("myophagocytosis").[40,41] Satellite cells proliferate and generate new myoblasts that form myotubes that fuse with the ends of damaged myofibers to close the necrotic gaps.[39,41] Regenerating myocytes have more basophilic cytoplasm than normal cells and enlarged nuclei that may have distinct nucleoli.[40] Over time, muscle damage exceeds regeneration and may result in extensive muscle replacement by fibrosis and adipose tissue (Figure 11.4A).[40] Chronic myopathy also features marked muscle fiber size variation with atrophic and hypertrophic fibers, prominently increased internal nuclei, and fiber splitting (Figure 11.4A and B).[40] Inflammation may accompany some muscular dystrophies,[38] while others have distinctive cytoplasmic inclusions or vacuoles.[40] For example, Pompe disease (infantile-onset glycogen storage disease type II) exhibits vacuolar myopathy of extraocular muscles due to distention of muscle fibers by glycogen (Figure 11.5).[42]

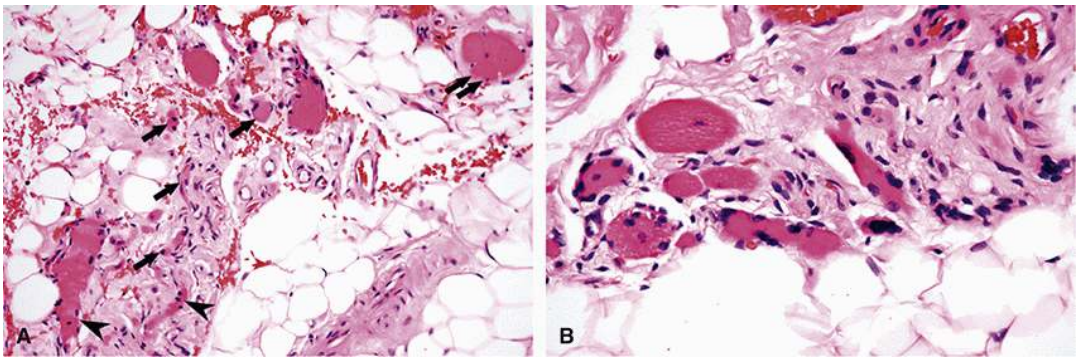

FIGURE 11.4 This levator palpebrae superioris muscle biopsy from an elderly individual with chronic progressive external ophthalmoplegia exhibits changes typical of chronic muscular dystrophies. A, There are atrophic fibers (arrows), fibers with internal nuclei (arrowheads), and a split fiber (double arrows) in a background of fibrosis and fatty replacement. B, Endomysial fibrosis surrounds atrophic muscle fibers with prominent internal nuclei.

Nuclear inclusions, identifiable by transmission electron microscopy[43,44] or immunohistochemistry,[45,46] are the pathological hallmark of OPMD. Tubular filaments, approximately 8.5 nm in outer diameter, 3.5 mm in inner diameter, and 250 nm in length,[43,44] composed of mutated poly(A) binding protein 2 (PABP2) with sequestered poly(A) RNA[45] form the inclusions. The nuclear inclusions are only in skeletal muscle fibers and are present in both clinically[43] and pathologically[46] affected and unaffected muscles. Cytoplasmic rimmed vacuoles, present in about 90% of muscle biopsies, are evident by light microscopy, and ultrastructurally resemble autophagic vacuoles.[43] Chronic myopathic changes in OPMD are similar to other myopathies and include muscle fiber degeneration and regeneration, marked variation in fiber size, split fibers, fatty infiltration, and fibrosis.[43,46,47,48] Levator palpebrae superioris muscle biopsies typically exhibit end-stage myopathy with severe atrophy and fibrosis.[28,48] Satellite cell number is increased in cricopharyngeal muscle but not clinically unaffected sternocleidomastoid, quadriceps, and deltoid muscles, suggesting a regeneration failure in affected muscles.[46]

The histological features of muscle biopsies from patients with MD type 1 and 2 are similar by routine light microscopy[49] and vary as the myopathy progresses.[50] Both MD types have nuclear inclusions of ribonucleic acid detectable by in situ hybridization[51] and a denervation-like pattern of *(Print pagebreak 93)* myopathic changes with fiber size variation (atrophy and hypertrophy), small angulated fibers, internal nuclei (central nucleation), and pyknotic nuclear clumps.[52,53,54,55] Atrophy preferentially affects type 1 muscle fibers in MD type 1 and type 2 fibers in MD type 2.[52,54,55,56] The presence of type 2 fiber atrophy and increased central nucleation should prompt genetic evaluation for MD type 2.[54]

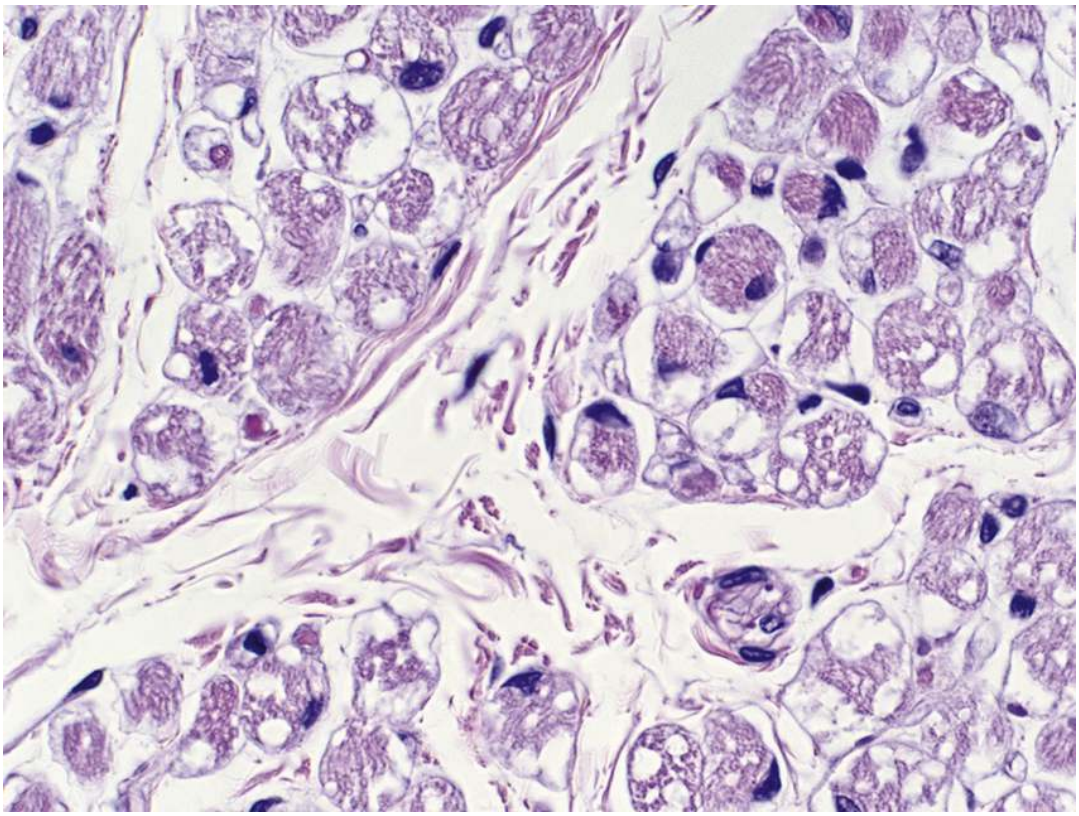

FIGURE 11.5 The inferior oblique muscle from a child with Pompe disease (infantile-onset glycogen storage disease type II) shows prominent vacuolar myopathy due to glycogen accumulation within muscle fibers.

COX-negative fibers and "ragged-red fibers" that represent the subsarcolemmal aggregation of proliferated mitochondria are the histological hallmarks of MMs.[18,40,57] Ragged-red fibers have rind-like thickening of fibers in hematoxylin and eosin-stained sections, and the subsarcolemmal mitochondrial aggregates stain bright red using modified Gomori trichrome stain.[40] The number of ragged red fibers differs among MMs.[18] They are less frequent in CPEO than other forms of MM,[18] and the presence of increased numbers of ragged red fibers and COX negative fibers in the orbicularis oculi muscle of normal older individuals warrants caution if interpreting muscle biopsies from this site.[15] Levator palpebrae biopsies may exhibit typical changes of MM or end-stage muscle myopathic changes (Figure 11.4).[58]

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CHAPTER 12

Blepharoptosis, Neurogenic

Key Points

- Neurogenic ptosis results from any pathologic process that disrupts the neural innervation of either the levator muscle or Müller muscle
- It is caused by myasthenia gravis, oculomotor nerve palsy, Horner syndrome, Marcus-Gunn Jaw wink syndrome, or iatrogenic neuromuscular blockade with botulinum toxin
- Myasthenia gravis initially presents with chronic remitting, but progressive, painless weakness of extraocular muscles manifesting with double vision and ptosis
- Oculomotor nerve palsy may be congenital or acquired, the latter due to microvascular infarct associated with diabetes mellitus, hypertension, atherosclerosis, or collagen vascular disease
- Horner syndrome results from interruption of the sympathetic nerve supply to the eyelids and orbit
- The clinical presentation and associated findings allow the differentiation of the various etiologic conditions
- Treatment depends on the underlying pathology; acetylcholinesterase inhibitors are the mainstay treatment modality in MG; most cases of oculomotor nerve paralysis improve spontaneously and do not require treatment; Horner syndrome is usually managed with aponeurotic advancement or Müller muscle-conjunctival resection; botulinum toxin-induced ptosis is typically temporary, resolving spontaneously after several months

Neurogenic ptosis is a type of eyelid drooping that usually results from any pathologic process that disrupts the innervation of either the levator muscle or Müller muscle.[1,2]

Etiology and Pathogenesis

There are five main causes of neurogenic blepharoptosis: myasthenia gravis (MG), oculomotor nerve palsy (ONP), Horner syndrome (HS), Marcus-Gunn Jaw wink (MGJW), and ptosis as inadvertent neurogenic etiology induced by botulinum toxin injections which is a relatively new addition to the list of causes of neurogenic ptosis.[3] MGJW is discussed separately in Chapter 38 .

Although MG is considered the archetypal example of an autoimmune disease involving the neuromuscular junction,[4,5,6] it is an etiologically as well as an immunologically heterogeneous disease.[6] While in the majority of patients IgG1 antibodies directed against acetylcholine receptors (AChRs) are responsible for the characteristic muscle fatigability, a smaller minority, the so-called seronegative MG, possess IgG4 antibodies to muscle-specific tyrosine kinase (MuSK), and not to AChRs.[5] Both antibodies probably represent two distinct immunopathologic mechanisms, as they are mutually exclusive and do not usually manifest simultaneously in the same patient.[6] Also, thymus pathology is different. In seropositive MG the thymus is frequently involved, whereas in MuSK MG it is not.[5,7]

The primary autoimmune form mentioned above is not the only underlying cause of MG. Thymic pathology, acute infections, and several medications may trigger or exacerbate myasthenia probably through presynaptic or even postsynaptic inhibition of acetylcholine release.[8] Pathological thymic changes, including thymic hyperplasia (follicular or diffuse thymitis) earlier in the course of the disease, and thymomas, as well as an atrophic thymus gland (late in the disease), are seen in 80% of seropositive myasthenia patients.[9] Systemic infections (viruses, bacteria, and even fungi) may trigger a myasthenic crisis.[10,11] The list of drugs inducing MG is extensive,[7] but drugs that are relevant to the current discussion are antibiotics including fluoroquinolones (ciprofloxacin and levofloxacin), macrolide antibiotics (telithromycin and azithromycin), and aminoglycosides (amikacin, and gentamycin).[8,12,13,14,15] Therefore, if a patient develops an acute exacerbation of MG due to a systemic infection, the very

antibiotics used to treat the infection may exacerbate the symptoms even more.[8]

ONP may be congenital or acquired. The most common cause of acquired ONP is a microvascular infarct which is commonly caused by systemic illnesses such as diabetes mellitus, hypertension, atherosclerosis, and collagen vascular disease. Direct or indirect compression by an intracranial posterior communicating artery, posterior cerebral artery, or superior cerebellar artery aneurysm is another common cause of isolated ONP.[16,17]

HS or oculosympathetic paresis results from interruption of the sympathetic nerve supply to the eye and orbit. The course of the three-neuron oculosympathetic pathway (central, presynaptic, and postsynaptic) is well established, arising from the hypothalamus and ultimately ending at the ipsilateral dilator muscle of the iris sphincter in a convoluted roughly U-shaped course.[18] The etiology of HS has traditionally been divided into congenital and acquired.[19] It may rarely present at birth due to head or neck trauma during delivery and may even be inherited in an autosomal dominant *(Print pagebreak 96)* fashion.[20] Acquired pediatric and adult HS is usually a sequela of trauma or surgery to the head, neck, or chest,[19,21] but an isolated HS without a history of trauma in children should always raise the suspicion of neuroblastoma.[19] The full list of etiologies causing HS is extensive and can be categorized according to the location of the lesion along the oculosympathetic chain. Central or first-order neuron lesions occur in the posterior hypothalamus, brain stem, or the cervical spine (C8-T2) and may be caused by skull base tumors, cerebrovascular accidents, demyelinating disease, or more commonly neck trauma. Preganglionic or second-order neuron lesions are usually caused by an apical lung mass (Pancoast tumor), aortic aneurysm, or aortic dissection. Postganglionic lesions include internal carotid artery disease (dissecting aneurysm or arteritis), Raeder syndrome (paratrigeminal syndrome), or carotid-cavernous fistula.[22]

Ptosis due to the inadvertent spread of the botulinum toxin is the most common complication in any esthetic practice.[3] While an inexperienced injector may primarily be responsible for this complication, other predisposing factors can facilitate the spread of the toxin to the eyelid, including excessive product dilution with injection of a large volume, a history of prior facial surgery, particularly recent eyelid surgery, as well as early massage or rubbing of the injected region.[3]

Clinical Presentation

The incidence of generalized MG is 5.3 per million person-years, and the estimated prevalence is 77.7 cases per million of the population.[6] MG affects all age groups, genders, and ethnicities; however, it has a bimodal age distribution, being more prevalent both in young females (less than 30 years of age) and older males (more than 50).[4,23] The exact incidence and prevalence of ocular MG (OMG) are largely unknown, and a recent meta-analysis of population-based epidemiological MG studies did not list a single study singularly concerned with OMG.[6] However, OMG is considered rarer than generalized disease[24] and shows a predilection for men.[25]

About 40% to 50% of MG patients initially present with purely ocular symptoms with a history of chronic remitting, but generally progressive, painless weakness or fatigability of the extraocular muscles manifesting with double vision and ptosis. Over the course of the disease, the symptoms may alternate between both eyes, and an acute onset may rarely be encountered.[4,25,26] Throughout the course of the disease, ocular muscles are involved in 90% of patients.[7] On the other hand, 50% to 80% of ocular myasthenics ultimately develop the generalized disease, which usually occurs within the first 2 years from onset. However, the use of immunosuppressants may reverse this trend.[5,7,27] On examination, OMG is hallmarked by the presence of pupil-sparing ptosis and extraocular muscle weakness, which is typically characterized by being variable, increasing with sustained muscle use even for brief periods, and improving with rest or sleep.[25] Ptosis may be unilateral or bilateral and usually asymmetrical (Figure 12.1).[28] When ptosis is unilateral or markedly asymmetrical, two phenomena may be observed, and both are attributable to the Hering law of equal innervation.[7,29] The first is apparent or "pseudoretraction" of the contralateral normal upper eyelid,[25,29] and the second phenomenon is "enhanced ptosis." After manually elevating the more ptotic eyelid, ptosis may appear to be increased or "enhanced" in the contralateral less ptotic eyelid.[7,30] A more characteristic, albeit rarer and more difficult to elicit phenomenon, is the Cogan's lid twitch sign, which is characterized by a brief episode of lid retraction after a vertical upward saccade from a downgaze position.[25] Clinicians should also be aware that MG may cause orbicularis muscle weakness.[25,31] When OMG patients are instructed to close their eyelids and keep them closed, a few seconds later the palpebral fissure widens and the cornea is exposed because of orbicularis fatigue.[31] This sign has been dubbed the "eyelid peek" or "peek-a-boo sign" because the patient appears to peep or peek at the examiner.[7,31] Orbicularis muscle weakness may also manifest with "afternoon ectropion" and "nocturnal lagophthalmos."[31,32]

Extraocular muscle involvement is also a common symptom in OMG and is found in as many as 90% of patients, usually associated with ptosis.[7] It can mimic any pupil-sparing ocular motility disorder, ranging from a single extraocular muscle paresis to complete external ophthalmoplegia, but OMG patients may also present with full ocular motility.[7]

Systemically, patients may complain of difficulty in chewing solid food, dysphagia, or dysarthria, as well as difficulty whistling, using straws, or inflating balloons. MG patients may exhibit a nasal tone of voice which becomes increasingly apparent if history taking is prolonged. Patients with generalized MG may also demonstrate a depressed or expressionless facial appearance, and the

characteristic myasthenic snarl may also be observed on attempted smile.[28] Air readily escapes through the lips, and liquid may escape through the nose during attempted swallowing with nasal regurgitation. Patients with limb weakness may complain of difficulty climbing the stairs or performing overhead tasks with their arms.[28]

The diagnosis of MG and in particular OMG is primarily a clinical one, but diagnostic tests are used to support the diagnosis and can be categorized into clinical, laboratory, electrophysiologic, pharmacologic, and radiologic tests.[33] The details of these tests are beyond the scope of the current discussion and are summarized in Table 12.1, but in general, the typical workup of suspected MG usually includes AChR antibody testing, single-fiber electromyography, and CT or MRI of the mediastinum.[23] One important clinical point that should not be overlooked is that 10% of MG patients will have a thymoma on chest radiology and 70% will have thymic hyperplasia. Those relatively high figures are not observed in healthy patients, which argues for a central role of the thymus gland in the pathogenesis of the disease.[36] More importantly, a negative antibody workup does not rule out MG/OMG if the clinical signs are highly suggestive.[7]

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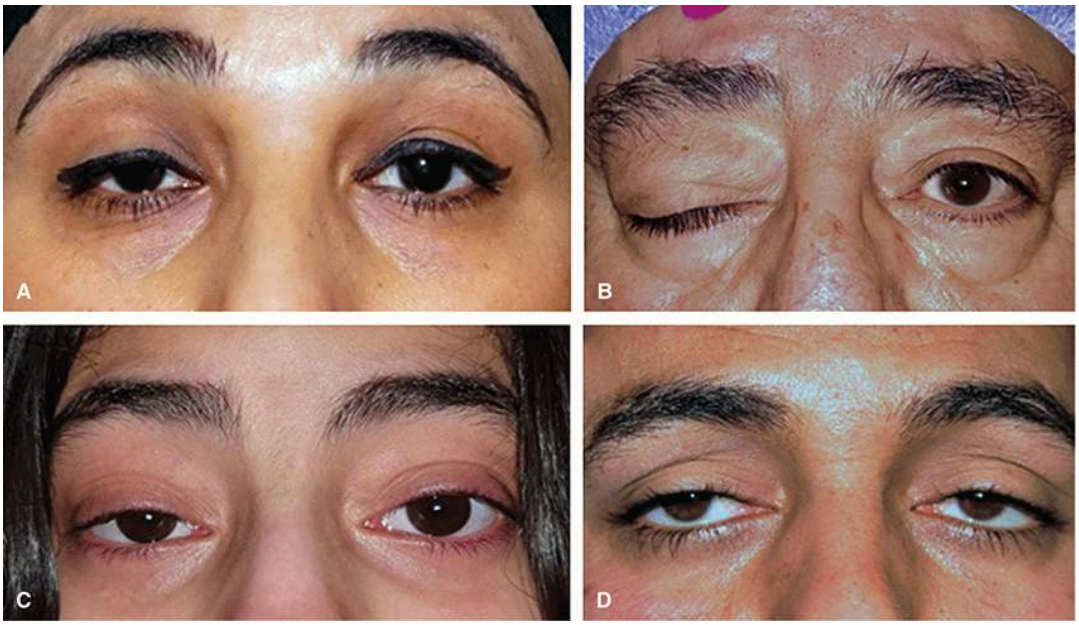

FIGURE 12.1 The spectrum of eyelid involvement in patients with myasthenia gravis. A, Moderate unilateral ptosis. B, Severe unilateral ptosis. C, Bilateral asymmetric ptosis. D, Bilateral symmetric ptosis.

TABLE 12.1 Summary of Tests Used to Help in the Diagnosis of MG/OMG

Test		Positive result	Notes
Clinical tests			
	Rest test	Improvement with rest	Moderately sensitive
	Ice test	Improvement with application of ice	Moderately sensitive
	Fatigue test	Worsening symptoms with sustained upward gaze	Moderately sensitive
Laboratory tests			
	Anti-AChR AB	Positive antibody test	Negative in 20% of MG
	Anti-MuSK AB	Positive antibody test	Negative in 40%-77% of OMG
	Lrp4	Positive antibody test	No correlation with clinical severity Positive in 40% of seronegative MG Correlates with clinical severity Positive in 2%-50% of double-seronegative MG
Electrophysiologic			
	RNS	↓ muscle action potential	
	Single-fiber EMG	Abnormal jitters	More sensitive than RNS

Pharmacologic			
	Tensilon test	Improvement with injection	Obsolete
Radiologic			
	Mediastinal CT/MRI	Thymic hyperplasia/thymoma	-

Anti-AChR AB, acetylcholine receptor antibody; EMG, electromyography; LRP4, low-density lipoprotein receptor related protein; MG, myasthenia gravis; MuSK, muscle-specific kinase; OMG, ocular myasthenia gravis; RNS, repetitive nerve stimulation.

Data compiled from[7,23,25,33,34,35]

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When ONP is associated with ischemic mononeuropathies such as diabetes or hypertension, it is usually pupil-sparing. There is little or no anisocoria and the pupil is normally reactive to light.[16] Involvement of the pupil (a dilated fixed ipsilateral pupil) usually signifies more sinister pathology such as an internal carotid-posterior communicating artery aneurysm (Figure 12.2).[16,37] Pain, in particular, is usually an ominous sign of a life-threatening aneurysm. Patients usually present with a specific pattern of ophthalmoplegia in the form of sudden onset of diplopia with the eye turned down and out, with partial or more commonly complete ptosis.[37] Angiographic imaging studies, as well as standard radiology (CT/MRI), are often required for diagnosis, but the best combination is to order a brain MRI with CT angiography.[37]

HS is classically characterized by a triad of miosis, partial ptosis, and ipsilateral anhidrosis, but this triad is rarely encountered all at once in clinical practice (Figure 12.3).[22] Ptosis may be minimal (1-2 mm) and may even be absent in 12% of patients. Anisocoria is more marked in the dark but is most obvious within the first 5 seconds of darkness, and it becomes less apparent after 10 to 15 seconds, a phenomenon known as dilation lag.[22] The distribution and extent of anhydrosis vary according to the location of the lesion, but because the majority of the examinations take place in an air-conditioned environment, disturbances in facial sweating are not always observed. Interruption of the sympathetic innervation to lower eyelid sympathetic muscle may result in lower lid elevation or “upside-down ptosis” and apparent enophthalmos.[22] Ipsilateral iris hypochromia (heterochromia iridis) may be observed in congenital HS because iris coloration, which normally occurs in early infancy, depends on the stimulation of melanophores by postganglionic sympathetic nerve fibers.[21]

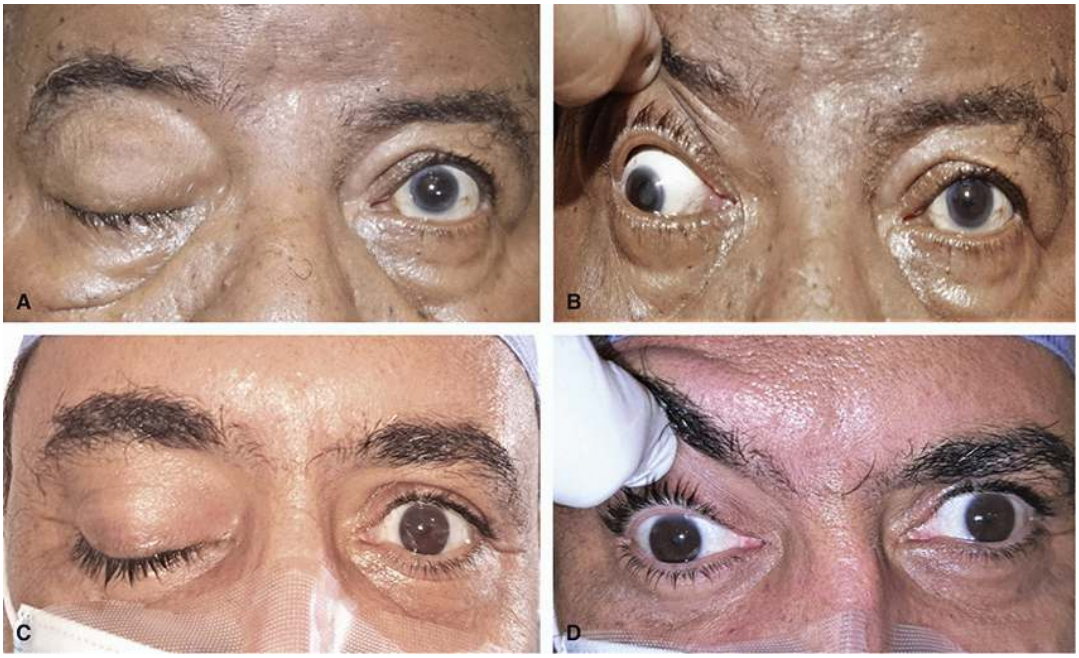

FIGURE 12.2 The spectrum of eyelid involvement in patients with oculomotor nerve palsy. A and B, Complete ptosis, extraocular motility disturbance, and pupillary abnormalities in a patient with an internal carotid-posterior

communicating artery dissecting aneurysm. C and D, Pupil-sparing oculomotor nerve palsy due to an ischemic etiology (diabetes).

The underlying pathology of HS is usually easily identified at the time of presentation in the majority of patients, but because of its long and circuitous anatomic three-neuron pathway, nontraumatic HS presents a diagnostic challenge with many disease entities that enter into the differential diagnosis.[22] Pharmacologic localization of the lesion, which has long been hailed as the gold standard for diagnosis, predates the era of modern neuroimaging, has confused clinicians for decades, and may not be very accurate.[22] However, several recent reports have highlighted the value of topical apraclonidine testing, a weak α-2 adrenergic receptor agonist which under physiologic conditions only manages to poorly dilate a normal pupil, but causes a marked dilatation of a Horner pupil because of denervation supersensitivity.[38,39,40] Although topical apraclonidine is a highly sensitive clinical test that helps in establishing the diagnosis of HS, it is not of much help in localizing a lesion. A safer more manageable approach to a patient with HS than the pharmacologic *(Print pagebreak 99)* route would preferentially rely on detailed history taking and routine radiology.[18,22] A detailed account of history taking in HS patients is beyond the scope of this chapter, but in general ancillary signs and symptoms may help the clinician direct their radiological workup. A painful HS may be an ominous sign of internal carotid artery dissection, and a CT angiogram of the aortic arch, carotid arteries, and intracranial vessels should be ordered immediately.[22] In addition, the presence of localizing central signs like contralateral ataxic hemiparesis or upper limb paresthesias may require an MRI of the brain. In case of a nonlocalizing HS, the MRI or CT protocol should include imaging of the head and neck regions, with additional imaging to the lung apex and the orbit.[22] Laboratory investigations are of little value in the diagnosis of HS except in a pediatric scenario where urinary catecholamine testing may help exclude neuroblastoma.[41] It should be noted that even after an exhaustive search, some cases of HS particularly in children (33%) are idiopathic with no apparent cause.[41]

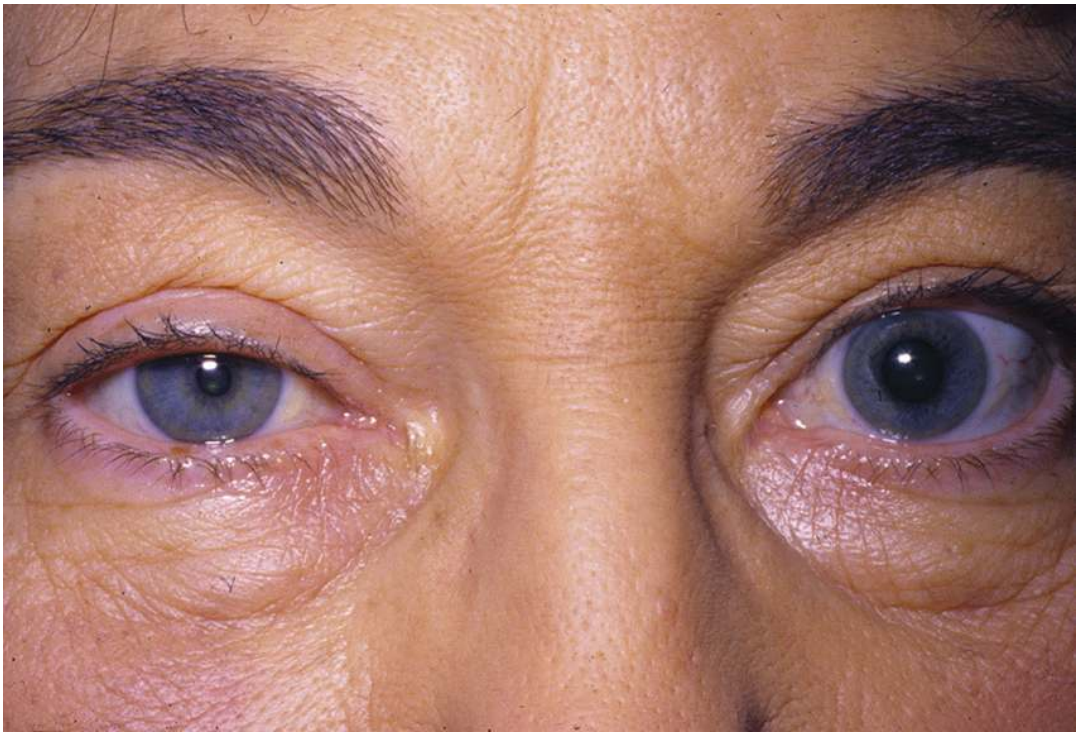

FIGURE 12.3 Horner syndrome with moderate ptosis and myosis.

Drooping of the upper eyelid following botulinum toxin injections may be acute or subacute and varies from mild to moderate. Ptosis is usually aesthetically displeasing, but it may rarely be severe enough to interfere with vision. Any patient presenting with sudden unexplained ptosis should be queried directly about a history of recent botulin toxin injection as they may not always spontaneously volunteer the information because patients are not usually aware of a causal association between ptosis and cosmetic injections. Occasionally, the patient may deny the episode due to social reasons if family members or friends are attending the examination (Figure 12.4).

Differential Diagnosis

The diagnosis of OMG is rarely in doubt when the patient presents with the proper history and characteristic clinical findings. Nevertheless, the list of simulating conditions is not short. Signs that should raise suspicion against a diagnosis of MG/OMG include the lack of variability or fatigability, pupillary abnormalities, diminution of vision, proptosis, the presence of pain, or strictly persistent unilateral signs and symptoms.[7] OMG may simulate virtually any pupil-sparing eye movement disorder like internuclear

ophthalmoplegia, and one-and-a-half syndrome because of its predilection to affect the medial rectus muscle particularly early in the course of the disease.[25] But because of the variable patterns of ocular motility disturbances encountered in OMG, it may also mimic trochlear, abducens, or even oculomotor nerve dysfunction.[7] On the other hand, many intracranial sinister etiologies may masquerade as MG (pseudomyasthenia).[31,42] Cogan lid twitch and the eyelid peek sign may help clinch the diagnosis,[31] but they are not 100% pathognomonic of MG and have been documented in other conditions.[7,42] The coexistence of poor eyelid closure and ptosis with ophthalmoparesis is strongly suggestive of OMG because the facial nerve does not course near the third cranial nerve,[7] but this combination has been observed in several types of myopathic ptosis as well[43] (see Chapter 11). Systemic features may not be of much help either because some symptoms such as dysphagia and dysarthria may also be shared with OMG and myopathic ptosis.[7,25] Although OMG patients may present with lid retraction due to the Hering law, thyroid eye disease should be ruled out in any known MG patient who presents with unilateral or bilateral retraction, because both conditions may coexist in 4% to 10% of patients.[7] It is also important to differentiate MG from paraneoplastic disease (Lambert-Eaton myasthenic syndrome [LEMS]) which is a distinct autoimmune disease of neuromuscular junction transmission caused by paraneoplastic antibodies directed against the presynaptic voltage-gated calcium channels (VGCC).[44] An aggressive search for an underlying malignancy is central to the management of LEMS as it is associated with a small lung cell cancer in approximately 40% to 50% of patients but other malignancies may be observed as well.[44,45] The initial presentation may be similar to MG/OMG with variable ptosis and diplopia which are not as rare as was previously thought.[7,44] Systemically, LEMS may suffer more proximal muscle weakness/fatigability, hyporeflexia, and an important *(Print pagebreak 100)* differentiating point is that LEMS may rarely manifest with autonomic dysfunction symptoms like pupillary abnormalities.[7,44] Antibodies to VGCCs may also clinch the diagnosis as they are positive in 75% to 100% of patients with LEMS and only 5% with MG, while the reverse is true if anti-AChR antibodies are tested.[45]

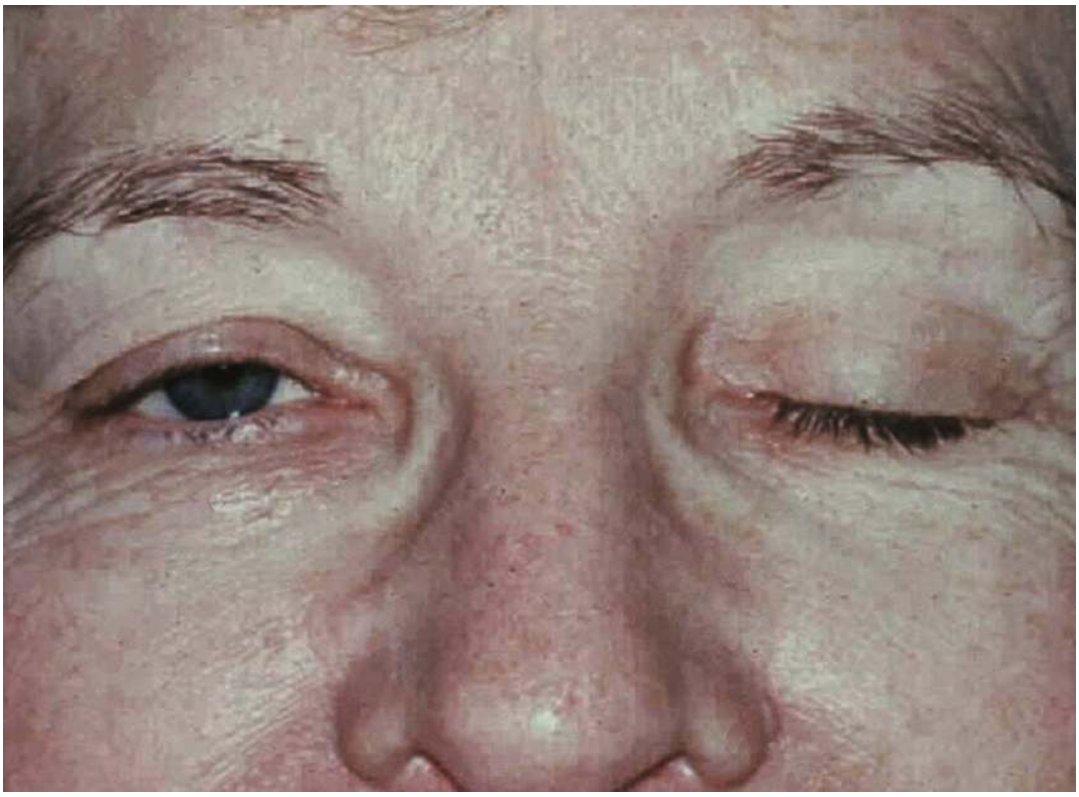

FIGURE 12.4 Drooping of the left upper eyelid following botulinum toxin injection.

Although the clinical presentation of ONP is instantly distinguishable, several caveats have to be noted. The “rule of the pupil” has several exceptions and does not always apply. 14% of patients with an aneurysm may counterintuitively present with a pupil-sparing ONP, at least at the onset of the disease while the aneurysm is still evolving.[16,37,46,47] Vice versa, an ischemic ONP due to diabetes may involve the pupil in 32% of patients.[47,48] Furthermore, 38% of ischemic ONP have pathologic anisocoria ≤2.5 mm.[48] Again, the presence of pain is not diagnostic of an aneurysm as it may be the presenting symptom of ONP associated with a mass lesion or ischemic vasculopathy just as well.[37,49]

HS may present several diagnostic challenges. Because many cases of HS are labeled idiopathic, even after an exhaustive workup, a congenital onset should always be ruled out first to avoid an exhaustive and costly workup, and in such cases, iris color, as well as old photographs, may help.[50] A particularly challenging situation in clinical practice is the young adult contact lens wearer with no history of trauma or surgery who presents with mild ptosis of unspecified duration. Although aponeurotic dehiscence immediately springs to mind, clinicians should always be on high alert for HS. A negative response to topical apraclonidine may help exclude HS.

Treatment

Acetylcholinesterase inhibitors remain the mainstay treatment modality in MG. However, any long-term treatment plan should include immunosuppression, which is required in generalized MG.[51] Glucocorticoids, azathioprine, cyclosporine A, mycophenolate mofetil, cyclophosphamide, methotrexate, and tacrolimus have all been tried as single agents or in combination.[51] In OMG, treatment with acetylcholinesterase inhibitors may be sufficient in milder cases, at least temporarily, but the indications for use of immune-modulating agents in OMG are less clear-cut.[51,52] A recent randomized, double-blind, placebo-controlled trial (the EPITOME study) showed a beneficial effect of an initial low dose of prednisone with gradual escalation when OMG is resistant to acetylcholinesterase inhibitors.[24] Immunosuppressants do not only ameliorate the symptoms of the disease but may also reduce the rate of progression of OMG to generalized MG.[7] In severe or drug-resistant cases, co-treatment with intravenous immunoglobulins or plasmapheresis may be considered.[51] More recently, rituximab,[52,53] and a newer monoclonal antibody, eculizumab (Soliris), have shown some promise in cases refractory to conventional treatment.[54]

Any thymic enlargement detected on CT scan or MRI should be removed. Some authorities recommend routine transsternal/endoscopic thymectomy even in nonthymoma patients, particularly children and adults up to the fifth decade, provided it is performed during the first year into the disease in the hope of achieving a medication-free remission.[28,36,50] A recent randomized clinical trial (the MGTX trial) conducted over 3 years has demonstrated clinically significant improvement in nonthymomatous MG patients and a more favorable outcome than prednisolone.[36] A 5-year follow-up study confirmed a continuous beneficial effect of thymic resection in nonthymoma patients[55]; however, MuSK positive patients may not benefit from the procedure.[5]

Most cases of ONP are ischemic and do not require treatment as they spontaneously improve, but the presence of a solid mass or aneurysm is treated emergently.[47] Similarly, the management of HS should be directed toward eradicating the lesion that is responsible for the syndrome.[50] Patients with an acute onset of painful HS should also be considered a neurological emergency, and carotid artery dissection, if present, should be managed immediately.

Nonsurgical management of neurogenic ptosis may involve taping the ptotic eyelid up (Figure 12.5) or the use of ptosis crutches, but these measures may exacerbate corneal dryness and corneal exposure,[7] and the crutches may cause chronic ocular pain. Ptosis due to botulinum toxin injections is managed conservatively. Patients should be reassured that the ptosis usually settles quickly within 3 to 4 weeks, and only rarely persists for the whole duration of the effect of the drug.[3] Nevertheless, anxious patients may be advised to stimulate or massage the levator muscle repeatedly with the back of an electric toothbrush for a few minutes each day, which allegedly lessens the duration of ptosis.[3] Alternatively, topical application of 0.5% apraclonidine eye drops can be prescribed at a dosage of 1 to 2 drops three times a day which causes contraction of the Müller muscle. This may elevate the eyelid by 1 to 2 mm and is usually well-tolerated.[3,56]

HS patients usually have good levator function and excellent eyelid protective mechanisms, and therefore surgical management either with aponeurotic advancement or *(Print pagebreak 101)* Müller muscle-conjunctival resection simply depends on the surgeon's preference.[50] What is indeed challenging in HS patients is the surgical correction of the slightly elevated lower eyelid which is very difficult to improve.[50]

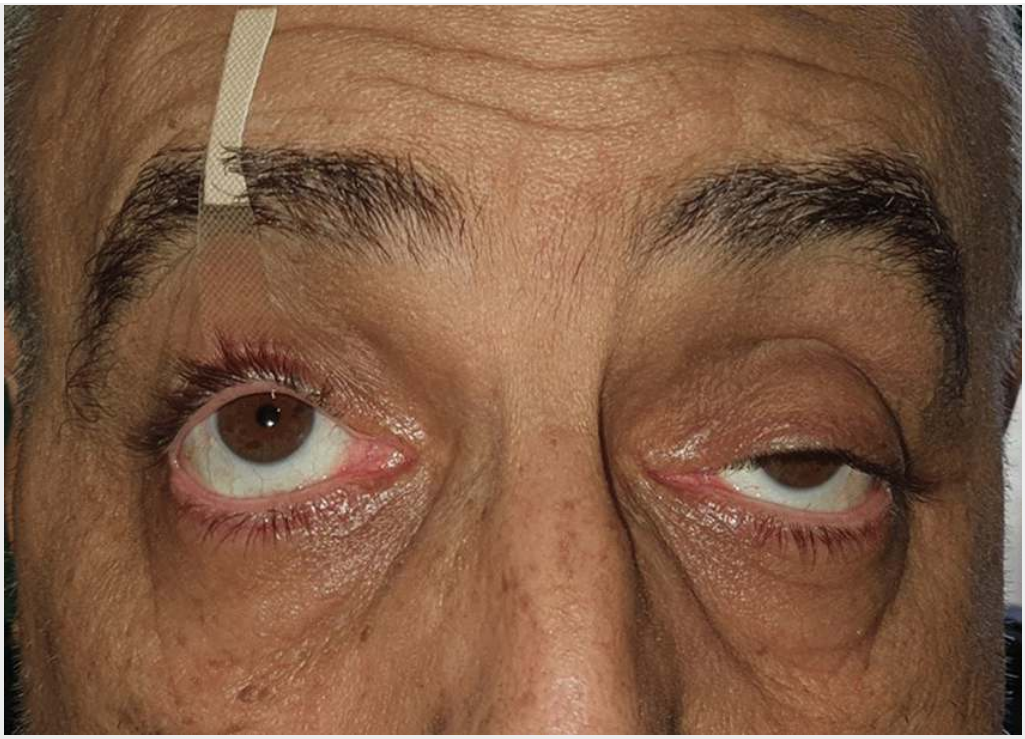

FIGURE 12.5 Taping of the eyelid to clear the visual axis as an alternative to surgery in a patient with neurogenic blepharoptosis.

On the other hand, ptosis surgery in OMG and ONP is considered high-risk due to a combination of poor ocular motility/poor Bell phenomenon. Also, in the case of OMG, the reduced orbicularis muscle strength weakening of eyelid closure mechanisms is an additional comorbidity.[57] Neurogenic ptosis patients with esthetic concerns pushing for full correction should be counseled that the main goal of surgery is to clear the pupillary axis while minimizing the risk of corneal exposure. When a frontalis suspension procedure is considered, because of its elastic nature, silicone reduces the risk of lagophthalmos compared with nonextensible materials and is, therefore, the preferred sling material to use.[57,58,59] However, patients undergoing silicone suspension should be advised that although silicone rods offer the unique advantage of the ease of readjustment and removal, the frequency of complications and the reoperation rate are high.[57,58] Complications include sling removal if severe corneal exposure is refractory to maximal lubrication, overcorrection, undercorrection, peaking, eyelash ptosis, poor symmetry, and unsightly sling visibility due to superficial placement under the skin.[60] Technical precision can reduce some of these complications. The open-sky technique[59,60] is generally favored over the closed Fox method for brow suspension,[57,58] both esthetically and functionally.[60] It allows the fixation of the silicone rod to the tarsal plate which decreases the rate of cheese wiring of the silicone rod through the delicate eyelid tissues, which ultimately reduces the risk of recurrence and minimizes the visibility of the sling through the eyelid skin. The eyelid crease is usually absent in neurogenic ptosis patients, and crease formation, which is only possible with the open-sky approach, helps minimize asymmetry and avoids the occurrence of eyelash ptosis.[60]

Perioperative considerations in the surgical management of OMG include the choice of anesthetics and the choice of postoperative antibiotics.[4] Although general anesthesia no longer poses an untenable risk to myasthenic patients, local anesthesia may be preferred as resistance to neuromuscular blocking agents may result in a higher likelihood of prolonged postoperative recovery.[4] Postoperatively, the choice of antibiotics used is another critical issue. As we mentioned earlier, fluoroquinolones, aminoglycosides, and macrolide antibiotics should be used with caution.

Prognosis

Although immunosuppressants may be required for life, most MG patients can lead essentially normal lives.[50] Thymoma patients pose a different problem as the prognosis is related to the histological staging of the tumor.[50,61] Patients with ischemic ONP may start to improve within 4 weeks of the onset of the disease, and full recovery without aberrant regeneration is expected within 4 months of the onset.[62] Immediate repair of an aneurysm causing an ONP with either surgical clipping or endovascular coiling within 3 days of onset is associated with a high probability of complete spontaneous improvement of oculomotor nerve function.[63,64] The prognosis of HS patients depends on the etiology.

Histopathology

To our knowledge, there are no descriptions of eyelid histopathological changes in neurogenic ptosis.

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CHAPTER 13

Brow Ptosis

Key Points

- Brow ptosis is a common phenomenon in the aging face and results from sagging of the forehead skin and loss of fascial support of the eyebrows to the frontal bone
- With aging in patients with brow ptosis, the lateral part of the brow usually shows the greatest degree of descent
- Other rarer causes of brow ptosis include myasthenia gravis, myotonic dystrophy, and oculopharyngeal muscular dystrophy
- Symptoms include loss of superior visual field, a tired appearance, and headaches due to compensatory contraction of the frontalis muscle
- Botulinum toxin to the lateral orbital portion of the orbicularis muscle, which acts as an eyebrow depressor, can be an effective treatment for mild lateral brow droop
- Transcutaneous browpexy with fixation sutures to underlying periosteum can also achieve adequate lateral brow elevation
- Direct surgical brow lift and forehead elevation are other more invasive procedures that are effective in more severe degrees of brow ptosis

The eyebrows frame the eyelids and are a powerful expression of emotions. Any change in their position may influence how other people judge our behavior and mood.[1] Brow ptosis results from sagging of the forehead skin and loss of fascial support of the eyebrows to the frontal bone. It is a common phenomenon in the aging face, and frequently accompanies laxity of other periorbital structures, such as the eyelid skin. A downward displacement of the eyebrows can accentuate the degree of redundancy of upper eyelid skin and result in significant loss of superior visual field. Often associated with brow ptosis is a descent of the subbrow fat pad, producing a thickened upper eyelid. Failure to recognize brow ptosis as a contributing factor in upper eyelid dermatochalasis can lead to a disappointing result following blepharoplasty.[1] There is no universally accepted definition of an ideal eyebrow position and contour, and ethnic variations, as well as cultural differences, may dictate different aesthetic preferences.[1,2,3,4,5,6,7]

Etiology and Pathogenesis

As age advances, the brow is under a constant “tug of war” between the combined forces of gravity and the periorbital protractor muscles (the orbicularis oculi, procerus, and corrugator supercilii) on one hand, which tend to pull the brows downward, and the frontalis muscle on the other, which elevates the brow.[7] The downward forces tend to prevail, and the brow is observed to descend in the majority of older patients.[7] However, paradoxical brow elevation is observed in a sizable proportion of individuals.[8] Some authors claim that the odds of brow elevation or descent with age are roughly equal and that in the majority of cases the brow level does not change appreciably with age.[9] This controversy probably depends on which part of the brow the observer is evaluating. The central and medial portions of the brow may remain constant in position or even elevate with age,[8] and one study failed to observe any age-related change in the position of the nasal part of the brow.[10] The lateral part of the brow, however, invariably shows age-related descent.[11] A recent study demonstrated that the distance between the nasal ala to the lateral brow decreases by 0.15 mm per year, accounting for an average descent of 3 mm over 20 years.[11] Therefore, it could be conceptualized that what is happening with aging is not an overall change in the position of the eyebrows, but rather a change in brow shape.[8] In younger individuals, the lateral brow usually is stationed at a higher position than the medial or the central parts of the brow, but as aging progresses, the brow acquires a flatter contour because of inevitable lateral descent. This may or may not be associated with paradoxical elevation of the rest of the brow.[8] These changes are more pronounced laterally because the lateral eyebrow is not densely attached to periosteum lateral to the supraorbital ridge,[11] and because the frontalis muscle stops short of the tail of the brow.[11,12] The lateral border of the frontalis muscle almost always ends, or becomes extremely attenuated, beyond the temporal fusion

line of the skull.[11,12] Therefore beyond this point, the gravitational effects, as well as the downward pull of the protractor muscles, are unchecked.[8,11,12]

Another frequently cited cause for involutional brow ptosis is volume loss and tissue deflation rather than actual tissue descent.[2,4,13,14] This has led to a trend in brow rejuvenation procedures focusing on volume replenishment instead *(Print pagebreak 104)* of brow elevation.[14,15] The existence of lateral brow drooping has been refuted, with the argument that hollowing of the eyelid-brow complex that occurs with age causes shadowing beneath the brow, causing an illusionary brow descent.[14] This concept has been challenged in a recent study that showed that total eyebrow volume does not decline with age and may slightly increase in males.[15] Furthermore, this same study showed a paradoxical increase in brow fat volume.[15] Although these findings may seem incompatible with clinical observations, the authors argue that the pseudodeflation that is observed in clinical practice is due to thinning and loss of skin elasticity, along with widening and deepening of the supraorbital rim with age.[15]

Brow ptosis may also occur secondary to paralysis or weakness of the frontalis muscle. The loss of frontalis tone that accompanies facial nerve paralysis generally causes a severe brow droop.[4,16,17] Other rarer causes include myasthenia gravis, myotonic dystrophy, and oculopharyngeal muscular dystrophy, although in these patients the frontalis muscle is less severely affected than the extraocular muscles.[4,18] Brow ptosis may also occur from the involuntary contraction of the orbicularis oculi in conditions such as blepharospasm or other facial dystonias.[4] Mechanical brow ptosis can also occur due to neoplasms involving the brow, like basal cell carcinoma, keratoacanthoma, melanoma, or squamous cell carcinoma.[4]

Clinical Presentation

Patients may not be aware of progressive brow ptosis and their presenting complaint may be drooping of the upper eyelids rather than drooping of the brows (Figure 13.1).[5] Patients may also complain of defective vision or loss of the superior visual field (Figure 13.2), a tired appearance, and more importantly, headaches or ocular discomfort.[5] Headache occurs because patients who have significant hooding are obliged to recruit their frontalis muscle to see clearly, and this may lead to frontalis muscle fatigue and subsequent headaches.[5]

FIGURE 13.1 Temporal brow hooding due to age-related descent of the brow.

FIGURE 13.2 Severe brow ptosis causing a significant loss of the superior visual field.

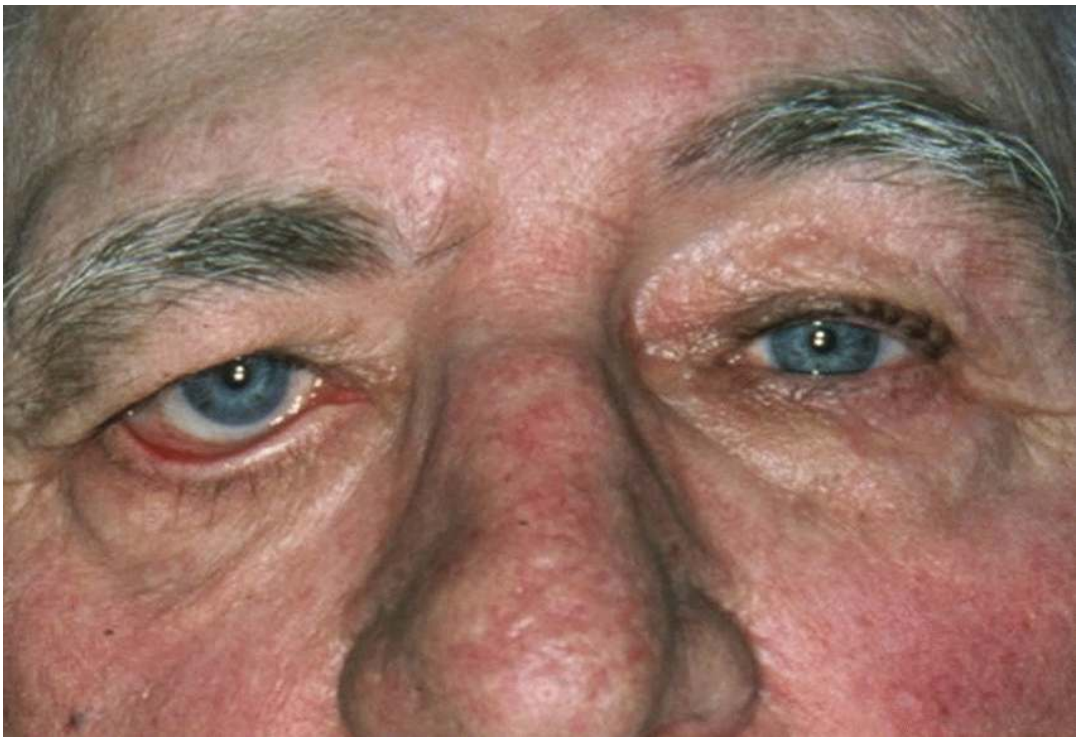

FIGURE 13.3 Facial nerve palsy causing significant unilateral brow ptosis with brow asymmetry and lower eyelid ectropion. (Courtesy of Dr. Ilya Leyngold.)

The history is very important in patients presenting with brow ptosis. Patients should specifically be asked about a recent history of botulinum toxin injections, as they may not volunteer the information spontaneously.[5] Elderly patients with a remote history of Bell palsy may have forgotten about it so any attending family member should be questioned if it is suspected. A history of trauma to the face, surgery for acoustic neuroma, or a history of stroke may also indicate facial nerve paralysis or injury (Figure 13.3).[6]

Patients with brow ptosis should be examined with the eyes looking straight ahead. The brow position, whether at, below, or above the superior orbital rim, should be noted in the medical record, together with a detailed outline of the position of the tail of the brow versus the rest of the brow. Photographic documentation is preferred if possible. Any brow asymmetry should be pointed out to the patient, and the eyelid position, as well as the palpebral fissure height, should be noted. In female patients who pluck their eyebrow

hairs or who have tattooed brows, it may be difficult to ascertain the true position of the eyebrow.[4,5] During examination, *(Print pagebreak 105)* any visible scar in the brow should also be noted. A temporal brow droop could cause significant dermatochalasis that may occasionally be so severe that it leads to a secondary mechanical misdirection of eyelashes or accentuate existing lash ptosis, causing ocular discomfort and tearing.[5,19] In patients with facial paralysis, secondary dermatochalasis may be more severe than in nonparalytic involutional brow ptosis.[20]

Differential Diagnosis

Because the management is different, patients with actual blepharoptosis or dermatochalasis should obviously be differentiated from patients with brow ptosis.[6] Of note is that these three conditions (brow ptosis, blepharoptosis, and dermatochalasis) are not mutually exclusive, as all of them may coexist together in the same patient to a varying degree in one or both eyes.

Treatment

A nonsurgical brow lift can be undertaken with judicious injections of botulinum toxin to the eyebrow depressors including the orbicularis muscle.[5] This so-called "chemical brow lift" may be indicated in patients who decline surgery, or who have mild to moderate brow ptosis with concomitant deep glabellar frown lines.[5] A temporal brow lift can be achieved with botulinum toxin injections into the superolateral orbicularis muscle just below the brow tail.[5,21,22,23,24] Botulinum toxin injections work by disrupting the balance between the eyebrow depressors and elevators, but a basic understanding of the anatomy of the eyebrow depressors is paramount to effect acceptable brow elevation with botulinum toxin.[24]

The brow and upper eyelids are interrelated and form a single aesthetic unit[2,3]; therefore, it is better to assess both components of this continuum together when planning periorbital rejuvenation.[3] Although temporal eyebrow drooping may indeed sabotage an otherwise excellent upper eyelid blepharoplasty, some authors have argued that brow ptosis should be addressed with caution, and it may be better to avoid the approach that all brow ptosis should be surgically corrected.[8,14] In older adults with brow ptosis, it may suffice to carry out an upper eyelid blepharoplasty to address dermatochalasis, while accepting a degree of uncorrected brow ptosis, provided the patient is offered all the alternatives preoperatively.[3] But if a brow lift is considered, it is important to point out that some procedures attempt to address the entire brow and not just lateral drooping. These may produce an unnatural appearance and are better avoided,[8] except in special situations like facial nerve paralysis.

There are several types of eyebrow elevation procedures described in the literature ranging from the maximally to the minimally invasive. The most effective procedure is the direct brow lift where skin is removed superior to the eyebrow. This technique offers the greatest brow elevation per millimeter of tissue excised, but the unsightly scar that may ensue limits its usefulness and popularity.[3,7] This procedure may be exceptionally valuable in patients with facial paralysis where brow skin excision, combined with posterior fixation to the periosteum, is the most commonly employed technique.[20] Variants of the direct brow lift include the "gull wing" direct brow lift, which extends the direct brow lift performed simultaneously on both sides into the glabellar region in a "gull wing" fashion.[5] This procedure produces a visible scar and might only be considered in elderly patients with marked generalized brow ptosis. However, it may be counterproductive as the descent of the medial part of the brow with age is a controversial issue.[10]

Other traditional brow lifting procedures include the endoscopic approach, the pretrichial, the mid-forehead, and coronal brow lift approaches.[5] A detailed description of those surgical techniques is beyond the scope of this chapter, but it may suffice to mention that the endoscopic approach has largely reduced the need for coronal or pretrichial brow lift procedures with their associated morbidities.[5] It should be also pointed out that an endoscopic brow lift is not indicated for every patient. Patients with minimal temporal brow ptosis, and alternately patients with very heavy brows, may not benefit from the procedure.[5]

On the other end of the surgical spectrum, minimally invasive techniques, such as the browpexy procedures, are usually combined with an upper blepharoplasty. In contrast to the more involved surgical approaches described above, browpexy techniques only achieve a more modest change in eyebrow position.[5,23,25] Nevertheless, three different techniques have enjoyed popularity in the last decade. The internal browpexy takes advantage of the eyelid blepharoplasty incision to fix the brow 1 cm above the level of the orbital rim with 4-0 polypropylene sutures.[25,26] The procedure can be combined with debulking of the lateral eyebrow fat to enhance the lifting effect.[25] Lateral orbicularis muscle fixation, originally introduced by Zarem et al. in 1997,[27] and later referred to as the "brassiere" suture technique by Varshney et al.,[28] is another useful technique. This restores a youthful appearance by elevating the brow fat pad and limiting its descent and unmasks the lateral tarsal platform.[25] Technically, this procedure does not raise the eyebrow at all, but rather camouflages it and is performed by dividing the orbicularis into superior and inferior halves. Two or three 5-0 sutures are then used to secure both the upper and

lower margins of the divided orbicularis to the periosteum of the lateral orbital rim.[25] The third technique is the external browpexy technique, which was introduced by Massry in 2012.[29] This straightforward technique is easily mastered and yields excellent outcomes with high patient satisfaction, at least temporarily.[25,29]

Prognosis

The goals, risks, and limitations of brow lifting procedures should be discussed in detail with the patient to have realistic expectations.[5] Patients should be informed of the potential *(Print pagebreak 106)* for scarring if a direct brow lifting procedure is chosen. Other complications include direct injury to the temporal branch of the facial nerve or sensory nerve damage with endoscopic procedures.[5] Patients should also be informed of the limitations of browpexy techniques. At best, browpexy can provide a subtle additional functional and cosmetic benefit.[25] Also, the long-term success of browpexy procedures is unknown and to the best of our knowledge no formal study has exceeded 6 months of follow-up.[29,30]

Histopathology

The etiology of brow ptosis is related to normal involutional laxity of the suspensory apparatus of the forehead or paralysis of the superior division of the seventh cranial nerve.

To our knowledge, there are no descriptions of brow histopathological changes for brow ptosis.

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CHAPTER 14

Congenital Tarsal Kink

Key Points

- Congenital tarsal kink is an exceedingly rare form of congenital entropion
- The condition is usually unilateral, but can be bilateral in 25% of cases
- Males are affected more frequently than females in a ratio of 3:1
- The etiology is unknown, but proposals include abnormal developmental horizontal fold deformity of the superior tarsal plate, direct mechanical pressure in utero with disinsertion of the levator aponeurosis, primary hypertrophy and contraction of the marginal orbicularis oculi muscle, defective insertion of the levator aponeurosis, and/or intrauterine inflammation of the fetal tarsus
- The upper eyelid margin usually shows severe entropion, with a prominent fold or kink across the posterior horizontal length of the tarsal plate
- A corneal ulcer or corneal infiltrate is usually observed in more than half of the reported cases at presentation and secondary blepharospasm is common
- The ocular surface can be protected temporarily with a soft contact or scleral lens until a more definitive procedure can be undertaken
- In most cases, surgical treatment will usually be required to prevent permanent damage to the cornea
- The prognosis for correcting the entropion is excellent with almost any surgical or suture procedure

Entropion is an in-turning of the eyelid margin associated with the eyelashes abrading the corneal surface with ulceration, and if left untreated, eventually opacification and visual loss. It can be seen as an acquired condition in adults, or as a congenital malposition. Congenital upper eyelid entropion, in general, was first described in 1841 by von Ammon.[1] Later cases were mentioned by Wilde,[2] Lippincott,[3] Chow,[4] and Redslob,[5] among others, but these early descriptions do not allow determination of specific etiologies.

Congenital entropion is typically present at birth or becomes evident within the first few weeks or months of life. It is exceedingly rare and mostly involves the lower eyelid in the form of epiblepharon. Congenital entropion of the upper eyelid is even rarer with only a small number of cases reported. The etiology can be secondary or primary. Secondary congenital entropion is acquired as a result of trauma, chemical conjunctival burns, infections, inflammatory conditions, and hereditary cicatricial disease, or it is associated with genetic anomalies such as cutis laxis[6,7] or progeroid syndrome.[8] Primary congenital upper eyelid entropion results from developmental or intrauterine processes and has been related to absent tarsal plates, fibrosis, and shortening of the levator aponeurosis, a thickened tarsus with an extra row of meibomian glands, or absence of the eyelid crease with loss of fixation of the anterior lamella to the tarsus.[9] When the tarsal plate is present, it usually is described as being normal.[10]

One well-defined form of primary congenital entropion has been referred to as the congenital horizontal tarsal kink, characterized by a horizontal depressed crease across all or part of the posterior surface of the upper tarsal plate. It was originally described in 1948 by Kettesy,[11] who speculated that inflammatory edema of the superior conjunctival fornix for several weeks in utero mechanically folded the tarsus into a fixed position. The tarsal deformity results in an inversion of the eyelid margin that causes corneal epithelial erosion, infectious keratitis, or corneal ulceration. The condition is usually diagnosed in children during the first several weeks or months of life. However, recognition of this condition is sometimes delayed, either because of initial misdiagnosis or because of subclinical findings that only progress with time.

Congenital tarsal kink is very rare with only about 48 cases described in the literature since 1948. Of the 25 cases where age data are available, the mean age at presentation was 24 weeks (range: birth to 240 weeks), with a median of 5 weeks. The condition is

bilateral in 25% of cases, and when unilateral, the condition involves the right side more frequently than the left (48% vs 27%). Of the 19 cases where the race was reported, 84% were in Caucasians. Males are affected more frequently than females in a ratio of 3:1 (74% male, 26% female).

In a review in 1969, Hiles and Wilder[12] reported six cases of primary congenital upper eyelid entropion associated with cardiovascular, musculoskeletal, and central nervous system abnormalities. Zak[13] also described a case of upper eyelid entropion associated with multiple systemic anomalies, including dysmorphic facies, micrognathia, abnormal feet, agenesis of the corpus callosum, and ventriculoseptal defect. Dailey et al[10] presented a case of congenital upper eyelid entropion associated with a congenital heart defect. It has been proposed that, unlike primary congenital upper eyelid *(Print pagebreak 108)* entropion, tarsal kink is not associated with systemic abnormalities.[14] However, Batur et al[15] reported a case of bilateral tarsal kink in an infant with Wiedemann-Rautenstrauch syndrome, an extremely rare, autosomal recessive disorder characterized by progeroid appearance, macrocephaly, wrinkled skin, reduced subcutaneous fat, and neonatal teeth. Lucci et al[16] described a case of unilateral tarsal kink in a child with trisomy 13 (Patau syndrome) having multiple craniofacial, cardiac, neurologic, and renal anomalies, and El-Mulki et al[17] presented a case of bilateral tarsal kink with hydronephrosis. Naik et al[18] and Pushker et al[19] provided one case each of tarsal kink associated with microphthalmos.

Etiology and Pathogenesis

The etiology of congenital tarsal kink is unknown. Proposed causes include an abnormal developmental horizontal fold or kink deformity of the superior tarsal plate,[20,21] direct mechanical pressure in utero with disinsertion of the levator aponeurosis,[14,16,22] primary hypertrophy and contraction of the marginal orbicularis oculi muscle,[13,20,21] a defect in and disinsertion of the levator aponeurosis,[13] and intrauterine inflammation of the fetal tarsus.[10] Absence of the eyelid crease without levator aponeurosis disinsertion in some cases supports the idea that dysgenesis of the terminal levator aponeurosis fibers in the orbicularis muscle and dermis may play a role in the pathogenesis of this disorder, and that the "kink" may be secondary to unopposed orbicularis muscle contraction.[14,23]

Sires[24] suggested that because right occiput anterior (ROA) vaginal deliveries are more frequent than left occiput anterior (LOA) deliveries, acute eyelid trauma during passage through the birth canal may account for the right-sided predominance of tarsal kink cases. However, Ghi et al[25] measured fetal head position during 80 births and reported that ROA and LOA positions were nearly equal, in 26.25% and 27.50%, respectively. Although there is no evidence of hereditary factors in humans, congenital entropion similar to horizontal kink was observed in a litter of New Zealand White rabbits containing one male and three females.[26]

Clinical Characteristics

The clinical findings in congenital horizontal tarsal kink have been well described.[10,12,13,14,16,17,20,21,22,23,27,28,29] Symptoms usually become manifest at birth or shortly thereafter when the infant cannot open one or both eyes, often with a mucoid discharge. In many cases, an initial diagnosis of infection is made, and the child is treated with topical antibiotics. When symptoms do not resolve or they progress and further evaluation is sought, the diagnosis is usually made several weeks or months later.

The upper eyelid margin usually shows severe entropion (Figure 14.1), with a prominent fold or kink across the posterior horizontal length of the tarsal plate. The diagnosis requires eversion of the upper eyelid to identify the kink and to distinguish it from other forms of congenital upper eyelid entropion. In some cases, a horizontal ridge can be palpated anteriorly beneath the skin. Naik et al[18] noted a more flattened obtuse tarsal bend instead of a sharp kink in two patients who presented after 3 and 5 years, respectively, and suggested that the tarsal kink might tend to stretch and flatten over time.

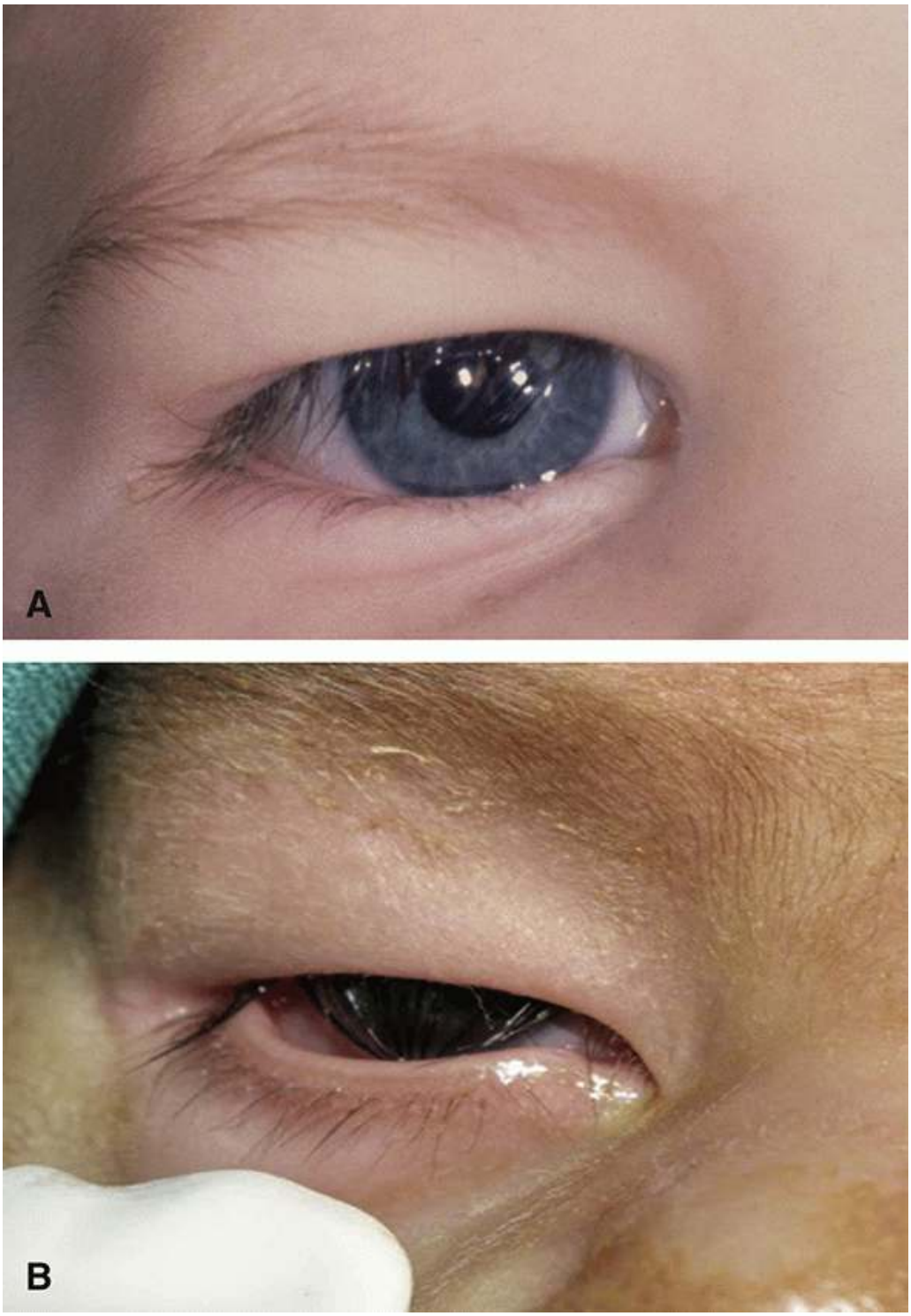

FIGURE 14.1 Spectrum of involvement of the upper eyelid in patients with congenital horizontal tarsal kink. A, Moderate entropion trichiasis. B, Severe entropion trichiasis with complete obliteration of the upper eyelid crease.

A significant proportion of cases have a corneal ulcer at presentation,[1,17,23] seen in 50% to 80% of patients, and 50% may have an active corneal infiltrate.[18,24] The ulcers are typically sterile, but this may be the result of treatment with topical antibiotics before culturing. The presence of corneal ulcers at birth in some cases suggests that the damage began in utero.

The upper eyelid crease usually is absent on the affected side. Blepharospasm is also a common finding, making it difficult for the clinician to open the eyes, and in part, this may be responsible for delayed diagnosis. Other findings can include mucoid discharge, conjunctival injection, trichiasis, eyelid edema, and secondary epiphora. Amblyopia has been reported in several cases.

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Differential Diagnosis

The differential diagnosis of congenital tarsal kink includes primary upper eyelid entropion such as epiblepharon, aponeurotic disinsertion, conjunctival cicatricial diseases with scaring and fornix shortening, as well as chemical burns. The corneal complications associated with tarsal kink can also be seen with infectious keratitis, trichiasis, distichiasis, and lower eyelid entropion.

Treatment

In children with tarsal kink, when the ocular surface is already compromised it can be protected temporarily with a soft contact or scleral lens until a more definitive procedure can be undertaken. Although short-term patching has been reported to successfully unfold the kink,[24] this is unlikely to be successful in any but very mild cases. Because most surgical procedures are destructive to the tarsal plate and meibomian glands, less invasive techniques have been sought. In cases where the kink can easily be reduced over a muscle hook, a temporary suture tarsorrhaphy has been used to splint the eyelid in a normal position to flatten the tarsal plate.[16,17] In his original description of this condition, Kettesy[11] treated his patient with everting sutures over a gauze roll for 5 days with resolution of the tarsal fold. One possible drawback to these suture techniques is the risk of amblyopia developing in an occluded eye in very young children. Other minimally invasive techniques involving everting sutures of various designs have been utilized as an initial procedure with good results reported.[16,17,19,22,30,31]

In most cases, surgical treatment will usually be required to prevent permanent damage to the cornea. Various surgical procedures have been described and include both anterior and posterior approaches. The surgical goal generally is weakening the kink with eyelid margin rotation and formation of the eyelid crease. McCarthy[28] described the lamellar tarsoplasty procedure where the anterior lamella of the tarsus from 1 mm below the superior border to just above the eyelash follicles is excised and reversed to apply enough traction to flatten the kink. But this is a difficult dissection and grossly disrupts the meibomian glands. Yuksel and Kosker[32] described a procedure of anterior tarsal face incision in the region of the kink, with advancement and reattachment of the levator aponeurosis to the tarsus and skin to strengthen the levator muscle. Anterior lamellar shortening, repositioning, and marginal eyelid rotation are also commonly used procedures with satisfactory results.[29]

Naik et al[18] utilized a transconjunctival horizontal tarsotomy with marginal rotation and reported a high success rate in repositioning the eyelid margin, improving corneal epitheliopathy, and reducing reflex epiphora. They argued that the transconjunctival approach may be better cosmetically in that it avoids a skin scar and may minimize blood loss. The posterior approach also addresses only the affected structure, the tarsal plate. Biglan and Buerger[20] also employed a full-thickness eyelid fracture with marginal eyelid rotation, as originally described by Ballen.[33]

Prognosis

The prognosis for correcting the entropion is excellent with almost any surgical or suture procedures mentioned above. It is important to reposition the eyelid as early as possible to prevent irreversible corneal scarring. Delayed cases and those with infectious keratitis carry a worse prognosis.

Histopathology

To the best of our knowledge, there are no histopathology reports related to this disease entity.

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CHAPTER 15

Dermatochalasis

Key Points

- Dermatochalasis is an age-related laxity of eyelid skin and loss of muscle tone resulting in redundancy of skin folds and subcutaneous tissue in the upper and lower eyelids
- Steatoblepharon is the prolapse of extraconal orbital fat into the eyelids related to laxity of the orbital septum
- The aging process of the skin is caused by both intrinsic (heritable) and extrinsic (environmental and personal) risk factors
- In the upper eyelid, clinical symptoms include excess eyelid skin overhanging the eyelid crease and sometimes the eyelashes as well and may reduce superior visual field
- Redundant skin is often associated with bulging fat pockets medially and laterally
- Brow ptosis is a common associated aging phenomenon that can exacerbate the appearance of excess upper eyelid skin
- The mainstay of therapy of dermatochalasis is surgical excision of excess skin with or without removal or repositioning of prolapsed fat pockets

The human face is composed of several functional and cosmetic units, but the dynamic periocular region constitutes the main point of focus in daily human interactions and occupies a pivotal point in relaying emotions and facial expressions.[1] Therefore, aging changes in the periocular region could lead to facial imbalance and functional disharmony.[1] Dermatochalasis refers to an age-related laxity of the eyelid skin and loss of muscle tone, with consequent redundancy of skin folds and subcutaneous tissue involving the upper and less commonly the lower eyelids.[1,2,3,4,5,6,7,8,9,10] Steatoblepharon (etymologically derived from the Greek word “steatos” or related to fat), which is casually referred to as “baggy eyes,”[7] is defined as the protrusion of eyelid fat pads and applies to the lower and less commonly the upper eyelids. Both conditions are usually observed starting from the fourth decade and maybe even earlier.[3] Although primarily a cosmetic problem, dermatochalasis can cause functional visual loss as well.[2]

Etiology and Pathogenesis

Several factors working together help to explain why the face ages. Similar to other organs, the skin including the eyelid skin simply ages over time,[10] and because sagging eyelids are considered a feature of the aging process of the skin in general,[6,11] the intrinsic (heritable) and extrinsic (nonheritable) risk factors for both conditions broadly overlap. It is a fact that age (per decade) is a major contributing factor to the development of dermatochalasis.[5,6,8] Other risk factors include a higher basal metabolic index, a lighter skin color, female sex, solar damage, and possibly smoking.[6,7,9] A recent epidemiological study conducted both in the Netherlands and the United Kingdom found that female sex is associated with a higher risk of mild sagging, while males have an increased risk of severe sagging.[6] Interestingly, the same study found that smoking only had borderline relevance, and that sun exposure was not a factor contributing to the development or progression of dermatochalasis.[6] These results are surprising because they contradict the long-held view that both cigarette smoking and sun exposure are detrimental to skin aging in general.[5,12]

What the results of this large level II study do suggest is that genetic or heritable factors do play a more significant role in the pathogenesis of dermatochalasis than was previously realized. One arm of this study was conducted on twins in the United Kingdom and found that heritability plays a role in the induction or prevention of dermatochalasis in 61% of patients.[6] Genetic analysis showed that a recessive gene located on the short arm of chromosome 18 (18p11) may have a defensive role against sagging eyelids.[6] An additional possible gene that could likely be biologically relevant to dermatochalasis is the *SMYD3 gene*, which is associated with matrix metalloproteinase (MMP-9) upregulation, a well-known modulator of the extracellular matrix.[6] Another recent genetic study conducted on middle-aged French females showed that two closely located genes may have a putative role in skin photoaging: the STXBP5L gene and the FBXO40 gene.[11] These studies suggest that future research should be directed further toward

investigating the molecular mechanisms of skin aging. It has been suggested that the inheritance of dermatochalasis resembles the inheritance pattern of other common complex traits in humans like body height, in that several DNA variants could each have a small additive or subtractive effect, ultimately determining the phenotype.[6]

Regardless of the actual role played by intrinsic or extrinsic etiologic factors, the actual events involved in the pathophysiology of dermatochalasis are not yet fully understood,[13] but suggested mechanisms explaining *how the face ages* include increased skin laxity, gravitational effects, and deflation (soft tissue as well as bone), which by working together *(Print pagebreak 112)* all underwrite the senescent eyelid changes that are observed in clinical practice.

Progressive skin laxity, which is a characteristic feature of the aging ocular adnexal tissue, both in the upper and lower eyelids, probably occurs due to a triad of increased elastolysis, increased collagenolytic activity, as well as lymphostasis.[13,14] This is supported by histopathologic findings that include an increase in the diameter and number of lymphatic vessels, a reduction in elastic fibers that are essential for the structure and function of the lymphatic system, disarrangement in collagen fibers with wide spacing between collagen bundles, stromal edema, and an increase in the number of macrophages, which suggest that subclinical inflammation may also play a role in the development or the initiation of dermatochalasis.[13,14,15] Lymphangiectasia, or dilatation of lymphatic vessels, is an indicator of lymphostasis. The stasis of interstitial fluid, which ensues, plays a pivotal role in the development of dermatochalasis.[13,15] Because dermal lymphatic capillaries are surrounded by an elastic network that is specialized in organizing the peristaltic activities of lymphatics, the breakdown of elastic fibers or the reduction in elastic fiber density may also play an important role in the pathogenesis of dermatochalasis,[13,15] as well as baggy eyelids.[13] There is also an increase in the diameter of collagen fibers and wide spacing between fibers suggesting stromal edema.[13,15] A unique study that was published recently compared the histologic findings in the skin versus the orbicularis oculi muscle and revealed that the orbicularis muscle remains relatively intact throughout the aging process.[16] As we shall see later, this is a major finding of significant clinical relevance.

In addition to progressive laxity, it should be realized that these effects are also weighed down by the effect of gravity,[14] which in the periocular region acts on the cephalocaudal axis causing tissue descent mainly in the upper eyelid-brow complex,[4,17,18] and to a lesser extent in the lower-eyelid-cheek complex.[19] The lateral aspect of the brow is not firmly attached to the supraorbital ridge, theoretically allowing its gradual descent due to gravitational effects. It has been calculated recently that the lateral tail of the brow may descend around 2.5 mm every 20 years.[18] The impact of gravity is less obvious in the lower eyelid where laxity of the skin, orbicularis muscle, and the orbital septum plays a more significant role.[19] The tighter arrangement of orbital retaining ligaments at the lid-cheek junction not only limits the effects of gravity but it also seals off the downward and forward prolapse of orbital fat attributable to laxity of the orbital septum. An additional factor that limits the effects of gravity in the lower eyelid is that it is suspended medially and laterally with the medial and lateral canthal tendons, respectively.[19]

In contrast to the effects of gravity, volume deflation has a greater impact on the lower eyelids than the upper, where it causes a tear trough deformity, a "*pseudo*" descent of the cheek, and skeletonization of the malar eminence.[4]

Clinical Presentation

Facial esthetic units are normally delineated by natural barriers, and because the eye is topographically located in the center of the face, it may be prudent to compartmentalize the periocular region into two distinct, yet not entirely separate, esthetic, and functional units.[4] The superior complex or unit includes the upper eyelids and the eyebrows, while the lower esthetic unit involves the lower eyelids and the cheeks.[4]

While patients seeking cosmetic rehabilitation of the lower eyelids have purely cosmetic concerns, patients seeking upper lid surgery may have significant functional concerns. They may complain of recurring bouts of frontal and/or migraine headaches or excessive fatigue when reading due to the chronic overuse of the frontalis muscle.[9] Relevant points during history taking should include anticoagulant use, as well as any recent injections of periocular neuromodulators in the weeks preceding the examination, which potentially could alter brow position. Patients complaining of puffy lower eyelids should specifically be asked about the tempo of onset. If an unsightly bulge has just evolved recently or progressed rapidly, an explicit inquiry should be made about the recent history of periocular filler injection in the lower eyelids or the whole face. Thyroid eye disease should also be excluded.

Well-recognized signs of upper eyelid aging include droopy eyebrows with excessive eyelid skin, especially laterally causing lateral hooding (Figure 15.1). The eyelid crease may no longer be visible or may be at least partially obscured by overhanging skin, and female patients may complain of the inability to apply makeup to the upper eyelids.[9,20] The nasal fat pad becomes more prominent with age, resulting in a localized spherical bulge medially, which if prominent may even alter the nasal contour (Figure 15.2).[5] The central pad of fat becomes less prominent with age causing hollowing of the superior sulcus. In mild cases, it may not be observed except when the patient looks down, but in more severe cases, it may cause a superior sulcus depression and skeletonization of the upper eyelid.[5] Upper eyelid height should also be checked thoroughly so as not to miss concomitant blepharoptosis, which may undermine the surgical outcome. With or without ptosis, dermatochalasis patients may have deep forehead furrows due to the

prolonged use of brow muscles.[9]

Functionally, upper lid hooding may be severe enough that patients may be forced to manually elevate the excess skin to clear the visual axis.[9] Patients with severe dermatochalasis may also suffer from a diminution of the central or more commonly the temporal visual field, which may impart a significant visual disability and could impair the patients' quality of life.[21] Excess upper eyelid skin may also overhang the eyelid margin causing entropion and eyelash ptosis, which could, in turn, cause corneal irritation (Figure 15.3).[9]

Examination of the lower lids usually reveals a separate set of distinct findings that are more of a cosmetic nature and these patients suffer little, if any, functional implications. Although patients may have various combinations of orbital *(Print pagebreak 113) (Print pagebreak 114)* fat herniation, fine wrinkles or rhytides, or an excess of lower eyelid skin forming a dewlap (Figure 15.4), a true or more commonly a pseudoherniation of fat usually predominates.[9,22] Skin discoloration and/or pigmentary changes may also occur.[8,9] It is of paramount importance to exclude lower eyelid laxity, as well as a preexisting lower eyelid retraction, which should be pointed out to the patient.[9] Because one of the marks of aging in the midface is the presence of a tear trough deformity or hollowness in the orbitomalar sulcus between the lower eyelid and the cheek, evaluation of the lid-cheek junction should not be overlooked. This sulcus is usually accentuated by fat herniating into the lower eyelid above it and by age-related deflation of the cheek malar fat pads below it.[22]

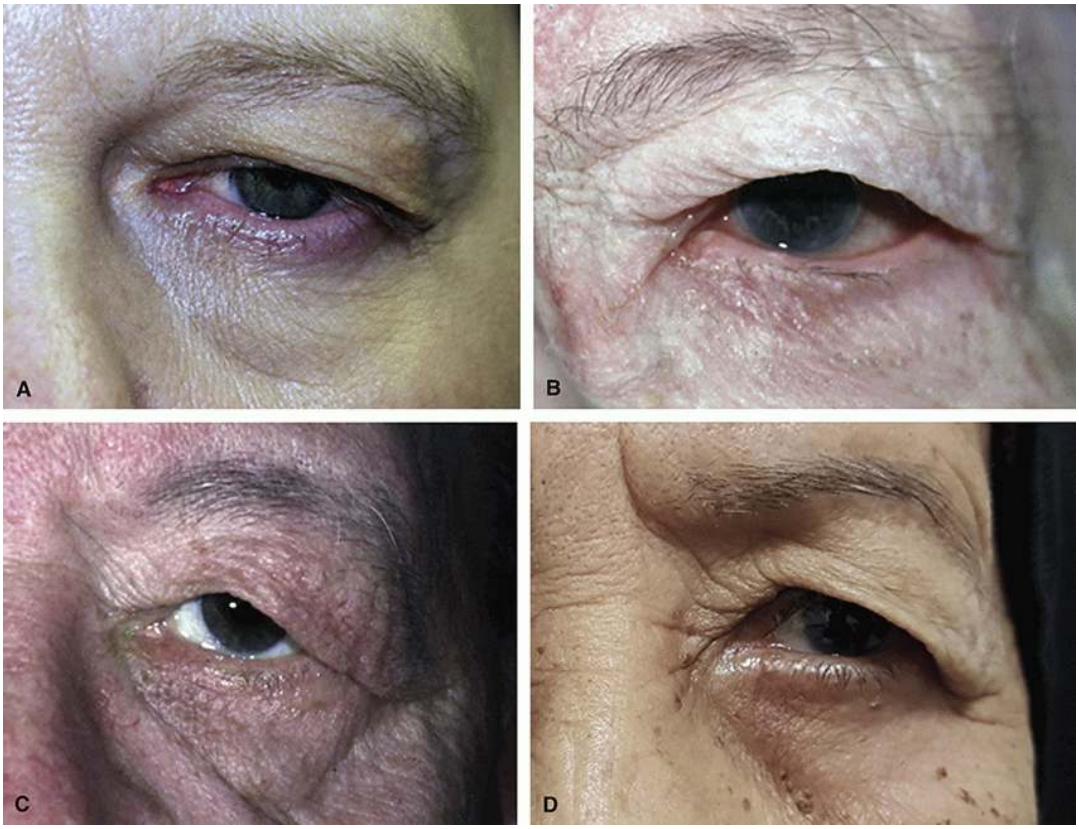

FIGURE 15.1 A-D, Upper lid dermatochalasis of varying degrees with significant lateral hooding.

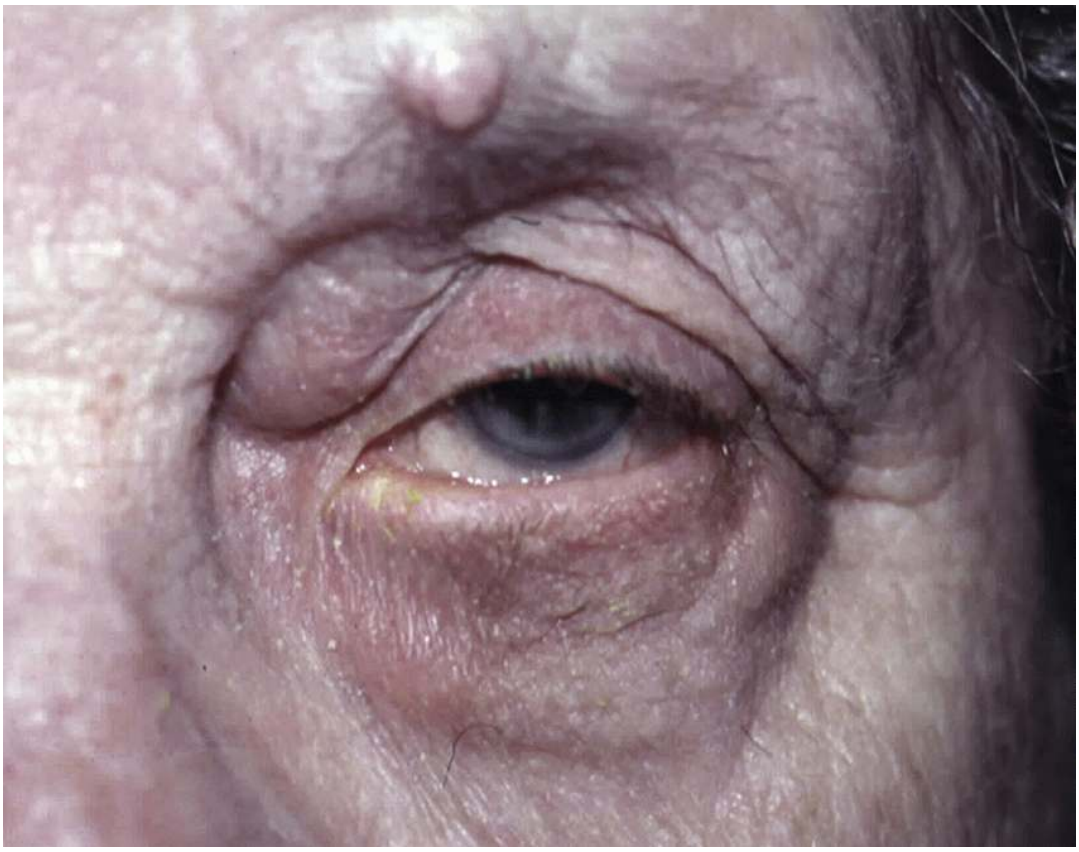

FIGURE 15.2 Dermatochalasis with prolapse of the upper eyelid medial fat pad.

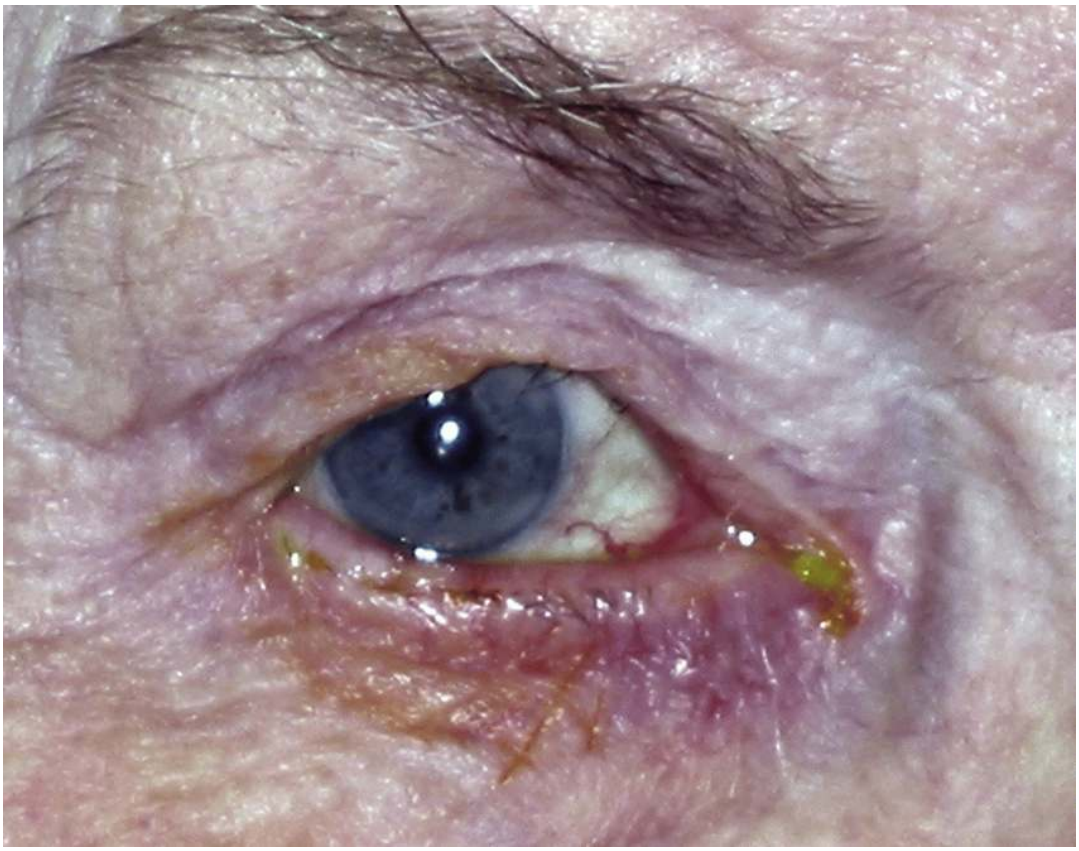

FIGURE 15.3 Upper eyelid dermatochalasis with eyelid margin entropion and secondary eyelash ptosis.

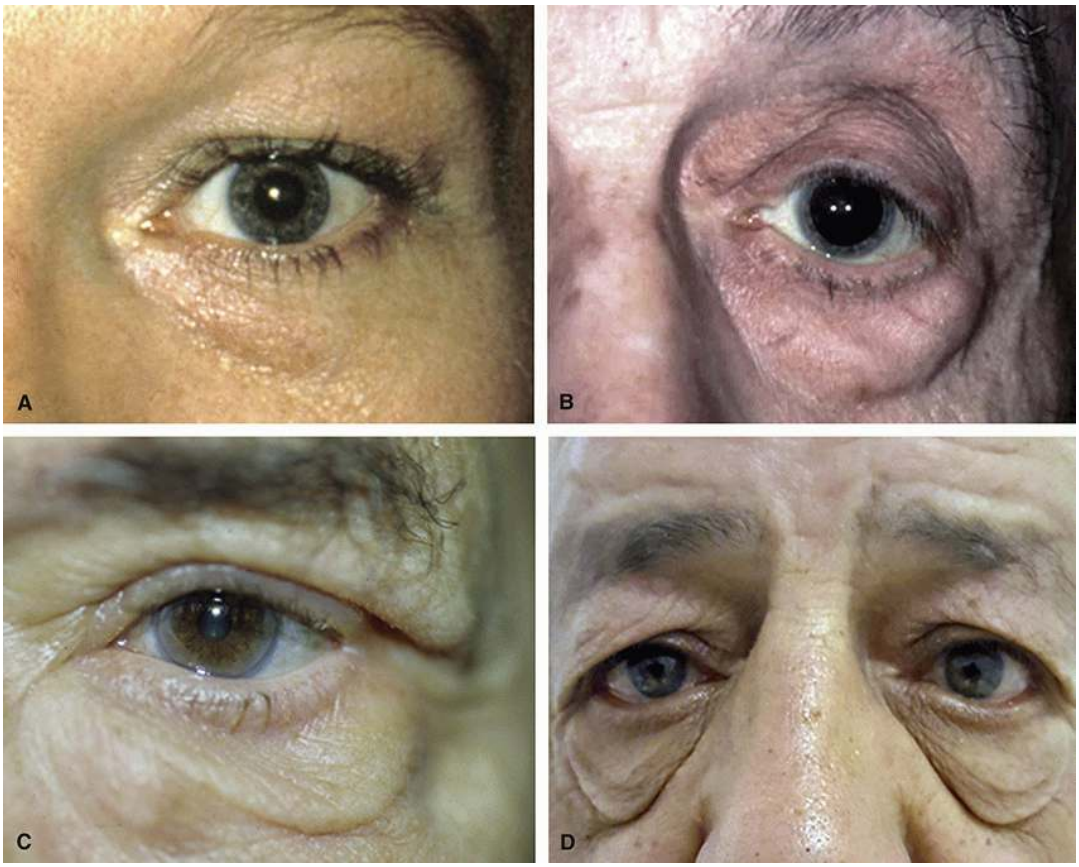

FIGURE 15.4 Lower eyelid dermatochalasis with mild (A) and marked (B) prolapse of fat pads and dewlap skin redundancy (C and D).

Differential Diagnosis

Two genodermatoses (inherited genetic skin conditions) should be differentiated from classic age-related dermatochalasis: cutis laxa (Figure 15.5) and Ehlers-Danlos syndromes. *(Print pagebreak 115)* Cutis laxa is a disorder of elastolysis and is characterized by premature sagging of the skin, including the eyelids. Eyelid sagging may also occur in association with the classic type of Ehlers-Danlos syndrome, a genetic disorder of collagen I and V, which is typically characterized by skin distensibility.[9]

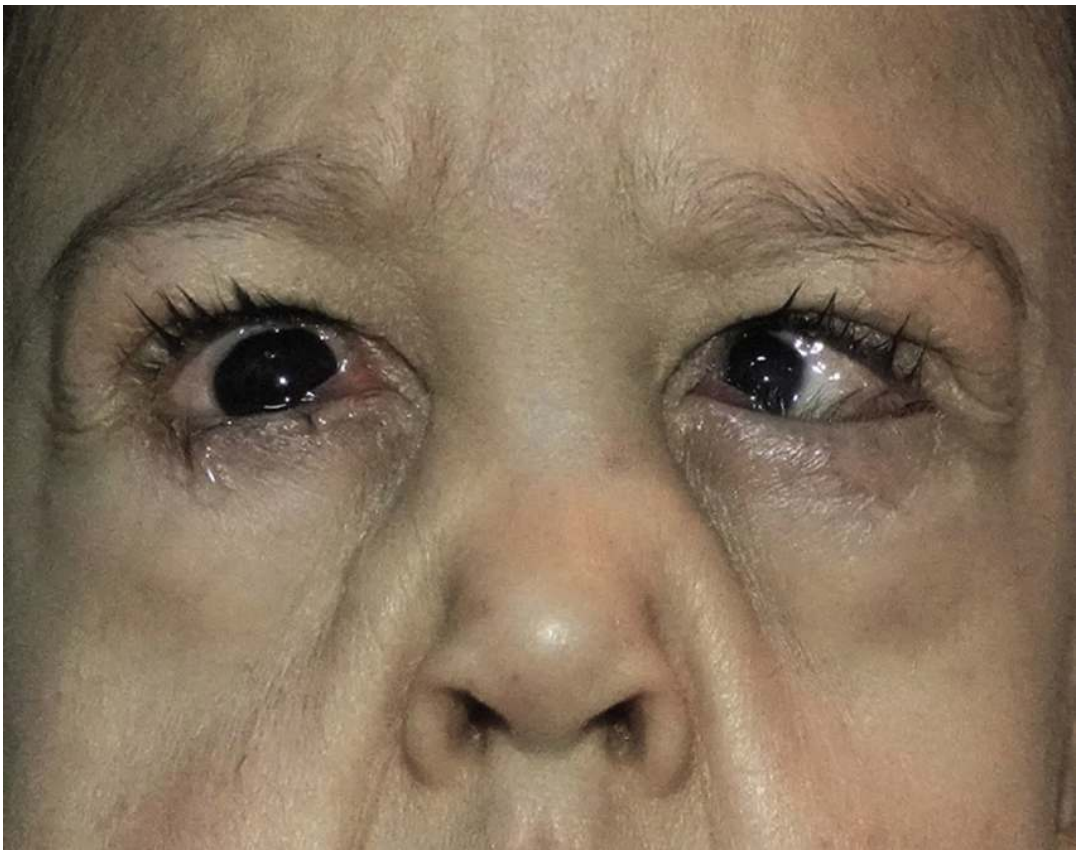

FIGURE 15.5 Premature aging and dermatochalasis in a patient with cutis laxa.

Another important entity to be differentiated from dermatochalasis is blepharochalasis. The redundant skin in blepharochalasis is induced by recurrent attacks of eyelid edema, while dermatochalasis patients do not suffer from such attacks. Although the clinical differentiation between both conditions is straightforward, the distinction between both is of a nomenclatorial nature, as both terms have incorrectly been used interchangeably by some dermatologists and general ophthalmologists to describe eyelid sagging.[9,10] Blepharochalasis is discussed separately in Chapter 27.

Treatment

Nonsurgical rejuvenation of the periocular region recently has enjoyed a surge in popularity and an expansion of its indications. Volumization with dermal fillers can positively augment or "soften" the periorbital region.[5,20] It is currently being used to correct tear trough deformity, or to increase the volume of the lateral subbrow region, providing mechanical support for the brow, or even to giving a browpexy effect, albeit being a temporary one.[5,20] Neuromodulation with botulinum toxin has an even more established role in modern oculofacial practice in the upper one-third of the face and is being used to treat not just dynamic rhytides but blunt static rhytides as well.[5] In addition, in experienced hands, mild lateral brow ptosis can temporarily be improved by injecting the superotemporal orbicularis oculi muscle.[5]

As of the time of this writing, the mainstay of therapy of dermatochalasis is still surgical, but the principles governing periocular rejuvenation continue to evolve. This is not solely attributable to the undisputed fact that esthetic ideals may be influenced by trends that change over the years, but more importantly because we now have a deeper understanding of the aging process in the periocular region and how to properly address it.[4] In the past, during the era of "subtractive surgery," surgeons were taught to direct their attention toward individual anatomical units and to deal with each separately.[4] Classical teaching dictated that blepharoplasty surgery was just about excising skin and muscle in the upper eyelids, or fat in the lower eyelids, and indeed such approaches usually provided an instantly gratifying outcome. But over time, concavity, hollowness, and skeletonization often ensued, reversing an initially acceptable outcome.[4,22]

Esthetically, a youthful upper eyelid is characterized by a well-defined brow of appropriate shape and height, together with the fullness of the upper periorbita, as well as a crisp and well-defined upper eyelid crease with minimal skin excess, and good skin quality.[20] To re-create this youthful appearance of natural contour and fullness, upper eyelid blepharoplasty surgery has recently enjoyed a paradigm shift from the classical mechanical excision of skin and muscle to fat preservation, transposition,

or even fat grafting.[23,24] The nasal fat pad could be transposed or excised if in excess,[24] but no fat beyond the medial compartment should be excised except in patients with thyroid eye disease. The orbicularis oculi muscle, which as we outlined earlier does not undergo any appreciable senescent changes, should be preserved.[23] The muscle can be incised and the edges resutured to the arcus marginalis to resuspend the temporal brow fat pad at a higher position. The term "brassiere suture" was coined as an adept description of the mechanics of this suture, which is an important step in most patients undergoing upper eyelid blepharoplasty.[23,25] Additional steps that should not be overlooked in upper eyelid blepharoplasty include repositioning of a prolapsed lacrimal gland, correction of concomitant blepharoptosis through the transcutaneous or the transconjunctival route according to the surgeon's preference, and lastly, any significant brow ptosis should be addressed either endoscopically, through the blepharoplasty incision, or directly.

Aesthetic lower eyelid rejuvenation has also recently evolved from the traditional cavalier attitude of fat excision and tissue redraping to a more modern outlook of fat preservation, as well as addressing the eyelid and the cheek as a single unit.[26] Fat repositioning has been popularized as an alternative to transconjunctival fat excision under the pretext that this approach will reduce the incidence of volume depletion or hollowness. This is better tailored toward restoring a natural and youthful surgical outcome, which is probably true in the majority of patients.[26] Recently, however, some authors have rekindled the interest in fat excision,[27] and rather than adopting a dogmatic approach that has prevailed recently against any fat excision at all, it should be pointed out that both techniques, if properly executed, can provide a pleasing outcome.[27] In patients with true herniation of fat, in particular, a modest amount of fat excision should be considered. Regardless of the surgeon's approach toward fat, lower eyelid blepharoplasty is performed through the transcutaneous, or preferably, the transconjunctival route. Redundant skin in the upper eyelid should always be excised in a conservative fashion using the pinch skin excision technique, and any concomitant horizontal eyelid laxity should also be addressed.[27]

Prognosis

The prognosis of dermatochalasis following surgery is excellent and most patients achieve a good cosmetic and functional outcome.

Histopathology

Dermatochalasis is an aging process in which gravity plays a supportive role. It is characterized by a redundancy of eyelid skin related to thinning of the epidermis, loss of elastic fibers, and weakening of connective tissue. Histopathology shows an increased number of lymphatic vessels, enlarged lymphatic diameters, a larger collagen stromal bed diameter, and *(Print pagebreak 116)* widely spaced collagen fibers suggestive of lymphedema.[13] There is also a markedly decreased density of elastic fibers, and macrophages are increased in number.

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CHAPTER 16

Ectropion, Cicatricial

Key Points

- Cicatricial ectropion is defined as a shortage of the anterior lamella of the eyelid
- Causes include congenital, traumatic, inflammatory, UV-related, infectious, neoplastic, and autoimmune etiologies
- The most common cause is trauma, but allergenic and irritant eyelid contact dermatitis can also lead to cicatricial ectropion
- Clinically, the eyelid margin is displaced away from the globe and the conjunctival surface is generally injected and thickened with varying degrees of keratinization and inflammation
- Cicatricial ectropion should be differentiated from noncicatricial causes of lower eyelid ectropion as well as from lower eyelid retraction
- In allergic dermatitis patients, prompt cessation of the offending agent together with topical steroid application is essential to prevent progression, and to induce a quick reversal of ectropion
- Surgery is the treatment of choice and should address both vertical and horizontal components
- Surgical options include multiple Z-plasties, lateral tarsal strip in combination with a cheek lift, or a full-thickness skin graft

Cicatricial ectropion is defined as a shortage of the anterior lamella of the eyelid, which causes outward rotation of the lash-bearing margin.[1,2] This leads to inadequate corneal protection due to a lack of apposition to the corneal surface. Chronic ocular discomfort results, and ultimately exposure causes corneal epithelial and stromal injury. Tear drainage dysfunction results from ectropion of the lacrimal punctum, and with time, the punctum may become occluded with an epithelial membrane.

Etiology and Pathogenesis

Cicatricial ectropion is a relative deficiency of eyelid skin and muscle that results from various causes. These causes are varied and include congenital, traumatic, inflammatory, ultraviolet (UV)-related, infectious, neoplastic, and autoimmune etiologies (Figures 16.1 and 16.2). Diseases causing congenital eyelid skin shortening are discussed separately in Chapter 17.

Traumatic causes of cicatricial ectropion can be seen following eyelid trauma and with skin loss that persists following surgical repair. This is especially true when vertical scars or skin grafts contract (Figure 16.1A and B). Chemical injuries to the eyelids due to acids and more commonly alkali agents are often also associated with ocular injury. On the eyelids, alkali can cause tissue saponification or hydrolysis of lipids and liquefaction of proteins resulting in cell death and tissue loss.[3] They can occur as industrial accidents, or even after relatively trivial domestic injuries with household chemicals. Thermal burns are common injuries that can result from hot surfaces, liquids, steam, and open flames (Figure 16.1C), and skin contracture can follow excessive radiotherapy (Figure 16.1D). Burn injuries can cause three levels of injury: superficial hyperemia with reversible vasodilation, deeper areas of ischemia, and deep levels of coagulation or necrosis resulting in contraction and loss of tissue.[4] Another source of eyelid skin shortening is surgical trauma from excessive removal of skin during lower eyelid blepharoplasty, or from cutaneous scarring following eyelid, orbital, or facial surgery (Figure 16.2B).[2,5]

Inflammatory causes of cicatricial ectropion include contact dermatitis and UV skin damage (Figure 16.2C and D). The eyelids are particularly susceptible to contact dermatitis because their skin is thinner (0.55 mm) than skin in the rest of the face (2.0 mm).[6,7,8,9] Eyelid contact dermatitis usually results from skin contact to exogenous substances, and two major forms have to be distinguished. The first or *allergic contact dermatitis* is less common and thus less likely to cause cicatricial ectropion. It usually develops as a

form of hypersensitivity reaction to allergenic chemicals like cosmetics, lotions, creams, or topical ophthalmic preparations.[10] The allergenic components in topical eye drops and ointments include either the preservative or the active principle, but it is not always possible to determine whether the offending agent is the active ingredient or the preservative used except with patch testing.[6,7,8,9] Topical antibiotics usually top the list with tobramycin as the most common allergenic agent, followed by preservatives or nonactive ingredients. Corticosteroids and mydriatics come next. Interestingly, antiglaucoma medications are at the bottom of the list.[10]

The second form, or *irritant contact dermatitis*, is four times more common around the eyes than allergic dermatitis, which is a frequently overlooked cause of lower eyelid ectropion. It can eventually lead to cicatricial ectropion, and usually results from a nonallergenic dose-dependent toxic effect typically resulting from the chronic use of topical eye drops, particularly antiglaucoma medications.[6,7,8,9]

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FIGURE 16.1 A, Cicatricial ectropion of the lower eyelid from a contracted scar. B, Upper eyelid cicatricial ectropion due to penetrating trauma. C, Cicatricial ectropion of the lower eyelid due to burn injury. D, Upper eyelid cicatricial ectropion due to excessive radiotherapy as a child.

The other inflammatory cause is chronic sun or UV light exposure in fair-skinned individuals. These result in actinic changes, which are more pronounced in the lower eyelids, and are clinically distinct from the normal chronological processes of aging skin.[11] Sun-damaged or photoaged skin typically exhibits inflammatory hypertrophy of elastic tissue, with an accumulation of thickened elastic fibers and amorphous elastotic material in the dermis.[8] With prolonged exposure and diffuse actinic damage to the lower eyelid skin, the skin becomes taut, exerting a downward tractional force on the anterior lamella, pulling the eyelid margin away from the globe and resulting in ectropion (Figure 16.2C and D).[2,11,12]

Cicatricial ectropion has rarely been reported in association with systemic infections like paracoccidioidomycosis.[13] Upper eyelid cicatricial ectropion may also rarely result from scar contracture in association with a fistulous tract from the frontal sinus, although a more common presentation would be cicatricial retraction rather than ectropion.[14]

Benign and malignant eyelid neoplasms may rarely cause cicatricial ectropion (Figure 16.2A)[15,16,17,18,19]; however, a "mechanical" displacement of the eyelid is a more likely mechanism for the ectropion associated with periocular neoplasms.

Several autoimmune dermatologic disorders, like discoid lupus erythematosus and psoriasis, may also cause cicatricial ectropion

although other eyelid margin abnormalities like entropion trichiasis and madarosis have also been reported with both conditions.[20,21] The rash associated with lupus and the plaques associated with psoriasis could result in chronic blepharitis and scarring, eventually ending in ectropion.[20,21]

Several systemic medications have been associated with the development of cicatricial ectropion including systemic 5-fluorouracil and epidermal growth factor receptor (EGFR) *(Print pagebreak 119)* inhibitors (erlotinib, cetuximab, and panitumumab), which are used as chemotherapeutic agents in the management of colorectal cancer.[22,23,24,25] The underlying mechanism is probably related to inhibition of EGFR in skin keratocytes, which express similar levels of EGFR as the targeted cancer.[23]

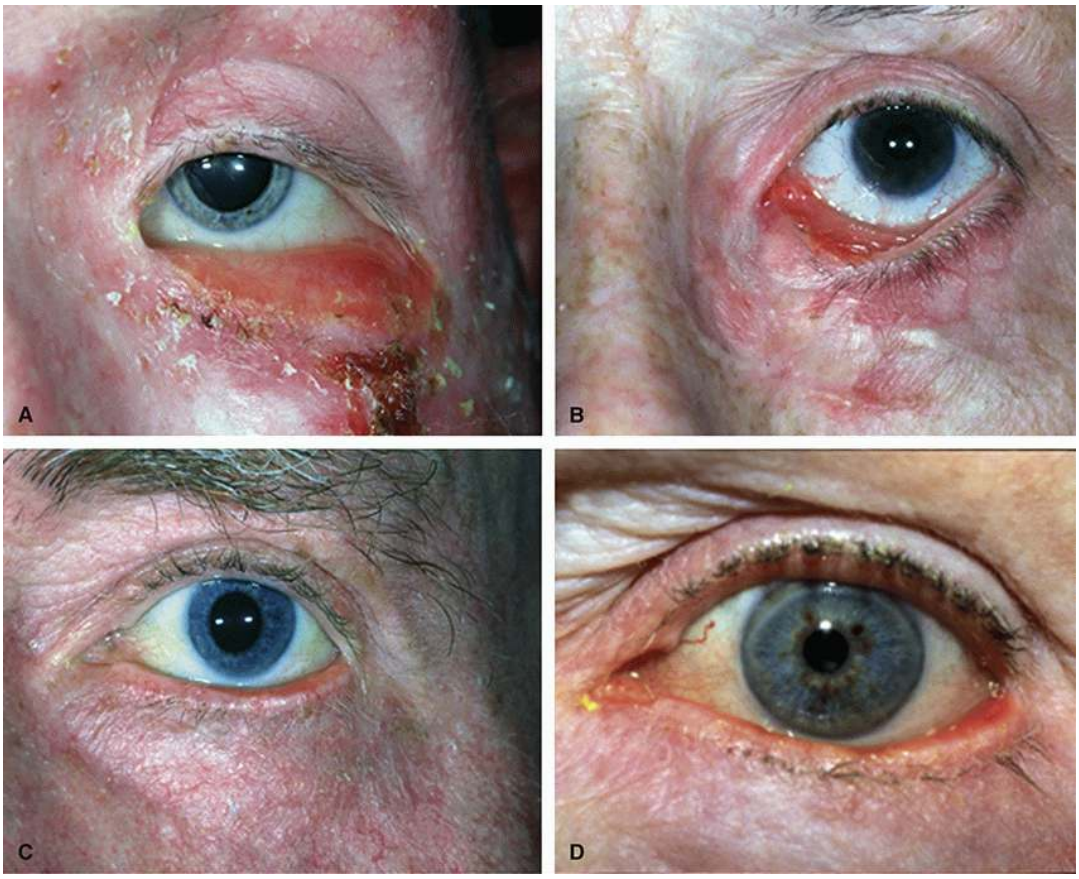

FIGURE 16.2 A, Severe lower eyelid ectropion from a contracted cutaneous malignant neoplasm. B, Cicatricial ectropion of the lower eyelid due to excision of skin neoplasm left to heal by granulation. C, Mild and (D) moderate lateral lower eyelid cicatricial ectropion from sun-exposed skin contracture.

Clinical Presentation

The eyelid margin is displaced away from the globe and the conjunctival surface is generally injected and thickened with varying degrees of keratinization and inflammation. This is usually associated with pooling of the tear lake, corneal dryness, and exposure. With prolonged ectropion, the inferior punctum often becomes stenotic, and it may even be occluded with a fibrotic membrane from disuse resulting in epiphora. These are general features shared by most types of ectropion, but in contrast to other etiologies where ectropion almost always involves the lower eyelid, cicatricial ectropion can involve both the upper and lower eyelids. Because the predominant etiology is usually traumatic (Figure 16.1A and B), cicatricial ectropion can present at any age, although patients with allergenic or irritant contact dermatitis are predominantly females in the age group between 20 and older than 60 years, and it is a very rare occurrence during childhood where alternative etiologies should be sought.[8,26] This bimodal presentation pattern is probably related to the use of cosmetics in younger individuals and glaucoma medications in the older age group.

Patients with contact dermatitis usually present with persistent symptoms for well over 1 year without a history of previous trauma or surgery. Patch testing is required for identification of the allergenic agents, if present, and the patch should remain on the back of the patient and be reread after 48 hours to avoid a false negative result.[6,7,8,9]

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Patients with actinic or solar damage may pose a diagnostic challenge and were probably labeled “idiopathic” or “involutional” in

former case series.[27] Ectropion may be the end stage of actinic skin damage, but earlier diagnostic signs of photoaged skin include unusual smoothness of the skin on palpation, irregular pigmentation, wrinkling, and occasionally scaling.[1]

Differential Diagnosis

Differentiating cicatricial from noncicatricial lower eyelid ectropion (discussed separately) should not typically pose a diagnostic dilemma, but there is some confusion in the literature regarding the use of the terms "cicatricial ectropion" and "lower eyelid retraction" interchangeably.[1] The former term should be restricted to patients whose anterior lamellar cicatrization causes outward rotation of the eyelid margin with exposure of the palpebral conjunctiva, while the latter term should be restricted to cases where cicatrization causes downward displacement of the lower eyelid, but with a noneverted lid margin.[1] Of note is that both conditions (cicatricial retraction with concomitant cicatricial ectropion) can coexist in clinical practice.[28]

Treatment

In patients with allergic dermatitis, prompt cessation of the offending agent together with topical steroid application is essential to prevent recurrences and to induce a quick reversal of ectropion.[6,7,8,9] However, prolonged topical steroid use may have unintended consequences of its own. In cases of irritant dermatitis from sustained use of glaucoma medications, lowering the frequency or concentration of the agent used and shifting to another agent are valid options.[7,8] However, this may not always help because some of these patients may have multiple drug allergies.[9] The underlying mechanism may be dose dependent and may not even be allergenic, but it may not be possible to discontinue the offending agents in conditions like glaucoma.[5,6]

Iatrogenic cicatricial ectropion caused by surgical trauma in the eyelid or midface region is usually a preventable complication. A careful surgical technique, coupled with prophylactic or preemptive measures in the form of lateral canthal tendon tightening, and/or orbicularis redraping to the lateral orbital rim may minimize the chances of developing cicatricial ectropion and the need for future corrective surgery.[29,30]

When cicatricial ectropion does develop, surgical correction is usually required for symptomatic relief and restoration of normal anatomy. An alternative to surgery has been proposed by injecting hyaluronic acid filler to stretch the tethered skin and act as a tissue expander, thus restoring lid-globe apposition.[31,32,33,34] Unfortunately, to cause a complete reversal of ectropion, overfilling of the eyelid is required, and the final cosmetic outcome is usually poor.[34] This limits the use of fillers only to patients who decline surgery or those who are deemed unfit for surgery.[34]

Strategies for surgical repair should provide both vertical and horizontal support to the lower eyelid to restore it to its normal anatomical position.[2,5] Several techniques are described for the repair of cicatricial ectropion. Single or multiple Z-plasties may be appropriate when a localized or focal cicatrix is encountered.[27] Lateral tarsal strip alone[35] or in combination with a cheek lift to recruit the midface skin vertically is a better procedure for mild cases in which the cicatricial element is more diffuse.[5] In more extensive cases of ectropion, either a local skin-muscle flap or a full-thickness skin graft is usually required for anatomic correction and symptomatic relief.[2,27]

Proponents of pedicled skin-muscle flaps argue that a deficiency of orbicularis muscle usually accompanies skin deficiency, and while a local flap could replace both components with tissues that are exactly similar to the missing tissue, a skin graft would only address the cutaneous component, resulting in an unsightly depression in the grafted region.[36,37] It should be noted however that recruiting local skin-muscle flaps may technically be more challenging than harvesting a skin graft, and it may not even be possible in cases when more generalized skin pathology involves the potential flap harvest sites, making flap design impossible. Local flaps, like the median forehead flap or flaps from the glabellar region, may also result in color and thickness mismatch with the lower eyelid. Flaps from the ipsilateral upper eyelid could potentially cause an asymmetrical tarsal platform show in comparison with the contralateral normal upper eyelid.[36] Another potential concern is that local flaps could leave additional unsightly scars in other visible regions of the face besides the initial scars resulting from the original trauma.[36,37] Therefore, a full-thickness skin graft combined with a horizontal eyelid tightening remains the mainstay of therapy.[36] Common donor sites for skin grafts include the ipsilateral or contralateral upper eyelid; skin from the retroauricular, preauricular, or supraclavicular regions; or the inner side of the arm. While the upper eyelid provides the perfect color match for the repair of a lower eyelid defect, there are caveats in harvesting upper eyelid skin. Besides the risk of causing further lagophthalmos in an eye with an already compromised eyelid closure mechanism, the upper eyelid skin could also be directly susceptible to solar damage, although to a much lesser extent than the lower. Therefore, it may be better to avoid using the upper eyelid skin in patients with ectropion resulting from photoaged skin.[12] Furthermore, in children, this source can rarely provide an adequate harvestable surface area.[38] Because of obvious anatomical limiting factors, the

preauricular region may not provide enough skin.[2] Therefore, for defects involving a single eyelid, a postauricular harvest site is preferred because it is least susceptible to sun damage, and the donor site scar is concealed.[12] In conditions where simultaneous repair of more than one eyelid is needed, the inner side of the arm may be more convenient. Regardless of the donor site, immobilizing the graft with quilt sutures to maximize graft-bed contact ensures better graft vascularization, and quilt sutures practically eliminate the *(Print pagebreak 121)* problem of graft failure or necrosis.[39] While some authors do not routinely combine a canthal tightening procedure along with skin grafting,[12] lateral canthal suspension with a lateral tarsal strip procedure is not just a useful adjunct, but a required prerequisite for all patients to counter downward traction on the graft that may occur while the graft is healing. Temporary lower eyelid traction sutures taped to the forehead at the conclusion of surgery could also counter the tendency for graft contraction in the early postoperative period.[40] Other ancillary procedures with skin grafts include lower eyelid retractor reattachment, excision of keratinized conjunctiva, and various lacrimal drainage pathway procedures if required.[12,38,41]

Prognosis

The prognosis of cicatricial ectropion is excellent when any of the abovementioned procedures are properly executed.

Histopathology

Cicatricial ectropion results from scarring, fibrosis, and shortening of the eyelid skin and anterior lamella. Aside from these skin changes, to our knowledge, there are no descriptions of other specific eyelid histopathological changes.

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CHAPTER 17

Ectropion, Congenital

Key Points

- Congenital ectropion is a complete eversion of the entire lower or upper eyelid margins or both and is usually present at birth
- It is theorized that birth trauma or pressure exerted during delivery may induce conjunctival chemosis and prolapse, which causes eyelid eversion
- Lamellar ichthyosis and Down syndrome can also be associated with congenital eyelid ectropion
- Congenital ectropion is a collective term used to describe a variety of heterogenous conditions
- In idiopathic congenital ectropion, the conjunctiva protrudes outside the eyelids, with complete eversion of the upper and occasionally lower eyelids
- In lamellar ichthyosis, blepharophimosis syndrome, and Down syndrome, there is contracture or shortening of the anterior skin lamella
- Treatment varies with the etiology and includes temporary tarsorrhaphy, fornix forming sutures, compression eyelid sutures, or skin grafts
- The prognosis is generally good for corneal protection and repositioning the eyelid against the globe

Congenital ectropion is defined as the complete eversion of the entire lower or upper eyelid margins or both and is usually present at birth.[1,2]

Etiology and Pathogenesis

Congenital ectropion is not a single disease and therefore it is difficult to define a single genetic error or a solitary etiopathogenic event as a causative factor; hence, respective etiologies or genetic mechanisms will be discussed briefly.

The cause of congenital upper eyelid eversion with conjunctival chemosis is unknown, but it is theorized that birth trauma or pressure exerted on the baby during delivery may induce venous stasis, leading to conjunctival chemosis and subsequent prolapse, which causes eyelid eversion. This mechanical eyelid eversion causes secondary orbicularis spasm, which may act as a sphincter at the base of the everted eyelid causing a domino effect of conjunctival strangulation and further edema.[3,4,5] In our opinion, this "birth trauma" theory needs to be revised. Several other authors have also reported similar cases in children delivered through uneventful vaginal delivery,[5,6] and even more interestingly, this theory is further challenged by a single case report from Russian literature, wherein neonatal lid eversion occurred in a child born by cesarean section.[7]

Lamellar ichthyosis is a hereditary condition commonly transmitted in an autosomal recessive fashion, whereby several different genetic mutations particularly in the TGM1 gene (chromosome 14q11), or in the long arm of chromosome 2 (2q33), alter the normal development and function of keratinocytes, causing a defect in skin desquamation.[8,9,10,11,12,13] Although there are other types of congenital ichthyosis, their clinical picture varies widely, and eyelid changes are only found in classic lamellar ichthyosis[14] and its phenotypic or genotypic variants, congenital (nonbullous) ichthyosiform erythroderma (CIE), and harlequin ichthyosis, which all fall under the umbrella term "autosomal recessive congenital ichthyosis."[15]

Down syndrome, or trisomy 21, is the most common nonheritable chromosomal disorder associated with mental and growth retardation, affecting approximately 1 in 600 live births. Several ocular and adnexal sequelae are reported with Down syndrome.[16]

Clinical Presentation

Because congenital ectropion is a rare entity, and because the literature is rather confusing, the incidence is largely unknown. The term “congenital ectropion” itself is a collective one used to describe a variety of heterogenous conditions under a universal banner; therefore, several classifications have been put forward to better understand the disease and to reduce confusion. Based on a clinicopathological study in a family pedigree, Picò in 1959 first attempted to classify the disease into four types, followed by França in 1997 who refined the classification.[17,18] According to Picó, group 1 encompasses patients with true congenital ectropion due to tarsal dysgenesis, group 2 occurs due to birth trauma, group 3 occurs as a result of anterior lamellar shortening, and group 4 includes cases secondary to abnormalities in the size or position of the globe or orbit. Because the presence of group 1 is uncertain, and because cases that fall into group 4 do not represent true ectropion and may be reversible with treatment of the original condition, we believe that both *(Print pagebreak 123)* classifications may be unsatisfactory and, in our experience, congenital ectropion falls into three simple categories:

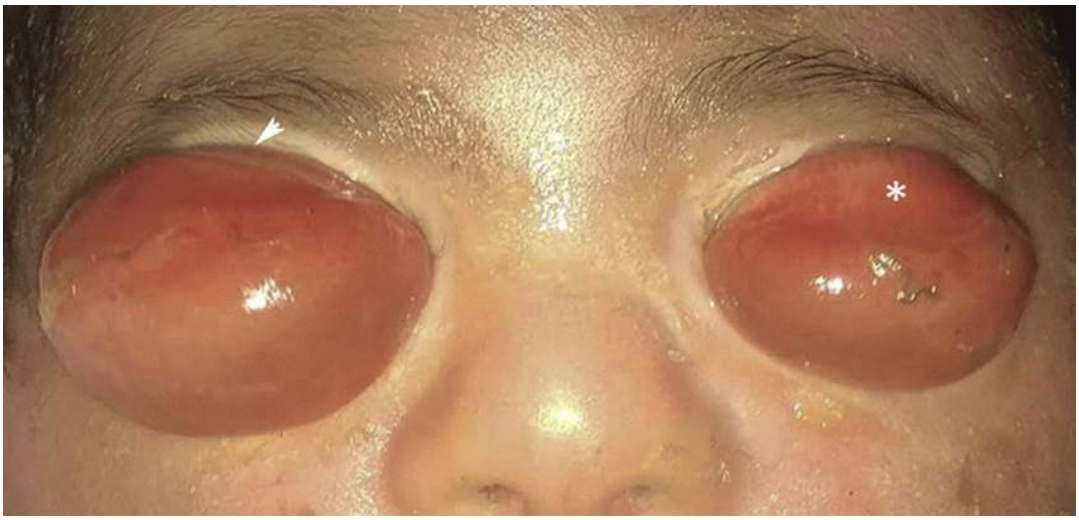

FIGURE 17.1 Congenital upper eyelid eversion with severe conjunctival chemosis. The eyelid margin is completely everted (arrowhead), and the meibomian glands are clearly visible (asterisk). (Courtesy of Dr. Elshaimaa Taher.)

1. Idiopathic congenital upper eyelid eversion with or without conjunctival chemosis and prolapse (Figures 17.1 and 17.2).
2. Congenital ectropion secondary to skin shortening conditions like lamellar ichthyosis and blepharophimosis syndrome (discussed in Chapters 28 and 71).
3. Congenital ectropion associated with Down syndrome (Figure 17.3).

Although we do not include it in our simple classification, group 1 in Picó’s original description deserves special mention. It was termed “true congenital ectropion” because it allegedly occurs due to congenital absence or dysgenesis of the tarsus and is an extremely rare entity.[17] Picó described eight patients where no tarsus was felt on palpation of the eyelid, either during surgery or on histopathological examination.[17] Interestingly, he extensively studied the literature before his 1959 paper and failed to find a single case report where the tarsus was truly congenitally absent. We conducted an extensive literature search from 1959 till the present, and to the best of our knowledge at least at the time of writing, tarsal dysgenesis causing true congenital ectropion was never described again after his initial report. Whether this entity truly exists or not is unknown, but its existence is disputed by other authors as well.[1]

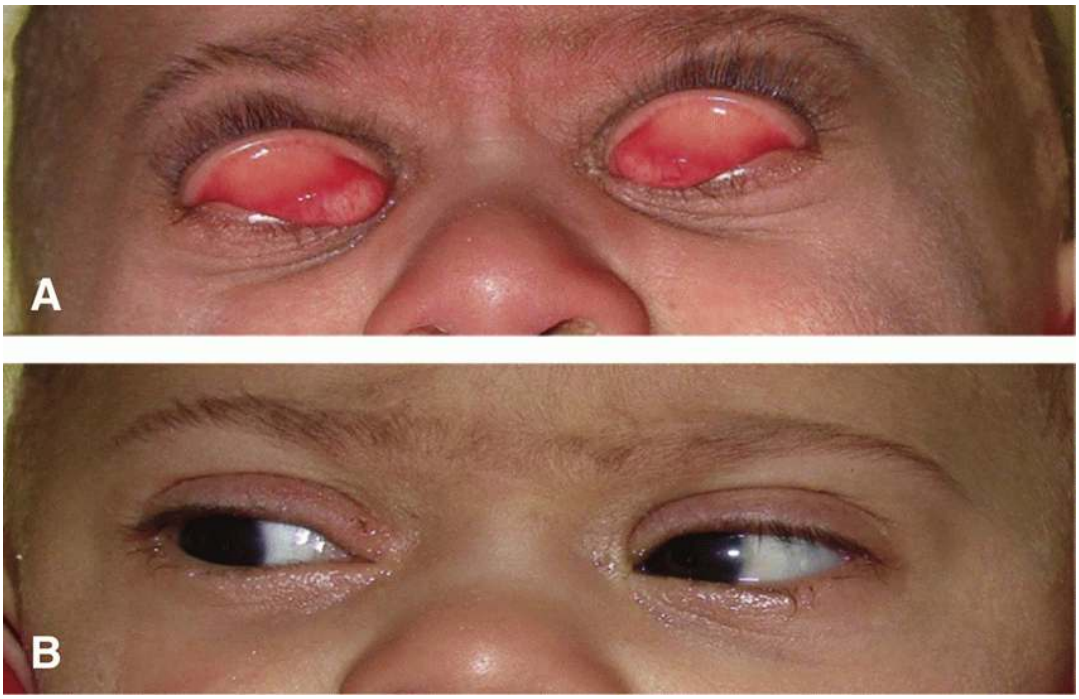

FIGURE 17.2 A, Congenital upper eyelid eversion without conjunctival chemosis 1 week after birth. B, Complete spontaneous resolution at 4 weeks of age.

FIGURE 17.3 Congenital ectropion involving the upper and lower eyelids in Down syndrome.

Idiopathic congenital bilateral upper eyelid eversion (Figures 17.1 and 17.2) is a benign self-limiting and extremely rare condition except in African black neonates where the condition is not uncommon, as evidenced by the large number of cases reported in Africa.[5,6] It even poses a sociocultural problem there, wherein parents are forced to apply unsafe traditional medicinal practices.[5,6,18] These patients who are usually systemically free typically present immediately after birth with bilateral fleshy masses, completely or less commonly partially covering the eyeballs. The conjunctiva protrudes well outside the confines of the eyelid margin, with complete eversion of the upper and occasionally lower eyelids.[5,6,19,20,21,22] Because the ocular surface is technically protected by the protruding conjunctiva, corneal problems are not observed. The upper eyelid may be more predisposed to congenital eversion because of its wider tarsal plate, which may be difficult to reinvert spontaneously once everted.[23] The condition is usually self-limited within 2 to 3 weeks.[5,6]

Congenital skin shortening from diseases like lamellar ichthyosis and blepharophimosis syndrome comprises the second group of patients. Blepharophimosis syndrome is discussed separately in Chapter 28. Lamellar ichthyosis has an estimated incidence of 1:250,000 to 300,000 live births.[8] The disease is immediately recognizable at birth because these neonates are typically embedded in an inelastic tight shiny membrane that looks rather like a cast that encases the newborn, thus the disease acquired the name "collodion baby."[8,14,15,24] This membrane is progressively shed and starts to crack and exfoliate in the first few days or weeks of life, and the skin develops platelike scales. During this process of continuous desquamation and shedding, these neonates are particularly vulnerable to dehydration and infection.[8,14,15,24,25,26] As these children grow older, ectropion progresses due to excessive dryness of the skin and subsequent skin contracture.[14,26,27] This cicatricial form of ectropion is more frequently bilateral and occurs in 45% to 80% of patients with *(Print pagebreak 124)* lamellar ichthyosis.[27] Although some authors believe the lower lid is usually more severely affected than the upper,[26] in our experience as well as others',[28] the upper eyelids may equally be affected. The severity of ectropion may range from mild punctal or medial ectropion to severe tarsal eversion and eyelid retraction and could be dependent on the type of ichthyosis. It is hypothesized that ectropion could be more severe in classic lamellar ichthyosis than in patients with CIE.[8] Based upon our limited experience with both conditions, we tend to agree with Cruz and associates[8] that patients with CIE may suffer from less severe palpebral changes and consequently less severe ocular surface abnormalities. It appears that ectropion and subsequent lagophthalmos may lead to chronic conjunctivitis, keratitis, corneal ulceration, and occasionally perforation.[8,14,26,27] Progressive anterior lamellar contraction could lead to tarsal eversion, which reduces the palpebral aperture and together with a preserved Bell phenomenon could impart protection of the cornea which could explain why some older patients only present with a cosmetic complaint while the ocular surface is in perfect health.[8] Other palpebral abnormalities include scales on the eyelashes, meibomian gland dysfunction, madarosis, and even entropion.[26,28]

Patients with Down syndrome, who constitute the third type in our simplified classification, usually present with bilateral upper and lower eyelid ectropion with poor eyelid closure (Figure 17.3), and an inadequate blink response. In more severe cases, they may develop spontaneous eversion of the eyelids during sleep and on crying and may suffer from signs of bilateral corneal exposure, which may progress to corneal scarring or a corneal abscess (Figure 17.4).[21,29] The eyelids, particularly the upper, appear to be larger than normal (megaloblepharon), and quite lax.[23] Other associated palpebral findings include a mongoloid (upward) slant of the palpebral fissure, epicanthal folds, blepharitis, and, counterintuitively, trichiasis with or without entropion. Entropion is more commonly observed in older patients and is attributed to chronic blepharoconjunctivitis.[23,29]

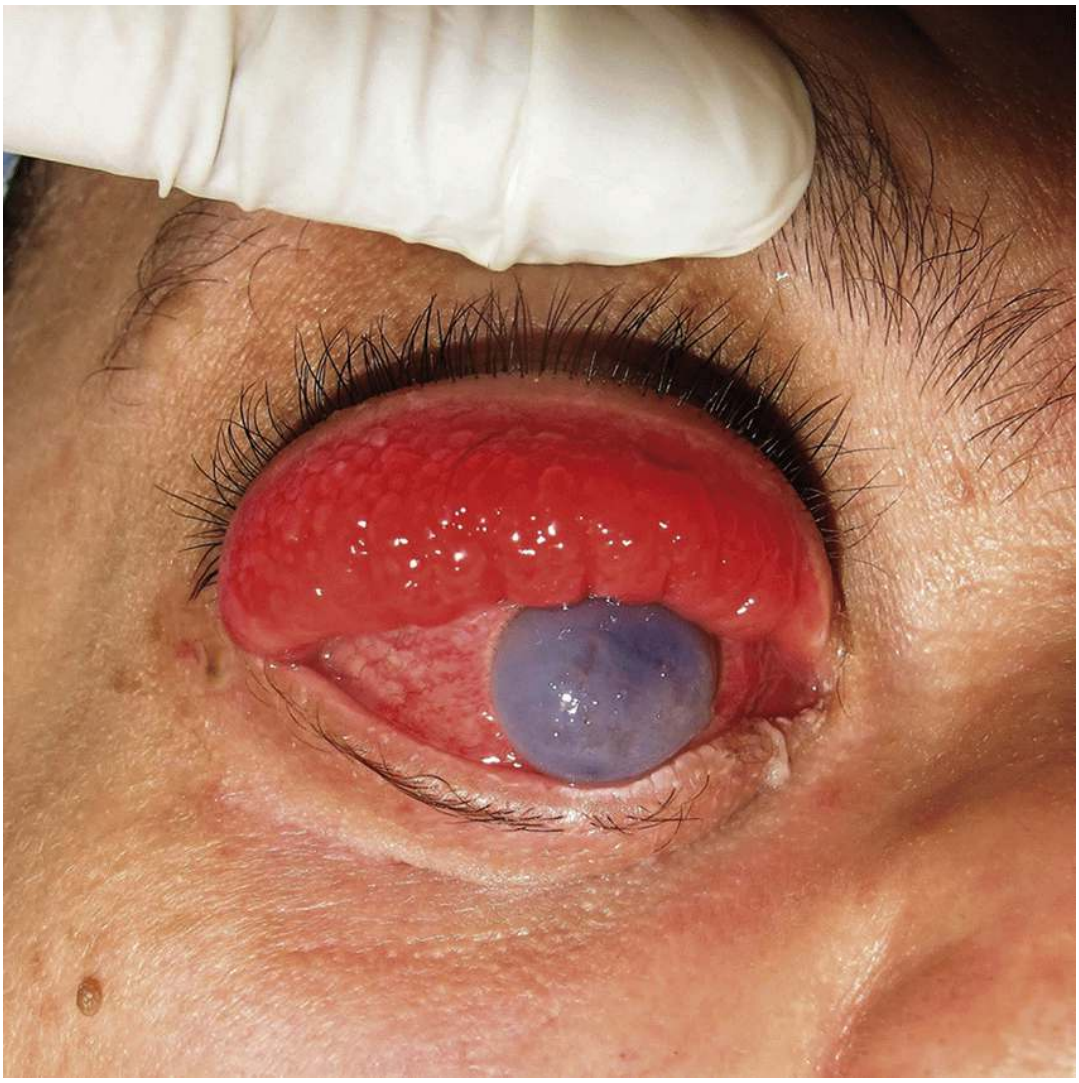

FIGURE 17.4 Chronic conjunctivitis and corneal scarring in an 18-year-old female patient with Down syndrome and neglected upper eyelid ectropion.

Vertical shortening of the skin is traditionally considered to contribute a predominant role in the pathogenesis of ectropion in Down syndrome patients, with horizontal lid laxity considered a secondary or delayed etiopathogenic mechanism developing after years of chronic ocular exposure, conjunctival irritation, and subsequent eye rubbing.[29] However, the generalized connective tissue laxity or reduced body tone in Down syndrome may be expressed in the eyelids as horizontal lid laxity and orbicularis hypotonia,[21] and both factors may contribute to the peculiar palpebral fissure appearance in patients with Down syndrome.[23] This congenital laxity could explain why in contrast to the first two types of congenital ectropion where manual repositioning of the eyelids is not possible, the eyelids in Down syndrome can easily be repositioned to their normal anatomical location in the clinic, but they snap back instantly upon finger release. Other possible mechanisms include vertical as well as horizontal elongation of the posterior lamella of the eyelid, particularly laterally, or the absence of an effective lateral canthal ligament.[30,31] Again, the confusion in the literature in explaining the mechanisms underlying congenital ectropion is that some authors try to explain different pathologies with singular etiologic mechanisms.

Differential Diagnosis

The most important differential diagnosis of congenital ectropion is euryblepharon, where the defining feature is ectropion involving only the lateral part of the lower eyelid. Euryblepharon is discussed in detail in Chapter 33.

Few other disorders give a clinical picture similar to ichthyosis. Most notably the differential diagnosis includes other conditions of cornification like eczema, psoriasis, or exfoliative dermatitis. Unlike those seen in blepharitis, scales on the lashes associated with lamellar ichthyosis are asymptomatic and are not associated with inflammation or redness of the eyelid margin.[28]

Treatment

In patients with neonatal eversion of the upper eyelid, the cornea is usually protected by the prolapsed conjunctiva, and management is usually conservative with the overarching goal to interrupt the eversion-chemosis cycle and to enhance speedy resorption of conjunctival edema. Conservative measures include topical lubrication along with topical antibiotic and anti-inflammatory lubricants or hypertonic saline, in addition to moist dressings, eyelid taping, or firm bandage.[5,6,18,32] Hypertonic saline-soaked gauze works through a process of osmosis, which sucks fluid from the edematous *(Print pagebreak 125)* eyelid tissues through the semipermeable conjunctiva membrane.[20] If all these conservative measures fail to break the cycle and stabilize the eyelids, temporary tarsorrhaphy, fornix forming sutures, or compression eyelid sutures may be indicated.[6] However, in our limited experience, conservative measures usually suffice.

In patients with lamellar ichthyosis, management decision is guided by corneal health, but because of the significant variability in clinical presentation, it must be individualized.[8,33] In mild or asymptomatic patients, the integrity of the ocular surface could be maintained with conservative measures, which include vigorous ocular and eyelid lubrication, topical application of N-acetylcysteine emollients, topical or systemic retinoids, hyaluronic acid injections in the pretarsal plane, and lid massage.[14,28,34,35,36] Continuous eyelid massage and stretching in a vertical direction throughout life may allegedly halt progression or even postsurgical recurrence of cicatricial ectropion if anterior lamellar lengthening is eventually required.[28] In those patients with severe generalized lamellar ichthyosis in whom skin grafting is necessary, there may be limited options for harvesting healthy unaffected skin.[27] If no area of suitable donor skin is available, an alternative approach may be to use a combination of inversion sutures, and lateral canthal suspension,[33] although in our experience, these measures are usually inadequate. Another alternative option that was reported with success is the use of an oral mucous membrane graft instead of skin[37,38] because mucosal surface involvement is not reported in association with lamellar ichthyosis.[14] Otherwise, if definitive surgical correction is pursued, the least affected suitable donor area is chosen, and donor skin should be prepared weeks ahead of surgery with topical emollient creams. Typical donor sites include the inner part of the arm, retroauricular area, supraclavicular area, or even the groin.[39] Recurrence of ectropion after initial successful skin grafting in patients with lamellar ichthyosis is not uncommon.[33,39] This is probably because patients with lamellar ichthyosis endure a chronic progressive form of skin change and cicatrization. Furthermore, graft contracture may be intensified by the child's growth if patients are operated upon in early childhood.[39] Therefore, it may be advised to delay surgery if ocular surface health can be maintained with conservative measures. A temporary partial see-through tarsorrhaphy that is only divided 3 months postoperatively was advocated in the past to keep the skin taught and reduce the recurrence of ectropion in the early postoperative period.[27] However, a more practical measure would be to aim for an initial overcorrection and to place the graft under tension with traction sutures for up to 1 week or even more. Postoperative care may also help reduce recurrence as these patients may require lifelong massage, postoperative topical application of emollient creams, and keratolytics on the grafted eyelids. This would not cause a problem if topical cream is applied to the lower eyelids but could be problematic and cause ocular irritation if carelessly applied to the upper eyelid. Eventually, if all these caveats are avoided, excellent corneal health can be maintained, and the visual potential is excellent.[33]

Milder cases of ectropion associated with Down syndrome may respond to conservative measures with vigorous lubrication. Patients with persistent symptoms may benefit from a four-lid horizontal lid shortening with a lateral tarsal strip or wedge resection of the lateral part of the eyelids.[23] A tarsorrhaphy may be indicated if a horizontal lid shortening procedure breaks down, or does not provide adequate ocular surface protection. Our preferred technique is a four-lid lateral tarsal strip, combined with resection of the posterior lamellae in older patients where chronic exposure of the conjunctiva may have contributed to significant conjunctival keratinization. If symptoms of ocular exposure persist, a full-thickness skin graft may be required.[29]

Prognosis

The prognosis for correction of eyelid position is excellent in most cases.

Histopathology

The histopathology of ichthyosis is discussed in Chapter 71. There are no other examples of histopathology related to congenital ectropion.

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CHAPTER 18

Ectropion, Involutional

Key Points

- Involutional ectropion is the most common type of ectropion seen in clinical practice
- It is generally attributed to aging changes and tissue laxity in the eyelid
- A primary etiopathogenetic causation is canthal tendon laxity, which more commonly involves the lateral canthal tendon in the lower eyelid
- Clinically, the eyelid margin is rotated away from the globe, often associated with punctal eversion and an increased lateral canthal angle
- Chronic conjunctivitis is not uncommon, and the conjunctival surface generally is injected and thickened, with varying degrees of keratinization and inflammation
- Surgical treatment is usually with horizontal eyelid tightening of the lateral canthal tendon or wedge resection of a block of eyelid tissue
- The prognosis for repositioning the eyelid is generally excellent

The most common type of ectropion encountered in clinical practice is involutional. This type of ectropion develops when the eyelid margin moves away from the globe as a result of senescent eyelid changes. As life expectancy is increasing on a global scale, the elderly population is expected to suffer from more involutional eyelid pathologies, most commonly involutional ectropion, but the progressive increase in ocular adnexal tissue laxity and the decrease in tone could also lead to other eyelid margin malpositions like involutional entropion.[1]

Etiology and Pathogenesis

By definition, the multifactorial etiology of involutional ectropion is generally attributed to aging changes in the lid and orbit.[1,2,3] Because several anatomic and ultrastructural features are shared between both entropion and ectropion,[4] an understanding of the vector forces involved in maintaining lower eyelid stability is paramount to appreciate the abnormalities that would eventually lead to either one or the other, and therefore these factors should be discussed together. Unfortunately, the question that has eluded researchers for decades—"Why would some eyelids turn in, while others turn out?"—still lingers unanswered in the literature,[5,6,7,8] and the ultimate decisive factor or more accurate factors remain elusive.[4,8] It should be realized, however, that for the eyelid margin to turn inward or outward, two critical etiologic events should occur: horizontal lower eyelid laxity and retractor dehiscence.[6] Although the other factors that are also discussed below reportedly play a less significant role, nevertheless, they might tip the scale toward either ectropion or entropion.

The normal lower eyelid position depends on firm anchoring of the lateral and medial canthal tendons to the bony orbital rim,[9] and therefore a primary etiopathogenetic event is canthal tendon laxity, which more commonly involves the lateral canthal tendon,[10] and allegedly plays a more significant role in ectropion than entropion.[3,11] The lateral canthal tendon is more frequently involved because it is inherently weaker than the medial,[12] more anatomically susceptible to clinically significant displacement, and is more exposed to chronic repetitive trauma.[9]

The second crucial anatomic event is disinsertion or attenuation of the lower eyelid retractors, which also makes the lid unstable.[2,13,14] However, in contrast to the ligamentous weakening outlined above, lower lid retractor dehiscence plays a more significant role in entropion than ectropion,[2,7,15] although the location and extent of the disinsertion of the retractors will determine clinically whether the patient will have isolated punctal eversion or frank tarsal ectropion.[14] In patients with tarsal ectropion, retractor disinsertion allegedly plays a more important pathogenetic role than horizontal lid laxity, which is also present but is not the striking

feature.[13,14,16,17,18] It was Jones in 1960 who first theorized that retractor disinsertion would allow the inferior border of the tarsus to rotate either outward or inward and likened it to levator aponeurosis dehiscence in the upper eyelid.[19]

An unchecked orbicularis oculi muscle that overrides the lower border of the tarsus is another vital event involved in the pathogenesis of entropion, but not in ectropion where it remains well tethered and does not roll upward.[20] Atrophy and hypertrophy of the orbicularis muscle have been demonstrated in involutional entropion and ectropion, respectively.[21,22] Earlier authors hypothesized that this is a primary pathogenetic event and that the variability in muscle bulk could explain the ability or failure of the orbicularis muscle to contract and override the tarsus, consequently causing either pathology.[21,22] An arteriosclerotic or a partially occluded marginal artery has been implicated in the atrophy of the muscle.[21] It should be noted, however, that more recent studies failed to reproduce those earlier results, and *(Print pagebreak 128)* accordingly, these studies do not support the hypothesis that a primary change in orbicularis muscle fibers is responsible for either disease.[23,24]

Tarsal size may also play an important role in turning the eyelids to the inside or out. In the presence of lateral canthal tendon laxity, a large or thickened tarsus overcomes the tone of the preseptal orbicularis resulting in ectropion, while a small, shrunken, or atrophic tarsus may be overcome by the same muscle resulting in involutional entropion.[5,24,25]

A larger globe or an increase in axial length correlates directly with involutional ectropion, while smaller eyes are more prone to develop entropion.[4] Another factor of significance is the globe position. The consensus is that an increase in exophthalmometry measurements also correlates directly with the development of ectropion, while enophthalmos correlates more with involutional entropion.[4,6,26] However, other researchers have failed to observe a direct causal relation between axial length and globe position,[27,28,29] and some authorities argue that this postulated association with globe position or size only demonstrates that a tighter eyelid-globe apposition simply prevents the eyelid from rotating inward or outward.[20] Midface descent is an often overlooked factor that may also mechanically aggravate preexisting ectropion due to downward gravitational vectors.[30,31,32]

Ultrastructurally, the composition of the "younger" tarsus is mostly collagenous fibers with scattered elastic fibers. Collagen fibers are essential for tensile strength, while elastic fibers are a source of tarsal resilience.[25,33,34] With advancing age, there is a significant and generalized reduction in both collagen and elastic fibers throughout all eyelid layers including the skin, orbicularis, and the tarsal stroma.[21,22,25,33,34] There is a relative increase in collagen fiber content in eyelid specimens from patients with involutional ectropion compared to patients with involutional entropion.[33,34] Whether this is the underlying factor explaining the greater tendency toward tarsal hypertrophy in patients with involutional ectropion is unknown.[35] Upregulation of key elastolytic enzymes like matrix metalloproteinase MMP-2, MMP-7, and MMP-9 in eyelid tissues is responsible for enzymatic degradation of elastic tissue, and consequently, a significant reduction in elastic fiber content, as well as substantial ultrastructural abnormalities in the residual elastin tissue, has been demonstrated both in ectropion and entropion.[33,34] The cause of this overexpression of elastin-degrading enzymes with advancing age is unknown but may be the consequence of local ischemia resulting from arteriosclerosis of the marginal arcade, chronic mechanical stress, or local inflammation.[33,34]

Clinical Presentation

Demographically, the prevalence of involutional ectropion in the elderly is around 2.9%,[26] with a sharp increase in prevalence after the age of 80 years (16.7%).[36] Involutional ectropion is slightly more common than involutional entropion[1] and is more prevalent in males than females (male prevalence is 5.1%, vs 1.5% in females), which is a reversal of the pattern observed in involutional entropion where females are more commonly affected.[26] This gender difference could be related to tarsal size, axial globe position, or possibly globe size.[1,4,5,6,26] Involutional ectropion almost always involves the lower eyelid and is more commonly bilateral (70% of patients).[36]

A large proportion of patients may have mild ectropion, which is only discovered during a routine examination, and therefore may be completely asymptomatic, but in symptomatic patients, the main presenting symptom is tearing. What makes tearing the most common complaint is that normal blink dynamics, as well as a uniform distribution of tears, are largely dependent on the normal apposition between the eyelid and the globe.[9] The pattern of epiphora may vary according to the location of ectropion. Medial ectropion causes eversion of the lacrimal punctum or punctal ectropion (Figure 18.1A), and observant patients usually comment that tearing is more common medially, which is usually their only symptom, while lateral ectropion causes pooling of the tears laterally (Figure 18.1B). Patients with a more generalized horizontal lid laxity also complain of epiphora, but those patients may also suffer from lagophthalmos at night, and the sagging eyelids may pose a significant cosmetic problem as well (Figure 18.1C and D).[37,38]

The eyelid should be evaluated both statically and dynamically with the anterior, medial, and lateral distraction tests, as well as the snap back test.[39,40] The so-called anterior eyelid distraction test is performed by pulling the eyelid away from the globe centrally and is judged as positive when the lower eyelid margin retracts from the globe a distance of more than 8 mm (Figure 18.2A).

Patients with medial canthal tendon laxity may present a diagnostic as well as a therapeutic challenge, and to assess the integrity of the medial canthal tendon properly, a lateral distraction test is performed by pulling the lower eyelid laterally, and if the punctum is

pulled with ease beyond the plica and toward the medial corneal limbus, it is judged as positive.[40] Based on the results of this test, O'Donnell et al qualitatively classified medial ectropion into mild, moderate, and severe.[12] Patients with isolated punctal eversion with no or minimal displacement are classified as mild, those with only a few mm of displacement are classified as moderate, and patients where the punctum is displaced to the medial limbus or beyond constitute the severe variety.[12] Moderate and severe cases are easy to diagnose, but patients with mild medial ectropion may be missed during a cursory examination, and the diagnosis may only be clenched by asking the patient to blink to induce maximal punctal eversion.[38]

A medial distraction test is more difficult to evaluate and is possibly of lesser clinical significance. If the punctum is pulled beyond the midpoint of the lacrimal caruncle when the lower eyelid was pulled medially, the lateral distraction test is judged as positive.[40] The eyelid snap back test is positive when the lower eyelid returns to normal position only after several blinks and not spontaneously when an examiner pulls the lower eyelid inferiorly (Figure 18.2B).[40] As was mentioned earlier, the location of retractor weakness or *(Print pagebreak 129)* disinsertion is usually greatest corresponding to the location of the ectropion.[3,40,41] The four classical signs of retractor dehiscence include inferior fornix deepening, upside-down ptosis, diminished excursion of the lower eyelid, and visualization of the retracted edge as a lustrous white line nearer to the fornix when retractor disinsertion is complete,[2,14,42] or as a V-shaped convex line pointing toward the tarsus when disinsertion is incomplete.[15] However, these may be difficult to identify and may not be demonstrated clinically in every case.

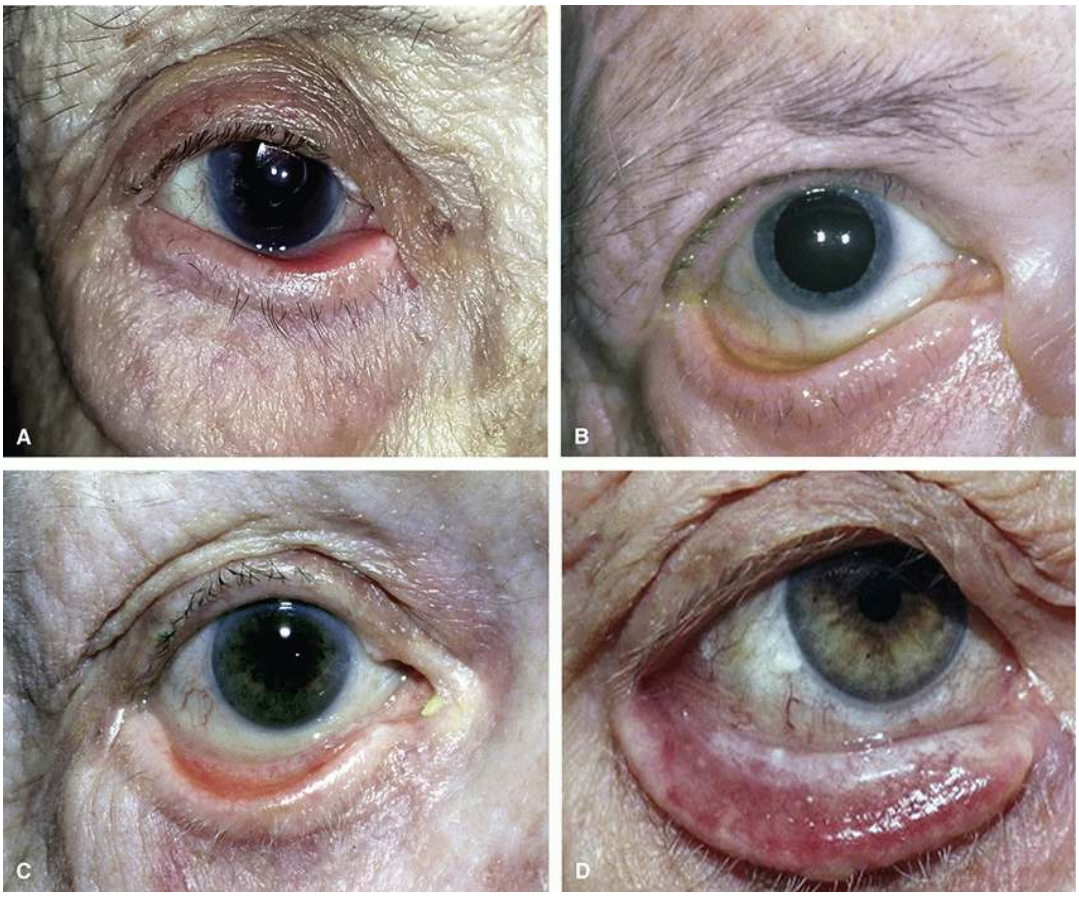

FIGURE 18.1 A, Medial ectropion with punctal eversion. B, Ectropion involving the lateral part of the lower eyelid. C, Generalized ectropion involving all parts of the lower eyelid. D, Tarsal ectropion with complete 180° eversion of the lower eyelid.

The inferior punctum often becomes stenotic, eventually even can become fibrotic or occluded with a superficial membrane, which is only secondary to punctal disuse. Although this secondary punctal stenosis usually improves after the eyelid position is corrected surgically,[37,38,43] formal evaluation of the entire lacrimal system is mandatory so as not to miss an unrelated nasolacrimal duct obstruction. Chronic conjunctivitis is not uncommon, and the conjunctival surface generally is injected and thickened, with varying degrees of keratinization and inflammation. There is usually an increased tear lake along the entire eyelid, and some evidence of corneal dryness or even ulceration from exposure may be encountered occasionally. However, corneal morbidity generally is more common in patients with tarsal ectropion, particularly if a cicatricial element coexists with the involutional changes. Tarsal ectropion represents an unusually striking form of ectropion where the ectropic state involves the entire lower eyelid and is not focal (Figure 18.1D).[14,18] These patients typically present at an older age with a completely everted lower eyelid. The tarsal plate is turned upside down and the lower border of the tarsus is flipped up toward the level of the inferior limbal margin, with outward eversion of the palpebral conjunctiva.[14]

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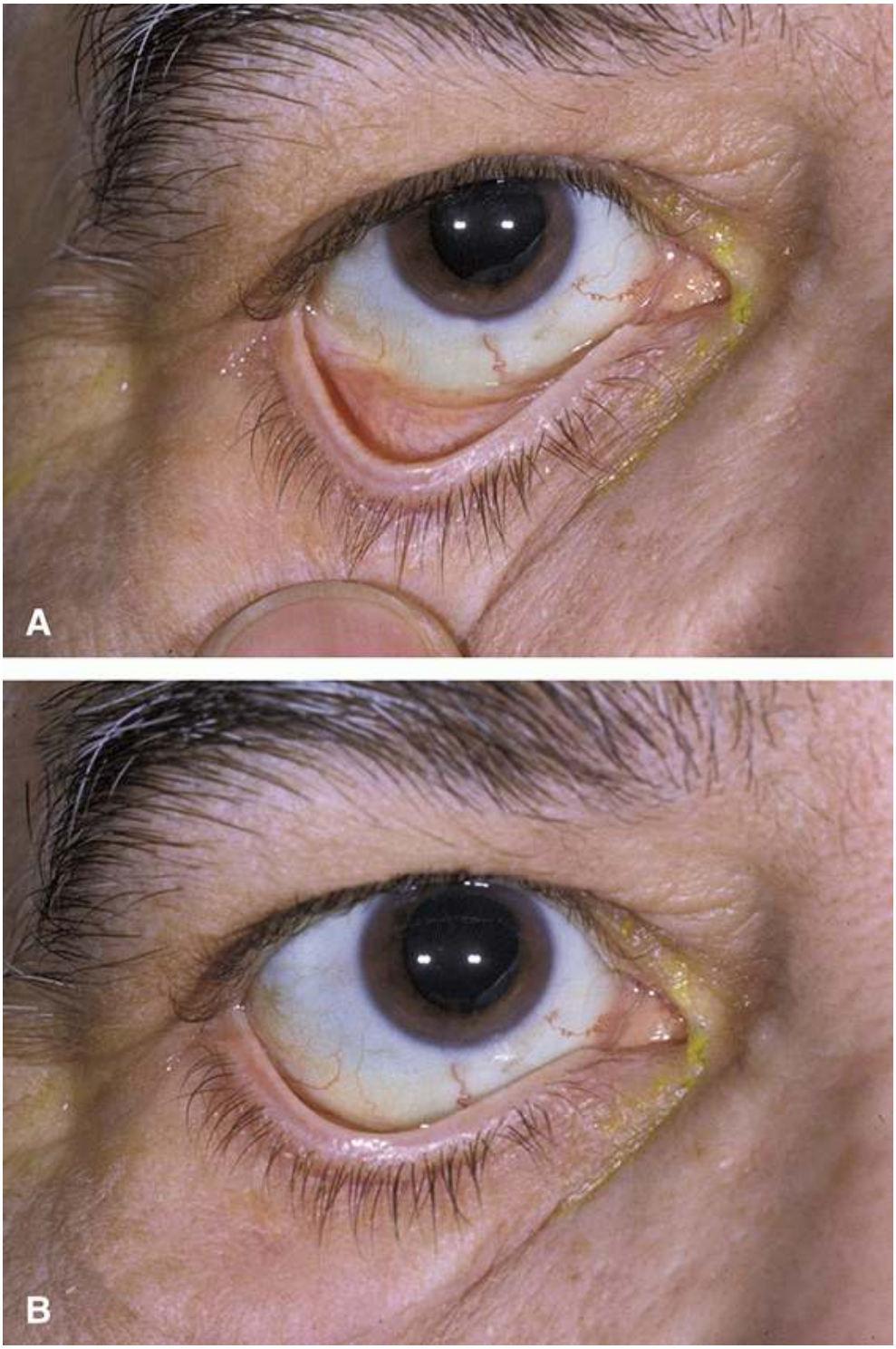

FIGURE 18.2 Snap back or distraction test. A, The eyelid is pulled away the globe centrally; a distance of 8 mm or more is a positive test for eyelid laxity. B, When released, the eyelid does not immediately retract to its normal position, but slowly drifts back.

Differential Diagnosis

The etiology of involutional ectropion encountered in clinical practice is often multifactorial, and a combination of involutional, cicatricial, paralytic, and even mechanical factors could coexist.[31] Establishing the diagnosis may be challenging at times, and unfortunately, age may not always be a clue because the two other conditions that may be clinically confused with involutional ectropion, namely the cicatricial and paralytic types, are not uncommon in the elderly. Chronic actinic sun damage, which is usually observed in the elderly, is more of a cicatricial nature and would not lend itself to surgical approaches addressing laxity problems

only. It is particularly crucial to rule out a cicatricial element in patients with tarsal ectropion.[17] To differentiate, the involutional type would be easily corrected by manually elevating the eyelid upward, while in the cicatricial variety, it can only be corrected by manually pushing the entire cheek-eyelid complex upward to the lower orbital rim to recruit skin and compensate for shortage.[38]

If a shortage of skin is not demonstrated, then a useful test to differentiate involutional ectropion from the paralytic variety would be to ask the patient to close the eyelids forcefully. Patients with involutional ectropion would not suffer from poor eyelid closure. It might appear rather redundant to try to differentiate an obvious clinical diagnosis as facial nerve paralysis from involutional ectropion through clinical evaluation, but it should be remembered that some elderly patients may fail to recall remote events particularly if Bell palsy has occurred decades ago and most of the signs and symptoms are already gone.

Treatment

In contrast to involutional entropion, which if left untreated could lead to serious corneal injury, patients with mild involutional ectropion who only complain of epiphora may be left untreated or given a trial of artificial tears. Although tearing may be symptomatically bothersome, it is not morbidly threatening to the cornea,[44] and symptomatic improvement after surgery may not always be complete. Surgical treatment of involutional ectropion should be considered if concurrent corneal exposure, chronic conjunctivitis, or significant tearing is attributable to the eyelid deformation.

Surgical approaches designed to address involutional ectropion generally involve a horizontal eyelid tightening procedure and can be classified into two groups, those that involve resecuring attachment of the canthal tendons to the bony orbital rim and those that involve resection of a block of eyelid tissue.[10] Because weakening of the lower orbital ligamentous support is a major factor in the pathogenesis of ectropion and entropion, failure to address even the mildest degree of horizontal laxity may lead to an unsuccessful result.[22] This is the reason why reestablishing a firm eyelid-globe apposition with a lateral tarsal strip procedure has consistently shown a high success rate in the management of both conditions, even if performed alone.[1,26] Although often overlooked in the literature, surgical repair of lateral canthal tendon laxity should identify and repair the entire lateral canthal tendon as a single unit, and not just the inferior crus. Failure to do so may cause lateral canthal angle contour abnormalities or even eyelid length disparity between the upper and lower eyelids.[9] The lack of relationship with the lacrimal system simplifies surgical maneuvers around the lateral canthus.[9] In patients with significant midface descent, the reconstructive role of a transcanthotomy midface lift or cheek resuspension, as an adjunct to standard surgical procedures for involutional ectropion, should be considered.[31,32]

Fortunately, the occurrence of a lax medial canthal tendon that requires reattachment is less frequently encountered in clinical practice.[9,12] Milder cases of isolated punctal eversion where the medial canthal tendon is intact can be repaired with the tarsoconjunctival diamond excision, with care to avoid injuring the lower canaliculus.[38] The sutures used to close the diamond should incorporate the lower eyelid retractors to prevent punctal eversion during blinking.[38] *(Print pagebreak 131)* Recently, Kenichi Kokubo and associates described an alternative technique whereby the lower eyelid retractors are separated medially from the conjunctiva, resected (shortened), and then reattached to the tarsus.[45] Moderate degrees of medial ectropion would benefit from combining a lateral tarsal strip with a medial spindle diamond excision.[46] While the medial spindle works by restoring the normal anatomical position of the punctum, the lateral tarsal strip would help by straightening a flaccid lower canaliculus and symptomatic epiphora will improve.[12] More severe cases will require a more involved reconstruction of the medial canthal tendon.[38,43,47,48,49] The consensus is that the threshold for operating on the medial canthal tendon should be high[12,50] because these techniques usually require an anterior orbitotomy approach. They may also entail sacrificing the lower or even the common canaliculus, which disregards obvious anatomical and physiological basics for tear outflow mechanisms.[12,51] More importantly, these techniques may be technically difficult with less than a perfect outcome.[43] Addressing the medial canthal tendon surgically is only indicated if the lateral distraction test pulls the punctum well beyond the nasal corneal limbus because in these cases a lateral tarsal strip would relocate the punctum too far laterally leading to an undesirable cosmetic as well as the functional outcome.[12] In these cases, the posterior limb and not the anterior limb of the medial canthal tendon should be addressed to avoid moving the eyelid away from the globe and rendering the surgery pointless. Again, plication of the posterior limb is technically difficult, and a unique problem not infrequently encountered during the procedure is the lack of robust tissue that will hold sutures in place in the vicinity of the posterior lacrimal crest. In these cases, a Mitek anchor, microplate fixation, and even transnasal wiring have been described.[12,43] Even if addressing the medial canthal tendon is inevitable, most patients will still require an adjunctive lateral tarsal strip procedure.

Operating on patients with tarsal ectropion represents a special challenge, and surgery may be fraught with failures. Because retractor disinsertion plays a more significant role in these patients than horizontal laxity, plication of the retractors or their reattachment to the inferior tarsal border stabilizes the posterior lamella, thus preventing the eyelid from spontaneously rotating along its horizontal axis.[14] Reattaching the lower eyelid retractors has been described as a remedy with good success, both through the transconjunctival or the transcutaneous routes.[13,16,42] Because retractor disinsertion is likened to

aponeurotic levator dehiscence, a posterior approach lower eyelid retractor repair analogous to a Müller muscle conjunctival resection was described recently.[18,19] This technique reestablishes normal anatomic alignment using the Putterman clamp to excise a block of the conjunctiva, and the lower eyelid retractors.[18,19] It should be noted, however, that because the block of excised tissue includes conjunctiva, there is a potential risk of shortening the lower fornix,[42] which normally averages only about 10 mm in depth in the center and progressively shallows further medially and laterally.[52] Regardless of the technique used for reattaching the lower lid retractors, it should be combined with horizontal eyelid tightening in all cases to address both postulated mechanisms responsible for tarsal ectropion.[19,42]

Prognosis

The prognosis for correction of involutional ectropion is excellent following any of the usual surgical approaches.[53] From an aesthetic point of view, lower eyelid ectropion repair using any of the abovementioned tightening techniques (eg, lateral tarsal strip) does not merely improve lower eyelid function but it may re-create a youthful appearance as well.[54]

Histopathology

Stefanyszyn, Hidayat, and Flanagan examined twenty eyelid specimens from patients with involutional ectropion.[21] "The main histopathological features included: (1) collagen degeneration and elastosis of the tarsal plate; (2) increased amounts of adipose tissue in the distal tarsus and capsulopalpebral fascia; (3) subacute inflammation and epidermalization of the tarsal conjunctiva; (4) focal degeneration, fibrosis and elastosis of pretarsal orbicularis, and occasionally minimal change in the muscle of Riolan; and (5) arteriosclerosis of the marginal artery."[21] Kocaoglu and coworkers noted similar histopathological changes.[35]

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CHAPTER 19

Entropion, Cicatricial

Key Points

- Cicatricial entropion is an acquired eyelid malposition characterized by tarsoconjunctival scarring resulting in an inward rotation of the eyelid margin
- It may be accompanied by trichiasis, distichiasis, or conjunctival epithelial metaplasia
- The underlying causes may be classified into progressive and nonprogressive cicatrizing diseases
- Progressive causes include trachoma, mucous membrane pemphigoid, and Stevens-Johnson syndrome
- Nonprogressive conditions include trauma, surgery, chemical injuries, severe blepharitis, or severe meibomian gland dysfunction
- Symptoms include foreign body sensation, tearing, pain, photophobia and eventually corneal abrasion, infection, and neovascularization
- The management of cicatricial entropion is essentially surgical with anterior lamellar repositioning or posterior lamellar grafting
- The overall prognosis generally is excellent

Cicatricial entropion is a commonly acquired eyelid malposition characterized by tarsoconjunctival scarring, which creates an imbalance between the anterior and posterior eyelid lamellae, resulting in an inward rotation or angulation of the posterior lid margin, which may be accompanied by trichiasis, distichiasis, or conjunctival epithelial metaplasia.[1,2,3,4,5,6,7,8,9,10] In developing countries, where trachoma is endemic, cicatricial entropion remains one of the more challenging eyelid disorders in terms of morbidity and proper management, and the terms cicatricial entropion and trachomatous trichiasis (TT) are even used interchangeably in these countries.[1,2]

Etiology and Pathogenesis

The underlying causes of cicatricial entropion may broadly be classified into progressive and nonprogressive cicatrizing diseases, all having a common end point, which is relentless and irreversible scarring of the posterior lid lamellae, and ultimately the ocular surface.[9] Progressive causes include infectious conditions like trachoma or leprosy, autoimmune processes like mucous membrane pemphigoid, Stevens-Johnson syndrome (SJS), and rarely thyroid eye disease. Nonprogressive conditions include trauma, surgery, chemical injuries, severe blepharitis, or severe meibomian gland dysfunction.[7]

Trachoma usually starts with repeated childhood infections with *Chlamydia trachomatis* serovars A-C (see Chapter 121).[6,11] Recurrent episodes of infection eventually result in entropion and trichiasis many years later, and ultimately corneal opacification and blindness.[6] Mucous membrane pemphigoid is a life-threatening and occasionally blinding autoimmune disorder,[9,12,13,14,15,16,17,18,19] and if the clinical manifestations primarily involve the eyes, the term ocular cicatricial pemphigoid (OCP) is often used (see Chapter 98).[14,15] SJS is a drug-induced acute blistering disease of the skin and at least two mucosal surfaces, which may be complicated with high mortality or significant long-term ocular morbidity (see Chapter 117).[20,21,22,23,24,25,26,27,28,29] It is important not to overlook other less frequent causes of cicatricial entropion like penetrating trauma, chemical injuries, prior surgical trauma, linear IgA disease, atopic keratoconjunctivitis, graft-versus-host disease, IgG4-related disease, and dysthyroid ophthalmopathy.[30,31]

Clinical Presentation

Patients are usually aware of their condition, and the main presenting complaint is "lashes rubbing against the eye."[6] Additionally, they may complain of general symptoms like foreign body sensation, tearing, pain, or photophobia, but in rare situations, they may be completely asymptomatic.[6] Patients should specifically be asked about a history of self-epilation, which would mislead the surgeon toward underrating the severity of entropion. They should also be questioned about previous eyelid surgery, which could undermine forthcoming surgical efforts.[6] An inquiry should also be made about a history of drug intake, penetrating trauma, or chemical injuries, or a history of orbital floor fracture repair. Cicatricial entropion may involve the upper or lower eyelids and may affect male or female patients at any age, but there are specific demographic patterns related to certain diseases. Palpebral deformities in trachoma predominantly involve the upper eyelid and are more common in females in endemic areas of the world. TT is virtually absent in the Western Hemisphere except among migrants.[4,7] Lower eyelid TT is less common than its upper eyelid counterpart, but it is not as rare as was previously thought,[6] occurring in *(Print pagebreak 134)* up to 11% of TT patients.[2] Cicatrizing disorders from cutaneous drug reactions, as with SJS, can occur at any age,[20] and OCP is a disease more common in the elderly.[15,19]

When evaluating patients with cicatricial entropion, it is not only the eyelid position or the number of lashes in contact with the cornea that should be examined, but the tarsal conjunctiva, the lacrimal system, and the cornea should be examined as well.[6] The palpebral manifestations embody a full spectrum of disease ranging at one end from simple trichiasis, where no entropion is observed (see Chapter 22), to frank entropion, where the entire eyelid margin rolls inward and may potentially be blinding (Figure 19.1).[4,7] The location of the eyelashes rubbing against the cornea may be a general indicator for the later development of corneal blindness, with more remote eyelashes away from the center posing a lesser grave danger (Figure 19.2).[6] However, it is important to remember that the eye is not a static structure and as the globe moves, contact between the eyelashes and the cornea will repeatedly take place.[4] There is also "rounding" or loss of the sharp boundary of the posterior eyelid margin in milder cases, but this posterior lid margin may completely disappear from view in more severe cases.[2,6] The eyelids may appear structurally deformed with loss of normal architecture, which may be accompanied by conjunctivalization or keratinization of the mucocutaneous junction or lagophthalmos in severe or recurrent cases.[2]

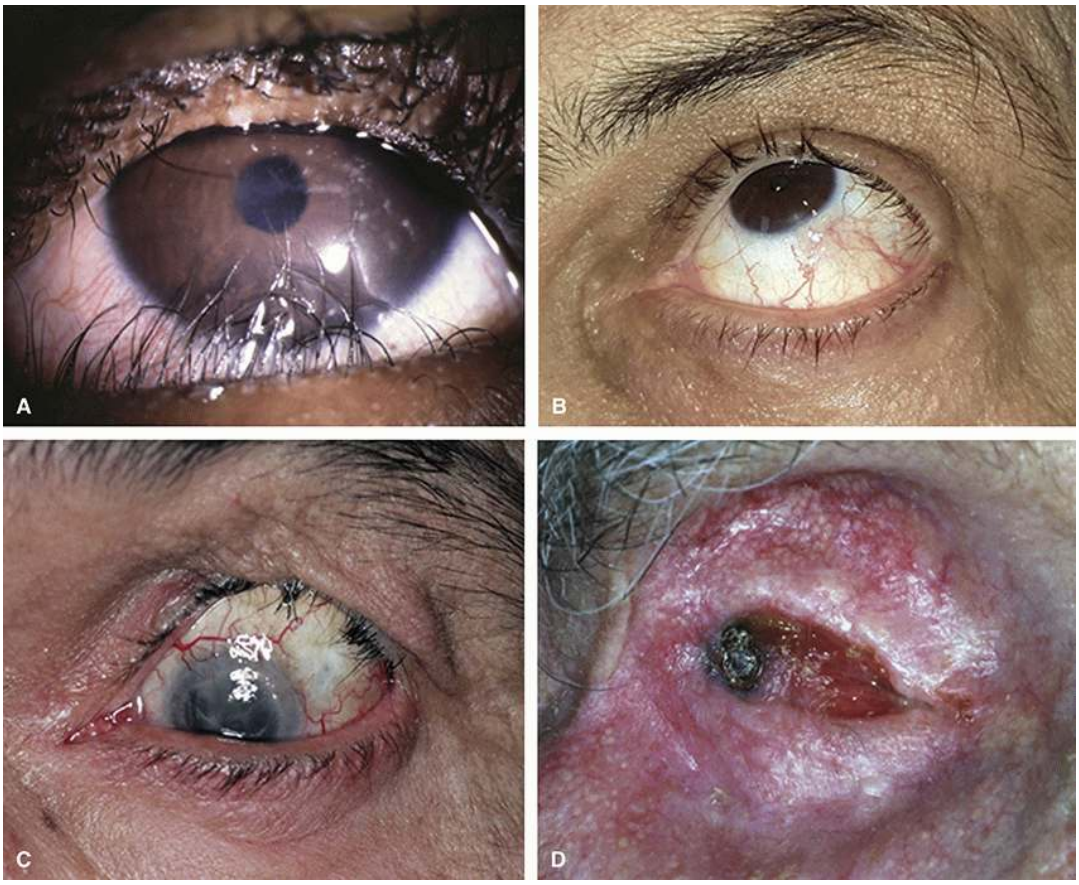

FIGURE 19.1 Cicatricial entropion. A, Mild entropion with secondary trichiasis from Stevens-Johnson syndrome. B, Lateral upper eyelid entropion in a case of trachoma. C, Cicatricial entropion with retraction of the upper eyelid from severe conjunctival scarring. D, Severe entropion of upper and lower eyelids from ocular cicatricial pemphigoid.

The conjunctiva shows a variable degree of scarring, which ranges from a few white lines to dense scar tissue and symblepharon formation (Figure 19.3), but the pattern of scarring may vary according to the etiology. Severe dryness with reduction of both the aqueous and lipid layers is frequently encountered especially in SJS and OCP and is multifactorial, occurring as a result of scarring

of the lacrimal ducts, chronic reduction of lacrimal gland function, meibomian *(Print pagebreak 135)* gland atrophy/orifice metaplasia, or reduction in conjunctival goblet cells.[17,21,22,27] This vicious cycle of entropion trichiasis, dry eyes, and lagophthalmos may lead to repeated corneal abrasions, infections, and neovascularization and could eventually lead to corneal scarring and blindness. In severe cases, the cornea may even perforate due to repeated infections and the globe becomes phthisical.[6,17,21,22]

FIGURE 19.2 Segmental cicatricial entropion. A, Medial lower eyelid entropion following trauma. B, Medial upper eyelid entropion and corneal scarring resulting from an alkali burn.

Differential Diagnosis

Cicatricial entropion is usually clinically evident, and it should not be difficult to distinguish from other causes of entropion; however, the biggest challenge facing an oculoplastic surgeon might be the difficulty differentiating one cause of cicatricial

entropion from the other. While clinching the diagnosis of traumatic cicatricial entropion or SJS may be self-evident from the history, differentiating trachomatous entropion trichiasis from OCP may be challenging, although the presence of symblepharon or ankyloblepharon may favor the diagnosis of OCP.[32,33]

Treatment

Through its Global Elimination of Trachoma initiative, the World Health Organization (WHO) is aiming to eliminate trachoma from the world by 2020 through its SAFE strategy: Surgery for entropion and trichiasis, Antibiotics distribution, Facial cleanliness, and Environmental improvements to suppress transmission.[4,10,34,35] Unfortunately, at the time of writing of this chapter, only 12 countries have successfully eliminated trachoma as a public health problem.[9]

The management of cicatricial entropion is essentially surgical, and surgery is broadly classified into two categories: minor procedures (discussed in detail in Chapters 22 and 41), which only address the aberrant eyelashes and are the generally preferred approaches in patients with focal trichiasis without entropion, and major procedures, which include corrective surgery for the eyelid malposition. These procedures correct the underlying anatomical eyelid abnormality and subsequently reposition the lashes away from the globe.[6]

The consensus is that corrective eyelid surgery is a key component in the management of cicatricial entropion to prevent potentially blinding corneal scarring.[3,6] Over the years, a plethora of surgical procedures have been described, but they can be summarily categorized into three groups: (1) eyelid shortening procedures that involve a tarsotomy/tarsectomy, (2) rotational procedures, or tarsal-sparing techniques that involve recession of the anterior lamella, or advancement of the posterior, and (3) lengthening of the posterior lamella with a spacer graft.[36] This large variety of procedures underlies the complexity of the disease and is a testament that the ideal procedure for cicatricial entropion is yet to be described.[3] All of them aim at achieving the same goal, which is to mobilize the entropic eyelid away from the cornea, but the consensus in modern oculoplastic practice is to move away from more involved procedures that require either excision/shortening of the eyelid tissue or eyelid lengthening using a graft.[6] Although the WHO recommends bilamellar tarsal rotation, or posterior lamellar tarsal rotation for TT, tarsal-sparing procedures like anterior lamellar recession (ALR) or reposition with a gray line split may be the preferred approach in the majority of TT patients, as well as those suffering from chronic autoimmune processes like OCP or SJS because neither tissue resection nor a conjunctival incision is required.[3,6,7] Both anterior lamellar reposition and ALR techniques are discussed in detail elsewhere,[3,6,7,30] but briefly the anterior lamellar reposition procedure is usually performed as follows: a lid crease incision is made with exposure of the anterior surface of the tarsus, and dissection is carried out inferiorly for several millimeters. Because one of the few complications of ALR/reposition is mild upper eyelid retraction, the levator is exposed and may be recessed away from the tarsus. This is important particularly *(Print pagebreak 136)* in patients with recurrent entropion and lagophthalmos and in younger patients where a cosmetically unsightly eyelid retraction may pose a problem for the patient. Several single-armed 5-0 polyglactin sutures are initially passed through the anterior lamella from the skin side close to the upper eyelid margin 1 or 2 mms above the lash line. They are then secured horizontally in a partial thickness manner through the tarsal plate, before finally exiting the skin again at the same plane of initial entry but a few millimeters away, and then both ends are tied, thus rotating the eyelid in a horizontal mattress fashion. This is followed by creating a superficial incision of the eyelid margin at the gray line to separate the anterior and posterior lamella, and the bare eyelid margin is allowed to epithelialize. The skin crease is reformed using 6-0 polyglactin sutures and the bites should also be passed through the tarsus to further augment the upward vector of traction of the 5-0 stitches. Unfortunately, several authors use the terms ALR and anterior lamellar reposition interchangeably,[7] although they are two distinct procedures.[3] While anterior lamellar repositioning does not entail complete lamellar division, a complete lid split into anterior and posterior lamellae is the hallmark of ALR, and if ALR is chosen, blunt dissection should extend from the skin crease incision to directly communicate with the gray line incision.[3,7] Obviously if ALR is to be performed, the gray line incision should precede the skin crease incision because if it is deferred till the end of surgery as described above, this may risk violating the preplaced 5-0 stitches. Some authors recommend ALR over anterior lamellar reposition, on the basis that without a complete lid split and lamellar division, the sutures will not be able to overcome the underlying cicatricial forces at the eyelid margin effectively.[3]

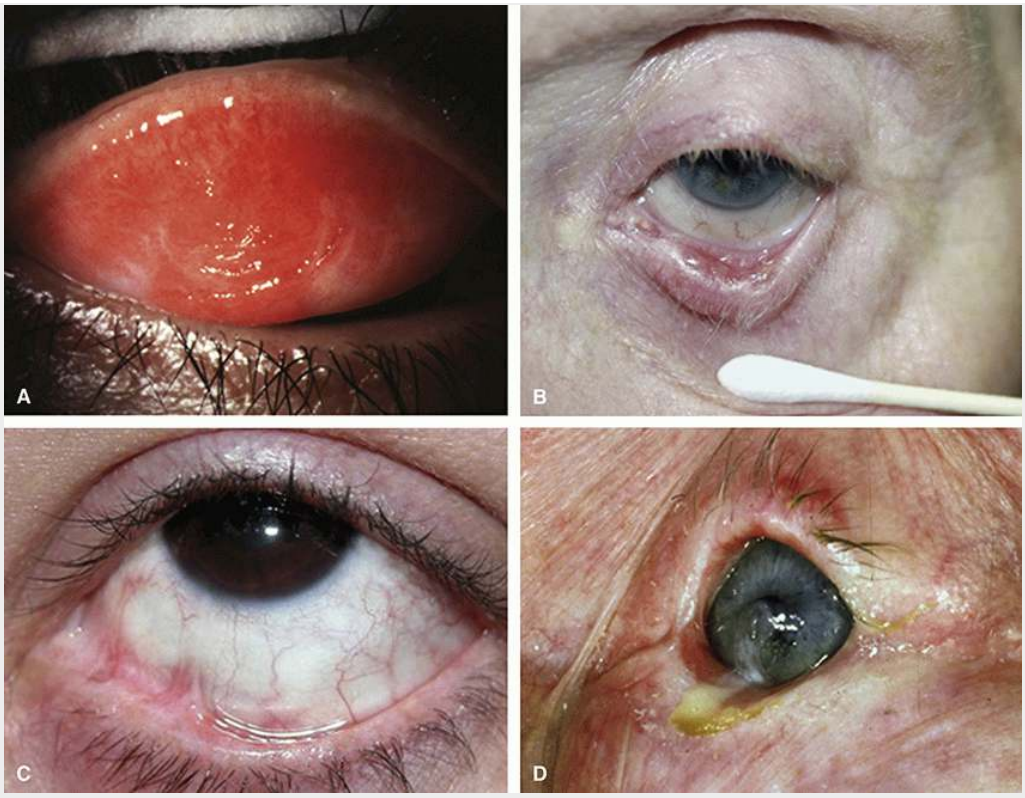

FIGURE 19.3 Conjunctival scarring associated with cicatricial entropion. A, Mild scarring of the upper eyelid conjunctiva. B, Symblepharon and shortening of the fornix of the lower eyelid. C, Medial symblepharon of the lower eyelid. D, Marked loss of the conjunctiva from ocular cicatricial pemphigoid.

It should be pointed out that lengthening of the eyelid with a spacer graft may still be required in three unique situations: (1) in patients with severe lagophthalmos or a very short tarsus where tarsal lengthening may be required, *(Print pagebreak 137)* (2) in SJS/OCP patients where a posterior lamellar graft may be needed to address symblepharon and entropion simultaneously, or (3) in SJS patients with tarsal margin keratinization if concomitant entropion is observed and both need to be addressed.[7,26,37] A short or scarred tarsus causing significant lagophthalmos may be encountered as part of the cicatrizing disease process itself, but it is more commonly encountered in parts of the world where tarsectomy (Snellen procedure) is still incorrectly performed with resection of a block of tarsus instead of a wedge, which may cause lid retraction/lagophthalmos rather than addressing the entropion,[38,39,40] which is a further argument against tarsectomy procedures in general. The management of lower eyelid entropion is less clear-cut as there are no formal guidelines set by the WHO, and the literature is also lacking in this regard. However, because of obvious anatomical reasons, tarsotomy/tarsectomy procedures are also better avoided in the lower eyelids as the risk for vascular compromise is real; therefore, a modified form of anterior lamellar reposition may be the preferred approach in the lower eyelid to avoid a tarsal incision.[37]

Unfortunately, recurrence of cicatricial entropion is not uncommon and is multifactorial, and while earlier recurrences are technique related,[3,41] late recurrences may result from progression of the original disease process itself.[6] Several technique-related issues need to be discussed. First, techniques that involve a tarsotomy like the WHO-endorsed procedures usually require a conjunctival incision; therefore, these techniques may trigger conjunctival inflammation, or aggravate tarsal cicatrization, eventually resulting in surgical failure not just in OCP or SJS but in trachoma patients as well.[3,41] Also, the long-term effects of these procedures on the integrity of the cornea and meibomian gland function are legitimate concerns.[2] Second, regardless of the technique used, a significant degree of surgical overcorrection of the lid margin is a prerequisite for the long-term success of surgery; otherwise, recurrence is inevitable.[2] A notable exception to this rule may lie in younger patients with cicatricial entropion who are naturally more cosmetically concerned than their older counterparts.[2] Third, even if sufficient overcorrection has been achieved at the end of the surgery, focal recurrences may still be observed due to inadequate peripheral dissection. Undercorrection after entropion surgery occurs more frequently in the temporal and nasal portions of the upper eyelid.[3,4] On the nasal side, surgeons may be reluctant to extend the incision and spread out the stitches further medially to avoid injuring the lacrimal system, while on the temporal side, it may be technically challenging to strategically place the stitches. The fourth and final factor is the surgeon themselves, as the surgeon's technical expertise is instrumental in reducing recurrence.[6]

Prognosis

Despite a large number of different surgical techniques used in the management of cicatricial entropion, the overall prognosis generally is excellent. In an examination of 11 reports published during the past decade totaling 472 patients, employing various combinations of the surgical approach described above, and with follow-up periods of 6 to 67 months (mean = 29 months), the overall success rate following one surgical session was 74% to 100%, with a mean of 90%.[5,7,37,42,43,44,45,46,47,48,49] Recurrences were reported in 11% to 38%, with a mean of 20.5% within 4 to 12 months. Of these, 15% required a second procedure and 3% a third intervention.

Histopathology

Cicatricial entropion results from scarring and shortening of the posterior tarsoconjunctival lamella from a variety of causes. The histopathology is varied depending upon the specific cause. For example, eyelids with cicatricial entropion from trachoma have a thick, compact, subepithelial fibrous membrane adherent to the tarsal plate, atrophy of Meibomian glands, conjunctival squamous metaplasia and loss of goblet cells, subepithelial lymphocytic inflammation, and tarsal degeneration with focal replacement by adipose tissue.[50,51]

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CHAPTER 20

Entropion, Involutional

Key Points

- Involutional entropion is an in-turning of the eyelid margin against the corneal and conjunctival surfaces
- It results from horizontal lower eyelid laxity of the lateral canthal tendon, and vertical attenuation, dehiscence, or disinsertion of the lower eyelid retractors
- The in-turned eyelid margin causes irritation, tearing, redness, and photophobia as a result of eyelash and skin friction against the corneal surface
- Simple everting sutures are a minimally invasive procedure that can be effective in some cases
- The definitive management is to address any horizontal eyelid laxity along with vertical laxity by reattachment or tightening of the lower eyelid retractors
- With appropriate surgery, the prognosis is excellent

Involutional entropion, a condition that is commonly encountered in the elderly, is induced by progressive thinning and attenuation of lower eyelid tissues, with subsequent in-turning of the eyelid margin against the corneal and conjunctival surfaces. This causes irritation, tearing, redness, and photophobia as a result of eyelash and skin friction.[1,2,3] Of all the periocular aging changes related to dehiscence or separation of anatomical tissues, none causes more discomfort and ocular morbidity than involutional entropion.[3]

Etiology and Pathogenesis

A basic understanding of lower eyelid anatomy is pertinent to understand the pathogenesis of involutional entropion. The lower eyelid retractors are a definite double layer, and both layers are responsible for maintaining the stability of the tarsal plate. Because of a motor component contribution from the inferior rectus muscle, the posterior layer of the lower lid retractors is also responsible for a lower eyelid excursion or vertical traction of 3 to 5 mm in downgaze.[1,4,5] In younger patients, the pretarsal muscle is normally firmly adherent to the tarsus, while its preseptal counterpart is weakly adherent to the septum, and involution makes these connections even weaker.[1]

Progressive age-related thinning and attenuation of eyelid tissues predispose the preseptal orbicularis muscle to migrate upward and override its pretarsal counterpart so that the lower eyelid turns in.[2,6,7,8,9] This is mediated by a combination of horizontal and vertical lower eyelid laxity in the form of lateral canthal tendon laxity, attenuation, dehiscence, or disinsertion of the lower eyelid retractors, and age-related atrophy of orbital fat and enophthalmos. Involutional entropion and ectropion are characterized by their "mirrored" clinical presentation, and they share similar age-related changes on both the anatomical as well as the ultrastructural levels,[10,11] see Chapter 18 for a detailed review and a more thorough discussion of those collective predisposing factors.

Clinical Presentation

The involutional type is by far the commonest type of entropion,[12] except in regions of the world where trachoma is endemic. An unprecedented number of people around the world are growing older, and the current number is expected to double by 2050.[13] The prevalence of involutional entropion in the elderly is currently 2.1%, and likewise is also on the rise.[14] This figure surges to 7.6% in patients older than 80 years.[14] Involutional entropion, which is more frequently bilateral, is slightly more common in white females, with a prevalence of 2.4%, compared with 1.9% in men. The incidence is very low in elderly blacks (0.8%).[14] The difference in sex prevalence could be attributed to tarsal size, axial globe position, or possibly the size of the globe itself.[10,14,15,16,17]

Patients typically present with significant ocular irritative symptoms and discharge. But because the symptoms and signs are initially intermittent, some cases may remain undiagnosed for months or even years or be mislabeled as dry eye or meibomian gland

dysfunction.[3] The frequency of the attacks gradually increases over time, and entropion becomes more permanent.[3,18] Similar to other types of entropion, the entire mucocutaneous border of the eyelid, together with the eyelashes, is directed toward the globe, with subsequent corneal touch secondary to the eyelid malposition (Figure 20.1). Other eyelid and ocular surface abnormalities in patients with involutional entropion include lower retractor laxity, lateral canthal tendon laxity, chronic blepharitis, chronic conjunctivitis, dry eyes, and superficial punctate keratopathy. If left untreated, entropion could potentially lead to corneal ulceration.[3,14,15] A specific variant of involutional entropion, the so-called "spastic entropion," typically follows a definitive inflammatory ocular event in the elderly, like intraocular surgery. This initiates a vicious cycle of ocular irritation, *(Print pagebreak 140)* reflex blepharospasm, and entropion. The resulting mechanical irritation exacerbates the eyelid malposition problem even further.[19,20]

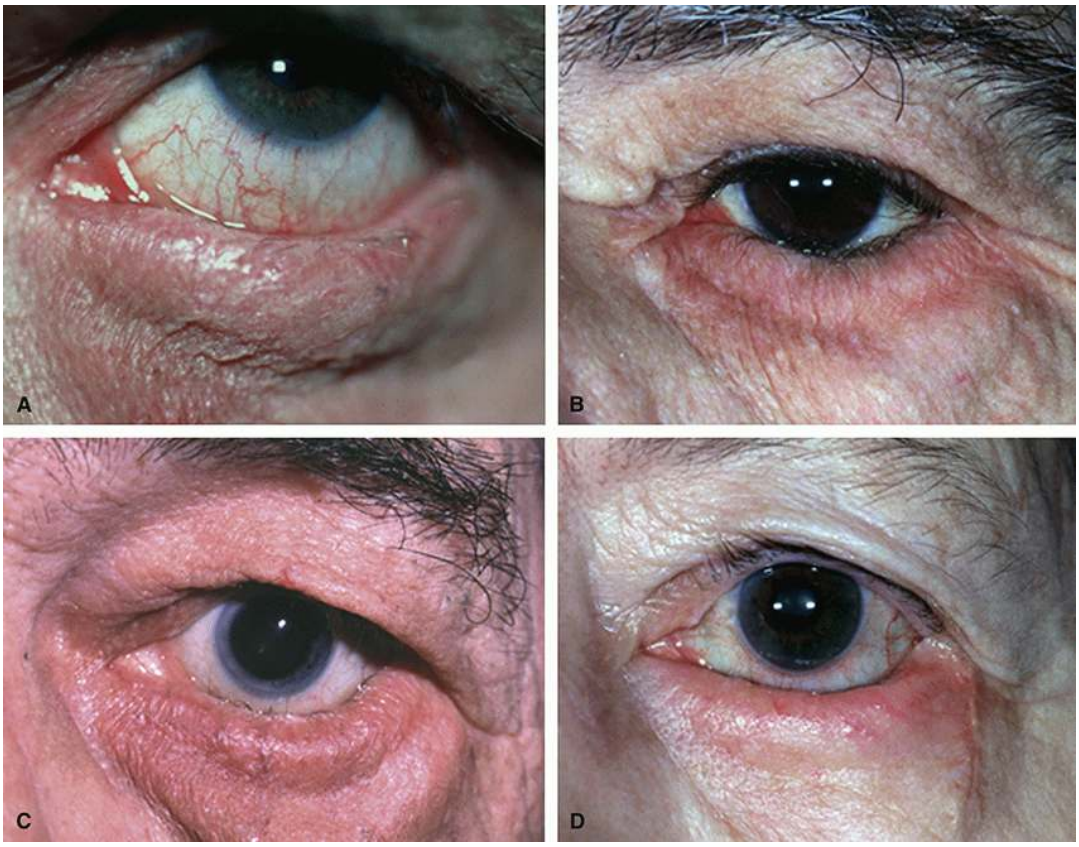

FIGURE 20.1 Spectrum of involvement of the lower eyelid in involutional entropion. A, Mild entropion with eyelashes anterior to the corneal surface. B, Moderate entropion where the eyelashes approach the globe with intermittent corneal touch. C, Advanced involutional entropion with most of the eyelashes directed toward the ocular surface. D, Severe involutional entropion with inversion of the tarsal plate and the entire mucocutaneous border of the eyelid, together with the eyelashes, is directed against the globe. A prominent preseptal orbicularis oculi muscle completely overrides its pretarsal counterpart.

Differential Diagnosis

Differentiating involutional lower eyelid entropion from the cicatricial type may be challenging, particularly in cases where entropion is recurrent. A cicatricial element may have been introduced due to fibrosis and scarring in the posterior lamella from the previous surgery.[21,22] To exclude cicatrization, the eyelid must be assessed carefully, and in that regard, the "snap back test" may be useful.[23] To perform this test, the lower eyelid should gently be pulled away from the globe. Upon release, the eyelid should promptly, albeit transiently, return to its normal anatomical position with a temporary resolution of entropion.[23] If the entropion persists, then a cicatricial element should be suspected. Another important sign to exclude a cicatricial element is to ask the patient to look downward. In a patient with involutional entropion, the lower eyelid would invert rather than retract. However, if the lower eyelid does not invert but retracts instead, then the diagnosis is probably cicatricial rather than involutional entropion.[6]

Treatment

Involutional entropion is a surgical condition. As early as 1972, Lester Jones estimated that more than 80 different papers had already been published on the subject,[6] and at the time of writing of this chapter, a quick Medline search elicited close to 200

results. Classical thinking might suggest that such a large number of published papers on a single *(Print pagebreak 141)* etiology that describe different surgical techniques might reflect the high recurrence rate or futility of previous surgical approaches that encourage surgeons to innovate. However, the situation with involutional entropion is rather different, and standard techniques that have been tried and tested for decades could easily reduce the recurrence rate to zero.

In earlier stages of the disease, where entropion is still intermittent, the condition may unknowingly be self-corrected by the patient simply by wiping the eyelid, which usually repositions the tissues, temporarily eliminating the symptoms.[3] Unfortunately, entropion almost always recurs. Various nonsurgical options such as eyelid taping, ocular lubrication, contact lens placement, or botulinum toxin injections have been used to alleviate symptoms while waiting for definitive surgical treatment, or even as a wholesale alternative to surgery.[23,24] Unfortunately, ocular lubrication and mechanical taping do not permanently address the anatomical basis of the condition. Patients may be unable to place the tape properly. Corneal ulceration can develop in more than half of these patients[24] despite, or even because of, wrong application of the tape, and the tape itself may mechanically abrade the cornea causing marginal ulceration.[24] Even if the tape is properly applied, it is unsightly, and chronic use could result in skin excoriation. Botulinum toxin might provide a temporary paralysis of the overriding preseptal orbicularis oculi muscle without compromising the cornea or disfiguring the patient. But then again, this option is only temporarily effective.[20] Therefore, the best long-term results are achieved with surgery.[2,18]

Minimally invasive procedures in the form of simple everting sutures alone are still advertised as a simple and effective remedy for the management of involutional entropion,[3] despite the reported rate of recurrence in more than 20% of patients.[18,25] For them to induce effective tightening of the lower lid retractors, the sutures must be placed obliquely through the full-thickness eyelid from a lower position in the fornix through the skin at a higher level closer to the eyelashes. This will prevent the preseptal orbicularis muscle from overriding the pretarsal portion.[23] This procedure was advocated for many decades,[25] but with the sharp increase in life expectancy, this semi-invasive but often temporary procedure might be argued not to have a place in modern ophthalmic practice. Exceptions might be patients who cannot be temporarily taken off their anticoagulant medications or terminally ill patients with a life expectancy of fewer than 6 months, which is the expected average period where everting sutures will probably remain effective,[23] or bed-ridden patients who cannot undertake more invasive surgery. Recently, another minimally invasive procedure was proposed whereby two mini-conjunctival incisions were used for reattachment of the lower eyelid retractors, and two mini-skin incisions were used for correcting the orbicularis oculi override.[26]

The definitive management of involutional entropion should address both the horizontal and vertical elements, and in that regard, the ideal surgical procedure should combine both horizontal eyelid shortening in the form of a lateral tarsal strip procedure, combined with plication or reinsertion of the lower eyelid retractors to address both elements, respectively.[5,21] However, the ideal operation should not only be effective and aesthetically acceptable, but it should also be simple and reproducible, especially for disorders like involutional entropion that are not uncommonly encountered in general ophthalmic practice.[2] The combination of a lateral tarsal strip and everting sutures may fulfill all criteria as the ideal procedure for involutional entropion. Horizontal shortening addresses horizontal laxity, while everting sutures address the vertical element through tightening of the retractors and indirect fixation or stabilization of the orbicularis muscle. Merging a lateral tarsal strip with everting sutures does not make this more challenging surgery, but in fact, the technique is simple enough to be performed by the general ophthalmologist.[2] When a lateral tarsal strip is combined with everting sutures, both procedures are put to better use and the failure or recurrence rate drops from 20% for either procedure alone to a range of 0% to 2% when both techniques are combined. It appears that neither procedure is efficacious on its own.[2,18,19]

Other recommended procedures in the literature include the Wies and the Quickert procedures, which may be better suited if there is a cicatricial element. Because these techniques involve a horizontal full-thickness eyelid incision, but this may be overkill if either procedure is performed in involutional entropion. Other techniques have been proposed in an attempt to prevent the orbicularis muscle from riding upward. These include cauterization, fixation, or extirpation of the muscle,[27,28,29,30] but they often do not address the primary pathology (horizontal and vertical eyelid laxity), but only deal with the secondary manifestation of the disease. Therefore, they should not be performed in isolation; otherwise, they may be fraught with failure.[22]

More technically involved procedures include combining horizontal eyelid shortening with reinsertion of the lower eyelid retractors to the lower border of the tarsus through a transconjunctival or a transcutaneous approach.[1,5,23,31,32] This is based on the concept that surgery for involutional entropion should address each etiologic anatomical factor.[22] While this technique may technically be more challenging for the noneyelid surgical specialist who may not be familiar with eyelid anatomy, it is the most anatomically appropriate operation. As with any procedure, potential complications may be seen including overcorrection or even cicatricial ectropion when the procedure is performed through the cutaneous route, or recurrence or cicatricial entropion with the transconjunctival approach.[21,22] For the noneyelid specialist, however, simpler effective alternatives exist with minimal complications.[21]

Prognosis

The prognosis for repositioning the eyelid using any of the available surgical techniques is generally excellent.

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Histopathology

Full-thickness eyelid specimens from patients with involutional entropion exhibit tarsal plate collagen fragmentation, increased adipose tissue in the distal tarsus, and tarsal conjunctival inflammation and epidermalization.[33] The histological changes in involutional entropion are similar to those of involutional ectropion but less severe.[33]

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(Print pagebreak 143)

CHAPTER 21

Epiblepharon

Key Points

- Epiblepharon is a developmental anomaly characterized by the presence of a redundant pretarsal skin fold that may extend over the lower eyelid margin
- Acquired epiblepharon can be seen in association with thyroid eye disease, following eyelid trauma, or lower eyelid surgery
- The eyelashes can be inverted toward the cornea and conjunctiva causing irritation, especially in downgaze
- The abnormal skin fold results from absence of the lower eyelid skin crease due to loss of attachment of the eyelid retractors to the skin and tarsus
- Epiblepharon has a strong predilection in East Asian populations
- Most patients will spontaneously improve by several years of age and do not require intervention
- In symptomatic cases or where the condition persists, surgical management consists of excision of skin and fixation of orbicularis and skin to the eyelid retractors and tarsus to reform the eyelid crease
- The prognosis is excellent for spontaneous resolution in most cases or with surgery in older children

Epiblepharon is a developmental anomaly characterized by the presence of a redundant pretarsal skin fold that may extend over the lower eyelid margin and invert the eyelashes causing corneal and conjunctival irritation.[1] Although most cases resolve with facial growth, some cases do not improve and may result in serious corneal morbidity.

Etiology and Pathogenesis

Over the years, several pathogenetic mechanisms have been proposed to explain the clinical manifestations of epiblepharon. The traditional view that epiblepharon simply occurs due to a “mechanical” push of the lashes against the cornea by a horizontal fold of extra skin[2,3] has been questioned,[4,5] and this challenge has recently been renewed.[6] An alternative hypothesis suggests that the excess skin fold merely has a minor secondary etiopathogenic role and that the real culprit lies in the loss of attachment of the anterior layer of the lower eyelid retractors to the skin and tarsus.[4,5,6] It has recently been confirmed that the lower lid retractors are composed of a definite double layer and not just one layer as was previously thought.[7] The anterior layer emerges from the Lockwood ligament, fuses with the orbital septum, and terminates on the anterior surface of the tarsus, subcutaneous tissue, and skin up to the lid margin. Normally, this anterior insertion holds the pretarsal orbicularis and skin firmly against the tarsal plate, subsequently keeping the eyelashes in check in their normal horizontal position.[5] Therefore, the loss of this anterior insertion not only loosens the attachment of the skin and the pretarsal orbicularis to the tarsus but more importantly it causes the eyelashes to assume a vertical orientation. The unchecked fold of skin and orbicularis further enhances epiblepharon by pushing the cilia more toward the globe. Although the presumed role of orbicularis muscle hypertrophy in epiblepharon pathogenesis has been dismissed recently,[6] it is interesting to point out that epiblepharon is reduced by muscle relaxants that are used when the child is under general anesthesia,[8] which argues against total dismissal of an aggravating role of the orbicularis muscle.

Clinical Presentation

Epiblepharon, a disease with a strong East Asian predilection,[3,9,10,11] is characterized by the presence of a horizontal fold of skin of variable length that lies parallel to and partially overrides the lower eyelid margin (Figure 21.1). The eyelashes are either vertically oriented or inverted causing ciliocorneal touch, and frequently the latter is seen only in or more accentuated in downgaze (Figure 21.2). In its most typical form, this horizontal fold of skin usually assumes a tentlike appearance limited to the medial one-

third of the eyelid with a downward and lateral slant.[10] The more extensive the skin fold, the more the lower eyelid margin is concealed by the fold.[12] Epiblepharon is also associated with a faint or obliterated lower eyelid crease.

A classification system for epiblepharon based on the severity of keratopathy due to ciliocorneal touch where keratopathy is classified into four grades starting with grade 0, which shows no keratopathy, up to grade 3, where more than one-third of the cornea is involved, has been proposed.[1] However, it requires a slit lamp examination, which may not always be possible in younger children. An alternative classification system was designed to aid in clinical judgment and to lay the groundwork for proper management was proposed based on the horizontal extent of the skin fold and the degree of concealment of the lid margin.[1] In class I, the skin fold is *(Print pagebreak 144)* below the lower eyelid margin. In class II, the fold is at the level of the lower eyelid margin without concealing it. Class III is defined as the fold being above the level of the lower eyelid margin but concealing <one-third of the lid margin medially. The most severe case is class IV where the fold is above the level of the lower lid margin and conceals >one-third of the eyelid margin (Figure 21.3). We believe this classification system based on skin fold height is more clinically relevant and reportedly correlates well with the severity of ciliocorneal touch.[1] However, occasionally patients will be observed where the degree of ciliocorneal touch outweighs the skin fold grading.

FIGURE 21.1 Congenital epiblepharon with the absence of the lid crease and a fold of skin overriding the eyelid margin.

Infants and young children may not express their symptoms well, and even in older children or adults, epiblepharon may be completely asymptomatic.[9] In patients where there is significant ciliocorneal touch, photophobia, eye rubbing, and squeezing of the eyelids are frequent presenting symptoms. A more common, almost universal symptom is epiphora,[9] but it is important not to overlook congenital nasolacrimal duct obstruction as a possible cause for tearing.[13] Other less common symptoms only reported by older children include ocular pain and blurred vision.[9]

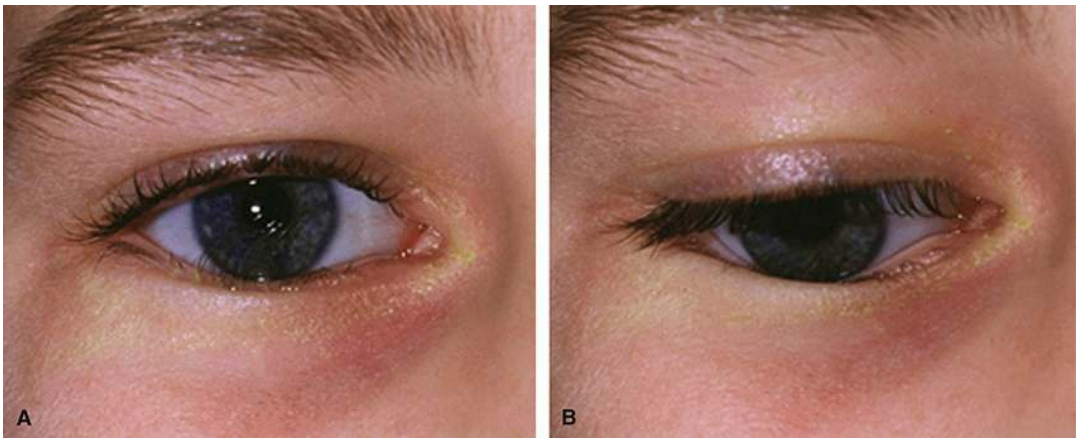

FIGURE 21.2 A and B, Epiblepharon in an older child with accentuated eyelid margin inturning during downgaze.

The natural history of epiblepharon is that most patients will spontaneously improve to the extent that by the time they reach high school, only 2% of children with untreated epiblepharon still have the condition,[14] but it cannot be directly inferred from the literature the exact percentage of patients who will ultimately require surgery. Indirect evidence could be deduced from age-matched prevalence studies. A landmark study conducted on Japanese children between the ages of 1 and 18 years showed a progressive decline with advancing age (24% at 1 year, 20% at 2 years, 7% at the age of 5-6 years, and 2% at 13-18 years).[9]

An unusual finding in patients with epiblepharon is the high incidence of clinically significant astigmatism, which affects between 44% and 52% of patients. It is usually in the form of with-the-rule astigmatism typically over 1.0 D and may even end up with astigmatic amblyopia.[10,15,16,17] The cause is unknown, but the most plausible explanation is that the change in corneal curvature is induced by a mechanical force created by the skin fold.[17] An alternative hypothesis is that astigmatism is due to pressure on the cornea from chronic squeezing and compulsive rubbing of the eyelids, both being natural sequelae of chronic ocular irritation, a situation not unlike the induction of keratoconus by frequent eye rubbing.[17] Another unusual association is the link to obesity where older children (6-15 years) with a higher body mass index have a higher incidence of symptomatic epiblepharon.[18,19] One study found a female predilection,[19] while another study did not find any sex predilection.[18] The cause is unknown.

Although epiblepharon is predominantly a developmental disease, an acquired form of secondary epiblepharon can be seen in association with thyroid eye disease, following eyelid trauma, or complicating lower eyelid surgical procedures where the eyelid crease is disrupted and is *(Print pagebreak 145)* not adequately reformed with fixation sutures.[20,21] Another unusual cause is mechanical epiblepharon caused by depression of the lower eyelid retractors from an oversized ocular prosthesis (Figure 21.4).

FIGURE 21.3 I-IV, Morphological classification of the lower lid epiblepharon according to the height of the lower lid skin fold. **Class I**. The fold is below the lower eyelid margin. **Class II**. The fold is at the level of the lower eyelid margin without concealing it. **Class III**. The fold is above the level of the lower lid margin but conceals <one-third of the lid margin medially. **Class IV**. The fold is above the level of the lower lid margin and conceals >one-third of the lid margin.

Differential Diagnosis

The most important differential diagnosis of epiblepharon is congenital entropion. True congenital entropion is quite rare. For a diagnosis of congenital ectropion to be truly made, it is imperative that the tarsal platform itself is inturned and not just the lashes. Once the posterior half of the eyelid margin rolls against the globe, epiblepharon is excluded.[4,5] Another defining feature of true congenital entropion is that contrary to epiblepharon, it does not improve with time.[22] Not all authors agree wholesale on this strict classification into either congenital entropion or epiblepharon, and the coexistence of both conditions in the same eyelid has been reported.[3,23] As was elegantly summarized by Jordan long before the dual nature of the lower eyelid retractors had been confirmed, if the anterior layer of the lower lid retractors is deficient, epiblepharon will occur, but if the posterior layer is disinserted, congenital entropion will ensue.[23]

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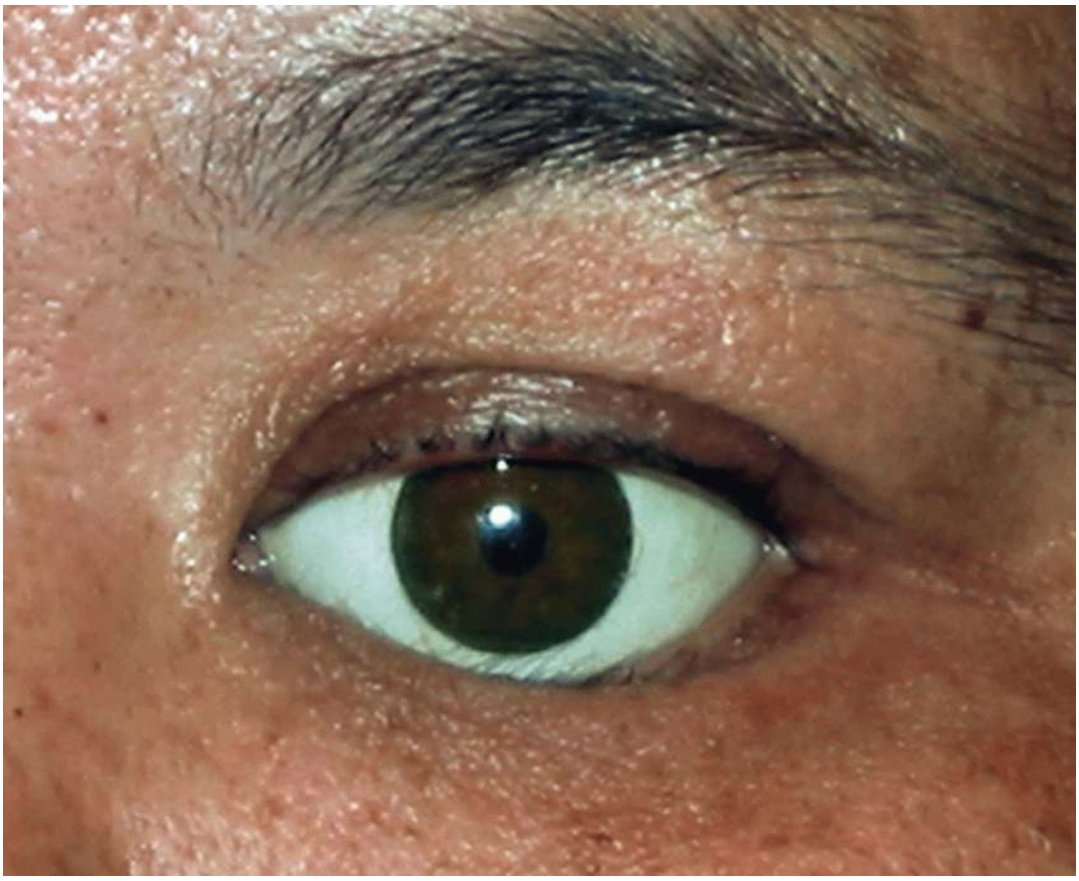

FIGURE 21.4 Acquired secondary epiblepharon from an oversized ocular prosthesis.

There is some confusion in the literature about the occurrence of epiblepharon in the upper eyelid.[22] It is important to realize that epicanthus tarsalis is the upper eyelid counterpart of epiblepharon and is a normal asymptomatic finding in Asians.[22,24] An exaggerated symptomatic form of epicanthus tarsalis may occur and in such cases may be termed epiblepharon of the upper eyelid.[22,24]

Treatment

Because most patients with epiblepharon will improve spontaneously and do not require surgery, epiblepharon is not generally regarded as a surgical emergency. A trial of topical antibiotic ointment or ocular lubricants should be tried at least initially in all patients,[13] although we have observed on more than one occasion significant corneal scarring when adopting this laissez-faire approach. When exactly to operate or how frequently surgery is required is not very clear in the literature. A recent study that recommended conservative treatment for all patients including patients with keratopathy and followed up patients up to 7 years (mean, 12.4 months) reported complete resolution of symptoms and signs in 94% of patients. A more logical approach would be to operate without delay on children with class IV epiblepharon, as well as in symptomatic children who fail to improve.[10] It should be borne in mind that significant astigmatism is another overlooked indication for surgery because if left untreated, astigmatic amblyopia will ensue.[17] Substantial astigmatic reduction was demonstrated after the surgical correction of epiblepharon.[17,25] Patients exhibiting higher baseline astigmatism are the ones who show the greatest astigmatic reduction after epiblepharon surgery.[17]

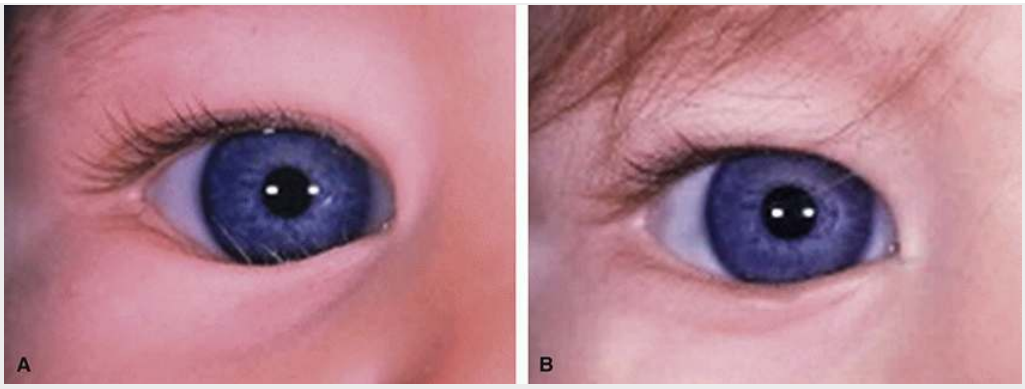

FIGURE 21.5 A, A young child with epiblepharon and an inturned eyelid margin. B, The eyelid margin is repositioned into a normal orientation following crease reformation with full-thickness Quickert-Rathbun sutures.

It is also imperative to remember that if these children present with epiphora alone, congenital nasolacrimal duct obstruction should be ruled out first before jumping to surgical repair of epiblepharon, otherwise epiphora will persist after surgery. In a recent retrospective study that included 89 children with epiblepharon ranging from the age of 2 months to 14 years, 5 patients required probing for the management of congenital nasolacrimal duct obstruction, 1 of whom was operated concomitantly for epiblepharon as well.[13]

Despite the high incidence of spontaneous resolution, in some young children, corneal touch by eyelashes may be symptomatic and present a significant clinical problem. Such cases can be managed with full-thickness Quickert-Rathbun sutures to reform the eyelid crease by forming an internal scar (Figure 21.5). Although such sutures may not result in a permanent solution, they tend to provide sufficient correction of eyelid position until the child outgrows the epiblepharon.

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For older symptomatic children where the condition has not resolved, the most commonly practiced surgical procedure is a modification of a technique that is almost 140 years old and involves excision of skin and orbicularis with tarsal fixation.[10,26,27,28,29] This modified Hotz procedure or Hotz-Celsus procedure includes an infralash skin incision, removal of a strip of orbicularis oculi muscle with or without excising skin (Figure 21.6). 6-0 polyglactin sutures are passed through the upper and lower edges of the skin, essentially incorporating the tarsus in between.[26] Some authors forego skin excision, but it is still practiced by most surgeons to a variable degree, although excessive skin excision may result in frank ectropion.[26,29,30] A graded approach to skin excision based on the original height of the skin fold has been recommended.[12] Although undercorrections and overcorrections are frequently reported with the modified Hotz procedure,[10,31] the main complication is medial undercorrection[30] (Figure 21.7). To avoid medial undercorrections, Ni and associates[30] recommend combining the modified Hotz procedure with a modified Z-plasty, which translocates horizontal redundant skin to the medial canthus. However, the verdict is still out if combining both techniques would truly reduce undercorrections or would result in unnecessary scarring without improving the success rate.[10]

An alternative surgical approach that anatomically addresses the alleged role of lower eyelid retractors in the pathogenesis of epiblepharon has been suggested by several authors.[10,23,26,32] These techniques aim to reattach the anterior layer of the lower lid retractors to the skin and tarsus with 6-0 polyglactin sutures. Despite its high success rate, this technique is not recommended in Asians because a well-formed crease is a natural by-product of the procedure.[10] According to the extensive Asian literature on epiblepharon, this is not a desirable outcome in Asians.

Nonincisional correction of epiblepharon is not new and the technique was described decades ago with the premise of correcting the basic anatomic defect of retractor disinsertion.[4,5] Full-thickness everting sutures typically using fast-absorbing 4-0 chromic gut were placed from the conjunctival side at the inferior border of the tarsus to exit the skin of the eyelid at the same horizontal plane. The technique was not very popular because previous authors either used fast-absorbing sutures or nonabsorbable sutures that were removed after 1 week and broadly applied their suture techniques in all classes of epiblepharon regardless of severity; therefore, they obtained lackluster results.[33] These nonincisional techniques have enjoyed a recent comeback with excellent reported success rates.[33,34] But the more favorable outcome could be attributed to the fact that those more recent articles judiciously narrowed down the inclusion criteria, restricting the use of everting sutures to milder cases where it was performed as an office procedure under local anesthesia, or as an ancillary procedure if the child was to be operated upon under general anesthesia for another indication like ptosis or strabismus.[33,34] Also, 6-0 polyglactin sutures were used instead of chromic sutures, which would take a significantly longer time to degrade, thus creating more scarring. Nonsurgical alternatives including the use of hyaluronic acid fillers or botulinum toxin are only of a temporary nature if parents refuse surgery.[10]

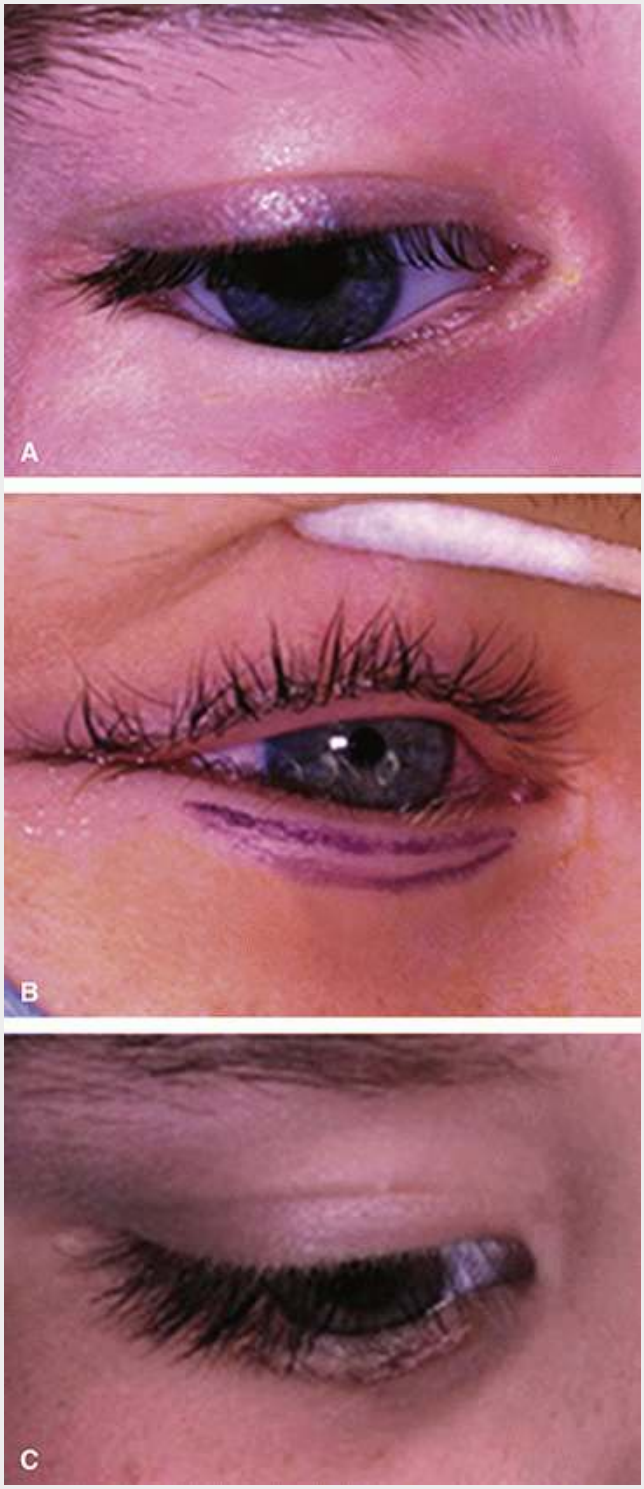

FIGURE 21.6 A-C, Surgical excision of a strip of skin and orbicularis muscle for correction of epiblepharon in an older child.

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FIGURE 21.7 Recurrence of epiblepharon restricted to the medial side of the eyelid as a complication of the modified Hotz procedure.

Prognosis

With appropriate surgery, the prognosis for reducing the folds is generally excellent.

Histopathology

Epiblepharon is a developmental anomaly and there are no histopathology sections relevant to this condition to our knowledge.

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CHAPTER 22

Eyelid Retraction

Key Points

- Eyelid retraction is an upper eyelid that is higher than normal or a lower eyelid that is lower than normal with respect to the corneal limbus
- Eyelid retraction can be classified as neurogenic, myogenic, mechanistic, and miscellaneous in etiology
- Myogenic etiologies are the most common causes, seen most frequently with thyroid eye disease (TED)
- The etiology of eyelid retraction is multifactorial, related to eyelid fibrosis, Hering law-induced pseudoretraction from asymmetric ptosis, or in cases of TED caused by sympathetic or levator muscle overaction, or globe proptosis
- In upper eyelid retraction, the eyelid margin is elevated above the superior corneal limbus, often associated with an incomplete blink, lagophthalmos, and corneal exposure
- Nonsurgical treatment includes injections of hydroxyapatite gel to lengthen the retractors, botulinum toxin to weaken the levator muscle, or steroids to reduce the inflammation associated with TED
- Surgical treatment includes lengthening of the levator aponeurosis or full-thickness blepharotomy
- The prognosis for patients with eyelid retraction is generally excellent following surgical or nonsurgical treatment

Eyelid position measured with respect to the cornea is influenced by age, involutional changes affecting eyelid anatomy, and other factors. In adults, the normal upper eyelid margin crosses the cornea approximately 2 mm below the superior limbus when the eye is in primary gaze. The lower eyelid margin is usually situated at the level of the inferior corneal limbus at the 6-o'clock position. The normal adult palpebral fissure is typically 8 to 10 mm in vertical height at the level of the midpupil.[1,2,3,4,5,6,7,8,9,10,11] Usually, there is no visible sclera between the eyelid margins and the upper and lower cornea limbus; however, lower eyelid retraction may be a normal anatomic variant.[9]

Eyelid retraction is defined as an upper eyelid that is higher than normal or a lower eyelid that is lower than normal with sclera showing between the corneal limbus and the eyelid margins. A classification scheme proposed by Bartley[1] separates eyelid retraction into neurogenic, myogenic, mechanistic, and miscellaneous etiologies.

Neurogenic eyelid retraction is usually acquired and can be present as a congenital condition. Premature infants sometimes have a transient downward conjugate gaze associated with upper eyelid retraction.[2] Other neurogenic causes of eyelid retraction include dorsal midbrain syndrome as well as pseudoretraction associated with contralateral ptosis resulting from the Hering law.[3]

Mechanical causes of upper eyelid retraction can be related to globe protuberance. Prominence of the globe can occur from high myopia, buphthalmos, and proptosis from orbital pathology. Mechanical causes also include scarring of the lids from previous surgery, tumors involving the eyelid retractors, eyelid burns, and other causes of anterior lamella contraction.

Lower eyelid retraction can be seen with hypertropia or prominence of the globe. Another cause of lower eyelid retraction is laxity of the lower eyelid from the involution of anatomical structures combined with gravitational effects. Contraction of lower eyelid skin from burns, tumors, or chronic skin disorders can also affect lower eyelid position. Recession of the inferior rectus muscle for vertical strabismus may also cause lower lid retraction because of the anatomic relationship between the inferior rectus and inferior oblique muscles and the lower eyelid capsulopalpebral fascia (retractor). Lower eyelid blepharoplasty with excessive excision of skin is also a common cause of retraction and inferior scleral show.[9]

Myogenic etiologies are the most common causes of eyelid retraction, and transient retraction can be seen with myasthenia gravis.[4] Congenital fibrosis of the eyelid muscles can also cause eyelid retraction.[5] Upper eyelid retraction is the most frequent eye finding in patients with Graves disease, seen in up to 90% of these patients.[6] Thyroid eye disease (TED) is one of the most common

autoimmune inflammatory disorders involving the eyelids and orbit. It is also known in the literature as thyroid-associated ophthalmopathy, Graves ophthalmopathy, or thyroid orbitopathy. Most commonly, TED occurs in association with Graves disease or Hashimoto thyroiditis, but can also occur in primary hyperthyroidism and euthyroid patients. The pathological changes of TED affect periorbital and orbital connective tissue, extraocular muscles, and orbital fat, resulting in symptoms ranging from mild ocular irritation to severe proptosis, motility restriction, and eyelid retraction. Visual loss from corneal exposure or compressive optic neuropathy can be seen in 3% to 5% of patients.[7] TED occurs in 25% to 50% of patients with *(Print pagebreak 150)* Graves disease and about a third of patients with Hashimoto thyroiditis.[8] Approximately 90% of TED cases are associated with hyperthyroidism, 5% with hypothyroidism, and about 5% in patients who are euthyroid.[6] Eyelid and orbital involvement is usually bilateral, but is often asymmetric, so much so that one side may clinically appear nearly normal.

Lower eyelid retraction is of equal or even greater concern than retraction of the upper eyelid since it is more frequently associated with lagophthalmos, exposure keratitis, tearing, and photophobia. Symptoms include ocular discomfort, decreased vision, and poor cosmesis.

Etiology and Pathogenesis

Eyelid retraction is the most common eyelid manifestation of TED. This is important not only because of its aesthetic implications for the patient but also because of its relation to corneal exposure and its potential for causing visual loss.[6,7,8,10,11] Several theories have been proposed to explain the etiology of eyelid retraction, although none have been universally accepted. The first is a mechanical factor resulting from globe proptosis, affecting how the eyelid drapes over the corneal surface. In an evaluation of 166 TED eyes by Rajabi et al,[10] a significant correlation was found between proptosis and the degree of upper eyelid retraction. These authors concluded that the mechanical draping of the eyelid over a proptotic globe was likely the principal cause of upper eyelid retraction. Although proptosis might play a role in some patients, other authors have considered this to be a very minor factor.[11]

Another proposal for the occurrence of upper eyelid retraction involves the Müller smooth muscles in the upper and lower eyelids, which are innervated by sympathetic nerve fibers.[12] In 1939, Pochin[13] first proposed sympathetic overaction as a contributing factor to eyelid retraction. Supporting this concept is the notion that many of the clinical symptoms seen in hyperthyroidism, such as palpitations, tachycardia, tremor, sweating, and heat intolerance, are related to hyperadrenergic activity,[14] and the observation that β-adrenergic blockade is known to modify these symptoms in Graves patients.[15] Nevertheless, although sympathetic overactivity has been reported in the intraocular muscles of hyperthyroid patients,[16] there is no difference in this activity between patients with or without eyelid retraction. It, therefore, appears that sympathetic overactivity may not be a major factor, although it might be contributing along with other factors. In this regard, Esmaeli-Gutstein et al[17] reported that the eyelid retractors show different distributions of adrenergic receptor subtypes with α2 receptors predominating in Müller muscle and β1 receptors in the levator palpebrae superioris. These authors proposed that these two muscles and their respective receptor profiles interacting together may play an important role in the control of eyelid position and that overstimulation may contribute to the development of TED-related eyelid retraction. Anatomically, Morton et al[18] demonstrated a lateral extension of Müller muscle fibers along the lateral horn of the levator aponeurosis between the lobes of the lacrimal gland. They proposed that this portion could contribute to the lateral flare or retraction frequently seen in TED patients. Other factors that might contribute to upper eyelid retraction are inflammation and fibrosis of Müller muscle, but the histologic data are inconsistent. While Cockerham et al[19] and Shih et al[20] found increased inflammation, fibrosis, and fat infiltration in the Müller muscles of inactive euthyroid TED patients, Lowinger et al[21] found no significant histologic difference in Müller muscle specimens from inactive TED patients compared with normal controls.

Overaction of the levator palpebrae superioris muscle has also been proposed to contribute to upper eyelid retraction. Small[22] and Ohnishi et al[23] reported imaging evidence of an enlarged levator palpebrae superioris muscle proximal to the Whitnall ligament in TED patients compared with controls. They proposed that upper eyelid retraction was likely the result of levator muscle hypertrophy. Wesley and Bond[24] also demonstrated levator enlargement and suggested that inferior rectus muscle restriction resulted in overaction of the superior rectus and levator muscles based on the Hering law. Fibrosis of the connective tissue system supporting the levator system and suspensory ligaments of the superior conjunctival fornix also may be at least partially responsible for upper eyelid retraction. It is not uncommon to find persistent retraction during recession surgery even when the levator aponeurosis and Müller muscle are completely detached up to the level of Whitnall ligament. Diminished levator excursion associated with increasing levels of lid lag and lagophthalmos supports this concept.[25] One final mechanism for eyelid retraction was suggested by Harrison and McLoon[26] who found a reduction of myofibers in the preseptal orbicularis muscle of hyperthyroid rabbits compared with controls. Orbicularis muscle tone weakening could allow relative overaction of the less opposed levator muscle.

Upper eyelid retraction has also been reported as a rare postsurgical sequel to enucleation surgery[27] and has been reported in 3.5% to 32% of anophthalmic sockets.[28] The cause is unclear, but it has been proposed to result from orbital volume deficiency with downward displacement of the superior rectus/levator muscle complex[29] or from an oversized ocular implant.[27]

Another rare mechanical cause of upper eyelid retraction is a large cystic glaucoma filtering bleb.[30,31] The pathogenesis of eyelid

retraction in patients with glaucoma filtering blebs remains unknown, but mechanical and chemical causes have been suggested. A mechanical mechanism seems unlikely since the eyelid resumes a retracted position after being pulled down over the bleb.[31] The chemical theory proposes Müller muscle overaction due to sympathetic overstimulation. Chronic conjunctival inflammation from a large diffuse bleb has also been suggested to cause Müller muscle fibrosis.[30]

Pseudoretraction of the upper eyelid is a common finding in patients with unilateral or bilateral but asymmetric ptosis where the uninvolved or lesser involved eyelid is retracted as a result of the Hering law of equal innervation.[32]

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Lower eyelid retraction in TED has been related to an increase of muscle tone in the inferior rectus muscle, which is commonly enlarged in TED patients. Fibrosis of the capsulopalpebral fascia could also retract the eyelid margin due to excessive tension on the lower eyelid tarsus. The relationship between lower eyelid retraction and proptosis was supported by several authors,[33] but supporting data are inconclusive.[34]

Associated with eyelid retraction, TED patients often have ocular surface changes related to an unstable tear film and manifestations of dry eyes. The etiology is not understood, and there are conflicting studies. Gürdal et al[35] demonstrated increased conjunctival squamous metaplasia associated with a decreased Schirmer tear test and increased tear breakup time in Graves patients compared with normal controls. They attributed the damage to ocular surface inflammation. However, Kikkawa[36] reported only a trend toward higher inflammation in TED patients, but this was not significant when compared with normal controls.

Clinical Presentation

In patients with eyelid retraction, the upper eyelid margin lies at or above the superior corneal limbus, and/or the lower eyelid margin lies below the inferior corneal limbus (Figure 22.1). In both cases, white sclera is typically seen between the cornea and the eyelid margins (called scleral show). The most common clinical symptoms are an excessively wide palpebral fissure with an unnatural rounded eye appearance, dry eye syndrome, excessive tearing, conjunctival erythema, a burning sensation, and blurred vision.

The most severe consequences of eyelid retraction result from corneal exposure due to an incomplete blink and lagophthalmos. In cases where eyelid retraction occurs with proptosis, globe subluxation can be a serious complication, where forward displacement of the globe from elevated orbital pressure occurs when the extraocular muscles cannot exert sufficient force to hold the globe in place.[37]

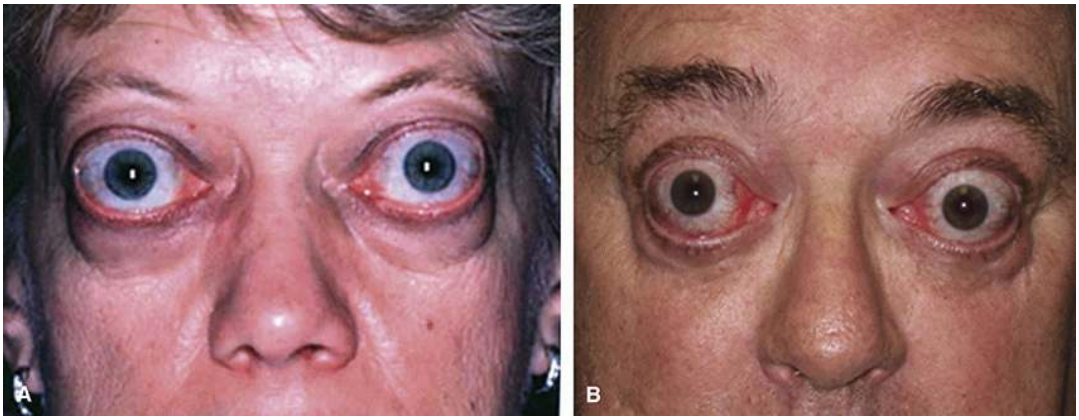

FIGURE 22.1 A and B, Eyelid retraction in thyroid eye disease with equal retraction of both the upper and lower eyelids.

In cases of eyelid retraction from TED, the clinical presentation is often variable. The eyelid and orbital manifestations may occur simultaneously with systemic Graves disease and hyperthyroidism, or it can occur before or after the onset of thyroid dysfunction.[38] Ophthalmic manifestations typically begin with an initial active inflammatory phase characterized by eyelid and conjunctival edema, erythema and chemosis, eyelid retraction, proptosis, and motility restriction, followed by a period of stabilization and finally an inactive chronic fibrotic phase. The active phase is said to have a mean duration of about 18 months but can persist for several years in some cases, and in rare instances, the chronic phase can be seen in the absence of any history of the active phase. In most cases of TED, eyelid retraction involves both the upper and lower eyelids, but in some cases, it can involve only the upper or lower eyelid (Figure 22.2).

In cases of traumatic eyelid retraction, including postoperative scarring, the elevated eyelid is usually associated with severe

lagophthalmos and corneal exposure (Figure 22.3).

Differential Diagnosis

A long list of conditions can cause eyelid retraction in addition to TED. In the upper eyelid, these can include cicatricial skin disorders such as ichthyosis and dermatoses,[39] tumors, trauma, previous eyelid surgery,[40] proptosis, and orbital fibrosis.[41] In the lower eyelid, retraction can be caused by cutaneous tumors, lower eyelid surgery,[42] trauma,[43] eyelid burn injuries,[44] or orbital floor fracture surgery.[41]

Treatment

Numerous surgical procedures have been proposed for the management of upper eyelid retraction.[45] In 1965, Henderson described disinsertion of the levator aponeurosis and Müller muscle.[46] Subsequent modifications and proposed novel techniques included Müller muscle recession or excision,[47] *(Print pagebreak 152)* anterior or posterior levator recession with or without adjustable sutures,[48] marginal myotomy,[49] and placement of natural or synthetic spacer grafts.[50] In 2003, Elner et al[51] reported results using a graded full-thickness anterior blepharotomy procedure first communicated, but not published, by Koornneef in 1999. In this procedure, an upper eyelid crease incision in the area of greatest eyelid retraction is made, followed by dissection through orbicularis oculi muscle, orbital septum, levator aponeurosis, Müller muscle, and conjunctiva just superior to the tarsal plate. The eyelid height and contour are observed in primary gaze, and the full-thickness incision is gradually extended nasally and temporally to achieve the desired margin-reflex distance (MRD1), contour, and symmetry with the contralateral eyelid.[51,52] Based on subsequent experience, it is now recommended that a central bridge of intact conjunctiva be left to prevent central flattening of the eyelid contour. When the appropriate eyelid position is achieved, only the skin is reapproximated, and the posterior *(Print pagebreak 153)* separation is left unrepaired. Using this technique, 93% of 50 retracted eyelids were improved or corrected. Postoperative complications included one patient each experiencing ptosis, wound dehiscence, full-thickness eyelid hole, and abnormal contour after suture removal. This technique addresses the diffuse, full-thickness alterations of the eyelid, including those of the skin and conjunctiva, which together result in the degree of upper eyelid retraction seen clinically.

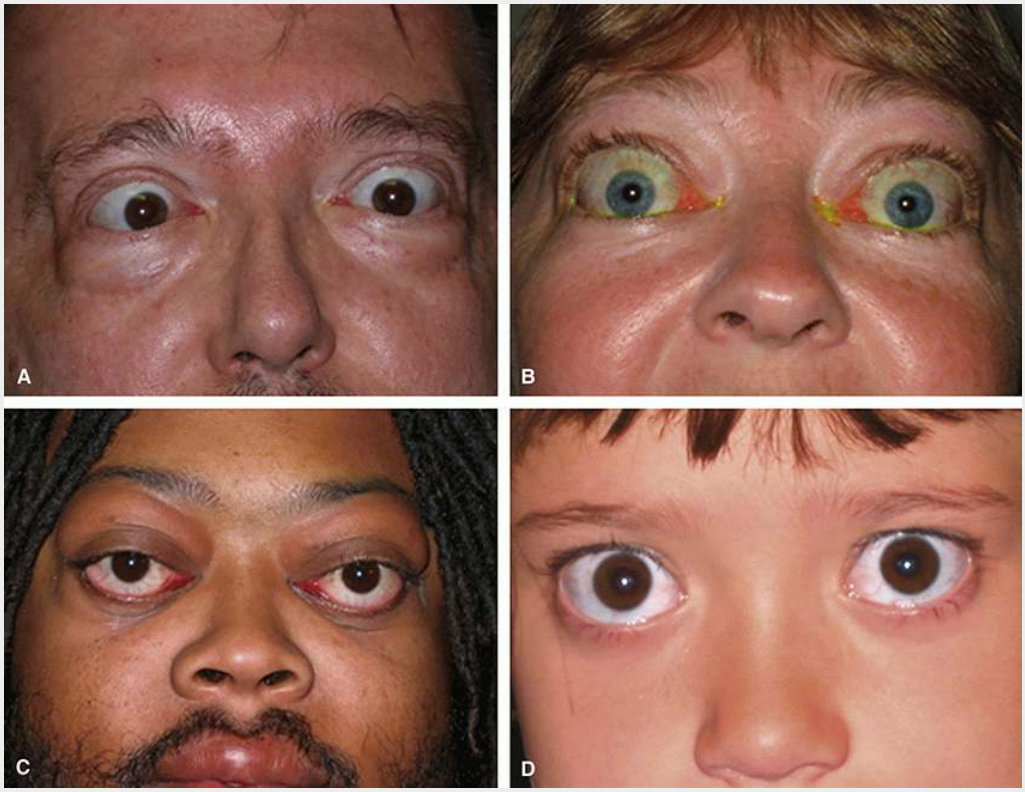

FIGURE 22.2 Variations in the pattern of eyelid retraction in thyroid eye disease. A and B, Upper eyelid retraction. C and D, Lower eyelid retraction.

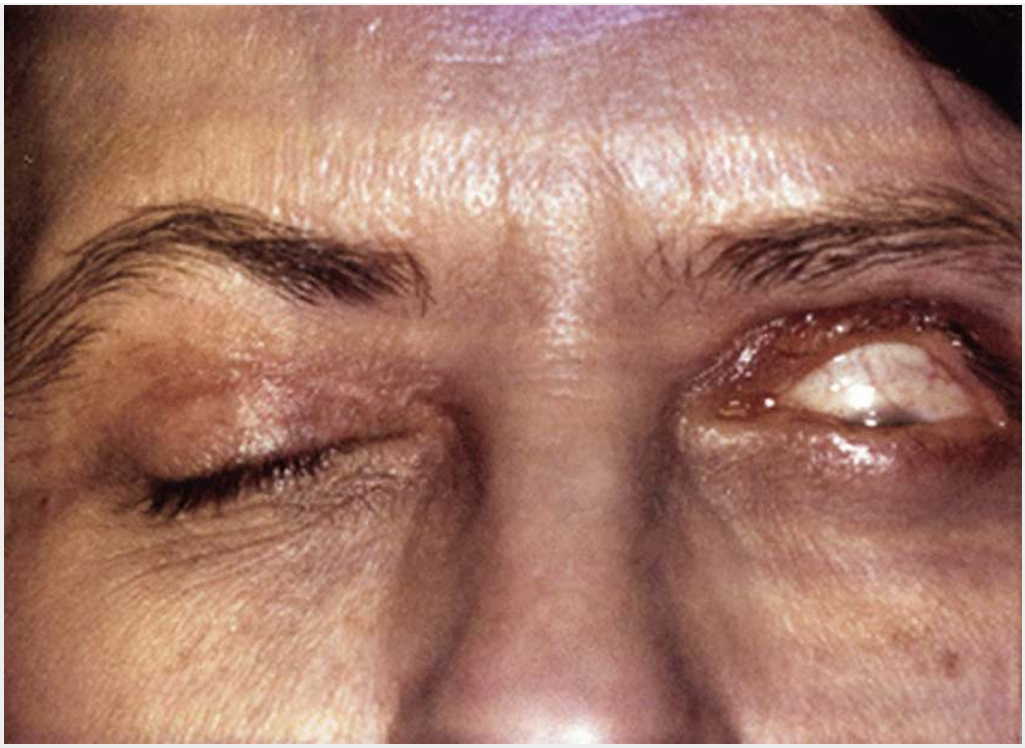

FIGURE 22.3 Left eyelid retraction in a patient with marked left upper eyelid aponeurosis from orbital septum fibrosis and contraction following multiple failed ptosis procedures.

Unlike the upper eyelid, the lower eyelid is affected by factors such as gravity and the position of the globe, both of which contribute to retraction and make management more challenging. Gravity can have a more significant effect when horizontal laxity is also present in the eyelid. In the lower eyelid, correction of the retraction is directed at repair of the underlying cause. In patients with postblepharoplasty lower eyelid retraction, scars are excised or revised, and a variety of approaches have been recommended to restore the normal anatomical position of the eyelid including horizontal eyelid tightening procedures in milder cases and/or a mid-facelift in more involved cases.[9]

In more advanced cases of postblepharoplasty lower eyelid retraction, or in patients with proptosis due to TED, lower eyelid tightening may in fact aggravate eyelid retraction.[9] Furthermore, the cicatricial elements are more commonly observed in the vertical plane.[9] In these patients, the lower eyelid should be lengthened either through an anterior or posterior approach. Numerous types of spacer grafts have been used to aid in the stability of the posterior lamella against the forces of gravity.[53] Autologous grafts include fascia lata,[54] auricular cartilage,[55] free tarsoconjunctival grafts,[56] hard palate mucosa,[57] and dermis.[58] Homologous grafts, such as eye bank sclera,[59] tarsus,[60] and acellular cadaveric dermis,[61] are acceptable alternatives and do not require additional surgery with resultant scaring on the patient. Synthetic alloplastic materials such as polyester mesh,[62] polytetrafluoroethylene,[63] and high-density porous polyethylene[64] have also been reported with good results. Additional skin for lengthening the lower eyelid can also be recruited from the cheek by elevating the midface soft tissue.[65] It has recently been suggested that in severe or recurrent cases of lower eyelid retraction when the retraction is associated with concomitant cicatricial ectropion, the condition can be successfully treated using a modified Hughes tarsoconjunctival flap with an overlying full-thickness skin graft.[66]

In addition to surgical treatment of eyelid retraction, a variety of nonsurgical methods have been proposed. Hydroxyapatite (HA) gel has been used for the treatment of upper eyelid retraction with immediate results after injection.[67,68] Transient complications including erythema, edema, and ecchymosis may occur. The injections can be delivered by either the transcutaneous or transconjunctival approaches to deposit the filler at the level of the eyelid retractors to lengthen them and to add weight to the upper eyelid. For the lower eyelid, injection of filler aims to lengthen the retractors and to provide support to elevate the lid and compress it against the inferior orbital rim. The volume of HA injected is titrated during the procedure for maximum effect and generally requires 0.2 to 0.5 mL. Upper eyelid injection can result in a reduction of the MRD1 of 0.5 to 1.0 mm and the result may persist for 12 months or more.[69] Ultrasound studies have shown that the filler is mostly localized in the preaponeurotic space.[70] In the lower eyelid, HA injection for retraction from various causes has shown improvement in scleral show, eyelid position, and ocular exposure symptoms.[71]

Botulinum toxin type A (BTA) acts on the motor end plates in the neuromuscular junction to prevent release of acetylcholine, resulting in a temporary muscle weakening or paralysis.[72] Common complications of injection include bruising, edema, and upper eyelid ptosis, and if toxin is injected into the orbit, weakening of extraocular muscles can cause diplopia.[73] While ptosis

is considered a complication of BTA when it is used for cosmetic purposes or facial movement disorders, it has been considered the desired result when used for treating upper eyelid retraction in TED patients, successfully reducing eyelid height, and improving ocular exposure symptoms.[74,75] Improvement in eyelid retraction following BTA injection has been reported in more than 90% of patients,[74] with a reduction in MRD1 of 3 to 4 mm lasting 3 to 4 months.[75]

Glucocorticoids are an important treatment option for patients with moderate to severe TED,[76] promoting a quick reduction in orbital inflammation and related symptoms. Steroids, either locally injected or administered intravenously, may also have a beneficial effect on eyelid retraction.[77] Following subconjunctival injections of triamcinolone, Chee and Chee[78] reported up to 2 mm reduction in MRD1 and improvement in lagophthalmos was reported over 6 to 12 months. A better response was obtained in patients in the active phase of the disease compared with those in the chronic phase. Similar findings were reported by Lee et al[79] where 86% of 22 patients in the active phase responded, compared with only 25% in the fibrotic phase. Xu et al[80] reported beneficial results in 21 patients with better results in patients having eyelid retraction for less than 6 months (83.3%) compared with those having symptoms for greater than 6 months (36.4%). All of these studies suggest that eyelid retraction is better treated with steroids in the active inflammatory stage of the disease, as would be expected. Complications of steroid injection into the eyelid include thinning of the superior rectus/levator muscle complex, elevation of intraocular pressure, and menstrual cycle disturbance.[79,80,81]

Prognosis

The prognosis for patients with eyelid retraction is generally excellent following surgical or nonsurgical treatment. Repositioning the eyelids to a more normal position will reduce the palpebral fissure, resultant lagophthalmos, improve corneal exposure and keratopathy, and enhance cosmetic appearance.

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Histopathology

There are no specific histopathology descriptions for eyelid retraction, except in cases where it might result from fibrosis or a scar.

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CHAPTER 23

Facial Nerve Paralysis

Key Points

- Facial nerve paralysis is a disfiguring facial weakness with various etiologies
- It is the most common cranial nerve palsy encountered in clinical practice
- The etiology is varied, and may be central or peripheral
- Central causes include stroke, brain tumor, or trauma
- Peripheral causes include infections, Bell palsy, Ramsay Hunt syndrome, or compression of the facial nerve by a tumor mass
- Facial nerve palsy can present with upper eyelid retraction, lower eyelid paralytic ectropion, adynamic brow ptosis, lagophthalmos, epiphora, and chronic exposure keratopathy
- In the majority of patients with Bell palsy, the condition resolves spontaneously without any intervention
- Synkinetic movements during voluntary expressions caused by aberrant regeneration of the facial nerve is a significant sequela seen in many patients
- Medical management is initially directed at protection of the globe with topical lubricants, botulinum toxin to induce ptosis, or the use of internal or external lid weights
- For cases persistent or residual facial paralysis, canthoplasty, tarsorrhaphy, or reanimation procedures can protect the eye or provide some improvement in facial motility
- For Bell palsy, the rate of spontaneous recovery is 70%, with most occurring within 3 weeks, and 15% after 3 to 5 months

Facial nerve paralysis (FNP) is an acute, disfiguring facial nerve weakness with various etiologies, which if idiopathic is termed Bell palsy, and is the commonest cranial nerve (CN) palsy encountered in clinical practice.[1,2,3,4,5,6,7,8,9,10,11,12,13] Although the management of patients with facial paralysis may be a multispecialty endeavor, it is the ophthalmologist who is probably the first clinician to encounter a patient with FNP. Some clinicians use the terms “Bell palsy” and “facial palsy” interchangeably,[13] and consequently a few patients may be erroneously presumed to have a Bell palsy although they may have a treatable lesion.[2] Aside from its clinical implications, patients with facial paralysis suffer a significant social torment, which may create difficulties in communication both at a personal and a professional level.[3,4]

Etiology and Pathogenesis

Before discussing the etiological causes of facial paralysis, some peculiar anatomical features of the facial nerve deserve at least a casual mention. Because of the unusual pattern of fiber crossing in the motor nucleus of the facial nerve, the upper half of the face which is supplied by the ventral portion of the motor nucleus receives innervation from both sides of the motor cortex, while the muscles of the lower half of the face are supplied by the dorsal portion of the nucleus, which is mainly controlled by fibers from the contralateral side of the brain. Therefore, an important clinical sign distinguishing a central from a peripheral etiology affecting the facial nerve is that a supranuclear or upper motor neuron lesion would present with weakness in the contralateral lower face associated with normal tone and movement of both sides of the forehead. However, a peripheral nuclear or infranuclear lower motor neuron lesion will result in an ipsilateral abnormal movement of the entire side of the face including the forehead.[6,14] The facial nerve also has the longest intraosseous route of any CN and is therefore particularly vulnerable to trauma or infections along its unusually long and tortuous course.[6,7,10,11]

A comprehensive assessment of all the etiological factors causing FNP is beyond the scope of this chapter as more than 100 different causes have been identified so far,[2] but briefly speaking, they can be categorized as central or peripheral causes.[6] Central causes include stroke, brain tumor, or trauma, while peripheral causes include congenital and hereditary causes, infections, Bell palsy, Ramsay Hunt syndrome, or compression of the facial nerve by a tumor mass.[6,10,13] By far, the commonest etiology is Bell palsy, which is responsible for 51% of cases of facial weakness, followed by facial nerve trauma (22%), and Ramsay Hunt syndrome (7%).[10] Because the classic textbook example of facial paralysis is Bell palsy, it will be the main focus of this chapter. Bell palsy is an acute peripheral facial mononeuropathy without a confirmed cause and is the most common cause associated with facial nerve weakness.[1,2,3,4,5,6,7,8,9,10] Although the evidence is piling up for a viral etiology that has long been suspected as the underlying cause, the exact mechanism of Bell palsy is currently unknown.[8,9] Many viruses including herpes simplex virus types 1 and 2 (HSV-1, 2), varicella zoster virus (VZV), adenovirus, influenza B virus, coxsackie virus, and Epstein-Barr virus have been linked to the development of Bell palsy, but it is believed that HSV-1 is the one that is responsible *(Print pagebreak 157)* for idiopathic facial palsy.[10] The proposed pathophysiology is that HSV-1 remains latent in the geniculate ganglia, and when it is reactivated, this causes inflammation, edema, and compression of CN V-VII as it exits the skull through the stylomastoid foramen.[8,11] While the evidence for a viral etiology in Bell palsy is anecdotal, herpes zoster virus is a confirmed viral agent responsible for FNP in Ramsay Hunt syndrome (herpes zoster oticus), which occurs due to reactivation of a latent herpes zoster virus in the geniculate ganglion.[10] Other infective agents include *Borrelia burgdorferi* (Lyme disease), and rarely Epstein-Barr virus, cytomegalovirus, leprosy, HIV, and polio.[10]

Although laceration injuries/blunt trauma to the craniofacial region close to the course of the facial nerve or direct trauma to the temporal bone may be implicated in several cases of facial weakness, the two most commonly encountered traumatic causes include trauma during delivery either due to forceps delivery or birth canal trauma.[7] Surgical trauma during removal of an acoustic neuroma is also the second most common cause of facial palsy because the facial nerve may be manipulated or occasionally sacrificed.[15] Even before surgery, 5% and 17% of acoustic neuroma patients show symptoms and signs of facial nerve weakness, respectively.[15] Other mass lesions that may cause facial weakness include meningiomas of the cerebellopontine angle, parotid tumors, facial nerve schwannomas, nasopharyngeal carcinomas, external meatus tumors, and even sarcoidosis.[10] Rarely, patients may present with congenital or hereditary facial paralysis. The list includes familial facial paralysis, Treacher Collins syndrome, Moebius syndrome, and Goldenhar syndrome.[10,16]

Several hypotheses have been put forward to try to explain the synkinetic movements that may accompany an incomplete recovery of the facial nerve, which will be discussed later in detail. The most accepted theory is that misdirected peripheral regeneration of the damaged facial nerve causes such aberrant movements.[17] After nerve injury, proximal axons regenerate, and then subsequently reroute or sprout to overinnervate an anatomically correct muscle or aberrantly innervate an incorrect one.[2,17] Other less plausible mechanisms include hyperexcitability of the facial nucleus or the possibility that neighboring axons may be stimulating each other.[2]

Clinical Presentation

Because the list of etiologies responsible for facial nerve palsy is long, an accurate estimate of its overall incidence is difficult.[10] It is estimated that between 7 and 50 patients per 100,000 person-years are affected annually by facial paralysis in different populations[4,5,10]; however, the incidence of idiopathic causes ranges between 13.1/100,000 and 20.2/100,000.[10] Children are less frequently affected with a gradual rise in incidence with increasing age, but with a higher incidence in females across all age strata.[4] In children younger than 10 years, the incidence is significantly lower (2.7 per 100,000 annually), compared to children older than 10 years, where the annual incidence is estimated to be 10.1 per 100,000.[4] The most common age at presentation is between 15 and 40 years,[10,12] but there is a disagreement regarding the sexual preponderance in FNP. While some authors failed to demonstrate a sex preference, other conflicting reports claimed more prevalence in either males or females.[5,10,12,13]

Detailed history taking and a thorough clinical examination are of paramount importance in patients with facial paralysis and may spare the patient unnecessary radiological or laboratory investigations.[8] Ideally, history taking should establish whether the onset was acute or chronic, unilateral or bilateral, and whether the lesion is proximal or distal.[10] Alarmed Bell palsy patients may complain that the onset of facial paralysis was sudden, and in such a scenario, the symptoms peak after 2 to 3 days.[10] Severe facial or postauricular pain, which typically precedes the onset of facial paralysis by 2 to 3 days or occurs at the day of onset, usually suggests Ramsay Hunt syndrome. This may or may not be associated with the typical vesicular rash.[10] Ramsay Hunt syndrome may also be associated with vestibuloauditory symptoms because of the proximity of the vestibulocochlear nerve (CN VIII) to the geniculate ganglion.[7] Patients may also present with a painful red eye, watering, or complain of cosmetic disfigurement.

The functional and debilitating effects of facial palsy are variable from mild to severe (Figure 23.1). This makes facial paralysis challenging to quantify, and up to the present day, the main obstacle to achieving evidence-based and reproducible management decisions is the subjective nature of assessment.[18] Therefore, numerous grading systems for FNP have been devised to establish standardization of facial functional assessment, improve the reporting of outcomes, and facilitate communication between professionals.[18] The most popular grading systems among clinicians are the House-Brackmann scale, the Sunnybrook grading

system, and the Facial Nerve Grading Scale 2.0 (FNGS 2.0).[18] The House-Brackmann grading scale, which was adopted by the American Academy of Otolaryngology in 1985, is widely used because of its relative ease and simplicity and subjectively classifies facial nerve function into six grades: ***grade I***, normal function; ***grade II***, mild dysfunction; ***grade III***, reduced forehead movement, noticeable synkinesis, and contracture; ***grade IV***, no forehead movement, incomplete eye closure, asymmetric mouth, and disfiguring asymmetry; ***grade V***, minimal movement; and ***grade VI***, no movement.[10,18,19,20] Other systems like the Sunnybrook grading system and the FNGS 2.0 incorporate synkinetic movements as one of their grading criteria or characteristics. Any of these grading systems would have been ideal if the sole purpose of such grading instruments was diagnostic, although preferably any grading system should also help in the management plan as well.[18]

Unfortunately, at least from an ophthalmological perspective, those grading systems would not aid in the management *(Print pagebreak 158)* plan because they mostly grade the whole face, as they were not designed by ophthalmologists; therefore, corneal assessment is usually neglected.[20] To adequately encompass the ocular sequelae of facial nerve dysfunction, the CADS grading system was recently proposed. It attempts to quantify the ophthalmic sequelae based on several parameters including **C**orneal involvement, static **A**symmetry in the periorbital region, **D**ynamic functioning of periorbital muscles, and **S**ynkinesis involving the orbital region.[21] In a separate study by the same group of authors, the CADS grading system reliability was rated from good to very good.[22] There are several perceived limitations with all these systems. None of the proposed generalized or arguably regional grading systems are truly quantitative, and instead, at best, they merely rely on or attempt to adopt some sort of subjective methodology.[18] The perfect facial nerve grading system should make use of current advances in digital photography to quantitate ocular and periocular defects, and to the best of our knowledge, this has not been designed yet.

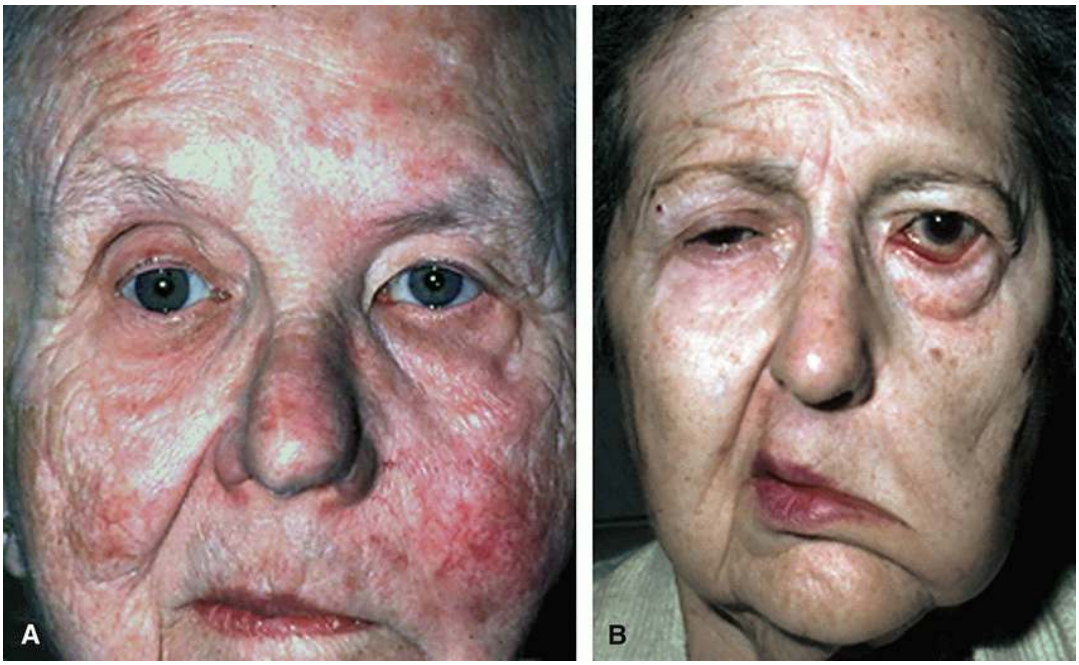

FIGURE 23.1 Degrees of facial paralysis. A, Mild paralysis (House-Brackmann grade II) with minimal weakness of facial muscles. B, Severe facial paralysis (House-Brackmann grade IV) with loss of all tone in facial muscles and disfiguring asymmetry. (Courtesy of Dr. Allen Putterman.)

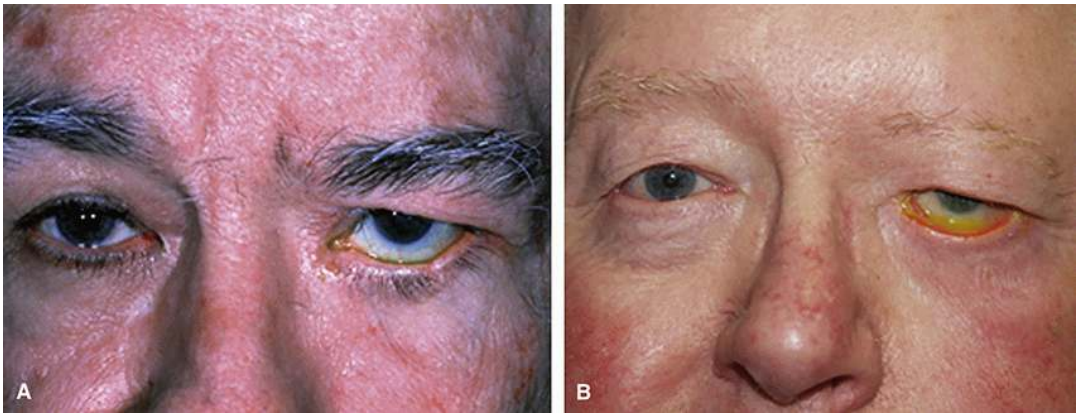

FIGURE 23.2 A and B, Ophthalmic manifestations of facial nerve palsy with brow ptosis, secondary dermatochalasis, and lower eyelid laxity.

In the periocular region, FNP typically presents with several worrying signs, including upper eyelid retraction from loss of orbicularis muscle tone, lower eyelid laxity, paralytic ectropion (Figure 23.2), adynamic ptotic brow with loss of forehead wrinkling, a variable degree of *(Print pagebreak 159)* lagophthalmos on attempted eyelid closure with or without a good Bell phenomenon, excessive tearing or occasionally dry eyes, and chronic inferior exposure keratopathy. If neglected, this could result in corneal abscess/perforation or endophthalmitis.[23] The size of the palpebral fissure in acute FNP is variable. Typically, although far from being the rule, the palpebral fissure is wider than the contralateral normal side not just because the upper eyelid is higher than the normal side but because the lower eyelid also sits below its normal position.[24]

Evaluation of a patient with acute facial paralysis should include a thorough assessment of all muscles of facial expression to determine if the patient has paresis or paralysis,[23] and the degree of paralysis could be graded with one of the abovementioned general or locoregional grading systems. The frontalis muscle should be assessed dynamically to differentiate an upper from a lower motor neuron lesion,[14] and the eyebrow position should be noted in the resting state as well. The degree of passive lagophthalmos, as well as the extent of forced eyelid closure, is examined as well (Figure 23.3). The degree of upper eyelid retraction, dermatochalasis, lower eyelid laxity/ectropion, and Bell phenomenon are also noted.[23,25,26] The sensation along the distribution of the trigeminal nerve is also evaluated,[23] as well as the ocular motility because the abducens nerve lies in close proximity intracranially to the facial nerve nucleus.[26] A red eye is a red alert sign in patients with facial palsy[8,25] and requires a careful slit lamp examination, that should include assessment of corneal sensation, which may be reduced after acoustic neuroma surgery.[23] The tear film and the tear meniscus should be examined with Schirmer test or Lissamine green to quantify tear production, and exposure keratopathy should be ruled out with fluorescein staining. The slit lamp is also an ideal tool to closely observe the impact of the patient's incomplete blink and Bell phenomenon on the cornea.[23,25,26]

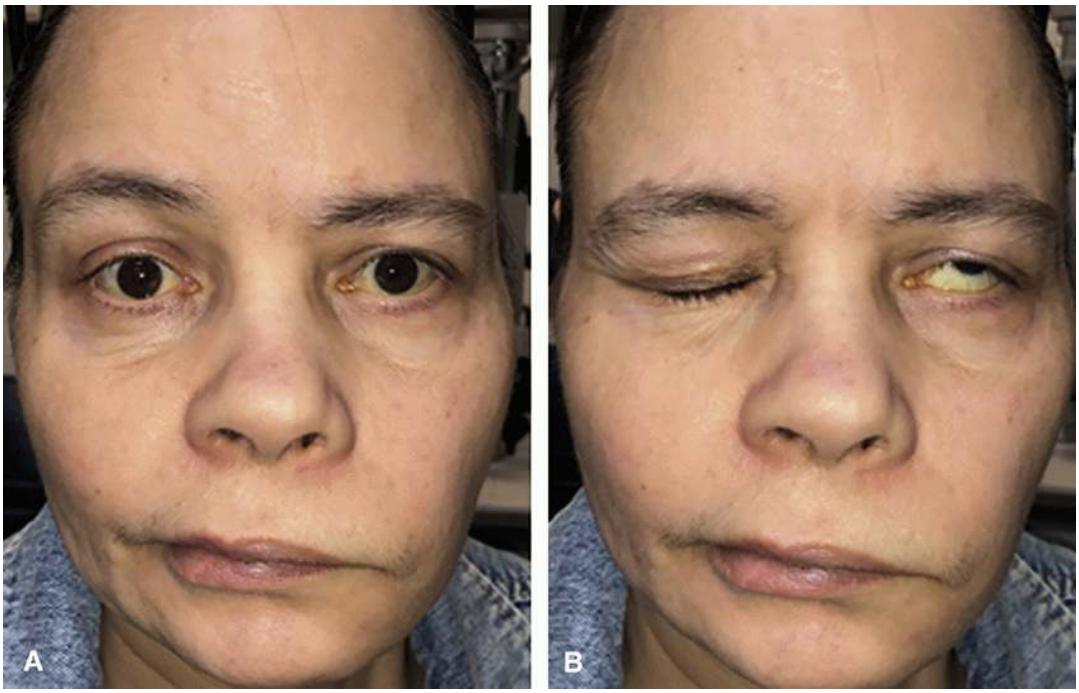

FIGURE 23.3 Facial paralysis. A, Left facial muscle weakness and mouth droop. B, Marked lagophthalmos and corneal exposure on attempted eyelid closure. (Courtesy of Dr. Kyle Godfrey.)

As was mentioned earlier, one of the more common ophthalmic presenting symptoms is epiphora, which has a multifactorial etiology in facial palsy patients. Lagophthalmos can cause an increase in tear production but decreased tear drainage due to atonicity of the orbicularis oculi and weakness or failure of the lacrimal pump, as well as eversion of the lower lacrimal punctum, can all contribute.[24,26] Epiphora usually regresses with a resolution of the palsy. It is pertinent to evaluate the lacrimal system carefully in all cases to avoid missing a coexistent nasolacrimal duct pathology. Conversely, tear production may be reduced in facial palsy patients if the lesion is proximal to the geniculate ganglion. Severe dryness and not tearing may be observed in those patients.[26]

Several imaging procedures and diagnostic tests have been used to evaluate patients with acute facial paralysis to help look for an identifiable cause, but a gold standard is yet to be defined, and the choice of radiology or laboratory investigations should be individualized.[8,10] The take-home message is that "any presentation of facial paresis/paralysis inconsistent with Bell palsy should be further evaluated by imaging."[8] Computed tomography may help in localizing the whereabouts of a nerve injury in cases of trauma, while magnetic resonance imaging (MRI) of the entire course of the facial nerve may help if a tumor mass or an infectious process is suspected and should include imaging of both the internal auditory canal and face.[7,8,10] However, if the diagnosis of Bell palsy is established, radiology does not usually provide any added benefit and may confuse the clinician *(Print pagebreak 160)*

because MRI may show enhancement along the involved facial nerve, which may be confused with a small mass compressing the nerve.[10]

The natural history of Bell palsy is that the majority of patients could recover completely without any intervention at all. Unfortunately, the story of facial palsy does not usually end there as nearly one-third of patients do not recover fully. Estimates vary [2] but approximately half of those patients with incomplete recovery develop a nonflaccid form of facial paralysis with varying degrees of static or kinetic hyperactivity or hypoactivity. This causes facial asymmetry at rest or during movement, along with synkinetic movements, which occur during voluntary expressions caused by aberrant regeneration of the facial nerve.[17,27,28,29] This outcome is usually a psychologically devastating problem in FNP[17] and is more typically encountered in patients sustaining a severe (>95%) nerve injury.[26] Synkinesis is defined as an involuntary undesired movement of the face, which typically accompanies a voluntary desired movement in the same or another region of the face.[17,27] It should be pointed out that synkinetic movements may occur in the direction of the agonist muscle either due to overinnervation of the paralyzed muscle or aberrant regeneration of an agonist muscle. Alternatively, they may occur in the opposite direction if an antagonist muscle is aberrantly reinnervated.[2,17,27,28,29] The former is more commonly encountered,[27] but in the rarer situation where an antagonist muscle is involved, the actions of both muscles may cancel each other out resulting in a complete stoppage of the originally intended movement, or the so-called autoparalytic syndrome.[27,30] Any combination of facial muscles can be involved in synkinetic action,[29] and the periocular region is a common area where those aberrant movements occur.[27] The most frequently encountered movement is the oculo-oral synkinesis (movement of the oral commissure with voluntary eye closure). Conversely, Marin-Amat syndrome manifests with narrowing of the palpebral fissure during opening of the mouth or mastication.[29] Other less frequent periocular synkinetic movements include paradoxical frontalis activation on attempted closure of the eyes[27] and gustatory epiphora (crocodile tears syndrome). After CN VII palsy, the nerves destined for the facial muscles may be misdirected to innervate the lacrimal gland, which leads to hypersecretion of tears, while chewing or talking.[31]

Synkinetic movements are not the only long-term sequela of FNP. While in acute paralysis, the upper eyelid retracts because of the unopposed action of the levator muscle due to orbicularis weakness (Sherrington's law of reciprocal innervation),[32,33,34] in chronic FNP, upper eyelid retraction and lagophthalmos could result from "thixotropy" or stiffness of the levator muscle.[32,33] It should be realized that normally under physiologic conditions, it is not the active contraction of the orbicularis but rather the passive relaxation or the active inhibition of the levator muscle that plays a pivotal role in the blink response and eyelid closure during sleep, respectively.[35,36] In facial palsy patients, the levator muscle suffers from chronic interruption of this normal physiologic pattern of tonic contraction and relaxation, which results in the formation of irreversibly tight cross-bridges between the actin and myosin filaments within the muscle fibers, ultimately resulting in levator muscle stiffness.[32,33]

Another feature that was recently documented is contracture or shortening of the upper and/or lower eyelid skin in patients with chronic facial palsy. In a recent study, more than two-thirds of FNP patients showed ipsilateral skin shortening, which exceeded more than 5 mm in 17% of patients.[37] Also, chronic FNP patients may suffer from a deflated atrophic appearance of the eyelids due to an associated volumetric loss (subcutaneous tissue and muscle/fat atrophy) resulting from muscular denervation of the orbicularis.[34,37] Paradoxical narrowing of the palpebral fissure at rest can occur in chronic FNP,[24,38] although in the majority of patients with a presumably narrow palpebral fissure, the upper eyelid is retracted. An untrained observer may misinterpret an upper eyelid skin fold exacerbated by brow ptosis as a narrow palpebral fissure.[37] This should be differentiated from the synkinetic narrowing of the palpebral fissure on attempted smiling.[14,37]

Differential Diagnosis

It could be argued that the diagnosis of FNP is a straightforward one, and indeed this is the case; however, because the list of etiologies underlying facial palsy is long, it is up to the clinician not to overlook obvious ancillary clinical signs or comorbidities and to avoid the tendency to mislabel every paralytic ectropion patient as a Bell palsy patient. Alternative underlying etiologies should not be missed; otherwise, patients may suffer from an unnecessary delay in diagnosis.[8] A slow onset, a recurrent or bilateral FNP, polyneuropathy, a more indolent or chronic onset, or failure to improve in the expected time frame should call for prompt reevaluation, and in these cases, radiology should be ordered if this has not been done already.[8] The age of presentation could also help. Although Bell palsy can affect any age including children, age of onset beyond the typical 15 to 45 years should raise suspicion.[8] Only then can the diagnosis of Bell palsy be established, which essentially makes it a diagnosis of exclusion.[8]

As noted earlier, the presence of severe pain, rash, or vestibulo-auricular symptoms should alert the clinician to Ramsay Hunt syndrome and not Bell palsy; however, it should be pointed out that some patients with Ramsay Hunt syndrome only present with facial palsy, combined with a zoster-like neuropathic pain, which follows a dermatomal distribution, but does not present with any vesicular rash at all, a rare condition which is termed Ramsay Hunt syndrome zoster sine herpete.[10,39,40] Therefore, it could be argued that some patients with presumed Bell palsy are Ramsay Hunt syndrome patients.[10] In these patients, serological assays of herpes zoster antibody titers in the blood or polymerase chain reaction (PCR) to detect VZV in exudates from the ear, blood, or even tears may help in establishing the diagnosis.[39,40]

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Treatment

The ultimate goal in the management of FNP is preservation of the globe,[10] and a combination of upper and lower lid procedures may be to restore the integrity of the palpebral fissure and salvage the eye.[41] But surgery is not the only option in FNP, and salvaging the eye can begin as soon a diagnosis of Bell palsy is made. Medical therapy should be started immediately after establishing the diagnosis. As mentioned earlier, the pathogenesis of Bell palsy is probably a cell-mediated inflammatory response due to a herpes simplex viral insult to CN VII; therefore, it should seem like a logical choice to start antivirals plus corticosteroids immediately following the diagnosis of Bell palsy. However, most authorities do not support this line of thinking, and prefer giving steroids alone.[8,10,42] A recent Cochrane meta-analysis that reviewed 10 clinical trials and included 2280 FNP patients showed a treatment benefit (higher percentage of complete recovery of nerve function and reduction of synkinesis) when antivirals were added to corticosteroids in comparison with corticosteroids alone for patients with complete or incomplete Bell palsy.[43] The study also found that the outcome for the participants receiving corticosteroids alone was significantly better than for those receiving antivirals alone. Interestingly, antivirals alone produced no benefit over placebo and therefore are not recommended as monotherapy.[10,43] Therefore, it could be cautiously recommended to commence a combination of acyclovir (2000 mg/d) or valacyclovir (1000 mg/d) for 5 to 10 days, and prednisone (1 mg/kg for 5 days followed by rapid tapering) within the first 3 days of onset.[43,44,45] This 3-day time limit is especially important with antivirals, which only act on replicating viruses.[10] The same beneficial effect of a steroid/antiviral combination was also observed in Ramsay Hunt syndrome.[10,39,46] Therefore, it may be safe to recommend a combination of antivirals and corticosteroids in any patient with idiopathic facial paralysis.[10,39]

Other conservative measures may also help in acute and even chronic FNP patients. Patients with mild or no exposure keratopathy can be managed conservatively with lubricants and possibly eyelid taping. While extensive lubrication is undoubtedly the mainstay of therapy in patients with acute paralysis,[10] the role of eyelid taping or patching at night is controversial and may inflict more harm than good.[10] However, if lubricants are inadequate in protecting the cornea while the improvement of facial nerve function is anticipated, mechanical protective ptosis can be achieved by paralyzing the levator muscle with botulinum toxin injections.[10,26,47]

The full length of a 27-gauge needle containing 5 to 7.5 units of botulinum toxin type A is injected through the eyelid adjacent to the midpoint of the superior orbital rim close to the orbital roof adjacent to the levator palpebrae superior muscle.[47] Botulinum toxin injections can also be administered in chronic facial palsy patients beyond the acute phase as a bedside procedure in patients who are deemed poor surgical candidates or those with a limited functional capacity.[48] This technique would pose less risk to the superior rectus muscle than direct transcutaneous or transconjunctival injection of the toxin into the levator.[26] Another temporizing measure is the use of external eyelid weights, which are attached to the pretarsal skin using double-sided tape.[48] Ideally, those external eyelids weights that are manufactured with a variety of skin tones and weights should induce a 1-mm of ptosis while sitting comfortably 3 mm above the lash line. However, contact dermatitis from the adhesive tape remains a concern.[48] Finally, some authors recommend that all FNP patients should be routinely advised to passively stretch their upper eyelids as well as their lower eyelids to prevent further skin contracture or to minimize existing lagophthalmos.[32,33,34,49]

Surgical intervention remains the backbone of therapy of FNP patients if conservative measures fail and the cornea is threatened. Lagophthalmos and eyelid retraction have been treated with several methods including passive upper eyelid reanimation with partial-thickness levator recession or a graded full-thickness blepharotomy.[10,50] These techniques may reduce palpebral fissure height to some degree because they may help counteract levator stiffness or thixotropy.[32,33] However, upper eyelid loading with gold or platinum weights has been the mainstay of treatment of lagophthalmos for several decades.[51,52,53,54,55,56,57,58,59,60,61,62] To the best of our knowledge, it was Bromley S. Freeman who first implanted a tantalum implant in the upper eyelid, a technique which was later refined and popularized by Gavin D. Smellie in 1966.[51] This technique works through passive reanimation of the upper eyelid, whereby gravitational pull greatly reduces lagophthalmos and improves voluntary eyelid closure.[10] The choice of the material (gold or platinum) and its physical weight are determined preoperatively in the clinic.[53] After a routine lid crease incision, the pretarsal orbicularis is dissected over the upper half of the tarsus, followed by the opening of the septum to recess the levator. The lower border of the platinum or gold weight is sutured to the tarsus at this higher location with 6-0 polyglactin 910 or nylon sutures. The recessed levator is then sutured to the top border of the implant partially draping the anterior surface.[53] The orbicularis oculi should be closed as a separate layer with 6-0 polyglactin sutures to help secure the implantable weight in place.[53] In the past, those implantable devices were placed at a lower pretarsal location[52]; however this low position usually results in a bulky or unsightly lid appearance particularly on downgaze and induces more astigmatism than if placed at a higher position.[61] Also, it may cause a higher rate of implant extrusion and migration.[53,60] Higher positioning of a heavier weight coupled with levator recession may provide better cosmesis and reduce the rate of extrusion,[53,59] but implant prominence remains a problem because of the

associated atrophy of subcutaneous tissues.[53,59] A third yet questionable alternative is supratarsal placement of the implant superior to the upper tarsal border so that the implant acts as a spacer between the tarsus and the recessed levator[56]; however, posterior extrusion of the weight remains a real concern, as only the conjunctiva and Müller muscle separate the weight from the surface of the globe.[56]

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The choice of implant material has also changed over the years. Although excellent results have been reported with gold weights, gold is not inert, and even if 99.99% pure, a certain subset of the population (5%-8%) may be allergic to it.[53,58] A delayed (type IV) hypersensitivity reaction may develop 1 to 2 weeks after implantation and may be misdiagnosed as wound/implant infection, with subsequent partial or complete extrusion. Therefore, a personal or family history of allergy to gold should skew the clinician toward recommending platinum, which is an inert metal.[53,58] Platinum, which is available in two forms (solid weight or platinum chains), is currently the preferred material of choice for lid loading not just because it is inert [53] but because as a metal it is denser than gold and therefore occupies less space and consequently reduces the possibility of a bulky eyelid.[62]

It is of paramount importance to rule out levator stiffness (thixotropy) as a cause of lid retraction or lagophthalmos before embarking on a lid loading procedure; otherwise, the outcome of surgery will be underwhelming.[63] This is probably the reason why combining both techniques (levator recession/lid loading) provides a favorable outcome.[53,62] Contracture or shortening of the upper eyelid skin is also an overlooked cause for a disappointing outcome, which may be occasionally observed after lid loading with gold/platinum weights. This could mislead the surgeon into replacing a properly chosen weight with a heavier one, which may cause extrusion or a poor contour.[37] In such cases where eyelid closure is insufficient following eyelid loading, an upper eyelid full-thickness skin graft could improve lagophthalmos if skin contraction is demonstrated.[49] Autologous fat grafting has been used successfully to improve the quality of the skin and to replenish the atrophied fat and may even reduce the lagophthalmos.[34]

Reconstruction of the lower eyelid is the second crucial step in reanimation of the periocular region in FNP.[10,63] There are different vectors at play that ultimately decide the position of the lower eyelid; therefore, the management plan should be individualized and multiple repeated procedures may be required if this multifactorial etiology is to be fully addressed.[10,63,64,65,66,67,68,69,70,71] The factors at play include the degree of gravitational or paralytic ectropion of the lower lid, the status of the medial and lateral canthal tendons, and the extent or degree of midface descent or ptosis.[63,64,65,66,67,68,69,70,71] The sheer weight or size of the tarsus may also play a minor role by further weakening the medial and lateral canthal ligaments.[67]

In patients with a partial impairment of orbicularis function, a simple lateral canthoplasty may suffice to restore an atonic lower lid into its proper anatomical position.[10] However, the lateral tarsal strip (LTS) procedure remains the most commonly performed procedure for patients with more severe weakness of the orbicularis, and it frequently works well at least initially although it tends to weaken over time and understandably does not fully correct medial canthal laxity.[7] LTS may be combined with recession and extirpation of the lower eyelid retractors if patients present with a concomitant yet mild lower eyelid retraction.[65] In patients with more severe lower eyelid retraction/ectropion, attention should be directed to the midface. Functionally, the lower eyelid does not end at the lid-cheek junction but is thought to form an anatomic continuum with midface structures down to the level of the upper lip.[7,71] The constant gravitational pull on the paralyzed midface structures causes them to sag and drag the lower eyelid margin even further down.[7] In these patients, a subperiosteal midface lift or a SOOF lift (suborbicularis oculi fat pad) may provide further vertical lift or support to the lower eyelid and could be used as an adjunct to LTS with or without a spacer graft. This superolateral myocutaneous redraping serves another important function. By raising the upper part of the cheek, the palpebromalar and nasojugal sulci are pushed upwards, which improves midfacial symmetry and confers a strategic cosmetic advantage.[66,68] The addition of a hard palate graft may be indicated if there is significant lower eyelid retraction.[7,68]

Medial canthal tendon laxity can be difficult to correct, and an ideal solution is yet to be published.[7] In milder cases, a lateral canthal resuspension may be all that is required[7]; however, if significant medial tendon laxity is encountered, this should be addressed surgically although it should be understood if a decision is made to address the medial canthal tendon, it should be done concurrently with lateral canthal tightening in the same procedure, although it should precede lateral canthal tightening to counter the tendency of lateral canthal procedures to pull the punctum laterally.[10] Addressing the medial canthal tendon in FNP may not only improve cosmesis and reduce lagophthalmos but also help reduce excessive watering induced by orbicularis weakness.[10]

Counterintuitively, and despite its cosmetically poor outcome and the loss of the peripheral field of vision, a permanent lateral tarsorrhaphy may still have a role in modern ophthalmic management of FNP albeit being a minor one.[10] The ultimate goal of all the abovementioned procedures is the preservation of vision, but if upper and lower eyelid reconstructive procedures have failed, a permanent lateral tarsorrhaphy may be indicated.[10] An additional possible indication is when there is a combined

paralysis of CN V and CN VII because corneal sensation may be compromised.[10] What is to be condemned, however, is the use of a permanent lateral tarsorrhaphy as a first-line measure without addressing the multifaceted etiology of paralytic lower eyelid ectropion first. This hurried or simplistic approach is not only ineffectual but may even be harmful as corneal integrity may still be compromised on top of a tarsorrhaphy.[63,64]

Brow ptosis, which occurs due to paralysis of the frontal branch of the facial nerve, may cause a significant cosmetic deformity and loss of the superior visual field. However, cosmetic rehabilitation of the ptotic brow should only be undertaken when the cornea is well protected to improve cosmesis and vision.[10] A direct brow lift with fixation to the underlying periosteum is commonly performed, but patients seeking brow lift solely for cosmetic reasons should be warned that it usually leaves behind a poor unsightly scar.[10] Another complication of a direct brow lift is the occurrence of paresthesias and numbness in the brow region in up to 75% of *(Print pagebreak 163)* patients.[72] Alternative techniques include an endoscopic, mid-forehead, coronal, or pretrichial brow lift, but they are less effective than a direct brow lift.[10,71] Either way, if an upper eyelid blepharoplasty is planned along with a brow lift, it should be performed with the most conservative means possible.[10] In a recent paper, Sonali Nagendran et al. utilized the excised brow skin from a direct brow lift procedure as a full-thickness skin graft to correct lower eyelid skin contracture, ectropion, and retraction with good functional outcomes.[73] Reanimation of the lower face is as important as reconstruction of the upper half, but it is beyond the scope of this chapter and is summarized elsewhere.[71]

Prognosis

The overall rate for spontaneous complete recovery is 70% within 6 months, with a 94% recovery rate in those with incomplete palsy, compared to a 60% recovery rate in patients with complete paralysis.[10] Of those patients who fully recover, 85% recover in the first 3 weeks,[13] while the remaining 15% only recover after 3 to 5 months.[13] Interestingly, patients are not usually expected to show signs of spontaneous recovery in the interim period between the first 3 weeks and the second peak of recovery at 3 to 5 months, a period which has been dubbed “hibernation of the facial nerve,”[13] where the facial nerve falsely appears to be dead. This bimodal pattern of recovery is explained by the fact that patients who recovered early only had partial paresis, while patients who recovered late had complete axonal degeneration.[13] In general, children and patients with incomplete Bell palsy have a better prognosis.[10,13] The poorest prognosis occurs in older patients,[10] patients with total degeneration, patients with Ramsay Hunt syndrome, and in patients with a late return of function as the possibility of normalization is very small after 3 months, and nil beyond 6 months.[13] Bell palsy may recur on the same or the opposite side of the face in 7% of patients.[13] Patients with Ramsay Hunt syndrome do not only have a poorer prognosis but a more severe and painful paralysis as well, and only 21% of patients achieve total remission.[13] In patients with acoustic neuroma, a careful dissection, preservation, or reconstruction of the facial nerve during surgery could reduce the overall incidence of postoperative paralysis at 1 year to less than 2%.[74]

Histopathology

We are not aware of any histopathology sections relevant to facial paralysis.

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CHAPTER 24

Ablepharon

Key Points

- Ablepharon is a term used to denote the absence or severe shortness of the eyelids
- It is usually associated with macrostomia and other congenital abnormalities
- Ablepharon-macrostomia syndrome is an extremely rare congenital disorder caused by a dominant mutation in the TWIST2 gene, which regulates mesenchymal stem cell differentiation and directs the development of chondrogenic and dermal tissues
- Affected individuals have an extremely shortened anterior eyelid lamella with a hypoplastic tarsal plate
- The upper eyelid margin is very close to the eyebrows, and there are usually no eyelashes
- Medical treatment is with intensive lubrication started from the moment of birth
- Surgical intervention consists of levator aponeurosis recession and full-thickness skin grafts

By definition, ablepharon is a term used to denote the absence or severe shortness of the eyelids. It is seldom a solitary anomaly and is usually associated with macrostomia as well as other congenital abnormalities in the setting of the so-called ablepharon-macrostomia syndrome.[1,2,3,4] In 1977, two pediatricians described this previously unrecognized condition with presumably absent eyelids, a large mouth, and multiple other congenital anomalies.[1]

Etiology and Pathogenesis

Ablepharon-macrostomia syndrome is an extremely rare congenital disorder that is caused by a dominant mutation in the TWIST2 gene, which is highly expressed in the craniofacial mesenchyme, controls the development of mesenchymal tissues, and is also overly expressed during embryonic development in the craniofacial region.[3,4,5] The TWIST2 gene thus regulates mesenchymal stem cell differentiation and directs the development of chondrogenic and dermal tissues.[5]

Clinical Presentation

Only 21 cases of ablepharon-macrostomia syndrome are reported in the literature.[3,4,5,6,7] The affected individuals present with ablepharon or more correctly microblepharon.[3] Affected individuals have extremely shortened anterior lamellae with a well-formed mucocutaneous junction at the upper as well as the lower eyelid margins (Figure 24.1). The tarsal plates are hypoplastic and redundant, and chemotic palpebral conjunctiva is universally observed.[3] The orbital septum and the levator aponeurosis are usually spared but may be thinned.[3,6] In light of these findings, some authors believe that the name ablepharon-macrostomia syndrome is a misnomer and recommend changing the name to microblepharon-macrostomia.[3,4] Because of marked anterior lamellar shortening, the upper eyelid margin is very close to the eyebrows, and there are usually no eyelashes.[6] These neonates are also typically born with corneal exposure.[3] Corneal erosions develop on postnatal day 1 or 2, proceeding very rapidly to corneal opacification and possibly perforation.[7] Other ocular abnormalities include nystagmus and strabismus.[4]

In addition to the striking ocular features, these patients exhibit a wide fishlike mouth (macrostomia) (Figure 24.2); microtia; attached ear lobes; hypertelorism with a wide nasal bridge and wide nasal tip; lax or redundant skin; sparse hair; variable abnormalities of the nipples, fingers, and hands (camptodactyly), as well as ambiguous genitalia.[5,7] Intellectual and motor development are usually normal.[3,4,5]

Differential Diagnosis

Barber-Say syndrome (BSS) is another very rare ectodermal dysplasia syndrome with significant genotypic as well as phenotypic overlap with ablepharon-macrostomia syndrome.[3,4,5] Clinically, both show macrostomia as well as microtia; however, the palpebral features of BSS are milder as these patients only present with ectropion with mild corneal exposure.[3] Eyebrows and eyelashes are sparse in BSS, but they are typically absent in ablepharon-macrostomia syndrome.[4] Genotypically, both conditions share a defect in the same gene (TWIST2), and the same location (residue 75).[5] The sole difference lies in a single amino acid alteration. A lysine at TWIST2 residue 75 results in ablepharon-macrostomia syndrome, while glutamine or alanine results in BSS.[5]

Another ectodermal dysplasia syndrome that shares other mutations in the same TWIST2 gene, albeit having a recessive pattern of inheritance, is the Setleis syndrome (bitemporal "forceps marks" syndrome). The palpebral fissures, though, are quite different as these patients present with congenital distichiasis of the upper eyelids and astichiasis (absent eyelashes) in the lower eyelids.[5,8,9] It should be *(Print pagebreak 168)* noted that some patients with BSS share the same eyelash changes with Setleis syndrome, and some authorities believe the three syndromes represent a continuum.[4]

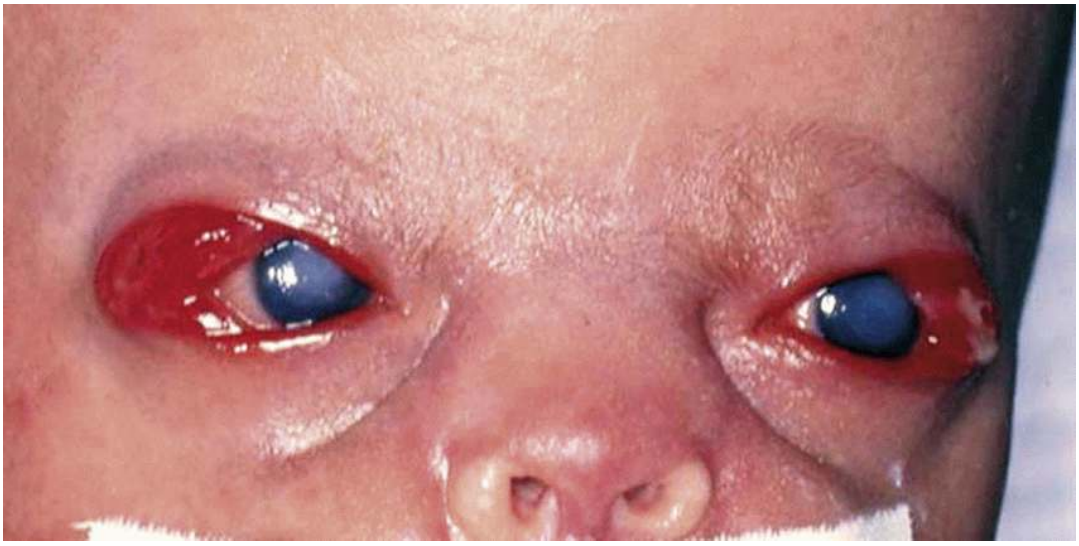

FIGURE 24.1 Ablepharon. Severe anterior lamellar shortening is seen, and the upper eyelid margin is very close to the eyebrows. (Courtesy of Dr. Antonio Augusto Cruz.)

It should not be difficult to discern simple eyelid colobomata that are not associated with corneopalpebral adhesions from patients with ablepharon/microblepharon, yet the phenotypic overlap with eyelid colobomata associated with corneopalpebral adhesions (cryptophthalmos) is a potential source of confusion, and it should be noted that both eyelid colobomata and ablepharon-macrostomia syndrome may occur in the same family.[10,11,12] The current consensus is that they are distinct entities,[3] a claim that is further supported by genetic evidence.[4,5] Technically speaking, it could be argued that complete cryptophthalmos, a condition where the forehead skin extends over the globe and onto the cheek without any discernable differentiation of eyelid tissue at all, is the only *true* ablepharon that exists in the human body. Please refer to Chapter 29 for a detailed discussion of eyelid colobomata.

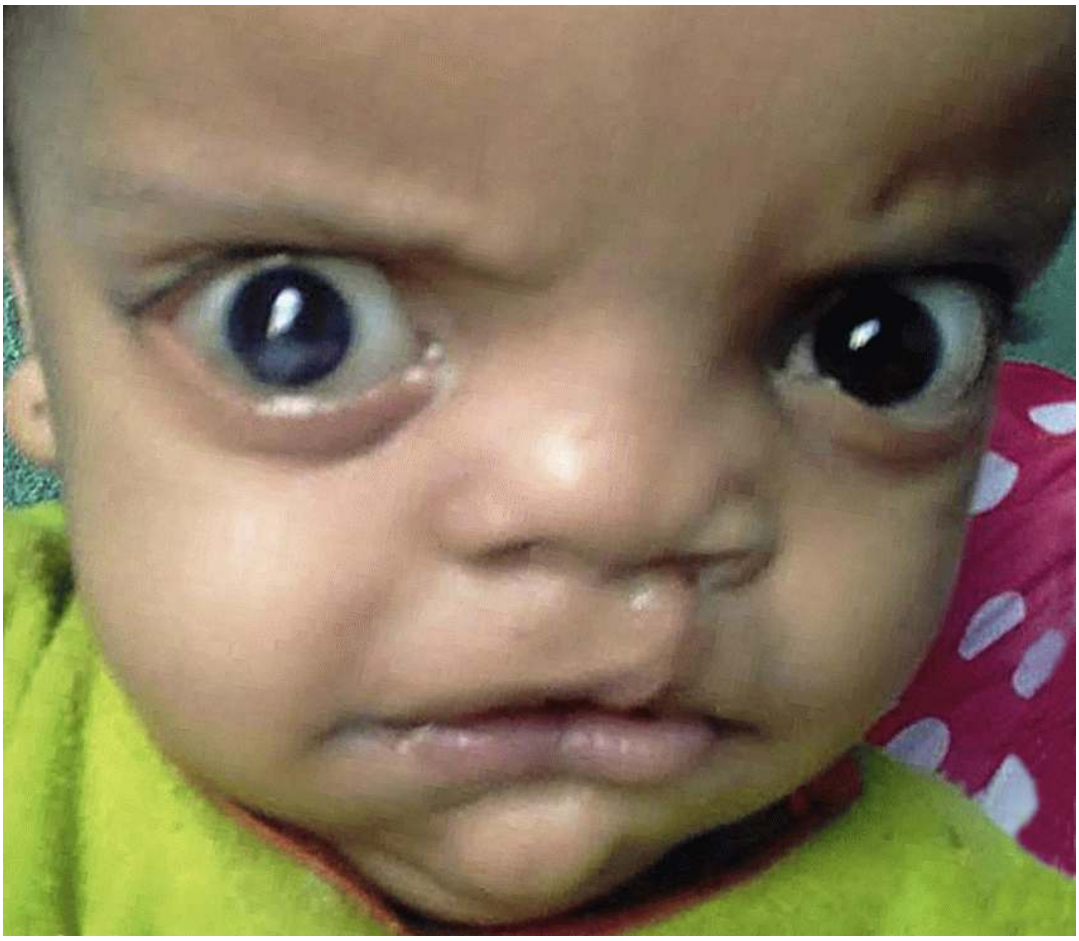

FIGURE 24.2 Ablepharon-macrostomia syndrome. In addition to the severe anterior lamellar lid shortening, these patients exhibit a wide fishlike mouth (macrostomia).

Treatment

Ablepharon-macrostomia syndrome is one of the actual few oculoplastic emergencies because these neonates are born with bilateral corneal exposure or ulceration.[3,7] Intensive lubrication should be started from the moment of birth with paraffin-based ointments, together with patching the eyes with Vaseline-soaked gauzes.[7] Conservative measures have no real place in management, and these patients do need immediate surgical intervention.[3] Because ablepharon-macrostomia syndrome is uniquely characterized by a vertical microblepharon of the anterior lamella while the posterior lamellae are more or less preserved,[3] major reconstructive procedures like the Cutler-Beard procedure or masquerade flaps should not be used because these local flaps may have a minimal effect on lowering the upper lids and keratopathy would persist.[3] In a recent paper, Cruz et al[3] summarized the surgical approach and surmised that once this unique pathology is understood, reconstruction is simple. A horizontal incision is made between the upper lid margin and the orbital rim. The orbicularis oculi muscle is then incised and the shortened septum is identified and widely opened. The preaponeurotic fat is then retracted upward and the levator aponeurosis is freely recessed or disinserted to bring down the eyelid margin. The resulting anterior cutaneous defect is replaced with a full-thickness skin graft.

Prognosis

Once the eyelids are adequately and promptly lengthened with a skin graft, visual recovery is good to excellent, and residual lagophthalmos is acceptable and usually inconsequential.[3] However, a delay in management may result in profound visual loss in up to one-third of the patients.[4]

Histopathology

There are no reports of eyelid histopathology in ablepharon-macrostomia syndrome or BSS, to our knowledge. A skin biopsy from the thigh of a 1-week-old male infant with BSS had atrophic, slightly orthohyperkeratotic epidermis; a thin reticular dermis; and a paucity of dermal elastic fibers with fragmentation.[13] A skin biopsy from an unspecified site in an 11-year-old boy with BSS also showed decreased dermal elastic fibers, along with decreased collagen.[14]

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CHAPTER 25

Ankyloblepharon

Key Points

- In ankyloblepharon, the eyelid margins are entirely or partially fused by full-thickness bands or partial filiform synechiae
- Ankyloblepharon can be congenital and can be isolated or syndromic
- Acquired ankyloblepharon can result from chemical trauma, burns, physical injuries, or cicatrizing diseases
- The condition is characterized by full-thickness fusion of upper and lower eyelids at the inner or outer canthi or both
- The full-thickness adhesions in congenital ankyloblepharon are severed through a lateral or medial canthotomy
- Acquired ankyloblepharon due to ocular cicatrizing disease may require ocular surface reconstruction, lysis of adherent bands, and fornix reconstruction
- Timely separation of bands results in an excellent visual and cosmetic outcome
- The bands consist of a fibrovascular core surrounded by epidermis

Ankyloblepharon is a condition in which the eyelid margins are entirely or partially fused by full-thickness bands or partial filiform synechiae.[1,2,3,4,5,6,7,8,9,10,11]

Etiology and Pathogenesis

The fusion of the eyelids is an integral part of the embryologic development of the human eyelid. This remarkable process, which starts in the 8th week of gestational life, involves only the peridermal and epidermal layers, whereas the mesenchyme remains intact and unfused. The eyelids remain fused until the 18th-20th week of fetal life when they start to separate. This is a slow, painstaking process that continues until the 24th week of fetal life. When the eyelids are still fused at birth, ankyloblepharon occurs.[1,2] Eyelid fusion at birth has also been reported in the context of significant prematurity as a normal physiologic phenomenon.[2]

Ankyloblepharon can be congenital or acquired. There are two distinct types of congenital ankyloblepharon. When there is a full-thickness fusion of the eyelids, the condition is termed congenital or classic ankyloblepharon (Figure 25.1).[6,7] However, when both eyelids are only partially fused by fine bands or skin tags, the condition is termed ankyloblepharon filiforme adnatum (AFA), a term that was coined by von Hasner in 1881 to set this condition apart from classic ankyloblepharon (Figure 25.2).[6,7,8] AFA can be isolated or syndromic. In its syndromic form, AFA is mostly associated with ectodermal dysplasias, which are a group of about 180 conditions characterized by abnormal development of ectodermal tissue including the skin, teeth, nails, hair, and sweat glands.[13,14] AFA is classified according to its systemic associations into six subtypes that are summarized in Table 25.1.

Acquired causes of ankyloblepharon include chemical trauma, burns, or physical injuries, cicatrizing diseases of the conjunctiva like Stevens-Johnson syndrome or ocular cicatricial pemphigoid, and inflammatory diseases such as herpes simplex blepharoconjunctivitis, particularly when it occurs in immunocompromised patients, and may rarely occur following lacrimal or eyelid surgery. Other rare causes include ulcerative blepharitis, diphtheritic conjunctivitis, trachomatous conjunctivitis, or systemic 5-fluorouracil treatment (Figure 25.3).[17,18,19,20,21,22,23] Ankyloblepharon can also occur temporarily from cyanoacrylate glue.[24,25] In a sense, a permanent tarsorrhaphy is an acquired surgically induced ankyloblepharon.

Clinical Presentation

Congenital ankyloblepharon is characterized by full-thickness inner canthal or outer canthal fusion of both upper and lower eyelids (

Figure 25.1).[7] When it occurs laterally, pseudoexotropia is observed. When it occurs medially, fusion usually occurs to the lacrimal puncta. The plica semilunaris and caruncle may be absent, the lacrimal passages are rudimentary, and there is an apparent esotropia. The eye is usually normal, but the condition may be associated with microphthalmia or anophthalmos.[7]

AFA may occur sporadically or be transmitted in an autosomal dominant fashion.[4] It classically manifests as unilateral or bilateral elastic or distensible strands or bands of tissue that partially fuse the upper and lower eyelids.[13] These bands typically originate from the gray line between the cilia anteriorly and the orifices of the meibomian glands posteriorly.[3,6,7] They vary from 0.5 to 5 mm in width and may range from 1 to 10 mm in length (Figure 25.2). In contrast to the classic congenital ankyloblepharon, the adhesions in AFA are usually observed in the central two-thirds of both eyelids and are not encountered near the medial or lateral canthi.[6,8]

Other ocular abnormalities are rarely associated with congenital ankyloblepharon and AFA, with only one case *(Print pagebreak 171)* report of iridodysgenesis and juvenile glaucoma with AFA.[26] Despite the apparent simplicity of the condition and the scarcity of associated ophthalmic anomalies, patients with AFA should promptly be referred to a pediatrician to exclude systemic associations that frequently may be fatal (see Table 25.1).

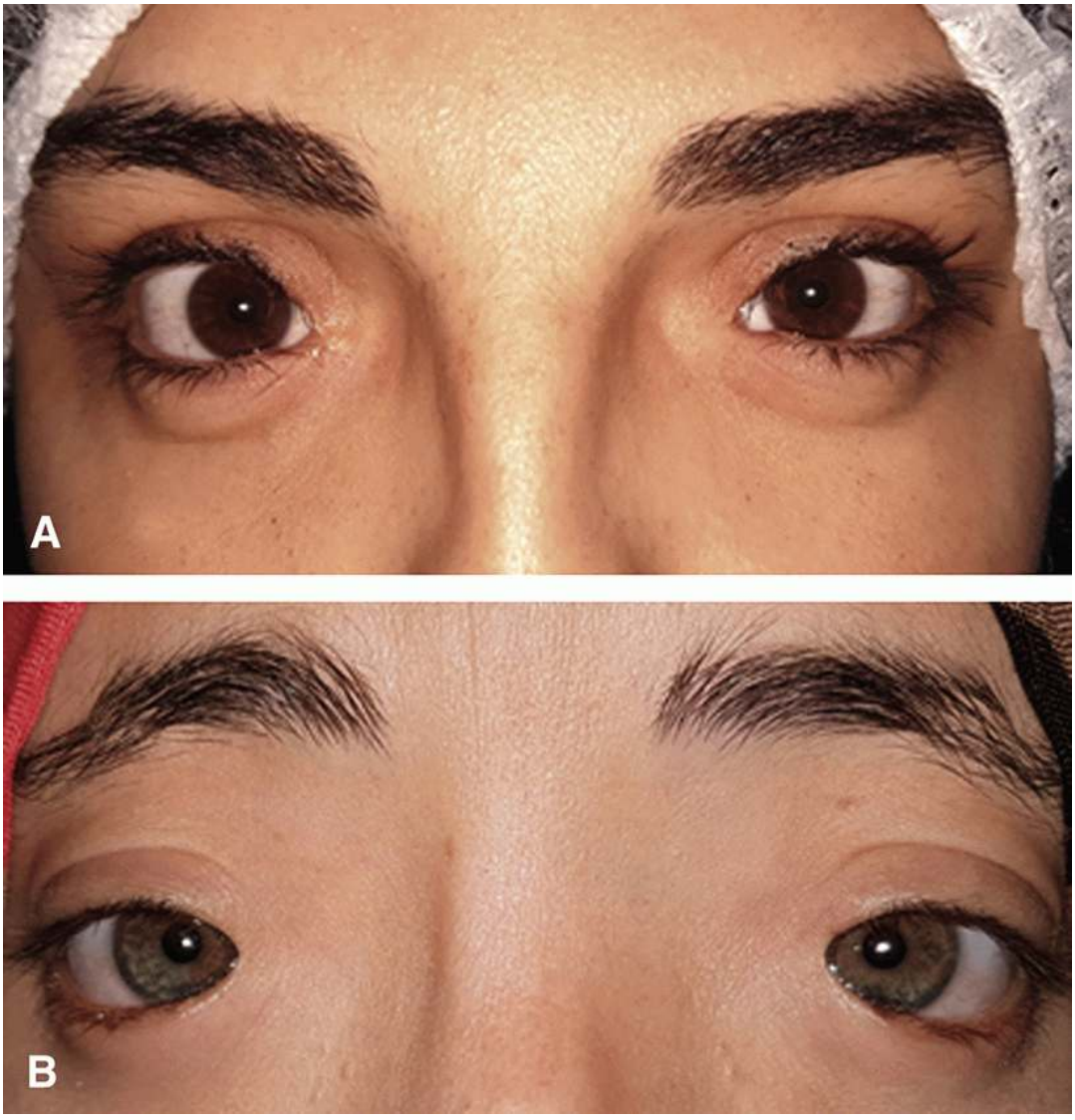

FIGURE 25.1 Two female siblings with classic congenital ankyloblepharon involving the medial canthal region. A, A milder form of medial ankyloblepharon. The lacrimal passages are patent. B, Severe medial ankyloblepharon. The plica semilunaris and caruncle are absent, and the lacrimal passages are rudimentary.

Differential Diagnosis

When present at birth, the systemic associations of AFA have to be recognized to identify any syndromic condition properly.[14] The presence of popliteal pterygia, syndactyly, abnormal external genitalia, cutaneous webbing, or intraoral adhesions suggests an *IRF6* -related disorder like popliteal pterygium syndrome (PPS), or its lethal variant the Bartsocas-Pappas syndrome.[14] The triad of AFA,

skin lesions (ulceration, hypo- or hyperpigmentation), and lip/palate clefting is highly suggestive of a *TP63*-related disorder like ankyloblepharon-ectodermal defects-cleft lip/palate syndrome (AEC, or Hay-Wells syndrome).[5] AEC is also characterized by the presence of curly or sparse wiry hair, maxillary hypoplasia, a small mandible, a broad nasal bridge, microstomia, trismus, or hypospadias.[13,27] Patients with the curly hair-ankyloblepharon-nail dysplasia syndrome (CHANDS syndrome) have several overlapping features with AEC like ankyloblepharon and hair changes but lack facial or oral clefting or the skin erosions that are virtually pathognomonic of AEC syndrome.[13] Patients with Edwards syndrome (trisomy 18) have multiple life-threatening congenital defects, and only 5% to 10% survive beyond the first year of life typically with severe mental disabilities.[7,28]

Congenital ankyloblepharon should be differentiated from complete cryptophthalmos, which was erroneously termed congenital ankyloblepharon in the past.[29] In patients with complete cryptophthalmos, the forehead skin extends over the globe and onto the cheek without any discernible differentiation of the eyelids.[30] Histopathologically, the eyelids are absent and are replaced by undifferentiated fibrous tissue with a total absence of the conjunctiva, tarsus, meibomian glands, cilia, and lacrimal glands.[30] Blepharophimosis is a condition characterized by a considerable reduction in the horizontal and vertical dimensions of the palpebral fissure usually associated with telecanthus, which may be confused with ankyloblepharon at least to the untrained eye.[19]

Treatment

The full-thickness adhesions in congenital ankyloblepharon are severed through a lateral or medial canthotomy. The bare tarsus or the gaps in the eyelid margin should be covered with a conjunctival flap and closed with 6-0 plain catgut or polyglactin sutures.[7]

In the majority of AFA cases, the bands are barely perceptible and may autolyze spontaneously.[13] Timely separation of larger bands or bands that do not lyse on their own is important to avoid occlusion amblyopia.[31] This only requires a minor surgical procedure with or without sedation to separate both eyelids gently with the help of Westcott scissors.[13] Because the eyelids retract away from each other and the defects in the upper and lower eyelid margins are small, there usually is no need to resuture those defects.

Patients with ankyloblepharon due to severe ocular cicatrizing disease may require ocular surface reconstruction with lysis of the adherent bands followed by fornix reconstruction with an amniotic membrane, nasal mucosal cartilage graft, or a mucous membrane graft.[17] Topical and systemic immunosuppression may be required to prevent a recurrence.[17] In the majority of cyanoacrylate injuries, only a few lashes are glued together, and conservative management in the form of topical antibiotic eyedrops coupled with frequent rinsing with fresh water usually allows the superglue to fall off on its own. However, more severe injuries with significant ankyloblepharon may require trimming or cutting of the adherent lashes.[32,33] Occasionally in more severe cases, peeling off the glue from the eyelid margins may be required.[32,33]

Prognosis

In AFA, timely separation of the bands will result in an excellent visual and cosmetic outcome. From a cosmetic point of view, the prognosis of congenital ankyloblepharon is also excellent. In acquired ankyloblepharon, the prognosis depends on the original cause.

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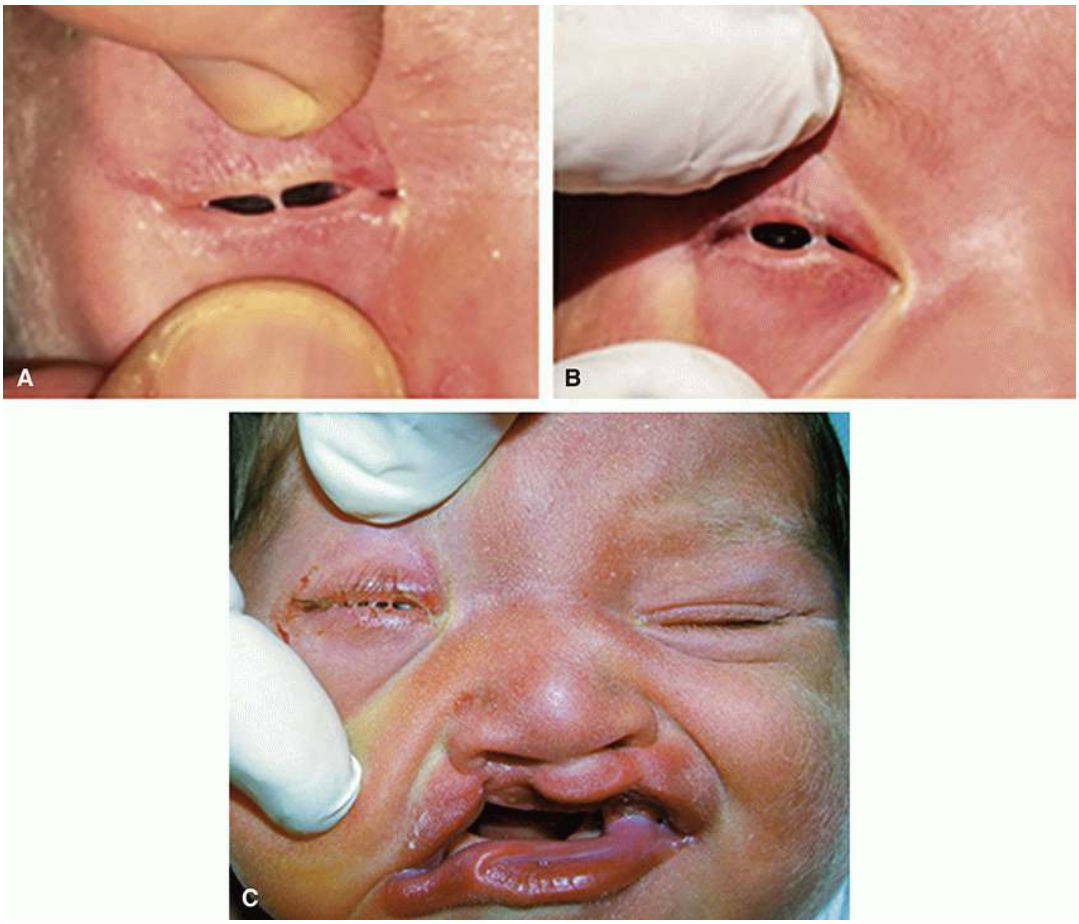

FIGURE 25.2 Ankyloblepharon filiforme adnatum (AFA). A, Type I or isolated nonsyndromic ankyloblepharon. A single central thin band can be observed. B, Another example of type I ankyloblepharon. Multiple broader bands can be seen. C, Type IV AFA. Multiple ankyloblepharon bands associated with cleft lip/palate. (Courtesy of Dr. Alan McNab.)

TABLE 25.1 Classification of AFA According to Systemic Associations

AFA Type	Systemic Associations
Type I	• Isolated nonsyndromic
Type II	• CNS malformations (myelomeningocele) • Cardiac malformations (persistent ductus arteriosus, septal defect) • Gastrointestinal malformations (imperforate anus)
Type III	Ectodermal malformations • AEC syndrome • PPS syndrome • Cleft lip/palate syndromes
Type IV	• Cleft lip/palate
Type V	• Trisomy 18 (Edwards syndrome)
Type VI	• Autosomal dominant AFA

AEC or ankyloblepharon-ectodermal defects-cleft lip/palate syndrome is also known as Hay-Wells syndrome. CNS, central nervous system; PPS, popliteal pterygium syndrome.
Data compiled from references 4, 10, 11, 15, and 16.

Histopathology

The bands in AFA have a variable histological appearance. The most common appearance is a fibrovascular core surrounded by epidermis (stratified squamous epithelium), with less common findings being a connective tissue devoid of blood vessels or bands of multilayered epithelium.[34,35] The connective tissue core is hypercellular with an embryonic appearance.[34] The eyelid adjacent to the band may lack Riolan muscle with embryonal connective tissue in its place, or it may be normal.[35]

We are not aware of any reports on the histopathology of the eyelid or the bands in syndromic AFA. Skin biopsies from affected (n = 2) and unaffected (n = 17) sites in people with AEC showed a variety of abnormalities including superficial perivascular lymphocytes (89% of biopsies), dermal melanophages/pigment incontinence (79%), a prominent superficial vascular plexus (58%), mild hyperkeratosis (47%), mild papillomatosis (16%), mild epidermal atrophy (42%), irregularity and bridging of rete ridges (32%), focal *(Print pagebreak 173)* interface dermatitis (32%), and mild papillomatosis (16%).[36] Enlarged, coarse, irregularly shaped keratohyalin granules were found in a child with AEC syndrome due to a novel *TP63* mutation.[37]

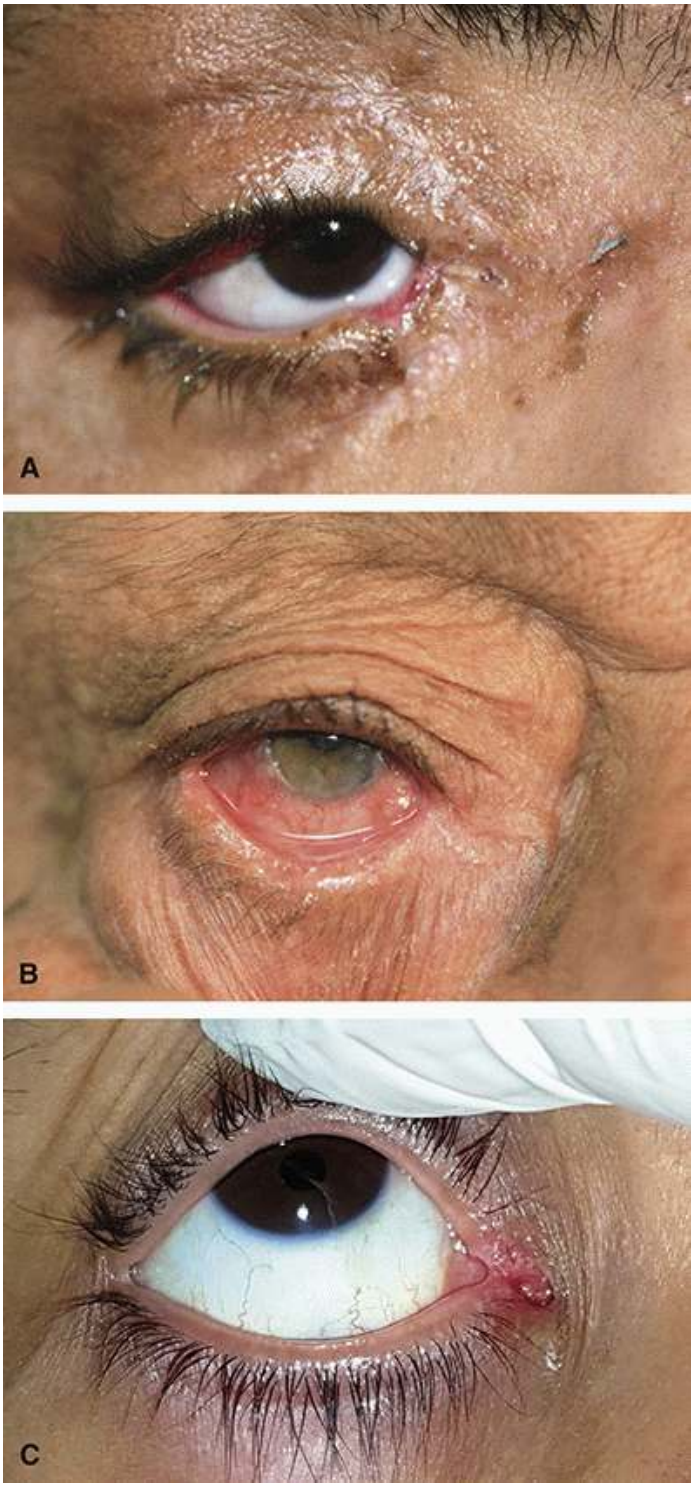

FIGURE 25.3 Acquired ankyloblepharon. A, Traumatic ankyloblepharon involving the medial canthus. B, Ankyloblepharon due to ocular cicatricial pemphigoid. C, Ankyloblepharon following bicanalicular lacrimal system

intubation.

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CHAPTER 26

Apraxia of Eyelid Opening

Key Points

- Apraxia is a neurologic movement disorder characterized by the inability to carry out learned, skilled motor acts
- Apraxia of eyelid opening is characterized by inability to open the eyes, with no clinical sign of orbicularis muscle contraction, no lowering of the brows, marked frontalis muscle contraction, and no dysfunction of the ocular motor nerves
- The basal ganglia appear to be involved in the translation of action plans to motor acts, and dysfunction of the basal ganglia plus higher neural networks appear to lead to praxis errors
- Evidence suggests that apraxia of eyelid opening most often occurs from prolonged inhibition of the levator muscle
- There is no cure for AEO, but treatment is most often with botulinum toxin as small 1 - to 2-unit doses into the pretarsal orbicularis muscle along the eyelid margin
- When AEO is combined with blepharospasm, botulinum toxin is given in the standard eyelid locations in addition to injections into the marginal orbicularis muscle
- The prognosis is generally good with botulinum toxin, but resistant cases may benefit from frontalis suspension or orbicularis muscle myectomy

Praxis is the ability to perform skilled or learned movements. Apraxia is a neurologic movement disorder characterized by the inability to carry out such learned, skilled motor acts, even though the command is understood, the patient is willing to perform the task, and the muscles and sensory systems needed to perform the action are intact.[1] Apraxia is further classified into subtypes such as ideomotor, ideational, and limb-kinetic apraxia and is seen in a variety of neurological disorders.[2,3]

Apraxia of eyelid opening (AEO) is a nonparalytic inability to initiate eyelid opening in the absence of clinically evident contraction of the orbicularis muscle, ocular motor nerve or sympathetic nerve dysfunction, or myopathy of the levator palpebral superior muscle.[4] A variety of different names have been used for this condition, attributed to different proposed etiologies. Goldstein and Cogan[5] first introduced the term apraxia of eyelid opening in 1965, based on four patients with basal ganglia disease who experienced difficulty in initiating the act of eyelid elevation. Nearly 40 years earlier, Schilder[6] described two patients with difficulty of eyelid opening who also had difficulty closing their eyes, and 3 years later, Riese[7] reported a similar condition in a patient with a frontotemporal injury. Subsequent reports have demonstrated AEO associated with extrapyramidal diseases such as multiple system atrophy, Parkinson disease, MPTP (1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine) intoxication, and progressive supranuclear palsy.[8,9,10] Boghen[11] first drew attention to the association between AEO and blepharospasm, with which it is often confused. The occurrence of AEO in patients with blepharospasm was reported as 7% in one study[9] and 10% in another.[12] Tolosa et al[13] found AEO in 12 of 22 (55%) consecutive patients with blepharospasm. AEO can also occur in isolation, not associated with any other central nervous system abnormalities.[9,14,15,16,17]

AEO is a very rare condition. In a study of three neighboring towns in Italy with a combined population of 67,606, only four cases of AEO were identified, giving a crude prevalence rate of 59 per million population.[18] In that study of 34 clinical cases of AEO, about 30% were isolated and 30% were associated with blepharospasm, 10% each with other dystonias, 10% with Parkinson disease and 18% with progressive supranuclear palsy.[18]

The diagnosis of AEO is usually made according to clinical criteria outlined in 1985 by Lepore and Duvoisin.[8] These include no clinical signs of orbicularis oculi muscle contraction, no lowering of the brows beneath the superior orbital margins (Charcot sign) as seen with blepharospasm, marked frontalis muscle overaction and brow elevation during the period of eyelid elevation failure, and no dysfunction of the ocular motor or ocular sympathetic nerves. Some authors also include transient failure to sustain eyelid elevation, although this condition is not included among these criteria for the diagnosis of AEO.[4,19]

Several different terms, besides AEO, have been used for this condition, none of them adequate to represent the presumed pathophysiology of the condition. One term, "focal eyelid dystonia,"[9] was based on the assumption that the syndrome is a dystonia and not an apraxia. The term "involuntary levator palpebrae inhibition"[8] was based on the concept of a supranuclear inhibition of levator muscle function. "Blepharocolysis"[20] and "pretarsal blepharospasm"[14] were based on the observation that the levator muscle is reciprocally inhibited by subclinical contractions of the pretarsal orbicularis muscle. Even though AEO does not adequately conform to the usual definitions of apraxia, where there is a dissociation between the praxis action plan and its execution, the term "apraxia of eyelid opening" remains widely embedded in the literature and is still the most commonly used term for this disorder.

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Etiology and Pathogenesis

Praxis is defined as the ability to perform skilled or learned actions. Apraxia, on the other hand, refers to the inability to carry out such praxis movements in the absence of elementary motor, sensory, or coordination deficits.[21] The praxis system is composed of functions associated with several regions of the brain that work in a coordinated fashion to process a planned action. The regions underlying praxis include the frontal and parietal cortex, basal ganglia, and white matter tracts containing projections between these areas.[22]

In 1908, Liepmann[23] outlined his concept of the praxis pathway and proposed that, to perform an action, a "space-time plan" has to be developed in the left parietal lobe and conveyed to the right central region (precentral and postcentral gyri, middle and superior frontal gyri, and their underlying white matter tracts) through association fibers and the corpus callosum. The action plan is coordinated in the basal ganglia where stimulatory and inhibitory signals are decided, projected to the primary motor cortex, and then projected to the motor nerves via the final common pathway of the pyramidal tract.[23,24] This has since been confirmed in other studies.[25,26,27] In 1985, Roy and Square[28] proposed a two-part model for the praxis pathway. First, a conceptual component forms an action plan or blueprint for execution of the task, establishing a sequence of individual actions. This is followed by a production component that develops sensorimotor information on how to perform this action plan and then translates them into coordinated actions.

Apraxia, or different types of praxis errors, depends upon abnormalities in the specific anatomic regions and neural networks involved.[22] The most widely recognized type of apraxia is ideomotor apraxia, or impaired performance of skilled motor acts, where patients show temporal and spatial errors affecting timing, sequencing, amplitude, configuration, and limb position in space.[1] In ideational apraxia, patients have difficulty carrying out a sequence of actions necessary to perform a complex, multistep action.[1,29] Orofacial apraxia is characterized by an inability to perform skilled movements involving the face, mouth, tongue, larynx, and pharynx.[30] The term limb-kinetic apraxia has been used to describe inaccurate or clumsy distal limb movements.[22,31,32,33]

The basal ganglia play an important role in praxis, probably through connections with the frontal and parietal cortex.[3,34,35] The basal ganglia are believed to contribute to sequencing, fine-tuning of movements, coordination of competing muscle contractions, and performance of automatic movements to praxis actions.[36]

Although apraxia has not been considered to result from dysfunction of isolated basal ganglia,[32,37] it does occur in association with extrapyramidal diseases involving the basal ganglia, including Parkinson disease, progressive supranuclear palsy, and Huntington disease. Since the basal ganglia appear to be involved in the translation of action plans into motor acts, it seems probable that dysfunction of the basal ganglia might lead to praxis errors.[38,39,40,41] However, it is generally believed that dysfunction of the basal ganglia alone is not sufficient to cause apraxia and lesions in the left hemisphere and disruption of association fibers are likely also to be involved.[37]

With respect to AEO, the exact nature of the responsible central disturbance is not known. However, evidence suggests that this involves abnormal supranuclear control of eyelid movement.[42] This is based on the occurrence of AEO in association with diseases affecting the extrapyramidal system,[4,5,8] such as Parkinson disease, or lesions involving the rostral brainstem,[43] or the right hemisphere.[44,45] This suggests a possible involvement of these anatomical structures and their neural networks.[46]

AEO can result from stroke; neurodegenerative disorders of the left inferior parietal lobe or frontal lobes; disruption of fibers in the corpus callosum; and extrapyramidal disorders believed to involve the rostral midbrain, that are thought to mediate supranuclear control of the levator palpebrae nucleus.[8] In addition, an idiopathic form of AEO has also been described without any underlying neurologic disease.[17,47]

Rare cases of a transient inability to open the eye after awakening from sleep have been described, not associated with known neurological or ophthalmological causes of ptosis.[48,49] This condition was first mentioned in 1897 by Silas Weir Mitchell,[50] involving three patients. Since then, a total of 20 cases have been recorded in the literature, of which 90% were female with a

median age of 63 years and 70% were unilateral. Patients can forcibly open their eyelids with their fingers, after which voluntary control of eyelid opening returns to normal. In the majority of cases, the condition spontaneously resolves without treatment within 18 months.[48] Although it has been argued that this might be attributed to the overnight effects of dry eye with the lids sticking together,[49] this seems unlikely because of its unilateral presentation and the fact that lubricating ointment instilled before sleep does not prevent its occurrence. Although it has been suggested that this condition may be a rare variant of AEO,[48,49,51] it is widely believed that this sleep ptosis results from the continuation of focal sleep-related muscular atonia of the levator muscle into the initial wakeful state.[49,51,52]

Initiation of eyelid elevation requires reciprocal inhibition, with activation of the levator palpebrae superioris muscle and the concurrent inhibition of orbicularis oculi activity. During eyelid closure the reverse is true. There is accumulating evidence that what is called apraxia of eyelid opening most often occurs from prolonged involuntary inhibition of the levator muscle.[19] Despite the absence of concurrent clinically evident contraction of the orbicularis oculi muscle, subclinical persistent contraction of the pretarsal portion of the muscle has been detected with electromyography which has led some authors to suggest that "pretarsal blepharospasm", a subtype of blepharospasm is a distinct entity that may simulate AEO clinically.[14,19,20,53,55] Of interest, one patient with AEO discussed by Aramideh et al[56] showed electromyographic (EMG) evidence of levator inhibition but no *(Print pagebreak 177)* simultaneous activity in the orbicularis muscle. It is unclear if this occurrence represents a rare instance of true apraxia rather than reciprocal inhibition. However, a study on eyelid movements and the startle response showed that, even in the absence of EMG evidence of orbicularis oculi contraction, cessation of tonic activity in the levator palpebrae can still occur, thereby permitting the eyelid to drop.[57]

Clinical Characteristics

In AEO, patients have a transitory inability to initiate eyelid opening on command in the absence of obvious orbicularis oculi muscle contraction. To initiate eyelid opening, patients with AEO sometimes use sensory tricks like looking up, throwing up the chin, and touching their face. There is no evidence of oculomotor nerve dysfunction, strabismus, or pupillary abnormalities and no symptoms suggestive of myasthenia gravis. Unlike in blepharospasm, where the brows typically move downward coincident with eyelid closure, in AEO the frontalis muscles contract in an attempt to open the eyes causing marked elevation of the eyebrows (Figure 26.1).[19,58] After a period with the eyes closed, the levator muscle contracts and the eyelids elevate. Unlike blepharospasm, in isolated AEO, increased blinking and photophobia are not prominent clinical findings. A novel clinical finding that may help differentiate AEO from pretarsal blepharospasm is that, on attempting to open the eyes, the lower eyelids do not elevate, whereas in patients with pretarsal blepharospasm, the lower eyelid may go up due to spasm of the pretarsal orbicularis muscle.[19]

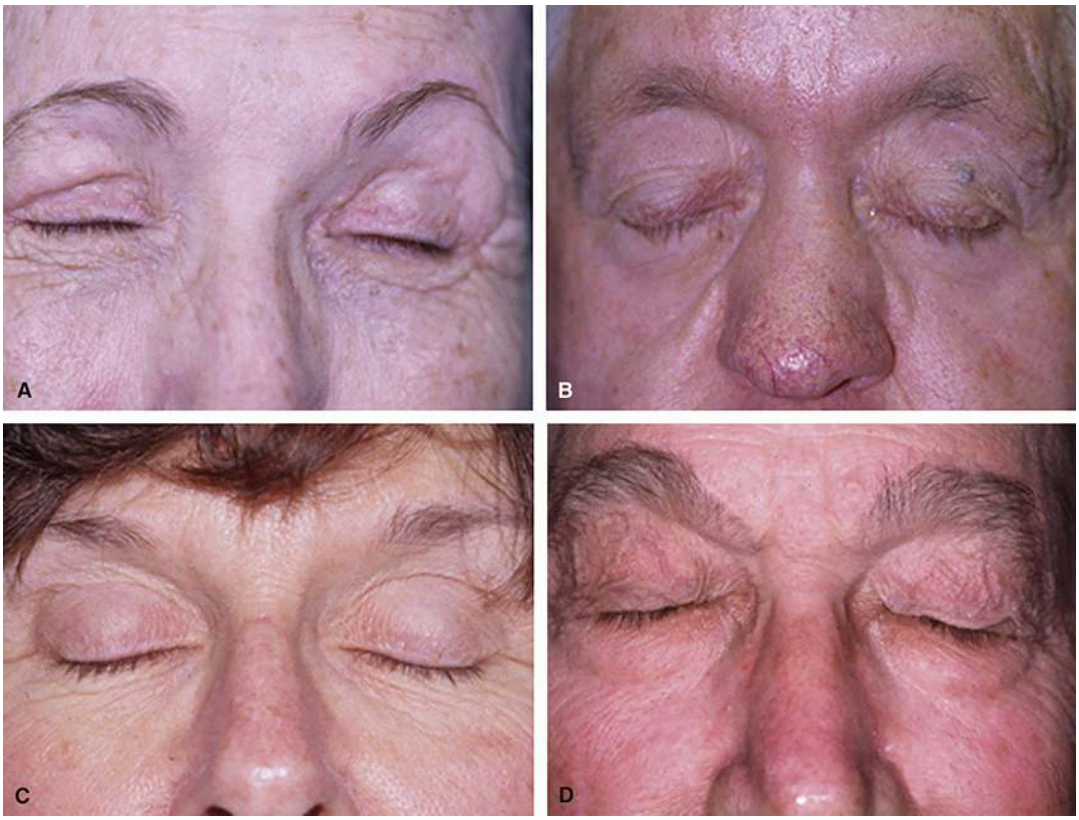

FIGURE 26.1 A-D, Apraxia of eyelid opening; there is involuntary eyelid closure without forceful orbicularis muscle contraction and with elevation of the brows.

In 5% to 30% of patients, AEO can be associated with blepharospasm, which can confuse the diagnosis.[19] Here, episodes of eyelid squeezing with a forceful contraction of the orbicularis oculi muscle may be interspersed with inability to open the eyes on command with the absence of orbicularis contraction.[59] On rare occasions, these patients may manifest clinically with blepharospasm alone, but the AEO is unmasked after the patient receives botulinum toxin therapy.[19]

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Differential Diagnosis

There are a large number of neurologic disorders that can be considered in the differential diagnosis of AEO. Blepharospasm is probably the most common condition that is often confused with AEO, and the two disorders often occur together in individual patients. The major distinguishing features are the clinically observable orbicularis muscle contraction and downward displacement of the brows which can be observed in blepharospasm, but not in AEO. Of note is that both features are also absent in pretarsal blepharospasm. Severe bilateral blepharoptosis also presents with an inability to voluntarily elevate the eyelids in the absence of orbicularis muscle contraction. Like AEO, it is also associated with brow elevation in an attempt to open the eyes. But unlike AEO, it is not episodic and there are no periods of normal open eyelids.

Other rare causes of involuntary eyelid closure include hemispheric infarcts,[60,61] diplopia-induced brain stem mechanisms subserving unilateral eyelid closure resulting in inability to elevate the eyelid,[62] blepharoclonus from Arnold-Chiari malformation,[63] monocular involuntary eyelid closure secondary to ocular pathology such as thyroid eye disease and retinal hemorrhage,[64] eyelid closure associated with normal pressure hydrocephalus,[65] following deep brain stimulation for Parkinson disease,[66] from synkinesis after facial nerve paralysis with aberrant regeneration,[67] gaze-evoked involuntary contraction of the orbicularis oculi muscle,[68] or as a complication of dental anesthesia.[69]

Treatment

There is no definitive treatment for AEO as it can occur as an isolated condition or can be associated with a large variety of concurrent neurological disorders. In cases of AEO associated with blepharospasm, it was proposed that myectomy is the only definitive treatment and that there is no other predictable successful treatment available.[70] This is followed by frontalis suspension if myectomy fails. However, well-placed botulinum toxin in the standard eyelid locations for blepharospasm plus one or two additional small 1- to 2-unit doses along the eyelid margin can be a very effective option for many patients and carries fewer potential risks and complications than myectomy surgery.

For isolated AEO without blepharospasm, a frontalis suspension may be a reasonable option,[71] and even in cases of AEO combined with blepharospasm, good results have been reported with frontalis suspension combined with botulinum toxin.[72,73]

In a case of AEO following traumatic injury to the bilateral frontal and right temporal lobes, and another case of putamen hemorrhage, eyelid symptoms resolved on a regimen of levodopa.[74,75] In another case of AEO from a deep right frontal subcortical lesion consistent with an internal carotid artery border-zone infarction, symptoms spontaneously disappeared 6 days later.[76]

Aripiprazole is an antipsychotic drug that acts as a partial agonist of dopamine D2 and D3 receptors and an antagonist of serotonin 5-HT1A and 5-HT2A receptors. It was shown to be effective in treating AEO associated with Parkinson disease in a small series. Deep brain stimulation targeting the subthalamic nucleus is an effective treatment for patients with advanced Parkinson disease, but the most frequent side effects are worsening of dysarthria and AEO seen in approximately 5% of the patients.[77] However, it has been reported that an increase in frequency and bandwidth of the deep brain stimulation can have a positive effect in reducing the symptoms of AEO.[78,79,80]

Sensory tricks, or *geste antagonistique,* such as touching the eyelids or the temporal regions, have been used as a strategy to facilitate eye opening in many patients with AEO.[9,16] Two patients with AEO were reported to have improvement of symptoms on wearing goggles, believed to simulate a sensory trick by contacting the periorbital skin. Although the mechanism of action is not known, it was suggested that proprioceptive input to the central nervous system might modulate the dystonic impulse in the basal ganglia leading to improvement of symptoms.[81]

Prognosis

The prognosis for AEO is difficult to determine given the wide variety of neurologic and other conditions associated with this entity. Cases stemming from an acute brain injury can sometimes resolve spontaneously. In those associated with extrapyramidal disorders, such as Parkinson disease, subthalamic deep brain stimulation can make AEO worse, but some studies have reported significant improvement in eyelid symptoms by manipulating the stimulation amplitude. Levodopa and the dopaminergic agent aripiprazole may also ameliorate AEO caused by levator inhibition. Botulinum toxin injected into traditional eyelid areas for blepharospasm is usually not effective, but smaller doses into the pretarsal orbicularis muscle can be effective in some patients. In cases resistant to more conservative treatment, frontalis suspension or orbicularis muscle myectomy may provide adequate amelioration of symptoms. Overall, the prognosis is fair, and in many cases, the symptoms can be managed effectively.

Histopathology

The authors are not aware of any histopathological studies of the levator palpebrae or orbicularis oculi muscles or other eyelid structures in patients with AEO. The histopathological changes in the central nervous system reflect the disease process underlying the apraxia.

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CHAPTER 27

Blepharochalasis

Key Points

- Blepharochalasis is a rare eyelid disorder characterized by recurrent episodes of painless eyelid edema, eventually leading to atrophy of periorbital tissues
- The pathophysiology remains largely unknown, but an immunologic mechanism is likely
- Trigger factors are unclear but may include menstruation, upper respiratory tract infection, beestings, sports, crying, fever, wind, emotional or psychological stress, and minor eyelid trauma
- Typical presentation is between the ages of 10 and 20 years
- Clinical features include skin that is thin, stretched, atrophic, redundant, loose, and discolored with abundant fine wrinkles
- It may be associated with lip edema, and nontoxic swelling of the thyroid gland
- There is no effective medical treatment for blepharochalasis, but oral doxycycline has been reported to be useful in some cases
- Late complications of blepharochalasis may include blepharophimosis, prolapsed lacrimal glands and orbital fat, and lower lid retraction

First reported more than two centuries ago, blepharochalasis is a rare eyelid disorder characterized by recurrent episodes of painless eyelid edema, eventually leading to atrophy of periorbital tissues.[1,2,3,4,5] While the disorder is well recognized, its exact etiology is yet to be fully elucidated.[1] Although he was not the first to describe the condition, it was Fuchs in 1895 who coined the term "blepharochalasis," which is etymologically derived from a Greek word meaning eyelid slackening. He also laid down the foundations for blepharochalasis as a separate clinical entity with a unique set of distinguishable characteristics.[2]

Etiology and Pathogenesis

Dermatologic literature frequently reiterates the dictum that blepharochalasis is a very localized form of cutis laxa,[6,7,8,9] and indeed the clinical as well as the histopathological features of blepharochalasis may partly resemble the elastolytic features of type I (but not type II) acquired cutis laxa.[10] Nevertheless, the pathophysiology of blepharochalasis remains largely unknown, although several theories have been proposed. The postpubertal onset may suggest a hormonal cause,[4] while an underlying vascular etiology is strongly supported by the redness and hyperemia of the skin during the attacks.[2] This vascular etiology is further reinforced by the clinical features of the disease.[1] An onset without an identifiable cause followed by spontaneous resolution is reminiscent of idiopathic angioedema.[1]

An immunologic mechanism that involves matrix metalloproteinases (MMPs) has long been suspected.[11] Postinflammatory release of MMPs hypothetically upregulates elastolytic and collagenolytic activity in blepharochalasis patients.[11,12] This immunologic mechanism is supported by several recent studies that demonstrate that blepharochalasis patients have immunoglobulin A (IgA) antibodies directed against elastic fibers in the dermis,[1,8,9,13] although a recent study failed to detect dermal IgA staining.[12] A reduction in the blood levels of complement C4 lends further credibility to an immunologic mechanism.[8] Yet it is still difficult to comprehend why a purported immune mechanism against elastic fibers would lead only to such localized disease. Because several familial cases have been reported,[4] and because no one knows exactly why elastic fibers are still not reassembled in the dermis, or why IgA staining persists even after prolonged periods of quiescence of the disease, the occurrence of a yet unknown hereditary factor cannot be excluded.[6]

What exactly triggers the inflammatory response in the first place is also a matter of debate, and a recent literature review failed to

identify a verifiable inciting factor in more than half the patients.[1] A large number of poorly documented trigger factors have been reported in the literature, including menstruation, upper respiratory tract infection, a beesting, sports, crying, fever, wind, emotional or psychological stress, and even minor eyelid trauma.[1] However, what complicates matters further is the loose definition of blepharochalasis, as some of the reported cases even in recent literature may not be patients with blepharochalasis after all.[1,3,14]

Clinical Presentation

Because of the rarity of blepharochalasis, robust demographic data are lacking. However, the typical presentation is between the ages of 10 and 20 years.[4] Although previously thought to be more common in females,[1] the reported male-to-female ratio is 1:1.[1,2,4,7] The active stage of blepharochalasis is characterized by recurrent episodes *(Print pagebreak 182)* of nonpainful, nonerythematous, and nonpitting edema of both upper eyelids (Figure 27.1), and this edema is relatively resistant to antihistamines and corticosteroids.[1,4,5] Unilateral involvement and involvement of the lower eyelids is less common,[1,2,8] but in more severe cases, the attacks may occasionally be observed in the lower eyelids.[1,2] The frequency of the episodic attacks varies from one patient to the other, but initially, it occurs around three to four times a year and then gradually declines as the patient grows older until the attacks completely subside.[1,4] However, the frequency and nature of the attacks are too variable for any meaningful analysis or standardization.[2] They can occur monthly or annually, lasting from several hours to several weeks, and can persist for only a year or 2, or recur over several decades.[2] After multiple attacks of eyelid edema, the eyelid suffers significant damage and enters a chronic phase of the disease, which is defined as the cessation of any episodic attacks for 2 years.[2] After the acute phase, the eyelid acquires either an atrophic or a hypertrophic appearance.[4] However, based on a series of 30 cases, Collin[2] rejected this classification scheme and questioned the existence of a hypertrophic type in the quiescent or chronic phase of the disease. Instead, he proposed that the hypertrophic phase is a misnomer that occurs when patients are observed by clinicians while they are still in an acute phase, which may indeed be quite prolonged in some patients. He further argued that all patients would invariably progress to atrophy. The authors' experience does not fully support these findings, as older patients are occasionally seen with recalcitrant hypertrophic changes that can persist for decades (Figure 27.1C).

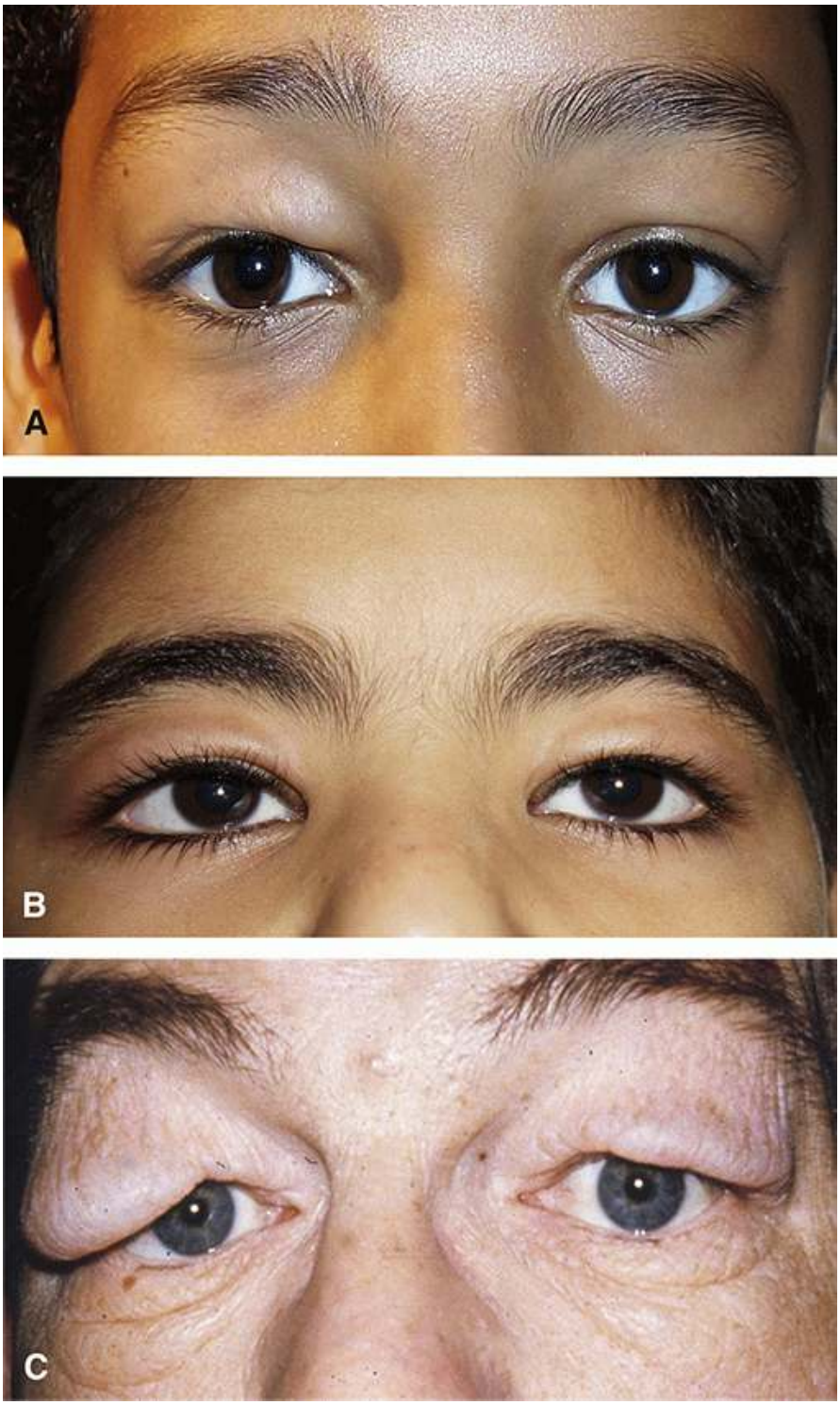

FIGURE 27.1 Hypertrophic changes in blepharochalasis. A, Asymmetrical fat bulge with predominant protrusion of the nasal pad of fat. B, Bilateral hypertrophic changes with a generalized fat bulge. C, An unusual case of persistence of hypertrophic eyelid changes through old age with asymmetrical generalized fat bulging.

In the acute phase of the disease or in the hypertrophic variety,[2] a massive prolapse of orbital fat and the lacrimal glands can occur due to weakness of the orbital septum.[4] However, in the atrophic variety or as the disease quiesces and reaches the chronic phase, the skin becomes thin, stretched, atrophic, redundant, loose, and discolored with abundant fine wrinkles acquiring the appearance of a "wrinkled cigarette paper" (Figure 27.2).[5,6] The skin may attain a reddish hue and telangiectatic vessels may be visible under the skin,[4] or it may show areas of hyper- or hypopigmentation. Ptosis is very commonly encountered in both varieties due to attenuation or disinsertion of the levator aponeurosis (Figure 27.3).[1,4]

Less commonly encountered features include a horizontal laxity of the upper as well as the lower eyelids due to dehiscence or disinsertion of the lateral or the medial canthal tendons.[2,4] Interestingly, the loss of fixation occurs at the distal attachment between the tendons and the tarsus, but the tendon remains firmly attached to the periosteum at the orbital rims, eventually ending in

rounding of the lateral canthal angle, and a horizontally shortened palpebral fissure, that may simulate blepharophimosis.[1,2,4] In severe cases, the globe may acquire a hollow sunken appearance due to marked atrophy of orbital fat.[4] Less frequently, these patients can develop a pseudoepicanthal fold due to the loss or atrophy of the nasal pad of fat (Figure 27.2C).[1,15]

Systemic associations are not common, but when blepharophimosis is accompanied by lip edema (double lips), and nontoxic swelling of the thyroid gland, the diagnosis of Ascher syndrome or Ascher triad should be considered.[16,17] It is estimated that blepharochalasis is a consistent finding in 80% of patients with Ascher syndrome.[17] Other rare associations of blepharochalasis include acute lymphocytic leukemia, unilateral renal agenesis, congenital heart disease with a left-to-right shunt, and multiple vertebral anomalies.[16]

Differential Diagnosis

Several entities can simulate blepharochalasis. It may be more difficult to identify the condition in the acute phase of the disease when the inflammatory episodes begin because *(Print pagebreak 183)* the list of causes of acute and chronic eyelid swelling is extensive. In the chronic phase, when disease activity quiesces, identification may be easier.[18]

FIGURE 27.2 Atrophic changes in blepharochalasis. A, Blepharochalasis patients show signs of premature aging with marked thinning of the skin, acquiring the landmark sign, "wrinkled cigarette paper skin." B, There is partial atrophy of orbital fat, and the skin is thin, stretched, atrophic, and redundant. C, In severe cases, a pseudoepicanthal fold can be observed due to marked atrophy of the nasal pad of fat. Again, the skin is loose, and discolored with abundant fine wrinkles.

In the acute phase, blepharochalasis can be confused with other conditions that lead to transient eyelid edema. Periorbital edema is commonly encountered in clinical practice and the list of causes is large, and although the diagnosis may be straightforward in some cases, others may be missed in actual clinical practice.[18,19] In general, the causes of periorbital edema can be classified broadly into four groups: infectious, inflammatory, tumors, or postsurgery/trauma. While tumor masses or trauma can be easily differentiated from blepharochalasis, certain other disease conditions may confuse the clinician, most commonly recurrent angioedema, hereditary angioedema, lymphedema, contact dermatitis, Melkersson-Rosenthal syndrome, rosacea, sarcoidosis, Sjögren syndrome, Ehlers-Danlos syndrome, and lower eyelid festoons.[1,5,19,20]

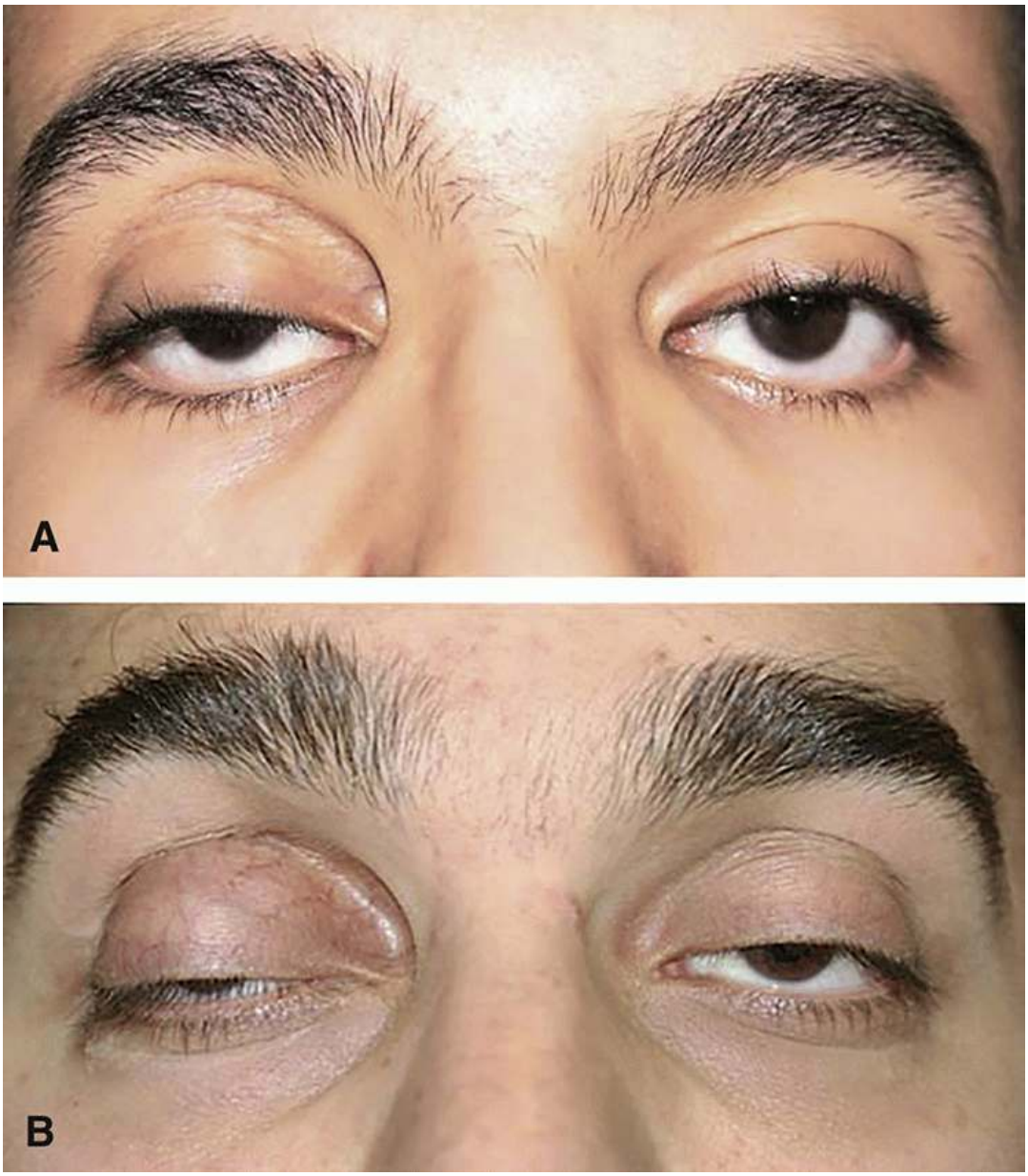

FIGURE 27.3 Ptosis in patients with blepharochalasis. A, Severe ptosis which is more marked in the OD can be seen. This is associated with severe wrinkling of the skin as well as a pseudoepicanthal fold. B, Another patient with more advanced ptosis completely occluding the visual axis. (Courtesy of Dr. Alan McNab.)

Recurrent angioedema is a transient event with no permanent sequelae in the skin. Systemic involvement in the form of urticaria, pruritus, or swelling of extremities and a favorable response to antihistaminics or corticosteroids are important differentiating points.[15] Recurrent contact dermatitis can simply be excluded by the cessation of the possible offending agent. Lymphedema, which occurs due to obstruction of lymphatic drainage,[2] could involve the upper lids and is similarly nonpitting, but the onset occurs later in life than in blepharochalasis, and the eyelid tissue is thick and bulky and not thinned.[2] Recurrent facial paralysis, a fissured tongue, or a granulomatous reaction on histopathology may help confirm the diagnosis of Melkersson-Rosenthal syndrome, while the presence of blepharitis, conjunctivitis, and facial erythema argues more in favor of rosacea.[1,21] Malar festoons, however, represent a chronic form of noninflammatory edema involving the lower eyelids and not the upper. Clinically, they resemble "cascading hammocks" with or without herniated fat.[15] Ehlers-Danlos syndrome is a genetic disorder with features of generalized cutaneous or ligamentous laxity in other parts of the body. Sarcoidosis can be excluded by histopathology and by its systemic features, while Sjögren syndrome, which can also present with eyelid edema, can be excluded by the absence of dry mouth, and negative antinuclear and SSA antibodies.[20]

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In the chronic phase of the disease, blepharochalasis should be differentiated from dermatochalasis, floppy eyelid syndrome, other causes of ptosis, as well as acquired cutis laxa.[18] Dermatochalasis, which is an exaggeration of the normal aging changes in the eyelid skin, is typically seen in the elderly, and usually occurs without any prior episodic edema attacks.[2,15] The ptosis associated

with blepharochalasis could be easily confused with aponeurotic ptosis or with other sinister causes of ptosis like myasthenia gravis, but awareness of the subtle clinical signs, which are so characteristic of blepharochalasis (atrophic skin, and a pseudoepicanthal fold), can help in the diagnosis and spare the patient unnecessary investigations.[15] Acquired forms of cutis laxa, which are exceedingly rare, may also be confused with blepharochalasis.[1,15]

Until our understanding of the etiology and pathogenesis of blepharochalasis increases, cases of blepharochalasis will be overdiagnosed by oculoplastic surgeons who are aware of the condition or will be mislabeled with an alternative etiology by ophthalmologists and dermatologists who are not. In general, signs that should warrant an alternative diagnosis include a unilateral disease process, a chronic and progressive course of the disease without acute exacerbations, or an atypical age at presentation, and most importantly the lack of any associated thinning of the skin.[2,3,22]

Treatment

No medical treatment has thus far proven effective for blepharochalasis, but some patients have reported subjective improvement with cold compresses during the attacks.[2] Two recent and frequently referenced papers from the same group of authors reported successful medical treatment with a combination of oral acetazolamide and topical steroids.[3,14] However, at closer inspection, the age group, as well as the age of onset in the patients reported in both papers, were in the 4th-8th decades, which does not fit the usual demographics of blepharochalasis. Also, the pictures provided do not show any eyelid skin thinning or other features of this condition.[3,14]

Based on the successful use of oral doxycycline in chronic blepharitis,[23] a condition which is also associated with MMP overexpression, the successful use of oral doxycycline with an initial loading dose of 50 mg once daily, and tapered over 10 months, has been reported. Although the follow-up was sufficient in one patient (18 months), in the other patient, it was much shorter (4 months).[11] A more recent paper reported only partial success with doxycycline.[15]

Surgery should not be performed in the acute phase, and patients who push for earlier surgery should be warned that it might have to be repeated later[2,5] because recurrent episodic attacks after a premature surgery could sabotage previous repair attempts.[11] Premature ptosis surgery could be followed by a redehiscence of the levator aponeurosis, while a patient with a protruded nasal pad of fat that is prematurely excised could develop a pseudoepicanthal fold later if the orbital fat progressively atrophies.[2] That said, it should be mentioned that the surgeon should not be dogmatic, and a decision to proceed with surgery earlier rather than later should be tailored to patients' functional needs and cosmetic concerns.[2]

Although ptosis surgery could at least in theory be performed through the conjunctival route, an anterior approach is generally recommended because this allows the surgeon to combine ptosis surgery with excision of the redundant skin, along with fat grafting and/or resuspension of the lacrimal gland.[1,2,4] Patients should be warned that ptosis surgery in blepharochalasis patients is unpredictable,[1,4,24] and the reasons for this are twofold. First and foremost, surgeons should watch out for a lateral canthal tendon laxity, which could lead to temporal peaking.[2] Whether to tighten the lateral canthal tendon before ptosis surgery or to defer and combine both surgeries is debatable.[1,2] Second, recurrent bouts of edema and stretching may have destroyed the lower portion of the aponeurosis, making it exceedingly difficult for the surgeon to identify its true edge.[1] Patients should also be warned that surgery may be complicated by prolonged periods of postoperative edema against which pharmacologic agents do not seem to be of much help.[4] The timing of surgery is also critical. To reduce the rate of recurrences, surgery is preferably deferred until blepharochalasis is stable or inactive because recurrent bouts of postoperative eyelid edema may lead to recurrence of ptosis.[24]

Prognosis

Late complications of blepharochalasis that are attributable to continuous underlying structural tissue destruction include blepharophimosis, prolapsed lacrimal tissue and orbital fat, lower lid retraction, and pseudoepicanthal folds. Treatments with local and systemic corticosteroids and antihistamines generally do not decrease the incidence, frequency, or duration of attacks and recurrent attacks of eyelid edema are common.

Histopathology

Histopathologically, the excised tissue usually shows epidermal atrophy with a marked decrease or fragmentation of elastic fibers.[1,2,5,8] Histological studies in more advanced cases demonstrate that elastic fibers have completely vanished as revealed by van

Gieson staining of the dermis.[6,13] Capillaries are dilated and increased in numbers with an occasional perivascular inflammatory infiltrate.[1,2,5,8] Collagen is also atrophic probably due to the collagenolytic activity mediated by MMPs[1,2]; however, the destruction of collagen fibers is an epiphenomenon that is less pronounced than and possibly secondary to elastolysis.[13] Chronic inflammatory changes were also demonstrated in the orbicularis oculi, the levator muscle, as well as the tarsus, and not just circumscribed to the dermis.[1,2]

The histopathologic changes in prolapsed lacrimal glands in patients with blepharochalasis have been researched recently in the Chinese literature and include elastic fiber *(Print pagebreak 185)* degeneration, inflammatory infiltration of the lacrimal glands, marked loosening of the supporting fascial tissues, and raised levels of immunologic markers (IgA, $CD3^+$ T cells, MMP-3, and MMP-9).[25] What these findings suggest is that in blepharochalasis patients, lacrimal gland prolapse may not just stem from mechanical causes but may have an underlying immunopathogenetic mechanism as well.[25]

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CHAPTER 28

Blepharophimosis Syndrome

Key Points

- Blepharophimosis syndrome is genetically and phenotypically distinct from simple congenital ptosis
- Blepharophimosis inheritance is usually autosomal dominant, and approximately 75% of cases have a positive family history
- The responsible gene is the forkhead transcription factor gene 2 (*FOXL2*), which is strongly expressed in the developing as well as the adult eyelids
- Most patients have severe, bilateral, and usually symmetric upper eyelid ptosis with very poor to absent levator muscle function
- Other findings include epicanthus inversus, telecanthus, refractive errors, and bilateral agenesis of the lacrimal gland, which occurs in more than 50% of patients
- Treatment is surgical to repair the epicanthus, telecanthus, and ptosis, either in several stages or in a single stage

Blepharophimosis syndrome is genetically and phenotypically distinct from simple congenital ptosis. It consists of a constellation of clinical findings, which altogether define the syndrome.[1,2] It was probably first described by Von Ammon in 1841[3] and was further defined by Vignes in 1889.[4] It took another 30 years for a more formal description to appear as a triad of ptosis, blepharophimosis, and epicanthus inversus,[5] establishing the term blepharophimosis-ptosis-epicanthus inversus syndrome with the acronym BPES. Later in the same year (1921), the hereditary pattern was described by Dimitry.[6] In 1971, telecanthus was added to the triad, making it a tetrad of signs (Figure 28.1).[7] It is imperative to be aware of the syndrome because of its genetic, surgical, and fertility implications.[8]

Etiology and Pathogenesis

Approximately 75% of cases of blepharophimosis have a positive family history, and inheritance is usually autosomal dominant, mostly through the father.[9] The remaining cases are sporadic, where the proband acquires the syndrome through a de novo mutation in the afflicted child or one of its parents. These figures, however, are not universal. In a recent study in the Indian population, only 23% of the affected patients showed a positive family history and 24% of patients showed chromosomal anomalies on cytogenetic analysis.[10]

The gene responsible for the clinical manifestations of the syndrome, the FOXL2 gene (forkhead transcription factor gene 2), is strongly expressed in the developing as well as the adult eyelids, in the pituitary gland, and the ovaries, but not in the testes, which explains the female, not male, infertility. It is located on the long arm of chromosome 3 (3q22-26).[10,11,12] Approximately 5% of the mutations occur outside the designated region of FOXL2, which may explain the occasional finding of atypical associated conditions like mental retardation.[10,11,12,13,14,15,16] In general, a sibling of a patient with BPES has minimal risk of developing the disease if the eyelids of both parents are normal[13]; however, it should be noted that because germline mosaicism has been documented with BPES, the exact risk of having another child with blepharophimosis should depend upon the results of genetic testing of both parents.[13] If a parent has a FOXL2 mutation, the risk of transmission is 50%, but if the parents are free, the risk of developing another de novo mutation in a sibling is exceedingly low.[14]

The existence of two types of blepharophimosis based on female infertility was proposed in 1983.[15] In type I, the syndrome is transmitted only by males with 100% penetrance, as affected females are infertile. In type II, females are fertile, and the genetic defect is transmitted by both affected males and females with a 96.5% penetrance.[15] The distinction between types I and II is mainly based on genetic testing. So far, 271 different mutations or allelic variables have been reported to cause blepharophimosis syndrome.[16] In general, type 1 mutations usually result from deletions in the FOXL2 gene and cause complete loss of gene

function, whereas type 2 mutations usually result from an extended or an elongated FOXL2 gene causing a partial loss of gene function.[10,11,12,13,14,15,16] Recently, however, the concept of two distinct types of blepharophimosis has been challenged. Even when sharing the same mutation, intrafamilial phenotypic variability, as well as the genotypic overlap between types I and II, have been demonstrated,[17,18,19] calling into question the strict classification of blepharophimosis syndrome into types 1 and 2.

Clinical Presentation

Blepharophimosis syndrome is not uncommon, with a reported incidence of 1/50,000 live births.[20] Because of the peculiar features that are instantly obvious at birth, patients typically present very early in life. Blepharophimosis, or narrowing of the horizontal palpebral fissure, is profound.[21] In the adult blepharophimosis patient, palpebral fissure length *(Print pagebreak 187)* is reduced and ranges from 20 to 22 mm (normal range 25-30 mm).[8,10,21]

Most patients with blepharophimosis have severe, bilateral, and usually symmetric upper eyelid ptosis with very poor to absent levator muscle function. Ptosis is usually so severe that most of these children assume the typical chin-up head position with pronounced high arched eyebrows from frontalis contraction (Figure 28.2). In the past, this led some researchers to erroneously postulate a bony abnormality of the supraorbital rim.[9,20] Factors underlying this severe ptosis in blepharophimosis syndrome remain unexplained.[22] Until recently, this was simply attributed to severe dysplasia or even absence of the levator muscle,[8,21] but this concept was recently challenged by demonstrating that, contrary to simple congenital ptosis, there was a significant improvement in levator function after supramaximal levator resections.[22] In a subsequent paper, the authors offered new insights into the pathophysiologic mechanisms leading to severe ptosis.[23] On preoperative MRI scans the levator aponeurosis was unusually thinned and elongated (25 mm). This finding was also supported intraoperatively, and histopathology showed a disorganized, exceedingly long aponeurosis with a healthy-looking well-defined muscle belly posteriorly. However, this normal muscle portion was situated too deep in the orbit and was poorly connected to the tarsal plate through the abnormal aponeurosis.[23]

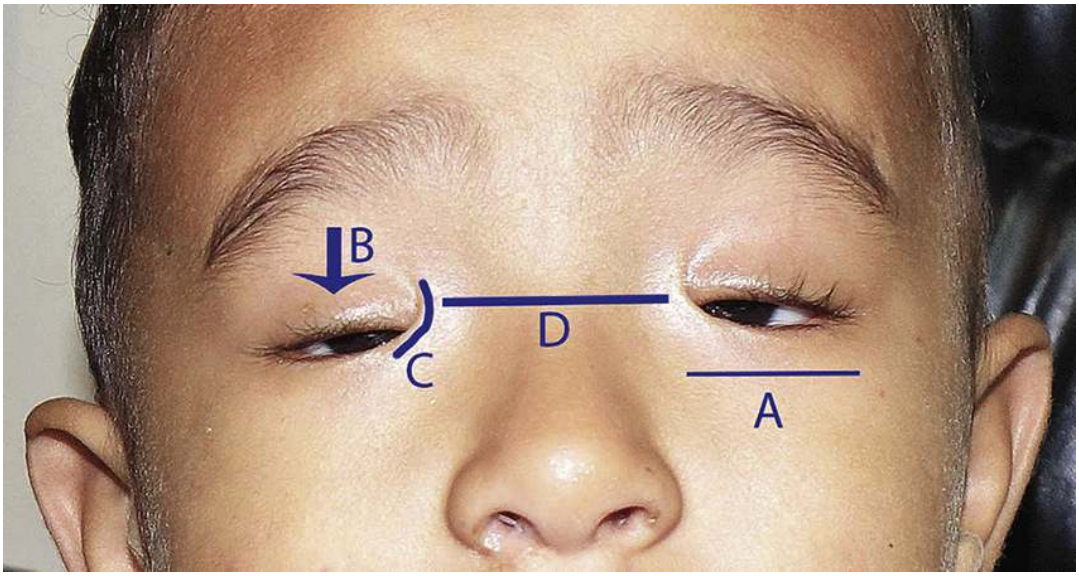

FIGURE 28.1 Typical findings of blepharophimosis syndrome. A, Blepharophimosis. B, Ptosis. C, Epicanthus inversus. D, Telecanthus.

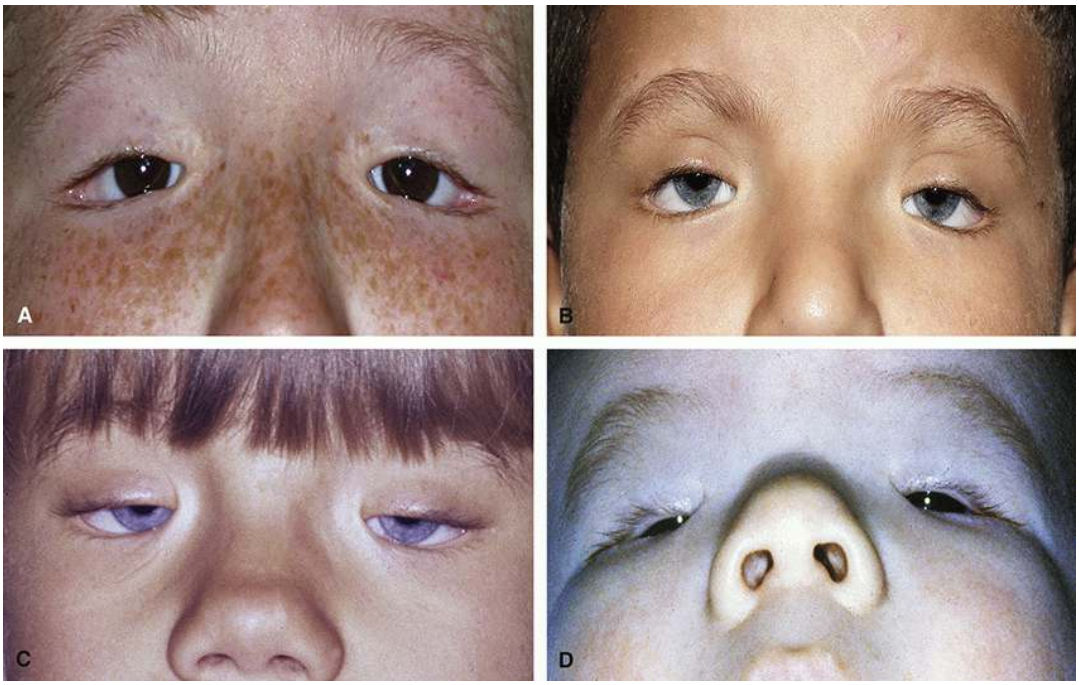

FIGURE 28.2 Variable degrees of ptosis in blepharophimosis syndrome. A, Moderate ptosis without obstruction of the visual axis. B, Moderate ptosis with bisection of the visual axis. C, Severe ptosis obstructing the visual axis. D, Severe profound ptosis completely obliterating the visual axis with the typical chin-up head position.

Epicanthus inversus is defined as an epicanthal fold emerging from the lower eyelid and curving upward obliterating the regular concavity in the medial canthal area. It is usually more pronounced at a very young age but tends to improve with age.[8,24] Telecanthus or lateral displacement of the medial canthus is observed in the vast majority of patients with subsequent lateral displacement of the inferior punctum.[1,24,25,26] This is classically attributed to an abnormally long inferior crus of the medial canthal *(Print pagebreak 188)* tendon (MCT).[1] Recently, however, it was hypothesized that a loose attachment of the MCT to the lower eyelid or an abnormal bifurcation of the medial canthal tendon is the underlying anatomical cause for the peculiar deformities of BPES that are classically observed in the medial canthal region.[24] The authors noticed that, in patients with BPES, the normal temporal fork-like splitting of the medial canthal tendon is not observed. Instead, the lower crus seemed to be markedly less formed and the medial canthal tendon, which was unusually thin, appeared to be mainly connected to the upper eyelid without the classic Y-shaped bifurcation.[24] Of note is that because of the associated phimosis of the palpebral fissure, hypertelorism is not observed in patients with BPES.[8]

Other ocular features of significance include refractive errors, which are almost a universal finding in blepharophimosis. This is usually simple hyperopia or with-the-rule astigmatism.[10] There is also a very high rate of strabismus, which ranges from 20% to 40%, compared with 2% to 4% in the general population.[10,21,27] Strabismus is usually horizontal (esodeviations are more common than exodeviations),[10] whereas vertical deviations are rare.[9,10] An alarmingly high rate of amblyopia ranging from 39% to 60% is also reported in patients with blepharophimosis and is multifactorial, resulting from profound ptosis, strabismus, and possibly a refractive error.[9,10,21] In contrast, the rate of amblyopia in patients with congenital ptosis is around 19%,[28] whereas in the general population the rate is 3.2%.[21] Associated lower eyelid anomalies include lower eyelid ectropion that may be more pronounced laterally resembling euryblepharon, and distichiasis or entropion of the medial part (Figure 28.3).[10,20] A novel clinical finding in blepharophimosis syndrome is unilateral, or more commonly bilateral, agenesis of the lacrimal gland, which occurs in more than 50% of patients. This is associated with a significant reduction in Schirmer scores. In the remaining 50%, the lacrimal gland is hypovolemic.[2] Because of this finding, plus the unusually high rate of amblyopia in these patients, ptosis surgery remains controversial.[2,29] In our experience this may be overstated because the palpebral fissure is narrow both horizontally and vertically, which may protect against corneal exposure. Less common ocular findings include lacrimal drainage system anomalies, angle dysgenesis, choroidal colobomas, optic nerve hypoplasia, and microcornea, or microphthalmos.[8,30,31] Less common associated facial features include a flattened depressed nasal bridge, high arched palate, and low set or cup-shaped ears.[21]

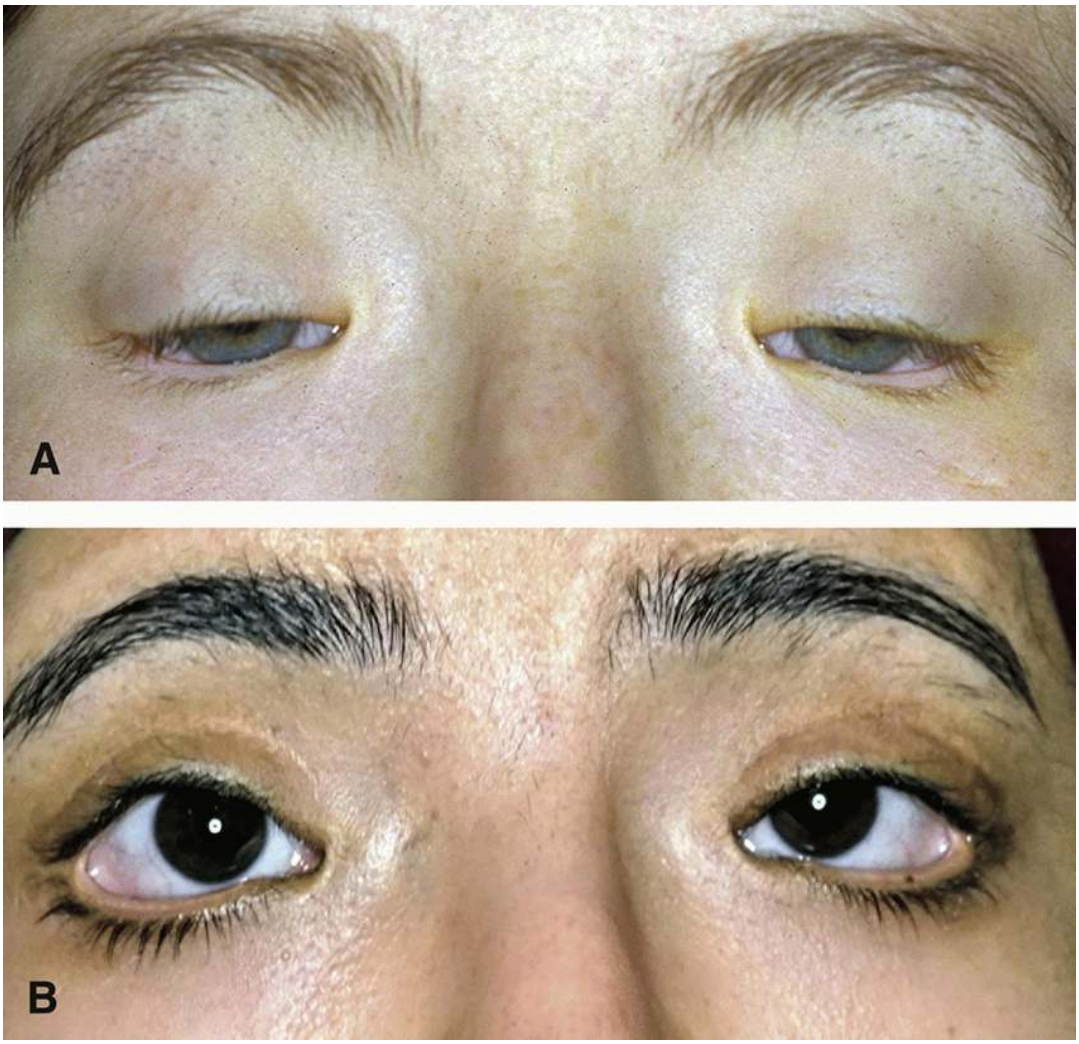

FIGURE 28.3 Variable degrees of lower eyelid ectropion in blepharophimosis syndrome. A, Mild ectropion. B, Moderate-severe ectropion. Anterior lamellar shortening is obvious particularly laterally.

In general, some females may have normal menarche in their early reproductive years, but they soon develop either ovarian resistance to gonadotropins (resistant ovary syndrome), irregular cycles, or true premature ovarian failure manifested by primary or secondary amenorrhea.

Differential Diagnosis

The most important differential diagnostic disease is simple congenital ptosis. Although it could be argued that it is easy to differentiate both conditions, it is important to remember that epicanthal folds are a normal finding in Asians and up to 30% of occidental infants usually in the form of epicanthus tarsalis or epicanthus palpebralis.[32] Therefore, not every infant with ptosis and epicanthus is a patient with blepharophimosis. As a clinical sign, blepharophimosis may be a harbinger of several systemic genetic disorders; therefore, the clinical findings of phimotic eyelids should not be automatically considered as a sine qua non for isolated BPES.[33] These syndromic blepharophimosis cases are dubbed "blepharophimosis-plus" genetic disorders and are observed in 7% of patients with blepharophimosis and are all exceedingly rare syndromes; nevertheless, they should be promptly excluded based on their associated systemic findings so that prompt referral may be advised.[33] These syndromes include Noonan syndrome (short stature, bleeding problems, and developmental delay), Marden-Walker syndrome (multiple joint contractures), Waardenburg syndrome (pale blue eyes, profound hearing loss), Williams syndrome (intellectual disability, heart problems), fetal alcohol syndrome, Dubowitz syndrome (mental retardation, microencephaly), trisomy 18, Ohdo syndrome (male genital abnormalities, missing patella, mental retardation), and Nicolaides-Baraitser syndrome (blepharophimosis, mental retardation, early-onset seizures, short stature, dysmorphic facial features, and sparse hair).[9,21,33] Etiologically, blepharophimosis-plus syndromes can be divided into those that result from a non-*FOXL2* etiology (78% of patients) and those associated with more extensive or multigene deletions involving the *FOXL2* gene itself (22%).[13,33]

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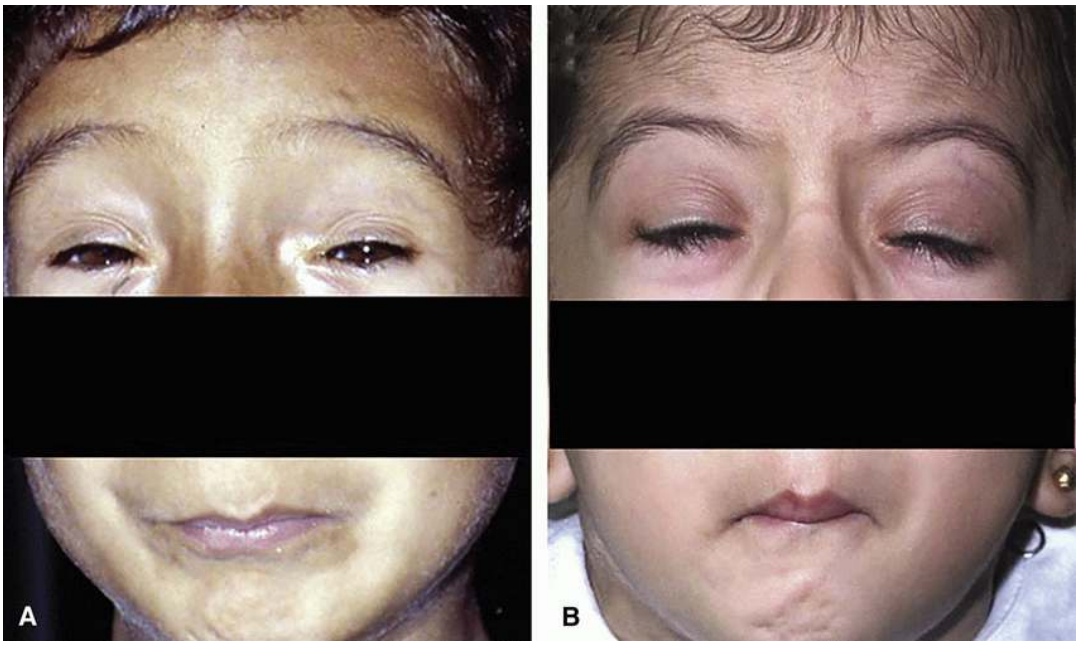

FIGURE 28.4 Schwartz-Jampel syndrome (SJS). A, The fixed facial features of Schwartz-Jampel syndrome (ptosis, blepharophimosis, and a puckered mouth) are related to the chronic contracture of the periocular as well as the perioral muscles. (Courtesy of Dr. Antonio Augusto Cruz.) B, A more severe example of SJS with more marked puckering of the mouth. Blepharophimosis is also more pronounced.

A relatively new entity, blepharophimosis–ptosis–intellectual disability syndromes (BID) refer to a group of more than a hundred phenotypically overlapping clinical syndromes including Kaufman oculocerebrofacial syndrome and OHDO syndrome. BID syndromes are distinct both genetically and clinically from BPES and are characterized by distinct morphological findings (blepharophimosis) plus intellectual disability.[34] One of the hallmark syndromes of BID is Kaufman oculo–cerebro–facial syndrome (KOS), which is also referred to as blepharophimosis–ptosis–intellectual disability (BPID) syndrome and is characterized by the typical dysmorphic features of blepharophimosis in addition to intellectual disability, microcephaly, microcornea, pale optic discs, flat philtrum, preauricular skin tags, and a high arched palate.[34,35]

Schwartz-Jampel syndrome is a rare autosomal recessive disease that may be more common in the Middle East and is characterized by generalized myotonia, muscle stiffness, weakness, joint deformities, short stature, blepharospasm, as well as acquired ptosis/blepharophimosis.[36,37,38,39] The fixed facial features of Schwartz-Jampel syndrome (SJS) are related to the chronic contracture of the periocular as well as the perioral muscles (Figure 28.4). Of note is that malignant hyperthermia and difficult intubation are potential complications of general anesthesia in patients with SJS.[36,37,38,39]

Treatment

Currently, the only treatment of blepharophimosis syndrome is surgical; however, it is one of the most complex procedures in the field of eyelid surgery owing to the presence of coexisting multiple deformities making the exact timing, sequence, and surgical technique controversial. The classical approach is to repair epicanthus and telecanthus first followed by repair of ptosis 3 to 6 months later. This is based on the premise that reconstruction of the medial canthus can worsen ptosis because the eyelids are tethered medially in telecanthus surgery (Figure 28.5A).[20,21,32,40] This epicanthus-first approach seems rather counterintuitive in light of the high rate of amblyopia in these patients.[10] Therefore, some authors reverse the sequence and start with surgical correction of ptosis and defer canthal surgery for later (Figure 28.5B).[9] Exactly how early ptosis should be corrected is also a matter of debate. A recent study on patients with severe ptosis who were operated upon at the age of 2 years, and patients with moderate ptosis who were operated upon around the age of 5 years reported an overall incidence of amblyopia of 30.4%.[9] It could be argued that this unusually high rate of amblyopia could be attributed to the coexistence of strabismus. However, patients with severe ptosis who were operated upon earlier in this study had lower rates of amblyopia than patients with moderate ptosis. This argues in favor of earlier intervention. When such an approach is implemented, some patients are satisfied with their appearance and do not accept a second-stage correction for epicanthal folds and telecanthus, because both of them tend to improve with time.[8,9,25,41] Bilateral frontalis suspension with autogenous fascia lata is the gold standard for this surgery. However, the need for early surgery may prompt the use of other materials like silicone or donor fascia lata from one of the parents. Other alternatives include levator muscle resection[22,23,42,43] or a frontalis muscle flap.[44]

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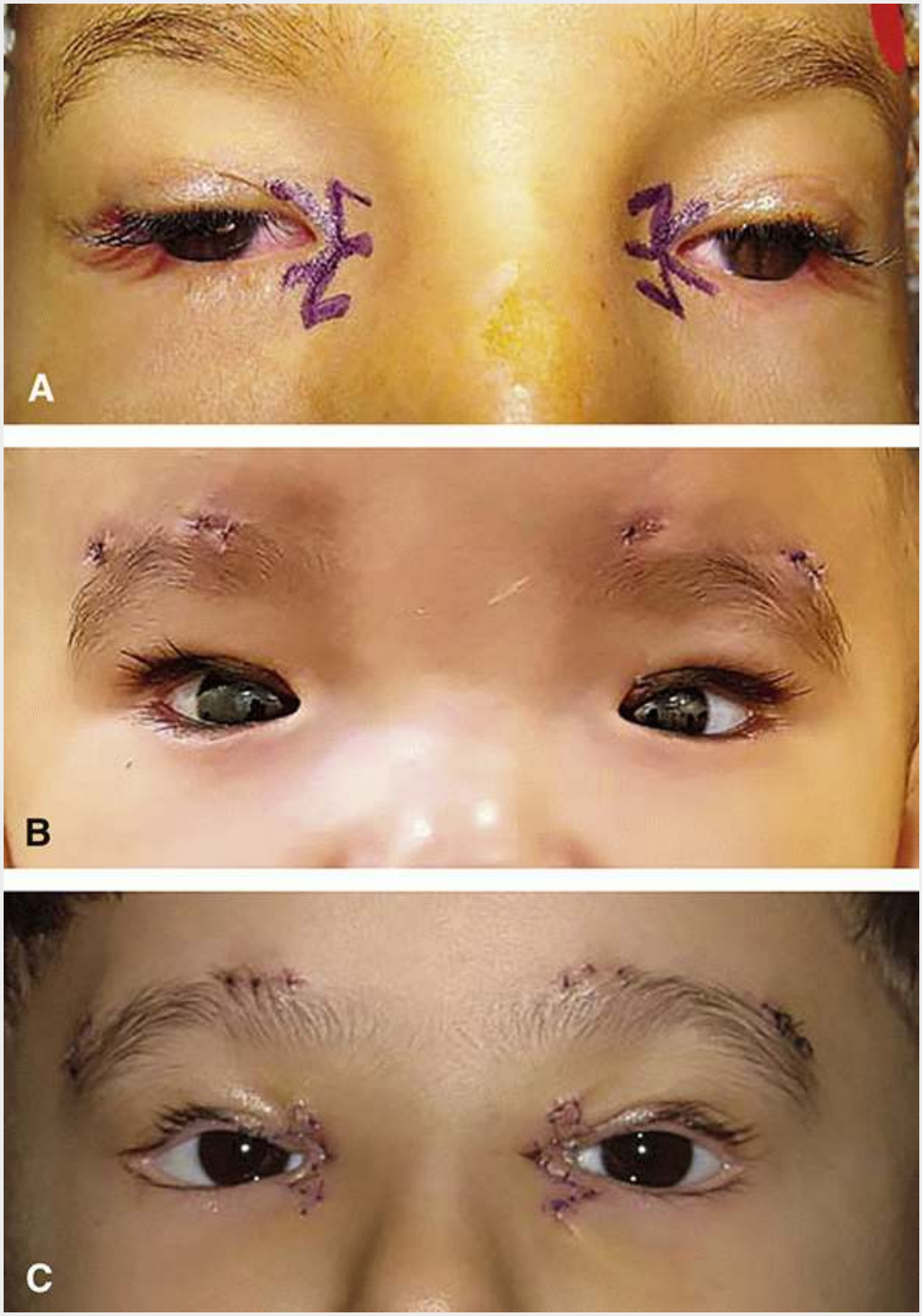

FIGURE 28.5 Three different surgical approaches for blepharophimosis syndrome. A, The traditional or *epicanthus-first* approach starts with the repair of the epicanthus and telecanthus first followed by repair of ptosis 3-6 months later. B, In the *ptosis-first* approach, the sequence may be reversed. Ptosis is corrected first and canthal surgery is deferred for later. C, The *one-stage* approach. Ptosis together with epicanthus and telecanthus are repaired simultaneously in the same setting, which may result in a temporary medial undercorrection.

Several surgical techniques have been proposed for telecanthus and epicanthal fold repair. The basic concepts underlying most of these techniques involve different designs of multiple Z-plasties, all aiming at redistribution of tissue, debulking of the abnormal subcutaneous fat beneath the epicanthal fold, and fixation of the medial canthal tendon to the periosteum at a position posterior to its original abnormal insertion.[40] Suggested techniques to address the epicanthus include the Mustardé jumping man technique, the Anderson five flap technique, or a simple Y-V plasty.[32] Although the intercanthal distance is significantly reduced after these techniques, they never achieve normalcy.[40] Therefore, to specifically address the telecanthus, transnasal wiring or anchoring the medial canthal tendon to the medial orbital rim with titanium microplate and screws could

be applied.[26,32,39,42] Combining the Y-V flap with microplate reconstruction of the medial canthal tendon is a simple and effective alternative to more involved techniques.[26]

Most authors recommend a multistage approach,[26,45] whereas some authors recommend a one-stage approach,[42,43] whereby ptosis together with epicanthus and telecanthus are repaired in the same setting (Figure 28.5C). It is important to understand that the direction of pull affected by both procedures is in opposite directions and tends to cancel each other out, especially medially.[42,43] It is also important to remember that the abnormalities observed in blepharophimosis, including epicanthal folds, result from an abnormal skin shortening rather than a surplus of skin.[32] Therefore, this approach could theoretically work in older children where ample skin is available to enable operating on the eyelids on two perpendicular planes simultaneously. The one paper that is frequently cited by proponents of the single-stage approach only cautiously recommends this approach and warns against its use if ptosis is severe.[43] If the surgeon elects to choose a one-stage procedure, the parents should be notified of the possibility of medial undercorrection that could persist for weeks.[42,43]

Lateral lower eyelid ectropion does not typically require correction in patients with blepharophimosis. If surgical correction is to be undertaken, a skin graft is needed because this outward position is due to a shortage of the anterior lamellae and is not due to a lateral canthal abnormality. Therefore, lateral canthal surgery would not work and, in fact, should be avoided.[40,43]

Prognosis

The natural history of untreated blepharophimosis syndrome is that the telecanthus and epicanthal folds may improve with time in some patients but the ptosis and blepharophimosis do not improve (Figure 28.6).[9,25] This should not imply that surgery should be deferred. Instead, surgery, particularly ptosis surgery, should be performed as early as possible because of the unusually high risk of amblyopia and the associated strabismus.[9] However, owing to the very nature of the disease and the presence of multiple associated deformities, full surgical correction that addresses all the eyelid anomalies associated with BPES may be more complex than the correction of other types of ptosis.[44,45]

A sensitive issue when dealing with parents of an afflicted female patient with blepharophimosis is the fertility issue. Parents typically present to the oculoplastic surgeon when their child is at a very early age, alarmed by their infant's appearance. Providing information on the possibility of future infertility and ordering molecular analysis of FOXL2 remain contentious. This is compounded by the fact that the correlation between FOXL2 allelic variants and phenotypes of blepharophimosis syndrome still awaits full clarification making exact genetic counseling difficult.[2,10,12] Generally, it may be preferable to delay discussing this issue until the child is a little older unless parents are planning a second child, where molecular genetic testing may be advisable earlier.

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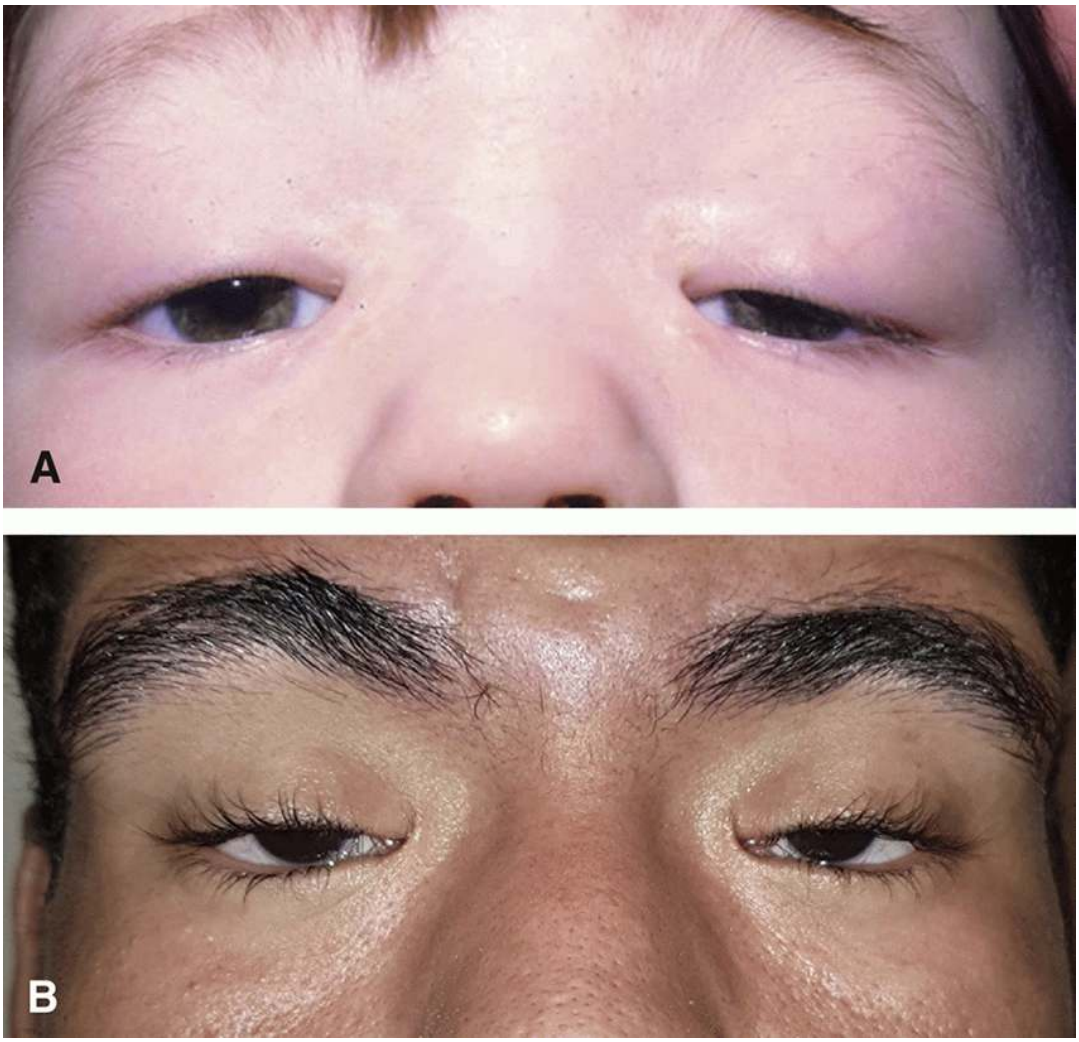

FIGURE 28.6 The natural history of untreated blepharophimosis syndrome according to the age of the patient. A, In infants and children, the full spectrum of the disorder can be observed. B, In older individuals presenting with untreated blepharophimosis, there may be a slight or moderate improvement in epicanthus and telecanthus, but the ptosis persists and dominates the picture. (Courtesy of Dr. Allen Putterman.)

Histopathology

Histopathology descriptions for blepharophimosis syndrome are limited. Huang et al[46] reported the morphological and histological findings in 30 patients, which showed that the medial canthal ligament of patients with BPES might have congenital dysplasia. By light microscopy, the anterior limbs of the medial canthal ligament were composed of collagen fibers intermingled with a few elastic fibers and striated muscle. The collagen fibers were disorganized, and the fibrous connective tissues exhibited hyaline degeneration. Fibroblasts among the collagen fibrils had pyknotic nuclei and were decreased in number. Striated muscle cells appeared to be degenerating with indistinct cell borders. Scanning electron microscopy showed enlarged disorganized with cracks and degenerative surface deposits. Transmission electron microscopy revealed irregular and disorganized collagen fibrils, some of which were torn and loose with increased spacing between fibrils. The fibroblasts were in varying stages of cell death with diminished cytoplasm, nuclear pyknosis, and cell membrane degeneration. Decock and coworkers examined the levator muscle from eight patients with BPES.[23] They identified disorganized connective tissue replacing the normal aponeurosis and increased connective and fatty tissue in the levator muscle.

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CHAPTER 29

Congenital Upper and Lower Eyelid Coloboma

Key Points

- A congenital eyelid coloboma is a full-thickness defect that can be unilateral or bilateral
- It may present with or without corneopalpebral adhesions and can be associated with anomalies such as Fraser syndrome, Goldenhar syndrome, or Treacher Collins syndrome
- The defect involves conjunctiva, tarsal plate, orbicularis muscle, and skin and leaves the cornea exposed
- The etiology is varied and multifactorial, with a genetic basis in associated syndromes and possibly craniofacial clefts and developmental factors such as abnormal neural crest cell migration, anomalous vascular development, defective migration and fusion of mesoderm, or amniotic bands
- The clinical features of eyelid coloboma vary from a simple limited defect with minimal adhesions to the cornea to complete absence of the eyelid as in cryptophthalmos
- Small and moderate-sized upper eyelid colobomas can usually be closed primarily or with simple reconstructive techniques
- Larger defects or those associated with corneopalpebral adhesions and craniofacial clefts will require more major reconstructive procedures including grafts and flaps
- The cosmetic and functional prognosis for simple colobomas is usually excellent, but when associated with facial clefts or various syndromes, multiple surgical procedures are usually necessary to achieve a fair to good outcome

Coloboma (plural, colobomas, colobomata) implies a full-thickness, curtailed structure, or a hole or a defect in a tissue,[1,2] and is a term that is almost exclusively used in ophthalmology.[1] First described in the iris in 1673 by Bartholin the younger, ocular colobomata can involve any layer of the eye[3] and usually result from defective closure of the embryonic fissure.[3] Eyelid colobomata, on the other hand, may involve the upper or the lower eyelids; can be unilateral or bilateral, symmetrical or asymmetrical; and can involve animals or humans. They may present with or without corneopalpebral adhesions (CPAs) and may be an isolated finding or be part of a larger spectrum of congenital anomalies as in the case of Fraser syndrome, Goldenhar syndrome, or Treacher Collins syndrome.[4] Congenital upper eyelid coloboma, in particular, may threaten vision at a very early age and is one of the few true nontraumatic oculoplastic emergencies that require prompt management when it presents in the first few days of life with a corneal ulcer or impending perforation. The classic congenital eyelid defect includes a shortage of conjunctiva, tarsal plate, orbicularis muscle, and skin, which leaves the cornea unprotected, resulting in possible exposure keratopathy. Even after closing the defect, close monitoring of visual function is of paramount importance because of the very high risk of amblyopia.[4]

Each of the disorders described below is given a large number of different names in the literature. Cryptophthalmos (CO) and its syndromic counterpart, Fraser syndrome (FS), have been assigned 17 different names.[5,6,7] Goldenhar syndrome (GS) has also been christened with at least 16 different names, the most famous of which are craniofacial microsomia and oculoauriculovertebral spectrum (OAVS).[8,9,10]
Treacher Collins syndrome (TCS) also goes by the names of mandibulofacial dysostosis or Franceschetti-Zwahlen-Klein syndrome.[11,12] Craniofacial clefts have also been described under at least 10 different names the most popular name being Tessier clefts (TCs), and in the case of clefts involving the eyelids, the term oblique facial clefts is also a popular name.[13,14,15] For practical purposes, we have retained the use of the terms CO, FS, GS, TCS, and TC throughout this chapter until a single orthonym is universally adopted for each of these disorders.[16]

Etiology and Pathogenesis

To date, the network of genetic mutations responsible for eyelid colobomas is largely unknown. Quite possibly, environmental factors or mechanical events during pregnancy may contribute to their development. FS and TCS are probably primary genetic abnormalities defined as a defect in the gene structure of an organ or part of an organ.[9,12] On the other hand, GS may be a secondary disruption anomaly or an interruption of the normal development of an organ that can be attributed to mechanical or teratogenic factors or may be of multifactorial origin where several genes and/or environmental factors influence the phenotype.[9,12] Facial clefting syndromes may also belong to the latter variety, although a genetic defect has been demonstrated recently.[17]

The exact etiopathogenetic events in FS are largely unknown; however, an insight into the genetics of FS has greatly been increased with the study of a certain family of mice mutants termed "bleb mice." In patients with FS as well as in bleb mice, the shared defect is a profound loss of adhesions *(Print pagebreak 194)* of the epidermis to the underlying basement membrane that results in abnormal epidermal blistering in the mouse embryo and hypothetically in FS/CO.[18] In normal mouse and human embryos, a group of closely related proteins called the FRAS/FREM protein family are universally present in all basement membranes throughout the body. They contribute to embryonic epithelial-mesenchymal integrity and tight adhesions during embryogenesis.[19,20,21,22] When this intricate process of epithelial-mesenchymal protein trafficking is interrupted by a genetic knockout, either experimentally (*Fras1−/−* mice) or in humans with a genetic defect on chromosome 4q21 or 13q13.1 (which encode FRAS1 or FREM2, respectively),[23] the most common resulting phenotype is composed of renal anomalies, abnormal fusion of the digits as well as the eyelids, in addition to subcutaneous hemorrhagic blisters in mice. Mutations in either of these two autosomal recessive genes were demonstrated in 50% of patients with FS. However, other genes have also been implicated recently.[23,24,25,26]

GS is an enigmatic heterogeneous disease the exact etiology of which is still not clear. The disease is usually sporadic, although familial instances have been demonstrated suggesting sometimes an autosomal dominant or autosomal recessive inheritance.[27] Various chromosomal abnormalities have been found in GS such as trisomy 7, 9 or trisomy 22 mosaicisms, deletions at chromosome 18q or 22q, and unbalanced translocations between chromosomes 5 and 8.[27,28,29,30,31] The most commonly accepted theory is that GS develops as a result of an interaction between environmental factors and some unknown submicroscopic genetic factors.[9] Disturbances in the migration, proliferation, or differentiation of the cranial neural crest cells have been proposed as a possible mechanism for GS.[32] A long list of possible teratogenic environmental factors includes smoking, cocaine use during pregnancy, diabetic embryopathy, primidone, retinoic acid or thalidomide use during pregnancy, and an unknown toxin during the Gulf war.[9,32,33] All these genetic-environmental factors ultimately converge toward a final common vascular perturbation event that dictates the phenotype.[9]

The question that remains is how and why colobomata develop in the context of GS. Smith et al[34] hypothesized that this may reflect a minor abnormality with entrapment of epidermal cells along the fusion lines of the medial and lateral protuberances of the frontonasal process late enough and insufficient enough to adversely affect the development of the cornea and conjunctiva, yet representing a weak point leading to an abnormal focal defect during the process of eyelid separation.[34,35]

TCS is a rare congenital disorder of craniofacial morphogenesis.[36] Mutations in the TCOF1 gene (autosomal dominant [AD], chromosome 5q32), the POLR1C gene (autosomal recessive, chromosome 6p21), or the POLR1D gene (AD, on chromosome 13q12) may all cause TCS. More than 80% of cases are due to defects in the TCOF1 gene where more than 120 different mutations have been described.[12] All of these genes interrupt ribosomal biogenesis, and since ribosomes produce proteins, the synthesis of proteins encoded by these genes is interrupted. The proteins produced from the TCOF1, POLR1C, and POLR1D genes are involved in early craniofacial morphogenesis of both bones and overlying cartilage and connective tissue.[36]

The pathogenesis of the rare craniofacial clefts is not yet fully understood and several theories have been proposed. Classical teaching dictates that TCs are multifactorial in origin and etiologically heterogeneous, with both environmental and genetic factors involved.[37,38] Existing theories include abnormal neural crest cell migration, anomalous vascular development (embryonic hematoma), defective migration and fusion of mesoderm, or a mechanical disruptive event due to amniotic bands or otherwise.[15,39] Although the cellular/genetic basis for TC remains unclear, recent studies have confirmed that a defect or mutation in the SPECC1L gene is contributory to the pathogenesis of TC.[39] SPECC1L encodes a novel cytoskeletal cross-linking protein, which is required for the integration of frontonasal and maxillary elements and convergence of mandibular prominences.[40] This important gene discovery raises the possibility that other genes might also contribute to TC.[39] Therefore it is entirely plausible to hypothesize that the ultimate pathogenetic event may have to do with a failure of cranial neural crest cell migration, with resultant failure of proliferation or fusion of maxillary and lateral nasal prominences.[34]

Clinical Presentation

Classification of Colobomas

The genetic makeup of several syndromic and isolated eyelid colobomata outlined above suggests that in the future a categorization of eyelid colobomas may be based on the genetic or molecular signatures of each particular anomaly. But until the unique genetic

bases of these misleadingly similar phenotypes are completely understood, the authors adopt a simple classification scheme solely for the present discussion, which is modified and updated from a previous classification schema that was previously suggested.[4]

1. Upper eyelid
    I. Isolated coloboma
        A. Coloboma associated with corneopalpebral adhesions (CPA) (for example, cryptophthalmos [CO])
            a. Complete: No discernible eyelid differentiation and the eyes are completely covered with skin
            b. Incomplete: A skin fold devoid of tarsus covers the medial aspect of the palpebral aperture associated with significant corneopalpebral adhesions
            c. Abortive type/congenital symblepharon variant (CSV) or partial CO: True coloboma of variable sizes with a diverse range of CPA. The lower fornix and lateral upper eyelids are usually spared

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        B. Simple coloboma: Upper eyelid coloboma in isolation, not associated with CPA
        C. Coloboma associated with Tessier clefts (TC) 9,10,11
    II. Syndromic variants
        - Fraser syndrome (FS)
        - Goldenhar syndrome (GS)/oculoauriculovertebral spectrum (OAVS)
        - Rare syndromes: Manitoba oculotrichoanal syndrome, nasopalpebral lipoma-coloboma syndrome
2. Lower eyelid
    I. Isolated coloboma
    II. Coloboma associated with Treacher Collins syndrome (TCS)
    III. Coloboma associated with Tessier clefts 3,4,5.
    IV. Rare conditions: Proboscis lateralis

The clinical features of isolated or syndromic CO vary from a simple coloboma with minimal adhesions to the cornea to a truly "hidden" eye or complete CO. François[41] subclassified cases with CO into complete CO, incomplete CO, and CSV, all of which may coexist in both eyes of the same patient or in siblings.[42] Although it is believed that the clinical spectrum of CO represents a continuum, probably resulting from the same genetic defect that may not uniformly lend itself to a rigid clinical classification schema,[43] for the current discussion, Francois' subclassification is adopted.

In patients with complete CO (Figure 29.1), the forehead skin extends over the globe and onto the cheek without any discernible differentiation of eyelids.[44,45] The ocular structures in complete CO are usually atrophic and grossly disorganized, but the eye may be normal in size or even enlarged, may occasionally present as a cyst,[44,45,46,47] and may rarely express a reaction to light.[44] The extraocular muscles may be of normal size for age or may be ill-defined with limited ocular motility, which can be seen and felt with palpation.[41,47] The globe may be central or may be displaced horizontally or vertically. The eyebrows are seldom normally developed,[36] and more commonly the entire eyebrow, its medial two-thirds, or its lateral one-third is absent.[44,47,48] A tongue of hair, which is not yet quite distinct at birth, may be seen extending from the scalp hair into the lateral one-third of the eyebrow.[47,48] In complete CO, the conjunctiva is also wholly absent and the skin is completely adherent to the anterior surface of the sclera and cornea by fibrous tissue. The condition may be unilateral or bilateral.[47] Histopathologically, the eyelids are replaced by undifferentiated fibrous tissue, with a total absence of the tarsus, meibomian glands, cilia, and lacrimal glands,[41,46,47] but the orbicularis oculi and the levator muscles are usually preserved, and the extraocular muscles may be present or absent.[41] The conjunctiva is usually absent in histologic sections, and the cornea is usually replaced with "intertwining collagen bundles" with no epithelial or endothelial lining.[41,47] Although the anterior segment might be malformed, the choroid, retina, and optic nerves appear to be normally formed.[47]

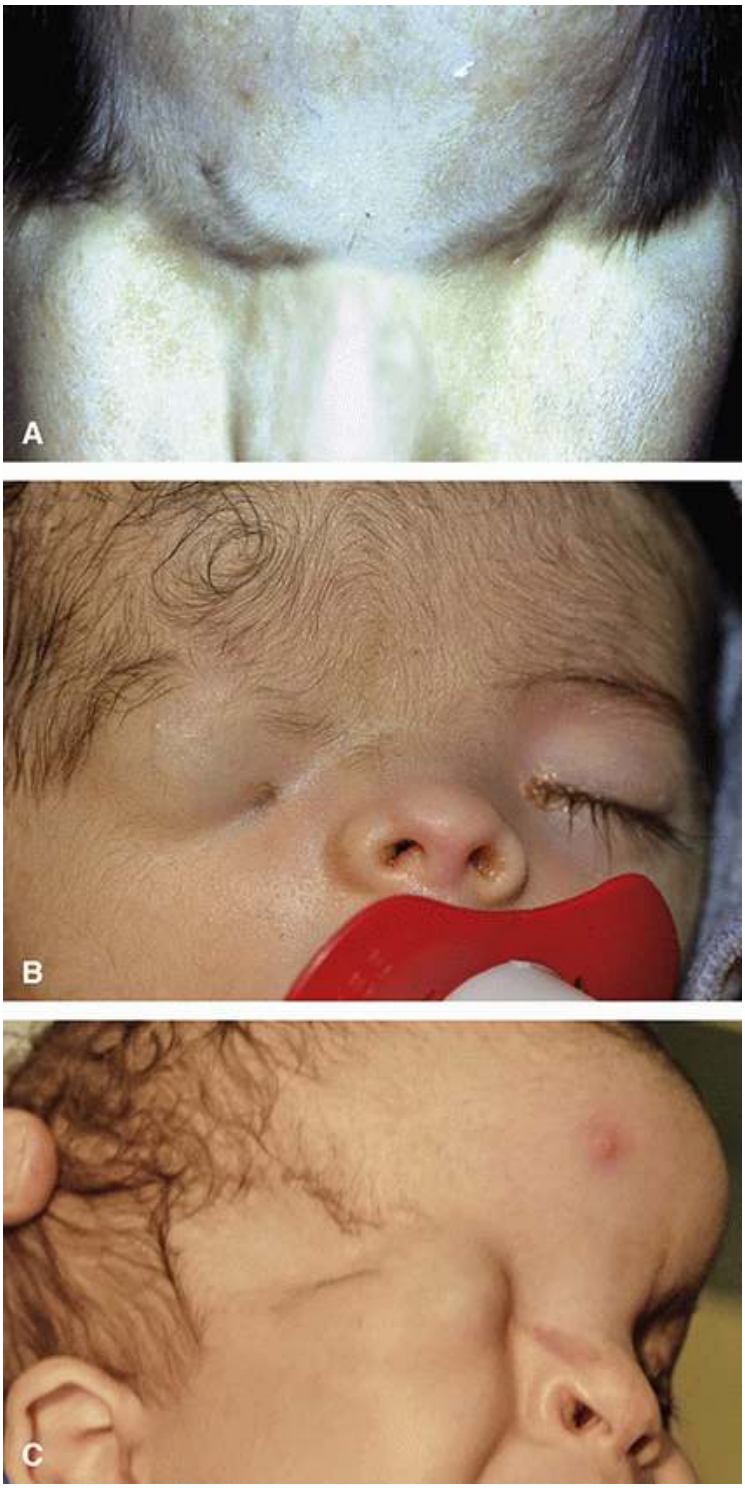

FIGURE 29.1 Clinical spectrum of complete cryptophthalmos. A, Bilateral cryptophthalmos. The lateral two-thirds of the eyebrows is absent and an abnormal tongue of hair is seen extending from the scalp hairline to the brows. B, Unilateral cryptophthalmos. A tuft of eyelashes can be seen at the presumed junction between the undeveloped upper and lower eyelids. C, Unilateral cryptophthalmos. No rudimentary lashes can be seen but a tongue of hair extending from the hairline to the brow can be observed. (A, Courtesy of Dr. Alan McNab.)

In incomplete CO (Figure 29.2), patients have an ill-defined upper eyelid or an incomplete skin fold devoid of tarsus covering almost the entire cornea.[4] This fold is fused to the underlying keratinized cornea along the entire length and width of the fold and may or may not extend downward to *(Print pagebreak 196)* fuse with the lower eyelid. This abnormal fold does not cover the entire eye, hence the partial or incomplete designation in François' clinical observations. These patients usually have a deceptively insignificant upper eyelid coloboma because the colobomatous part of the eyelid is partly replaced by the oversized skin fold.[4] There may be a rudimentary presence of the lateral eyelid structures and conjunctival fornix, which is almost a constant feature in incomplete CO and in CSV even in its most severe forms.[41,48] A small lip of normal rudimentary upper eyelid may be present nasally, together with a functioning upper punctum and canaliculus.[4] The inferior fornix may or may not be spared depending on

the inferior extent of the abnormal skin fold. Patients with incomplete CO may have microphthalmic eyes or eyes that are of normal size echographically. Incomplete CO is the rarest of the three subtypes and is usually unilateral.[49]

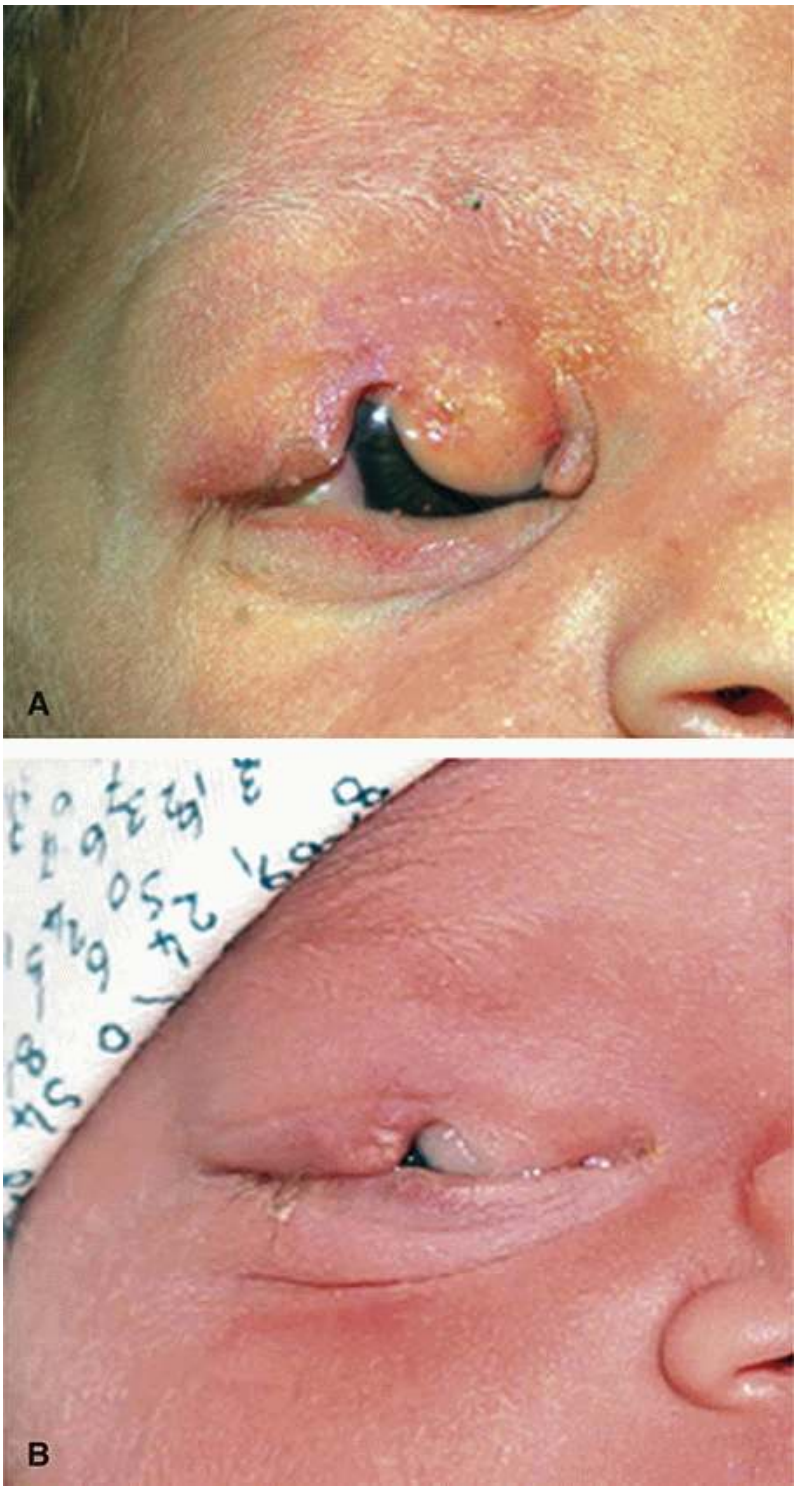

FIGURE 29.2 Incomplete cryptophthalmos. A, The patient has a deceptively insignificant upper eyelid coloboma because the colobomatous part of the eyelid is largely replaced by the oversized skin fold. The lateral eyelid structures are normal, and the medial lip of the upper eyelid including the lacrimal system is also preserved. The concealed part of the cornea is mostly keratinized, and the prognosis for functional reconstruction/visual development is dismal. B, The lateral eyelid structures are also preserved but the lacrimal system is absent because the abnormal skin fold in this patient also involves the medial part of the upper eyelid.

In patients with CSV (Figure 29.3), which is also referred to as abortive CO or partial CO, the upper eyelid skin is deficient and its remnants are visibly adherent to the globe, hence the decades old designation “congenital symblepharon.” The lower eyelid is usually spared, and corneal involvement depends on the extent and severity of CPAs.[48] Subramanian et al subclassified CSV into mild, moderate, and severe grades based on the extent of the coloboma and the severity of corneal adhesions,[48] and the defect may

indeed range from a minor notch in the eyelid margin associated with minimal CPA overlying the coloboma or even adhesions confined to the limbus to patients in whom there is a near-total eyelid colobomatous defect with extensive involvement of the cornea. The term CSV is a relic of late-nineteenth-century medicine[50] and possibly should be abandoned as it may erroneously imply that in the other two varieties (complete and incomplete CO), the cornea is spared or is at least less affected than in CSV. However, CPA is a universal finding in all three types of CO, without which the diagnosis should be called into question. The extent of CPA is less in CSV than in complete or incomplete CO where the conjunctival sac may be absent.[41,47] It should be remembered that prior to eyelid fusion, the corneal epithelium is fused with the surface ectoderm,[51] and only after eyelid fusion do they separate and the cornea takes its normal developmental course. Consequently, by definition, a patient with CO will not have a normal cornea at least in the area of the cornea corresponding to the CPA.[4]

The major feature of FS, which is the syndromic counterpart of cryptophthalmos, is CO (85%-93%) and is considered the syndrome's single most common anomaly.[52,53,54,55] If CO is not observed, the diagnosis of FS should be called into question.[53] Complete CO is the most common subtype in patients with FS. Other major nonocular features include cutaneous syndactyly of the hands and feet (62%-95%) and ambiguous genitalia (40%-66%).[52,53,54,55] Urinary tract abnormalities are also quite common (37%-80%) and usually take the form of unilateral or bilateral renal agenesis, renal hypoplasia, ureteral agenesis, or less commonly bladder abnormalities.[52,53,54,55] A positive family history of the disease (40%-60%) is also an important finding in the diagnosis of FS.[53,55] Respiratory tract abnormalities in the form of laryngeal and/or tracheal stenosis are also very frequent findings.[56,57] Minor features are not infrequent and include congenital malformations of the ears (75%), nasal malformations (˜50%),[52,53,54,55] cleft lip/palate, and skeletal abnormalities, which may manifest in the skull, ribs, or limbs.[52,53,54,55]

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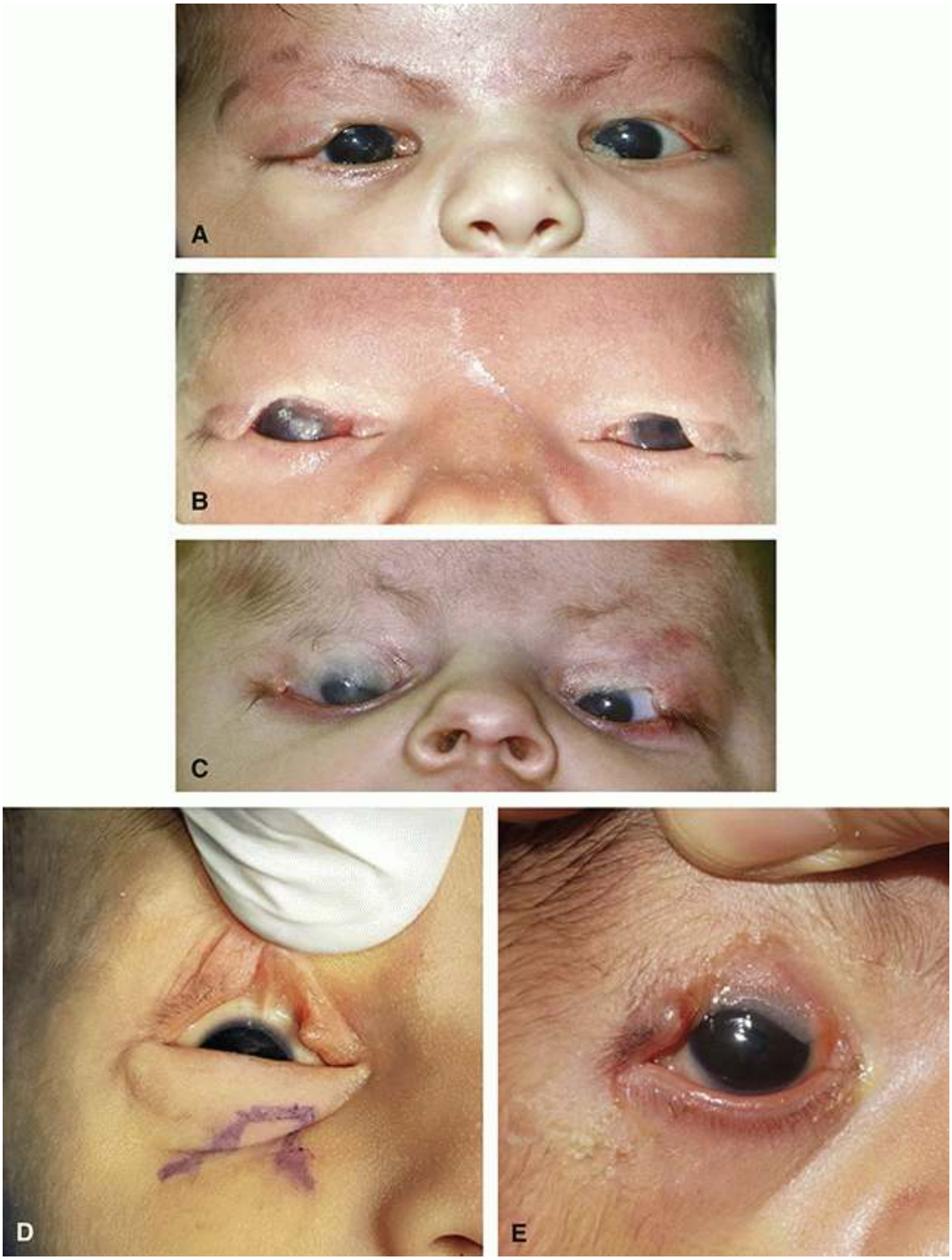

FIGURE 29.3 Spectrum of involvement of the upper eyelid in congenital symblepharon variant (CSV), which is usually bilateral. A, Bilateral moderately sized coloboma with mild corneal involvement. The cornea is relatively spared. B, A 2-week-old infant presenting with a bilateral corneal abscess. The moderately sized eyelid defect is associated with significant corneal adhesions that are responsible for extensive corneal morbidity. C, Asymmetrical presentation with a near-total eyelid colobomatous defect (OD) and a moderately sized defect in the OS. D, Close-up view of corneopalpebral adhesions, which are a universal finding in CSV but is minimal to moderate in this particular case. E, Close-up of extensive corneo-palpebral adhesions (CPA) involving the entire colobomatous defect.

Simple colobomas not associated with corneal adhesions may be isolated or associated with GS (Figure 29.4). In their nonsyndromic form, those "pure colobomas" are strictly unilateral, have no associated systemic findings, and do not usually present with significant keratopathy despite the corneal exposure, and the upper fornix is always well formed with normal depth. The shape of these colobomas is typically quadrangular, but they may also assume a triangular configuration, and for unknown reasons, they are almost exclusively confined to the junction of the medial and central parts of the eyelid.[46,58] The actual size of the defect is difficult to ascertain because the edges are pulled in opposite directions by *(Print pagebreak 198)* the separated parts of the orbicularis muscle, which is contracting freely because the eyelids in these patients are not tethered to the globe in any way.[58] This fact may explain why corneal exposure may be less pronounced than would be expected even with a large eyelid defect.[59,60]

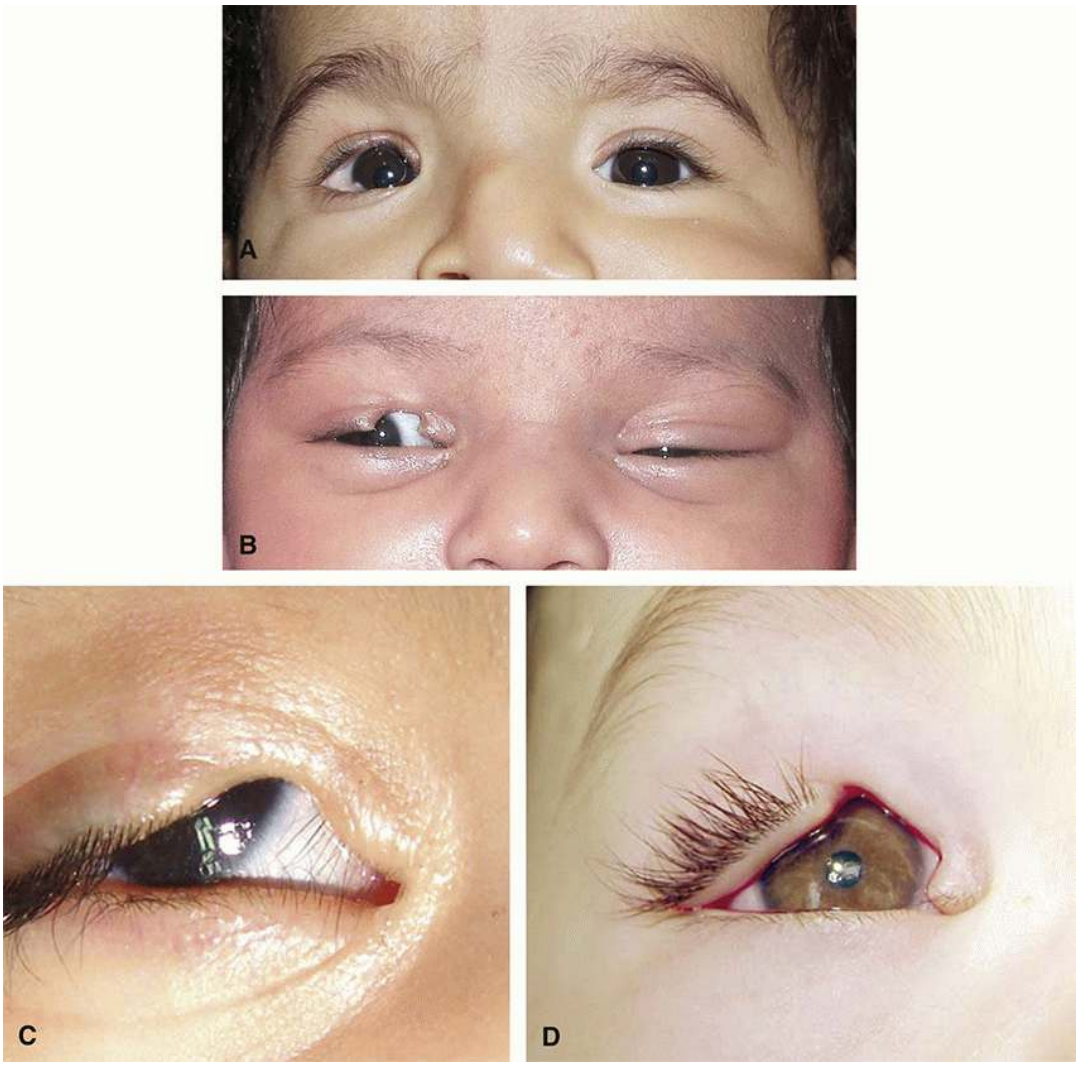

FIGURE 29.4 Simple colobomas involving the upper eyelid are usually unilateral and may assume a triangular or quadrangular shape. A, Simple coloboma associated with Goldenhar syndrome. B, Simple isolated coloboma without a syndromic association. C, Close-up view of a triangular coloboma. D, Close-up view of a quadrangular coloboma.

The syndromic counterpart of isolated or simple upper eyelid colobomas is GS. The estimated incidence of GS varies between 1:5600 and 1:26,550 live births.[34] GS has a causally heterogeneous etiology and pleiotropic clinical features. This pleiotropism probably depends upon how the expression and activation of certain developmental genes and proteins have been differentially disrupted during embryonic and fetal development.[32] The hallmark ocular feature of GS is the presence of a coloboma plus an eccentric or limbal epibulbar dermoid. This is far more common than a simple coloboma alone, which is seen in only 11% of patients with GS and is usually unilateral.[34] The coexistence of a limbal dermoid together with an eyelid coloboma is highly suggestive of GS.[4,61,62]

Ocular anomalies associated with GS are diverse, and because of this diversity, there have been several attempts to classify ocular and periocular manifestations of GS into distinct groups or types. One recent large systematic review divided them into four distinct groups or types.[8] **Type I anomalies** are defined as anatomical ocular or adnexal anomalies that in general do not tend to impair vision (orbital dystopia, lipodermoids, telecanthus, epicanthus, and lacrimal system anomalies). **Type II ocular anomalies** are those anatomical ocular or adnexal anomalies that could potentially impair vision (epibulbar dermoids, anophthalmia, microphthalmia, or optic nerve hypoplasia). **Type III ocular anomalies** include neurologic deficits or motility disorders of the eye (anomalies of the oculomotor, trigeminal, or facial nerves; Duane syndrome; superior oblique muscle palsy; and monofixation syndrome). Refractive errors were separately categorized as **type IV ocular anomalies** (irregular astigmatism, anisometropia, hyperopia, or myopia).[8]

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Systemic manifestations include flattening of one half of the face causing marked facial asymmetry (hemifacial microsomia), cervical spine abnormalities, deafness, facial clefting, facial nerve paralysis, urogenital anomalies, brain anomalies, congenital heart defects, delayed motor development, short stature, delayed speech development, and microcephaly.[63] As a syndrome with such a

diverse spectrum of systemic features, there exists a single feature that is almost mandatory for diagnosis, that is microtia and/or preauricular tags (composed of skin and cartilage), which are present in 95% to 100% of patients and may be bilateral in up to 50% of patients even if other manifestations are strictly unilateral.[27,63] In familial cases, the diagnosis is considered even if preauricular tags are the only manifestation of the disease.[63] Lower eyelid colobomata are rarer than their upper eyelid counterpart (Figure 29.5A).

Colobomata in TCS are usually bilateral notches occurring on the lateral one-third of the lower eyelid and not usually associated with CPAs.[64] Although these are frequently described as small insignificant notches, the stark appearance of these eyelid notches is usually augmented by the lack of underlying bony support.[11] They are not uncommon, occurring in 69% of patients with TCS, yet they are infrequently recognized in ophthalmic practice simply because they are of lesser clinical and aesthetic significance than the other facial features of TCS.[12,34] Those focal notches usually are associated with a paucity of lashes medial to the coloboma, and in general, the medial two-thirds of the lower eyelid is hypoplastic.[11] The lateral canthal tendon and the tarsus are hypoplastic, and the periosteum as well the superficial musculoaponeurotic systems are also deficient.[11] A more common eyelid defect (89%) is the characteristic downward and lateral (antimongoloid) slanting of the palpebral fissure, which is almost pathognomonic of the condition and gives these patients the characteristic "sad-looking eyes" (Figure 29.5B).[11,12] Other ocular features include an intermittent divergent squint.[64] Systemically, other developmental abnormalities in TCS are restricted to the head and neck. These include aplastic/hypoplastic zygomas as well as mandibular and midface hypoplasia resulting in the characteristic sunken cheekbones and fish facies (retruded chin).[11,12] A high arched palate, bifid uvula, crowding of the teeth, external ear deformities (microtia), hearing loss, and airway obstruction are also frequently encountered.[11,12] From birth, the adequacy of the airway is of primary concern and is probably attributed to micrognathia and tongue obstruction of the hypopharynx.[11,12] Congenital heart disease has been described in patients with TCS, but it is uncommon. Developmental delay is also uncommon in this population.

The incidence of TCs or oblique craniofacial clefts is extremely rare, comprising only 0.25% to 1% of the overall incidence of facial clefts, which accounts for an overall incidence of around 1/200,000 live births.[38,39,65,66] The actual incidence of eyelid colobomas associated with clefting disorders is not known, but the incidence may be underreported because these cases are typically managed by some surgeons who may elect to report on the more severe associated defects.[34] TCs are more commonly associated with lower eyelid colobomas, but they may rarely involve the upper eyelid (Figure 29.6). Most known cases are sporadic with no sex predilection[15] and, usually, are strictly unilateral.[34,64] Craniofacial clefting disorders are extremely disfiguring and complex malformations that involve the skeleton of the *(Print pagebreak 200)* face, as well as the mouth, nose, eyelids, and brow.[67] Several classification systems have been described over the years for categorization of these rare conditions. However, one classification that has stood the test of time is the Tessier classification system.[13] Clefts may asymmetrically involve bone and soft tissue, but both skeletal and soft tissue defects should be present, although they may not coexist on the same plane.[13] Clefts may also cross both hemispheres, and a craniofacial or a combination cleft involving the upper and lower half of the face is thus produced.[13] Classical combinations of craniofacial clefts are 0/14, 1/13, 2/12, 3/11, 4/10, and 5/9.[67] TC clefts associated with eyelid colobomas typically involve the lower eyelids (Tessier clefts #3,4,5,6)[34]; however, their northbound counterparts (Tessier clefts #9,10,11) may involve the upper eyelids on very rare occasions (Figure 29.6).[67,68]

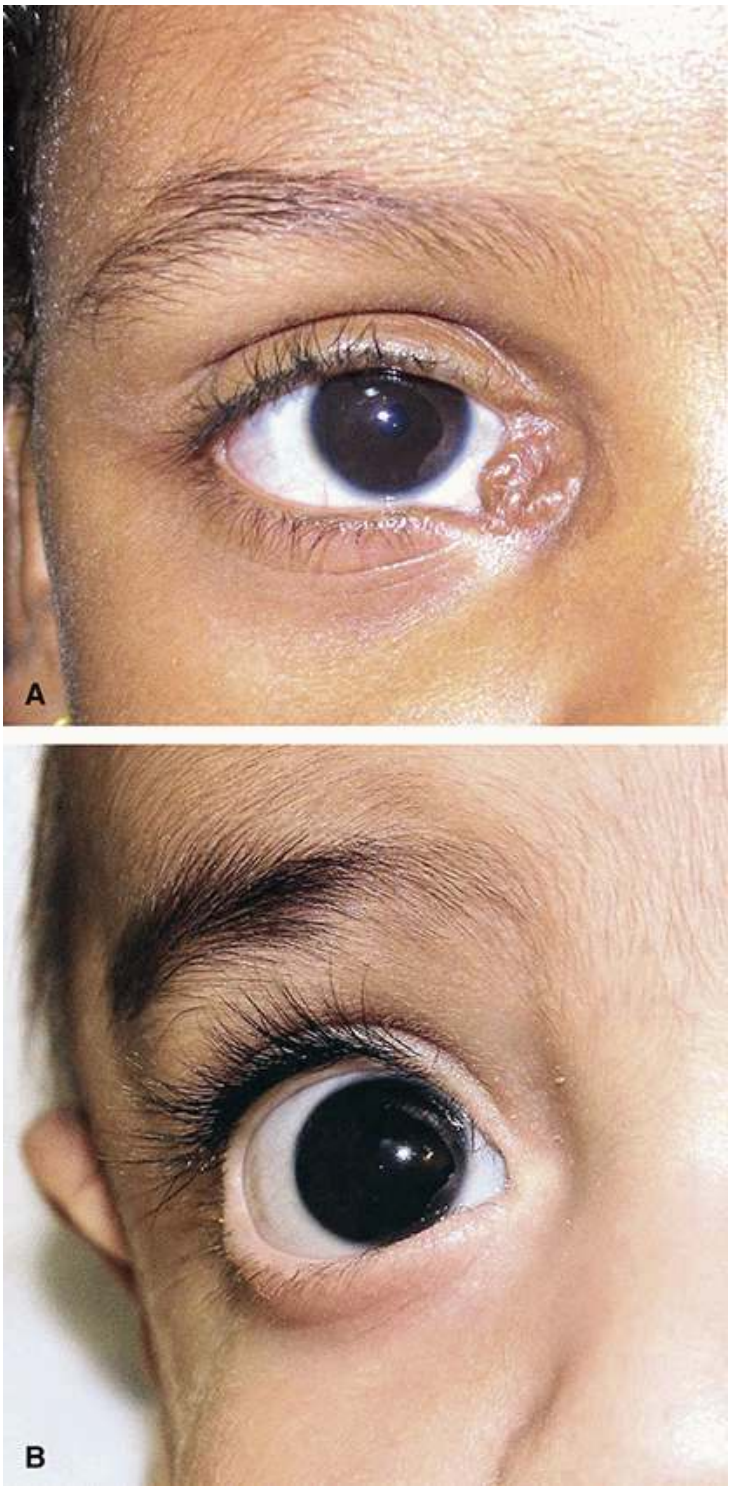

FIGURE 29.5 Lower eyelid colobomata. A, Simple isolated lower eyelid coloboma with tissue maldevelopment in the medial canthal region. Neither a syndromic association nor a craniofacial cleft could be demonstrated. B, Patients with Treacher Collins syndrome show the characteristic downward and lateral (antimongoloid) slanting of the palpebral fissure, which is almost pathognomonic of the condition and gives these patients the characteristic "sad-looking eyes." Mid-facial hypoplasia can be seen.

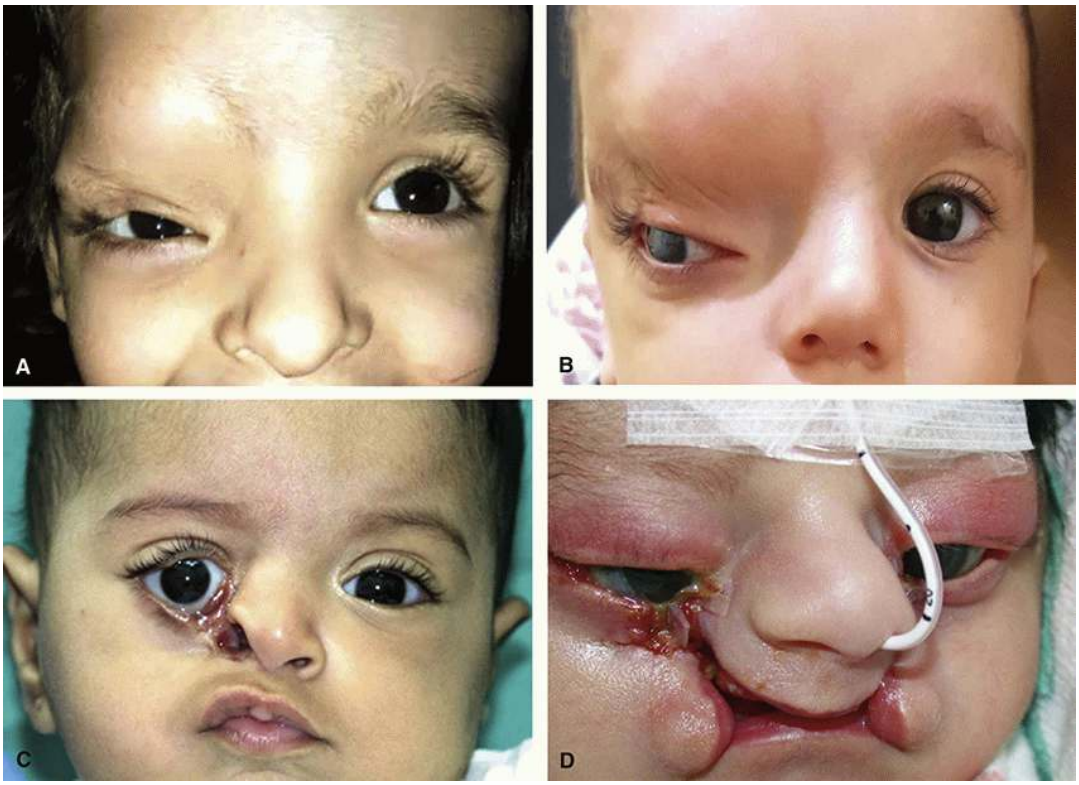

FIGURE 29.6 Spectrum of involvement of the eyelids in patients with Tessier clefts (oblique facial clefts). A, Tessier cleft #9 with a paramedian coloboma and frontal encephalocele. The lateral two-thirds of the ipsilateral eyebrow is absent. B, TC #10 with a frontal encephalocele, and an eccentric coloboma of the upper eyelid that was inadequately repaired. The orbital roof is absent as well as the entire ipsilateral eyebrow. C, Unilateral TC #3 with an extensive medial lower eyelid defect but without an associated cleft lip. D, A rare case of bilateral TC #3 with bilateral cleft lip and palate, and a predominantly unilateral extensive medial lower eyelid defect. (C, Courtesy of Dr. Amir Elbarbary.)

The detailed discussion of TC is beyond the scope of this chapter but those of ophthalmic significance will be briefly outlined. Tessier numbered his clefts in an anatomical fashion in a counterclockwise fashion from 0 to 14 centered on the orbit and radiating out like spokes of a wheel or watch dials.[13] The lower numbers (0-7) represent facial clefts, whereas the higher numbers (8-14) represent their cranial counterparts. TCs of ophthalmic importance are TC #3,4,5,6,8,9,10, and 11. In a counterclockwise fashion, the most medial variety, TC #3, extends from the philtrum of the lip to the medial canthus of the eye, with foreshortening of the medial canthal region and absence of the ipsilateral nasolacrimal system.[15] TC #4 involves a central coloboma of the lower eyelid, whereas TC #5 usually involves the eyelid lateral to the infraorbital foramen.[15] TC #6 is usually associated with a small notch in the lateral part of the lower eyelid and is considered synonymous with TCS.[68]

Because of its horizontal orientation, TC #8 is not considered one of the oblique clefts, but it may still be associated with significant palpebral morbidity in the form of a lateral canthal coloboma and is more commonly observed in clinical *(Print pagebreak 201)* practice than its oblique counterparts.[69] It is characterized by the lack of fusion of the upper and lower lids at the lateral canthus with the consequent absence of a lateral canthus, as well as the presence of an epibulbar dermoid or dermolipoma, and is usually associated with GS.[69] In the absence of an associated bony skeletal defect, whether colobomatous soft tissue defects involving the lateral canthal region should be regarded as part of the spectrum of craniofacial clefts[69] or not remains a matter of controversy; therefore, the term lateral canthal clefts or lateral canthal coloboma may be preferred (Figure 29.7).

TC #9 is the northbound counterpart of #5 and is even rarer with only nine confirmed cases and usually involves the lateral part of the upper eyelid.[67] TC #10 is also extremely rare, usually involves the central part of the upper eyelid, and may be associated with CPAs, and despite their central location, they are not quite dissimilar from colobomata associated with FS/CO, which usually assume a more medial location[4]; however, in contrast to FS/CO, they are universally associated with a skeletal or bony component.[13,70] Those bony clefts include a large defect in the frontal bone, supraorbital rim, and orbital roof, which may cause a frontotemporal encephalomalacia. Tessier #10 clefts are also associated with an arachnoid cyst in the middle cranial fossa and occasionally dystopia and lateral rotation of the orbit.[13,71] TC #11 is the northbound counterpart of #3 and is associated with coloboma in the medial part of the eyelid.[13] To the best of our knowledge, the skeletal component of TC #11 is unknown.

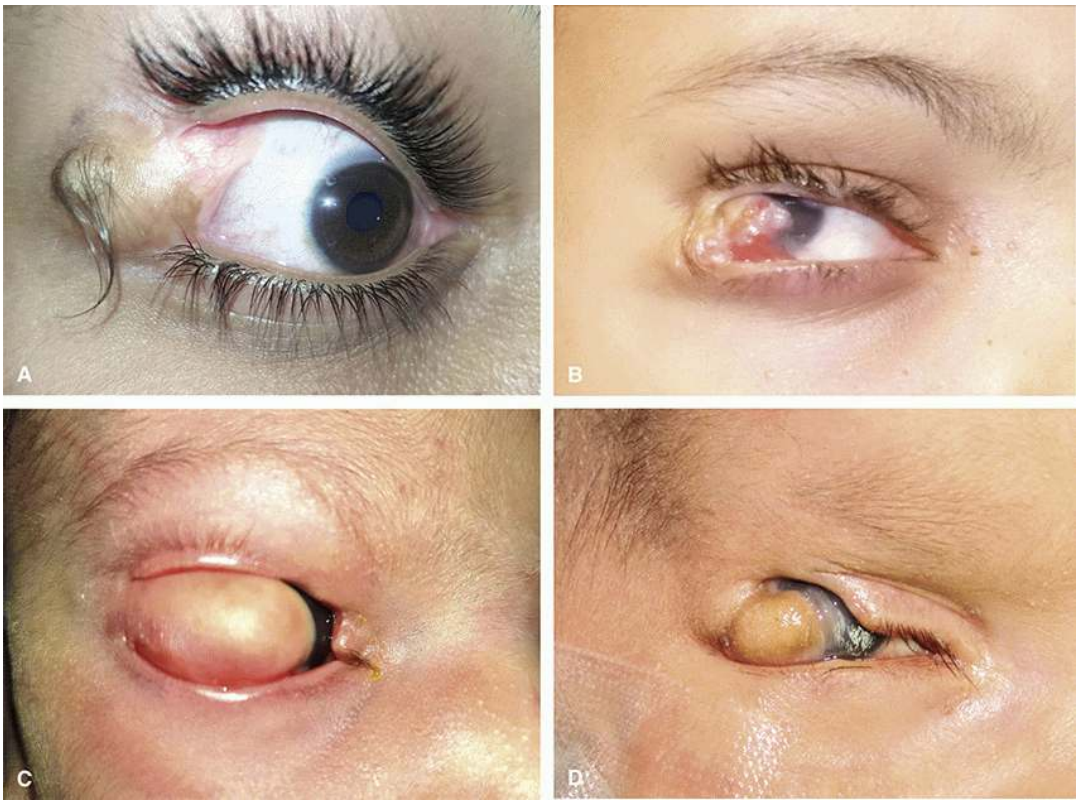

FIGURE 29.7 Spectrum of involvement of the eyelids in lateral canthal clefts or lateral canthal colobomata (the so-called Tessier cleft #8). All patients have Goldenhar syndrome, but none of the patients had an associated bony defect. A and B, True lateral commissure colobomata with a maldeveloped (absent) lateral canthus and an associated dermolipoma. The rest of the upper and lower eyelids are normal. C, An extensive dermolipoma is associated with a strip of skin that disrupts the normal anatomy of the lateral canthus. Another coloboma in the medial part of the upper eyelid can be seen. D, A lateral canthal coloboma in the lateral half of the upper eyelid. An extensive dermolipoma can be seen.

Proboscis lateralis is a rare congenital craniofacial abnormality with a birth prevalence of 1/100,000 to 1/1,000,000. It is characterized by the presence of a nose-like, tube-like, or trunk-like appendage arising from the surface of the face, most frequently located in the vicinity of the medial canthal region (Figure 29.8).[72,73,74,75,76] The etiology is unknown, but it *(Print pagebreak 202)* is generally believed to develop secondary to fusion defects involving the embryonic maxillary process.[72,73,74,75,76] As per the Boo Chai classification, proboscis lateralis is classified into four groups according to the location of the lesion: (1) group I, normal nose; (2) group II, nasal irregularities; (3) group III, nasal and eyelid irregularities including eyelid colobomas; and (4) group IV, nasal and eyelid abnormalities associated with orofacial clefting.[75] The condition is associated with multiple craniofacial anomalies, which vary according to the location in which the lesion arises, but the most commonly encountered anomaly that is observed in clinical practice is partial or complete heminasal aplasia, the presence of which is an indication that the ipsilateral nasal cavity is completely closed at the piriform aperture. Lower eyelid colobomata are common, but colobomas of the upper eyelid have also been reported. Additional ocular/periocular anomalies include multiple lacrimal system anomalies, a cyclopean eye, microphthalmia, anophthalmia, as well as colobomas of the iris or the retina.[72,73,74,75,76]

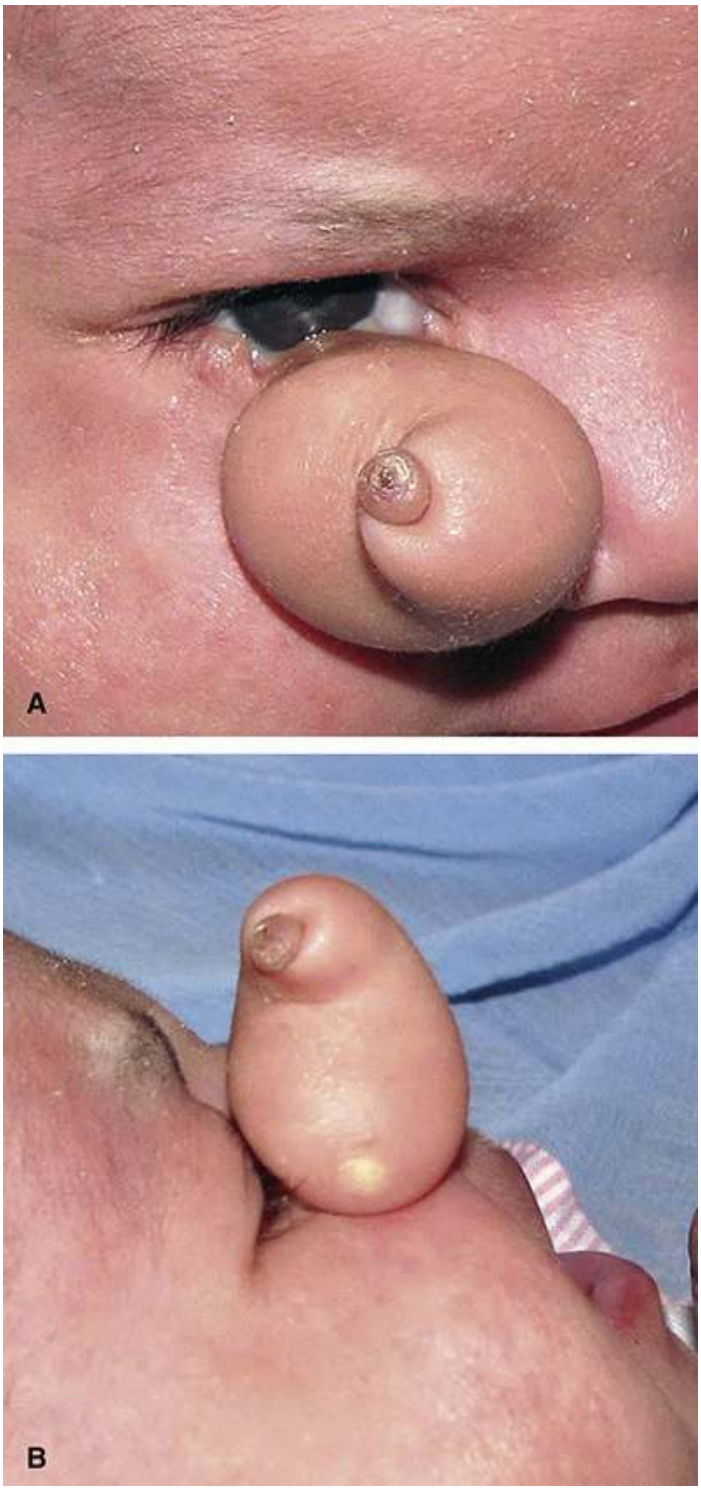

FIGURE 29.8 A rare case of group I proboscis lateralis arising exclusively from the lower eyelid. A, Frontal view. B, Lateral view.

Differential Diagnosis

The combination of syndactyly, renal agenesis, and laryngeal or tracheal anomalies does not only occur in FS. Three other syndromes share those features including cutis aplasia-total, Nager acrofacial dysostosis, and Pallister-Hall syndrome, but the presence of CO excludes these syndromes.[53,55]

It may not be difficult to differentiate GS from TCS based on the facies alone. However, several other syndromes need to be differentiated from GS. These include CHARGE association, VACTERL association, Townes-Brocks syndrome, Wolf-Hirschhorn syndrome, Hallermann-Streiff syndrome (mandibulo-oculodyscephaly), as well as Delleman and Seckel syndromes.[32] The detailed discussion of this large list of simulating disorders is beyond the scope of this chapter, but the characteristic facial appearance,

mental and developmental growth patterns, intellectual disability, and the presence or absence of other systemic features may help establish the diagnosis.

It is important to differentiate Nager and Miller syndromes from TCS.[12] Nager acrofacial dysostosis syndrome may have facial features similar to that of TCS, but lower eyelid colobomas are rare. Both Miller and Nager syndromes share many clinical features with TCS, but they are differentiated by the presence of upper and less commonly lower limb abnormalities.[12,77]

Although they are all included under the same rubric, it is not difficult to differentiate TCs from the far more common clefts of the embryonic primary (cleft lip) and secondary palate (cleft palate), or the rarer but far more treacherous median clefting disorders that are not associated with eyelid colobomata but may be associated with hypotelorism (holoprosencephaly), or hypertelorism (median cleft face syndrome or frontonasal dysplasia).[15,38]

It should not be difficult to differentiate a congenital upper or lower eyelid coloboma from acquired eyelid defects. A history of prior eyelid surgery or trauma should easily differentiate both conditions.

Treatment

Eyelid colobomata may represent one of the few oculoplastic emergencies that may have to be faced at a very early age. Operating on such young infants with multiple congenital anomalies with attendant possible anesthetic risks and with little tissue available for reconstruction may be *(Print pagebreak 203)* challenging.[52,53,55,56,57] Irrespective of the type or location of the coloboma, the basic management principles are similar, the only major difference being the presence or lack of corneal adhesions. Although the basic principles of management are outlined below, detailed discussions of the management options are detailed elsewhere.[4,11,48,57]

For small (25%) upper eyelid colobomatous defects not associated with CPAs (simple coloboma/GS) direct closure may suffice, although for moderately sized defects (25%-50%), severing of the upper crus of the lateral canthal tendon may be required for satisfactory closure.[4] Because of the relative lack of underlying laxity in infants,[4,78] direct approximation, even if technically feasible, may not always be the best therapeutic option as it may, at least in larger defects, result in severe mechanical ptosis that may persist for several months obstructing the visual axis, which is potentially amblyogenic.[29] For larger defects (50% or more of the eyelid), available options include the Cutler-Beard procedure or an eyelid rotational (switch) flap, but both are also potentially amblyogenic.[79,80] Alternatively, the use of a tarsomarginal graft covered with an overlying skin-muscle advancement flap, which does not occlude the pupil, may be a better option than eyelid sharing procedures.[78]

The management of colobomas associated with CPA (CO/FS) presents an additional challenge, as the fornix needs to be reconstructed during the same procedure or preferably separately. In patients with CSV, upper eyelid colobomas are potentially vision threatening and should promptly be treated at the earliest. The same basic reconstructive management principles apply. When the defect is very small, direct primary layered closure is appropriate, but larger defects better lend themselves to eyelid sharing procedures. For reasons that are not entirely understood, recurrence of CPA is less frequent when an eyelid sharing procedure is undertaken. It could be theorized that, when an eyelid sharing procedure is employed, the area of the cornea that was adherent to the eyelid remnants is no longer in contact with the diseased upper eyelid but rather faces the overlying normal conjunctiva and tarsus from the unaffected lower eyelid.[4] For fornix reconstruction, an amniotic membrane graft can be used. The graft should be large enough to cover the entire fornix and should be secured with fibrin glue and not with sutures to reduce irritation and postoperative inflammation, followed by placement of a symblepharon ring or a conformer.[4]

Incomplete CO sometimes poses a challenging problem in trying to explain to the parents why a poor visual potential is expected. To the parents' eyes, it may look less devastating than either complete CO or CSV. The coloboma looks small and is fictitiously reduced in size by the oversized skin fold adherent to the cornea, so that the diseased part of the cornea is completely concealed. Keratopathy is unusual, the eye is painless, and the remaining exposed part of the cornea usually looks normal. Rushing to early surgery is not indicated because most of the cornea is keratinized and the prognosis for functional reconstruction is dismal at best. Besides, the risk of corneal exposure and perforation is minimal. Therefore, in contrast to CSV, incomplete CO does not pose a surgical emergency, but when surgery is indicated on cosmetic grounds alone direct closure usually is not effective because the actual defect after resection of the abnormal skin is usually more than 50% of the eyelid. An eyelid sharing procedure or an eyelid switch flap should be used. Patients with complete CO deserve a special category on their own because technically there is no coloboma, the eye is painless with no risk of impending perforation, and normal development of the cornea is impossible. Fornix reconstruction for the accommodation of a prosthetic shell is extremely challenging because both a fornix and eyelids must be reconstructed.[81] In these cases, it is preferable to defer

surgery since the ultimate visual, cosmetic, and reconstructive outcomes are generally poor. If surgery is to be undertaken, it should be performed in a stepwise fashion and the first objective is the creation of a conjunctival sac.[4,44] The skin covering the ocular remnants is divided followed by placement of a conformer covered with a mucous membrane graft. Eyelid reconstruction with stiffening of the posterior lamella and possibly further socket mucous membrane grafting could be carried out 1 year later.[4] An alternative source for socket reconstruction if mucous membrane grafting fails is the preputial skin in uncircumcised children.[82,83]

The surgical management of TCS is by definition staged because of the enormous amount of facial soft tissue and bony reconstruction required.[11] Lower eyelid colobomas associated with TCS pose a lesser risk to the cornea than an equivalent defect in the upper eyelid, and very small defects could be left untreated.[11] Larger defects may need prompt management. Owing to the extensive concomitant involvement of the midface and the lack of bony support for eyelid structures, these larger defects may not always be amenable to direct closure or tightening of the lateral canthal tendon,[11,64] and transposition flaps from the upper eyelid coupled with posterior lamellar grafting and tightening of the lateral canthal tendon may be required.[11]

A detailed discussion of the surgical management of craniofacial clefts is beyond the scope of this chapter but suffice to state that, because of their rarity and their complexity, craniofacial clefts pose the most significant reconstructive challenge to the craniofacial surgeon today. Also, reaching a management consensus is difficult because of the variability in presentation from one patient to the other. In brief, the primary aim of repair in TC is to simultaneously reconstruct the face and the eyelids, and in the majority of cases, local tissue mobilization is enough to close the defect.[67,84]

Prognosis

Except for simple isolated colobomas involving the upper eyelid where cosmesis and visual potential are expected to be excellent, families should be counseled that several procedures may be required, and in cases of CO/FS/TC, the visual potential may be poor despite these multiple surgeries. Parents should also realize that, even in the absence of a *(Print pagebreak 204)* good visual outcome, cosmetic rehabilitation might not be perfect.[4] Patients with complete and incomplete CO, in particular, should be reminded that they do not have a normal cornea. Accordingly, parents should be informed that complete and incomplete CO are conditions that are incompatible with normal vision. On the other hand, the visual potential in CSV is dependent on the extent of adhesions at the initial presentation.[4] Dealing with the shocked and grieved parents of a blind and disfigured child could be a major challenge and may require counseling for the parents and the patients themselves later as they mature.

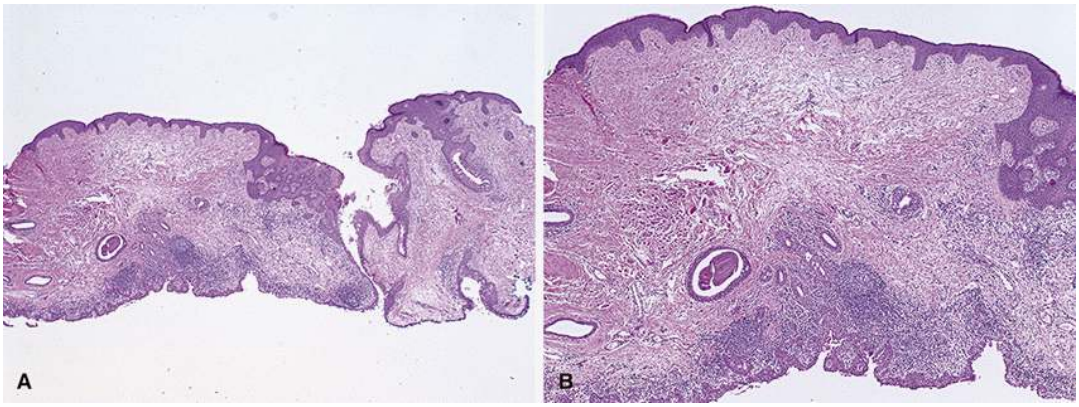

FIGURE 29.9 This left upper eyelid coloboma was removed at the age of 3 years. It was part of a facial deformity incompletely repaired at 2 days of age. A, A mixture of epidermis and conjunctival epithelium lines the coloboma. B, At the edge of the coloboma, the eyelid has pseudoepitheliomatous hyperplasia of the epidermis, only a focus of atrophic orbicularis oculi muscle, and lacks tarsus.

Histopathology

There is scant information on the histopathological features of colobomas since eyelid tissue is rarely submitted for histopathological examination. Al Essa and coworkers examined tissue from the upper eyelid adjacent to colobomas in 10 children and found similar pathological changes.[85] The eyelid tissue at the coloboma edge had abnormal dermis with thick collagen fibrils and varying degrees of atrophy of the orbicularis oculi muscle and tarsus.[85] The epidermis and conjunctiva were normal except in congenital upper eyelid colobomas with corneal adhesion. In these cases, the conjunctiva and tarsus were absent at the edge of the

coloboma.[85] We have examined tissue from only one eyelid coloboma, and the changes were similar to those described by Al Essa et al[85] (Figure 29.9).

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CHAPTER 30

Distichiasis

Key Points

- Distichiasis is a rare disorder where there is an abnormal growth of eyelashes from the orifices of the meibomian glands behind the normal row of eyelashes
- Distichiasis may be congenital or acquired
- Metaplasia of the meibomian glands due to the long-standing cicatrizing eyelid and ocular surface disease is probably responsible for acquired distichiasis
- The congenital variety, termed lymphedema-distichiasis syndrome, is a dominantly inherited disorder that presents with distichiasis in early childhood and lymphedema at puberty
- The aberrant eyelashes may be just a few cilia or a regular well-formed row growing out of the meibomian gland orifices near the posterior lid margin, parallel to the normal eyelashes
- Treatment is indicated for significant corneal abrasion or ulceration with the goal of destroying the cells that have the potential to regenerate new follicles
- Treatment can be achieved with the use of cryotherapy, electrocautery, or surgery

Distichiasis is a rare disorder where there is an abnormal growth of eyelashes from the orifices of the meibomian glands resulting in an accessory row or several rows of lashes behind the normal one, hence the prefix di in distichiasis,[1] to differentiate it from the even rarer tristichiasis and tetrastichiasis.[1,2] As Sidney Fox remarked decades ago, owing to the rarity of distichiasis most papers studying the condition blend the discussion of trichiasis and distichiasis together, and consequently, robust or useful information is generally lacking in the literature.[1]

Etiology and Pathogenesis

Distichiasis may be congenital or acquired. Although metaplasia of the meibomian glands due to a long-standing cicatrizing eyelid and ocular surface disease is probably responsible for acquired distichiasis,[3] it is the congenital variety that deserves special mention. The congenital variety, which is termed lymphedema-distichiasis (LD) syndrome, is a dominantly inherited disorder with high penetrance and variable expressivity, but it may also occur de novo, with an estimated rate of new-onset mutations of around 30%.[4] LD syndrome typically presents with distichiasis at birth and lymphedema at puberty,[5,6] and males suffer the greater brunt of this disease.[6] Embryologically, the meibomian gland analgen, which are a derivative of the surface ectoderm, appear around week 11. It is important to understand that early during embryonic life, the meibomian gland analgen are fundamentally similar to the eyelash analgen, albeit developing in a much slower fashion.[7] This embryologic mimicry is the reason why the meibomian glands are sometimes referred to as a "*hair follicle without a hair shaft*."[8] According to Samuel Whitnall, the occurrence of congenital distichiasis should not be surprising because the meibomian glands represent a primitive vestigial remnant of a secondary row of eyelashes that have disappeared in humans during evolution.[9] Congenital distichiasis, therefore, is probably an atavistic phenomenon that develops when the primary epithelial germ cells in the meibomian gland analgen develop into a complete pilosebaceous unit instead of a specialized tarsal gland.[10,11,12]

In 1999, the gene for LD syndrome was identified as the FOXC2 gene and mapped to chromosome 16q24.[13] Several mutations have been reported in the FOXC2 gene, a forkhead transcription factor gene, formerly known as the mesenchyme forkhead 1 (MFH1) gene, which as of the time of this writing is the only gene decisively linked to LD syndrome.[14,15] Recent evidence from animal knockout mutation models suggests that FOXC2 is normally expressed in the endothelial and smooth muscle cells of developing venous and lymphatic vessels, particularly the valvular leaflets, which control vascular outflow.[16,17,18,19] It is also expressed in neural crest-derived mesenchymal cells, and is necessary for normal meibomian gland development through

mechanisms that are not yet entirely clear.[20,21] It should be noted that abnormalities in the FOXC2 gene not only affect the meibomian glands but may also result in abnormal thickening of the corneal stroma, corneal neovascularization, as well as corneal conjunctivalization.[20] Therefore, some of the symptoms encountered in patients with congenital distichiasis, such as photophobia, may be due to corneal abnormalities and may not be entirely attributable to rubbing lashes.

Clinical Presentation

Although patients with LD syndrome are born with distichiatic lashes, they typically present around the age of 4 or 5 years and not at birth. This is because these lashes are initially lanugo-like, finer, thinner, well-tolerated and may *(Print pagebreak 208)* not cause ocular irritation at the outset.[1,6,11] Occasionally, distichiasis could be accidently discovered earlier by the ophthalmologist or even by an observant parent who occasionally may present with the child commenting on the presence of a double row of lashes parallel to each other. As the child grows, the patient may experience significant photophobia and ocular irritation symptoms. The aberrant eyelashes may be represented by a few cilia forming a discontinuous row or as a regular well-formed row parallel to the normal eyelashes (Figure 30.1A).[6] Lashes can be observed growing out of the meibomian gland orifices near the posterior lid margin. These lashes are straight, pigmented, and rub against the cornea. The aberrant eyelashes are more commonly observed emerging from all four eyelids,[22] but occasionally they may be seen emerging exclusively from the lower or upper eyelids.[1,22] Distichiatic lashes in patients with LD syndrome are more common in the central and lateral parts of the eyelid than in the medial part.[6] Other ocular associations include blepharophimosis syndrome, blepharoptosis, strabismus, and rarely keratoconus.[6,22]

Primary lymphedema, which is the second cardinal symptom of LD syndrome, is also highly penetrant but usually develops around the age of 10 years in males and even later in females.[6] This is the reason why distichiasis may present in clinical practice without lymphedema and may have led some authors to contemplate the occurrence of distichiasis in isolation without lymphedema, a scenario that is rejected by geneticists.[6,10,23]

Because FOXC2 mutations affect both lymphatic and venous morphogenesis, patients with LD syndrome suffer not only from lymphedema but from varicose veins as well. This affects up to 50% of individuals with LD syndrome,[6] and even if not clinically evident, a recent color Duplex ultrasound study has shown that every single participant with a mutation in FOXC2 showed reflux in the great saphenous vein.[17] Other systemic associations include congenital heart disease (ventricular septal defect, tetralogy of Fallot, or patent ductus arteriosus, 6.8%), cleft lip and/or palate (4%), and less commonly scoliosis, renal abnormalities, spinal epidural cysts, learning difficulties, and autism.[6,14,24]

Acquired distichiasis (Figure 30.1B and C) may be observed as an intermediate or long-term sequela of chronic inflammatory conditions in the eyelids, like ocular cicatricial pemphigoid, Stevens-Johnson syndrome, trachoma, or following chemical injuries, but they rarely if ever form a regular row of lashes, and contrary to congenital distichiasis, these lashes tend to be shorter, finer, nonpigmented, or faintly pigmented.[11,25] Recently PTD combination chemotherapy (pertuzumab + trastuzumab + docetaxel) in a patient with HER2-positive metastatic breast cancer resulted in bilateral lower eyelid distichiasis and mild cicatricial lower eyelid entropion as an ocular side effect.[26] The specific chemotherapeutic agent responsible for the eyelid changes is unknown but docetaxel is the likely culprit.[27]

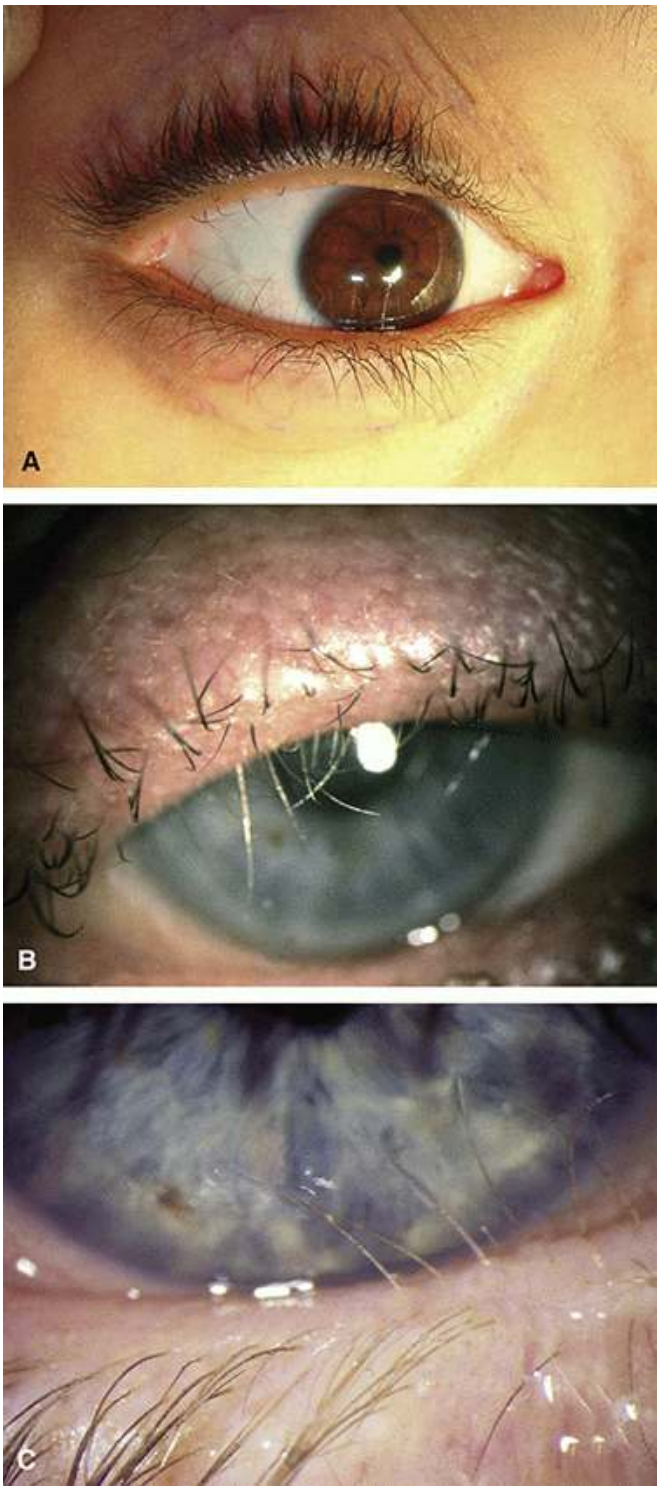

FIGURE 30.1 Distichiasis. A, Congenital distichiasis of the upper and lower eyelids. B, Acquired distichiasis of the upper eyelid. C, Acquired distichiasis of the lower eyelid.

Differential Diagnosis

LD syndrome may be confused with other causes of hereditary lymphedema like Meige disease and Milroy disease. Although Meige disease has a pubertal onset similar to LD syndrome, it is more common in females than males.[6] *(Print pagebreak 209)* Patients with Milroy disease typically present with lymphedema at a very early age.[28] Yellow nail syndrome is another hereditary disease also linked with anomalies in the FOXC2 gene, but lymphedema has a much later onset and is typically associated with onycholysis and respiratory problems.[28] None of the above-mentioned conditions have associated eyelash anomalies.[6,14,28]

A unique condition with aberrant eyelashes that may be confused with distichiasis is cilia incarnata. Cilia incarnata is an acquired condition that is defined by the misdirection of eyelashes whereby the eyelashes grow either anteriorly under the skin (cilium

incarnatum externum) or posteriorly through the conjunctival surface (cilium incarnatum internum) instead of emerging normally from the eyelid margin (Figure 30.2).[29]

Another rare congenital condition with aberrant cilia, which does not fit the description of distichiasis but may cause a diagnostic dilemma because of its rarity, is a condition termed ectopic cilia whereby a bunch of eyelashes is found grouped entirely outside the eyelid margin. Ectopic cilia are usually a congenital condition, although acquired cases have been described (Figure 30.3A).[29,30,31] Of note is that aberrant eyelashes may also be observed arising from the conjunctiva in patients with a conjunctival dermoid, a limbal dermoid, or lipodermoid, but then again, this should not pose a diagnostic difficulty at all (Figure 30.3B).[32]

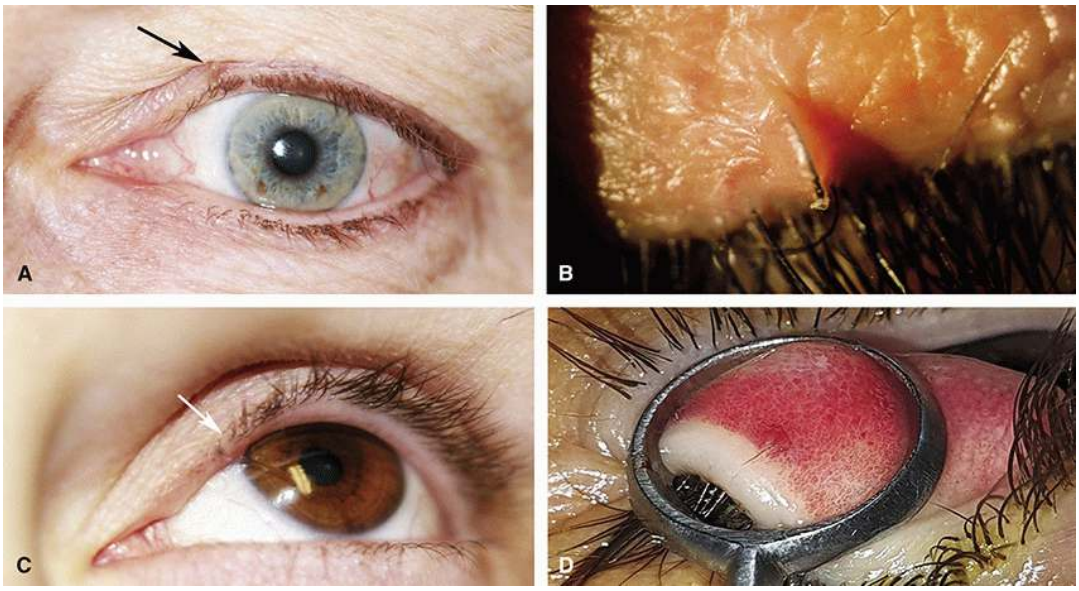

FIGURE 30.2 A, Cilium incarnatum externum. A single lash is seen buried beneath the skin (black arrow). B, High magnification view (slit lamp photomicrograph) of another patient with cilium incarnatum externum showing the buried lash. C and D, Cilium incarnatum internum. An eyelash can be observed extending into the undersurface of the eyelid beyond the eyelid margin (white arrow). (A and C, Courtesy of Drs. Bhupendra Patel and Raman Malhotra.)

Treatment

The decision to treat and the choice of the modality of treatment used depend on the number as well as the location of the aberrant eyelashes.[21,22] Few authors have suggested an algorithm for the management of distichiasis.[22] Treatment is indicated if symptoms are present or if significant corneal staining or ulceration is observed.[22] The ultimate objective is to destroy all the cells that have the potential to regenerate and form new follicles.[12,33] This can be achieved with the use of heat, cold, electricity, radiation, or less commonly, surgically.[12] It should be pointed out that surgical approaches primarily designed for entropion repair, which may have been mistakenly used in the past to treat distichiasis,[22,34,35] are of little additional benefit in distichiasis because the eyelid margin is normal in position. Therefore, treatment is normally focused only on the distichiatic eyelashes, and a graded approach is recommended according to the number and extent of the distichiatic lashes.[22,34,35] The therapeutic modalities currently available range from temporary relief measures like contact lens wear or mechanical epilation of the abnormal eyelashes[36] and minimally invasive procedures like electrolysis, radiosurgery, cryotherapy, or argon laser[12] to more involved surgical procedures including eyelid splitting with direct internal eyelash bulb extirpation or surgical excision of the entire second row of distichiatic lashes.[23,37]

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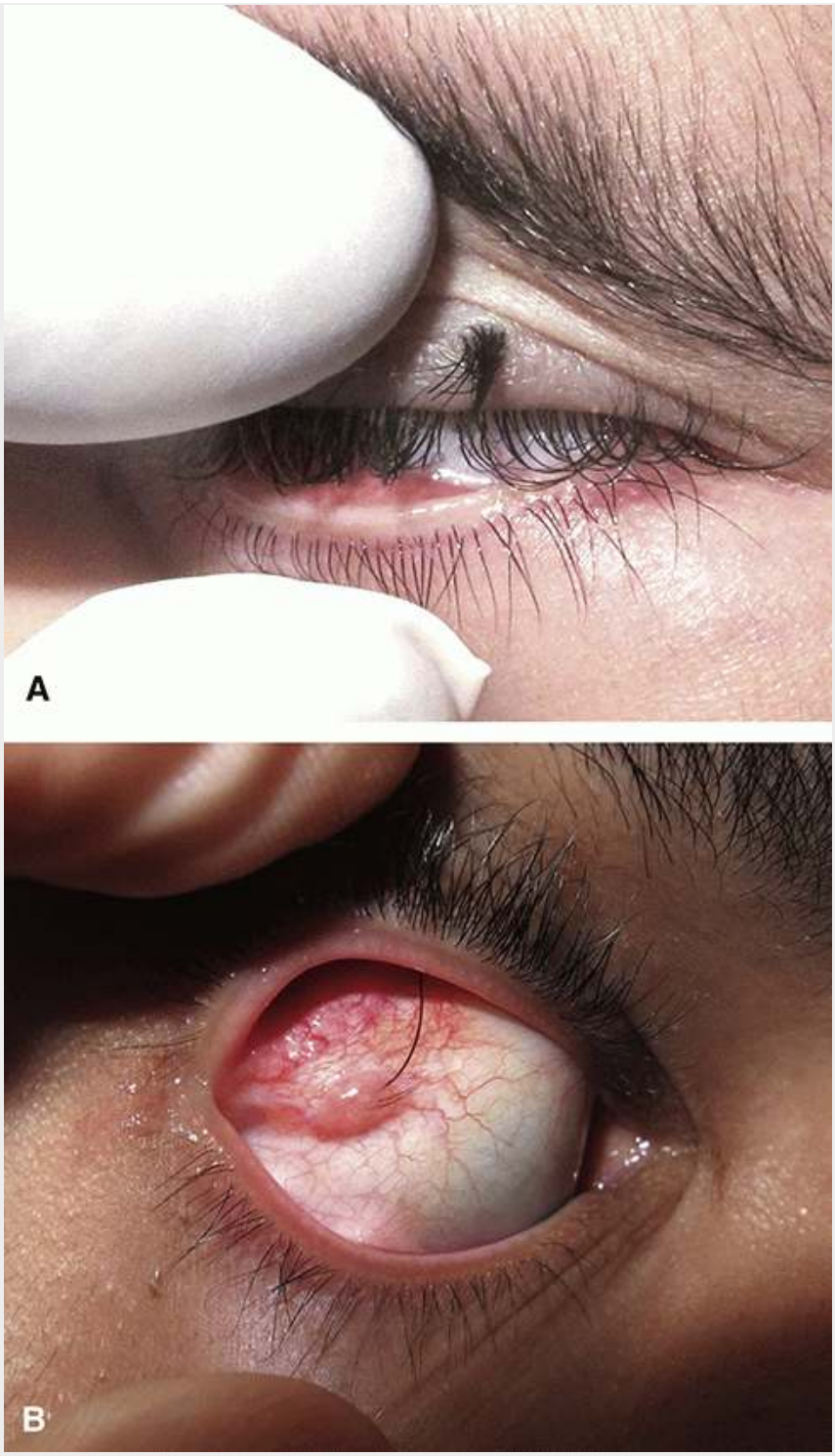

FIGURE 30.3 A, Ectopic cilia. B, Eyelashes arising from a conjunctival lipodermoid. Both conditions are away from the eyelid margin and should not be confused with distichiasis.

Contact lens wear may provide immediate relief but may not be of practical value in children and may even predispose the patient to bacterial infection and a reduction in goblet cell counts further exacerbating symptoms.[36] Epilation also provides temporary relief, but eyelashes typically regrow in 4 to 6 weeks.[36] Because the above temporary measures do not provide long-lasting relief, a definitive surgical approach is preferred. If only a few aberrant lashes are observed, electroepilation is preferred over cryotherapy because it affords a more focused individualized approach toward the individual distichiatic lashes. To minimize recurrences, it has been suggested that electroepilation should be performed using the operating microscope under high magnification[12] rather than with the surgical loupe. Minimal current is applied until bubbles of coagulated tissue appear on the surface, and the lash is manually removed.[36] If any tension is felt while trying to manually remove a lash this indicates that immediate retreatment with a higher power setting is required.[12] Electroepilation or electrocautery may be associated with the risk of loss or ablation of normal eyelashes.

Cryotherapy may be indicated if more than one-quarter of the lid margin is involved or if previous electrolysis has failed.[22] However, this modality may be associated with eyelid margin depigmentation, which may not be desirable particularly in children and in darkly pigmented individuals.[22] Cryotherapy may also cause focal eyelid margin abnormalities or trichiasis.[23,38]

Unfortunately, minimally invasive procedures do not always produce a favorable outcome. Therefore, if they are complicated by recurrence, or if the disease initially involves more than half the eyelid margin, an eyelid splitting procedure may be indicated with the eradication of the eyelash follicles under direct observation. If a lid splitting procedure is considered, the use of a super sharp microfeather blade is preferable over the standard no. 11 scalpel blade, and the incision placement immediately anterior to the abnormal eyelash line is of paramount importance to reflect the normal eyelashes away from the distichiatic lashes.[12,21,23] An incision depth of around 3 mm is also critical because, with a shallow incision, some eyelash follicles may be missed.[12,37] The eyelash follicles can then be destroyed with a monopolar or a bipolar cautery or with radiosurgery or cryotherapy, or excised with a surgical blade.[12,37] It should be pointed out, however, that these patients may develop entropion as a direct consequence of the procedure.[23,36] More extensive approaches like full-thickness excision of the distichiatic eyelashes are not recommended especially in cases of acquired distichiasis because this may aggravate any cicatrizing eyelid disease that might be present.[36]

Prognosis

Parents should be notified that distichiasis is difficult to treat, that most of the treatment measures only provide temporary relief, and that more than half of the patients treated for the first time will require retreatment at some point.[22] Also, they should be made aware that any of the above-mentioned procedures could induce eyelid malpositions, cosmetic deformities, and loss or misdirection of the normal eyelashes.[6,23,37]

Histopathology

There are only a few reports on eyelid histopathology in congenital distichiasis, and Picó reviewed the cases published before 1957.[39] The first histological study was by Nicati in 1880; he observed aberrant cilia emerging from meibomian gland openings in eyelid margin tissue.[39] Herrnheiser (1891) used serial sections to demonstrate that aberrant eyelashes corresponded to the location of glands whose excretory duct opened into a hair follicle.[40] "The number of both cilia and glands corresponded to the normal number of meibomian glands."[40] Herrnheiser did not identify any actual meibomian glands, and he interpreted the slightly *(Print pagebreak 211)* developed sebaceous glands as appendages of the abnormal cilia.[40] Kuhnt[41] examined full-thickness wedge resections from the upper and lower eyelids of a 52-year-old woman with distichiasis since childhood, treated by epilation for many years.[39] Kuhnt reported that meibomian glands were absent, with replacement by an "accessory row of cilia having sebaceous glands opening into their follicles."[42] "Moll's glands were hypertrophied, and there was a second row of Krauss' glands in the middle of the tarsus."[43] Erdmann (1904) identified moderately thickened tarsus with scanty sebaceous gland alveoli connected to hair follicles that had rudimentary cilia of smaller-than-normal diameter.[44] Moll's glands opened into the hair follicles.[44] Brailey, in 1906, reported a normal thickness and density of the tarsus but "absolutely no trace of the Meibomian glands or any epithelial cells whatever …, nor was there anything to suggest that any morbid process had previously taken place leading to the subsequent atrophy of the glandular elements."[45] The accessory row of cilia could not be examined by Brailey since they had been removed by electrolysis.[45] Begle (1913) also noted the absence of meibomian glands with hyperplastic sebaceous glands discharging into follicles of accessory cilia and independent sebaceous glands beneath the eyelid margin discharging upon its surface.[46] von Szily[47] noted posterior cilia emerging from orifices of rudimentary meibomian glands.[48]

Recently, Alkatan and colleagues reported the histological findings in three children with congenital distichiasis, one who had undergone repeated epilation and the other two who had electrolysis.[49] Excised eyelid tissue from the child who had repeated epilation disclosed "numerous aberrant hair follicles adjacent to the sebaceous glands located in the posterior lamella" along with "significant" fibrosis and chronic inflammation around the follicles and sebaceous glands.[49] Excised full-thickness eyelid tissue from two brothers who had been treated with electrolysis showed "several hair follicles within the posterior lamellae surrounded by extensive fibrosis likely due to cautery, which had also affected both the epithelium and the subepithelial tissue in the form of absence of most of the meibomian glands and focal chronic infiltration mainly around the follicles."[49] Based on the older studies reviewed above, this absence of meibomian glands may be a primary, not a secondary, abnormality.

Raymond-Letron and coworkers examined eyelid tissue from 20 dogs with distichiasis and control eyelid tissue from 11 dogs.[50] All dogs with distichiasis had normal tarsal sebaceous glands with serial sections disclosing hair follicles, with or without hair shafts, within the tarsus near or among the tarsal glands.[50] The hair follicles connected to the excretory ducts of the tarsal glands, allowing the cilia to emerge from the openings of the tarsal glands on the eyelid margin.[50] The difference in the histological appearance of

the eyelid tissue from dogs and humans may represent a species difference and/or possibly acquired versus congenital distichiasis.

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CHAPTER 31

Epicanthal Folds

Key Points

- Epicanthal folds are small crescentic webs of skin that contour around the medial canthal region with their concavity directed toward the inner canthus
- They can be congenital or acquired and can be seen as an isolated, or racial finding or in association with several facial anomalies
- Acquired epicanthal folds can result from trauma or surgical complications
- Congenital epicanthal folds are caused by vertical shortening of the medial canthal skin and an abnormal oblique distribution of the preseptal orbicularis muscle
- Clinically they are characterized by an extra fold of skin in the medial canthal area obscuring a portion of the medial canthus and the lacrimal caruncle and are categorized by their anatomic location based on the origin and insertion of the fold
- The four types include epicanthus supraciliaris, epicanthus palpebralis, epicanthus tarsalis, and epicanthus inversus
- The management of epicanthal folds is surgical skin rearrangement designed to lengthen the skin vertically, often combined with debulking of the underlying preseptal orbicularis muscle and subcutaneous tissue
- The prognosis is generally good, but surgical reduction can result in minor medial canthal scarring

Epicanthal folds are small crescentic webs of skin that contour around the medial canthal region with their concavity directed toward the inner canthus. They can be seen as an isolated, or racial finding or in association with several facial anomalies.[1,2,3,4,5,6]

Etiology and Pathogenesis

Epicanthal folds can be congenital or acquired. Congenital epicanthal folds can be observed in young children of all races as a normal finding before the nasal bridge elevates, or it can be seen as a normal racial variation, particularly in East Asians, Eskimos, Native Americans, and some Southern African tribes, where it usually persists with no attenuation.[2] In a recent study that surveyed the normative periocular anthropometric values in children versus young adults from the Chinese Han population, the authors demonstrated that with advancing age, epicanthal folds do tend to regress and are less frequently observed in young adults.[5] Several syndromes are also associated with epicanthal folds, such as the blepharophimosis syndrome (see Chapter 28) or Down syndrome.

Acquired causes include penetrating injury or burn trauma to the medial canthal region. An iatrogenic epicanthal fold or cicatricial canthal web may also occur during aggressive excision of grade II or III xanthelasma if the surgeon bridges the medial canthal region with the same incision and may also occur due to an abnormally curved or unusually high dacryocystorhinostomy incision. In these patients, severe webbing of the medial canthal region may result in vertical skin contracture and a hypertrophic semilunar skin fold that closely resembles an epicanthal fold.[5,7,8,9] Acquired cicatricial webbing may also occur laterally at the lateral canthal region following trauma or an aggressive combined upper and lower eyelid blepharoplasty.[8,10,11]

The main underlying topographic abnormality in acquired cicatricial webs, and to a lesser extent in congenital epicanthal folds, is a localized vertical deficiency of the skin with a concomitant relative horizontal skin excess.[8] In patients with congenital folds, it is important to remember that the vertical skin shortening is not the sole etiopathogenetic mechanism causing an epicanthal fold, as these congenital folds are also associated with an abnormal oblique redistribution of the preseptal orbicularis, the direction of which coincides with the direction of the epicanthal fold like the underlying events in epiblepharon.[12,13] This abnormal preseptal orbicularis extends further downward to connect with its preseptal counterpart in the lower eyelid inside the epicanthal fold, a

unique finding that is not observed in the normal population.[14] The pretarsal portion of the orbicularis is not involved.[14] Histopathologically, an epicanthal fold is therefore composed of three compartments: an outer skin lining, a fibromuscular core structure (preseptal orbicularis and fibrotic tissue), and an inner skin lining.[14]

Clinical Presentation

Epicanthus is characterized by an extra fold of skin in the medial canthal area that can obscure a portion of the medial canthus and the lacrimal caruncle (Figure 31.1).[6] The condition usually affects about 20% to 30% of the general occidental population at birth, but as the bridge of the nose elevates, it usually starts to get attenuated and mostly disappears around puberty; however, it may persist in some form or another in 2% to 5% of the population.[1,2,3,4] It is *(Print pagebreak 214)* important to realize that epicanthal folds are a normal finding in 40% to 90% of Asians where the *normal* appearance is hallmarked by an epicanthal fold that covers the medial part of the eyelids giving the illusion of telecanthus and horizontal phimosis, whereas in non-Asian races a *normal* appearance is defined by a rounded medial canthal angle coupled with total visualization of the caruncle and plica semilunaris.[12,14,15]

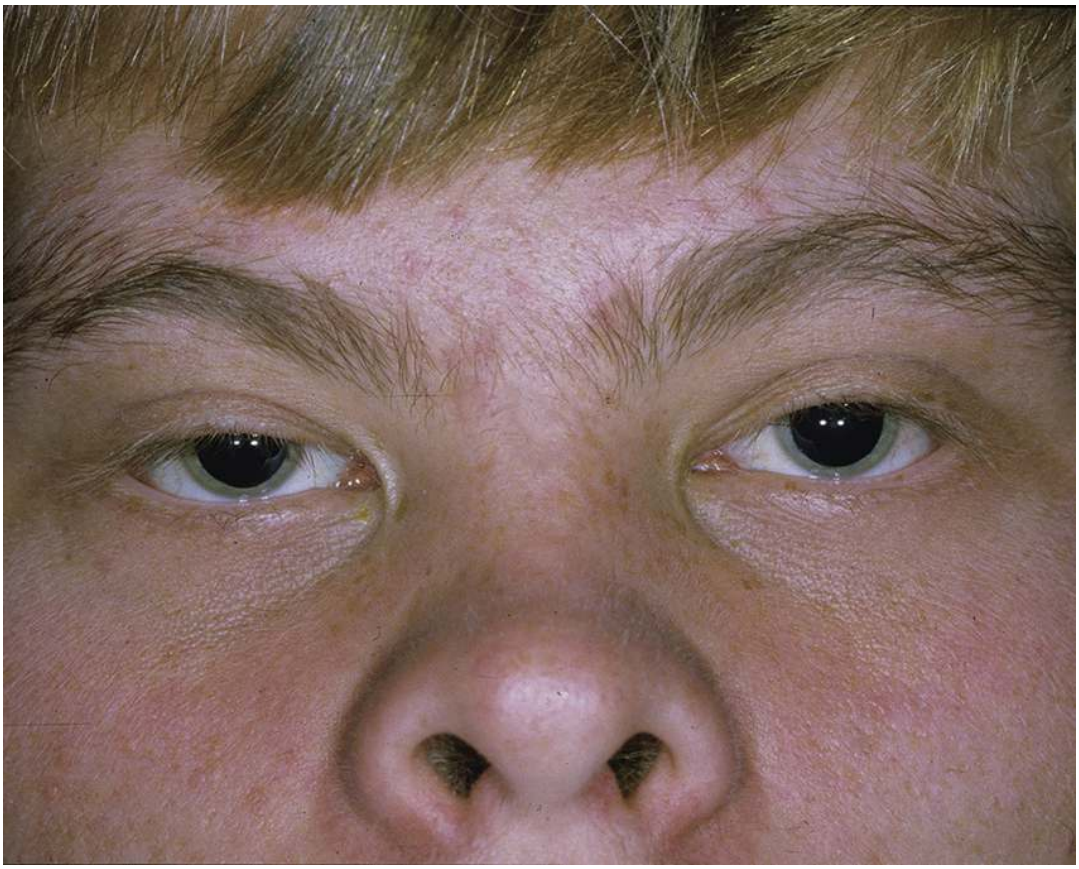

FIGURE 31.1 Epicanthal folds obscuring part of the medial upper eyelid and medial canthus.

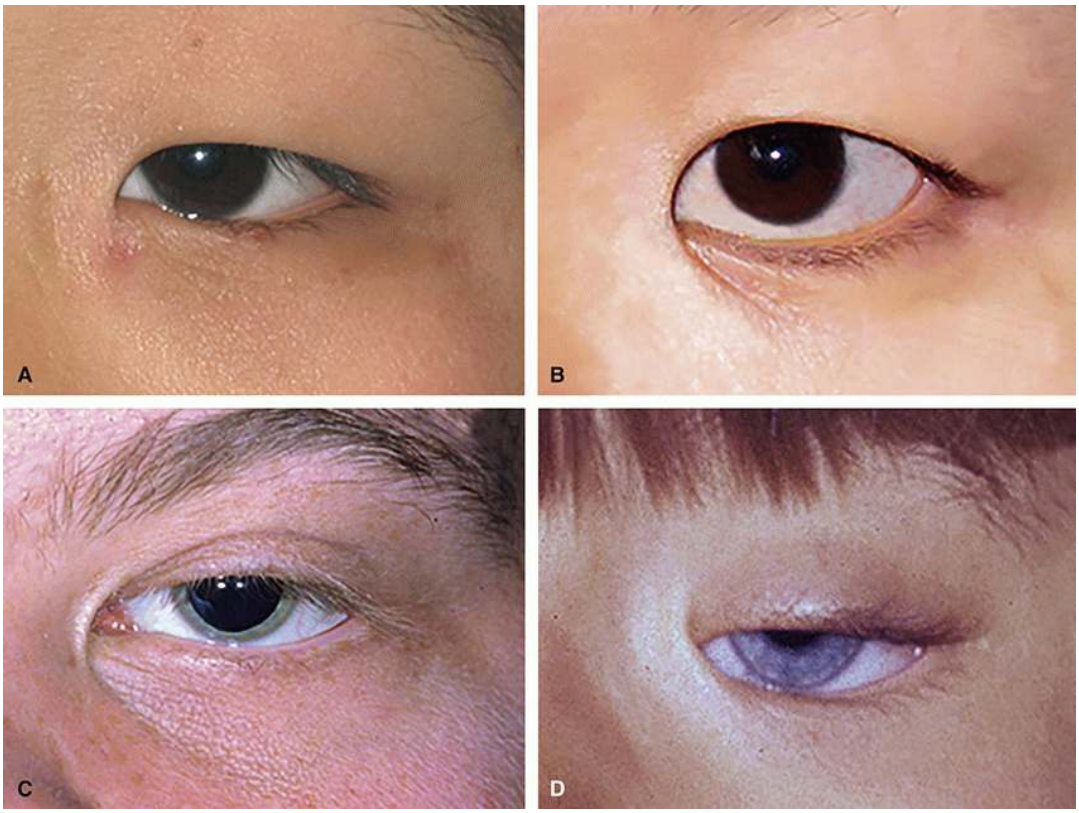

FIGURE 31.2 Types of epicanthal folds. A, Epicanthus supraciliaris. B, Epicanthus palpebralis. C, Epicanthus tarsalis. D, Epicanthus inversus.

Four configurations of epicanthal folds exist and are categorized by their anatomic location based on the origin and insertion of the fold (Figure 31.2). They are termed (1) epicanthus supraciliaris, where the skin fold originates from the upper lid close to the eyebrows and runs downward toward the lacrimal sac; (2) epicanthus palpebralis, which may be similar to the first type but the fold originates at a lower level in the upper eyelid and also ends at a lower level in the lower eyelid close to the anterior lacrimal crest; (3) epicanthus tarsalis, which presents as a fold of skin arising from the upper lid and extending inferiorly but with minimal involvement of the lower lid and is the most common type observed in children of East Asian descent; and (4) epicanthus inversus, where the redundant fold arises from the lower lid and is one of the defining features of blepharophimosis.[1,2,3,4,5,6]

Acquired cases usually present with historic and clinical evidence of prior trauma or surgery, coupled with extensive scarring in the medial or lateral periorbital region with or without cicatricial ectropion of the lower or upper eyelids.[8,16]

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Differential Diagnosis

John Mustardé suggested that, from a practical and clinical point of view, it may be difficult to differentiate the first three types of congenital epicanthal folds from each other[4,6] and preferred to use the term simple or Mongolian epicanthal folds to collectively describe those three types.[4] On the other hand, the fourth type (epicanthus inversus), which is a component of blepharophimosis syndrome, can be easily differentiated by the concomitant presence of telecanthus and ptosis.[4]

Because of an antecedent history of trauma, surgery, or burn, it is usually easy to differentiate a congenital canthal fold from an acquired cicatricial web. If the history is vague, it can still be easily differentiated on clinical grounds. A congenital epicanthal fold only occurs medially, whereas an acquired defect can involve either the medial or lateral canthi. Also, acquired defects are more commonly associated with more significant scarring and distortion of anatomy.[8]

Treatment

The management of congenital epicanthal folds is essentially surgical, and they are not particularly difficult to treat, although the surgical management in the first three types should be deferred until the child is older. It is important to realize that,

regardless of etiology, epicanthal folds arise as a result of a shortening of the skin rather than a skin redundancy; therefore, the ultimate role of the surgeon is to rearrange or redistribute tissue rather than perform a skin excision, which should be avoided, if at all possible, except for a minimal excision of a dog ear after wound closure.[4,17]

Although surgical repair is not particularly challenging, because of the ubiquity of the condition in Asians, well over 70 different epicanthoplasty techniques have been described from 1841 till 2019, and the treatment is far from being standardized. Most of those techniques employ geometric configurations that may look different on casual observation, but they can be broadly classified into two groups, variations of the Y-V flap to redistribute tissue, or transposition flaps which are largely based on Z-plasties.[12,18,19,20,21] Any of the above skin rearrangement techniques that aim at lengthening the skin should be combined with debulking or thinning of the underlying preseptal orbicularis fibers and subcutaneous tissue. This step (orbicularis myectomy) is crucial for the success of the procedure regardless of the exact epicanthoplasty technique adopted by the surgeon, as it releases vertical tension caused by the underlying orbicularis muscle, thereby facilitating tissue redistribution.[12,22]

An alternative technique that does not involve an epicanthoplasty, which may subsequently provide a better cosmetic outcome, has been pioneered by David Jordan and Richard Anderson,[3] where a standard eyelid crease incision is made and extended medially along the crest of the fold, followed by debulking of subcutaneous tissue and orbicularis fibers. A small strip of skin may be excised followed by securing both edges of the skin over the fold to the periosteum along the lateral side of the nose. The rest of the eyelid crease incision is closed to continue the deep crease fixation.[3] Although this technique is recommended for the first three types of epicanthal folds,[3] it works best with epicanthus tarsalis.[12] Recently, subtle variations of this elegant technique were reintroduced in Asian countries and popularized in the media as "magic epicanthoplasty."[12] Although the surgical details of the so-called Asian blepharoplasty are beyond the scope of this chapter,[23,24] if an epicanthal fold is present and an epicanthoplasty is considered, it should be combined with double-eyelid blepharoplasty surgery in the same setting to achieve the desired appearance of folded eyelids.[6]

The surgical correction of epicanthus inversus is more complicated because it typically involves simultaneous repair of the telecanthus and epicanthal folds.[17]
The most popular technique is the multiflap technique proposed by John Mustardé (the so-called Mustardé's jumping or dancing man technique). This technique simultaneously corrects the epicanthal fold with telecanthus and is done in all patients with epicanthus inversus in a standardized fashion regardless of the extent or exact orientation of the inverted epicanthal fold.[4,17] Alternative techniques that include the Anderson five flap technique, the del Campo technique, and Y-V plasty are detailed elsewhere,[17] but the underlying concept in all those techniques is tissue redistribution in the medial canthal region that combines the use of a Y-V plasty and multiple Z-plasties with orbicularis debulking.[8] The use of a simple Y-V plasty alone has been advocated recently as a simple, protocolled, and reproducible alternative to more complicated reconstructive procedures with the added benefit of reduced visible postoperative scarring as the scars lie in a cosmetically favorable position.[25]

In milder cases with an acquired medial or lateral epicanthal fold (cicatricial webs), multiple Z-plasties or local transposition flaps may be useful in correcting those linear contractions and flattening the fold if the wounds are relatively soft and not overly scarred.[7,8] This may or may not be combined with postoperative serial injections of a combination of Kenalog and 5-fluorouracil to help reduce scarring.[8] More commonly, however, skin shortening is marked and more favorable results could be obtained by excising the scar web, releasing the canthus, and placing a full-thickness skin graft.[4,5,7,11,26,27]

Prognosis

The surgical management of congenital epicanthal folds is usually satisfactory and is generally easier than correction of the telecanthus that may be associated with it. However, most of the procedures described in the literature tend to result in hypertrophic scarring on the nasal skin near the medial canthus making surgeons hesitant to employ these procedures on a wider basis.[6,12] Concerned parents of children with congenital epicanthal folds from certain ethnicities (eg, East Asians) may be advised that epicanthal folds tend to regress with advancing age.[5]

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Histopathology

Park and Hwang examined epicanthal folds from two epicanthoplasties and 15 cadavers.[14] The folds consisted of a core of intermingled skeletal muscle fibers and fibrous tissue with epidermis covering the outer and inner surfaces.

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CHAPTER 32

Essential Blepharospasm

Key Points

- Essential blepharospasm (EB) is a complex neurologic condition
- Secondary, or reflex, blepharospasm is due to ocular surface disease, such as keratitis or blepharitis, or with eyelid conditions such as trichiasis or entropion
- EB begins as a focal dystonia involving only the eyelid muscles, but in 50% to 70% of patients, it spreads to adjacent muscle areas of the mid and lower face and neck
- Meige syndrome is a segmental craniocervical dystonia comprising two focal areas, blepharospasm and involuntary movements of the mid-and lower facial muscles
- Basal ganglion dysfunction is thought to play a major role in the pathogenesis of dystonias including EB
- Symptoms of EB range from increased frequency of blinking to sustained forceful, sometimes painful, squeezing of the eyelids that can lead to functional blindness
- The photophobia in EB can be reduced significantly by photochromatic modulation with specially tinted lenses
- Many systemic drugs have been reported to be partially effective for dystonias, including dopamine agonists, GABA agonists, and anticholinergic agents
- Botulinum toxin injection has become the mainstay of treatment for EB by blocking acetylcholine release at the neuromuscular junction
- The prognosis for improved quality of life is generally very good

Fssential blepharospasm (EB), first reported by MacKenzie[1] in 1857, is a focal cranial dystonia characterized by involuntary, symmetrical eyelid closure. It affects approximately 1.4 to 13.3 cases per 100,000 population, with women more commonly affected than men in a ratio of approximately 2.5-3:1.[2,3,4] In the United States, it is estimated that at least 50,000 people are affected, with 1500 to 2000 new cases diagnosed annually. The condition is seen most often in middle-aged to older individuals in the sixth to seventh decades of life. Photophobia is a major trigger that exacerbates symptoms in a significant percentage of patients.[5]

Primary blepharospasm (BSM) is a complex neurologic condition and should not be confused with secondary, or reflex, blepharospasm due to ocular surface disease, such as keratitis or blepharitis, or with eyelid conditions such as trichiasis or entropion. Management of these conditions will usually resolve the secondary blepharospasm.[6]

Predisposing factors for primary blepharospasm may include recent stressful events, a history of dry eyes or keratitis, and head trauma.[7] In most cases, EB begins as a focal dystonia involving only the eyelid muscles. However, in 50% to 70% of patients, it spreads to adjacent muscle areas as a segmental or regional dystonia. In these cases, the mid-and lower face becomes involved in 85%, cervical muscles in 33%, and laryngeal muscles in about 10%.[8,9] Of those who do progress to adjacent regions, 20% will do so within 1 year, 55% within 2 years, and 90% within 5 years.[8,9]

A phenomenon often seen with dystonias is the use of sensory tricks, which are purposeful maneuvers that can temporarily reduce the severity of the abnormal dystonic posturing.[10,11,12,13] Previous studies suggest that 55% to 72% of patients with EB and 40% to 55% of patients with hemifacial spasm use such trick maneuvers to alleviate their symptoms.[11,14] A variety of different sensory trick maneuvers have been described, with the most common being touching specific areas of the face and upper eyelid. Others include humming, whistling, coughing, and yawning.[13] Approximately 45% to 65% of patients who use alleviating maneuvers report that their maneuver either abolishes or reduces their symptoms by 50% or more. Several authors[15,16] emphasized that these maneuvers could involve not only sensory but also motor stimulation, and they referred to these tricks more accurately as alleviating

maneuvers. The mechanisms underlying alleviating maneuvers are not clearly understood, but they appear to reduce cortical activity, perhaps by altering central processing.[17]

Meige syndrome is a segmental craniocervical dystonia comprising two focal areas, blepharospasm and involuntary movements of the mid-and lower facial muscles. In 1910, Henri Meige, a French neurologist, provided a detailed description of 10 patients with this condition,[18] and since then, the condition has been referred to under the eponym of Meige syndrome. However, this dystonia was first described by Talkow in Germany in 1870, and Wood in the US in 1887, so that the term Meige syndrome is inappropriate. Although the condition is accommodated under the broad term craniocervical dystonia,[19] various other included conditions also involve blepharospasm and other facial and cervical muscle combinations. So, despite its limitations, the term Meige syndrome remains in common usage.

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Etiology and Pathophysiology

Blepharospasm is considered to be a defect in the central neurological circuit that controls eyelid muscle activity and coordination.[20] This circuit has sensory input, central coordination control in the basal ganglia, and motor output components. Input factors such as light, ocular surface irritation, pain, emotion, and stress send sensory impulses to the central control center. A defect in this control center, presumably in the striatal dopamine 2 receptors,[21,22] results in altered functional connectivity in widespread areas of the brain including the thalamus and cerebellum.

The corticobasal ganglia-thalamocortical loop is thought to be responsible for the regulation of voluntary movement. This motor circuitry is segregated into direct and indirect pathways that regulate stimulatory and inhibitory effects mediated and coordinated in the basal ganglia.[23] The direct pathway connects the motor cortex and caudate and putamen of the basal ganglia. Inhibitory signals are then sent to the globus pallidus internus (GPi) and substantia nigra that suppress the thalamus through gamma-aminobutyric acid (GABA)-mediated signals. This excites projections to the motor cortex, promoting muscle movement. The indirect pathway inhibits signals through the basal ganglia. It is responsible for disinhibiting the subthalamic nucleus, which ordinarily stimulates the GPi. This inhibitory signal suppresses muscle movement. In dystonia, it has been proposed that there is an imbalance between the direct and indirect pathways so that the indirect pathway becomes dysfunctional. This results in uninhibited stimulation of the direct pathway and muscle hypertonicity.[23]

Basal ganglion dysfunction is thought to play a major role in the pathogenesis of dystonias. In EB, decreased gray matter has been found in structures related to sensorimotor processing, particularly in the putamen, caudate nucleus, and thalamus.[24] In case reports of focal dystonias, striatal gliosis and putaminal degeneration have been identified.[25,26,27] Also, studies on experimentally induced dystonias in animals suggest a role for the putamen and corpus striatum in blepharospasm.[28,29] Positron emission tomography scans,[30] and diffusion tensor magnetic resonance imaging of the putamen, corpus callosum, pallidum, and caudate nuclei in EB patients support a role for the basal ganglion in a variety of focal dystonias.[31] These findings support the hypothesis that increased activity in the direct striatopallidal pathway inhibits the internal globus pallidus, resulting in increased inhibition in the medial globus pallidus and reduced activity in pallidal output to the thalamus.[32] The result is decreased inhibition of competitor muscles associated with the spastic muscles. Several studies have shown improvement in EB symptoms with the administration of oral methylphenidate, a drug that increases intrasynaptic dopamine by blocking dopamine transmitters.[33,34] Some evidence has suggested that two factors, environmental and genetic, jointly underlie the pathophysiology of dystonia.[35] Environmental factors include things like local injury.[36,37] In EB, up to 20% of patients have one or more family members with focal dystonia, essential tremor, or Parkinson disease.[38,39] This suggests a genetic predisposition. Animal models and population studies have suggested that predisposing genes are inherited in an autosomal dominant fashion with low penetrance.[40,41,42] Studies have also shown polymorphisms in the D5 dopamine receptor (DRD5), and a group of DYT gene polymorphisms has been linked to some inherited dystonias.[42,43,44] However, no specific genetic factors have been identified specifically for EB.

Clinical Presentation

EB is seen primarily among older individuals at a mean age of 64 years but rarely can be seen in children and adolescents.[45] Females are affected 2.5 times more frequently than males and tend on average to be 4 to 5 years older. Symptoms of EB range from increased frequency of blinking to sustained forceful, sometimes painful, squeezing of the eyelids that can lead to functional blindness. In many cases, the spasms may be localized to the eyelid protractor muscles alone as a focal dystonia (Figure 32.1). But with progression, spasms may also involve adjacent areas of the head and neck. Midfacial or lower-facial spasms are most often involved as a segmental dystonia (Figure 32.2A) or may spread even further to the neck as a regional dystonia (Figure 32.2B). Eyelid closure is bilateral and symmetrical and can range from increased frequency of blinking to occasional mild intermittent closure, to persistent forceful squeezing that may be difficult to overcome manually. Long-standing blepharospasm may be associated with anatomic eyelid changes, including dermatochalasis, eyelid and brow ptosis, entropion, and ectropion.[5,46] These

frequently result from patients trying to manually open their eyes with their fingers or other devices such as tape or ptosis crutches (Figure 32.3). Upon careful questioning, patients frequently report certain precipitating factors such as driving, reading, stress, and bright lights.

In a study of 120 Chinese patients with blepharospasm or cervical dystonia using validated rating instruments, Yang et al[47] reported a significant increase in depression, anxiety, and sleep disorders and cognitive decline compared with normal controls. But there was no significant correlation between these nonmotor symptoms and motor severity in these two forms of dystonia.

The diagnosis of blepharospasm can sometimes be difficult, and eyelid closure alone may not be sufficient. In 2013, Defazio et al[48] introduced a validated algorithm for diagnosis of blepharospasm based on a seven-item guide including stereotyped, bilateral, and synchronous orbicularis oculi spasms inducing eyelid narrowing or closure, associated with a sensory trick, or increased resting blink rate. This algorithm yielded a 93% sensitivity and 90% specificity for the diagnosis of blepharospasm. In addition, contrary to apraxia of eyelid opening, in EB the eyebrows are pulled downward without frontalis muscle contraction elevating them. This phenomenon is termed Charcot's sign.

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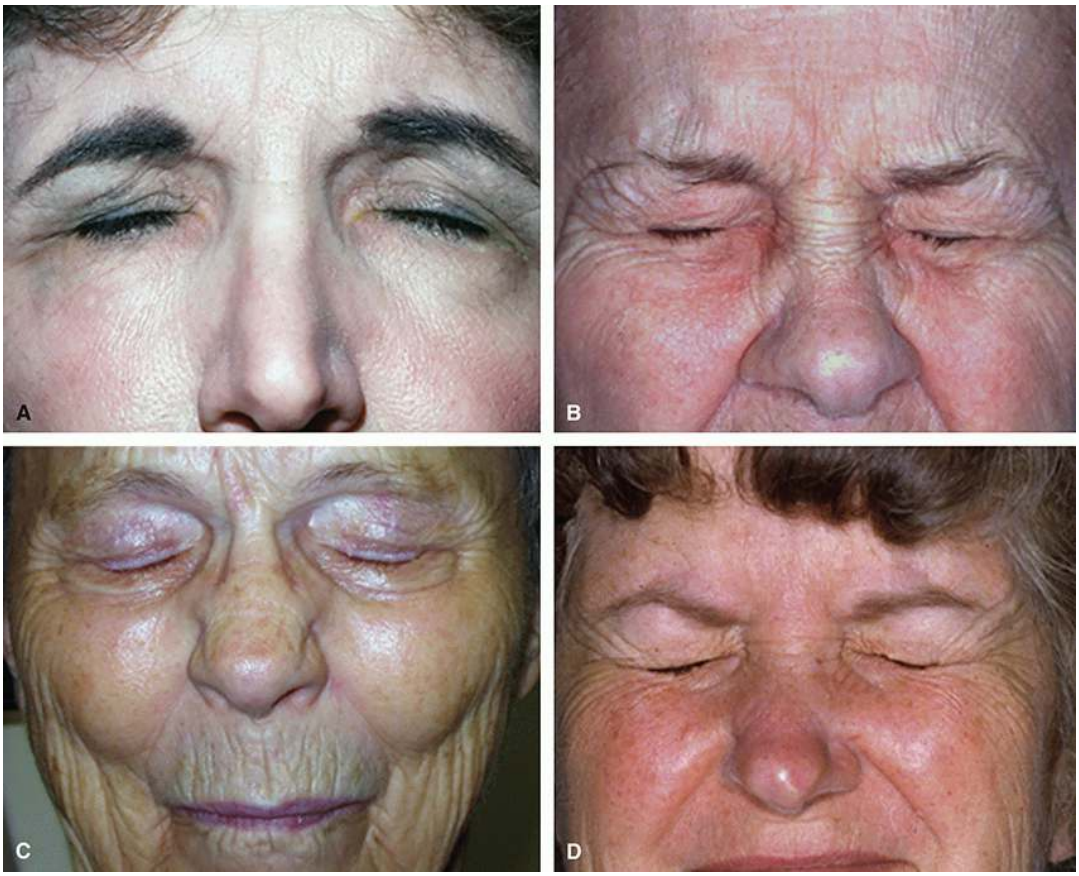

FIGURE 32.1 A-D, Essential blepharospasm as a focal dystonia involving the eyelids. Note contraction of the orbicularis muscle and downward traction on the eyebrows.

Several clinical rating scales have been developed to measure the severity of EB. The most important are the Jankovic Rating Scale, the Blepharospasm Disability Scale, the Functional Disability Score, the Blepharospasm Disability Index, and the Burke-Fahn-Marsden Dystonia Rating Scale.[49,50,51,52] More recently, Defazio et al introduced a validated severity scale based on the most relevant blepharospasm motor abnormalities and objective criteria that the authors say yields moderate to almost perfect reliability, and acceptable internal consistency, and that can reliably be administered by people without high levels of movement disorders experience.[53]

Differential Diagnosis

The diagnosis of blepharospasm is one of exclusion. Conditions that cause ocular surface irritation or corneal abrasions such as trichiasis or severe blepharitis may induce secondary reflex blepharospasm (Figure 32.4). A careful examination of the eyelid margins and cornea must be made to rule out such causes of eyelid spasms. Neurodegenerative disorders, such as Parkinson disease,

Huntington disease, and Wilson disease, may be associated with blepharospasm.[54] Apraxia of eyelid opening (AEO), is seen in extrapyramidal diseases, such as supranuclear palsy and Shy-Drager syndrome, and in AEO patients cannot open the eyelids in the absence of clinically evident orbicularis muscle contraction.[55] Also, in apraxia of eyelid opening, the eyebrows typically are elevated, whereas in blepharospasm, they are contracted downward. Some patients with EB have a component of apraxia of eyelid opening that may confuse the diagnosis. Hemifacial spasm is a unilateral disorder that affects the facial muscles innervated by the seventh cranial nerve. In rare cases of bilateral hemifacial spasm, both sides of the face are affected, superficially resembling EB, but the spasms on each side are asynchronous, in contrast to the synchronous *(Print pagebreak 220) (Print pagebreak 221)* spasms in EB. Eyelid tics are the most common ophthalmic manifestation of Gilles de la Tourette syndrome, seen in more than 50% of such cases, but unlike blepharospasm, Tourette syndrome starts in early childhood with a peak in severity between 10 and 12 years of age. It is also associated with vocal tics.[56]

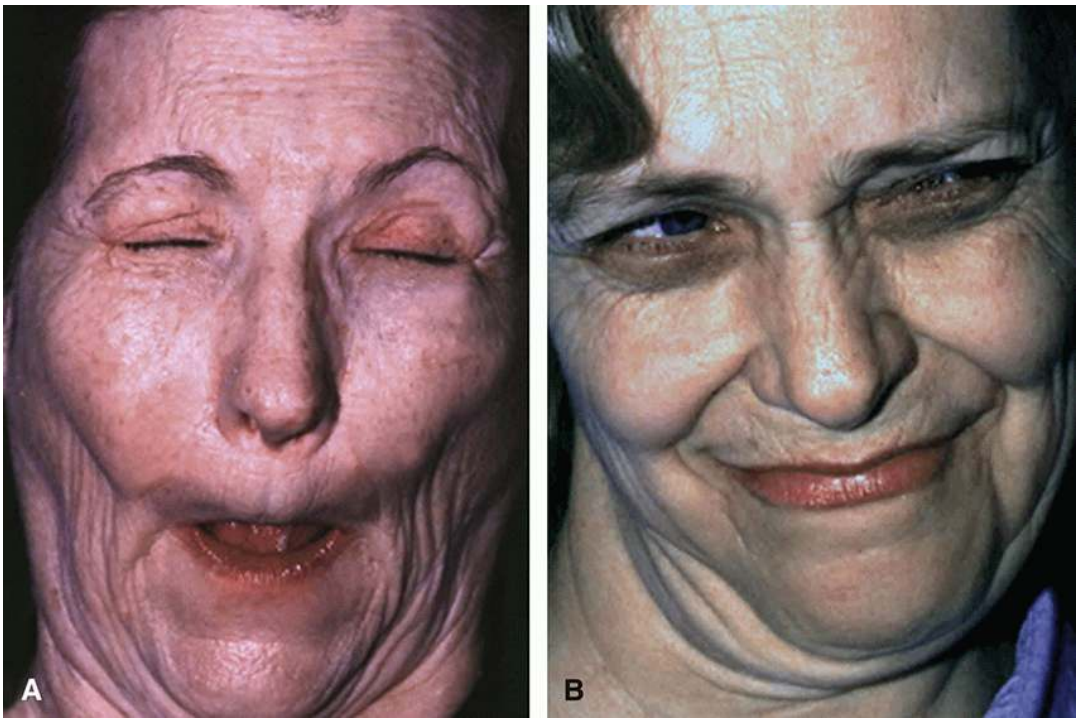

FIGURE 32.2 A, Segmental dystonia of EB and midfacial dystonia (Meige syndrome). B, Regional dystonia with EB, midfacial dystonia, and torticollis.

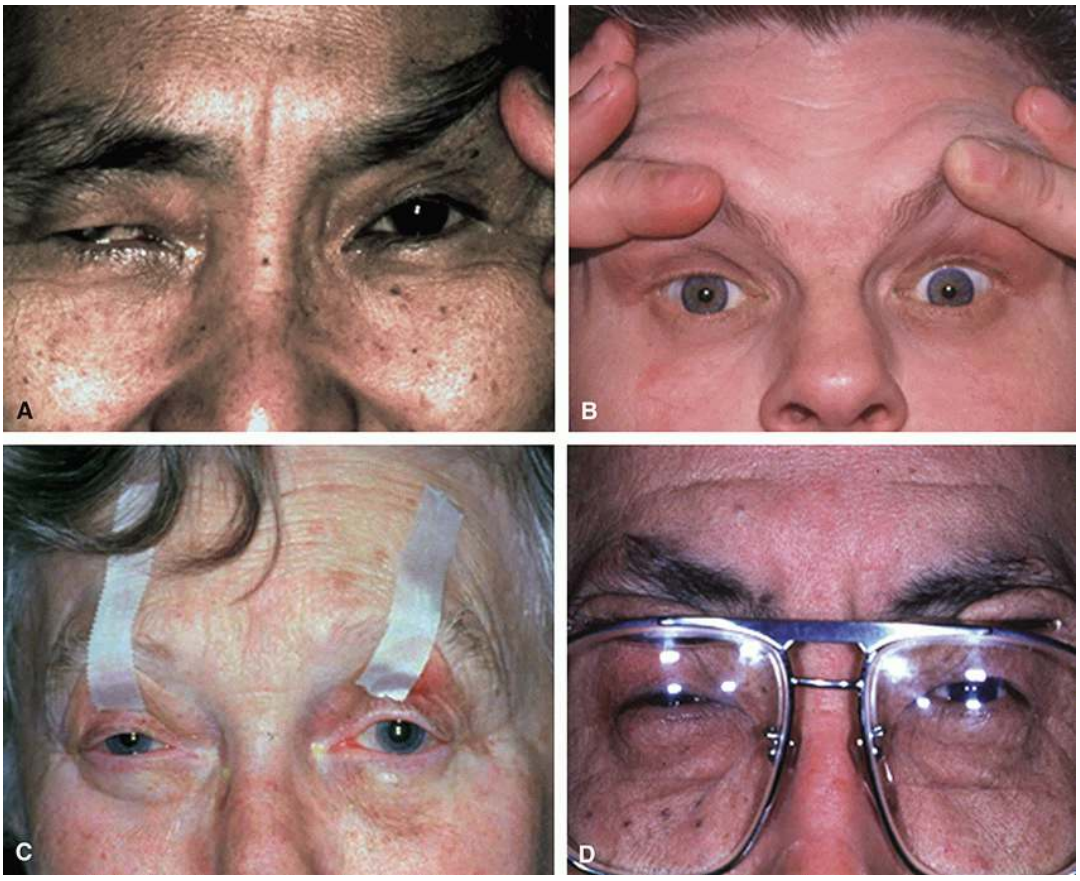

FIGURE 32.3 Various mechanisms used by patients to maintain some visual function with EB. A and B, Manual elevation of the eyelids with fingers. C, Eyelid taped to the forehead. D, Ptosis crutches fixed to eyeglasses.

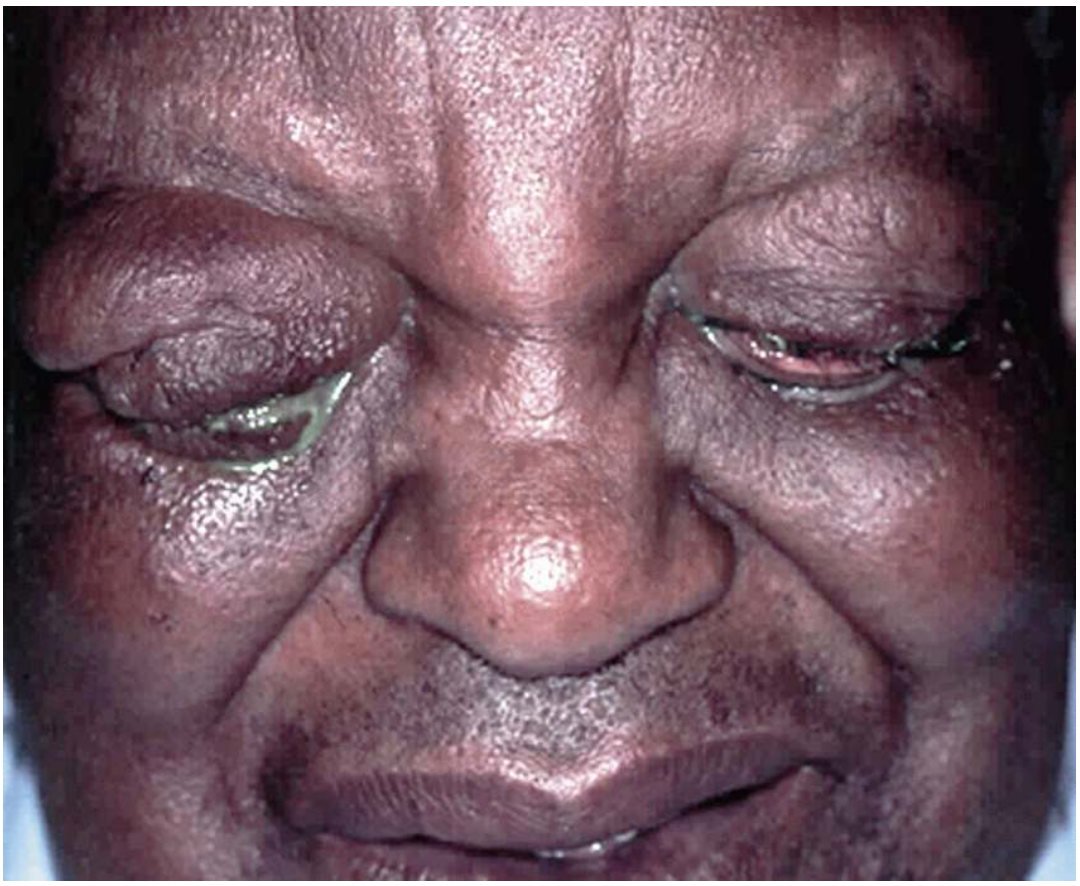

FIGURE 32.4 Secondary reflex blepharospasm from severe blepharitis simulating essential blepharospasm.

Treatment

The photophobia in EB can be reduced significantly by photochromatic modulation with specially tinted lenses.[57] Glasses tinted with FL-41 have been shown to provide improved subjective and objective benefit in the management of photophobia in EB, compared with standard gray-tinted lenses.[58] Excessive sensory input from ocular surface irritation, such as blepharitis or dry eyes, can be managed with topical antibiotics and lid scrubs, artificial tears, and punctal occlusion.

Many systemic drugs have been reported to be effective for dystonias, but specific pharmacologic therapy for the control center of blepharospasm has not yet been determined. With most drugs, effects are only partial and short lived. For this reason, pharmacotherapy is usually reserved as an adjunct to botulinum toxin injections where its effect alone is not satisfactory. The most common agents reported to be effective for EB include dopaminergic agents, GABA agonists, and anticholinergic agents.[59]

Dopamine deficiency in the basal ganglia has been implicated in EB and other forms of dystonia, and dopamine agonists and dopamine uptake inhibitors, such as methylphenidate, have been reported to reduce eyelid spasms in EB.[33,34] GABA agonists, such as benzodiazepines, have sedating effects and muscle relaxing properties. Anticholinergics are a commonly used class of medications in EB and act as central nervous system depressants. All of these pharmacologic agents have significant side-effect profiles including confusion, sedation, drowsiness, lightheadedness, and hallucinations that may limit their use in many patients.[59]

Over the past 3 decades, botulinum toxin injection has become the mainstay of treatment for EB. The serotype A toxin of *Clostridium botulinum* weakens muscles by inhibiting the release of acetylcholine from the presynaptic nerve terminal of the neuromuscular junction. Muscle weakness usually begins in 2 to 7 days after the injection and on average lasts 3 months in 90% of patients.[60,61,62] In some patients, it may last as long as 4 to 6 months or as little as 1 to 2 months. Five units of botulinum toxin are typically injected with a 30-gauge needle on a tuberculin syringe. Injections are made superficially into the orbicularis oculi, corrugator, and procerus muscles. The most common side effect of the injection is swelling of the eyelid, sometimes accompanied by bruising. Injections that are too deep, beneath the orbital septum, could spread to the levator muscle, causing eyelid ptosis. This can usually be avoided by sparing the central portion of the upper eyelid and injecting only in the medial and lateral eyelid. Other side effects include lagophthalmos with corneal exposure, ectropion, entropion, epiphora, diplopia, and lower facial weakness. All such side effects are temporary and typically last only 3 to 4 weeks. Contraindications to botulinum toxin injections include allergies to the drug, infection at the injection site, coagulopathies, myasthenia gravis, pregnancy, and breastfeeding. Ninety percent or more of patients will develop weakness of the orbicularis oculi muscle after injection of botulinum toxin with partial to complete relief of eyelid spasms. Repeat injections are usually required every 3 to 4 months, but repeat injections are not always as effective as the first injection.

For patients with spasms who do not respond to multiple sessions of botulinum toxin injection, or who show a good response initially but later develop resistance, surgery may be appropriate. In some cases, the spasms are relatively mild, and since the frontalis muscle is not involved in the spasms, a frontalis suspension procedure has been shown to provide at least some improvement in eyelid closure in 73% of treated patients, although most required additional botulinum toxin injections in order to increase the desired effect.[63]

Surgical myectomy involves removal of the pretarsal, preseptal, and orbital portions of the upper eyelid orbicularis oculi muscles.[64,65] Extended myectomy could also include removal of the procerus and corrugator muscles. Upper and lower eyelid myectomy surgery should be staged separately to avoid chronic lymphedema that is common with simultaneous surgery. Orbicularis myectomy surgery can be performed through an upper eyelid crease incision. The pretarsal orbicularis between the eyelid crease incision and a position several millimeters above the lashes is dissected and removed. The muscle from the superior edge of the incision to the inferior edge of the eyebrow is also dissected away. Finally, the orbital portion of the orbicularis muscle over the temporal raphe is resected. The procerus and corrugator *(Print pagebreak 222)* muscles can be accessed through the skin crease incision and divided between the supraorbital and supratrochlear neurovascular bundles when indicated. Of note is that the associated anatomic eyelid changes that may accompany long-standing EB such as dermatochalasis, eyelid ptosis, brow ptosis, entropion, or ectropion should be managed accordingly.[66]

Deep brain stimulation (DBS) is a safe, low-risk, and reversible intervention using electrical impulses that alter neural signals in specific subcortical regions of the brain.[23] Electrodes are implanted and connected to a subcutaneous pacemaker and are effective in primary generalized and cervical dystonia.[67,68,69,70] Pallidal DBS for Meige syndrome has been described in single case reports and small case series, with improvement in severity scales ranging from 45% to 89% over follow-ups of 1 to 6 years.[71,72] GPi DBS has been used for isolated blepharospasm with encouraging results.[71,73,74,75,76,77,78,79] Recently, deep transcranial magnetic stimulation, which is a noninvasive alternative to DBS whereby patients receive brain stimulation with a helmet that is fitted with electric coils, has been advocated in combination with botulinum toxin injections

in patients with blepharospasm to alleviate depression, anxiety, or other nervous system disorders that may be associated with EB.[80]

Prognosis

There is no cure for EB, and management is directed only at the management of visually debilitating eyelid spasms. With botulinum toxin, the prognosis for improved quality of life is very good.[81,82,83,84,85] Most patients can return to work, drive, and resume other normal functions, and their improved social interaction often leads to less depression.[86] For the 2% to 4% of patients who do not respond to chemodenervation alone, the addition of pharmacologic agents or selective surgery is usually effective.

Histopathology

There are no reports of eyelid histopathology in patients with blepharospasm, to our knowledge, unless long-standing blepharospasm results in dermatochalasis, entropion, or ectropion.

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CHAPTER 33

Euryblepharon

Key Points

- Euryblepharon is a horizontal enlargement of the palpebral aperture
- The etiology of euryblepharon is unknown, but theories include shortening of the anterior lamella, partial or complete developmental hypoplasia of the palpebral portion of the orbicularis oculi, or abnormally elongated lateral canthal tendon
- The clinical manifestation is an increased length of the palpebral aperture with a lateral ectropion of the lower eyelid hanging away from the globe
- It may occasionally be seen concurrently with ptosis, distichiasis, telecanthus, strabismus, or abortive cryptophthalmos
- Treatment is surgical with a lateral canthal resuspension in milder cases, but more severe cases may require an advancement flap, skin graft, or a midface lift procedure
- The prognosis is good following surgical repair, but some scarring may result from more extensive surgical procedures

Euryblepharon is defined as a horizontal enlargement of the palpebral aperture with subsequent eversion of the lateral part of the lower eyelid. Vertical shortening of the skin is a common association.[1] This condition was first described by Desmarres[2] in 1854; several other earlier case reports have also been cited by Duke Elder[3] in 1963, who modernized the definition of euryblepharon.

Etiology and Pathogenesis

Although the exact etiology of euryblepharon is largely unknown and no specific genes or loci have been observed,[1,4] several pathogenetic mechanisms may help explain the clinical manifestations of this condition. A short anterior lamella, partial or complete developmental hypoplasia of the palpebral portion of the orbicularis oculi causing undue tension on the skin, or an abnormally elongated lateral canthal tendon are among the more plausible theories. Other less conceivable etiopathogenetic mechanisms include indirect pull of the platysma on the eyelid, defective fetal separation of the lids, and localized congenital displacement of the lateral canthi.[4,5,6,7,8,9]

Clinical Presentation

The most obvious clinical manifestation of euryblepharon is increased length and width of the palpebral aperture. A typical clinical sign is that the lower lid and less commonly the upper lid appears to “hang away” from the globe laterally,[6] as if the eyelid is “too big” for the globe (Figure 33.1). This may be an inaccurate description because euryblepharon is typically associated with a vertical lower eyelid shortening rather than lengthening. Whether this vertical shortening is also associated with horizontal shortening[8] or paradoxical horizontal lengthening of the lower eyelid[7] is contentious in the literature. Typically, euryblepharon symmetrically involves both lower eyelids but asymmetric cases have been described.[5] Euryblepharon may occur in isolation without any ocular or systemic associations, or may be associated with several different local or systemic anomalies.

Locally, it may occasionally be observed concurrently with ptosis, distichiasis, telecanthus, strabismus, or abortive cryptophthalmos.[1,5,10] Systemically, euryblepharon is the quintessential defining feature of blepharocheilodontic (BCD) syndrome (Figure 33.2) and Kabuki-makeup syndrome.[5,6] It has rarely been described with Noonan[11] and Barber-Say syndromes[12] and multiple endocrine neoplasia syndrome type 2B (MEN 2B).[13] BCD syndrome is a rare disorder characterized by lower eyelid euryblepharon, upper eyelid megaloblepharon, distichiasis, bilateral cleft lip and palate, hypodontia, conical teeth, and imperforate anus. The syndrome is inherited in an autosomal dominant fashion with incomplete penetrance, but de novo mutations have also been described. Two genetic loci have been identified so far for the disease (16q[22] and 11q12).[14,15,16] Kabuki syndrome (also known as Kabuki-

makeup syndrome or Niikawa-Kuroki syndrome) derives its name from the peculiar characteristic dysmorphic facial features that are highly reminiscent of the makeup pattern of Kabuki artists, the ancient theatrical form of Japanese opera. Hallmarks of this genetic disease include euryblepharon, high arched eyebrows, depressed nasal tip, and prominent ears. Systemic features include skeletal anomalies (brachydactyly, spinal anomalies, and a short fifth finger), cleft lip and palate, mental retardation, postnatal growth retardation (short stature), and dermatologic anomalies (persistent fetal pads on the fingertips). The syndrome *(Print pagebreak 226)* more commonly occurs in children of Japanese ancestry in a sporadic fashion, but other ethnicities have been described. The full phenotype appears to evolve, compounding the early diagnosis of the disease.[17,18,19]

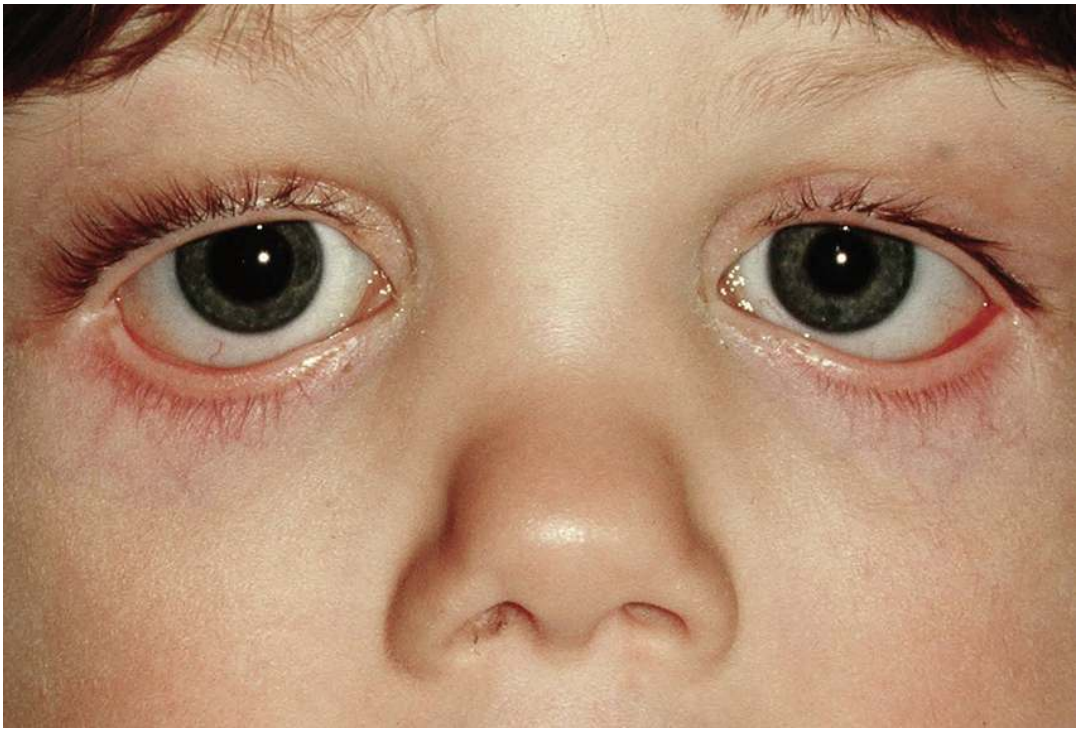

FIGURE 33.1 Isolated euryblepharon. (Courtesy of Dr. Alan McNab.)

Differential Diagnosis

The most important differential diagnosis of euryblepharon is congenital ectropion. True congenital ectropion is also very rare and usually syndromic. The defining feature of congenital ectropion is ectropion involving the entire upper and/or lower eyelid and not circumscribed to the lateral part like euryblepharon. Possible associated syndromes include Down syndrome and blepharophimosis-ptosis-epicanthus inversus syndrome. Euryblepharon may occasionally be a feature of Down syndrome, although congenital ectropion of the upper and lower eyelids and upward slanting of the palpebral fissure is a more cardinal oculoplastic feature.[5]

Although temporal displacement of the lower eyelids is a common finding in patients with the blepharophimosis-ptosis-epicanthus inversus syndrome, generalized ectropion is more common, with lateral displacement of the lower punctum with or without punctal eversion being more defining features of the syndrome. The pathogenesis is also different. An abnormally developed lower crus of the medial canthal tendon rather than an abnormality in the lateral canthal tendon or an abnormal attachment of the lower eyelid to the medial canthal tendon could explain the peculiar features of blepharophimosis syndrome.[20]

Although inferomedial displacement of the lateral canthal tendon in milder cases of mandibulofacial dysostosis (Treacher Collins syndrome) could simulate isolated euryblepharon, the hallmarks of that disease, including the hypoplastic cheek-lower lid complex and the exaggerated antimongoloid slant of the palpebral fissure, can easily differentiate both conditions (Figure 33.3).[21]

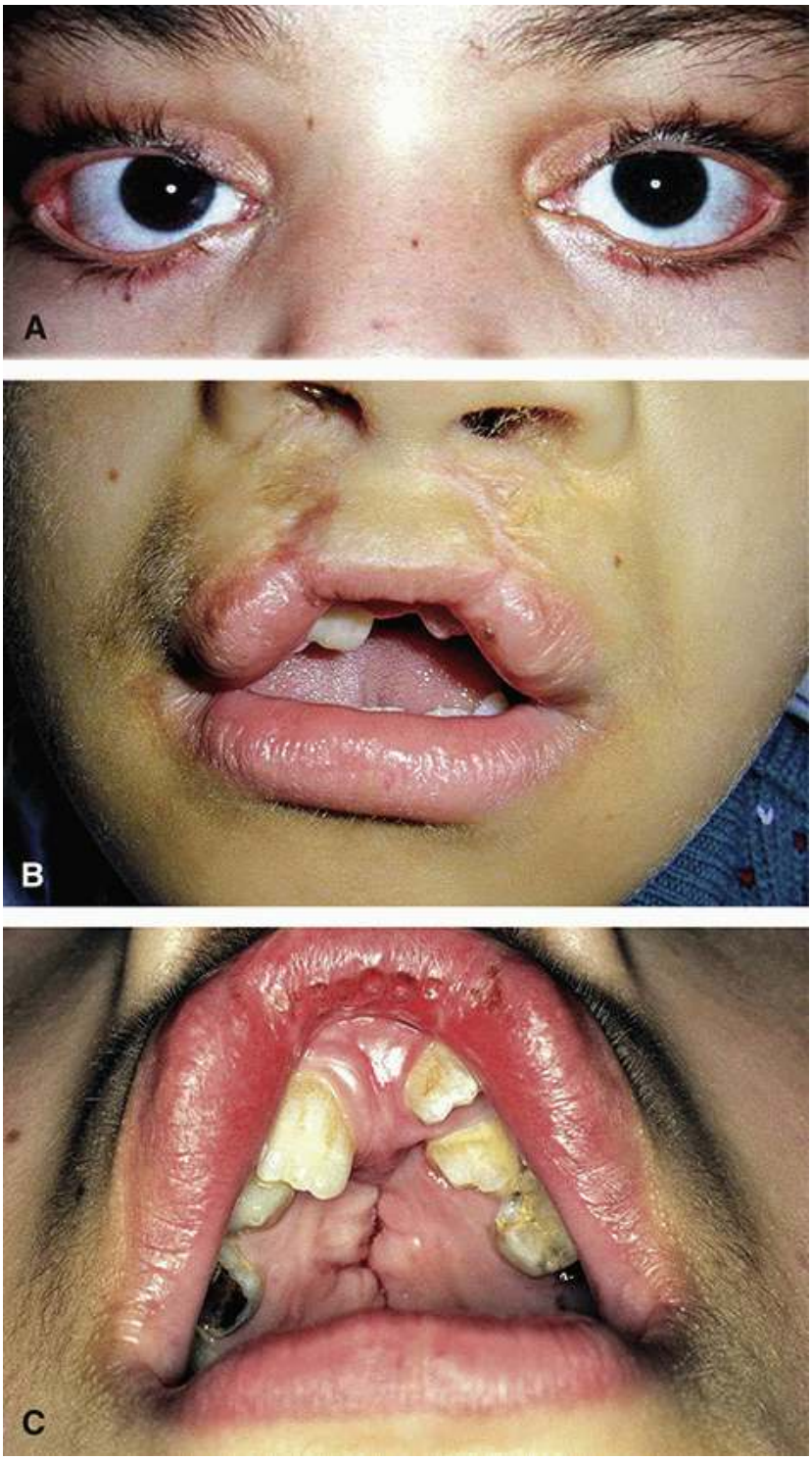

FIGURE 33.2 Cardinal features of the blepharocheilodontic syndrome (BCD syndrome). A, Euryblepharon. B, Cleft lip. C, Hypodontia and conical teeth.

Treatment

Although the obvious remedy for euryblepharon is surgical, nonsurgical expansion or reinforcement of the lower eyelid with a pretarsal injection of hyaluronic acid gel has been described in milder cases using a layered approach with multiple threadlike injections under topical lidocaine sedation. The desired endpoint is resolution of lagophthalmos without occlusion of the visual axis.[22] Lateral canthal resuspension is an obvious first-line surgical option in milder cases, but it may fail to restore the functional anatomy fully in more severe cases because of the shortened anterior lamella. In these cases, an advancement flap,[1] a skin graft,[8] or recruitment of cheek skin through midface lifting may be required.[7]

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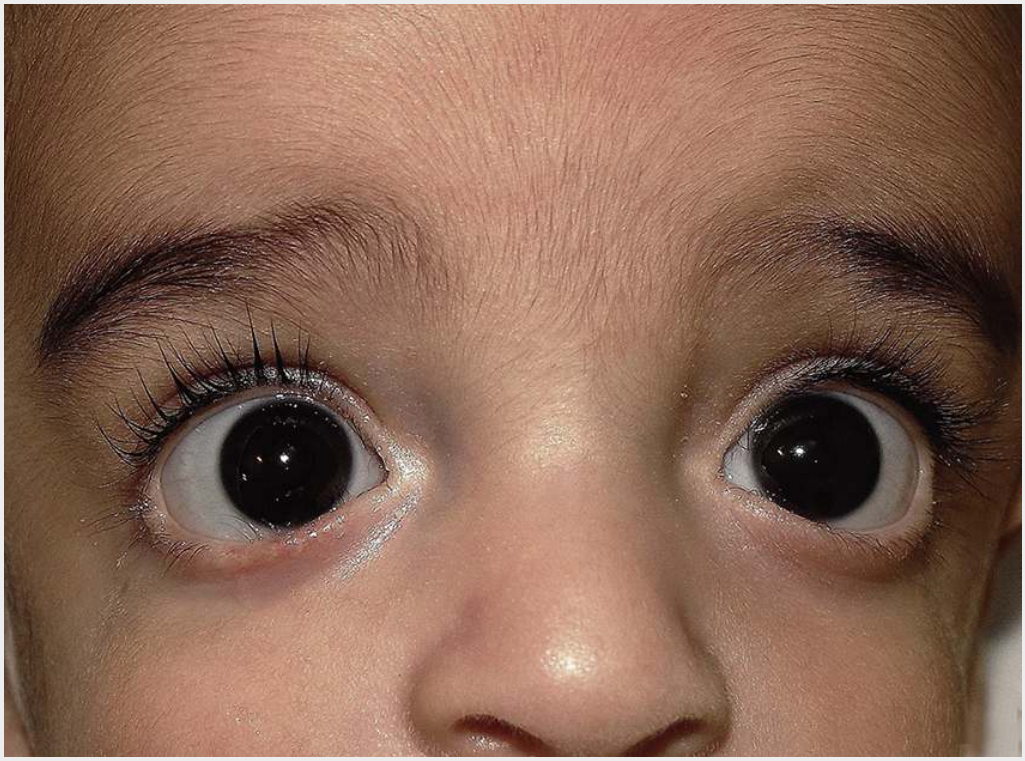

FIGURE 33.3 Marked cheek and lower eyelid hypoplasia with the typical antimongoloid slant but not euryblepharon in a patient with Treacher Collins syndrome.

Prognosis

In most cases, the prognosis is good following surgical repair, although more severe cases will sometimes require more extensive reconstructive surgery with some scarring.

Histopathology

Euryblepharon is a developmental anomaly for which we are not aware of any specific histopathology descriptions.

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CHAPTER 34

Floppy Eyelid Syndrome

Key Points

- Floppy eyelid syndrome is an acquired condition
- It is characterized by hyperelastic, floppy, or rubbery eyelids that evert spontaneously during sleep causing exposure symptoms
- The etiology is unclear, but a mechanical theory proposes that the tarsus suffers biomechanical change from repeated pillow/eyelid pressure during sleep
- The ischemia-reperfusion theory proposes that sleeping on one side leads to pressure-induced ischemia of the tarsal plate
- This syndrome mostly affects the upper eyelids in obese males but is less frequently reported in females and may affects the lower eyelids
- Clinically, the upper eyelids are very elastic and become grossly distorted and are easily everted away from the globe with very slight traction
- The condition is typically associated with severe papillary conjunctivitis, meibomianitis, blepharitis, and tear film instability
- The majority of patients with floppy eyelid syndrome have associated obstructive sleep apnea, but the etiologic relationship is not clear
- Conservative treatments include patching, taping, and shielding the eyes at night
- Surgical correction with horizontal shortening of the eyelid is usually required to reestablish firm apposition between the eyelids and the globe
- The long-term results of surgery are often disappointing, achieving an overall success of only 42%

In its most classic and strict definition, floppy eyelid syndrome (FES) describes obese males with an acquired hyperelastic, floppy, or rubbery upper eyelid that everts spontaneously during sleep, causing exposure symptoms.[1,2,3,4,5] This condition was first described in 1981; further research over the ensuing 4 decades has on occasion enriched the original description. At other times it has confused the clinician by overusing the term FES, and blurring the line between FES and simulating conditions with an ever-increasing range of uncertain ocular and systemic associations.[2,3,4]

Etiology and Pathogenesis

The upper eyelid is a composite structure supported by a stiff tarsal plate, which under normal conditions is a dense rigid fibrous structure composed mainly of collagen types I and III and thus provides a strong structural framework for the upper eyelid.[1,3,5]

The etiology of the condition is unknown, but there are three competing theories to explain the loss of this intrinsic rigidity in FES: the mechanical theory, the ischemia-reperfusion theory, and the leptin resistance theory, which is related to obesity.[2,3,6,7] The mechanical theory implies that the eyelids become vulnerable to repeated mechanical stress because of recurrent pathologic cyclic eyelid loading resulting from repeated pillow to eyelid interaction during sleep. The tarsus consequently suffers dramatic biomechanical changes becoming pliant and overly flexible. This allows easy eversion of the upper eyelid and chronic exposure of the ocular surface. A positive cycle of morbid events is thus initiated.[5] This cyclic tissue stress results in the inability of the tarsus to maintain tensional homeostasis between external mechanical stimuli and internal (cytoskeletal) tension with a definite alteration in

the mechanical properties of the affected tarsus.[8] Recent evidence is more in favor of the mechanical theory, where there is an upregulation of elastic matrix metalloproteinase activity, especially matrix metalloproteinase-7 (MMP-7) and matrix metalloproteinase-9 (MMP-9). This results in a subsequent reduction or depletion in mature elastic fiber abundance within the tarsus; a paradoxical increase in the contractility of tarsal fibroblasts, which is probably an adaptive response; and surprisingly, upregulation of V-CAM1 and PPP1R3C genes in tarsal fibroblasts.[3,5,9,10,11]

The ischemia-reperfusion theory is supported by the association with of FES obstructive sleep apnea (OSA).[3] According to this theory, sleeping on one side leads to pressure-induced ischemia of the tarsal plate. But when the patient suddenly awakes, the immediate reperfusion of the tarsal plate causes free radical release that damages the tarsal stroma and quite possibly induces corneal ectatic changes as well.[3,12] This theory is supported by the significant association with obstructive sleep apnea and the laterality of FES with the sleeping side.[2,12] It is also supported by an increase in inflammatory markers in the blood as well as the tear film (MMP-9), possibly induced by local tarsal ischemia.[12] Some authors maintain that the hypoperfusion theory is a less likely alternative to the mechanical stress theory because the upper eyelids are richly perfused with blood and, *(Print pagebreak 229)* more importantly, because a reciprocal association between both FES and OSA is currently disputed.[12,13] Of note is that hyperpeptinemia is associated with up-regulation of MMP-9 and is also closely associated with OSA.[2,3,6,7] Therefore, it is interesting to speculate that the etiology of FES may be multifactorial and that all three theories may contribute to a final common pathway at the molecular level resulting in tarsal elastin depletion, which eventually leads to the development of FES.[2,7]

Two and half decades ago, Van der Bosch and Lemij introduced another term for a broader or a closely related condition called the *lax eyelid syndrome*, which is characterized by similar symptomatology irrespective of age, sex, or basal metabolic index of the patient. By definition, these patients, who may be young and healthy, may also suffer from ptosis, canthal tendon laxity, laxity of the upper and lower eyelids, as well as ectropion or even entropion.[13,14,15] Furthermore, because there is an additional subset of individuals with lid hyperlaxity, which may also occur at any age but without any symptomatology or conjunctival reaction, Fowler and Dutton coined an all-encompassing term *lax eyelid condition* as a catchall term to describe all the aforementioned conditions.[2] According to the authors, it is important to differentiate between a (1) lax eyelid condition, which is any condition of eyelid laxity caused by cutaneous or systemic disease and without papillary conjunctivitis or dry eye symptoms; (2) lax eyelid syndrome, which is a subset of lax eyelid condition but is associated with papillary conjunctivitis or dry eye symptoms, which may occur at any age and may affect either sex; and (3) floppy eyelid syndrome, which they consider as a specific subset of lax eyelid syndrome. The term (FES) is therefore reserved for patients with obesity and obstructive sleep apnea with a strong male predominance.[2] Of note is that the terms lax eyelid syndrome and lax eyelid condition have not yet achieved broad recognition, and the term FES is still widely used in the literature.

Clinical Presentation

The most commonly affected demographic age group is obese males with a high body mass index from the 5th till the 8th decade, with or without a history of sleep problems.[2,3] However, it has been reported in children,[16] as well as in females.[6]

Patients usually present with symptoms of ocular discomfort, bilateral ocular redness, ropy discharge, and chronic eye rubbing that are more severe upon awakening in the morning.[1] These symptoms are usually nonspecific, which explains why in some patients the condition may linger undiagnosed or can be mislabeled as chronic infective conjunctivitis for up to 10 years unless the clinician directly looks for eyelid laxity.[1,3,17] Therefore, in any obese patient with chronic recalcitrant conjunctivitis, family members should specifically be asked if the patient wakes up frequently during sleep, whether they sleep with their eyelids everted against the pillow, or whether the ocular surface is exposed during sleep.

In the resting awake state, the eyelids may look entirely normal, although an astute observer can notice there is usually some skin redundancy (dermatochalasis) that is out of proportion to the age of the patient, along with a significant amount of whitish mucous discharge around the corners of the eye.[1,3,17] But more importantly, the upper eyelids are very elastic, and with very slight effort and a bare minimum of superotemporal traction, the upper eyelids become grossly distorted and everted, easily exposing the conjunctiva and the globe (Figure 34.1).[1,3] The tarsal plates are rubbery and pliant with a loss of intrinsic rigidity, which allows them to be folded with ease. Symptoms and signs are bilateral; however, because the pivotal event in FES is upper eyelid nocturnal eversion, the condition is usually asymmetrical with the more severely affected side corresponding to the side on which the patient preferentially sleeps. Both sides may be affected equally if the patient frequently reverses their position during sleep.[3]

The lower eyelids may be affected as well, although this is less frequently identified as a part of FES (Figure 34.2A).[13] Other associated palpebral findings include blepharitis, blepharoptosis (Figure 34.2B), entropion, or ectropion.[13] An additional important yet subtle finding is the presence of eyelash ptosis and possibly loss of eyelash alignment (Figure 34.2C). In more severe cases, the upper eyelid is so lax that it overhangs the lower eyelid during sleep causing significant ocular irritation. This condition is termed eyelid imbrication (Figure 34.2D).[14,18]

Few studies in the literature have attempted quantification of the eyelid laxity in patients with FES, or a systematic grading of the eyelid abnormalities.[13] A vertical upper eyelid distraction of 15 to 25 mm or a horizontal lid distraction of ≥5 mm is strongly suggestive of FES.[13] The vertical eyelid pull is calculated by measuring the difference between the resting position of the upper eyelid and its position with a maximum pull.[13] On the other hand, Ricardo Salinas and associates reviewed and summarized the different grading systems for FES. Several grading systems are available, but they are all limited by the subjective identification of hyperlaxity. One of the more commonly applied grading systems that has been used among several clinical studies is a crude screening test that assesses the degree of exposure of the tarsal conjunctiva upon lifting the upper eyelid skin with the examiner's thumb while the patient is looking downward. Grade 0 patients do not have FES (the tarsal conjunctiva is not visible upon lifting the eyelids). Patients are classified as grade 1 (mild FES) if less than one-third of the upper conjunctiva is visible and grade 2 (moderate FES) if one-third to half of the upper tarsal conjunctiva is exposed, whereas in grade 3 patients (severe FES), more than half of the tarsal conjunctiva is visible (Figure 34.1).[13]

Ocular surface abnormalities include moderate to severe papillary conjunctivitis, which is almost a universal finding; meibomianitis; blepharitis; and tear film instability.[3,15] Patients with FES may have associated corneal abnormalities, observed in almost 70% of patients,[6,7] including widespread punctate keratopathy, filamentary keratitis, recurrent corneal erosions, corneal vascularization, severe exposure keratopathy, corneal scarring, thinning, and very rarely ulcerative microbial keratitis and even corneal perforation.[4,17] Therefore, FES is a potentially blinding condition and patients may indeed experience a drop in visual acuity.[1,2,3] Another enigmatic association between FES and *(Print pagebreak 230)* the cornea is an increased incidence of overt keratoconus seen in roughly 10% to 20% of patients.[6,7,19] All the aforementioned corneal problems are related to nocturnal eversion, whereas keratoconus is attributed to eye rubbing.[3,20] Other postulated ocular associations include normal-tension glaucoma and nonarteritic anterior ischemic optic neuropathy. To the best of our knowledge, a causal association between FES and either condition (glaucoma and ischemic optic neuropathy) is not clear and it may be indirectly attributable to the association of FES with sleep apnea because a relation with both conditions has statistically been shown with obstructive sleep apnea and not with FES.[13,21] Irrespective of the exact cause, it has been suggested that, when a patient is diagnosed with FES, they should be screened for glaucoma.[13]

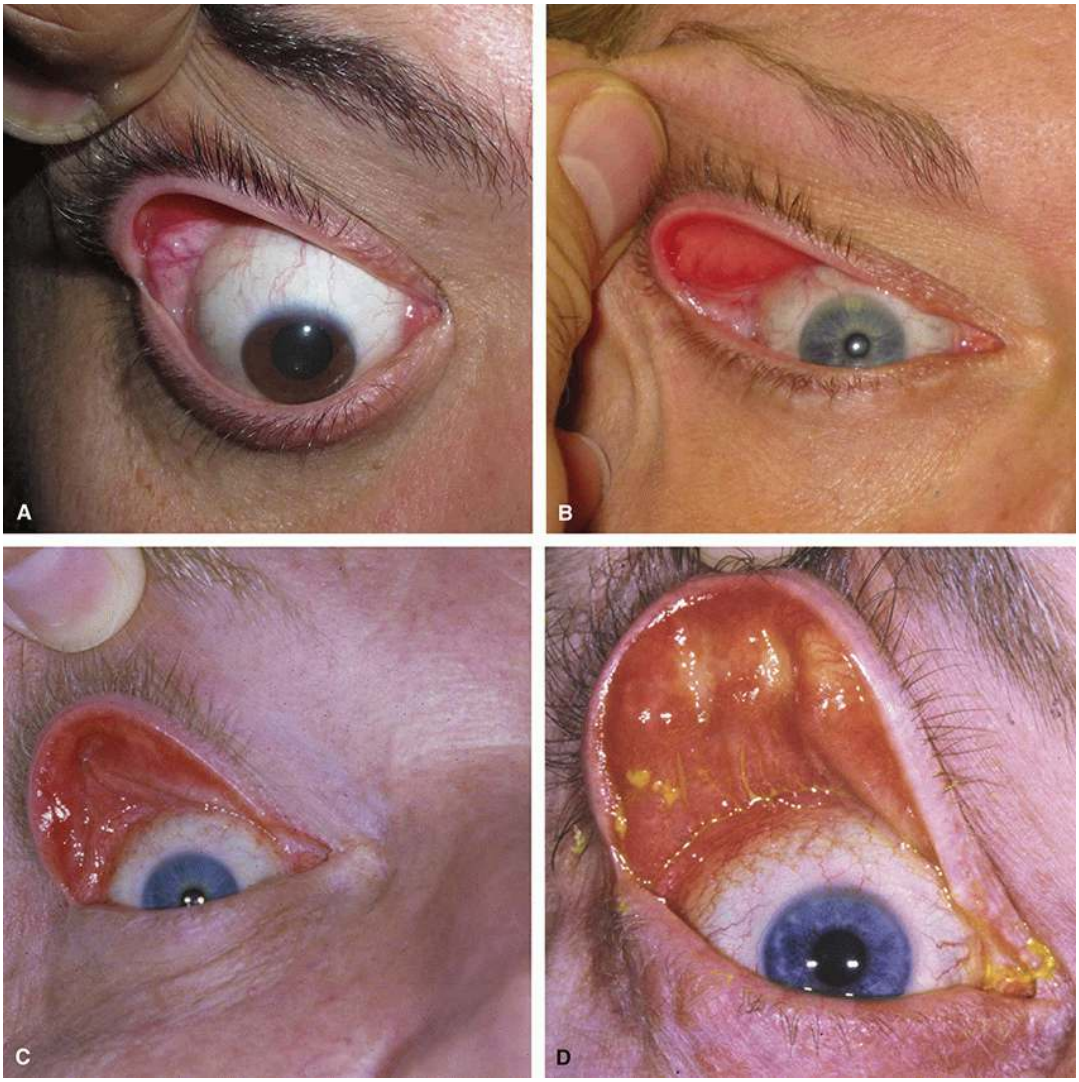

FIGURE 34.1 Spectrum of involvement of the upper eyelid in patients with floppy eyelid syndrome. A, Grade 1 (mild

FES): One-third of the tarsal conjunctiva is exposed upon eyelid eversion. B, Grade 2 (moderate FES): Between one-third and half of the tarsal conjunctiva is exposed with eyelid eversion. C, Grade 3 (severe FES): More than half of the tarsal conjunctiva is exposed. D, Grade 3 with severe conjunctivitis.

Systemically, FES is associated with obesity and obstructive sleep apnea (OSA).[3,7,22] OSA is characterized by a recurrent interruption of ventilation for periods of *(Print pagebreak 231)* more than 10 seconds due to airway collapse,[2,12] which places the individual at an increased risk for significant cardiovascular morbidity (ischemic heart disease), diabetes, and hypertension, probably due to a repetitive pattern of chronic hypoventilation.[12,23] The vast majority of patients with FES have associated OSA,[2,12,22,24,25,26] whereas the reverse is not true. Only a tiny minority of patients with sleep apnea have a floppy eyelid,[24] although a recent metanalysis did show that patients with OSA do have a 4.12 times higher FES risk compared with normal individuals.[27] Therefore, the association is hard to ignore and needs further evaluation.[12]

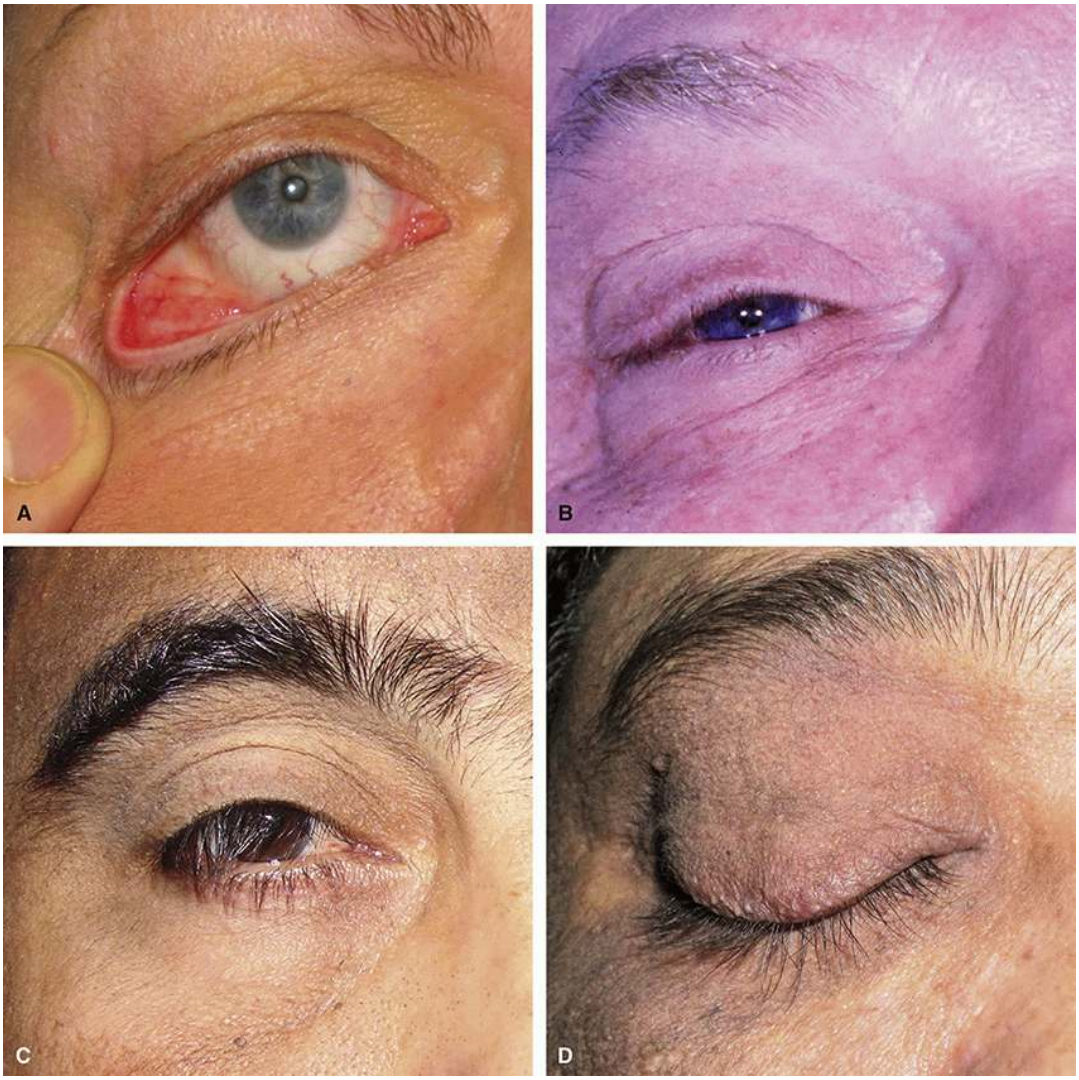

FIGURE 34.2 Additional palpebral features of floppy eyelid syndrome. A, Involvement of the lower eyelid in floppy eyelid syndrome. B, Blepharoptosis C, Eyelash ptosis and loss of eyelash alignment. D, Eyelid imbrication (overhanging of the upper eyelid over the lower eyelid).

Differential Diagnosis

FES is one of the more relevant and frequently missed entities in the differential diagnostic list of recalcitrant conjunctivitis, as well as chronic epiphora.[3,14,28,29] The diagnosis should particularly be considered in patients with chronic conjunctivitis refractory to multiple treatments. All patients with *idiopathic* or *recalcitrant* conjunctivitis should be screened for FES during their initial or routine ophthalmological examination.[13] Other entities that may also cause chronic intractable conjunctivitis include a retained foreign body, nasolacrimal duct obstruction, or the giant fornix syndrome,[28,30,31] but *(Print pagebreak 232)* more sinister etiologies include neoplastic or masquerade syndromes and carotid or dural sinus fistulas.[28]

Although FES ranks on top of the list of lax eyelid conditions, eyelid laxity may have protean causes with a variety of clinical

presentations, and as was mentioned earlier, not every patient with a lax eyelid should be automatically diagnosed with FES.[2] Younger nonobese patients whose eyelid laxity is preceded by years of recurrent attacks of eyelid edema of an unknown etiology could be suffering from blepharochalasis.[14] Other causes of a lax eyelid condition include congenital conditions like Ehlers-Danlos syndrome, or congenital cutis laxa whereas acquired causes include postinflammatory mid-dermal elastolysis or acquired cutis laxa. But in general, these conditions are usually associated with a generalized skin laxity all over the body and the diagnosis is not difficult to make.[3,14]

A rare yet frequently overlooked cause of eyelid laxity is pachydermoperiostosis. Pachydermoperiostosis, or Touraine-Solente-Golé syndrome, is a primary familial (autosomal dominant) form of hypertrophic osteoarthropathy that involves the bones and the skin and is associated with a 9:1 male preponderance. One-third of patients have a family member with the same condition.[32,33,34,35,36,37] The condition is characterized by digital clubbing, periostosis, and facial skin thickening or enlargement (pachydermia), hence the term pachydermoperiostosis.[32,33,34,35,36,37] Genes encoding the enzyme 15-hydroxyprostaglandin dehydrogenase, which is the main enzyme involved in prostaglandin degradation, are directly linked to the syndrome, which results in a disruptive effect on the clearance of prostaglandin E2, which subsequently accumulates in tissues and causes the classic manifestations. Ophthalmic features include ptosis, floppy eyelids, enlargement of the tarsal plates with accompanying diffuse sebaceous gland hyperplasia, as well as massive eyelid thickening (Figure 34.3).[32,33,36,37]

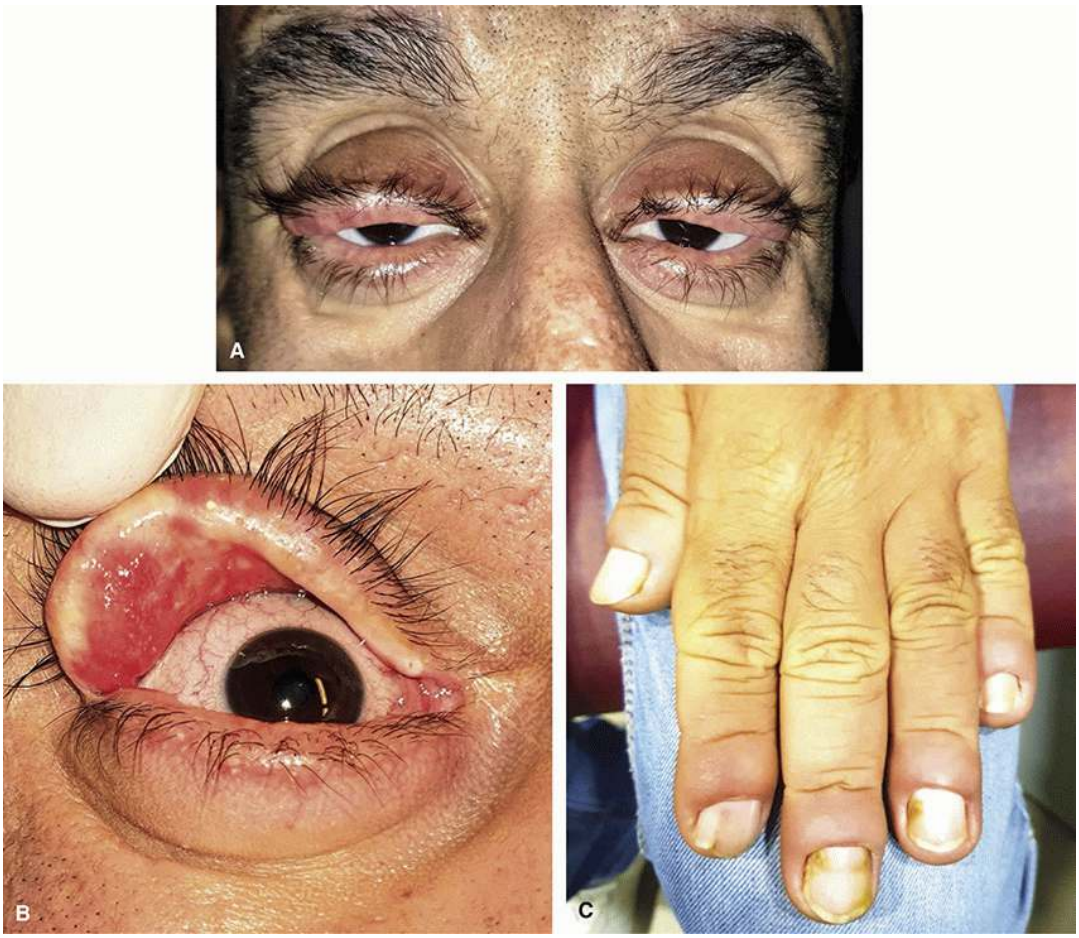

FIGURE 34.3 Features of pachydermoperiostosis. A, Severe ptosis and massive eyelid thickening. B, Floppy eyelids. C, Digital clubbing.

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Treatment

Conservative measures, which include patching, taping, shielding the eyes at night, weight reduction, as well as sleeping on the back, have all been tried with variable degrees of success.[22,38] Although McNab and others[39,40] reported reversal of FES with treatment of OSA with continuous positive airway pressure (CPAP), it cannot firmly be established whether the beneficial effect of CPAP is attributable to improvement of the disease condition itself or due to the supine sleeping position that patients with CPAP are instructed to adopt.[40] Although bariatric surgery is known to have a positive beneficial effect on sleep apnea,[41] it has not been evaluated in relation to patients with FES.

These temporizing measures rarely succeed in controlling the symptoms, and surgical correction of the laxity is usually required to reestablish a firm apposition between the eyelids and the globe.[14] Lateral tarsal strip procedures, with or without a periosteal flap; full-thickness horizontal shortening of the lateral one-fourth to one-third of the eyelid margin; or block pentagonal excision; or full-thickness resection of the lateral part of the upper eyelid have all been described with variable success.[3,32,42,43,44,45,46,47] Patients with eyelid imbrication, in particular, may benefit from a horizontal tightening procedure.[14,18] Recently, several animal and human cadaver studies have demonstrated that photochemical cross-linking of tarsal collagen using ultraviolet A and riboflavin (vitamin B2) increases the stiffness of tarsal tissue.[48,49,50] In an in vitro study using vertical strips of central tarsus excised from human cadavers, the Young modulus, a measure of stiffness using the stress/strain ratio, was found to increase by 75% following photochemical cross-linking.[50] This same study also demonstrated that cross-linking reverses elastase-induced mechanical degradation of the upper eyelid tarsus.[50] Future in vivo studies are required to demonstrate whether tissue stiffening could be a safe procedure for treating lax eyelid conditions in human patients.[49,50]

Management of pachydermoperiostosis is essentially surgical and usually necessitates a horizontal eyelid shortening with an upper eyelid tarsal strip or preferably an upper eyelid vertical and horizontal en bloc resection, in addition to levator advancement.[32,36] Nonsteroidal anti-inflammatory drugs may help alleviate the chronic pain associated with the condition. Recently, the use of Etoricoxib, which is a potent prostaglandin inhibitor, was allegedly associated with the reversal of signs and symptoms, but this finding requires further study.[35]

Prognosis

Failure to consider FES as part of the differential diagnosis of chronic conjunctivitis or chronic epiphora can lead to an unnecessary delay in starting treatment[17] and may lead to performing unnecessary lacrimal surgery. FES is a severely underdiagnosed condition, and these significant delays in diagnosis may have a significant impact on the cornea that could subsequently cause impaired vision.[12]

Although no prospective studies or even long-term retrospective studies have been conducted to evaluate or compare the outcomes of the various surgical procedures, recent evidence suggests that the long-term results of surgery are disappointing, achieving an overall success of only 42%.[3]

Histopathology

The histopathological findings in FES were reviewed recently by Salinas et al.[13] Eyelid skin has decreased elastin demonstrable using van Gieson stain with transmission electron microscopy showing a diminished elastin core embedded in bundles of microfibrils with a moth-eaten pattern.[9] There was markedly decreased elastin around hair roots in 6 of 11 FES specimens examined by Schlötzer-Schrehardt and coworkers.[9] Immunohistochemical staining using antibodies to matrix metalloproteinase-2 (MMP-2; gelatinase A), MMP-9 (gelatinase B), and MMP-7 (matrilysin) shows increased MMP-2 in the dermal stroma and around hair follicles, increased MMP-9 in the walls of dermal blood vessels and the periphery of hair roots, and increased MMP-7 staining of the epidermis, blood vessel walls, and hair follicles. van Gieson stain shows decreased elastin in the orbicularis oculi muscle when compared with normal control eyelids.[9] The tarsus may appear unremarkable by routine light microscopy,[42] but decreased elastin is observable using histochemistry,[9,10] immunohistochemistry,[10] or transmission electron microscopy.[9] Immunostaining shows increased MMP-2, MMP-9, and MMP-7 in FES tarsal stroma and around blood vessels and increased MMP-7 around meibomian glands.[9] The meibomian glands may have duct dilation and thickened secretions.[9] The palpebral conjunctiva usually has nonspecific changes, including chronic inflammation,[9,10,42] thickened[9] and keratinized[9,42] epithelium, a diminished number of goblet cells,[42] and sometimes papillary hyperplasia.[9,10] Immunostaining shows increased MMP-2, MMP-9, and MMP-7 in FES conjunctival epithelium and increased MMP-7 in the conjunctival substantia propria.[9]

There are only a few reports concerning the histopathological findings in the eyelids of patients with pachydermoperiostosis. In the patient reported by Neufeld, Price, and Woodward (Figure 34.3),[37] the eyelid epidermis was of normal to slightly increased thickness without parakeratosis or hyperkeratosis. The dermal connective tissue was much denser than normal, with the loose connective tissue of the normal eyelid dermis replaced by thick bundles of dense collagen. Hyperplasia of hair follicles, sebaceous glands, eccrine glands, and apocrine glands markedly expanded the dermis (Figure 34.4A-C). There was mild perivascular chronic inflammation in the superficial dermis and mild to moderate ectasia of blood vessels, and the dilated vessels had plump endothelial cells with occasional endothelial cells being vacuolated and exhibiting formation of strands extending across the vessel lumen. Concentric lamellae of connective tissue with a mildly myxoid appearance surrounded one cluster of ectatic vessels. In contrast to the normal eyelid, which has mostly *(Print pagebreak 234)* anagen follicles, there was an increased number of follicles in the catagen and telogen phases of the growth cycle. The orbicularis oculi muscle appeared unremarkable. The connective tissue zone

between the orbicularis oculi and the tarsal plate was thickened by dense fibrous connective tissue with focal hyalinization. Sebaceous (meibomian) gland hyperplasia thickened the tarsal plate (Figure 34.4A). There was a focus of granulomatous inflammation in the tarsal plate, indicative of a ruptured sebaceous unit with a lipogranulomatous response. Dense collagenous tissue with foci of hyalinization thickened the palpebral conjunctiva substantia propria. The conjunctival epithelium was markedly thickened with superficial keratinization and a paucity of goblet cells (Figure 34.4D). The eyelid changes were similar to those described in the skin of other body sites.[51,52,53] The few reported eyelid specimens have noted dermal fibrosis, sebaceous gland hyperplasia, and focal accumulation of mucin around blood vessels.[54,55,56,57] Hyperplasia of hair follicles has not been reported in other eyelid specimens, but it was noted in the review by Vogl and Goldfischer[51] for other body sites. The thickening and sclerosis of the connective tissue between the orbicularis oculi muscle and the tarsal plate in our patient resembled that illustrated by Davidson and Smith.[56] Seven other papers have reported meibomian gland hyperplasia and tarsal thickening,[32,33,36,54,56,57,58] whereas one report observed a normal tarsus.[55] The conjunctival epithelial thickening, superficial keratinization, and decreased goblet cells were nonspecific results of reduced eyelid mobility and chronic irritation.

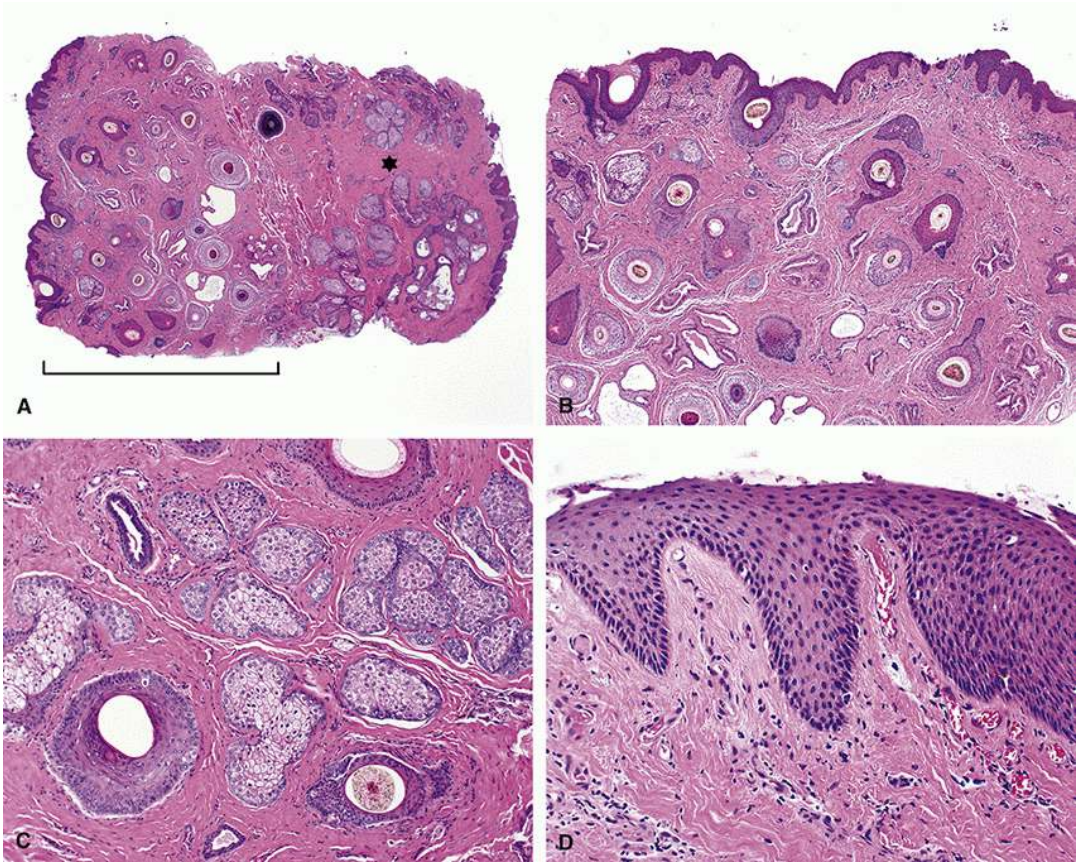

FIGURE 34.4 This left upper eyelid resection was from the 43-year-old man with pachydermoperiostosis reported by Neufeld and coworkers.[37] A, Full-thickness photomicrographic section of the eyelid with marked thickening of the dermis (bracket) due to sclerosis and hyperplasia of hair follicles, sebaceous glands, eccrine glands, and apocrine glands. Meibomian gland hyperplasia thickens the tarsal plate (★). B, Higher magnification of the dermis showing hyperplasia of hair follicles, apocrine glands, and eccrine glands. C, Sebaceous glands were focally hyperplastic within the dermis. D, The conjunctival epithelium is markedly thickened and has superficial keratinization with a paucity of goblet cells, the substantia propria is thickened by dense collagenous tissue with areas of hyalinization, and there is slight chronic inflammation.

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CHAPTER 35

Hemifacial Spasm

Key Points

- Hemifacial spasm is a movement disorder characterized by spasms of the muscles innervated by the facial nerve
- It typically begins in the fifth to sixth decades of life
- The most common cause for hemifacial spasm is an ectatic blood vessel that compresses the facial nerve at the root exit zone in the pons
- The most common offending vessels are the anterior inferior cerebellar artery, posterior inferior cerebellar artery, and the vertebrobasilar artery and vein
- Hemifacial spasms begin clinically as unilateral facial muscle fasciculations, which later become more pronounced contractions of the orbicularis oculi muscle and progressively spread to other facial muscles
- Several drugs have been reported to show some efficacy in the management of hemifacial spasm including carbamazepine, clonazepam, gabapentin, baclofen, and haloperidol
- Peripheral chemodenervation with botulinum toxin is the treatment of choice for most patients with hemifacial spasm
- Without treatment, hemifacial spasm can interfere with talking and eating and in rare cases lead to functional blindness
- With botulinum toxin injections, more than 80% of patients can experience significant relief of spasms for 12 to 16 weeks

Hemifacial spasm (HFS) is a movement disorder characterized by spasms of the muscles innervated by the facial nerve (CN 7). The major clinical manifestation is involuntary unilateral clonic and/or tonic contractions of the muscles of facial expression. Symptoms often begin in the periorbital muscles but later progress to involve muscles of the mid-and lower face and platysma. In severe cases, eyelid closure may result in functional blindness.

The condition was first described by Schultze in 1875, in a 56-year-old man with involuntary movements involving the left side of his face.[1] On postmortem examination, a giant aneurysm of the left vertebral artery was found compressing the left facial nerve. In 1886, Gowers expanded the definition and described the classical features of this condition.[2] Several years later, Édouard Brissaud presented a similar case in a 35-year-old female with clonic contractions of the muscles of the right half of her face that became worse at times of stress.[3] The name of this condition was introduced by Babinski in 1905 as hémispasme facial,[4] and he also reported that, when the orbicularis oculi muscle contracts, the frontalis muscle also contracts, raising the eyebrow, distinguishing HFS from blepharospasm (see Chapter 32).

The prevalence of HFS in the United States has been reported at 11 per 100,000 population, with a 2:1 female preponderance (14.5 per 100,000 in females and 7.4 per 100,000 in males).[5] Another study from Norway gave a similar prevalence of 9.8 per 100,000.[6] Few epidemiologic data are available, but HFS has been reported to be more common in some Asian populations than in Caucasians.[7]

Primary HFS typically begins in the fifth to sixth decades of life. Fewer than 6% of patients present before the age of 30 years,[8] and presentation before the age of 40 years should elicit a search for an underlying secondary cause. HFS is usually sporadic, but occasional familial cases have been described, with a maximum incidence of 2% to 3% in several large series.[9,10] There is a definite female predominance with reported ratios of 1.8:1,[11,12,13] to as much as 3:1.[14]

Bilateral cases have been reported, but are very rare, occurring in an estimated 0.6% to 5% of HFS patients.[11,15,16] In these cases the disease usually starts unilaterally and, only after several months to years, involves the contralateral side. Unlike essential blepharospasm, muscle contractions in bilateral HFS are asymmetrical, with the spasm on each side completely independent. One

case of presumed symmetrical bilateral HFS has been described, attributed to supposed anatomic connections between the bilateral facial nuclei.[17]

Etiology and Pathophysiology

The root exit or entry zone of a nerve is the junction between the central and the peripheral segments of a cranial nerve. In this zone, there is a transition from the central oligodendroglial cells to peripheral Schwann cells that are responsible for myelination of the nerve. The cranial nerves in this zone also lack an epineurium and are covered only by an arachnoid membrane. Because of this anatomic structure, in this zone the nerve fiber is more susceptible to mechanical injury.[18]

The most common cause for HFS is an ectatic blood vessel that compresses the facial nerve at this root exit zone.[19] In their review of 22 published reports, Miller and Miller[20] found the most common offending vessels to be the anterior inferior cerebellar artery (37%), the posterior inferior cerebellar artery (30%), and the vertebrobasilar artery and *(Print pagebreak 238)* veins (23%). Chronic compression by these vessels causes mechanical injury to the vulnerable nerve segment at the exit zone, resulting in local demyelination.[21] It has been proposed that this allows ephaptic transmission of impulses, or local exchange of electric fields, between neighboring neurons across these demyelinated segments, leading to excessive or abnormal firing.[9]

HFS can be either primary or secondary. Primary HFS results from compression of the seventh nerve at the root exit zone in the posterior cranial fossa by an aberrant or ectatic vessel. Secondary HFS can be caused by a wide variety of etiologies including cerebellopontine angle tumors, arteriovenous malformations, arterial aneurysms, cerebellopontine arachnoid cysts, stroke, trauma, demyelinating disorders, infections such as otitis media, tubercular meningitis, structural abnormalities of the posterior cranial fossa, and Bell palsy.[13] The incidence of posterior fossa tumors causing HFS is about 0.4%,[22] so that patients with new-onset HFS should be imaged before treatment.

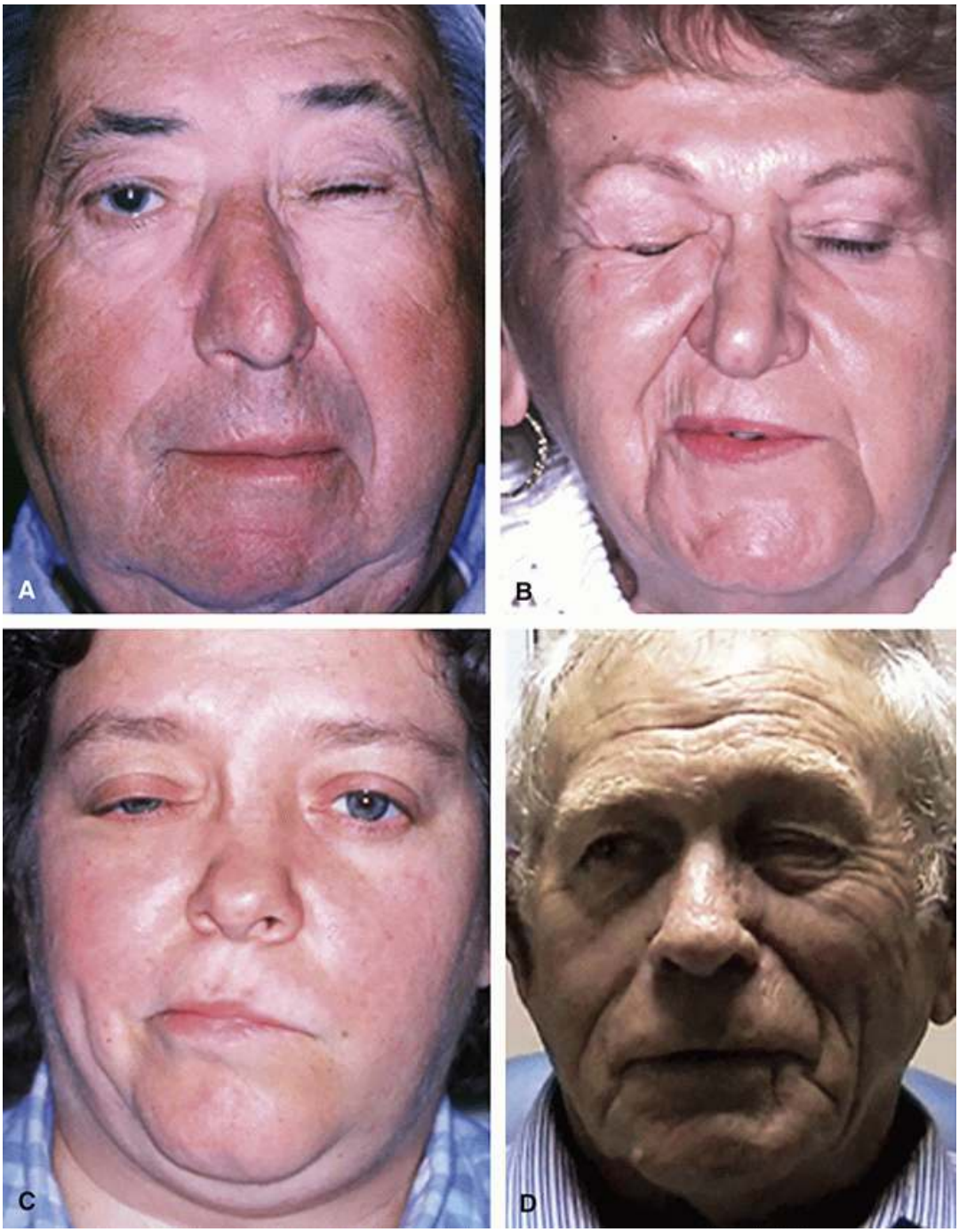

FIGURE 35.1 A-D, Clinical features of hemifacial spasm.

Clinical Presentation

Primary HFS usually begins with unilateral facial muscle fasciculations, followed later by more pronounced contractions of the orbicularis oculi muscle (Figure 35.1). In 80% to 90% of cases, the spasms are initially limited to the periocular *(Print pagebreak 239)* region but progressively spread thereafter to other facial nerve branches.[23,24,25]

In secondary HFS, the upper and lower facial muscles are usually involved simultaneously.[26,27] Contrary to blepharospasm, in which spasms disappear during sleep, contractions in HFS persist during sleep. Symptoms often increase during stress or when performing some routine functions such as reading, speaking, or eating.[3] But similar to blepharospasm, sensory tricks, such as touching the face, can reduce the spasms. Arterial hypertension has been reported to be an association with HFS in as many as 40% of cases,[28] presumably related to vessel ectasia and subsequent seventh nerve compression.

Although the disease is usually chronic with gradually worsening symptoms, Mauriello et al[29] reported 5 of 119 (4.6%) patients with HFS to show spontaneous resolution of symptoms following treatment with botulinum toxin.

Differential Diagnoses

The differential diagnosis of HFS includes a long list of disorders that can clinically be confused with it. These include essential blepharospasm, tardive dyskinesias, facial motor tics, psychogenic facial spasm, focal cortical seizures involving the facial muscles, and aberrant regeneration of the facial nerve after injury or Bell palsy. Blepharospasm is always bilateral, and the two sides show synchronous contractions of the orbicularis oculi muscles. Even when HFS is bilateral, the contractions on both sides of the face are always asynchronous. Tardive dyskinesia may be seen in some individuals with exposure to neuroleptic agents or dopaminergic antagonists. It manifests as facial grimacing with stereotypical stiff, jerky movements of the jaw, lips, tongue, neck, trunk, and limbs. Aberrant regeneration of the facial nerve after injury appears as synkinesis between muscle groups, such as orbicularis muscle contraction on attempted mouth opening. Unlike HFS, these abnormal movements are absent at rest. Myokymia is characterized by involuntary, nonsynchronous, fine, undulating fasciculations. In the eyelids, myokymia tends to be unilateral and most often affects the lower eyelid. The condition is usually transient over a few days or weeks, frequently associated with fatigue, stress, or excessive caffeine intake.

Treatment

Several drugs have been reported to show some efficacy in the management of HFS. These include carbamazepine, clonazepam, gabapentin, baclofen, and haloperidol.[13] However, their efficacy is inconsistent, and major side effects include sedation, fatigue, and exhaustion.[30]

As with essential blepharospasm, peripheral chemodenervation with botulinum toxin is the treatment of choice for most patients with HFS. A large number of trials have validated the value of this therapy, with improvement reported in 75% to 100% of patients.[31,32,33,34,35,36,37,38] Injection around the eyelids and upper face often will relieve spasms in the lower face as well. However, injection into the perioral muscles should be used with caution and only with small doses of 1 to 2 units, since these small muscles are more prone to excessive weakness resulting in mouth droop and drooling. A therapeutic effect is usually seen within several days to a week after injection, and muscle weakness usually lasts around 3 to 4 months, somewhat longer than for blepharospasm.[38] In some patients, the beneficial effects may be significantly shorter, in the range of 2 months or less.[39] Adverse effects of botulinum toxin are few but include temporary bruising at the injection site, upper eyelid ptosis, mild facial weakness, and, very rarely, diplopia.[40]

For patients who do not experience adequate relief from botulinum toxin or drug therapy, or for younger patients who may not want to undergo injections long term, surgery may be an appropriate option. The surgical procedure of choice is microvascular decompression of the facial nerve at its exit zone. This procedure aims to displace the aberrant or ectatic vessel away from the nerve. The surgical procedure has been reported to have a success rate of 85% to 90% in some series.[41] In up to 33% of cases the improvement may be delayed for months,[42] and following a cure, recurrences of 1% to 3% can be seen within 5 years.[43] Complications include recurrence of spasms,[44] hearing loss,[45] cerebrospinal fluid leakage, and facial nerve paralysis that can be transient or even permanent.

Prognosis

Despite the benign appearance of facial twitches in HFS, they can significantly interfere with normal functions such as talking and eating and in rare cases lead to functional blindness. Also, they often cause social embarrassment, psychological withdrawal, and depression. Early recognition and the institution of appropriate therapy are important. Botulinum toxin injections offer a simple, noninvasive therapy that is considered the treatment of choice for most patients. Improvement in spasms is usually seen in more than 80% of patients,[46] associated with a significant improvement in the quality of life, although the effect of toxin treatment is temporary, lasting only about 12 to 16 weeks, and may vary according to the type of botulinum toxin injection used (onabotulinum toxin A [Botox], abobotulinum toxin A [Dysport], or incobotulinum toxin A [Xeomin]).[47] The major complication of facial injections is a weakness of nontargeted muscles, such as the orbicularis oculi and orbicularis oris muscles, and lagophthalmos with possible corneal exposure.

Patients who do not respond to the botulinum toxin injections or who prefer a permanent cure are offered surgical options. Microvascular decompression is an effective long-term treatment for HFS with >85% of patients experiencing sustained improvement in symptomology for 20 years or more after surgery.[48,49,50,51] The overall complication rate is about 6%, with major neurologic complications of gait disturbance, diplopia, facial nerve palsy, and hearing loss seen in about 0.4% of cases.[48]

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Histopathology

Although it is widely believed that the etiology of HFS involves attrition at the neurovascular interface and the generation of ectopic action potentials from demyelinated facial nerve fibers at the seventh cranial nerve exit zone,[52] we are not aware of any histopathologic studies that support this notion.

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CHAPTER 36

Horner Syndrome

Key Points

- Horner syndrome (HS) results from the interruption of the oculosympathetic pathway
- Symptoms include ipsilateral ptosis, miosis, anhidrosis ± lateralizing signs
- A detailed knowledge of the anatomy of the pathway is imperative to localize the lesion
- Missing the subtle signs of HS may result in grave clinical consequences
- Central lesions are usually neoplastic, or due to a vascular occlusion
- Iatrogenic injuries are a common cause of preganglionic HS
- Postganglionic HS is usually associated with internal carotid artery pathology
- Radiologic evaluation is more clinically relevant than pharmacologic testing
- All diagnostic pharmacologic agents are sympathomimetics
- Apraclonidine 0.5% reverses the anisocoria in HS and can be used to establish the diagnosis instead of cocaine

The term Horner syndrome (HS) refers to the clinical condition of oculosympathetic paresis, which in its most typical form presents with a classic triad of ipsilateral miosis, ptosis, and impaired vasomotor/sudorific activity in the face and neck.[1,2,3,4,5] The syndrome results from interruption of the oculosympathetic pathway, which has a long, circuitous course with central, preganglionic, and postganglionic neurons.

Although the syndrome is credited to a Swiss ophthalmologist, Johann Friedrich Horner, who described the condition in 1869, it was discovered and rediscovered repeatedly before Horner himself, who admitted in his paper that several of his colleagues had prior knowledge of the condition. However, he was the first author to correctly attribute the symptoms to oculosympathetic paresis.[1,2] Although the French and Italian literature refer to Horner syndrome as Claude Bernard-Horner syndrome or Bernard syndrome, to give credit to the French ophthalmologist Claude Bernard, who described the condition in 1852, the credit for the first-ever description of this condition goes to François Pourfour du Petit in 1727 who did experimental sectioning of the sympathetic nerve trunk in dogs and recorded the clinical effects.[1]

Although this piece of history underlies the fact that a lone researcher is rarely responsible for the discovery of a single disease,[1] the eponymous term Horner syndrome immediately brings to mind an instantaneous link to a specific set of symptoms. Although some authors endorse the recommendations of the Federative Committee on Anatomical Terminology, which as early as 1950 repeatedly called for the rejection of the use of eponyms in medicine,[1,6] others cite Horner syndrome in particular as a classic example to defend eponyms.[7] At the time of writing of this chapter, the term Horner syndrome is still routinely used in the literature and will probably remain popular in the foreseeable future, simply because the term combines meaning and brevity.[8]

Etiology and Pathogenesis

Horner syndrome (HS) results from the interruption of the sympathetic supply to the eye (the oculosympathetic pathway). Throughout its long and circuitous route, it covers the entire ipsilateral anatomy of the head, neck, and upper chest. Therefore, before discussing the etiologic causes of HS, it is imperative to briefly outline in detail the three-neuron course of the sympathetic pathway until it reaches the eye and its adnexa.[4] A deep understanding of the anatomy will not only accurately confirm the location of the lesion, and condense the differential diagnosis, but would also help the physician choose the appropriate investigative tool.[8]

The first-order neuron (central neuron) originates in the posterolateral nuclei in the hypothalamus. It descends caudally through the tegmentum of the midbrain and pons in a diffuse manner. At the pontomedullary junction, the fibers merge into a discrete bundle and take an abrupt anterior turn to lie ventral to the inferior olivary nucleus of the medulla. The fibers course down the spinal cord, to terminate in the intermediolateral cell column (the ciliospinal center of Budge-Waller) between C8 and T2.[3,4,5,9]

The second-order neuron, or the preganglionic sympathetic fibers, takes a complicated course through the upper chest and neck. Most of these fibers exit the spinal cord rostrally through the ventral rami or anterior roots at the level of T1, although some fibers exit the ventral roots at C8 or T2. These anteriorly exiting neurons arch over the apex of the lung, before starting their ascent by joining the paravertebral sympathetic chains. The latter are paired bundles of nerve fibers that lie parallel to the vertebral bodies along the entire length of the spinal column. The fibers then pass through *(Print pagebreak 243)* the inferior cervical ganglion without synapsing. In 80% of individuals, the inferior cervical ganglion is found to be fused with the first thoracic ganglion to form the stellate or cervicothoracic ganglion.[9,10] The stellate ganglion is anteromedial to the vertebral artery, posteromedial to the common carotid artery and jugular vein, and lateral to the trachea and esophagus and is related inferiorly to the apex of the lung.[11,12] After they leave the inferior cervical/stellate ganglion, the oculosympathetic fibers split around the anterior subclavian artery into two separate tracts to form a complete loop. The first tract passes anterior to the subclavian artery, whereas the second tract loops posteriorly and encircles the vessel forming the ansa subclavia. The fibers then rejoin again and ascend uninterrupted through the middle cervical ganglion, which lies at the level of the C6 vertebra, to terminate and synapse in the superior cervical ganglion roughly at the level of the carotid bifurcation.[2] The superior cervical ganglion is the largest cervical sympathetic ganglion, as it may reach up to 2.5 to 3 cm in length.[8,10] It is situated anterior to the transverse processes of the C2 and C3 vertebrae, is roughly 1.5 cm posterior to the palatine tonsil, and lies directly posterior to the internal carotid artery and sheath.[2,8,10,12] To sum up the relevant surface anatomical landmarks, the stellate ganglion lies at the level of the neck of the first rib, the middle cervical ganglion is marked by the cricoid cartilage, whereas the level of the superior cervical ganglion is roughly approximated either by the hyoid bone or the angle of the jaw because it is a considerably longer structure.[12]

Each preganglionic neuron synapses with about 15 postganglionic or third-order neurons within the superior cervical ganglion.[8] A small number of these postganglionic fibers, the so-called sudomotor fibers, leave the main bulk of the axons with the sheath of the external carotid artery to supply the sweat glands on the face. However, most of the axons remain within the internal carotid artery sheath in their path toward the cavernous sinus. They exit the superior cervical ganglion via the internal carotid nerve, which ascends along the petrous segment of the internal carotid artery, and then branch into several bundles or two main branches, a larger lateral or anterosuperior bundle, and a smaller medial or posteroinferior one.[13,14] These bundles may stay separate or join the nerve plexus around the internal carotid artery.[13,14,15] Although the internal carotid nerve plexus is derived largely (but not exclusively) from the sympathetic nervous system, it also receives contributions from parasympathetic and sensory fibers.[14,16]

Although the topography, composition, and connections of the nerve plexus within the cavernous sinus have been extensively investigated, there is considerable disagreement about the exact course and relationships of the sympathetic fibers both within and beyond the cavernous sinus.[14,17] This disagreement may simply stem from the substantial variability of the course the sympathetic fibers take from this point onward to the orbit.[14] What has repeatedly been demonstrated is that within the cavernous sinus the greater part of the sympathetic nerve plexus along the internal carotid artery gives off filaments that either briefly hitchhike along the abducens nerve (VI), only to leave the nerve several millimeters later to join the ophthalmic division of the trigeminal nerve (V1),[9,14,15] or the fibers continue in their course uninterrupted along with the abducens nerve to the orbit.[14]

The fibers traveling along V1 join the nasociliary nerve, which is one of its three terminal branches, and enters the orbit through the superior orbital fissure, then pass on to the long ciliary nerves (2-3 in number), which penetrate the sclera adjacent to the optic nerve to supply the dilator pupillae muscle.[2,17] Alternatively, the ciliary ganglion may receive a tiny sympathetic rootlet within the orbit, which passes through the ganglion without synapsing and joins the short ciliary nerves before reaching their final destination to innervate the dilator pupillae muscle.[14,17,18] Sympathetic fibers may directly follow the course of cranial nerves III, IV, or V1, or they may accompany the ophthalmic artery. Therefore, sympathetic fibers may enter the orbit both through the superior orbital fissure or the optic canal, although access through the optic canal is controversial.[16,17,19,20,21]

Exactly how the unmyelinated postganglionic sympathetic efferent nerve fibers reach the Müller muscle in the upper lid or the inferior tarsal muscle in the lower lid is not entirely clear, but it appears that sympathetic fibers to both muscles also follows the motor and sensory nerves of the orbit (cranial nerves III, IV, V1, and VI),[17,19,22] although some authors insist that the sympathetic supply to Müller muscle reaches its destination through the superior division of the oculomotor nerve.[8] It remains controversial whether or not sympathetic fibers extend along the infraorbital nerve to the inferior sympathetic tarsal muscle.[17,19] It should be noted that, besides giving off the orbital branches, the sympathetic plexus around the internal carotid artery contributes to the autonomic supply of sweat glands in the medial part of the forehead probably via the supraorbital nerve, in contrast to the lateral part of the forehead, which, like the rest of the face, is supplied by the sympathetic plexus around the external carotid artery.[14,21,23]

HS can be congenital or acquired. Congenital causes of HS include labor trauma resulting from brachial plexus injury, which is exceedingly rare nowadays; malformations of the internal carotid artery; or congenital tumors along the course of the sympathetic

chain.[24,25] An upper thoracic or cervical neuroblastoma is the most common occult malignancy associated with HS in children as well as in congenital HS and is the presenting sign in 2% of individuals with neuroblastoma.[25,26,27] In adults, any lesion along the unusually long course of the oculosympathetic pathway can result in HS. The injury could be due to mechanical, traumatic, vascular, inflammatory, or neoplastic disorders near, or directly involving, any of the structures related to this U-shaped three-neuron pathway.[8,28] Central HS usually occurs as a result of vascular occlusion or a tumor, whereas preganglionic lesions are usually associated with iatrogenic injuries or an apical lung mass and postganglionic HS is usually associated with a pathology involving the internal carotid artery.[2] *(Print pagebreak 244)* It should be realized that, in up to 40% of patients, no cause is ever established and the condition is labeled idiopathic HS.[25,29,30]

Clinical Presentation

The main presenting symptom of HS is a unilateral mild drooping of the upper eyelid, although observant parents may notice that their child has unequal pupils or hemifacial sweating abnormalities.[31,32] In congenital HS, a history of birth trauma may be elicited, whereas in adults as well as in children without a congenital onset, inquiring about prior trauma or neck or chest surgery is important. As we shall see later, some specific symptoms may help localize the lesion; for example, the association of HS with acute pain may suggest the possibility of a dissecting carotid aneurysm. Patients should also be asked about the presence of palpable masses in the neck, axilla, and abdomen.[25]

On examination, the classic triad of ptosis, myosis, and facial anhidrosis is rarely observed in clinical practice, as anhidrosis may be absent.[4] When the sympathetic pupillomotor fibers are affected, the ipsilateral pupil becomes more miotic than the contralateral side (Figure 36.1), but the pupillary reflexes are equally preserved on both sides because they are parasympathetically controlled. Assessment of the size of both pupils should be carried out in the dark where anisocoria is expected to be at a maximum. Anisocoria is usually subtle, can easily be overlooked, and therefore should be specifically sought.[3] The pupil on the affected side also suffers a dilatation lag after cessation of a transient light stimulus.[4,33]

Interruption of the sympathetic innervation to the Müller muscle in the upper lid causes mild ptosis (1-2 mm) that persists in downgaze. In the lower eyelid, involvement of the sympathetically innervated fibers causes upside-down ptosis where the lower lid margin elevates by 1 to 2 mm. This results in narrowing of the palpebral fissure, or pseudoenophthalmos (Figure 36.1C).[34,35] HS is one of the few clinical situations where measurement of the margin-to-reflex distance 2 value (MRD2) has true clinical significance. MRD2 is defined as the distance between the central corneal reflex and the lower eyelid margin (normal value is 4-5 mm).[36]

Because the oculosympathetic pathway carries vasomotor fibers to the eye, acute disruption of these fibers may lead to mild conjunctival hyperemia, which is usually just a transient sign.[37] A relative and mild hypotony, as well as an increase in the accommodative amplitude, has also been reported in HS.[34,38]

The cervical sympathetic outflow is the main pathway for thermoregulatory sweating and flushing; therefore, interruption of the vasomotor and sudomotor fibers to the face would result in the inability of the facial skin to flush or sweat in response to thermal, emotional, or gustatory stimulation.[23,39] Furthermore, because of the loss of sweating, the ipsilateral skin is drier compared with the unaffected side.[38] Central lesions usually cause anhidrosis, which, if clinically detectable, would involve half of the body and not just half of the face. Any lesion proximal to the bifurcation of the common carotid artery produces ipsilateral anhidrosis involving the entire half of the face, whereas a lesion distal to the bifurcation causes anhidrosis confined to a small patch on the medial aspect of the forehead.[23,40,41] In general, the areas that do not sweat also do not blush, although the lack of blushing may be better observed clinically.[42]

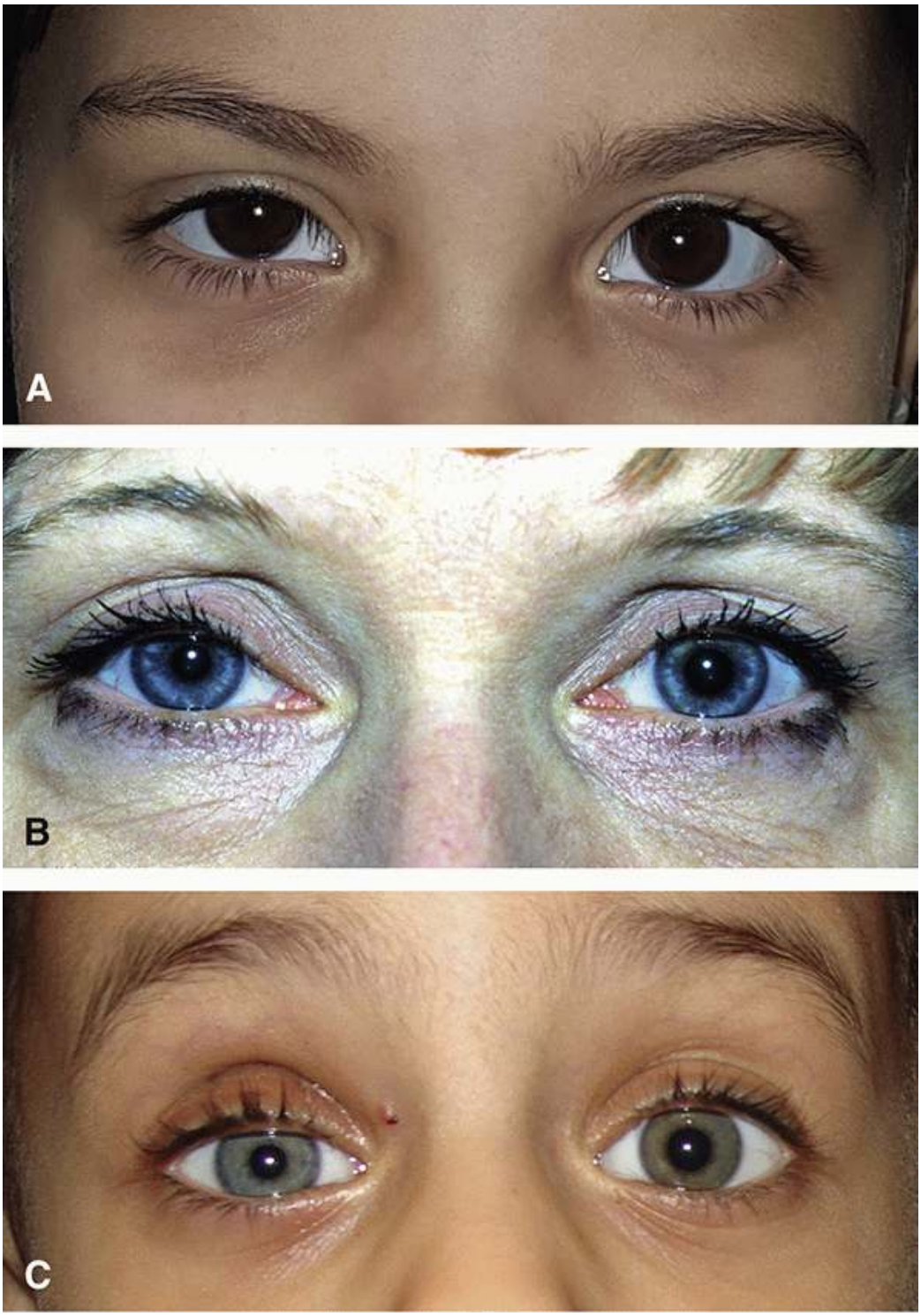

FIGURE 36.1 Spectrum of ocular and periocular involvement in patients with Horner syndrome. A, Isolated ptosis of the right eyelid. B, Right eyelid with ipsilateral miosis. C, Ptosis with ipsilateral miosis and pseudoenophthalmos due to subtle upside-down ptosis of the lower eyelid.

In children and less commonly adults, the harlequin sign or harlequin syndrome may occasionally be observed. It is characterized by an excessive reaction of compensatory facial flushing and sweating contralateral to the side of the lesion. Why this overreaction occurs is unknown.[42,43] An initial and transient reactive vasodilatation in the form of temporary flushing/sweating may rarely be observed on the ipsilateral side of the lesion immediately after cervical sympathectomy owing to a transient compensatory increase in the intrinsic vascular tone, but the dominant effect of sympathetic denervation is one of vasoconstriction from day 1.[39] It is worth considering that, because the majority of humans are currently living in modern temperature-controlled spaces, patients with HS rarely complain of disturbances of *(Print pagebreak 245)* sweating or facial flushing, although this could be perceived during physical exercise.[2,39,42]

In addition to the characteristic triad, patients who acquire HS at birth, or very early in life, develop iris heterochromia, with the

affected side having the lighter color. Coloration of the iris normally occurs during early infancy and is complete by the age of 2 years. It depends upon the stimulation of melanophores by postganglionic sympathetic fibers.[41,44] Therefore, in patients with congenital HS, the melanin is reduced, and the eye appears blue, and even in infants with light-colored irides, the iris on the affected side is of a lighter tint than the normal side.[41,44]

Lesion Localization

Depending upon the anatomic location of the underlying pathologic process, HS is usually associated with additional clinical signs that may be peculiar to the particular anatomic location, whether central, preganglionic, or postganglionic.[3] This can only be appreciated after thoroughly studying the complex anatomic pathway outlined above. A detailed discussion of the associated syndromes and neurologic findings is beyond the scope of this chapter, but several general rules should be borne in mind.

As we mentioned earlier, in central neuron lesions, anhidrosis, if present, should involve the entire ipsilateral half of the body. Crossed sensory or motor signs are highly suggestive of a central lesion. The combination of HS with contralateral trochlear nerve paresis suggests a lesion in the dorsal midbrain.[2] The association of HS with bilateral or less commonly unilateral abducens nerve paralysis usually suggests a pontine lesion.[2] Some syndromes are relatively common and may deserve special mention. Lateral medullary syndrome (Wallenberg syndrome), which occurs due to an ischemic infarction of the vertebrobasilar artery or the posterior inferior cerebellar artery causes a variety of symptoms including vertigo, swallowing difficulties, as well as a loss of pain and temperature sensation in the opposite limbs.[2,45]

The quintessential example of a preganglionic HS is a Pancoast tumor. Patients with a combination of shoulder pain and HS should be investigated thoroughly for a lung mass.[2] Pancoast syndrome or a Pancoast tumor is an apical lung neoplastic or infectious lesion that spreads locally to the region of the superior thoracic outlet, with involvement of the brachial plexus and the stellate ganglion, causing a constellation of signs including preganglionic HS, plus symptoms of ipsilateral shoulder pain; paresthesias along the medial arm, forearm, and fourth and fifth digits; and/or weakness or atrophy of the hand muscles.[2] It is usually caused by non-small cell lung carcinoma, but less common causes include lung adenoid cystic carcinoma, hemangiopericytoma, mesothelioma, plasmacytoma, non-Hodgkin lymphoma, pseudomonal and staphylococcal infections, tuberculosis, aspergillosis, and cryptococcosis.[2] Other causes of a preganglionic HS include chest trauma or hematoma and more importantly iatrogenic injuries, which are an important cause of preganglionic HS and which may occur following epidural anesthesia, coronary artery bypass surgery, lung surgery, carotid endarterectomy, pacemaker insertion, internal jugular catheterization, or stenting of the internal carotid artery.[2]

The anatomic distribution of postganglionic lesions extends from the internal carotid artery to the cavernous sinus and the orbital apex, and varies from the trivial to the life-threatening,[29] but the archetypal example is carotid artery dissection, which is often accompanied by acute face and neck pain (carotydynia).[29] The superior cervical ganglion can be injured in penetrating intraoral trauma or iatrogenically in procedures such as tonsillectomies.[2] Skull base tumors with or without involvement of the cavernous sinus can cause a postganglionic HS. Lesions within the cavernous sinus may have simultaneous involvement of cranial nerves III, IV, V, or VI to a variable degree. Patients who present with isolated HS without additional clinical features probably have a postganglionic lesion.[29,45]

Within the cavernous sinus, postganglionic lesions may be associated with irritation of the trigeminal nerve, which may result in Raeder's paratrigeminal syndrome, the main features of which include ptosis, miosis, and apparent enophthalmos, in addition to ipsilateral facial pain due to trigeminal irritation, but facial sweating is preserved.[8] Alternatively, lesions in the lateral sellar compartment (cavernous sinus) may be associated with a parasellar syndrome characterized by ipsilateral sensory disturbances over the distribution of the ophthalmic division of the trigeminal nerve coupled with HS.[8] The coexistence of a sixth nerve palsy with ipsilateral HS is called Parkinson sign and is highly suggestive of a parasellar lesion.[46] Cluster headache, one of the trigeminal autonomic cephalalgias, is characterized by severe unilateral, short-lived lancinating headaches localized to the orbital, temporal, and mid-face areas, accompanied by ipsilateral tearing, nasal stuffiness, conjunctival injection, and ptosis. Cluster headaches are thought to be due to a transient postganglionic HS probably due to injury of the sympathetic fibers within the bony carotid canal. The condition could progress to permanent oculosympathetic paresis in patients who experience repeated attacks.[2,28,29]

Historically, pharmacologic diagnosis and localization of HS was and still is an integral part of the diagnostic workup. All the drugs used in pharmacologic localization are sympathomimetics. The underlying *physiological* principle is their direct or indirect ability to release or synthesize norepinephrine from the *normal uninterrupted* postganglionic fibers into the nerve terminals.[8] This is a two-step process. The first step is to establish a diagnosis of HS, whereas the second step attempts at localizing the causative lesion.

For the first step, two competing drugs are available for a pharmacologic diagnosis of HS, cocaine and apraclonidine, but apraclonidine is rapidly replacing cocaine as the gold standard.[34] Apraclonidine (0.5%) is an α_2-adrenergic sympathomimetic agonist, which was repeatedly shown to reverse the anisocoria associated with HS.[34,47] The direct stimulation of α_1 receptors that are located in the iris dilator *(Print pagebreak 246)* muscle would cause mydriasis, whereas the stimulation of the α_2 receptors that

are located on the presynaptic terminals and not in the muscle itself are inhibitory pulses, which would cause miosis due to a reduction of norepinephrine production and release. Therefore, under normal conditions, apraclonidine would be expected to cause minimal miosis, which may not be clinically discernible.[8,31,48,49] However, in the pupil affected with HS, apraclonidine reverses the miosis because of the denervation hypersensitivity of the α_1 receptors on the iris dilator muscle.[8,31,48,49] Although this agent does not help localize the lesion, it is more readily available commercially than cocaine, and the reversal of anisocoria may be easier to observe in the clinic than cocaine's asymmetric mydriasis, and in contrast to cocaine, the color of the iris has no impact on the test results.[8,31,34,48,49] Brimonidine could also be used instead of apraclonidine, but it has a weaker effect.[49]

Alternatively, the application of one drop of topical cocaine (2%-10%) in the conjunctival sac may be used instead of apraclonidine. Under normal conditions, cocaine would be expected to dilate both pupils, because it inhibits the reuptake of norepinephrine both at postganglionic synapses and at the iris dilator muscle. This indirectly increases the amount of norepinephrine available to stimulate the muscle, thereby acting as an indirect sympathomimetic agent.[3,8] The Horner pupil would understandably fail to dilate because of the chronic deficiency of norepinephrine in the synapses (although it might minimally dilate in central lesions), while the contralateral normal pupil dilates. An anisocoria of more than 0.8 mm raises a strong suspicion of HS.[8] However, for more accurate observation of the asymmetric mydriasis caused by topical cocaine, the pupils should be evaluated at least 30 minutes after the installation as the maximal response is obtained 40 to 60 minutes after installation.[3,8] The drawbacks of cocaine are that cocaine drops are expensive, may be difficult to obtain, the test is less reliable the darker the iris color gets, and some patients may be uncomfortable with the nature of the substance itself.[8,34]

The second step is to differentiate a central or preganglionic lesion from a postganglionic one. Again, another indirect sympathomimetic agent, hydroxyamphetamine, can be used to exclude a postganglionic pathology. In contrast to the way cocaine works, hydroxyamphetamine works by stimulating the release of norepinephrine from nerve terminals; therefore, if these terminals are denervated, the pupil will not dilate and anisocoria will persist. But if the pupil dilates equally on both sides, then this suggests the postganglionic neurons are intact and they have the potential to produce the neurotransmitter, suggesting a first-or second-order neuron lesion. In short, hydroxyamphetamine is a test of the integrity of the postganglionic neuron, but it should be noted that norepinephrine stores may take around 1 week to be depleted after the insult, so that the hydroxyamphetamine test may not be of value if it is performed within this window.[50] It should also be borne in mind that cocaine reduces the clinical effect of hydroxyamphetamine, and if both tests are to be carried out they must be separated by 72 hours.[50] Unfortunately, neither hydroxyamphetamine nor any other sympathomimetic drug can differentiate a central from a preganglionic lesion.[50,51]

In real-world scenarios, the neuroradiologic evaluation may be more important clinically than pharmacologic testing, not just because pharmacologic tests mostly rely on controlled substances that may be difficult to obtain, let alone remembering their significance, but also because these tests are generally unreliable and may have their limitations, particularly in children.[8,29,42,52] Therefore, in modern clinical practice, localization of a lesion and the judicious ordering of ancillary radiologic investigations may more appropriately be based on the clinical features and a thorough understanding of the anatomy of the oculosympathetic pathway rather than pharmacologic testing.[8] Neuroradiologic evaluation should include magnetic resonance imaging (MRI) of the neck, brain, chest, or cervical spine, as well as magnetic resonance angiography (MRA) or computed tomography (CT) angiography of the head and neck.[3,29,51,53] If central or postganglionic HS is suspected, a brain MRI should be ordered.[3,29,50,51] If a preganglionic lesion is suspected, a CT of the chest should be ordered, and if a painful HS is encountered, an MRI/MRA of the neck is warranted.[2,3] If localizing or ancillary signs are not useful in the selective ordering of specific radiologic tests, a catchall approach may be to image the entire pathway from the hypothalamus down to the chest.[28] This holistic approach is particularly important in children where a diagnosis of HS should prompt immediate testing with MRI of the brain, neck, and chest, in addition to urinary catecholamines testing (homovanillic acid and vanillylmandelic acid).[2,54]

Differential Diagnosis

Because the ptosis in HS is usually subtle and rarely exceeds 1 or 2 mm, levator dehiscence should be ruled out,[2,3] but other causes of ptosis (neurologic, myopathic, mechanical, and neuromuscular conditions) should also be considered.[2] Moderate or severe ptosis should alert the clinician to an alternative diagnosis.[4] Two conditions that are frequently listed as prime simulating lesions (ocular myasthenia gravis and oculomotor nerve palsy) are not difficult to discern from HS. Ptosis in both conditions is usually more severe and is usually associated with ocular motility problems, and the ptosis in myasthenic patients is also variable.[50] It should be noted that not all patients with an asymmetry in eyelid position have true ptosis, and other conditions should be ruled out including dermatochalasis, contralateral lid retraction, and globe dystopia or globe asymmetry.[50] Acute HS ptosis should be differentiated from acute, unilateral transient blepharoptosis, which is of an unknown etiology, although a recent history of a viral upper respiratory tract infection may be elicited. As its name implies, this is a transient self-limiting condition and could easily be differentiated from HS owing to the lack of ancillary or localizing signs and symptoms.[55]

When anisocoria is observed in clinical practice, the next step in the clinical examination is to confirm that the *(Print pagebreak 247)* pupillary light reflexes are preserved on both sides; otherwise, other causes of anisocoria should be considered. Physiologic

anisocoria is the most common cause of pupil asymmetry and is observed in 15% to 30% of the general population; therefore, a busy ophthalmology practice is expected to see several cases every day.[28] Physiologic anisocoria should be no more than 1 mm and is stable in light and dark conditions. Old photographs may help confirm the diagnosis and exclude recent onset, more sinister pathologies.[28]

The list of causes of pathologic anisocoria involves conditions where the abnormal pupil is the larger one (pupil-involving oculomotor nerve paralysis, Adies pupil, or drug-induced) or the smaller one (pharmacologic blockade or the Argyll Robertson pupil).[28,56] As a general rule, if there is a greater anisocoria in light, the larger pupil is the abnormal one, whereas if there is a greater anisocoria in the dark, the smaller pupil is the abnormal one.[28] Also, a previous history of ocular surgery or iris atrophy following inflammation or trauma should be ruled out before a diagnosis of HS is made based on pupillary findings alone.[2]

A rare entity that is the exact opposite of HS is the Pourfour du Petit syndrome where an irritative lesion somewhere along the sympathetic pathway causes eyelid retraction, unilateral mydriasis, hemifacial hyperhidrosis, and occasionally iris hyperpigmentation. The condition may or may not be associated with cluster headache, recurrent paroxysmal right facial pain, or trigeminal neuralgia pain.[57]

Treatment

If an obvious cause is identified, appropriate and prompt referral is warranted, particularly in children and in situations like an acute painful HS, which is considered a neurological emergency, particularly if the patient presents within the first 4 weeks from onset.[50]

In patients with stable HS after life-threatening conditions have been stabilized or excluded, or when no identifiable cause is established (idiopathic HS), ptosis surgery is warranted for functional or cosmetic reasons. A satisfactory eyelid position can be obtained by aponeurotic advancement, aponeurotic resection, and counterintuitively by conjunctivomullerectomy, where it appears to work via advancement of the levator, a mechanism of action that is independent of the Müller muscle.[50,58,59,60,61]

Prognosis

Missing the subtle signs of HS could result in grave clinical consequences, as it is one of the few true "*red flags*" in oculoplastic surgery, a warning that somewhere along its path, the oculosympathetic pathway is interrupted by a serious underlying condition that may cost the patient their life or cause serious morbidity.[4,50]

Although a significant number of pediatric patients with HS have an unknown etiology,[25] the diagnosis of HS in a child may signify an underlying fatal pathology in 21% to 50% of children.[25,54] The majority of neuroblastomas responsible for HS are localized tumors arising in infants and younger children, which usually imparts a more favorable outcome.[25]

Histopathology

To our knowledge, there are no descriptions of eyelid histopathological changes in HS.

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CHAPTER 37

Madarosis

Key Points

- Madarosis is the complete loss of eyelashes or eyebrow hair due to a variety of causes
- This is generally distinct from hypotrichosis, which refers to a reduction in the number of eyelashes
- Causes are broadly classified into dermatologic diseases, infectious diseases, endocrine disorders, drugs, trauma, neoplastic processes, and congenital conditions
- Clinical appearance ranges from mild thinning to complete eyelash and eyebrow hair loss
- Treatment options include camouflage techniques with cosmetics, eyebrow pencils, eyeliner, eye shadow, or eyebrow or eyelid tattooing
- Prostaglandin F2α analogs are approved for the treatment of hypotrichosis possibly through stimulation of prostaglandin receptors in the dermal papillae
- Surgery may be indicated for brow madarosis as a last resort with follicular unit transplantation from the occipital area
- Scarring madarosis from deep dermal infections or following severe trauma are not expected to regrow any lashes, but madarosis from superficial inflammatory dermatoses, endocrinopathies, or chemotherapy are likely to be reversible

Madarosis is a general term that is used to describe the loss of eyelashes or eyebrow hair due to a variety of causes.[1,2,3,4] Other less frequently used synonyms of madarosis include milphosis, hypotrichosis, or alopecia adnata.[2,3] The term “milphosis” is restricted to the loss of eyelashes only and not eyebrow hair.[3] A reduction in the number of eyelashes, rather than a complete loss is termed hypotrichosis, whereas “alopecia adnata” is a term that is used to denote lash underdevelopment and is usually used in the context of congenital anomalies of hair.[3] Another term that is used in relation to eyelashes but in an opposite context is “hypertrichosis,” which in contrast to hypotrichosis denotes excessive eyelashes that may grow in 2, 3, or 4 rows.[3] Because cilia serve both protective and cosmetic functions, the consequences of their loss can be functional as well as esthetic.[2]

Etiology and Pathogenesis

There are 100 to 150 eyelashes in each upper eyelid, and every eyelash persists for 3 to 5 months before being shed.[3] Madarosis may occur as an isolated finding or may be part of a generalized loss of scalp or body hair.[1,2,3,4,5,6,7,8] The causes may be broadly classified into (1) dermatologic diseases, including alopecia areata, psoriasis, acne rosacea, discoid lupus erythematosus, cutaneous sarcoidosis, telogen effluvium, and en coup de sabre (localized scleroderma); (2) infectious diseases, including staphylococcal blepharitis, herpes simplex or zoster, HIV, and leprosy; (3) endocrine disease including hyper-and hypothyroidism; (4) drugs, including antithyroid drugs, anticoagulants, anticholesterol drugs, and antimetabolites such as cyclophosphamide, colchicine, or methotrexate; (5) trauma, including radiation for ocular tumors, thermal, chemical, or electrical burn, surgical trauma to the eyelids or the brow (direct brow lift), or eyelid tattooing; (6) neoplastic eyelid processes, particularly sebaceous cell carcinoma, squamous or basal cell carcinoma, malignant melanoma of the eyelid, or lymphoma; and least commonly (7) congenital conditions, including eyelid colobomas, cryptophthalmos, Ehlers-Danlos syndrome, acanthosis nigricans, and Treacher Collins syndrome.[1,2,3,4,5,6,7] Other atypical causes that cannot be categorized include substance abuse (cocaine vapor), which is associated with reversible madarosis[1,2,5]; the long-term daily use of mascara[4]; and Kawasaki disease.[8]

Madarosis can also be classified pathogenetically into scarring and nonscarring types, which is a useful tool to determine the prognosis.[2,3] In general, any of the above-mentioned conditions can lead to nonscarring madarosis if the inflammation they induce is superficial or transient with no fibrosing potential, whereas scarring or cicatricial madarosis is caused by a deep irreversible fibrotic process.[2]

Clinical Presentation

A detailed discussion of the entire range of causes of eyelash loss is beyond the scope of this chapter and is detailed elsewhere in the literature,[2] but the major causes include infections, inflammatory conditions such as rosacea and atopic dermatitis, nutritional deficiencies, trauma, and eyelid margin lesions.

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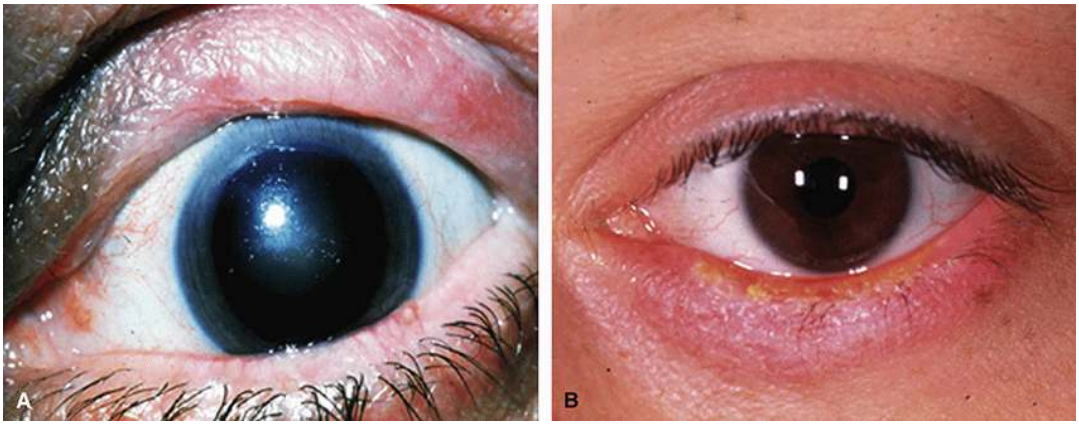

FIGURE 37.1 A and B, Madarosis associated with chronic blepharitis.

Depending on the etiology, patients with madarosis may report a range of hair loss experiences, from mild thinning to complete eyelash and eyebrow hair loss, as well as a reduction in the length of the remaining eyelashes and a change in color (depigmentation).[9]

Madarosis can be seen in cases of long-standing blepharitis with eyelid margin hypertrophy and scarring (Figure 37.1). Chronic eyelid rubbing can break the lashes at their base resulting in the apparent absence of lashes (Figure 37.2).

Alopecia areata, an autoimmune nonscarring type of hair loss, very rarely involves the eyelids exclusively and is more frequently observed in cases of alopecia totalis (scalp alopecia) or alopecia universalis (whole body alopecia).[2,9,10] Within the active patch of alopecia ariata, there is an inflammatory lymphocytic infiltration around the lower third of the eyelash that converts the growth phase of the eyelash from an anagen (growing phase) to a telogen (resting phase).[10] Telogen effluvium is the most common type of hair loss and is defined as an increased shedding of normal telogen hair. It may be associated with several systemic diseases or may occur after severe emotional trauma and rarely involves the brows.[1]

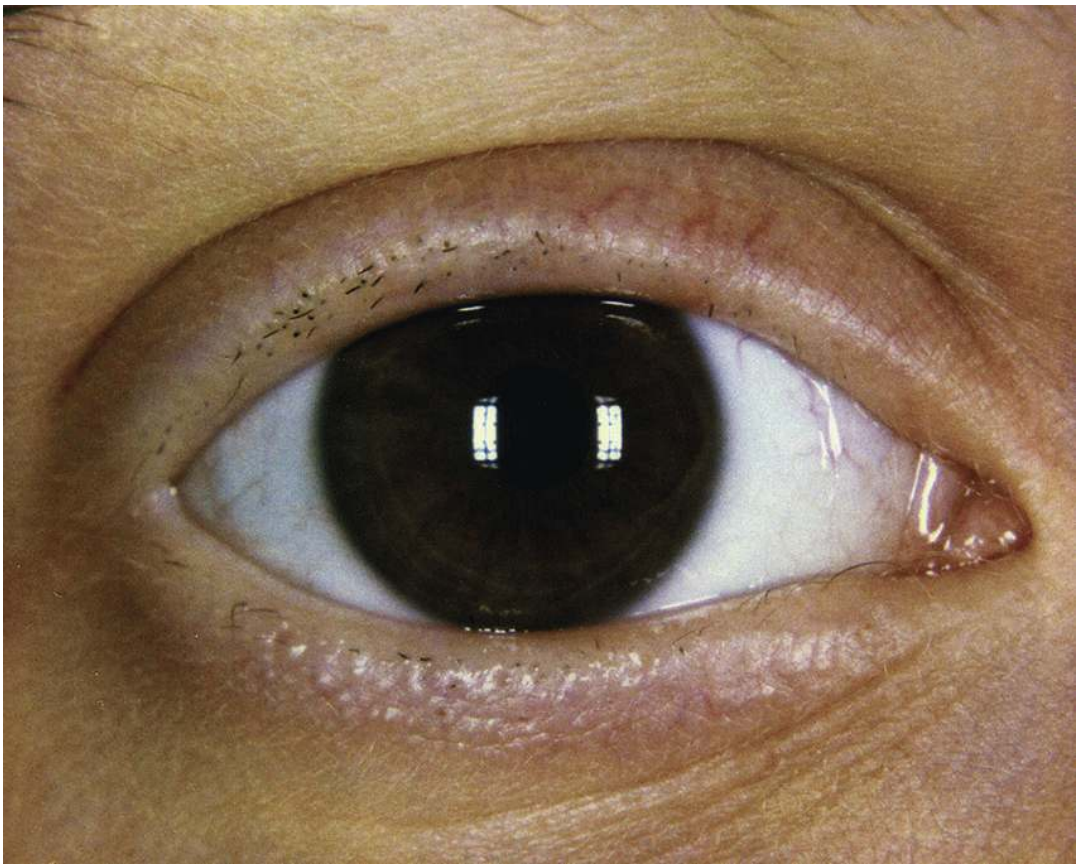

FIGURE 37.2 Chronic eyelid rubbing with breakage of eyelashes at their base.

A classic example of infectious agents causing alopecia is lepromatous or borderline leprosy, which may cause scarring madarosis due to histiocytic infiltration of the hair follicles.[1,2,3] Because thyroid hormone receptors are present in the pilosebaceous unit, hypo- and hyperthyroidism disorders can disrupt hair cell cycle kinetics possibly through an increase in the telogen:anagen ratio, causing madarosis or hypotrichosis.[1] One peculiar sign that is possibly suggestive of thyroid disease is the Hertoghe sign (Queen Anne sign), which is defined as madarosis circumscribed to the lateral one-third of the eyebrow and is typically associated with hypothyroidism. Madarosis can be the presenting sign in both hypothyroidism as well as in hyperthyroidism. The lashes may be coarse and short in hypothyroidism, whereas in hyperthyroidism there is thinning with breaking off and shortening of the hair.[1] As noted above, eyelash loss can be a valuable premonitory sign in various systemic disorders, and a full laboratory workup, with referral to an endocrinologist or a dermatologist, or a biopsy from the eyelid skin may help settle the occasional diagnostic dilemma when the exact cause of hair loss cannot be determined.

Eyelid or eyebrow madarosis may also occur as a side effect of multiple chemotherapeutic agents.[11] In chemotherapy-related madarosis, eyelash and eyebrow hair loss is usually preceded by scalp and body alopecia by weeks or even months.[11] In this particular subset of patients, eyebrow alopecia usually precedes eyelash madarosis.[11] Toxic madarosis due to radiation in the periocular region is usually reversible unless the dose exceeds 50 to 60 Gy.[12]

Malignant lesions such as sebaceous carcinoma that extends to the lash follicle may be associated with madarosis that tends to be more focal in location (Figure 37.3).[3] Although madarosis is frequently described as a clinical sign *(Print pagebreak 251)* that may help differentiate between a recurrent chalazion and sebaceous carcinoma,[1] lash hypotrichosis can still occur in the setting of a longstanding chronic or recurrent chalazion (Figure 37.4). Other benign lesions, such as eyelid marginal hemangioma, are often also associated with madarosis (Figure 37.5). Eyelid trauma, either natural or as a result of surgical procedures is also often associated with loss of eyelashes or absence of lashes because of the tissues used in eyelid reconstruction (Figure 37.6).

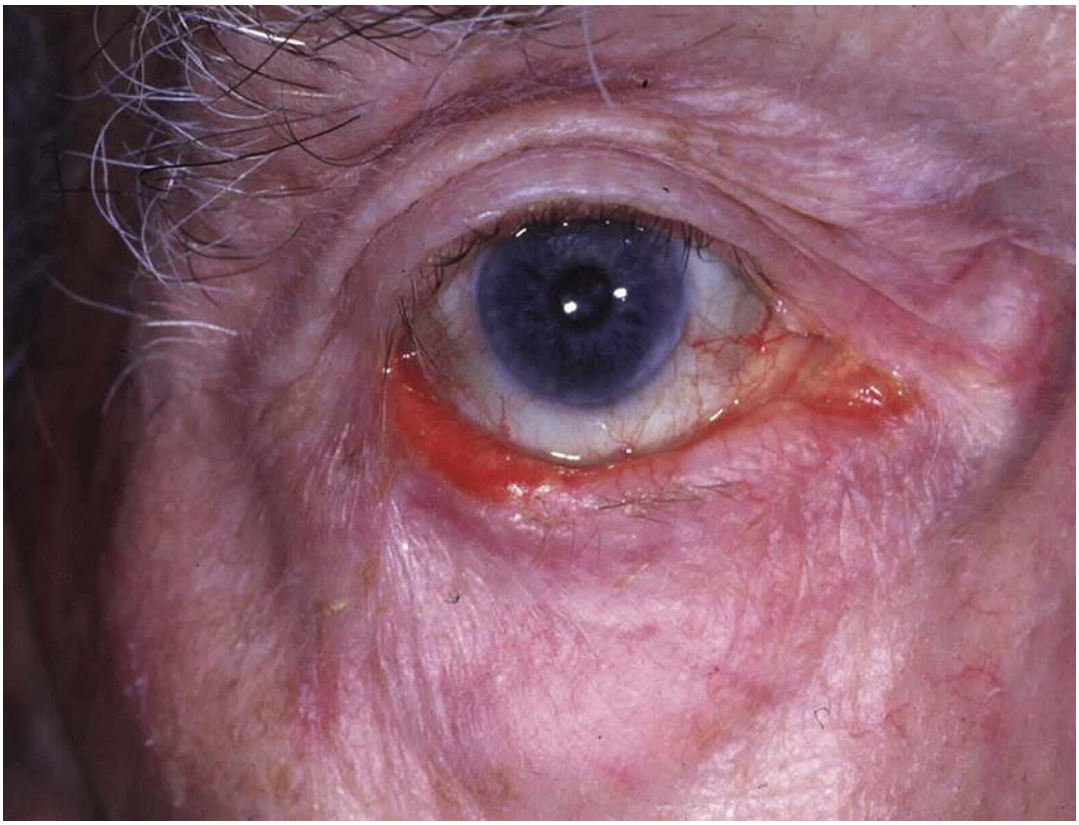

FIGURE 37.3 Sebaceous carcinoma along the lower eyelid margin with loss of eyelashes.

Patients with congenital eyelid coloboma of any type are naturally devoid of eyelashes in the colobomatous defect (Figure 37.7). Also, in patients with complete and incomplete cryptophthalmos, the eyebrows are seldom well developed, with complete or partial madarosis of the ipsilateral eyebrow.[13] This eyebrow madarosis simply occurs because any maldevelopment in the eyelid region suppresses hair growth in the eyebrows.[14]

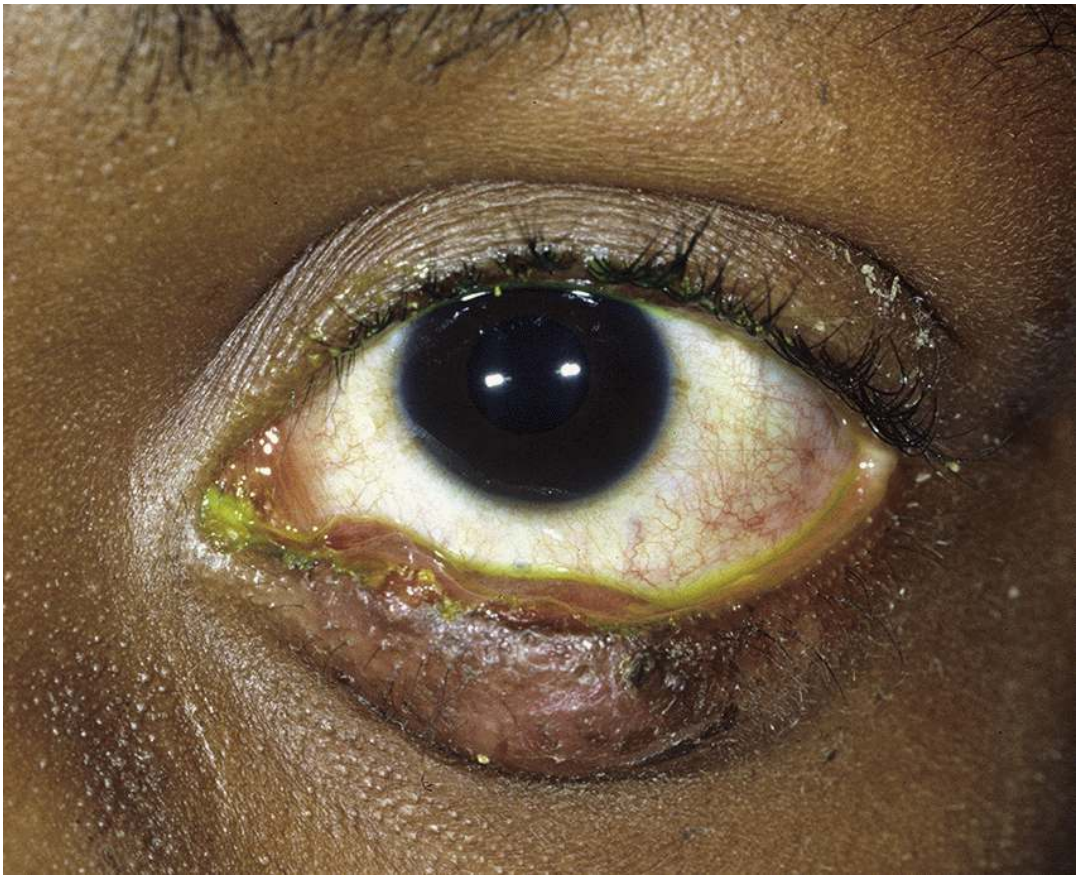

FIGURE 37.4 Recurrent lower eyelid chalazion with madarosis.

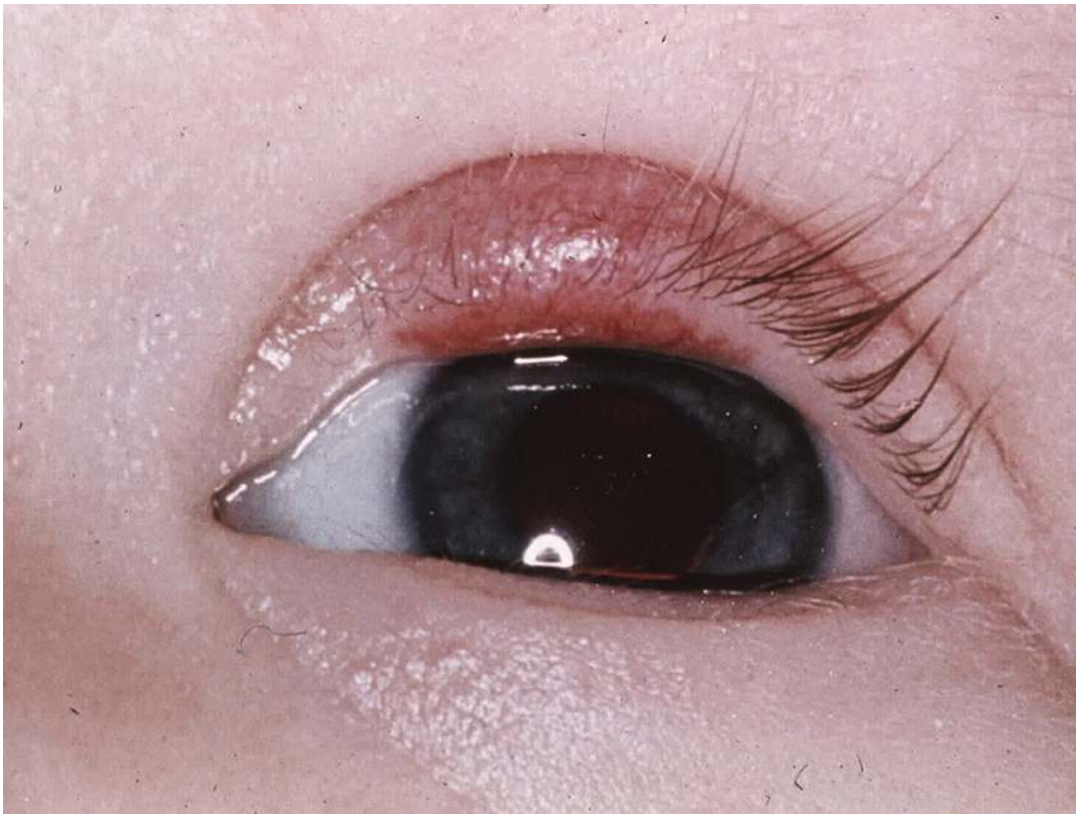

FIGURE 37.5 Marginal eyelid arteriovenous malformation associated with loss of eyelashes.

Differential Diagnosis

The differential diagnosis of madarosis is vast and includes more than 100 entities.[2] One peculiar condition to exclude when a bizarre pattern of eyelash loss is observed is trichotillomania. This is defined in the 4th edition of the Diagnostics and Statistic Manual of Mental Disorders (DSM-IV), as hair loss from a patient's repetitive self-pulling of hair.[15,16] The etiology is complex, but it is usually triggered by a psychosocial stressor within the family, although the patient usually denies it, and other family members may not have observed the problem firsthand. The diagnosis is usually easy as the hair loss is patchy and the eyelashes are broken at different levels, in addition to the characteristic age (school-aged children).[9] When in doubt, a negative hair pull test at the edges of the madarotic area will help clinch the diagnosis.[16] It should be noted that hypotrichosis of the lateral third of the *(Print pagebreak 252)* eyebrow is not specific for hypothyroidism and is a clinical sign shared by many maladies including atopic dermatitis, alopecia areata, and lupus.[17]

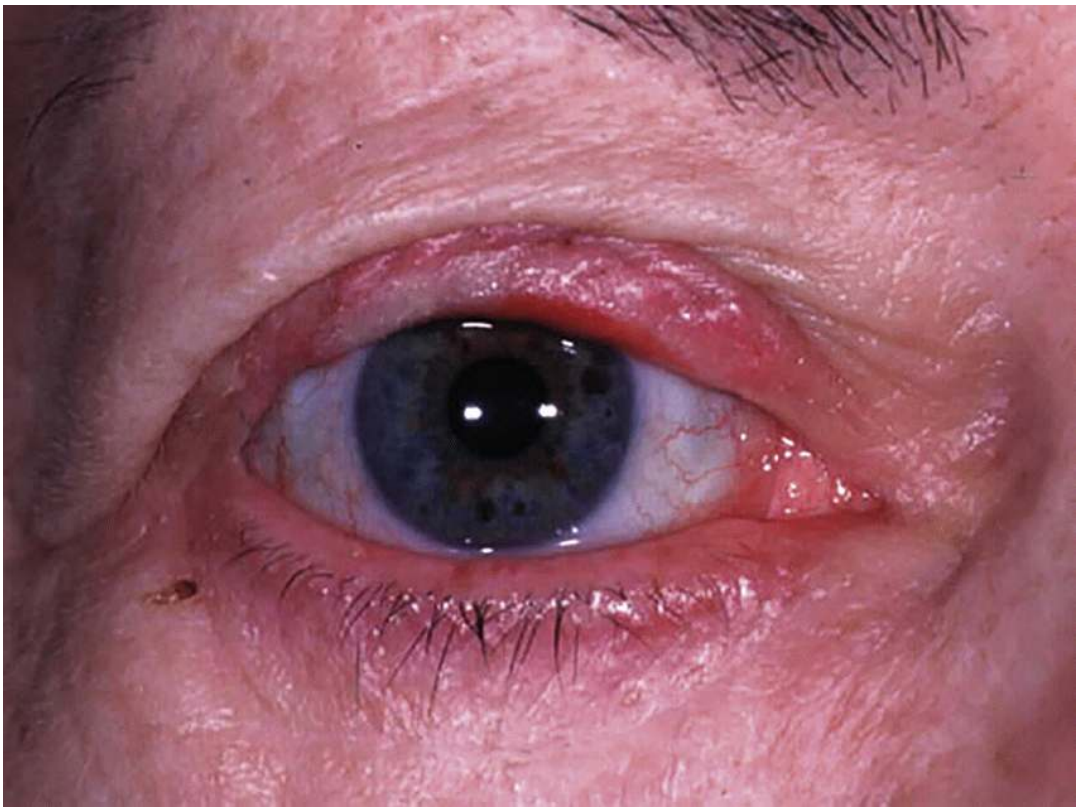

FIGURE 37.6 Reconstructed upper eyelid following Cutler-Beard procedure with absence of eyelashes.

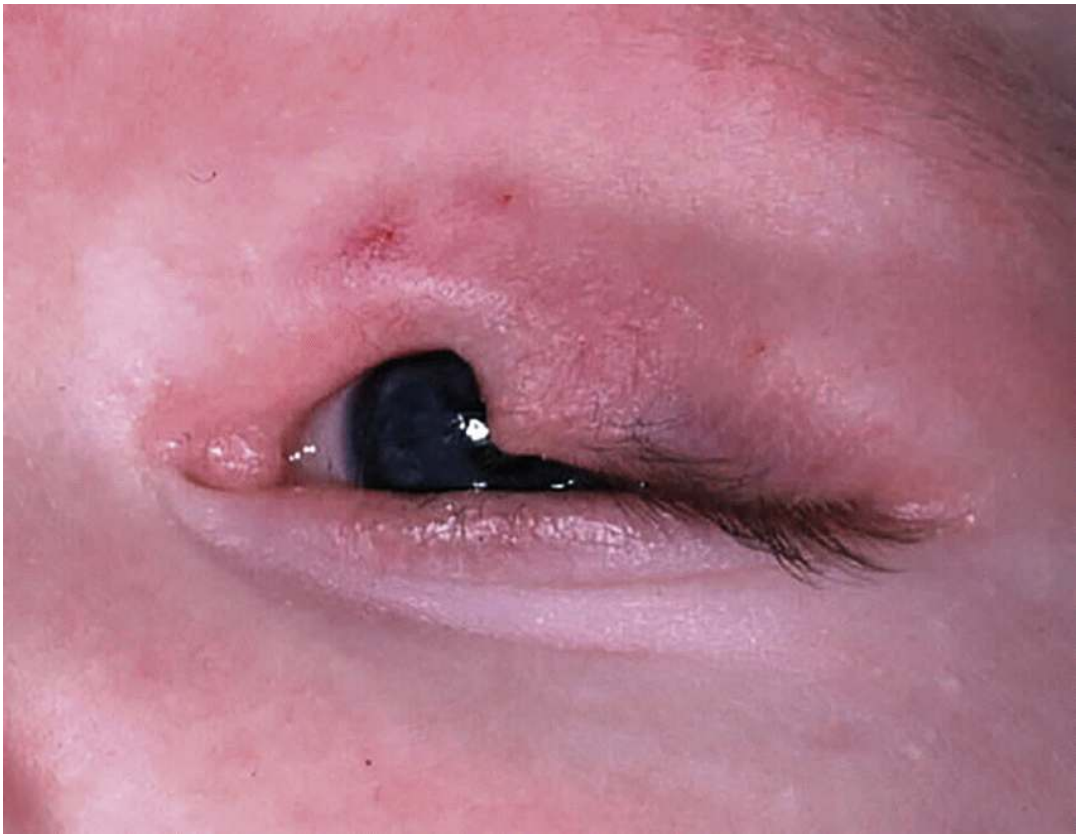

FIGURE 37.7 Congenital coloboma of the upper eyelid with absence of the eyelid margin and eyelashes.

Treatment

Unlike the scalp where several valid treatment options exist for alopecia, most of them do not apply to patients with eyelash

madarosis,[11] although some of those therapeutic modalities may be applicable in the brow.[2] Techniques that could work in the brow include intralesional injections of corticosteroid suspensions, topical steroid creams, or topical twice daily application of minoxidil 5%.[1,2]

Although patients may be comfortable concealing scalp alopecia with scarves or wigs, patients who attempt to camouflage madarosis with cosmetics such as eyebrow pencils, eyeliner, or eye shadow may not be as successful, and the esthetic outcome of camouflage techniques is limited and clumsy at best.[11] If there is a near-total loss of the eyelashes, an eyeliner may be a viable option, whereas if there is partial eyelash loss mascara may be more suitable.[2] Artificial eyelashes and eyebrow troupes may be tried with a complete or partial set of lashes, or lash singlets, but again, the outcome is not usually satisfactory, particularly in patients with partial hypotrichosis as the artificial lashes may need to be glued to the remaining natural ones.[2,11] Cutaneous irritation from allergic contact dermatitis may also occur from the glue or the artificial lashes themselves.[2,11] Eyebrow or eyelid tattooing (permanent makeup) may also be tried, but the complications of dermal tattooing are not uncommon including a further loss of hair follicles during tattoo laser removal if a patient elects to remove it later.[2,18]

In 2008, the US Food and Drug Administration (FDA) approved bimatoprost (0.03%), a prostaglandin F2α analog, for the treatment of hypotrichosis. Its mechanism of action is not fully understood, but it may stimulate prostaglandin receptors in the dermal papillae, prolong the anagen phase by converting telogen hair follicles to the anagen phase, or promote vellus to terminal hair differentiation.[2,17] It is applied once daily to the eyelid margin and reportedly increases length, thickness, darkness, and growth of eyelashes.[19] However, there is a growing body of evidence documenting the detrimental negative effects of bimatoprost on orbital soft tissues including periorbital lipodystrophy, enophthalmos, deepening of the superior sulcus, cicatricial ectropion, trichiasis, and rarely lid retraction.[20,21,22] In addition, the hypertrichosis pattern observed with its chronic use is characterized by a markedly irregular pattern of lash curling and possibly even trichiasis.[19] Most importantly, as the FDA approval demonstrates, bimatoprost is licensed for milder cases of lash hypotrichosis and not for severe cases of madarosis. Its use is reportedly ineffective particularly if there is >50% lash loss.[23,24] Apparently, an intact hair follicle is required for bimatoprost to work, but because hypertrichosis is frequently observed in patients receiving prostaglandin analogs as antiglaucoma medications, this lack of efficacy is surprising. An alternative hypothesis that is not entirely implausible is that local ocular topical application is more efficacious in promoting lash regrowth than cutaneous application using a cotton tip.[24] When applied to the brow, the tail of the brow is the area that shows the earliest and most profound favorable response to topical bimatoprost.[17] When all the above measures fail, surgery may be indicated as a last resort. In the brow, follicular unit transplantation from the occipital area may be tried. A 1 × 4-cm elliptical area of the skin containing a total of 150 hair follicles is required for each brow.[1,25] Eyelash transplantation may be attempted using various techniques of follicular unit grafting or using a strip composite graft preferably from the eyebrow because of the morphologic similarities between both hair types.[1] The outcome, however, is inferior to eyebrow hair transplantation due to the difficulty in handling and implanting the follicular units.[1,26,27,28]

In patients with trichotillomania, no topical therapy is effective and a placebo does not work. Psychotherapy is required, and the source of stress (usually a strict parent or a rival sibling) should be explored and managed by a psychiatrist.[9]

Prognosis

The potential for regrowth of the lashes depends on the reversibility of the underlying etiology.[2] Patients with scarring madarosis from deep dermal infections or following severe trauma are not expected to regrow any lashes, whereas patients with reversible madarosis from superficial inflammatory dermatoses, endocrinopathies, or chemotherapy are likely to recover.[2] Patients with cancer usually experience regrowth of the eyelashes within weeks after cessation of chemotherapy, but regrowth of the eyebrows may occur later,[11] although a certain degree of madarosis or hypotrichosis can persist, and may not fully recover.[11] Because *(Print pagebreak 253)* alopecia is identified socially with cancer, the psychological impact may be enormous,[11] and madarosis complicates matters even further because, although these patients may be prepared emotionally for chemotherapy-induced alopecia, they usually are not aware that eyelid and eyebrow madarosis may occur as well.[11]

Histopathology

Histopathology for madarosis is specific for the associated conditions associated with it, such as a tumor, chalazion, or inflammation.

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CHAPTER 38

Marcus Gunn Jaw Wink Ptosis

Key Points

- Marcus Gunn jaw wink ptosis (MGJWP) is one of the most common congenital synkinetic eyelid disorders, but it is not the only one
- The precise mechanism of MGJWP remains unclear, but the traditional thought is that it is caused by an abnormal branch of the trigeminal nerve congenitally misdirected to the oculomotor nerve
- An alternative theory is that the jaw wink is an exaggeration of a normal barely detectable physiologic cocontraction of the extraocular muscles innervated by the oculomotor nerve, and the muscles of mastication innervated by the trigeminal nerve
- MGJWP presents with unilateral ptosis at rest, with paradoxical lid elevation occurring with opening of the mouth, moving the mandible sideways, protruding the tongue, clenching the teeth, swallowing, or smiling
- In patients with minimal or no ptosis, observation may be appropriate
- To abolish the wink in these patients, extirpation of the levator aponeurosis can be performed with a subsequent frontalis suspension procedure
- With surgery, the synkinetic movement can be minimized and the ptosis corrected, but asymmetry in downgaze is expected

Synkinesis is defined as an aberrant innervation that results in an involuntary contraction of a muscle upon stimulation of a nerve that does not normally supply this muscle under physiologic conditions.[1,2,3,4,5] Marcus Gunn jaw wink ptosis (MGJWP) or trigemino-oculomotor synkinesis is one of the most common congenital synkinetic eyelid disorders. In 1883, Robert Marcus Gunn, a Scottish Ophthalmologist, skillfully observed one case of congenital ptosis that was associated with elevation of the ptotic lid when the jaw was moved, and the syndrome was pinned to his name ever since.[1,2,3]

Etiology and Pathogenesis

MGJWP is usually sporadic, but a specific hereditary pattern in the form of autosomal dominant inheritance with incomplete penetrance has been reported on more than one occasion.[1,4] The precise pathogenetic mechanism of MGJWP remains unclear, and the most plausible theory is the concept of aberrant connection; however, it is the location of this alleged neural misdirection that is controversial.[4] Traditionally, MGJWP was thought to occur when an abnormal branch of the trigeminal nerve is congenitally misdirected to the oculomotor nerve. This abnormal miswiring was thought to occur peripherally between the mandibular branch of the fifth cranial nerve or its anterior division, innervating the pterygoid muscles, and the superior branch of the third cranial nerve, innervating the levator muscle (trigemino-oculomotor synkinesis).[5,6,7] Although this etiopathogenetic mechanism fails to explain the coexistence of ptosis, which is the second key component in MGJWP, it still appears repeatedly in the literature.[6] Alternatively, the location of this aberrant connection or neural misdirection could be more central (cortical, internuclear, or infranuclear).[4] This has led some authors to include MGJWP under the category of congenital cranial dysinnervation disorders where aberrant innervation of the ocular and facial musculature generally arises from abnormal development of cranial nerve nuclei or their axonal connections.[8,9]

It should be noted, however, that as early as 1959 Sano proposed an alternative theory, demonstrating electromyographically that the jaw wink is an exaggeration of a normal barely detectable physiologic cocontraction of the extraocular muscles innervated by the oculomotor nerve on the one hand and the muscles of mastication innervated by the trigeminal nerve on the other.[10] Normally this primitive phylogenetic mechanism is kept in check by a higher central control. According to this hypothesis, this central inhibitory mechanism is “released” due to an unknown congenital brain stem lesion.[11] The presence of a primitive trigeminal-oculomotor

neural circuit has recently been verified in an animal model, which argues in favor of this "release hypothesis"[12]; however, this "ephaptic coupling" or cross talk between adjacent axons directed to the levator muscle and the pterygoids is controversial.[13]

Clinical Presentation

MGJWP accounts for 5% to 10% of all cases of congenital ptosis.[1,2,14] A slight preponderance for the left side has been noted by some authors,[5,15] and disputed by others,[1,2,16,17] but sex distribution is essentially equal. Parents usually present with the infant very early in life complaining of eyelid flickering or rhythmic eyelid movements with feeding.[18] Older children and adults usually present with partial unilateral *(Print pagebreak 255)* ptosis at rest, with paradoxical lid elevation occurring when moving the mandible sideways (Figure 38.1), with opening of the mouth (Figure 38.2), protruding the tongue, clenching the teeth, swallowing, or even when smiling (Figure 38.3).[1,2,19,20] There are two major types of synkinesis in MGJWP. The first type is termed external (lateral) pterygoid-levator synkinesis and is characterized by synkinetic lid elevations when the jaw is thrust to the opposite side, projected forward, or opened widely. The second type, or the internal (medial) pterygoid-levator synkinesis, which is quite rare,[3] is characterized by lid elevation that is triggered by clenching of the teeth, closing the mouth, or moving the jaw to the same side.[3,5,21] In very young children it may not be possible to determine the exact movement that induces the wink.[3] The degree of the synkinetic eyelid excursion varies from one patient to the other, often retracting the eyelid to a higher level than the normal unaffected side,[2,22,23] and usually being more evident in downgaze. Although it is difficult to accurately quantify the amount of lid excursion with jaw movement, some authors grade the jaw wink into mild (2 mm or less), moderate (approximately 5 mm), or severe (7-8 mm or more).[1] The natural history of the jaw wink is that patients often remark that the synkinesis seems less prominent as they get older. Whether the jaw wink truly improves with age or whether patients acquire the ability to mask it is still a heavily contested issue, but the majority consensus is that it does not diminish and instead patients learn to mask the movement.[1,2,16,17] However, on more than one occasion we have encountered an adult patient who presents with a history of MGJWP but on examination fails to elicit any jaw wink at all or only exhibits the slightest jaw wink.

The degree of ptosis may be mild, moderate, or severe, and although rare, the jaw wink may even be observed in normal eyelids without ptosis.[20,24,25] As the wink improves or appears to improve with maturity, patients also learn to diminish their true ptosis through subtle sustained contractions of the jaw muscles.[26] This "habitual ptosis" is often of a lesser degree than the patient's true ptosis.[5] By learning to hide their ptosis by habitually maintaining an altered jaw position, these patients could be unconsciously or involuntarily putting to good use the same intimate neural connections that led to the jaw wink in the first place.[26]

Irrespective of the presence or absence of habitual ptosis, any subtle movements of the jaw while the surgeon is assessing the levator may underestimate muscle function. Therefore, to get an accurate measure of levator function, it is important to assess levator excursion with the mouth closed[2] or better with the jaw completely immobilized by the examiner or an assistant.[26] In older individuals suspected of having habitual ptosis, it is important to instruct the patient to relax this isometric muscle contraction, although it is not always possible because some patients may be incapable of spontaneous relaxation of their jaw muscles after years of habitual contraction.[5,26]

Various motility disorders have been described with MGJWP, but the most common is ipsilateral superior rectus underaction occurring in up to 76% of patients and may or may not be associated with hypotropia.[1,5,16,17,22,23,25,27] Conversely, some patients with MGJWP may present with hypotropia without superior rectus weakness.[5] Less frequently reported ocular misalignment conditions include esotropia, exotropia, double elevator palsy, Duane retraction syndrome, and pseudo inferior oblique overaction.[1,2,3,28,29] Other associated ocular conditions include anisometropia in up to 25% of patients[1,17] and amblyopia in 30% to 60% of patients.[1,2,16,17] Amblyopia is multifactorial and is not exclusively of occlusive origin. Because eyelid drooping in MGJWP is not a constant phenomenon, amblyopia is rarely a consequence of the ptotic eyelid.[16,17] Systemic associations are a rare occurrence in patients with MGJWP; however, it has been reported with Waardenburg syndrome, Rubinstein-Taybi syndrome, Hirschsprung megacolon, neuroblastoma, melanosis coli, profound deafness, and neurofibromatosis type 1.[5,21,30,31]

Differential Diagnosis

Because of the unusual nature of the synkinetic movement, diagnosis of MGJWP is usually self-evident. However, the movement may be subtle and some patients may not necessarily be aware of it, and even when the condition is obvious, not all parents may volunteer the information.[6,18] Therefore, it is important to rule out a jaw wink in all patients presenting with congenital myopathic ptosis irrespective of the presenting complaint because the management is entirely different.

MGJWP should also be differentiated from other types of congenital and acquired facial synkinetic movements because, as was mentioned earlier, MGJWP may be the most common congenital miswiring eyelid disorder but it is not the only one.[24,32] A rare variety known as inverse Marcus Gunn jaw winking is characterized by eyelid drooping on opening the mouth and is believed to occur due to inhibition rather than stimulation of the levator muscle during external pterygoid contraction (Figure 38.4A and B).[33] An even rarer variety is the see-saw MGJWP, which is a bilateral phenomenon characterized by classic MGJWP on one side and

inverse Marcus Gunn on the other side.[33] Other congenital synkinetic eyelid movements include trigemino-oculomotor synkinesis involving the inferior division of the third cranial nerve,[34] superior oculomotor-inferior oculomotor synkinesis (levator-medial rectus synkinesis) (Figure 38.5A and B),[35] superior oculomotor-superior oculomotor synkinesis (superior rectus to levator synkinesis in patients with congenital oculomotor nerve paralysis),[36,37] trochlear-oculomotor synkinesis (lid retraction with depression of the eye in adduction) (Figure 38.5C and D),[38,39] and trigeminoabducens synkinesis.[7]

Acquired synkinetic eyelid movements may involve either the oculomotor or the facial nerves.[1,37,40] Synkinetic eyelid movements involving the oculomotor nerve usually occur following trauma or any long-standing acquired dysfunction of this nerve and typically involve a synkinetic *(Print pagebreak 256)* movement between the superior rectus and the levator, the cardinal feature of which is ptosis that diminishes or disappears in upgaze and increases in downgaze. This is neither a feature of MGJWP nor conventional congenital myopathic ptosis and could be easily misattributed to a good levator excursion on upgaze rather than a synkinetic movement. Therefore, it should be excluded in all patients with a history of distant trauma.[37]

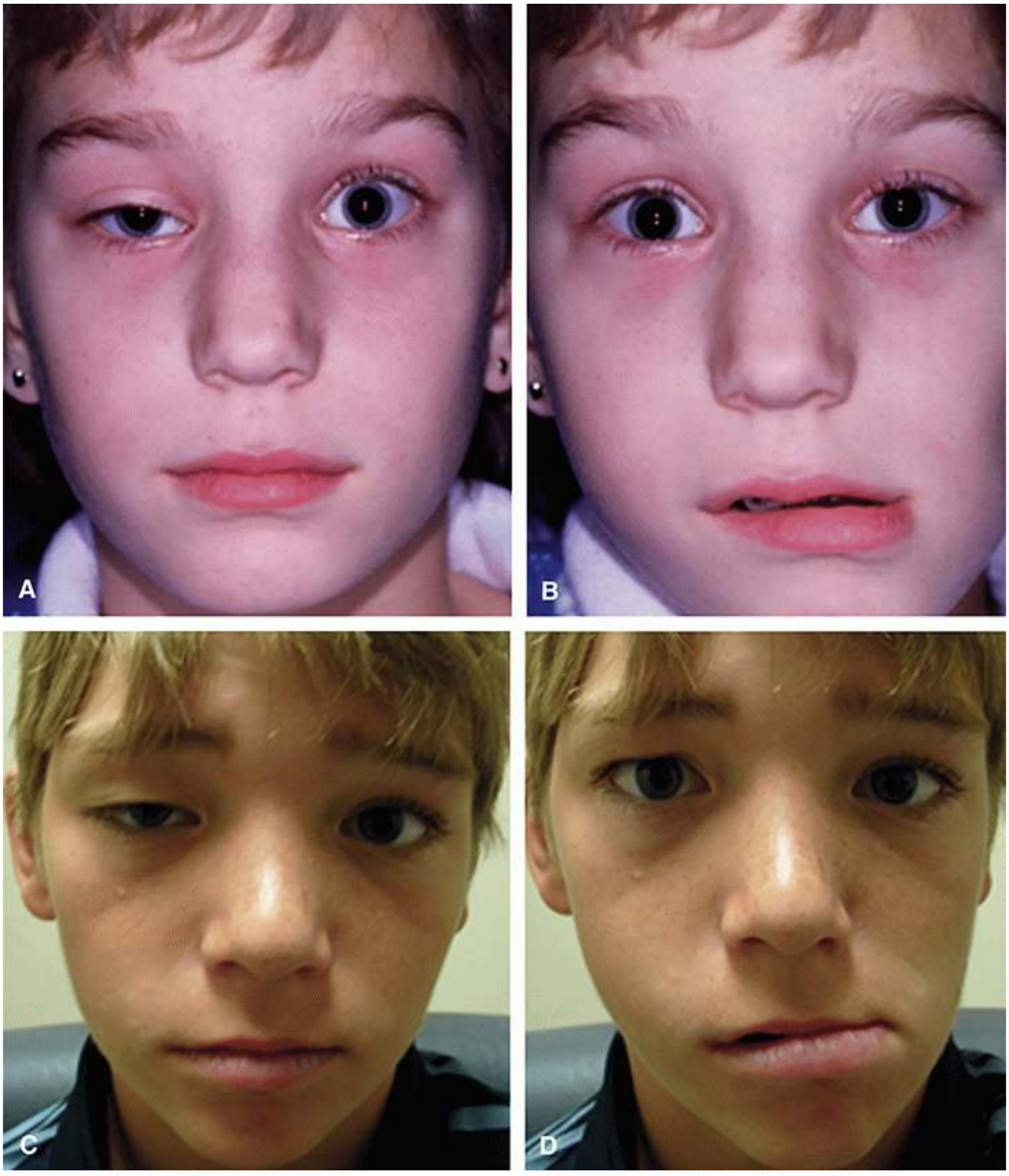

FIGURE 38.1 A-D, Type 1 MGJWP or external pterygoid-levator synkinesis with synkinetic eyelid elevation when the jaw is moved to the contralateral side.

Aberrant movements involving the facial nerve typically occur following peripheral-type facial nerve palsies (Bell palsy).[24,37,40] Marin-Amat syndrome, incorrectly referred to in the literature as inverse Marcus Gunn phenomenon, is an uncommon disorder where the upper eyelid drops resulting in an involuntary eye closure with opening of the mouth or with lateral movements of the jaw. This is an acquired condition and is usually observed as one of the rarer synkinetic sequelae after aberrant facial regeneration following peripheral facial nerve palsies.[21,40] Immediately following an acute facial nerve injury, Wallerian degeneration of the

injured axons occurs, but months later, axonal regrowth takes place. It is postulated that abnormal branching and/or abnormal target innervation of the regenerating axons is a likely cause of aberrant facial movements where the regenerating facial nerve axons responsible for contraction of the orbicularis oculi muscle develop a misconnection with the mandibular division of the trigeminal nerve.[40] The use of the term inverse *(Print pagebreak 257)* Marcus Gunn in the setting of Marin-Amat syndrome may be inaccurate because the condition results from contraction of the orbicularis oculi muscle and has nothing to do with inhibition or activation of the levator palpebrae superioris muscle.[40] This is evidenced by the fact that in these patients, the decrease in palpebral fissure height after jaw opening is a result of a reduction in both MRD-1 and MRD-2, and not MRD-1 alone. This argues against levator involvement (Figure 38.4C and D).[40] Also, the condition improves with botulinum toxin injections into the orbicularis muscle. In patients with Marin-Amat syndrome, symptoms begin after a mean period of 4.4 years (range, 12-10.5 years) following the onset of facial nerve palsy.[40] In patients with Marin-Amat syndrome, not only is there ptosis while eating, but also at rest due to orbicularis muscle spasm.[40]

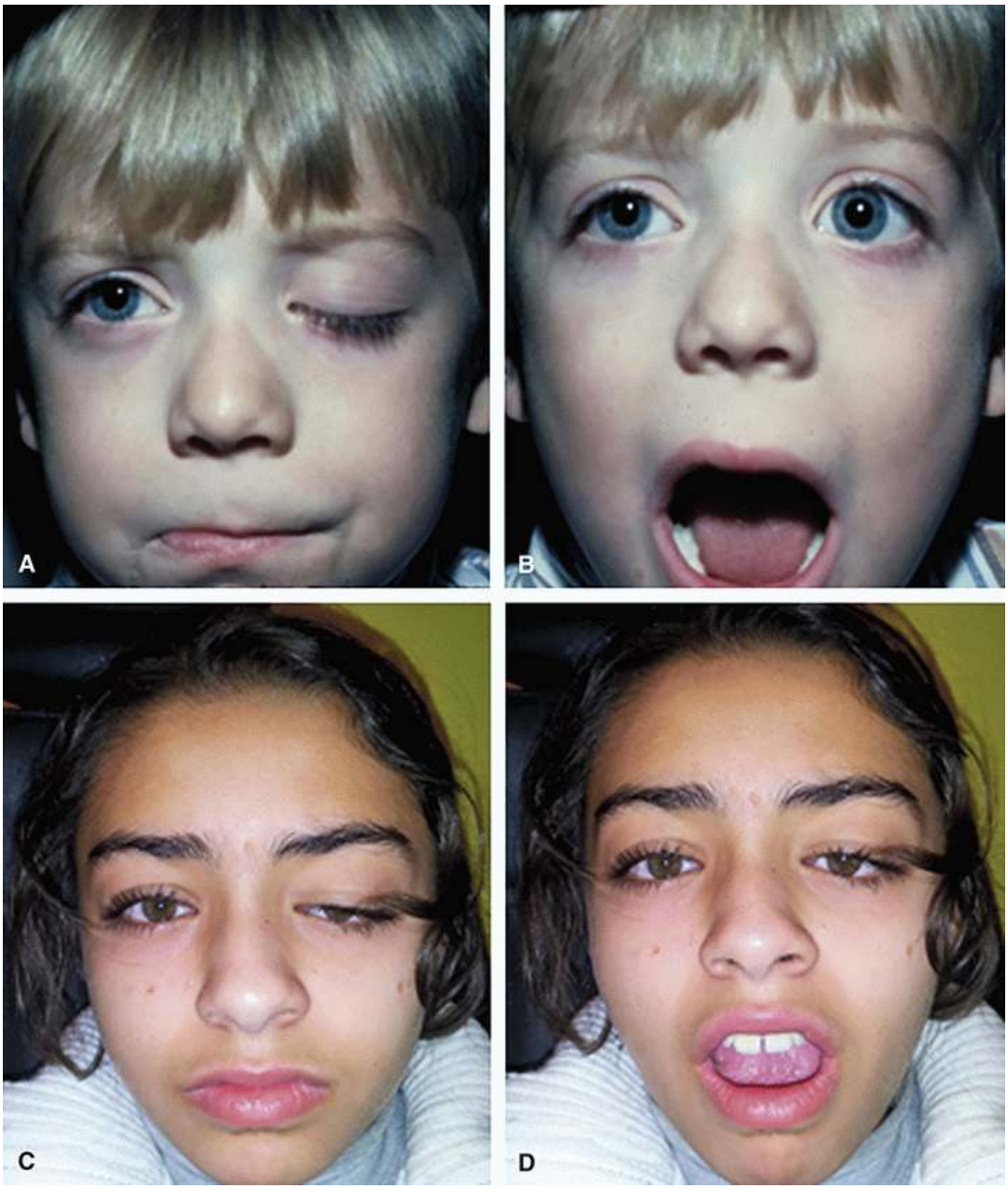

FIGURE 38.2 A-D, Type 1 synkinesis with eyelid elevation when the jaw is opened widely. (A, Courtesy of Dr. Allen Putterman.)

Treatment

The surgical management of MGJWP is still controversial and may not always be satisfactory.[16] There are several reasons

why the literature lacks a definitive management algorithm for MGJWP. The surgeon must deal with two separate problems (blepharoptosis and jaw winking) and not one, and the challenge is that the natural history of one of *(Print pagebreak 258)* these two problems (the jaw wink) is uncertain. The individual variability in the interplay between both phenomena and the relative rarity of the condition overall are additional factors that make standardized care difficult.[16] Management of amblyopia and vertical or horizontal strabismus, in the form of surgery or orthoptic/spectacle correction, should precede management of MGJWP.[1,2,17] In our opinion as well as others',[1] amblyopia should vigorously be addressed before surgery; otherwise, the outcome of ptosis surgery will be underwhelming.

FIGURE 38.3 A and B, Jaw wink synkinesis with smiling.

In patients with minimal or no ptosis, regardless of the degree of a wink, observation may be recommended and surgery is not usually required.[3,20] To abolish the wink in these patients would require extirpation of the levator, which in turn would necessitate a subsequent brow suspension procedure. This might result in greater asymmetry than the original preoperative state.[20] On the other hand, because the jaw wink declines with age, or at least appears to diminish, older patients with good levator function and minimal synkinesis may benefit from external levator resection.[1,2,22,23] However, parents of affected younger children may only be concerned with ptosis and not bothered by a minimally visible preoperative synkinetic movement. They should be warned that a levator resection ptosis procedure performed in children who have not yet consciously learned to conceal the movement may result in a much more obvious jaw wink after the surgery. The levator muscle is strengthened by the procedure, thus potentiating the eyelid excursion, which now initiates at a higher level and increases the amount of scleral show.[16] Therefore, it is not the case that the jaw wink would simply increase with levator resection but that it will be more noticeable as well.[1,22,23]

Few patients fall in the above-mentioned categories requiring only observation or levator resection surgery. The majority present with moderate to severe ptosis, associated with a significant wink. In these patients, bilateral or less commonly unilateral fascia lata sling suspension, combined with bilateral or preferably unilateral (Chicken-Beard) disinsertion of the levator muscle is a common practice.[16,22,23,41,42,43] To abolish the jaw wink, 1 to 2 cm must meticulously be excised from the levator and its aponeurosis.[42] The levator is dissected from the anterior surface of the tarsus and is followed superiorly beyond the Whitnall ligament with care to avoid damage to the superior rectus or the superior oblique muscles. The medial and lateral horns are incised, and the aponeurosis, together with the muscle, is transected.[3,22,23] To avoid reattachment to the tarsus some authors recommend suturing the proximal end of the severed levator to the arcus marginalis, although we find this step unnecessary if meticulous excision of the muscle was undertaken.[3,42]

Unilateral or bilateral brow suspension with autologous fascia lata is then performed in a standard fashion.[3] Whether to perform unilateral or bilateral ptosis surgery has been a contentious issue for decades.[41,42,43,44,45,46] Proponents of bilateral surgery argue that a major issue with unilateral surgery is asymmetry in downgaze,[22,23] but another legitimate concern is that there may be little incentive for the patient to recruit the frontalis muscle because the contralateral normal eyelid can be opened without the need for frontalis action.[44] On the other hand, proponents of unilateral surgery argue that bilateral surgery would convert the normal, dynamically mobile, pathologically free contralateral eyelid into a static, fixed eyelid and would, at least *(Print pagebreak 259)* in theory, impart some risk on the contralateral cornea.[45] Understandably, parents may be reluctant to entertain surgery on the normal eyelid and may accept a less-thanperfect cosmetic outcome on downgaze when surgery is limited to the ptotic lid.[5,42] Another advantage of unilateral surgery is that, if the patient is not satisfied with downgaze asymmetry, the possibility of subsequent contralateral surgery at a later date is always there.[45]

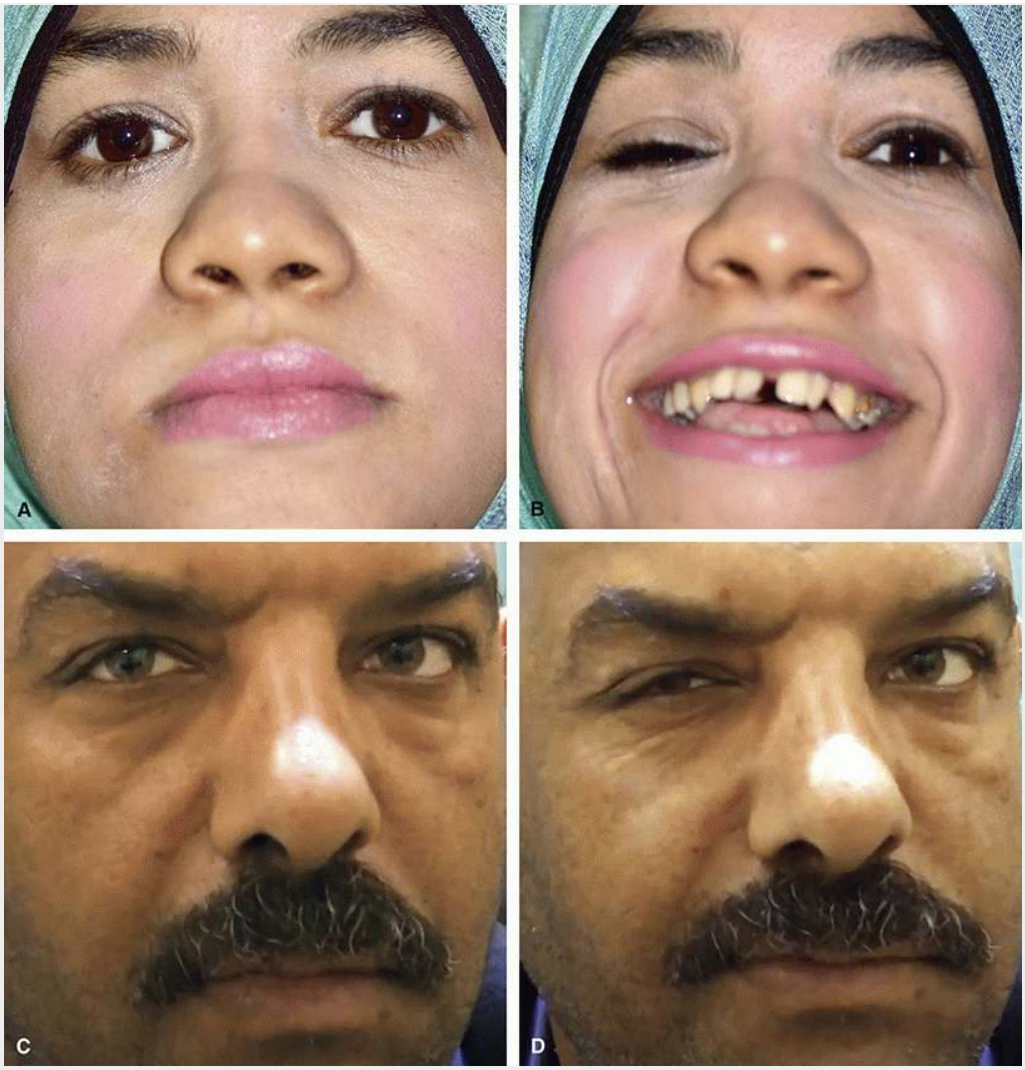

FIGURE 38.4 A, Inverse Marcus Gunn jaw winking with no ptosis at rest. B, The eyelid droops on opening the mouth and MRD-1 is reduced. C, Marin-Amat syndrome 5 years following facial nerve palsy in the right side with no ptosis at rest. D, The eyelid droops on attempted chewing and in contrast to inverse Marcus Gunn both MRD-1 and MRD-2 are reduced.

Prognosis

Patients should be warned that, because the simultaneous performance of levator extirpation and frontalis suspension is more complex than standard ptosis surgery, prolonged postoperative edema may ensue and may manifest as initial undercorrection that usually improves with time.[42] With a long-term recurrence rate of nearly 30%, and a reoperation *(Print pagebreak 260)* rate of up to 20%,[17] ptosis undercorrection that persists beyond the early postoperative period is a serious issue that is seldom reported in the literature in patients with MGJWP.[17,22,23,42] On the other hand, several large series have consistently demonstrated excellent results and failed to observe any undercorrection.[1,2,16]

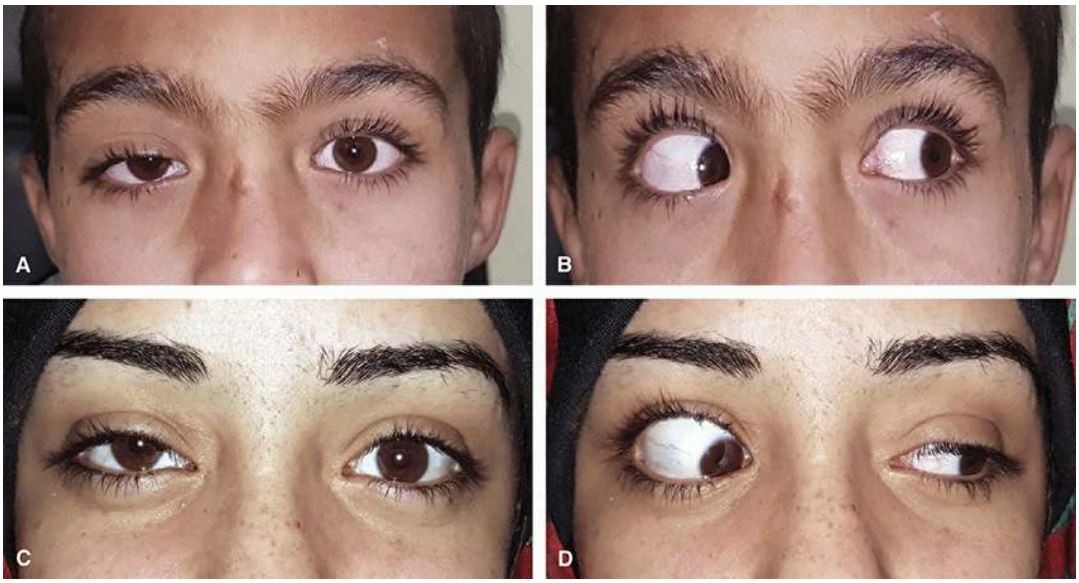

FIGURE 38.5 Rare synkinetic eyelid movements. A and B, Right-sided levator-medial rectus muscle synkinesis. The eyelid retracts and the ptosis disappears on attempted adduction. C and D, Trochlear-oculomotor synkinesis. The eyelid retracts with depression of the eye in adduction.

There are several possible causes for the occasional disappointing result in patients with MGJWP. Five decades ago, Crowell Beard argued that, if the superior rectus muscle is weak, the result of ptosis surgery with any technique will be disappointing.[22,23] As was mentioned earlier, an ipsilateral superior rectus underaction, which may or may not be associated with hypotropia, is not uncommon in patients with Marcus Gunn. A more plausible mechanism for failure is amblyopia that was not properly addressed before ptosis surgery. Another explanation for undercorrections in MGJWP is probably related to an improper examination technique that underestimates the severity of ptosis if the jaw is not completely immobilized, and unilateral levator resection is performed rather than a suspension procedure.[26]

Patients with MGJWP should also understand that it is not possible to completely restore the eyelid function to normal and that bilateral lid lag, or an asymmetrical lid lag in downgaze (if bilateral or unilateral surgery is performed, respectively) may be bothersome cosmetically. Nevertheless, when the proper surgical procedure is performed, the synkinetic movement can be minimized and the ptosis corrected, which is an acceptable compromise to most patients.

Histopathology

Lyness and coworkers examined the distal end of the levator palpebrae superioris muscle from the affected and clinically normal sides of 12 patients with MGJWP undergoing bilateral brow suspension.[47] The average age of the patients was 7 years (range 4-17 years), and there were cadaveric control muscles from a 10-year-old and a 15-year-old child. The levator muscles from both the affected and clinically normal sides of the MGJWP patients had a decreased muscle fiber density (fibers/mm^2) when compared to the normal cadaveric controls, and the decrease in fiber density was greater on the affected than the clinically normal side of the MGJWP patients. Morphometry suggested both atrophy and compensatory hypertrophy of the affected levator muscle fibers in comparison with the clinically normal side. Enzyme histochemistry showed muscle fiber type grouping, typical of neurogenic atrophy, on the affected side of the MGJWP patients. The authors suggested "that the process underlying the Marcus Gunn phenomenon is a neurogenic atrophy with aberrant reinnervation and that it is a bilateral process with one side being severely affected and the clinically normal side being affected to a lesser degree."[47]

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CHAPTER 39

Microblepharon

Key Points

- Microblepharon refers to a vertical shortening of the upper or lower eyelids
- The etiology is unknown, but it has been described as an isolated unilateral finding or in association with ablepharon-macrostomia syndrome, Barber-Say syndrome, and trisomy 21
- Affected individuals show a variable degree of shortened anterior lamella with a well-formed mucocutaneous junction
- In severe cases lagophthalmos results in corneal exposure and may proceed to corneal opacification
- Surgical management is with a full-thickness skin graft or hard-palate graft combined with a lateral tarsal strip procedure
- The prognosis in milder cases is usually excellent, but the cosmetic and visual outcome in more severe cases depends upon the promptness of surgical intervention

Microblepharon is a rare congenital abnormality first described in 1848 by Cornaz.[1] By definition, microblepharon is a term used to denote vertical shortening of the upper and/or lower eyelids.[2,3] Unfortunately, microblepharon is a term that is seldom used in the literature, whereas the more commonly used term ablepharon may be a misnomer.[4,5]

Etiology and Pathogenesis

Microblepharon results from faulty eyelid embryogenesis where the eyelid fold development is disrupted resulting in a number of eyelid anomalies. Anomalies can range from complete absence of the lids to nearly normal but short eyelids.[6] Microblepharon is the mildest form of this faulty development and has been described in association with ablepharon-macrostomia syndrome,[4] Barber-Say syndrome,[7] and trisomy 21 (Down syndrome)[2] or as an isolated unilateral finding.[4]

Clinical Presentation

Microblepharon is characterized by a vertical shortage of upper and lower eyelid skin resulting in various degrees of lagophthalmos, scleral show, and corneal exposure, depending on the severity of the defect (Figures 39.1, 39.2, 39.3). Affected individuals may show a variable degree of shortened anterior lamella with a well-formed mucocutaneous junction at the upper as well as the lower eyelid margins.[3,4] In milder cases (Figure 39.1), the vertical extent of the upper eyelid skin from the eyebrows to the eyelashes is moderately reduced[3] and the diagnosis may be elicited only by asking the child to look down (Figure 39.2), but in more severe cases (Figure 39.3) there is marked anterior lamellar shortening and the upper eyelid margin is very close to the eyebrows with sparse or absent eyelashes.[4,8] Severe cases may suffer from constant lagophthalmos even when asked to voluntarily close the eyelids, whereas milder cases may only suffer from lagophthalmos during sleep but not during voluntary closure.[3,4] Patients with mild to moderate shortening may present later in life with minimal or no exposure symptoms, whereas neonates with severe microblepharon may even be born with corneal exposure, which may proceed very rapidly to corneal opacification.[3,4,9]

Milder degrees of microblepharon are rarely syndromic except in the setting of trisomy 21.[2] More severe cases may exhibit systemic symptoms related to their syndromic association, including in the case of ablepharon-macrostomia syndrome a wide fish-like mouth (macrostomia); microtia; attached ear lobes; hypertelorism with a wide nasal bridge and wide nasal tip; lax or redundant skin; sparse hair; variable abnormalities of the nipples, fingers, and hands (camptodactyly); as well as ambiguous genitalia.[9,10] Alternatively, patients with Barber-Say syndrome may exhibit generalized hypertrichosis, dry lax skin, macrostomia, cup-shaped ears, a bulbous nose, hypoplastic nipples, as well as abnormal genitalia.[8] Both conditions phenotypically overlap, and some authorities believe they represent the same disease.[5,8]

Differential Diagnosis

A controversial issue in the literature is whether ablepharon and microblepharon represent the same disease or whether they are separate entities. Several authors maintain that the term ablepharon should be omitted from medical terminology and that all cases dubbed as “ablepharon” merely represent cases of severe microblepharon and that eyelid remnants are always present with preservation of the mucocutaneous junction.[4,5,11]

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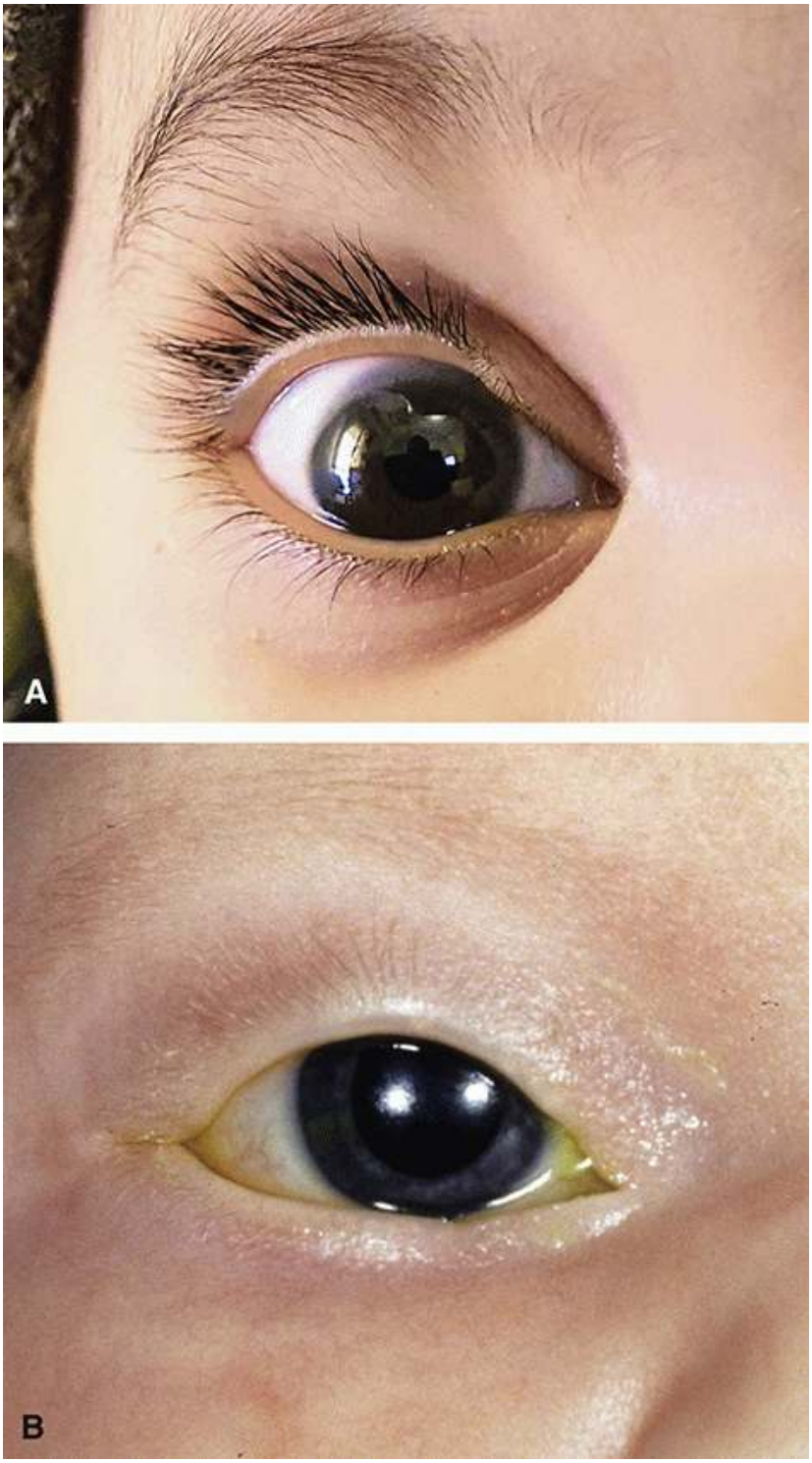

FIGURE 39.1 A, Mild microblepharon of the upper eyelid. B, A mild case of lower eyelid microblepharon.

FIGURE 39.2 In mild cases of microblepharon, the diagnosis may be elicited by asking the child to look down.

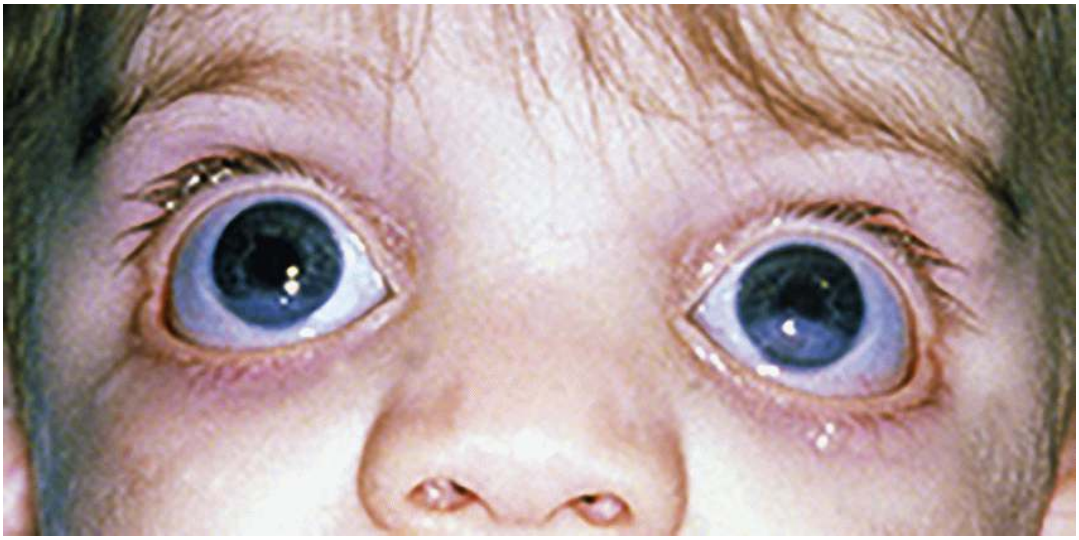

FIGURE 39.3 Severe upper and lower eyelid microblepharon.

Milder cases of microblepharon may be confused with euryblepharon, which is defined as a horizontal enlargement of the palpebral aperture with subsequent eversion of the lateral part of the lower eyelid. Although vertical shortening of the skin is a common association,[12] the defining feature of euryblepharon is an ectropion or eyelid eversion that is circumscribed to the lateral part of the lower eyelid (see Chapter 33).

Treatment

Milder cases may benefit from a full-thickness skin graft or hard-palate graft combined with a lateral tarsal strip procedure, which may be performed at ease except if the cornea is threatened.[3] More severe cases in the setting of ablepharon-macrostomia syndrome require immediate surgical intervention with a full-thickness skin graft.[4]

Prognosis

Although the prognosis in milder cases is usually excellent,[3] the cosmetic and visual outcome in more severe cases depends upon the promptness of the surgeon to proceed immediately with surgery and the choice of the surgical technique.[4]

Histopathology

In microblepahron there are developmental structural defects in eyelid anatomy. We are not aware of any specific eyelid histopathologic descriptions.

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CHAPTER 40

Myokymia

Key Points

- Eyelid myokymia is a form of involuntary muscle twitches localized to small bands of the orbicularis oculi beneath the skin
- Myokymia is a hyperexcitability disorder of the motor unit caused by excessive involuntary myokymic discharges of the facial nerve
- The cause of eyelid myokymia is not clear, and an etiologic cause is rarely found
- Facial and eyelid myokymia may be related to an unstable axon membrane acting as an ectopic generator of discharges associated with lesions in the ipsilateral pontine tegmentum in the vicinity of the facial motor nucleus
- Eyelid myokymia typically presents as unilateral, involuntary, transient, and intermittent twitches in the eyelid skin that give an undulating or rippling wave-like appearance to the overlying skin
- It is typically associated with stress, lack of sleep, fatigue, and excessive caffeine use
- Almost all patients with isolated eyelid myokymia respond to conservative measures including reassurance, rest, and elimination or reduction of possible risk factors
- For cases that persist more than 3 months, antiepileptic drugs or botulinum toxin injections may be tried
- Most cases resolve spontaneously and in the absence of involvement of other facial muscles do not require any further workup

Eyelid myokymia (EM), a term that is derived from the Greek root *kyma* or wave, is clinically defined as a form of involuntary undulating vermicular or wriggling wavelike muscle twitches localized to small bands of the orbicularis oculi beneath the skin.[1,2,3,4,5,6,7,8,9,10,11] EM is also referred to in the literature as eyelid twitches or eyelid tremors, which are less specific terms that can be used to describe both eyelid myokymia and blepharospasm.[4]

Etiology and Pathogenesis

All myokymias whether focal (facial myokymia, FM), or myokymia circumscribed to the eyelid (eyelid myokymia, EM) are hyperexcitability disorders of the motor unit caused by excessive involuntary myokymic discharges of the facial nerve.[11] It is hypothesized that EM is generally considered a *forme fruste* of FM, which in turn is considered a *forme fruste* of neuromyotonia; the difference lies in the frequency of myotonic discharges and the extent and severity of muscle involvement.[3,11,12]

The exact cause of EM is not clear, but the condition is usually considered benign, and an etiologic cause is rarely found. An insight into the etiopathogenesis of EM can be provided by a closer look at the pathogenesis and etiology of its more ominous counterpart, FM, which is a focal form of myokymia circumscribed to the facial nerve. The latter condition is characterized by extensive muscle involvement and involuntary muscle fiber activity in one-half of the face associated with distinctive electromyographic myokymic discharges.[2,11,13] FM is hypothesized to develop due to an unstable axon membrane acting as an ectopic generator of discharges, and it is typically associated with a lesion within or near the ipsilateral pontine tegmentum (dorsal pons) where the motor nucleus of the facial nerve is located.[10] Alternatively, other lesions in the vicinity of the facial motor nucleus (supranuclear, perinuclear, or infranuclear lesions) may also cause facial nerve hyperexcitability.[10,14] The underlying pathophysiology of EM is probably identical, and it may be safe to assume that in EM the underlying pathogenetic mechanism appears to be hyperexcitability of the peripheral motor nerve axons of the facial nerve.[1,2,3] The relatively chronic, localized, nonprogressive nature of EM, which rarely involves other facial muscles, probably corroborates this hypothesis[2]; however, it is not entirely implausible that a more central mechanism causing deafferentation of inhibitory pathways, and ultimately resulting in localized hyperexcitability of the orbicularis

muscle, is responsible for EM.[11]

The list of confirmed causes of EM is short. In chronic cases, It may rarely be indicative of an underlying neurological disease like multiple sclerosis.[3,10] EM has also been described in association with the use of an antiepileptic drug called topiramate, which has a variety of clinical applications including prophylaxis against migraine and binge eating.[15] EM was also reported in patients with leprosy and in patients subjected to an experimental noninvasive brain stimulation technique called anodal transcranial direct current stimulation, which has recently shown promise in the management of chronic pain, depression, and a variety of other conditions.[16,17] A recent systematic review has suggested that high cannabis consumption may lead to myokymia. Although a tetrahydrocannabinol (THC) serum level of more than 1 µg/L was associated with eyelid tremors in 86% of patients in one study, other studies showed different results.[4]

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On the other hand, the list of underlying causes of FM is extensive. The most common causes include multiple sclerosis, pontine glioma, and Guillain-Barré syndrome.[2,3] Other brainstem neoplasms (cerebellar astrocytoma, metastatic tumors, or acoustic neuroma) and infections (tuberculosis and cysticercosis) may also cause FM.[2,3,11,14] Rarer causes of FM may be genetic (hereditary channelopathy caused by a mutation in one of the voltage-gated potassium channel genes, KCNA1, and less commonly KCNQ2), autoimmune (antibodies to voltage-gated potassium channels [VGKCs]), toxic (rattlesnake venom), or drug-induced (flunarizine, clozapine, or gold salts).[12,13,15,18] Autoimmune voltage-gated potassium channelopathies are associated with a wide spectrum of peripheral as well as central hyperexcitability disorders.[12,18,19] To the best of our knowledge, this disorder has not been demonstrated in association with isolated EM,[20] and neither have most of the above-listed causes of FM with the exception of multiple sclerosis.[3,10] Of note is that anti-IgLON5 disease, a recently described neurological disease entity that develops due to an antibody-mediated disruption of IgLON5 (a curious cell adhesion protein of uncertain function), is frequently associated with FM.[21] Anti-IgLON5 disease possesses dual features of autoimmunity and neurodegeneration and manifests clinically with bulbar dysfunction (dysphagia, dysarthria, vocal cord palsy, and/or respiratory difficulties), gait difficulties, and sleep alterations in addition to hyperkinetic movements (myoclonus, myorhythmia, myokymia, etc.).[21]

Although electrophysiologic studies could afford a better localization, characterization, and understanding of neurologic disorders, electromyographic data are lacking in patients with EM.[1] Only two studies exist in the literature,[22,23] and surprisingly, according to these studies, the defect may be more centrally located in the brainstem than was previously thought, and at least in its chronic form, EM may not be as benign as was originally assumed.[22,23]

Clinical Presentation

Conditions associated with facial nerve hyperexcitability can assume a variety of clinical shapes and forms of which EM is the most common and mildest form.[1,2,3] Myokymia limited to the eyelid tends to affect healthy young subjects who typically present complaining of annoying twitches in the eyelid skin. These are experienced by the patient but may or may not be visually observed by others, but if they are visible, they give an undulating or rippling wave-like appearance to the overlying skin.[15] It is typically associated with stress, lack of sleep, fatigue, excessive caffeine use, or examinations, although a temporal relation between the onset of EM and those psychosocial factors is occasionally denied by the pat ient.[2,5,10,23,24] Some patients report that an attack can be initiated by rubbing the eyelids; conversely, others report that an EM attack can be aborted by rubbing the eyelids.[25]

The condition is commonly unilateral, involuntary, transient, and intermittent, more frequently affecting the lower eyelid, and is allegedly more common in fema les.[2,5,10,23,24] The coexistence of EM and droopiness of the eyelid should alert the clinician to the possibility of heavy cannabis use.[4] Myokymia initially presents as episodic twitches that last a few minutes and then disappear over days or weeks,[2,5,10,26] but solitary episodes may rarely last for hours rather than minutes.[2] In rare situations, myokymia becomes chronic and persists for months, yet even in these chronic cases, EM rarely progress to involve other muscles of the face or show a systemic association, and myokymia is still considered benign.[2] In those rare chronic situations, neurologic diseases like multiple sclerosis should be ruled out with neuroimaging.[2,5,9,10]

Differential Diagnosis

EM may clinically overlap with other causes of eyelid tremors or facial nerve hyperexcitability such as (1) blepharospasm (bilateral, spastic, dystonic movements of the orbicularis oculi muscle), (2) FM (continuous undulating movements of facial muscles), (3) hemifacial spasm (unilateral, intermittent, clonic, or tonic synchronous spasmodic contractions of muscles supplied by facial nerve), (4) aberrant regeneration with synkinesis after Bell palsy, (5) psychogenic spasm, or (6) facial tics (rapid stereotyped movements that could also involve muscles not supplied by the facial nerve).[27,28,29] Differentiating EM from these simulating conditions is not usually a challenging task and is simply based upon the pattern and extent of muscle involvement, as well as the triggering factors causing these tremors, and their social implications.[28,29]

Blepharospasm and hemifacial spasm generally occur in the elderly population, may be triggered with voluntary movements, and cause clinically visible involuntary eyelid closure, as well as intense social embarrassment. Of note is that hemifacial spasm often initially involves the orbicularis oculi muscle and gradually spreads to other parts of the face.[28,30] FM can be identified by its more extensive muscle involvement, as the wavelike twitches occur beneath different areas of the skin of the face.[2,3,10,11] Also, in patients where facial myotonia is caused by a pontine mass or multiple sclerosis, FM may be so pronounced that it results in a persistent facial contraction or focal neuromyotonia.[11] Psychogenic spasm is relieved with sleeping and improves with placebo treatment. EM can also be confused with superior oblique myokymia if it causes ocular oscillopsia or pseudonystagmus, which is exceedingly rare.[5,24,26,31] A final note should be made about dystonic blinks. One study which longitudinally followed-up patients who presented with increased blinking as their sole symptom for 5 years suggested that frequent blinking may occasionally be a precursor of blepharospasm.[32] Such condition is termed dystonic blinks (DBs) or eyelid flickering.[33,34] It should be noted, however, that patients with DBs are symptomatic for several years, in contrast to EM patients whose symptoms usually span a period of weeks.

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Treatment

Almost all patients with isolated EM respond to conservative measures including reassurance, rest, and elimination or reduction of possible risk factors.[2,10] If myokymia fails to abate after 3 months of onset, antiepileptic drugs like carbamazepine (800 mg/day) may be prescribed.[10] Alternatively, botulinum toxin injections may be tried, and a single injection may resolve the condition.[1,2] If more than one injection is required, the frequency of injections can often be limited to once or twice yearly.[2] It is difficult to determine whether this single dose of botulinum toxin is indeed curable or whether this unusually successful outcome just happens to coincide with the natural history of this benign, self-limiting condition.[2] In the past, limited myectomy was reportedly beneficial in refractory cases, although its use in current medical practice is questionable.[9]

Prognosis

EM can persist for several weeks to months, but most cases resolve spontaneously, and in the absence of involvement of other facial muscles does not require any further workup. FM is also a transient phenomenon except when it is associated with a pontine glioma or a high VGKC titer where it can persist for years.[18,35]

Histopathology

To our knowledge, there are no descriptions of eyelid histopathological changes in myokymia.

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CHAPTER 41

Telecanthus

Key Points

- Telecanthus is an abnormally wide distance between the medial canthi with a normal interpupillary distance
- It can be congenital, or acquired, or isolated, associated with many syndromes, most commonly blepharophimosis syndrome and Waardenburg syndrome type 1
- Secondary telecanthus is associated with detachment or rupture of the medial canthal tendon following trauma
- In congenital telecanthus the presenting symptom is principally cosmetic, the interpupillary distance is normal, and patients rarely complain of tearing
- In syndromic cases, there may be associated findings such as blepharophimosis, ptosis, epicanthus inversus, hearing impairment, hair albinism, or iris heterochromia
- The treatment of congenital telecanthus is surgical with shortening or tightening of the medial canthal tendons
- Traumatic telecanthus from naso-orbito-ethmoidal fractures usually requires repositioning of bony fragments and reattachment of the medial canthal tendon with transnasal wiring or microplating
- The prognosis is variable, and surgery often leaves some degree of scarring in the medial canthus

Telecanthus is defined as an abnormally wide distance between the medial canthi with a normal interpupillary distance.[1,2,3,4,5,6] The term was coined by Mustardé[2] and is derived from the Greek word *tele* or wide and the Latin word *canthus* or corner of the eye.

Etiology and Pathogenesis

Telecanthus is observed when there is an abnormal insertion or length of the medial canthal tendons and can be congenital or acquired. It can be an isolated finding, but it also occurs in the context of many syndromes, most commonly blepharophimosis syndrome and Waardenburg syndrome type 1. According to the Online Mendelian Inheritance In Man (OMIM) website, 156 additional syndromes may be associated with telecanthus,[7] including the telecanthus-hypospadias syndrome, Down syndrome, fetal alcohol syndrome, Cri du Chat syndrome, Klinefelter syndrome, Turner syndrome, frontonasal dysplasia with alar clefts, Opitz GBBB syndrome, nasopalpebral lipoma-coloboma syndrome, or Jacobsen syndrome.[7]

Primary telecanthus is defined as an increased distance between the inner canthi with a normal outer canthal distance and a normal interpupillary distance; secondary telecanthus, on the other hand, is characterized by an increase in all three parameters and is associated with ocular hypertelorism.[3,6] Hypertelorism (teleorbitism, or *ocular hypertelorism*) is a clinical-radiological term that is used in the literature to describe widely spaced orbits.[8,9]

The medial canthal tendon may also detach or rupture following trauma to the mid-face.[10] This usually occurs owing to disruption of the bony attachment of the medial tendon following naso-orbito-ethmoidal (NOE) fractures types II and III.[10,11,12] Disruption of the anterior limb of the medial canthal tendon alone does not produce telecanthus. For telecanthus to occur, this requires disruption of both the anterior and posterior limbs of the tendon.[10,13] A less frequent cause of traumatic telecanthus is a degloving injury where the skin with the underlying tissue is completely torn off in the medial canthal region. The subsequent shearing forces result in avulsion of the medial canthus. By definition, degloving injuries do not involve trauma to the bone.[10,14]

Clinical Presentation

The normal intercanthal distance usually is less than 20 mm in infants and less than 24 mm in older children, whereas in adults the normal range for intercanthal distance is 25 to 37 mm in women and 26 to 38 mm in men.[13,15] In the absence of strabismus, these values are typically half the interpupillary distance, and values that exceed this parameter are indicative of telecanthus.[15]

In patients with congenital telecanthus, the principal presenting symptom is cosmetic, and despite the unusually long medial canthal tendons, patients rarely complain of tearing. Clinically, the interpupillary distance is normal, but the intercanthal distance is wide (Figure 41.1). As a result, the eyes may appear somewhat esotropic since the amount of visible medial sclera is less than the lateral scleral width (Figure 41.2).

In syndromic cases, there may be associated findings such as blepharophimosis, ptosis, and epicanthus inversus in patients with blepharophimosis syndrome (Figure 41.1),[16] or severe hearing impairment, localized hair albinism (a white forelock of hair or early graying), bright hypochromic blue irides, or iris heterochromia in cases of Waardenburg syndrome type I.[17]

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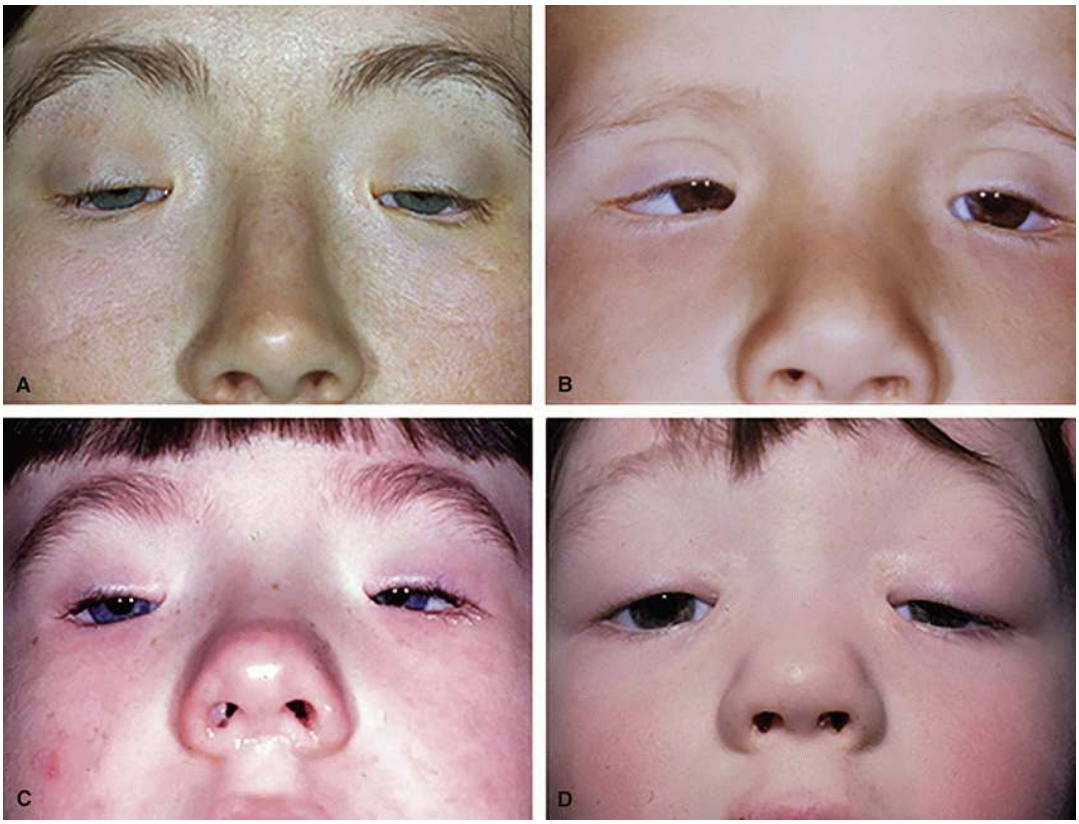

FIGURE 41.1 A-D, Congenital telecanthus associated with blepharophimosis syndrome. D, (Courtesy of Dr. Allen Putterman.)

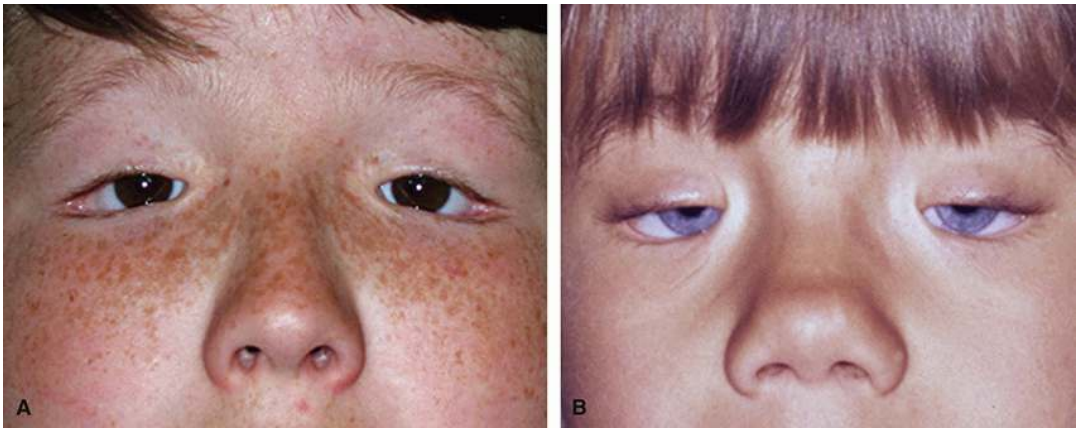

FIGURE 41.2 A and B, Pseudoesotropia due to telecanthus.

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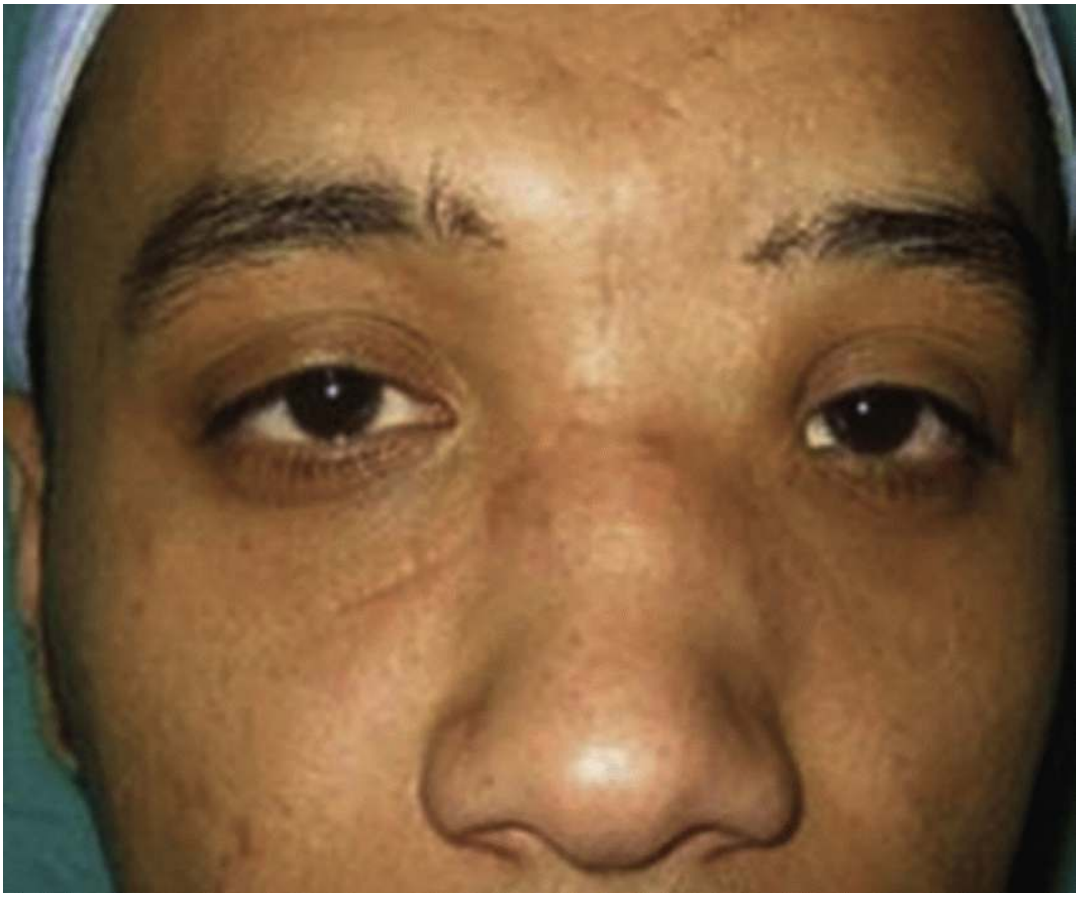

FIGURE 41.3 Traumatic telecanthus. (Reprinted with permission from Elbarbary AS, Ahmed AL. Medial canthopexy of old unrepaired Naso-orbital-ethmoid (NOE) traumatic telecanthus. *J Cranio-Maxillofacial Surg.* 2014; 42:106-112.)

Besides telecanthus, clinical signs typically associated with a naso-orbito-ethmoidal fracture include unilateral or bilateral rounding of the medial canthal angle with obliteration of its natural concavity, depressed and widened nasal bridge, irregular epicanthal fold, shortened horizontal palpebral fissure, obliteration, or posterolateral displacement of the caruncle, and epiphora (Figure 41.3).[13,14] Degloving injuries usually present with a triad of telecanthus, ptosis, and tearing.[14] The characteristic clinical finding in patients with degloving injuries is a vertically oriented wound beginning from the forehead or eyebrow region across the medial canthus and extending downward to the cheek region.[14] In either case, the medial canthal tendon does not merely shift laterally but is usually shifted downward as well (Figure 41.3).[10] A computed tomography (CT) scan is usually required to determine the cause. In both conditions, traumatic telecanthus is associated with damage to the lacrimal drainage system in at least 50% of patients[18] and probably even more.[14] This is an important association since it can lead to acute infections after a fracture or telecanthus repair.

Differential Diagnosis

Nonsyndromic telecanthus presenting as a singular phenomenon is rare, and in such cases, telecanthus must be differentiated from hypertelorism.[1] Hypertelorism is a condition characterized by lateralization of all orbital structures (the two bony orbits are set wide apart), with a secondary increase in both the inner and outer intercanthal distances.[3,4,5,6] There is confusion in the literature from the inappropriate use of the terms telecanthus, hypertelorism, and teleorbitism interchangeably. Although some cases of telecanthus may indeed give the impression of illusory hypertelorism, differentiation can be simply made by measuring the interpupillary distance; however, since an accurate definition of hypertelorism is based on bony landmarks, a CT scan is preferable to prove that bony teleorbitism truly exists.[3,8,9]

Dystopia canthorum lateroversa is another confusing term that is probably synonymous with the term telecanthus, although they are occasionally described as separate entities with the term dystopia canthorum vaguely described as lateral displacement of the inner canthi combined with lateral displacement of the lacrimal puncti.[5] The term is probably archaic[19] and predates the era before Mustadé coined the term telecanthus.[2] However, it is still used in the literature to describe telecanthus occurring in the setting of Waardenburg syndrome types I and III.[17,20]

Treatment

The treatment is essentially surgical through shortening or tightening of the medial canthal tendons while keeping the eyelid curvature conforming to the eyeball.[21] In milder cases medial canthal tendon plication alone may be effective. This is done with a 4-0 Polyglactin suture on a P2 needle to fold or compress the tendon.[21] More severe cases require transnasal wiring. A CT scan usually is required before performing this procedure to determine the level of the cribriform plate and to safeguard against intracranial penetration by the wire.[21] Positioning of the wire posterior to the lacrimal sac is essential to avoid injury to the lacrimal drainage system. Placement of the transnasal wire anterior to the lacrimal system would result in canthal angle dystopia and displacement of the eyelids away from the globe. Prophylactic intubation should be undertaken if there is concern about a potential injury to the lacrimal system.[21] Medialization of the canthal tendon could also be achieved via securing the tendon to the medial orbital wall with a titanium mini or microplate that is bent to conform to the contour of the medial wall.[22,23,24]

Since most of the above-mentioned procedures lead to the creation of new epicanthal skin folds, or accentuation of existing ones, transposition flaps should be undertaken simultaneously during telecanthus repair regardless of whether telecanthus is an isolated finding or repair is being carried out in the setting of blepharophimosis syndrome. In isolated cases, a simple Y-V flap design usually suffices.[22]

Traumatic telecanthus in the setting of naso-orbitoethmoidal fractures is usually complicated because the bone is severely fragmented and must simultaneously be rigidly and meticulously fixated.[10] Reattachment of the medial canthal tendon can be achieved with transnasal wiring or unilateral mini or microplating with a monofilament suture canthopexy passed through a hole in the microplate.[11] Although such unilateral techniques originally were designed to simplify the complicated transnasal wiring procedure, they require stable bone to fix the plate firmly, which may be difficult to find if a concomitant dacryocystorhinostomy is planned.[24] Strategic placement of the microplate posterior to the lacrimal fossa, and in a slightly cephalad direction, is also paramount.[10,11]

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Any attendant lacrimal system trauma should be addressed before or concomitant with telecanthus/fracture repair to reduce the postoperative bacterial load,[18,25] because, as mentioned earlier, ignoring lacrimal system problems could lead to acute infections after transnasal wiring or hardware placement for fracture repair. Performing lacrimal surgery later, with the hardware in place, is a challenging situation for the oculoplastic surgeon and may on occasion require removing the hardware if it interferes with the dacryocystorhinostomy. Conversely, performing lacrimal surgery in patients with mild traumatic telecanthus may provide a unique situation. Direct posterosuperior suture fixation of medial canthal tendon remnants to the periorbita near the region of the posterior lacrimal crest, coupled with redistribution of the superficial tissues to redirect the medial canthus upward, may obviate the need for more involved procedures. However, this soft-tissue approach lacks the rigidity of firm wire or plate anchoring.[24]

Prognosis

The optimal protocol for telecanthus repair is controversial. Simpler procedures are fraught with undercorrections usually producing suboptimal results. On the other hand, those procedures that do work are more involved techniques that require a learning curve and may carry a real risk of damage to the ocular and periocular structures.[22,26] Both approaches may produce unsightly scars, but these tend to fade with time. Traumatic telecanthus, in particular, is best treated early because the soft tissue and bony deformities that result from unrepaired naso-orbital ethmoid fractures are notoriously difficult to correct later.[10]

Histopathology

There are no histopathology descriptions for primary telecanthus, to our knowledge.

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CHAPTER 42

Trichiasis

Key Points

- Trichiasis is a disorder in which the eyelashes are misdirected toward the ocular surface, without an associated in-turning of the eyelid margin
- Trichiasis is an acquired condition caused by inflammatory or traumatic processes involving the eyelid margin
- Etiologies include trachoma, leprosy, measles, herpes zoster, chronic blepharitis, eczema, atopic diseases, Stevens-Johnson syndrome, ocular pemphigoid, and chemical or thermal burns and eyelid margin scars related to trauma or surgery
- Patients may present with ocular irritation, photophobia, tearing, pain, secondary blepharospasm, or conjunctival congestion with discharge
- Temporary relief measures include lubricants, or contact lens wear
- Optimal treatment is destruction of the cilia follicles responsible for the aberrant eyelash growth, with electrolysis, cryotherapy, or laser ablation
- Multiple recurrences may require more extensive surgery such as lid margin splitting with the excision of the entire lash-bearing area

Trichiasis is defined as a lid margin disorder in which the eyelashes are misdirected toward the ocular surface, without an associated in-turning of the eyelid margin, and is a major cause of ocular morbidity.[1,2,3,4]

Etiology and Pathogenesis

Trichiasis is essentially an acquired condition of a cicatricial nature,[4] and any inflammatory process involving the eyelid margin can deform the eyelashes.[4] The list of etiologies is extensive and includes infectious causes like trachoma, leprosy, measles, or herpes zoster; chronic inflammation of the eyelid margin including blepharitis or meibomianitis; skin diseases including actinic elastosis, eczema, or atopic diseases; diseases that involve the conjunctiva like Stevens-Johnson syndrome, ocular pemphigoid, or vernal keratoconjunctivitis; and chemical or physical burn injuries to the eyelid margin or eyelid margin scars related to trauma or surgery.[3,5,6,7,8,9,10] All these conditions fundamentally share a common final endpoint, which is inflammation and scarring of the eyelash follicles.[3]

Clinical Presentation

In general, trichiasis is rarely seen before the 3rd decade,[3] may be unilateral or bilateral, and could affect the central or the lateral portions of the upper or lower eyelids. In patients with trachoma, trichiasis is more frequent in women and predominantly involves the upper eyelids.[3,5,6,7] Trichiasis is frequently classified according to severity. Minor trichiasis involves the aberrant orientation of five or fewer eyelashes in any one eyelid (Figure 42.1), and major trichiasis involves six or more eyelashes (Figures 42.2 and 42.3).[5,7,11] Patients usually present with symptoms of ocular irritation including photophobia, tearing, dryness, burning pain, blepharospasm, or conjunctival congestion with discharge.[3] Diagnosis of trichiasis is easy and should not be hard to miss. However, it is important to exclude associated conditions that may alter the treatment strategy, including eyelid margin malpositions (entropion), symblepharon formation, or tarsal conjunctival scarring (trachoma).[3] All misdirected eyelashes should be mapped in the patient's chart, preferably with photographic documentation or a hand-drawn illustration.[3] Up to 70% of patients epilate their lashes[2]; therefore, they should specifically be asked about any recent episode of self-epilation. Clinically, evidence of epilation is recognized by the presence of broken or newly growing lashes, which are usually short and sharp, with or without areas of absent

lashes.[2]

Differential Diagnosis

The major confusion concerning trichiasis may be nomenclatorial.[3] The terms trichiasis, metaplastic lashes, or distichiasis are frequently used interchangeably. Distichiasis is specifically defined as an abnormal growth of one or several accessory rows of lashes behind the normal one and arising from the orifices of the meibomian glands (see Chapter 30). Eyelash metaplasia is a more general term loosely defined as any lash originating from a follicle that is in an abnormal location, and the term is more frequently used in reference to abnormally located eyelashes in trachoma.[7] Dystrichiasis is an archaic term that is still confusingly used in the literature, albeit infrequently,[12] and is an all-encompassing term that includes under its umbrella misdirected lashes of both varieties, the trichiatic and the aberrant ones.

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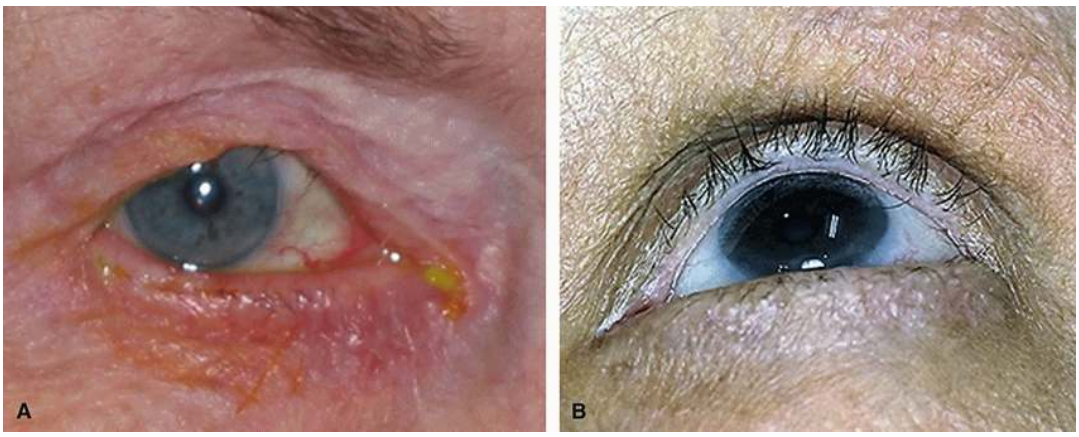

FIGURE 42.1 A and B, Minor trichiasis with fewer than six eyelashes touching the globe.

Treatment

Although centrally located lashes may impose more direct corneal damage,[7] all trichiatic lashes require prompt management, whether located centrally or in the peripheral regions of the eyelid because the eye is not a static structure. The treatment of true trichiasis without associated entropion is usually surgical with minor eyelash ablating procedures.[3] Temporary relief measures including lubricants, contact lens wear or manual epilation may have a limited role (Figure 42.4A). However, they may be of benefit in acute conditions or in autoimmune diseases such as ocular cicatricial pemphigoid, where systemic control of the disease may be preferable before eyelid surgery, or in rural areas with endemic trachoma, where access to surgical care facilities is not available.[2,3,13] As was mentioned earlier, patients with trichiasis often pull out their eyelashes,[2,7] and if a recent episode of epilation has taken place, surgery should be postponed at least temporarily, and the patient is instructed not to re-epilate the lashes until the next scheduled visit.

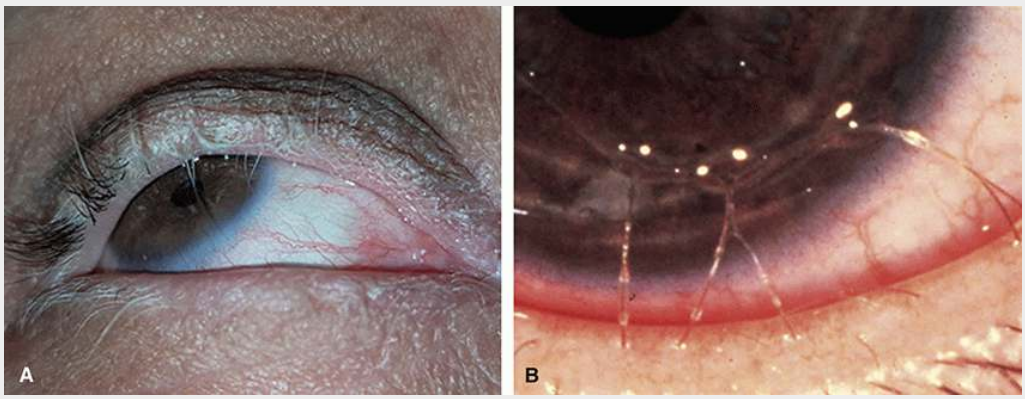

FIGURE 42.2 A and B, Minimal major trichiasis with six or more aberrant eyelashes. A, Six poliotic eyelashes on the upper eyelid contacting the cornea. The posterior eyelid margin is sharp and there is no entropion. B, Seven trichiatic eyelashes along the central lower eyelid.

Whether epilation is an effective measure in preventing corneal blindness or not is controversial as some studies have reported a favorable outcome, whereas other studies warn against it.[3,7] Classical teaching in trachoma-endemic regions maintains that patients should be informed that epilation is only a temporizing measure, and may even potentially be harmful, because in the ensuing weeks when the lashes are regrowing, they are usually short and sharp, and could, at least in theory, produce more damage before they have fully restored their original length. However, a recent study that was conducted in the Amhara province in Ethiopia challenged the modus operandi among ophthalmologists in those regions who consider epilation harmful.[14] Surprisingly, this study found that at 6 months postepilation, *(Print pagebreak 274)* trichiatic eyelashes were thinner, weaker, and nearly half the length of pre-epilation trichiatic lashes. Furthermore, the number of postepilation trichiatic eyelashes was significantly reduced by more than half at the last follow-up.[14] Therefore, frequent epilation may be recommended as a temporizing measure to control, or at least reduce, the burden of trichiasis in remote regions of the world where access to surgical facilities is difficult.[14]

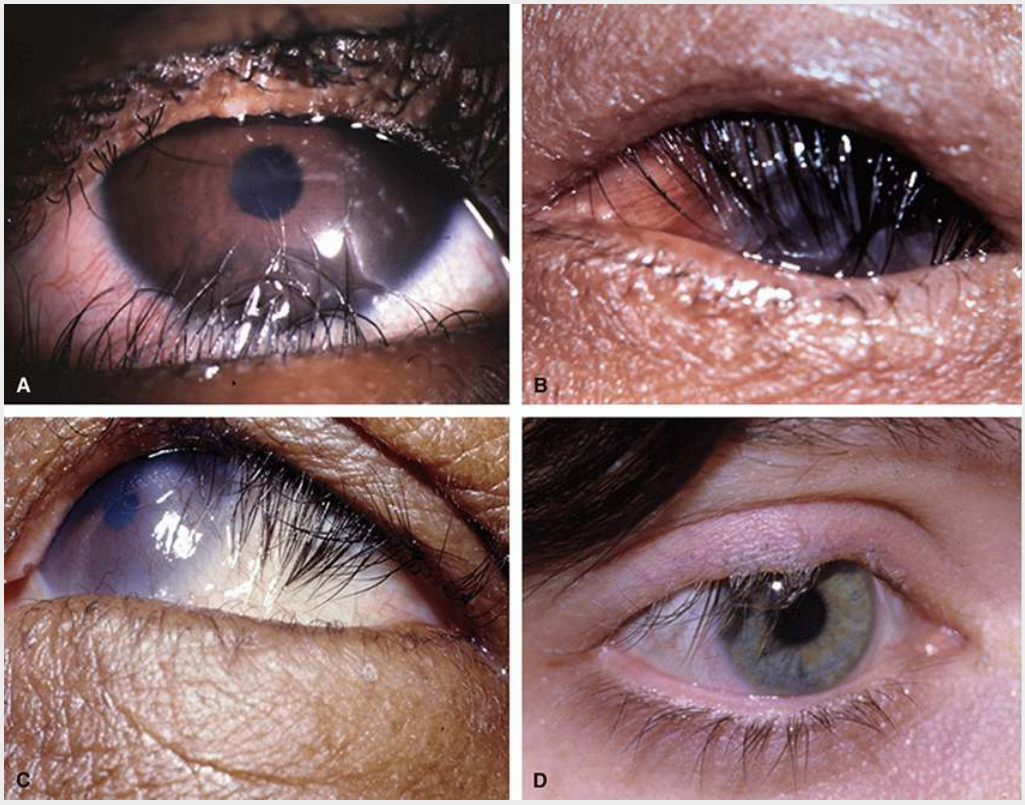

FIGURE 42.3 Major trichiasis with numerous aberrant eyelashes contacting the corneal surface. A, Lower eyelid trichiasis with Stevens-Johnson syndrome. B-D, Trichiasis from conjunctival scarring in a case of trachoma.

The optimal treatment for trichiasis is the destruction of the cilia follicles responsible for the aberrant eyelash growth, either with electrolysis, cryotherapy, or Argon laser.[3,13] Electrolysis or electroepilation with cautery or with a radiofrequency device is the gold standard for the management of minor trichiasis (Figure 42.4B).[3,5] The procedure preferably is performed under the operating microscope after the eyelid is anesthetized with local infiltration.[3] The radiofrequency unit is set to coagulation mode, and the electrolysis tip is inserted parallel to the eyelash shaft 3 to 4 mm down to the bulb. Minimal current is applied for 1 to 2 seconds until bubbling or frothing is seen at the base of the eyelash. The current is raised gradually if the initial setting fails to destroy the follicle. The use of the microscope allows the operating surgeon to trace the faint course of the trichiatic lash just beneath the eyelid margin for strategic placement of the electrolysis tip. When the eyelash follicle is destroyed successfully, the aberrant lash usually extrudes spontaneously while the electrolysis tip is being withdrawn from the eyelid margin. Alternatively, if it does not extrude spontaneously, it can be plucked provided that absolutely no effort is exerted or any force is applied while the lash is being removed.[3] If any tension is felt during attempted removal, the current should be reapplied.[15]

Hair follicles are more sensitive to the destructive effects of freezing than the conjunctiva or the skin, and therefore an alternative viable option is cryotherapy (Figure 42.4C). This may be the method of choice for segmental or diffuse trichiasis (major trichiasis).[3] The procedure should be performed under local anesthesia and the operating microscope *(Print pagebreak 275)* may not be required. The affected portion of the eyelid is frozen for 20 to 30 seconds in a double freeze-thaw method technique.[3] If more than one region of the eyelid is involved, applications are repeated along the affected portions of the eyelid.[1,3] The Argon laser spectral frequencies of 488 nm (green) and 514 nm (blue) are absorbed by melanin, and the output

energy, which is transformed into heat, can be used to destroy eyelash follicles (Figure 42.4D). However, the success rate is generally inferior to electroepilation or cryotherapy.[7]

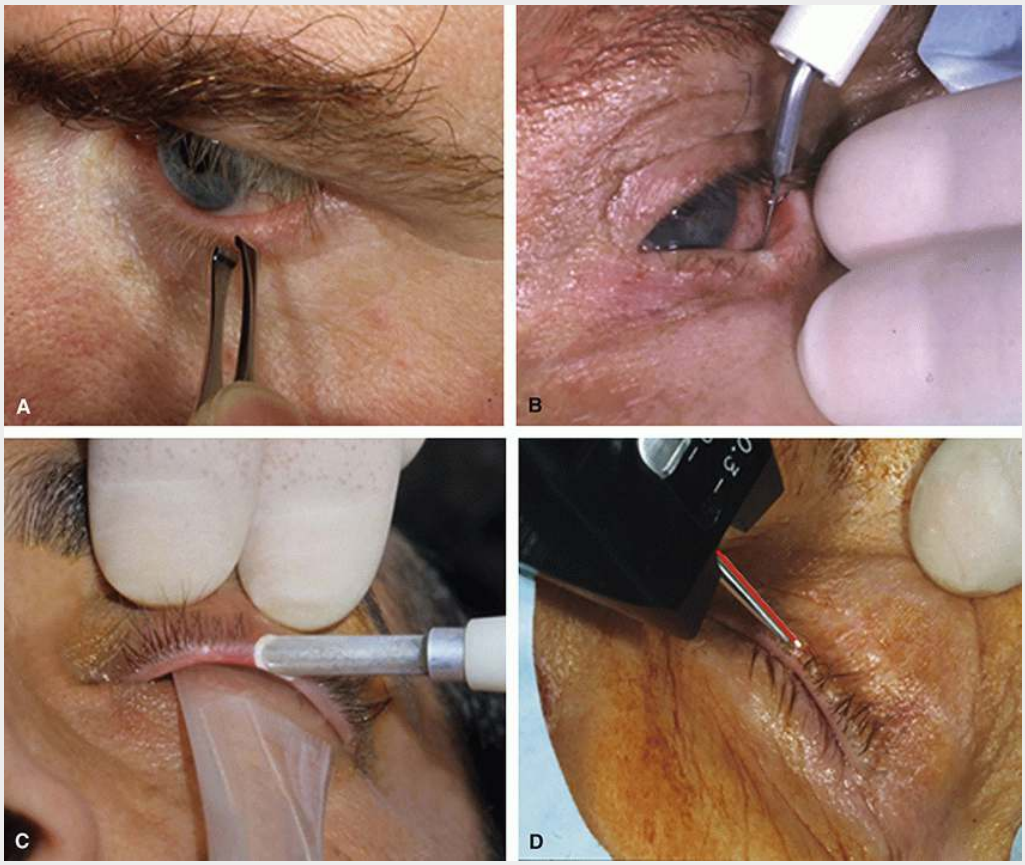

FIGURE 42.4 Management of trichiasis. A, Manual epilation. B, Electroepilation. C, Cryosurgery. D, Laser ablation.

Eyelid surgery may be indicated in patients with diffuse trichiasis, in patients with segmental trichiasis where a large number of trichiatic lashes are encountered, or after multiple recurrences following eyelash ablating procedures.[3] Surgery is also indicated in rural areas with endemic trachoma where the World Health Organization recommends formal tarsal rotation surgery and not focal therapy for individual eyelashes in all patients irrespective of the number of trichiatic lashes.[2] Proponents of this approach argue that patients living in remote rural areas may only rarely have the opportunity to receive proper medical care again if a less invasive policy is adopted and surgery is deferred until the development of more severe disease. Not all authorities agree on this strategy, arguing that asymptomatic patients may voluntarily choose to defer treatment if the only available option is surgery.[2,7] Several surgical procedures have been described specifically for trichiasis to permanently redirect trichiatic eyelashes away from the globe.[5] The most common procedure, which has enjoyed popularity in the past century, was the Van Millingen procedure described in 1887. This involves splitting the eyelid margin at the gray line and interposing a mucous membrane or hard palate graft in between, but the overall success rate is low.[5,16] A more recent procedure, which may be recommended as an end of the line approach after multiple recurrences, also involves a lid margin split *(Print pagebreak 276)* combined with the excision of the entire lash-bearing area[17] or advancement of the anterior lamella (Figure 42.5A). Direct excision or ablation of the trichiatic eyelash bulbs can also be performed through an eyelid crease incision with excellent results (Figure 42.5B).[18]

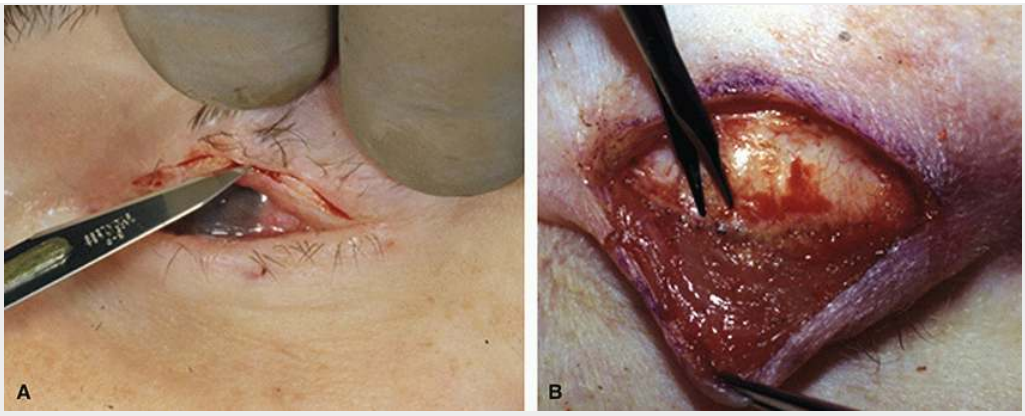

FIGURE 42.5 A, Lid splitting procedure with advancement of the anterior lamella. B, Direct internal eyelash bulb resection.

Prognosis

In mild cases with only a few aberrant lashes, periodic epilation may be sufficient to keep the patient comfortable and protect the cornea. With more extensive trichiasis, destruction of the cilia is usually necessary, but recurrences are common and multiple repeat treatments may be required.

Histopathology

The eyelid histopathological changes in trichiasis reflect the disease causing the eyelid scarring.

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CHAPTER 43

Trichomegaly

Key Points

- Trichomegaly is an abnormal increase in the length, thickness, or pigmentation of the eyelashes but not in their number
- The causes of trichomegaly are extensive and may be congenital, acquired, or drug induced
- Congenital trichomegaly may be isolated or associated with systemic syndromes
- Acquired ocular conditions associated with trichomegaly include nonspecific uveitis, Behçet disease, vernal keratoconjunctivitis, and enucleation or evisceration surgery
- Systemic conditions associated with trichomegaly include atopic dermatitis/allergic disease, HIV infection, alopecia areata, cancer metastasis, dermatomyositis, systemic lupus erythematosus, porphyria, malnutrition, anorexia nervosa, hypothyroidism, and pregnancy
- Eyelashes are unusually long, dense, crowded, and hyperpigmented
- Initial management should include evaluation of a relevant history of drug intake and a search for an underlying systemic disease
- Treatment can be by shortening or trimming of the offending eyelashes or by permanent hair removal using electrolysis, cryotherapy, or laser modalities
- Eyelash trichomegaly can socially be embarrassing, but if an underlying cause is identified, the condition may be reversible

Trichomegaly is defined as an abnormal increase in the length, thickness, or pigmentation of the eyelashes but not in their number.[1,2,3,4,5,6,7,8,9,10] Although it was first reported by Reiter in 1926 who attributed the condition to a hyperfunctioning adrenal gland,[5] it was Gray who coined the term trichomegaly in 1944 in a patient with lymphoma and likened the condition to "*movie lashes*" because long eyelashes were portrayed in Hollywood back then as a desirable aesthetic feature.[6]

The terms trichomegaly and hypertrichosis are frequently used interchangeably in the literature; however, they are not synonymous. Hypertrichosis is strictly defined as excessive hair growth anywhere in the body, where there is an actual increase in the number and not just the length of terminal or vellus hairs. In contrast, trichomegaly is a medical term used exclusively in the periocular region, where the number of hair follicles is normal but the length of the lashes is increased.[11] The term eyebrow trichomegaly is also used albeit infrequently when overgrowth of eyebrow hairs is observed.[7,8,12]

Etiology and Pathogenesis

In contrast to hair growth elsewhere in the body, very little is known about the biology of growth of the eyelashes, and knowledge in this field is still rudimentary. As a result, there are conflicting data in the literature about basic physiologic processes like the length of each phase of the eyelash growth cycle.[13,14] Confusion also exists about the exact number of eyelashes in each eyelid.[14,15] A brief overview of the physiology of eyelash growth may help shed some light on the underlying causes of hair follicle abnormalities.

Although the eyelid skin is the thinnest in the body, eyelashes are the thickest hairs in the body with the widest recorded diameter.[15,16] This is probably significant from an evolutionary point of view because eyelashes subserve an important protective function preventing debris from entering the eye.[17] The absolute number of eyelashes may vary according to the hair growth cycle but overall, the eyelashes are more or less constant in number from birth, and retain their pigmentation throughout life, therefore eyelashes are classified as terminal hairs (thick, coarse, pigmented hairs) and not vellus hairs (the fine short, nonpigmented hairs, which are observed elsewhere in the face before puberty).[11,18] There are approximately 75 to 150 eyelashes in each upper eyelid

arranged in multiple rows, whereas the eyelashes in the lower eyelid are lesser in number (75-80), arranged in fewer rows, and shorter in length than those in the upper eyelids (6-8 mm vs 8-12 mm).[9,12,15,17] Eyelashes are typically darker than eyebrow hairs and are resistant to graying.[9]

The human hair growth cycle is divided into three or four phases, anagen, telogen, catagen, and possibly the exogen phase.[17] The eyelash anagen phase (growth phase), which is a phase of rapid cellular growth and proliferation, is approximately 1 to 2 months long (25-70 days) wherein the eyelashes grow at a rate of 0.12 to 0.15 mm/day.[13,14,15] This contrasts with the arrested development during the apoptosis-driven catagen phase (involutional or transition phase) of eyelash growth, which takes about 15 days, during which keratinocytes (epithelial elements of the follicle) undergo apoptosis.[15] The telogen phase (resting or dormant phase) is the phase where no significant changes are observed, and is estimated *(Print pagebreak 278)* to last between 3 and 8 months (100-270 days).[15] Whether the exogen phase, where eyelash fallout or shedding is observed, is a separate phase or a part of the anagen or catagen phase is unknown.[13,19]

The total duration of the eyelash growth cycle is controversial in the literature as it reportedly varies between 3 and 12 months, but the average is around 5 to 7 months.[3,9,15,17,20] The cycle is asynchronous meaning that at any one moment in time, individual eyelashes are at different phases of the growth cycle.[17,20] Approximately 41% to 50% of upper eyelid lashes are in the anagen phase at all times, which contrasts with the denser scalp hairs where 85% to 90% of hair follicles are in the anagen phase at any point in time.[3] The anagen-totelogen ratio in the lower eyelids is even lower (14%).[14,15] It is the length of the anagen phase that determines the length of the eyelashes. Any process that leads to prolongation of the anagen phase will eventually result in trichomegaly.[15,18] A clear mechanistic distinction should be made here between trichomegaly and hypertrichosis, because as was mentioned earlier, the term hypertrichosis may also be associated with an actual increase in hair follicle density or number. This may result from a decrease in hair shedding because of a relative decline in the percentage of follicles in the telogen phase compared with the anagen phase. Therefore, in hypertrichosis, both mechanisms may be at play (prolongation of the anagen phase and an increase in the anagen-telogen ratio).[18] Vellus to terminal hair follicle differentiation is another mechanism that is used to explain hypertrichosis elsewhere in the body but may not play a significant pathogenetic role in the eyelids where lanugo/vellus hairs are absent except on the anterior surface of the eyelid skin and in the caruncle.[13,18,21,22]

The trigger factors that initiate the above-mentioned underlying etiopathogenetic mechanisms remain obscure. Although several hormones and chemical mediators are known to be involved in the body hair growth cycle including androgens, growth hormone, insulin, glucocorticoids, and prolactin, these growth factors are region specific, and as far as is known, there is no concrete evidence to support a similar role of any of the above hormones in the eyelids.[18,23,24]

The list of conditions causing trichomegaly is extensive and may be congenital, acquired, or drug-induced. Congenital trichomegaly may be isolated or associated with systemic syndromes. Isolated (also called familial or benign trichomegaly) is transmitted in an autosomal recessive fashion due to a homozygous mutation in the FGF5 gene.[25] Another congenital condition (hypertrichosis lanuginosa, werewolf syndrome), which is transmitted in an autosomal dominant or X-linked dominant fashion, is associated with generalized hypertrichosis throughout the body including hair follicle growth that covers the entire anterior surface of the upper and lower eyelids, eyelashes, and eyebrow hairs and results from a genetic defect that results in the persistence of fine lanugo hairs after birth.[11,18]

Trichomegaly is a constant feature of Cornelia de Lange syndrome or Brachmann-de Lange syndrome[26] and Oliver-McFarlane syndrome.[27] Other inconstant syndromic associations where trichomegaly may be observed but may not be a key feature of the syndrome include conerod dystrophy, tetralogy of Fallot, Macinnes syndrome, Hermansky-Pudlak syndrome, Aghaei-Dastgheib syndrome, Laurence-Moon syndrome, phylloid hypomelanosis, and congenital heart disease.[3,10,28,29,30,31,32] Of note is that more than 100 syndromes are associated with hypertrichosis all over the body, any of which, at least theoretically, may also show trichomegaly as an associated finding.[10,18]

Acquired ocular conditions associated with trichomegaly include nonspecific uveitis, Behçet disease, vernal keratoconjunctivitis, and enucleation or evisceration surgery.[15,23] The causal association between uveitis and trichomegaly is not clear, yet several molecular mediators of inflammation, which have been observed to contribute to uveitis, also have been demonstrated to significantly accelerate or prolong the anagen phase. These substances include substance P, tumor necrosis factor-alpha (TNF-α), insulin-like growth factor-13 (IGF-13), basic fibroblast growth factor (b-FGF), and transforming growth factor-beta 13 (TGF-β13).[23] The mechanism appears to be immune mediated as evidenced by the fact that trichomegaly is observed bilaterally in patients with unilateral uveitis.[23] Also, this association is more commonly observed in younger patients with uveitis where the immune response is usually more powerful.[23]

Trichomegaly following enucleation or evisceration surgery is probably attributed to repeated mechanical friction or trauma related to prosthetic wear.[33] A recent study demonstrated that following full-thickness wedge resection, the total number of eyelashes returns to normal in comparison with the contralateral unoperated eyelid.[15] This relative trichomegaly is theorized to be a compensatory mechanism that is probably attributed to a rebound increase in the baseline anagen/telogen ratio.[15]

Systemic conditions associated with trichomegaly include atopic dermatitis/allergic disease, HIV infection, alopecia areata, cancer metastasis (metastatic renal adenocarcinoma), dermatomyositis, systemic lupus erythematosus, porphyria, malnutrition, anorexia nervosa, hypothyroidism, and pregnancy.[3,4,9,23,34,35,36] The cause of long eyelashes in atopic dermatitis is unknown, but it is speculated that frequent rubbing of the eyes might be the contributing factor, as the itch-scratch cycle can result in repetitive inflammation or microtrauma, which may cause mast cell-mediated hypertrichosis.[34] Mast cells are abundant in the conjunctiva in patients with local or systemic allergy and are considered the switchboards for hair follicle remodeling in patients with atopic dermatitis.[34] These mast cells transform hair follicles from the resting telogen phase to the anagen phase.[34] An alternative mechanism is that mast cells secrete prostaglandins indirectly stimulating the growth of the eyelashes.[34] The etiopathogenic mechanism of eyelash trichomegaly in HIV infection is also unknown, but several theories have been proposed including the stimulation of keratinocyte and pilosebaceous unit growth due to high viral activity, immunological dysregulation, as a paraneoplastic feature, or due to caloric-protein malnutrition that appears *(Print pagebreak 279)* in advanced stages of HIV infection. But the most plausible mechanism is intense viral replication because trichomegaly is more commonly observed in end-stage disease where viral activity is high.[35] Recent studies have failed to demonstrate a relationship between HIV status and the length of lashes; however, this may simply be attributed to the improvements in the medical treatment of the condition.[3]

Trichomegaly may also develop as a nonintended adverse reaction to topical or systemic drugs.[3] The list of drugs causing trichomegaly is extensive, but the quintessential example is topical prostaglandin F2α analogs (latanoprost, bimatoprost) used for the treatment of glaucoma. Other causes of drug-induced lash trichomegaly and hypertrichosis include epidermal growth factor receptor inhibitors (erlotinib, cetuximab, gefitinib, and panitumumab), which are used in the treatment of a variety of tumors, including bladder, colorectal, head and neck, breast, and lung or ovarian cancers.[3] Other drugs include cycloserine, cyclosporine A, diazoxide, interferon-alpha/ribavirin, isopropyl unoprostone, methoxsalen, trioxsalen, minoxidil, penicillamine, phenytoin, psoralens, corticosteroids, streptomycin, tacrolimus, thiacetazone, or zidovudine.[3,4,9,23,37,38]

The exact mechanism by which prostaglandin analogs induce trichomegaly or hypertrichosis is unknown, but it is hypothesized that the stimulatory effect of these agents on the hair growth cycle is attributed to stimulation of prostaglandin receptors in the dermal papillae, which in turn would result in the prolongation of the anagen phase, recruitment of telogen phase hair follicles into the anagen phase, and promotion of vellus to terminal hair transformation.[16,39,40]

Clinical Presentation

The main presenting complaint of patients with trichomegaly is usually cosmetic,[41] and not infrequently, it may be an accidental finding during routine ophthalmological examination.[3] Alternatively, patients wearing eyeglasses may complain that the eyelashes frequently brush against the lenses of their glasses, which may require frequent daily lens cleaning.[42] To establish a diagnosis of trichomegaly, eyelashes should measure 12 mm in length or more (Figure 43.1).[3,9,35,42] Although this is an arbitrary number, it is universally adopted in the literature even in the pediatric population.[34] Although lower values (10.5 mm) have been occasionally described in the literature,[41] a cutoff number upward of 12 mm is more logical because as was mentioned earlier, the normal values of upper eyelash length range between 8 to 12 mm.[13] Likewise, a value more than 8 mm would be required for a diagnosis of lower eyelid trichomegaly, even though a cutoff point for lower eyelid trichomegaly is not mentioned explicitly in the literature.

In trichomegaly eyelashes are long, dense, crowded, and hyperpigmented (Figure 43.2),[3] and usually bilateral and symmetrical in distribution even in patients with uniocular uveitis.[23] Although the disease usually involves both the upper and lower eyelids, the upper eyelashes are significantly longer in comparison with the lower.[23] The condition may lead to corneal abrasions if the lashes are abnormally curly, and if the eyelashes become unusually thick and bushy. Trichomegaly may result in lash ptosis, which may interfere with vision, as well as the proper instillation of eye drops, and in extreme scenarios, may even result in mechanical ptosis.[3,43]

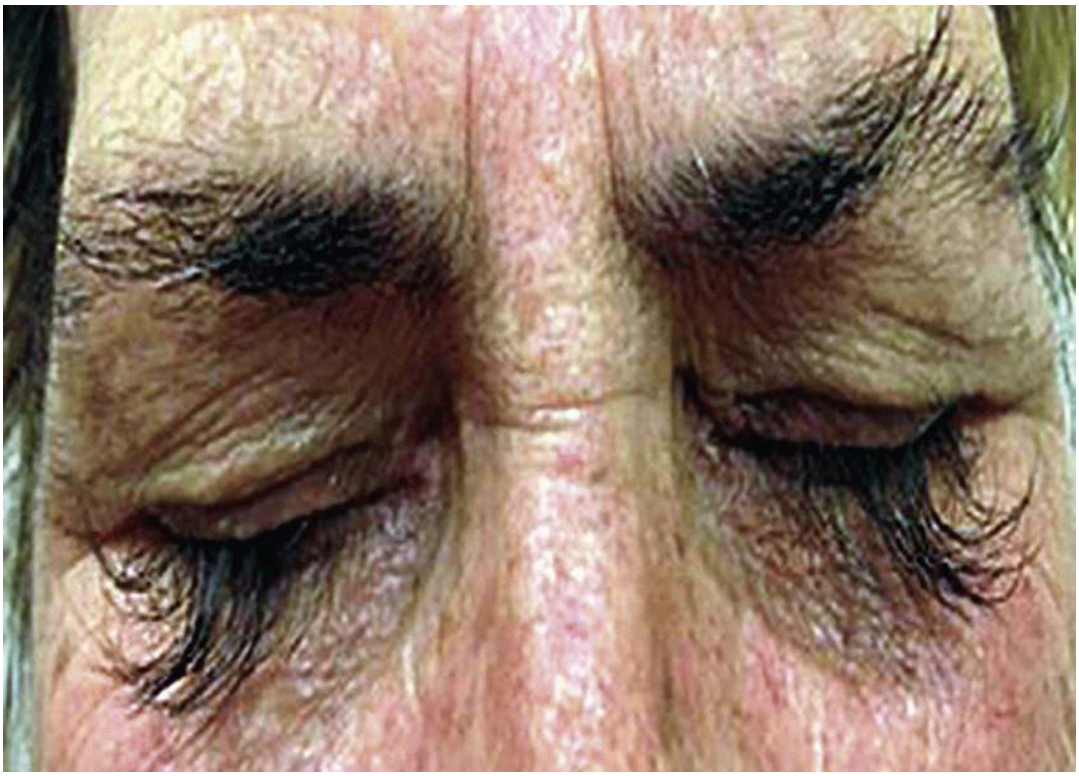

FIGURE 43.1 Excessive elongation of eyelashes in trichomegaly. (Reprinted with permission from Wolters Kluwer: Kosal UI, Pilanci KN, Ordu C, et al. Trichomegaly induced by cetuximab; case series and review of the literature. *Am J Therapeut*. 2016;23:e1226-e1229.)

FIGURE 43.2 Trichomegaly with dark, thick elongated lashes in the lateral half of the upper eyelid.

This increase in length is frequently associated with an increase in the number, thickness, and pigmentation of the eyelashes, as well as an increase in the number of rows of eyelashes. The chronic use of prostaglandin F2α analogues may also result in trichomegaly (Figure 43.3A) and the conversion of vellus to terminal hairs around the canthal areas and on the anterior surface of the lower eyelid skin, upper cheeks, as well as the malar area.[43,44,45] In addition, conjunctival hyperemia, increased iris pigmentation, and

periocular *(Print pagebreak 280)* hyperpigmentation of the skin are also observed with these topical glaucoma medications.[43,46] The condition is more frequently observed when prostaglandin analogues are used for longer periods, in darker-skinned individuals, or in older individuals who may inadvertently place the eyedrops outside the eyes thus inducing the periocular hair growth and pigmentary changes.[16,43] The long eyelashes may become adherent to the tear film with contact to the eye (Figure 43.3B). They can also trap eyedrops and interfere with the correct application of the antiglaucoma medications, and a vicious cycle is thus established.[47]

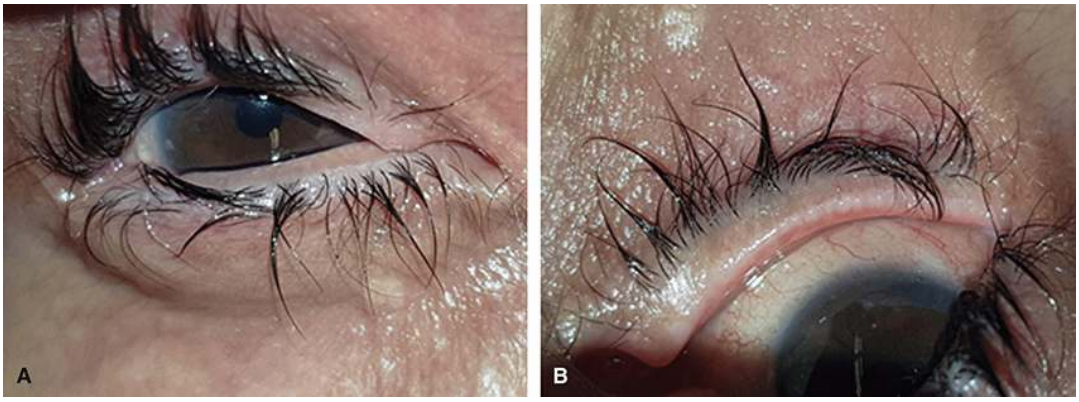

FIGURE 43.3 A, Trichomegaly associated with topical prostaglandin F2α analog use, resulting in increase in number, thickness, and pigmentation of the eyelashes. B, Long eyelashes in trichomegaly adherent to the tear film and in contact with the eye.

Cornelia de Lange syndrome is diagnosed primarily by the peculiar dysmorphic facial features. These include a low anterior hairline, bushy, high arched eyebrows, synophrys (eyebrows growing across the base of the nose), anteverted nares, maxillary prognathism, long philtrum, thin lips, and "carp" mouth, in association with prenatal and postnatal growth retardation, mental retardation, and upper limb anomalies. Trichomegaly is seen in 99% of patients.[3,26] Oliver-McFarlane syndrome is characterized by trichomegaly, severe chorioretinal atrophy, and multiple pituitary hormone deficiencies, including growth hormone, gonadotropins, and thyroid-stimulating hormone. If untreated, it may result in hypogonadism, intellectual impairment, and profound short stature.[27,48,49,50,51]

Differential Diagnosis

It may not be difficult to diagnose trichomegaly, but there are a few medical terms and conditions that are associated with an increase in eyelash density, or an abnormality in the position of the eyelashes, which may be confused with the condition including polytrichia, trichiasis, distichiasis, ectopic cilia, cilium incarnatum, and hirsutism.[9,21,52,53,54]

In the eyelids, the term polytrichia is strictly defined as an increase in the number of eyelashes.[9,52] Therefore, the term hypertrichosis, which is defined as an increase in the number and length of the eyelashes, can be subclassified into trichomegaly (increase in length) and polytrichia (increase in number).[52] Polytrichia is an archaic term that is rarely encountered in the literature today and generally is used to describe conditions like distichiasis and tristichiasis where lashes may grow abnormally in three or more rows.[9,52]

Trichiasis is an acquired lid margin disorder where the eyelashes are misdirected toward the ocular surface, without an associated in-turning of the eyelid margin itself, and in contrast to trichomegaly, it is a major cause of ocular morbidity (see Chapter 42).[52]

Eyelashes that are documented to grow in abnormal locations include distichiasis, ectopic cilia, and cilium incarnatum. Distichiasis is defined as an abnormal growth of lashes from the orifices of the meibomian glands resulting in an accessory row or several rows of lashes behind the normal one (Chapter 30). In its congenital form, the condition may be associated with late-onset hereditary lymphedema of the limbs.[52] Ectopic cilia is a condition characterized by lashes situated externally in the lateral aspect of the upper eyelid skin away from the lid margin.[21] Cilium incarnatum (see Chapter 30, Figure 30.2) is a benign lid condition where cilia grow subcutaneously under the lid skin (cilium incarnatum externum)[21] or subconjunctivally (cilium incarnatum internum).[53]

Hirsutism, a term which is seldom, if ever, used in the context of eyelid diseases except perhaps in error, refers to an androgen-induced, male-pattern hair growth in females (beard, mustache, etc.) and usually has an endocrinological cause like adrenal or ovarian dysfunction, micropolycystic ovaries, adrenal hyperplasia, androgen-producing tumors, severe insulin-resistance syndromes, hyperprolactinemia, or Cushing syndrome.[11,54] Of note is that there is a single case report where the use of topical prostaglandin analogs for glaucoma resulted in hirsutism around the chin and lips.[55]

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Treatment

The first line of therapy is to search for an underlying identifiable cause or an offending medication,[9] and if a drug is recognized, it should be stopped if possible. If there is no relevant history of drug intake, a search for an underlying systemic disease is warranted, and the patient should be referred to a dermatologist or an internist who is better able to identify the systemic or dermatological predisposing conditions.

If there is no identifiable systemic disease, or if cessation of the offending drug fails to reverse the condition, treatment may be indicated. Unfortunately, the wide variety of therapeutic modalities available for hypertrichosis that involves other areas of the body may not be viable options in the periocular region. These options are summarized elsewhere and are beyond the scope of interest for ophthalmic surgeons, but they are broadly classified into depilatory and epilatory methods.[18] Depilation involves shortening or trimming of the offending hair follicles at some point along their length, and indeed some patients may resort to self-trimming of the eyelashes with scissors.[18,38] Epilation is more definitive and can also be self-administered, but the effect is reversible and it is technically difficult in the crowded milieu of the eyelids. Patients may require the assistance of a family member who may have to use magnifying loops to pull out the offending eyelash. Most patients will experience mild to moderate pain during the process.[18]

Permanent hair removal can be achieved definitively only via destruction of the follicular germ cells using electrolysis, cryotherapy, or Argon laser modalities, which may only be indicated in severe cases causing significant mechanical abrasion of the cornea. It should be remembered that the underlying pathology (abnormal length and curliness of the eyelashes) is fundamentally different from true trichiasis where fibrosis and scarring of the lash follicle itself are present.[56] Consequently, the morbidity in patients with trichomegaly is milder, and most of these patients have no ocular symptoms at all, and the presenting complaint is usually only cosmetic. It should be remembered that excessive electrolysis is not without side effects, is still associated with recurrences, and can result in scarring of the thin eyelid skin.[9] If all other measures fail, anterior lamellar reposition surgery rarely may be required.[41]

Prognosis

Eyelash trichomegaly can socially be embarrassing or psychologically disturbing, and it may occasionally lead to visual obscurations or interfere with the proper installation of eye drops, but corneal morbidity is rare. If an underlying cause is identified, the condition may be reversible with treatment of the underlying condition. Unfortunately, a search for a cause may be elusive, and it may remain unidentified for years.

Furthermore, it is not entirely clear in the literature whether or not drug-induced trichomegaly is reversible with cessation of the offending agent.[41] In the case of prostaglandin-associated trichomegaly, the effects may be reversible if topical prostaglandin analogs are used for only brief periods (<21 days).[16] However, when the eye drops are used for longer periods, trichomegaly and hypertrichosis can be permanent,[57] partially reversible,[41] or completely reversible.[58] Even if trichomegaly were completely reversible after cessation of use, it still may be a nuisance because there are situations where the medication (topical or systemic) cannot be stopped or replaced. Nonetheless, further research into this undesirable side effect may provide significant insights that could result in the development of more effective medications for eyelash hypotrichosis in the future.[59]

It should be noted that, for the past few decades, trichomegaly was considered a poor prognostic sign in patients with HIV. However, because of the marked advancements in antiretroviral therapy and the general improvement in the immune status of patients with HIV, eyelash trichomegaly is no longer considered a poor prognostic sign in these patients.[35]

Histopathology

We are not aware of any reports on eyelid histopathology in patients with trichomegaly.

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CHAPTER 44

Abscess and Preseptal Cellulitis

Key Points

- Periocular superficial infections can be categorized broadly into cutaneous abscess and preseptal cellulitis
- An abscess is defined as a localized collection of pus involving the epidermis and dermis
- Preseptal cellulitis is a diffuse infection of soft tissues anterior to the orbital septum
- The principal underlying cause of preseptal cellulitis or abscess is trauma
- Patients with systemic diseases such as diabetes, renal failure, or malignancy or patients who are immunocompromised are at a higher risk
- Periorbital abscess and cellulitis are typically bacterial infections but may rarely be mycotic
- Presentation is with a painful erythematous swelling or mass
- Hematogenous dissemination can lead to sepsis
- Abscesses are treated with incision and drainage, whereas the preseptal cellulitis is managed with oral antibiotics

Superficial infections of the periocular region can be categorized broadly into a cutaneous abscess and preseptal cellulitis.[1,2,3,4,5] An abscess is defined as a localized collection of pus involving the epidermis and dermis, with or without subcutaneous tissue involvement,[1,2,3,4,6] whereas preseptal cellulitis (occasionally referred to as anterior orbital cellulitis) is a diffuse infection of the soft tissues anterior to the orbital septum. Both conditions are usually caused by bacterial pathogens.[6,7]

In the general medical and pediatric literature, cellulitis and abscesses are generally discussed together under the rubric of superficial skin and soft tissue infections[6] because the International Statistical Classification of Diseases and Related Health Problems (ICD) published by the World Health Organization did not make a clear distinction between cellulitis and abscess formation before its tenth iteration (ICD-10).[8] In the periorbital region, most of the causative organisms and some of the predisposing factors leading to preseptal cellulitis or abscess formation are shared. Therefore, these entities are discussed together.

Etiology and Pathogenesis

Anatomically, the orbital septum separates the eyelids from the orbital tissues. Superficial infections anterior to the orbital septum can cause an eyelid abscess or preseptal cellulitis, whereas infections posterior to the septum can cause orbital cellulitis.[3,5] Paranasal sinus disease is the most common cause of orbital cellulitis, whereas the principal underlying cause of preseptal cellulitis or abscess formation is a traumatic disruption of the protective layers of the skin.[1,9] Other underlying conditions include acute hordeolum, dacryocystitis, sinus disease, sinus surgery, upper respiratory tract infection, inflammatory skin conditions (eczema, radiation therapy, or psoriasis), lymphedema, a recent history of brow epilation (tweezing, plucking, threading, waxing, or shaving), manual manipulation of eyelid chronic skin lesions, scratching of eyebrow acne lesions, or dental procedures.[9,10,11,12,13,14]

Patients with systemic diseases such as diabetes, cirrhosis, end-stage renal failure, pulmonary diseases, or malignancy or patients who are immunocompromised are at a higher risk for developing an abscess or preseptal cellulitis following a relatively trivial trauma or from a surgical wound.[15] Warmer weather is associated with a higher incidence of cellulitis and abscess formation because colonization of the skin surface is reduced in low temperatures.[8] Predisposing factors peculiar to methicillin-resistant *Staphylococcus aureus* (MRSA) infections, which are increasing in frequency in the periorbital region, include recent hospital admission, intravenous drug use, newborn age range (<28 days), young age particularly in those practicing contact sports, male gender, low socioeconomic status, immunosuppression, military service/prison time, steam bath use, recent treatment with antimicrobials, and close contact with health care workers.[16,17,18]

A periorbital abscess or cellulitis is usually pyogenic (bacterial) in origin. Although relatively rare, a mycotic etiology is occasionally reported.[4,11,13] The most common organisms implicated in patients with preseptal cellulitis are beta-hemolytic streptococci (most commonly group A *Streptococcus* or *Streptococcus pyogenes*), or methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-sensitive *Staphylococcus aureus* (MSSA), and coagulase-negative staphylococci (CoNS).[8,12] On the other hand, *Staphylococcus* spp. (MRSA, MSSA, CoNS) are the predominant pathogens encountered in patients with a cutaneous abscess.[5,6,12,19] Other rarer organisms causing periorbital abscesses or cellulitis include *Pseudomonas* spp., *Streptococcus faecalis*, *Ekinella corrodens*, *Escherichia coli,* and anaerobes.[13,15,20,21]

MRSA infections have been on the rise in the general population in recent years,[10,16,22,23] and in the periocular region, the prevalence of *S. aureus* strains reported to be resistant to methicillin varies from 3% to 62%.[10,24] The type of injury can give a general idea about the pathogen involved. A *(Print pagebreak 286)* periorbital infection resulting from sinusitis or upper respiratory tract infection is usually caused by *Streptococcus* species, or less commonly by *Haemophilus influenzae*. The latter has declined in frequency since the introduction of the *H. influenzae* type B (Hib) vaccine.[12,14,25] On the other hand, a fungal infection may result from an injury that is contaminated with soil.

The pathogenetic events that lead to abscess formation or preseptal cellulitis are straightforward. Large eyelid lacerations may provide a point of entry to the organisms. Similarly, brow shaving, epilation, or scratching of eyelid or eyebrow lesions may cause smaller breaks in the skin that may likewise facilitate the subcutaneous entry of microbes. The source of the organisms is the exogenous or endogenous microflora, including skin commensals, native bacteria living around hair shafts, or the contaminated hands of the patients themselves.[12] When sinusitis is the primary cause of periorbital infection, the infection may have spread from the ethmoid sinuses through the lamina papyracea, the floor of the frontal sinus, the roof of the maxillary antrum, or through hematogenous spread. Although the virulence of a particular organism may be the principal factor thought to play a role in the development of preseptal infections, host immune responses also substantially participate in disease progression.[26]

Whether periorbital infections are caused by a local major or minor traumatic event, hematogenous dissemination through sepsis, or direct inoculation in sinusitis patients, the subsequent pathogenic events are the same. Local tissue cells are destroyed by bacterial enzymes and toxins, which in turn trigger an inflammatory response by attracting large numbers of white blood cells. Regional blood flow and vascular permeability are increased under the influence of released cytokines, causing erythema and tissue edema.[21]

Clinical Presentation

Patients usually present with a painful mass that is tender to touch. Although they may experience fever and generalized malaise, systemic symptoms may be absent. Because many cases of preseptal cellulitis and abscess are associated with human behavior, patients should specifically be asked about a history of trauma (skin abrasion, penetrating wound, an insect bite, brow epilation, or scratching a long-standing eyelid or brow skin lesion).[12] The clinician should not shy away from asking male patients about cosmetic brow hair removal as it is no longer a female-only practice.[12] In general, *S. aureus,* particularly MRSA infections, usually present with pain that is out of proportion to the clinical picture.[27] When an abscess or cellulitis develops following trauma, the inflammation is temporary (3-4 days) and spatially related to the original trauma.[10] For instance, following epilation of the eyebrow hairs, the abscess that develops is usually located temporally because this is where females tend to pluck their hairs.[10]

An eyelid abscess is a localized suppurative collection of pus that may or may not be pointing. The presenting features include an acute onset of eyelid edema, erythema, a fluctuant mass with surrounding cellulitis and warm skin, and conjunctival chemosis (Figure 44.1). Tenderness usually is maximum over the abscess, which may feel like a fluid-filled cavity upon palpation. Patients with preseptal cellulitis typically present with a diffusely red, swollen, and tender eyelid without a single focus of pointing pus, although on closer inspection a single point of a suppurative collection of pus may be observed. The skin findings in preseptal cellulitis are similar to the classic signs of cellulitis elsewhere in the body: dolor (pain), calor (heat), rubor (erythema), and tumor (swelling), in addition to mechanical ptosis if the upper eyelid is involved (Figure 44.2).[8]

The diagnosis of cellulitis and abscess essentially is a clinical one based on history and physical examination alone,[8] but radiology (computed tomography [CT]) may be needed if an orbital extension (orbital cellulitis) is suspected. Indications for performing a CT scan include swinging pyrexia that lasts for 36 hours, failure to improve within 24 to 36 hours of antibiotic treatment, or if examination of the eye is impossible because of massive edema.[13] A blood sample may be taken for a complete blood count, urea, electrolytes, and possibly blood culture. However, this laboratory workup is not routinely required to establish the diagnosis of abscess or cellulitis or to direct future therapy.[13] Prior identification of the causative organism with a conjunctival swab, skin swab, or even a sinus aspirate may be irrelevant, and waiting for the results of a culture and sensitivity test may be harmful because some of these infections may require immediate medical or surgical intervention. Furthermore, in most patients, conjunctival or skin swabs either will yield negative results, or when they are positive, the concentration of the bacterial load is often low and inaccurate. The results of some swab cultures may be polymicrobial owing to colonization with skin commensals that may not even be involved in the etiology of the underlying preseptal cellulitis or abscess.[8,13] Moreover, in a typical clinical scenario, by the time these

patients present to the oculoplastic service, they usually already have been preloaded with antibiotics.[8] Alternatively, the immune system could have already reduced the number of viable bacteria or a very small number of bacteria may be responsible for a robust inflammatory response due to bacterial toxins and other inflammatory mediators. These inflammatory mediators may contribute more to the pathogenesis of cellulitis than the bacterial load itself.[6,8,13,14] A blood culture may be more accurate, but in some studies, the yield was as low as 2%, and it is not indicated as part of the management except in infants <3 months of age.[6,13]

Differential Diagnosis

A patient presenting with an acute inflammatory condition involving the periorbital region can prove to be a diagnostic challenge. A misdiagnosis may result in subsequent mismanagement that may prove disastrous.[28] Although the diagnosis of an eyelid abscess may be difficult to miss, any condition *(Print pagebreak 287)* that simulates the four cardinal signs of cellulitis (dolor, calor, rubor, and tumor) may be confused with preseptal cellulitis.[8] There are many mimics of preseptal cellulitis (pseudocellulitis) in the periorbital region, and these are summarized below.

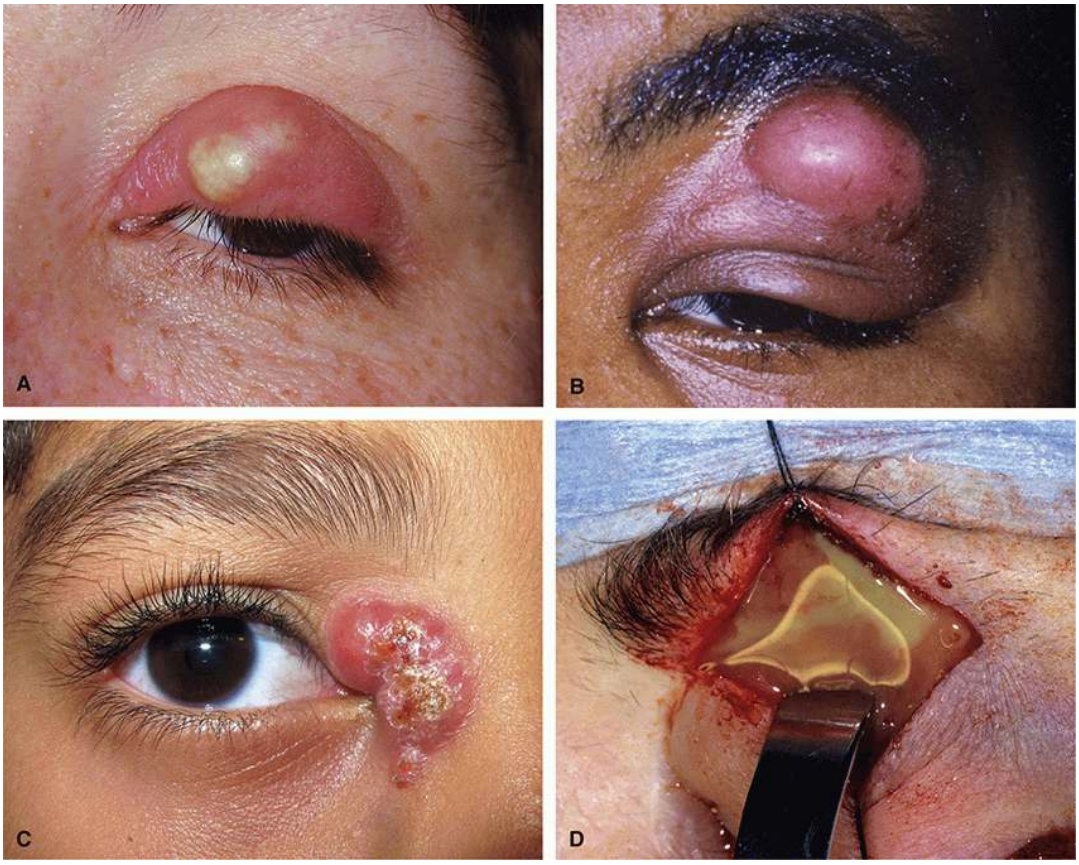

FIGURE 44.1 Eyelid abscess. A, Upper eyelid with surrounding cellulitis. B, Large upper eyelid and brow abscess. C, Abscess formation in the medial canthal region following minor trauma. D, Surgical drainage of a large upper eyelid and brow abscess with copious purulent material.

Although the majority of preseptal infections are bacterial in origin, mycotic, parasitic, and viral infections should always be considered in the differential diagnosis. A diagnosis of eyelid sporotrichosis caused by the fungus *Sporothrix schenckii* should be suspected if the lesion is papular, nodular, ulcerative, plaque-like, or verrucous, with characteristic satellite nodules along the lymph trajectory around the initial lesion.[26] Eyelid sporotrichosis is not uncommon, and several large case series have been published.[26,29,30] It may occasionally present with a classic eyelid abscess without the typical satellite lesions, but the diagnosis can still be suspected because the majority of patients are from rural areas with a history of exposure and trauma related to the soil.[26,29,30]

Because patients with herpes zoster ophthalmicus may acutely suffer from significant pain and eyelid edema, the differential diagnosis of preseptal cellulitis should exclude an early zoster infection. However, the characteristic neuropathic pain along the distribution of the ophthalmic division of the trigeminal nerve, which is usually followed by the typical dermatomal skin rash, may help establish the diagnosis. Preseptal cellulitis may be confused with orbital cellulitis.

History taking is important because a history of trauma usually precedes preseptal cellulitis, whereas a history of sinusitis often precedes infection posterior to the orbital septum.[3] Orbital cellulitis is often marked by changes in ocular motility and vision as opposed to preseptal cellulitis, where vision and ocular motility are characteristically normal. If the diagnosis is in doubt, CT of the

orbit with or without intravenous contrast would easily exclude orbital cellulitis.[3]

Idiopathic orbital inflammation (IOI) may present with lid swelling, erythema, and eye pain that may initially be *(Print pagebreak 288)* difficult to differentiate from an infectious process. Pain and tenderness may be more characteristic of infection, although the distinction can be quite difficult. If the condition progresses despite a brief course of antibiotics, IOI should be considered in the differential diagnosis.[3] In the lower eyelid, dacryocystitis may present with a tender infected mass and may cause diffuse cellulitis. If suspected, it should be ruled out with a proper evaluation of the lacrimal system.[3]

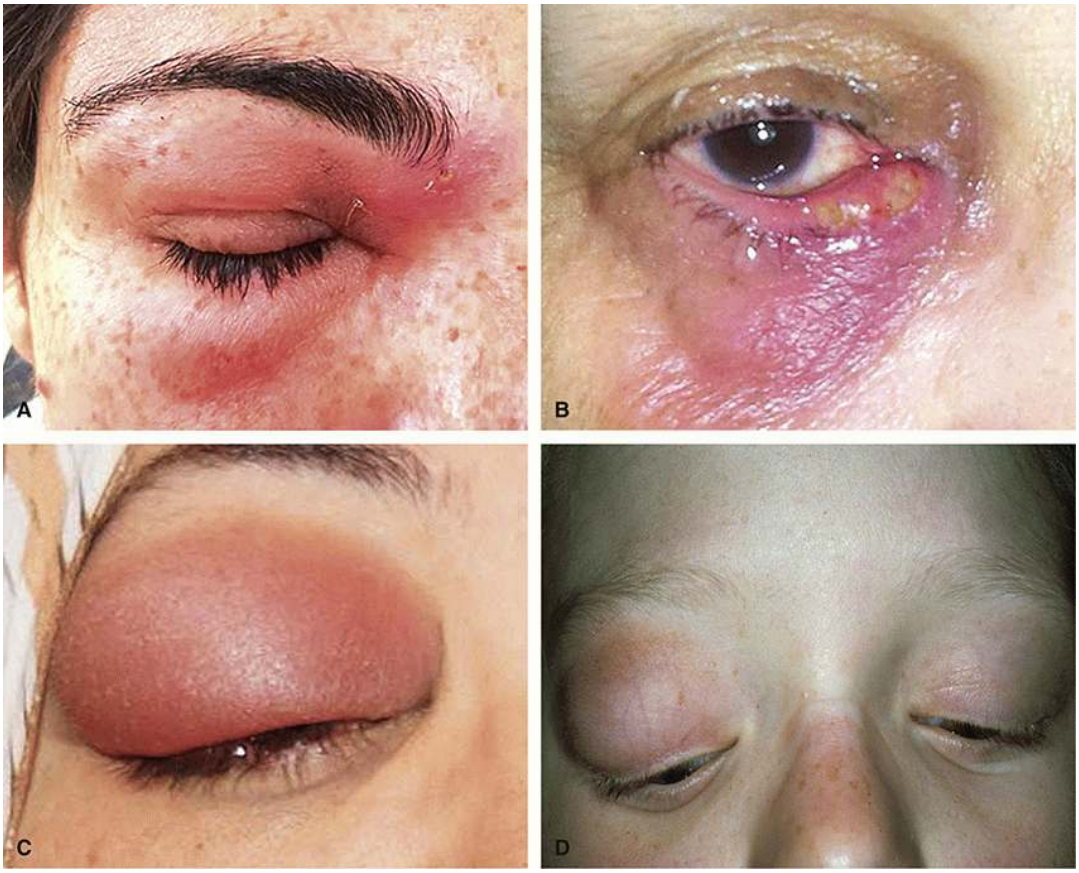

FIGURE 44.2 Preseptal cellulitis. A, Preseptal cellulitis following brow epilation involving the upper eyelid. B, Mild preseptal cellulitis involving the lower eyelid. C and D, Diffuse preseptal cellulitis involving the entire upper eyelid with secondary mechanical ptosis.

Preseptal cellulitis may also be confused with angioedema and allergic contact dermatitis.[2] Patients with angioedema usually present to the ophthalmologist with an alarming upper and lower eyelid swelling of rapid onset. A history of a known allergic reaction to food or medications may be extracted from the patient. Contact dermatitis is a type IV hypersensitivity eczematoid reaction of the skin that is triggered by chemicals like cosmetics, lotions, creams, or topical ophthalmic preparations. In addition to the red scaly itchy rash in the involved areas, contact dermatitis can cause severe swelling of the facial and periorbital skin and may be difficult to distinguish from cellulitis.

In contrast to the extensive list of lesions and conditions simulating preseptal cellulitis outlined above, fewer conditions may be confused with an eyelid abscess. A periorbital abscess should primarily be differentiated from necrotizing fasciitis (NF). NF is a rare, rapidly progressing bacterial infection that originates in the fascia, involves muscles and subcutaneous fat, and ultimately results in necrosis of the overlying eyelid skin.[31] It is conventionally classified into two types. Type 1 is uncommon in the head and neck region, whereas type 2, which is usually caused by group A *Streptococcus pyogenes,* commonly involves the eyelids.[31,32] The pathogenicity of NF is attributable to angiothrombotic microbial invasion and tissue liquefactive necrosis.[33] Similar to an eyelid abscess, NF also may be associated with a minor cutaneous injury; half of the patients have an underlying systemic condition, and 35% of patients have more than one comorbid *(Print pagebreak 289)* condition.[31,34] Although the early course of the disease may be similar to preseptal cellulitis or abscess (pain, tenderness, skin warmth, swelling), and may be impossible to differentiate, patients with NF later develop blisters or bullae, followed by crepitus, skin anesthesia, and skin necrosis with alternating patches of dusky skin erythema and discoloration.[31] Early clinical signs that may be suggestive of fasciitis include pain that is out of proportion of other physical findings, failure to respond to broad-spectrum antibiotics, skin bullae, and soft tissue gas on X-ray.[31,34] A laboratory workup also may help to distinguish necrotizing from nonnecrotizing soft-tissue infections. A white blood cell count >15,400 cells/mm,[3] a serum sodium level <135 mEq/L, a serum lactate level >2.0 mmol/L, a C-reactive protein ≥150 mg/L are suggestive of

tissue necrosis.[8,35,36,37]

Dacryoadenitis may present as a circumscribed tender mass in the outer part of the upper eyelid and may be confused with an eyelid abscess.[38] A lacrimal gland ductal cyst (dacryops) may be complicated by secondary infection and may simulate an eyelid abscess.[39] An anterior hordeolum or stye may present as a furuncle or an abscess on the lid margin. A hordeolum is an acute focal inflammation of the eyelid that develops due to microbial infection (usually *S. aureus)* of the meibomian or Zeis glands.[3,40]

An eyelid abscess may also be confused with pyoderma gangrenosum, as well as ecthyma gangrenosum. Pyoderma gangrenosum is a destructive, necrotizing, noninfective ulceration of the skin and is often associated with systemic diseases like inflammatory bowel disease, as well as some joint and blood diseases, but is quite rare in the periorbital region.[28] Ecthyma gangrenosum is one of the most characteristic cutaneous manifestations of *Pseudomonas aeruginosa*, as it occurs in approximately 13% of patients with *P. aeruginosa*-associated septicemia.[41] Rarely, a neoplastic process like orbital plasmacytoma may simulate a periorbital abscess.[42,43,44] An upper, or less commonly lower, eyelid recurrent abscess or fistulous tract may signal the presence of an underlying previously undetected sinus disease. Underlying sinusitis should be considered if a patient with a recurring eyelid fistula/abscess is suffering from chronic headache and/or chronic nasal discharge.[45,46]

Treatment

The distinction between an eyelid abscess (a localized collection of pus within the eyelid skin or subcutaneous space) and preseptal cellulitis, which is a rather more diffuse process, has important treatment implications.[8] Abscesses are primarily treated with incision and drainage (Figure 44.1D), whereas the mainstay of treatment of preseptal cellulitis is oral antibiotics, particularly those with anti-beta-lactamase activity (amoxicillin/clavulanate, or cefpodoxime).[8] An abscess may coexist with preseptal cellulitis, which may complicate the management plan.[8] The management of patients with preseptal cellulitis or abscess may require a multidisciplinary approach. If in doubt about the dosing of antibiotics, an infectious disease specialist or a pediatrician should be consulted. An ENT specialist should be consulted in patients where preseptal cellulitis originates from a sinus infection.[13,14] In contrast to patients with frank orbital cellulitis, patients with preseptal cellulitis or an eyelid abscess do not generally require hospital admission except when evolving signs indicate progression. These signs include acute exacerbation of the periorbital swelling despite treatment, diplopia, reduced visual acuity, abnormal pupillary light reflexes, proptosis, or ophthalmoplegia. Systemically unwell patients or patients with central signs or symptoms (drowsiness, vomiting, headache, seizure, or cranial nerve paresis) may also require admission.[13]

In patients with preseptal cellulitis, empiric antimicrobial therapy must be started immediately on an outpatient basis, coupled with the topical application of an antibiotic ointment or a steroid/antibiotic combination (neomycin-polymyxin B-dexamethasone).[3] The initial antibiotic may be modified later based on the progress of the disease or if a specific pathogen is cultured.[6] Unfortunately, little evidenced-based agreement exists on a preferred antibiotic approach in the initial management of cellulitis, as different studies used different treatment plans.[8,14] A multicenter Canadian emergency room study showed that 25 uniquely different antibiotic regimens were prescribed as initial treatment options and another 40 different regimens were prescribed on discharge.[47] If in doubt, an infectious disease specialist should be consulted before starting empiric antibiotic therapy.

Typical cases of nonpurulent preseptal cellulitis without localized abscess formation and without systemic signs of infection (mild cellulitis) may be treated with oral antistreptococcal antimicrobial agents (cephalexin, dicloxacillin, penicillin VK, or amoxicillin/clavulanate). In cases of penicillin allergy, clindamycin may be prescribed.[8] The decision to proceed with oral or intravenous antibiotics is also a critically unanswered question. Patients with preseptal cellulitis who meet a single SIRS (systemic inflammatory response syndrome) criterion should receive oral antibiotics.[8] SIRS criteria include a temperature greater than 38°C or less than 36°C, a heart rate greater than 90/min, a respiratory rate greater than 20/min, or white blood cell count greater than 12,000 cells/mm^3 or less than 4000 cells/mm^3.[8] Patients with more than one criterion or patients who have progressed despite oral therapy should receive an intravenous regimen (cefazolin, ceftriaxone, penicillin G, or clindamycin).[8] The standard duration of treatment should be between 5 and 10 days in immunocompetent patients and 7 to 14 days in immunocompromised individuals.[8]

Depending on the local community prevalence of MRSA, clinicians may choose to load their patients with an empiric antibiotic coverage for MRSA.[3] Alternatively, the lack of response to traditional antibiotic therapy that does not cover MRSA should prompt suspicion that an MRSA infection is taking place.[3] Community-associated MRSA is often susceptible to a range of antibiotics (trimethoprim-sulfamethoxazole, rifampin, clindamycin, or doxycycline), which is different from the antibiotics to which hospital-acquired MRSA is *(Print pagebreak 290)* sensitive (vancomycin and linezolid).[10] Vancomycin is effective against both MRSA and streptococci, and some authorities believe it should be prescribed as first-line therapy in cases of severe preseptal cellulitis, although others prefer to reserve vancomycin if safer less toxic alternatives are available.[8,

[24,48] Because some vancomycin treatment failures may be associated with increased weight or body mass index rather than vancomycin resistance, vancomycin dosing should be weight based (15-20 mg/kg per dose intravenously every 8-12 hours) rather than the standard dosing schedule of 1000 mg intravenously/12 hours.[8] Rifampin and linezolid may be highly efficacious in patients with refractory MRSA probably due to higher bioavailability in seemingly impregnable biofilms (a self-produced exopolysaccharide matrix that encases the bacteria protecting them from antibacterials), but systemic toxicity, particularly in the case of linezolid, may limit their use as a first-line drug.[22] Predictably, the traditional categorization of MRSA into the community-or hospital-acquired strains is not a rigid one as community-associated strains may be isolated in a hospital setting and vice versa.[23] As was mentioned earlier, one should exercise caution when interpreting the results of traditional culture methods, which may lead to the prescription of the wrong antibiotic.

Newer antibiotic agents such as telavancin, tedizolid, dalbavancin, and oritavancin recently have shown excellent results in skin and superficial tissue infections, including MRSA infections, but may be prohibitively expensive and some of these newer agents may have serious side effects.[8] A single dose of oritavancin had an efficacy comparable with a 7-to 10-day course of vancomycin.[49] If patients with preseptal cellulitis do not improve with medical therapy (oral or intravenous antibiotics), or if they are progressing to orbital cellulitis, surgical evacuation of the pus is warranted.[14]

Although patients with preseptal cellulitis may improve solely with antibiotics, a cutaneous abscess usually requires drainage, although a small abscess could resolve spontaneously without treatment or following a brief course of antibiotics.[13] If spontaneous rupture and drainage of the abscess does not occur, or if the abscess only partially evacuates and then recurs, incision and drainage (I&D) should be carried out promptly.[6] I&D has the added benefit of limiting the development of multidrug resistance in the community.[16,17,23,50] During surgery, the lesion should be explored thoroughly to exclude the presence of a foreign body.[4] Any purulent material is submitted for culture and sensitivity, which should routinely include culture for fungi particularly if the purulent material is unusually rare. The resultant defect may or may not be closed with sutures depending on the integrity of the surrounding eyelid or periocular skin.[4] If the surrounding skin is healthy, it may be better to approximate the skin edges with several 6-0 absorbable sutures.[4] Routine postoperative antibiotics are usually prescribed, and the regimen may be modified after the results of culture and sensitivity are obtained, particularly if incomplete healing or recurrence is observed. Although antibiotics are routinely prescribed following drainage of an abscess, there is no clear evidence to support their use.[51,52] Some authors have shown that a 7-to 10-day course of antibiotics after I&D is more effective in preventing recurrences compared with either placebo or a shorter (3-day) course of treatment.[6]

Patients with an extensive abscess or complicated preseptal cellulitis may benefit from negative pressure wound therapy, which promotes healing and stimulates granulation tissue formation through the application of subatmospheric wound pressure on the wound bed, although this may be a more appropriate modality in patients with NF.[53]

Although data from single-center studies suggest that the addition of systemic corticosteroids may hasten clinical improvement and reduce hospital length of stay (LOS) in pediatric patients with orbital cellulitis,[54,55] a recent survey using the Pediatric Health Information System registry data from 51 children's facilities in the United States failed to detect a reduction in LOS with corticosteroid use during hospitalization for orbital cellulitis.[55]

Prognosis

In contrast to patients with orbital cellulitis or mucormycosis or patients with a necrotizing strain of *Streptococcus pyogenes,* immunocompetent patients with an eyelid abscess or preseptal cellulitis generally fare well and have an excellent prognosis without the need for hospital admission, provided that they receive proper therapy. Failure to respond to medical treatment may be a signal that the disease is progressing into orbital cellulitis, which may result in blindness, and may even spread intracranially leading to an intracerebral abscess, bacterial meningitis, or cavernous sinus thrombosis.[13,53,56]

As mentioned earlier, an abscess ultimately requires drainage, and even in patients with MRSA or patients with other drug-resistant strains like VISA (vancomycin intermediate-resistant *S. aureus*), or VRSA (vancomycin-resistant *S. aureus*), proper drainage alone is curative even if the wrong postoperative antibiotic was prescribed before the results of culture were available.[56] Conversely, treatment failures may be observed if drainage is not performed at all, or if inadequate drainage is carried out by an inexperienced surgeon, even if the proper antibiotic was instituted from the start.[22,23,50,56] This is probably attributable to the fact that organisms like MRSA may survive within a biofilm, and therefore the antibiotic may fail to reach the organism in sufficient therapeutic concentrations.[22]

A higher rate of periorbital infections has not been observed in patients with compromised immunity or patients with comorbid conditions, but these patients are at a greater risk for developing either condition even from relatively trivial trauma or from a surgical wound. If preseptal cellulitis or an abscess does occur in this particular subset of patients, it may progress relentlessly, so

that the clinician should be particularly alert in patients with diabetes plus trauma.[3,10,15,23,56]

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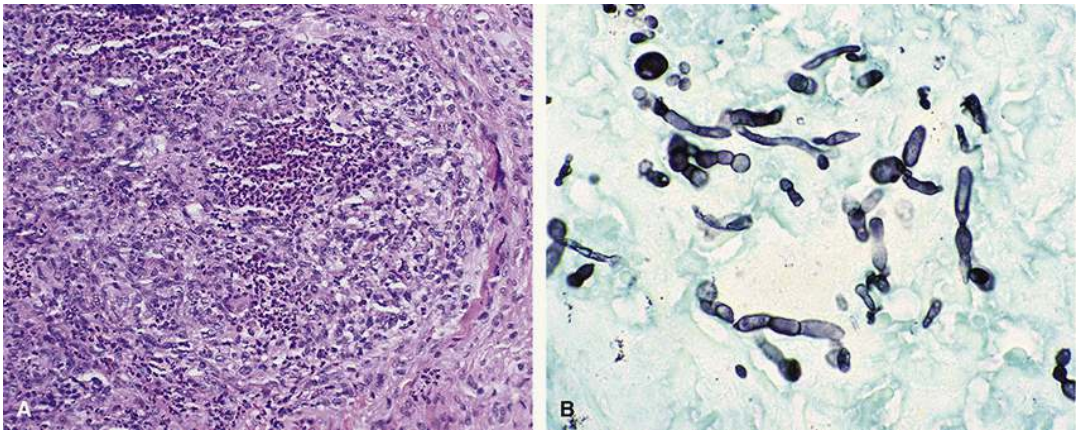

FIGURE 44.3 A, Suppurative granulomatous inflammation, with granulomatous inflammation surrounding a small abscess, is a feature of unusual skin infections such as this case resulting from *Purpureocillium lilacinum* (formerly termed *Paecilomyces lilacinus*) infection after a laceration contaminated by soil (hematoxylin and eosin). B, Staining with Grocott methenamine silver technique highlights septate hypha in the center of the suppurative granuloma. The morphology of the fungus is compatible with the culture growing *Purpureocillium lilacinum*, but *Aspergillus* spp., *Fusarium* spp., *Scedosporium* spp., *Trichoderma* spp., and other hyaline molds may appear similar.[66]

Histopathology

Abscesses are characterized histologically by a central area of necrosis containing leukocytes and degenerated tissue. Polymorphonuclear leukocytes (neutrophils) are the initial leukocyte within an abscess, but over time they are dominated by macrophages and lymphocytes. Leukocytes, similar to those in the necrotic center of the abscess, infiltrate the surrounding tissue, accompanied by vascular dilation and edema. Over time and with appropriate antibiotic treatment, abscesses resolve with replacement by fibrous connective tissue.[57] Small abscesses surrounded by granulomatous inflammation, termed "suppurative granulomatous inflammation," are a clue to look for unusual microorganisms such as *Actinomyces* spp., nontuberculous mycobacteria, and fungi (Figure 44.3).[58,59,60] The presence of suppurative granulomas should prompt histochemical stains for microorganisms, including an acid-fast stain (Ziehl-Neelsen, Fite-Faraco, or Kinyoun carbol fuchsin), periodic acid-Schiff stain, and a silver impregnation stain for fungi (Grocott or Gomori methenamine silver stain).[59] If thin filamentous organisms are apparent using a silver impregnation stain, then a bacterial stain is needed to support a diagnosis of *Actinomyces* spp.[61]

Cellulitis features perivascular and interstitial infiltration of leukocytes in the deep dermis that may extend into the subcutaneous tissue (Figure 44.4), accompanied by varying degrees of blood vessel and lymphatic dilation and edema.[8,62,63,64,65] Hemorrhage and necrosis may also be present. Neutrophils are the predominant leukocyte initially, with lymphocytes and macrophages increasing over the ensuing days. There may be only a few bacteria discernible using histochemical stains unless tissue necrosis is present or the patient is immunocompromised.[64] If the patient is immunocompromised, then histochemical stains for fungi are warranted.[65] Cellulitis usually resolves without scarring unless tissue necrosis has been present.[66]

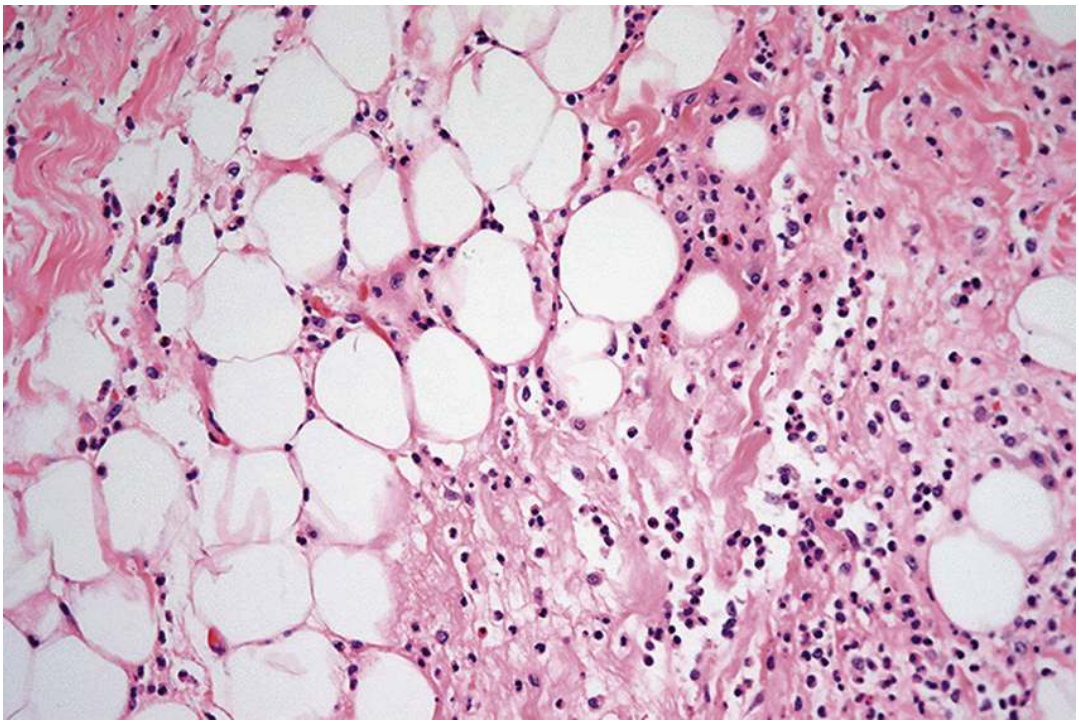

FIGURE 44.4 Acute cellulitis has neutrophils infiltrating the deep dermis and often the subcutaneous tissue (hematoxylin and eosin).

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CHAPTER 45

Acrochordon

Key Points

- An acrochordon (skin tag) is a benign fleshy tumor that is frequently acquired in adult life
- The condition is characterized histopathologically by a slightly hyperplastic epithelium covering a dermal connective tissue stalk
- The exact etiology is disputed, but known predisposing factors include aging, diabetes, obesity, hypertension, acromegaly, and chronic skin friction or irritation
- Acrochordons may be have several syndromic associations including the Birt-Hogg-Dubé syndrome, basal cell nevus syndrome (Gorlin-Goltz syndrome), or Cowden syndrome
- Clinically skin tags appear as a soft, flesh-colored, pedunculated papules that may be single or multiple
- A diagnosis of acrochordons in children should raise the possibility of Gorlin-Goltz syndrome/basal cell carcinoma
- The list of simulating eyelid lesions includes intradermal nevus, dermal neurofibromas, filiform warts, and quite rarely basal and squamous cell carcinoma
- Surgical excision under local anesthesia is the preferred method of treatment
- The lesions are benign with no possibility of malignant transformation

An acrochordon (plural, acrochorda, or acrochordons) is a benign fleshy tumor that is acquired in adult life and is frequently encountered in the eyelid skin, as well as in areas of friction like the axilla and groins.[1,2,3] Several alternative names for acrochordons exist in the literature including fibroepithelial polyp, fibroepithelial papilloma, and soft fibroma, besides the household name skin tag.[1,2,3,4,5]

Etiology and Pathogenesis

The etiology of acrochordons is unknown. It was hypothesized in the past that skin tags occur in areas where elastic tissue has been lost.[6,7] According to this concept, the loss or sparsity of elastic tissue, which is a normal consequence of aging, could result in the development of acrochordons; however, this theory is disputed.[8] Low-grade human papillomavirus (HPV 6 and 11) infections may be related to the genesis of skin tags,[9,10] but this relation is also disputed.[11]

A genetic etiology of acrochordons has not been established, although a link is possible because skin tags have several syndromic associations. Acrochordons may be part of the Birt-Hogg-Dubé syndrome (BHD syndrome, 17p11), basal cell nevus syndrome (Gorlin-Goltz syndrome, 1q34, 9q22, or 10q24), or Cowden syndrome (10q23).[12] Birt-Hogg-Dubé syndrome is a rare autosomal dominant genodermatosis caused by a mutation of the BHD gene and is hallmarked by a triad of multiple trichodiscomas, fibrofolliculomas, or acrochordons, and is also associated with several internal malignancies (kidney and less commonly thyroid cancer). However, this syndrome has not been reported in the periocular region, although a solitary eyelid trichodiscoma has been described.[13] Gorlin-Goltz syndrome is an autosomal dominant disease characterized by the early onset of multiple basal cell carcinomas, along with other findings including the childhood onset of acrochordon-like growths, which may occasionally harbor basal cell carcinoma.[3,14,15]

Other predisposing factors or associated conditions include obesity, pregnancy, diabetes, insulin resistance, and hyperlipidemia.[2,16,17] Acrochordons also appear to increase in number during periods of weight gain.[2,17] The relation to insulin resistance and type 2 diabetes appears to be robust,[18] and in addition, one recent study found that 45.8% of subjects with skin tags suffered from hyperlipidemia, 65.0% from hypertension, and 70.8% from obesity.[19] In short, the risk of developing a metabolic syndrome is

significantly higher in patients with skin tags.[17]

Elevated levels of growth hormone may also be associated with the development of fibroepithelial polyps as skin tags are one of the more frequent cutaneous manifestations of acromegaly.[20] It is not clear whether excessive levels of growth hormone per se are responsible for the evolution of skin tags directly or whether they develop as a consequence of insulin resistance and dyslipidemia.[20] Although a possible association between skin tags and colonic polyps has been proposed in the past, this relation is currently disputed by most researchers.[1,21,22]

An important but frequently overlooked possible predisposing factor is chronic friction or irritation of the skin, as acrochordons are well known to develop in friction-prone areas like the axilla, neck, trunk, or eyelids and are associated with activities like shaving, eye rubbing, or wearing jewelry.[23,24] A recent study found that the mast cell count in acrochorda was significantly higher than in controls.[23] Mast cells are increased in *(Print pagebreak 295)* number in many skin diseases, and they are particularly recruited to sites of injury as an early response to trauma. These mast cells subsequently upregulate their tumor necrosis factor α content to direct the tissue response to injury.[23,25]

Clinical Presentation

Acrochordons are extremely common in adulthood. It is an incidental finding in roughly 50% to 60% of patients older than 50 years presenting to a dermatology clinic. Nevertheless, the vast majority of these patients are not bothered by them, and only 0.5% may present to the clinician for excision of these lesions.[1,24] This is because the popular belief among patients is that skin tags are an acceptable sign of aging.[1] The condition is first observed in the second decade of life, after which there is a steady increase in frequency up to the 5th decade, then the number of individuals with skin tags starts to plateau.[1,26] There is no sex predilection, but as was mentioned earlier, fibroepithelial polyps are more common in obese diabetics.[1,2,3,4,16,17,18,19]

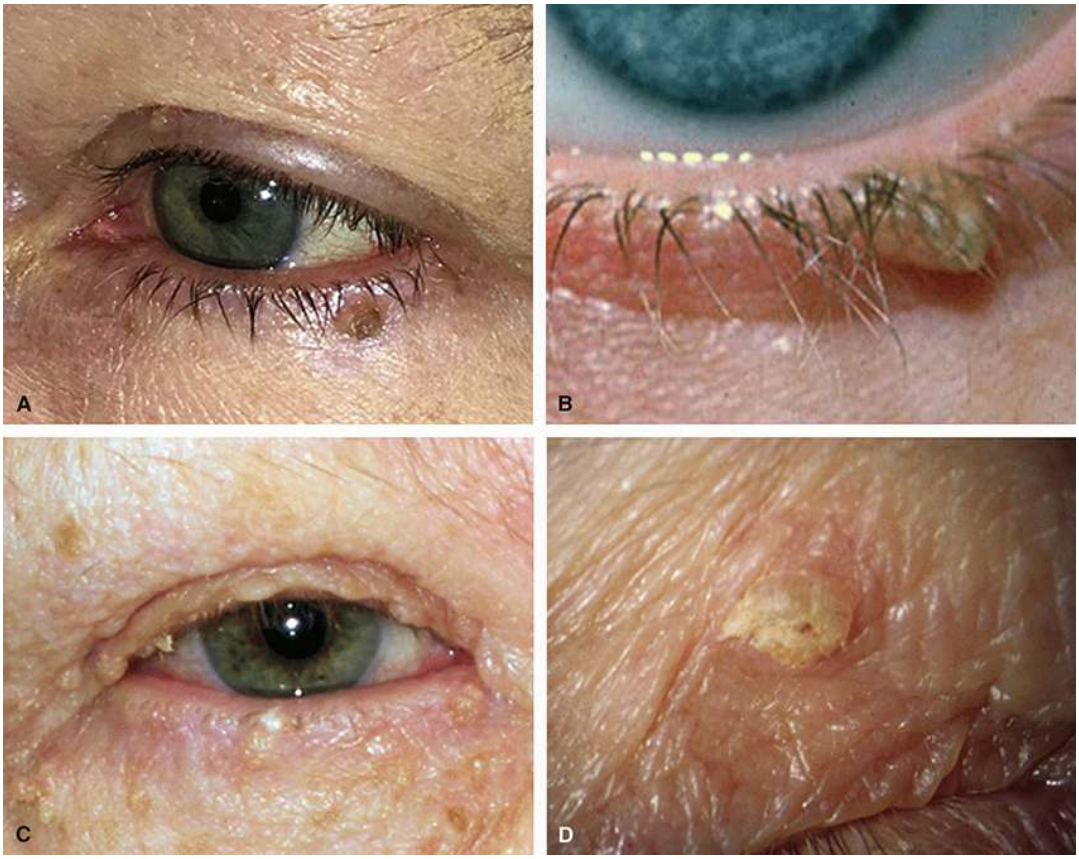

FIGURE 45.1 A-D, Sessile acrochordons on the eyelids.

The clinical appearance of acrochordons in the periocular region is similar to other skin tags in the rest of the body. They are soft, skin-or flesh-colored, sessile, or pedunculated papules that have a smooth, folded, boggy, or filiform (fingerlike) outer surface (Figures 45.1 and 45.2).[1] The lesions may be solitary or multiple, and they may vary in size from 1 to 5 mm but they can attain a larger size, which is an infrequent finding in the periocular region.[1,2] A solitary acrochordon may look and feel as if a small bag or a purse is hanging from the surface of the skin.[2] Although the eyelids are common sites for acrochordons, they also have a predilection for the axilla, neck, back, inframammary region, inguinal region, and groin.[1]

If the patient scratches the lesion or accidentally twists the pedicle, or if the lesions become irritated or mechanically injured, they can acquire the shape of a necrotic, crusted papule that may simulate a malignancy and may not be clinically distinctive.[1]

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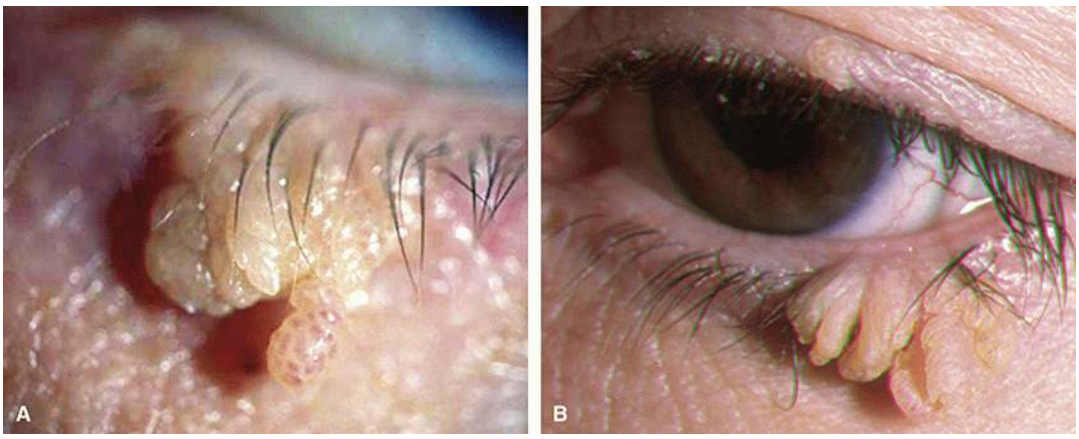

FIGURE 45.2 A and B, Pedunculated and filiform acrochordons. (B, Courtesy of Dr. Charles Soparkar.)

Differential Diagnosis

Entities that may be confused with skin tags include intradermal nevi, neurofibromas, verruca vulgaris (the common wart), nevus lipomatosis, dermatosis papulosa nigra (DPN), and some keratinocyte carcinomas (nonmelanoma skin cancers) including basal and squamous cell carcinoma.[1] Intradermal nevi may have a boggy, flesh-colored appearance, which may make differentiation from skin tags impossible except by histologic examination. Delayed age of onset may help establish a diagnosis of acrochordon rather than a nevus.[1] Dermal neurofibromas can resemble skin tags, but on palpation, the diagnosis of neurofibroma can be effortlessly made because of the "buttonhole sign," where neurofibromas can be invaginated inside the skin with relative ease.[2,27,28]

Verruca vulgaris (common warts) are benign tumor-like proliferations or viral papillomas caused by infection of the epidermal cells with the HPV. These lesions are rare in the eyelids; however, one variety, the filiform wart, occasionally may be observed in the periorificial areas of the face like the mouth, as well as in the eyelids, and could be confused with acrochorda.[1,4] In the eyelids, filiform warts are usually solitary lesions with fingerlike projections that are commonly interspersed between the eyelashes.[1,4] Another rare entity that may look similar to a large skin tag is nevus lipomatosus (pedunculated lipofibroma) of the eyelid.[5] Clinically, the larger size of nevus lipomatosus may help differentiate both lesions, but histopathology is usually required to confirm the diagnosis.[5]

DPN is a pigmented papular eruption of the face and neck, which is currently considered a variant of seborrheic keratosis and is commonly observed in patients with a darker skin complexion. It affects 35% of African Americans and is also observed in Asian populations, albeit less commonly.[28,29] The very first presentation is during adolescence where minute, round, skin-colored, or hyperpigmented macules or papules are observed in the malar region and/or the periorbital region singly or in limited numbers, but they increase in number and size and spread to the rest of the face very slowly over time. Ultimately, a single patient may have hundreds of these lesions.[28,29] They closely resemble seborrheic keratoses, and therefore they can be easily distinguished from acrochordons, as DPN lesions usually assume the form of multiple, sharply demarcated papules or plaques in contrast to acrochorda, which are commonly pedunculated, and are generally fewer in number.[28,29]

Less commonly, a skin tag may simulate malignant conditions like a basal cell or squamous cell carcinoma.[1] Since acrochordons are extremely rare in children, their presence in the pediatric population should alert the clinician to the possibility of basal cell nevus syndrome (Gorlin-Goltz syndrome). Therefore, a presumptive diagnosis of acrochordon in a child should be regarded with some degree of concern.[2,3]

Treatment

Acrochordons can be removed at the patient's request, mostly for cosmetic improvement or because of irritation. Small skin tags can be removed in the clinic by snipping them with very sharp scissors without local anesthesia or cautery. Severing the lesion quickly with ultrasharp scissors may limit pain, and the crushing action of the scissors usually results in little bleeding.[1] Nevertheless, minimal local anesthesia with adrenaline may be preferred in the sensitive skin of the periocular region. Larger

or confluent acrochordons may require more extensive local anesthesia and cautery, regardless of the location.[1,2] Alternatively, cryotherapy or electrodessication may be employed.[1,2]

In typical lesions in adults, no biopsy is needed, but a biopsy should be performed on acrochordons in children because the lesions are uncommonly encountered in this age group. Failure to do so may miss a diagnosis of basal cell nevus syndrome.[2]

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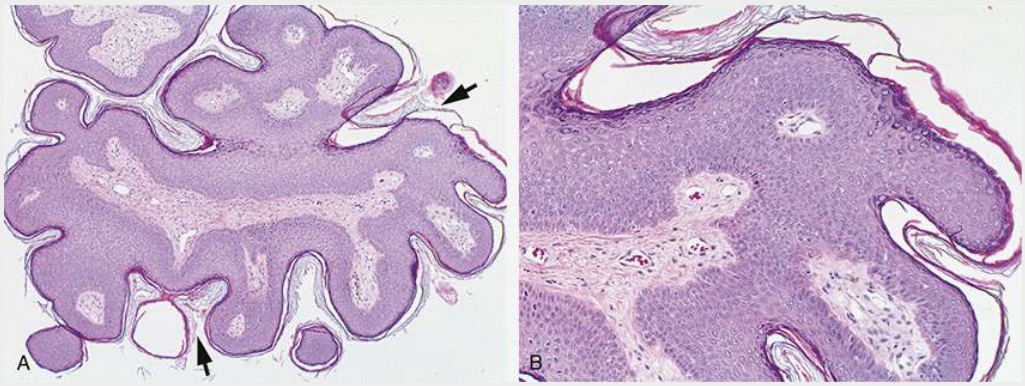

FIGURE 45.3 A and B, Eyelid acrochordons usually feature acanthotic epidermis forming interdigitating cords resembling those in seborrheic keratoses. The epidermis covers a fibrovascular core (✶) that may have loose or dense connective tissue. Several hyperkeratotic areas are evident (arrows).

Prognosis

Acrochordons are benign conditions with no possibility of malignant transformation.[2,3] Skin tags are of little consequence except for concerns that are of an esthetic nature.[6,7] Reassurance about the benign nature of these lesions should help minimize anxiety, but patients should also be informed that if left untreated, the number and size of skin tags are expected to progressively increase with age.[6,7] Patients should also be advised that skin tags may be an indicator that the patient could be more susceptible to a metabolic syndrome and its cardiovascular complications, so that lifestyle modifications may be required.

Histopathology

Acrochordons are highly variable histologically. They are sessile or pedunculated with a papillary configuration and a keratinized epidermis.[30] The epidermis may be normal or hyperplastic and covers a fibrovascular core of loose or dense collagen.[31] Acrochordons of the eyelid resemble those occurring on the neck[32,33]; they most often have acanthotic epidermis forming interdigitating cords resembling those in seborrheic keratoses (Figure 45.3). Horn cysts are uncommon in eyelid acrochordons. Hyperkeratosis may be diffuse, focal, or absent. Early lesions have less thickening of the epidermis with sparse or absent interdigitating epidermal cords. Larger lesions may have a flattened epithelium and a central core of adipose tissue.[34] With torsion, some lesions may develop ischemic necrosis. The principal histological differential diagnosis is with seborrheic keratosis, leading Waisman to classify neck acrochordons as “papillomatous seborrheic keratoses.”[33] In our experience, correlation of the clinical and pathological appearances is most useful to distinguish a seborrheic keratosis from an acrochordon. However, it is not always possible to differentiate these two entities histologically.

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CHAPTER 46

Actinic Keratosis

Key Points

- Alternative names in the literature include solar keratosis and senile keratosis
- Actinic keratosis (AK) results from the proliferation of epidermal keratinocytes with variable degrees of dysplasia
- AKs are one of the precancerous forms of squamous cell carcinoma
- They typically occur in older fair-skinned individuals with a history of chronic sun exposure and are rarely seen before the age of 45 years
- AK lesions typically feel rough on palpation
- Observation alone should not be an option in lesions that are near to the eyelid margin
- Excisional biopsy with permanent pathology is the recommended treatment of choice in the periorbital region
- Topical agents are only indicated if patients decline excision, or for residual lesions following surgery

Actinic keratoses (AKs) are red scaly lesions confined to the epidermis. They are commonly observed in older fair-skinned individuals with a history of chronic sun exposure, hence the alternative names solar keratosis or senile keratosis.[1,2,3,4,5,6,7,8,9,10] The term keratosis refers to a thickening of the stratum corneum in the epidermis, while the term actinic is a testament to its solar origin.[11]

Although a universally accepted agreement about the very nature of these lesions and their malignant potential is lacking, these dysplastic keratinocytic tumors have the potential to progress to in situ squamous cell carcinoma (SCC) (Bowen disease), invasive SCC, and quite possibly basal cell carcinoma (BCC).[1,2,3,4,5,6,7,8,9,10]

Etiology and Pathogenesis

AK is an epidermal proliferation of atypical keratinocytes that is induced by excessive exposure to nonionizing radiation, especially within the ultraviolet (UV) spectrum of sunlight, which generates a cascade of structural damage to a cell's DNA and membrane lipids.[2,11] UV-A radiation (320-400 nm) is responsible for 95% of the solar radiation that reaches the Earth and can penetrate deeply into the dermis having devastating effects.[11] Among other mechanisms, UV-A primarily induces indirect photooxidative damage via the generation of reactive oxygen species (ROS). Once these are generated, ROS damages cellular nuclei as well as cell membrane lipids. A secondary effect of UV-A is that it promotes guanine (G) to thymine (T) replacement mutations in DNA. Consequently, signal transduction and cellular interaction pathways are affected, and abnormal cellular proliferation ensues.[3,10,11,12,13,14,15] UV-B radiation (290-320 nm) constitutes just 5% of the solar radiation reaching the Earth's surface, but it penetrates the basal layer of the epidermis, so that its effect on keratinocytes is more devastating as it is directly absorbed by cellular DNA.[11] UV-B radiation causes replacement of the thymine and cytosine bases (C-T DNA substitutions) and promotes errors in the repair of cyclobutane thymidine dimers, with subsequent DNA damage.[11] The DNA mutations in these sun-damaged areas predominantly affect the p^{53} gene (*TP53*).[3,12,13,14,15] *TP53* is a tumor suppressor gene that interrupts the cell cycle to allow the repair of damaged DNA. The abnormal expression of *TP53* and its protein p^{53} are considered markers of premalignant conditions and play pivotal roles in the development of AK/SCC. Chromosomal mutations in this gene are found in 16% to 100% of AK lesions, but p53 mutations in AK are different from those associated with SCC.[5,10,16] Other oncogenes, particularly those along the mitogen-activated protein kinase pathway, may not be instrumental in AK per se but may play a pivotal role in the transition from AK to SCC.[16]

Other risk factors for the development of AK, besides solar radiation, include light skin, old age, male sex, and immunosuppression.[11,17] Patients with a light complexion (Fitzpatrick types I and II skin), light hair, or light iris color are more susceptible to develop

AK. This light complexion is why the condition is more common among people of European ancestry.[11,17] Patients older than 80 years are six times more likely to develop AK than patients in the sixth decade.[11] Increased prevalence in men may simply reflect their occupational exposure to solar radiation since men work outdoors more often than women. Immunosuppressed patients, such as organ transplant recipients, are also more susceptible to develop AK.[11,17] Other risk factors for AK include episodes of painful sunburn before the age of 20 years, never using sunscreen, and a positive family history of cutaneous neoplasms.[10] Multiple bouts of painful sunburn before the age of 20 years may initiate the carcinogenic cascade, which is an indication that acute recurrent exposure to UV radiation can also lead to p53 mutations and not just a chronic form of exposure.[10]

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The exact nature of AK is contested. Whether it is a premalignant condition (intraepithelial keratinocytic dysplasia), a malignant superficial SCC (in situ SCC), or merely a photoaging epiphenomenon resulting from chronic sun damage is uncertain.[3,5,6,9,15] Whether considered premalignant or malignant, the argument is rather semantic, because both conditions can potentially break through the basement membrane causing frank SCC.[15] Because all AK lesions show signs of cytologic atypia, the widely held view is that AK probably represents a premalignant condition that may progress to Bowen disease or SCC.[1,2] Proponents of the hypothesis that AKs are merely by-products of photodamage argue that AKs are fairly stable lesions that are neither malignant nor premalignant, as evidenced by the fact that most of the lesions do not routinely progress to SCC.[15] They contend that even when AKs progress to malignancy, the process follows a two-step model of carcinogenesis. An initial mutation in a tumor suppressor gene results in the development of AK, which in this scenario is merely an initiated or a precursor lesion insufficiently promoted to become malignant. In a second step, an additional or second carcinogenic hit leads to the acquisition of invasive properties and progression to SCC.[10,15] Whether the time factor (lesion duration) contributes to this second hit or not is controversial.[10]

The clinical significance of AKs stems from the fact that they are closely related to nonmelanoma skin cancers (NMSCs) or keratinocyte carcinomas (KCs).[10] Although both terms (NMSC and KC) are loosely used interchangeably in the literature, they are not identical, and the term KC is preferred over NMSC because AKs and other KCs universally arise from epidermal keratinocytes.[5,7] Furthermore, the ambiguous term NMSC also includes other nonkeratinocyte malignancies like basal cell, squamous cell, and Merkel cell carcinoma, cutaneous lymphoma, or sebaceous carcinoma. Therefore, the term KC rather than NMSC will be used throughout this chapter.[7]

AK may progress to SCC in one of the two ways. The classic pathway requires a stepwise development of full-thickness epidermal neoplasia, which should precede the development of invasive SCC. The alternative mechanism, termed the differentiated pathway, entails the direct invasion of proliferating atypical keratinocytes that are originally limited to the epidermal basal layer along the shafts of hair follicles and sweat ducts.[10,18] This adnexal invasion mode is far more aggressive than the classic or direct pathway.[10] However, there is an ongoing controversy regarding the possibility of progression of solar keratosis to BCC, and the mechanism of this alleged progression is not precisely known.[5,8] It could be argued that some early lesions, which were presumably diagnosed initially as AK, were BCCs from the start, previously mistaken for AKs.[5,8] Alternatively, an AK may be masking an underlying infiltrative or nodular BCC.[19] Adding to the confusion is that several other reports documented that solar keratosis may have histologic features suggestive of both SCC and BCC.[8,20]

Clinical Presentation

The epidemiology of AK is simply a reflection of the different nomenclatures it bears in the literature (actinic, solar, or senile).[17] AK is quite common and is the third most frequent cause for dermatologic consultations.[21] On an international level, the prevalence of AK is highest in subtropical and hot sunny regions like Australia. The condition affects approximately one in six North Americans during their lifetime, as well as 40% to 60% of Australians older than 40 years, and it has been calculated that up to 34% of males in the United Kingdom older than 70 years have at least one AK lesion.[4,10]

As was mentioned earlier, studies in Europe, Australia, and the United States have consistently shown that the disease is more common in males. Whether this has a prognostic significance or impacts on the progression of AK to SCC is debatable.[22,23,24,25,26,27] Because AK results from cumulative exposure to the sun, it is mainly a disease of individuals older than 45 years, and the incidence rises with advancing age.[1,2,3,4,5]

The body areas most affected include the forehead, balding scalp, ears, the vermilion of the lower lip (actinic cheilitis), forearms, and dorsal aspect of the hands.[4,5] AK is rarely reported in the periorbital region, though it accounts for 2% to 5% of eyelid tumors. Unfortunately, because of the rarity of the condition, and the subsequent lack of epidemiological studies about eyelid AK, it is not clear whether periorbital AK is more frequent in the upper or the lower eyelids. One clinicopathological study showed that 81% of periorbital AKs occur in the upper eyelid.[27] This finding is counterintuitive because the upper eyelids are considered a more sun-protected site in the face, compared with the lower eyelids.[28] Moreover, other KCs like SCC and BCC are more common in the lower eyelid and medial canthal region. In our experience, approximately 70% of eyelid AKs involve the lower eyelids, a proportion similar to periocular BCC and SCC. The 30% of AKs in the upper eyelids may be due, at least in part, to the upper eyelid skin being

the thinnest skin in the body, making it highly vulnerable to actinic damage despite its privileged location.[29]

Large or confluent lesions may cause cosmetic disfigurement or physical irritation, and some patients may notice an area of roughened skin, which may occasionally itch or become tender to touch, but otherwise, AK is usually asymptomatic.[4,5,30] In subtropical regions like Australia and New Zealand where individuals are generally more sun-aware, patients are more concerned about the malignant nature of the lesion and may present earlier.[17]

AKs may range in appearance from macular erythematous foci (Figure 46.1) to large hyperkeratotic plaques (Figure 46.2A). They are typically multiple, small in size, slightly raised, skin-colored, or yellowish-brown macules or papules, often with overlying dry adherent scales. They may feel rough on palpation, a feeling which is evocative of a sandpaper *(Print pagebreak 301) (Print pagebreak 302)* feel that is often more felt than seen.[5,31] Some lesions may have telangiectatic vessels on the surface, while others may be variably pigmented. Occasionally, AK may also proliferate and become exophytic to constitute a cutaneous horn, a condition that is termed verrucous keratosis, but it is more common on the ears than the eyelids (Figure 46.2B).[4,5] If an AK rapidly enlarges, suddenly becomes painful, eroded, indurated, or erythematous, or if the lesion is >1 cm in diameter, the clinician should suspect the rare development of SCC.[4,27,32] Furthermore, the presence of multiple and confluent AK lesions is termed field cancerization, which is an independent risk factor for the development of SCC.[10,11]

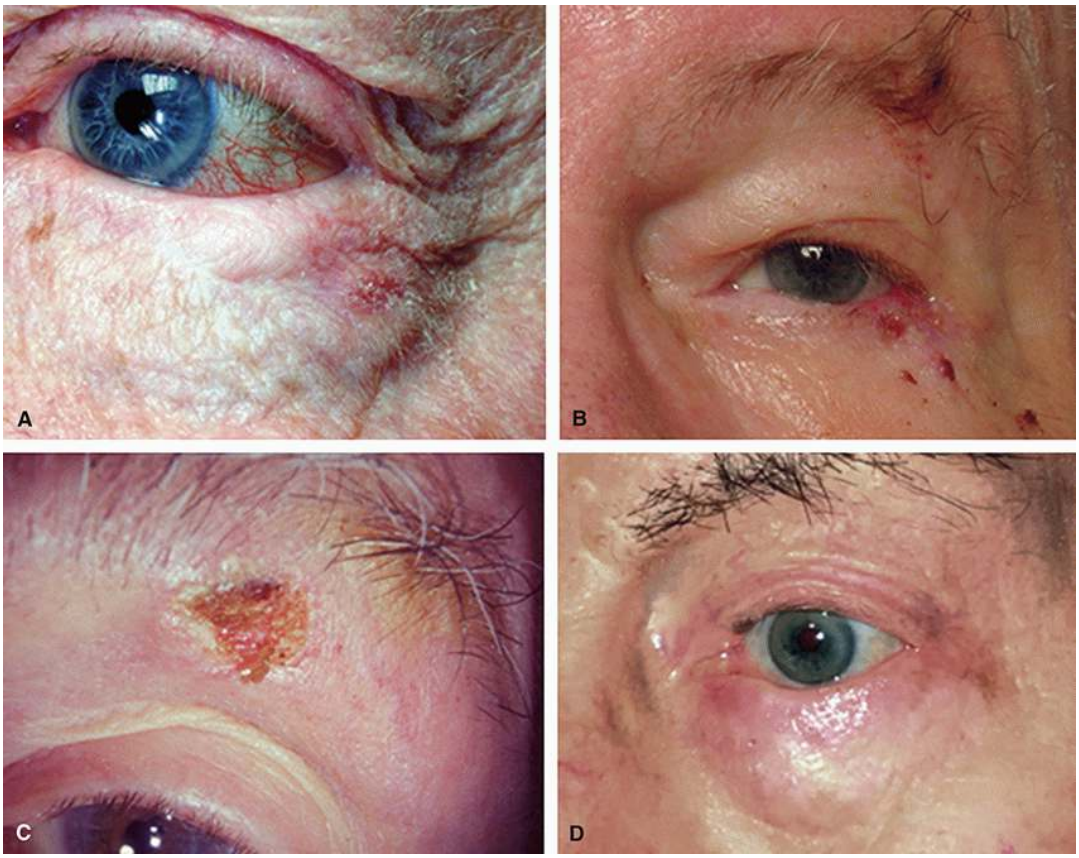

FIGURE 46.1 Actinic keratosis (AK) of the eyelids and brow. A and B, AK at the lateral lower eyelid. (Courtesy of Dr. Robert Goldberg). C, AK on the inferior brow with superficial scales. D, Erythematous macular AK on the medial lower eyelid.

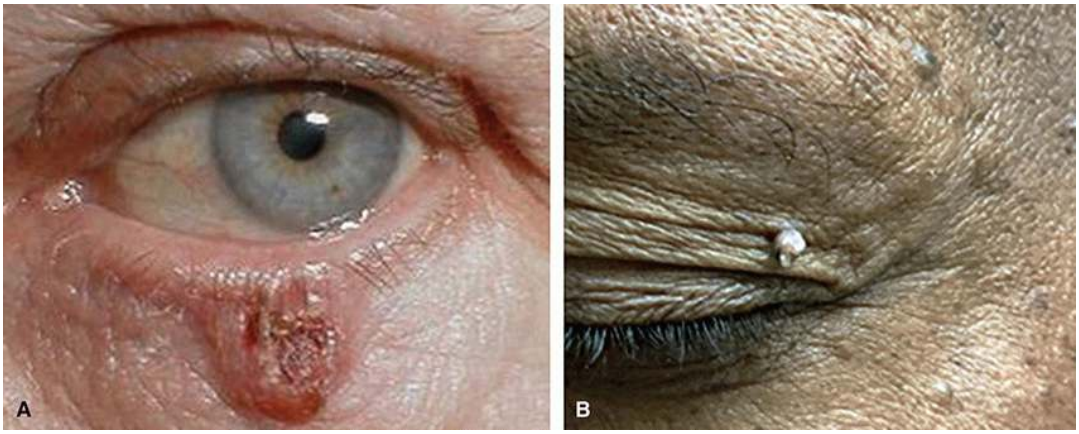

FIGURE 46.2 A, Large hyperkeratotic actinic keratosis (AK) on the central lower eyelid. B, Small AK on the lateral upper eyelid with a cutaneous horn.

On clinical grounds, AK may be classified according to the Olsen clinical classification scheme into grades I, II, and III, where grade I lesions are slightly palpable (better felt than seen), grade II lesions are moderately thick (easily felt and seen), and grade III lesions are hyperkeratotic.[33] Because of the rarity of eyelid AK, the distinction between these grades may be of lesser clinical relevance in the periorbital region. Morphological variation may affect our ability to diagnose AKs properly, as there are several different subtypes of AK (atrophic, Bowenoid, lichenoid, pigmented, or hypertrophic). These types can only be distinguished by dermoscopy or histopathology.[2,5,15]

Ocular and systemic examinations are usually unremarkable, but it should be noted that a history of solar keratosis is strongly associated with the development of ocular surface squamous neoplasia because solar UV radiation is considered a risk factor for both conditions; therefore, ocular surface examination should not be overlooked.[34,35]

Differential Diagnosis

AK should be differentiated from other benign skin conditions associated with aging, solar exposure, or both (photoaging), and in this regard, dermoscopy, a clinic diagnostic tool that is not frequently employed by ophthalmologists, has been repeatedly shown to be extremely important in the accurate diagnosis of equivocal lesions.[4,10] Dermoscopy utilizes a skin surface microscope, which is widely available in dermatology clinics, to examine the skin. Although it may occasionally obviate the need for a skin biopsy, clinicopathological correlation with histopathology remains the gold standard for diagnosis of cutaneous conditions.[36]

Seborrheic keratosis (Chapter 115) is a common skin condition that is easily confused with AK. In contrast to AK, seborrheic keratoses are raised (rarely flat), friable, verrucous, or "stuck-on" epidermal papules, which may be easily scraped off the skin surface, and they may be skin colored, or variably pigmented.[1] They are also age-related but may arise suddenly in large crops as a paraneoplastic sign of internal malignancy (Leser-Trélat sign).[2] Other conditions that may also be confused with AK include common warts (verruca vulgaris), stucco keratosis, arsenical keratosis, discoid lupus erythematosus, acantholytic acanthoma, psoriasis, and acrokeratosis verruciformis, although most of these lesions are rarely observed in the periocular region.[10,27,37,38] Pigmented AKs may also pose a diagnostic uncertainty and should be differentiated from other pigmented skin conditions like junctional nevi, melanocytic compound nevi, lentigo maligna, solar lentigo, and lichenoid keratosis.[10,38]

AK should also be differentiated from other nonpigmented premalignant conditions in the eyelids like Bowen disease and an evolving or developing keratoacanthoma.[39,40] Initially, Bowen disease may be similar in size and appearance to AK, but the former lesions are recalcitrant nonhealing ones, that by definition could grow in size to reach several centimeters, and they are typically more erythematous and scaly.[39] On a histological level, Bowen disease differs from AK in that it has full-thickness cytological atypia of the epithelium. Using immunohistochemical staining, the basal layer on Bowen disease is spared, whereas in AK it is routinely abnormal.[41] In contrast, the distinction between AK and keratoacanthomas is not usually difficult, except if the lesion is still evolving. Keratoacanthomas are rapidly progressive lesions that appear as raised flesh-colored papules with a central crater filled with keratin (Chapter 76). They are typically observed on the lower eyelids and may spontaneously involute.[39]

Clinically, BCC may also be mistaken for AK or vice versa, and the correct diagnosis may only be established with histopathology.[30,42] Both lesions may have telangiectatic vessels on the surface, but the characteristic rolled edges are usually more suggestive of BCC (Chapter 128).[30,43]

Treatment

Although the lack of consensus about the nature of AK and its malignant potential may have contributed to inconsistencies in management decisions in the past, the treatment strategy of AK has evolved from the traditional approach of observation and "treat as you go" to a more preemptive therapeutic strategy where all lesions are treated proactively to reduce the potential for progression to KCs.[10,44]

Before discussing treatment options, it is important to stress that prevention is of paramount importance. Increasing awareness and knowledge about AK and its malignant potential, as well as adopting a policy of lifelong sun protection strategy directed both against UV-A and UV-B, as well as regular examinations of the skin in susceptible individuals, may help reduce the prevalence of AKs or their progression to more ominous KCs.[45,46]

Although the treatment of AK in the periorbital region is not standardized,[9] its proximity to the eye, coupled with the fact that

it is impossible to predict which lesions will progress and which ones will not, mandates that observation of eyelid AKs as a primary mode of treatment is not an option as it can lead to devastating consequences. It is important *(Print pagebreak 303)* from a medical point of view to treat all of these lesions.[9,46] A lower threshold for biopsy of suspicious lesions is highly recommended in high-risk patients like organ transplant recipients, patients receiving chemotherapy, or patients with chronic lymphocytic leukemia.[46]

Treatment is indicated primarily to limit the potential for malignant transformation, but the cosmetic burden of AK should not be overlooked.[5,47,48] Therapeutic options can broadly be classified into surgical and nonsurgical treatment modalities. Surgical options can be further subclassified into excisional biopsy or nonscalpel surgical treatments.[9] Although excisional biopsy is the accepted method of choice in periorbital AK, a clear-cut approach to excision is lacking. A recent electronic survey that was distributed to members of the American Society of Ophthalmic Plastic and Reconstructive Surgery inquiring about their preferred practice pattern with regard to AK showed that the majority of respondents preferred to excise the lesion with permanent pathology. Others excised and then referred the patient to a Mohs surgeon, while some respondents excised the lesion under frozen section control.[9] The majority of eyelid AKs are small (<2 mm) and may not require extensive reconstruction, which may obviate the need for a Mohs surgeon.[9] Because these lesions are premalignant at best, even if one margin of the excised lesion is not cleared, there is no need for immediate reoperation, and observation is warranted, although reexcision may be indicated if a lesion persists or enlarges again.[9]

Nonscalpel surgical options include cryosurgery, curettage, electrosurgery, dermabrasion, chemical peels, laser therapy, and methyl aminolevulinate photodynamic therapy.[44,49,50,51] However, the use of some of these modalities may not be recommended in lesions that are close to the eyelid margin.[9] The use of any of these modalities limits the ability of the clinician to identify the nature of the lesion and leaves the clinician and patient with the burden of diagnostic uncertainty.[9]

There is a wide range of topical preparations that are used by dermatologists in the management of AK. Topical agents are indicated only if patients decline surgery, or if a biopsy shows a positive margin.[9] Even if a nonexcisional treatment is chosen, topical agents should be used with extreme caution, and the patient should be scheduled for a regular follow-up to reevaluate the lesion.[52] Unfortunately, patients may be more concerned with the cosmetic outcome and the side effects of surgery than the data about the potential for progression to invasive cancer.[53]

5-Fluorouracil (5-FU, 0.5%-5%) is a pyrimidine antimetabolite chemotherapeutic agent that is FDA approved for use in AK and superficial BCC. The mechanism of action of 5-FU in KCs is attributed to intracellular depletion of thymidine, which leads to decreased DNA synthesis, and eventually, cellular destruction.[54] The drug may be indicated in patients who decline surgery, or after incomplete excision of AK where an in situ residual component is observed histologically at the edges. However, it should be used with caution near the eyelid margin because it may lead to temporary conjunctival and ocular irritation, and rarely can lead to transient hair thinning or hair loss.[54] It is available as a cream or solution that is usually applied topically to the treatment area, twice daily for 2 to 4 weeks. Although some authors recommend a lower concentration (0.5%) for facial AK,[11] the 5% formulation is more widely available worldwide.[10]

Topical imiquimod 5% is also approved by the FDA for the treatment of AK. Although this drug was initially developed as an antiviral agent, its immunomodulatory activity prompted its use as a topical antitumoral agent. Imiquimod is a Toll-like receptor agonist (TLR-7 and TLR-8 receptors), inducing proinflammatory cytokines, which eventually mount a Th1 antitumor response. The drug also upregulates apoptotic activity.[54] Because of its hydrophobic nature and small size, it can penetrate the epidermis with relative ease, which makes it an ideal agent for topical application. It is usually used on a twice-weekly basis for 16 weeks, but several alternative regimens have been described. Imiquimod results in complete clearance in almost half of the treated lesions.[54,55,56,57] Patients should be informed that because the cream base contains both stearyl and benzyl alcohol, it is not generally recommended in the periocular region, which may result in ocular irritation, and itching may vary from mild to severe.[3] Patients may also complain of a burning ocular sensation or epiphora due to punctate keratitis.[58] Erythema, erosion, and a significant inflammatory reaction may be observed on the surface of the lesion, which usually resolves within 1 month after cessation of therapy.[58] However, patients should also be informed that a mild to moderate inflammatory reaction may be an acceptable collateral damage in treating a premalignant condition. Other possible but rare side effects include preseptal cellulitis and microbial keratitis.[58]

Diclofenac gel (3%) is a nonsteroidal anti-inflammatory agent that works via inhibition of cyclooxygenase 2, which in turn leads to a reduction in prostaglandin synthesis, induction of apoptosis, and inhibition of cell differentiation and angiogenesis.[10] It is applied twice daily for a minimum period of 60 to 90 days. The long-term efficacy is excellent, with very high remission rates 1 year after treatment in immunocompetent patients, although the results may be less stellar in immunosuppressed individuals.[10] Because of the relatively long duration of therapy, the main problem with diclofenac gel is that its efficacy is largely dependent on patient compliance.

Ingenol mebutate (Picato) is a macrocyclic diterpene ester derived from the sap of the plant *Euphorbia peplus*, which was

originally a traditional herbal medicine. The drug has two mechanisms of action, cytotoxic and immunomodulatory.[10,54] It works either by inducing primary necrosis of cell membranes and mitochondria or via a protein kinase C-mediated, antibody-dependent cellular cytotoxicity. Several *(Print pagebreak 304)* well-constructed studies have shown its benefit in AK.[54,55,56,57,59] However, in January 2020, the European Medicines Agency (EMA) suspended the drug following a recommendation by its Pharmacovigilance Risk Assessment Committee, citing reports of increased rates of skin cancer associated with the drug. Tirbanibulin 10 mg/g (1%) ointment, is a new topical formulation which has been approved by the EMA for the treatment of Olsen Grade 1 scalp and face AK, but to the best of our knowledge, its periocular use not been reported yet.[59]

Prognosis

The fate of AK is not a one-way track to malignancy. An untreated AK may take one of three courses, spontaneous remission (18%-63%), stable persistence (63%), or malignant transformation (0%-20%).[5,6,10] The reported rates of the three different courses that this disease may take are highly variable in the literature, but it is predominantly one of persistence or regression.[5] It has been estimated that between 60% and 80% of SCCs develop in areas of AK, but the exact rate of progression is variably documented in the literature, and the numbers range from 0% to 0.53% per year. However, some studies report higher yearly figures.[5,6,8,10] Higher rates are generally reported in patients where there is a history of recurrent AK, a prior history of another KC, or in high-risk patient populations.[5,6,46] Although yearly estimates of progression vary, they generally translate to a substantially high cumulative lifetime risk of progression from AK to SCC (10% and 20% at 10 years in immunocompetent and immunosuppressed individuals, respectively).[5,9,10,60] Spontaneous regression may be observed if the patient discontinues sun exposure.[39]

Despite its rarity in the periocular region, AK is one of the few red flags in oculoplastic surgery, and the reason for this is twofold. The potential ability of AK to transform to SCC is a matter of primary concern, but the mere presence of AK lesions is a biomarker or an indicator that the patient has sustained a large cumulative dose of UV radiation, which means that the patient is susceptible not only to KCs (SCC, Bowen disease, and BCC) but also to malignant melanoma (MM).[11,17] Indeed, several population-based studies that followed AK patients for periods of up to 10 years showed that the risk of developing skin cancers in AK patients is sixfold higher than in the population without AK.[61,62] The odds ratio for developing SCC is higher than the odds ratio for developing BCC or MM.[10,33]

Histopathology

The World Health Organization Classification of Skin Tumours lists seven histological variants of AK,[63] though there is variability in terminology among dermatopathology textbooks.[64,65,66,67] All of the histological variants have focal parakeratosis, dysplastic keratinocytes occupying at least the basal layer, dermal actinic elastosis, and a variable degree of dermal mononuclear inflammation. AKs may be an isolated lesion or associated with seborrheic keratosis, solar (senile) lentigo, melanocytic tumors, or in situ or invasive SCC.

Hypertrophic AK features orthokeratosis with alternating parakeratosis, acanthosis with mild or moderate papillomatosis, and dysplastic keratinocytes that may be minimal and confined to the basal layer. Hypertrophic AK is the variant most commonly seen in eyelid biopsies (Figure 46.3A and B); striking hyperkeratosis occasionally results in a cutaneous horn (Figure 46.3C and D).[31] In some cases of hypertrophic AK (sometimes termed proliferative AK), more pronounced cytological atypia and papillomatosis may simulate an invasive SCC.

Lichenoid AK is the second most common variant seen in the periocular region, in our experience, though it is much less common than hypertrophic AK. Lichenoid AK has dysplastic epidermal cells, irregular acanthosis, vacuolar change of basal cells, occasional apoptotic keratinocytes, hyperkeratosis and/or parakeratosis, along with a band-like (“lichenoid”) infiltrate of lymphocytes and macrophages in the superficial dermis abutting the epidermis (Figure 46.3E).

Bowenoid AK is characterized by dysplastic cells extending through almost the full thickness of the epidermis,[63,66] though some dermatopathology texts indicate that Bowenoid AK may have full-thickness dysplasia.[64] In the eyelid and periocular region, ophthalmic pathologists classify epidermal lesions with full-thickness dysplasia as SCC in situ or Bowen disease.[68]

Atrophic AK has a thinned epidermis, sometimes only a few cells thick, with cytologically atypical basal keratinocytes and parakeratosis. Acantholytic AK has dysplastic keratinocytes and suprabasal acantholysis leading to clefts.

Pigmented AK is distinguished by excessive melanin within keratinocytes of the lower epidermis and often in melanocytes and dermal macrophages (Figure 46.3F).

Epidermolytic AK has dysplastic keratinocytes together with features of epidermolytic hyperkeratosis: clear spaces around nuclei in

the spinous and granular layers, keratinocytes with pale staining cytoplasm with indistinct cell borders in the upper epidermis, marked thickening of the granular layer with irregularly shaped keratohyalin granules, and compact hyperkeratosis.[65,69,70]

Due to the multiple variants of AK, the histologic differential diagnosis is broad. In our experience, the most common issue is distinguishing hypertrophic AK from superficial BCC in tiny eyelid biopsies. Immunohistochemical stains using antibodies to Ber-EP4 resolve these cases since the atypical keratinocytes in BCC stain positively, while those in AK do not stain.[71] If the clinical diagnosis is SCC, then additional histological sections are warranted before diagnosing AK. Pigmented AK may simulate lentigo maligna but can be differentiated using immunohistochemical stains for melanocyte-inducing transcription factor (MITF; also termed microphthalmia-associated transcription factor) or SOX10.[66] MITF and SOX10 will stain the atypical melanocytes of lentigo maligna but not the dysplastic keratinocytes of AK.[64]

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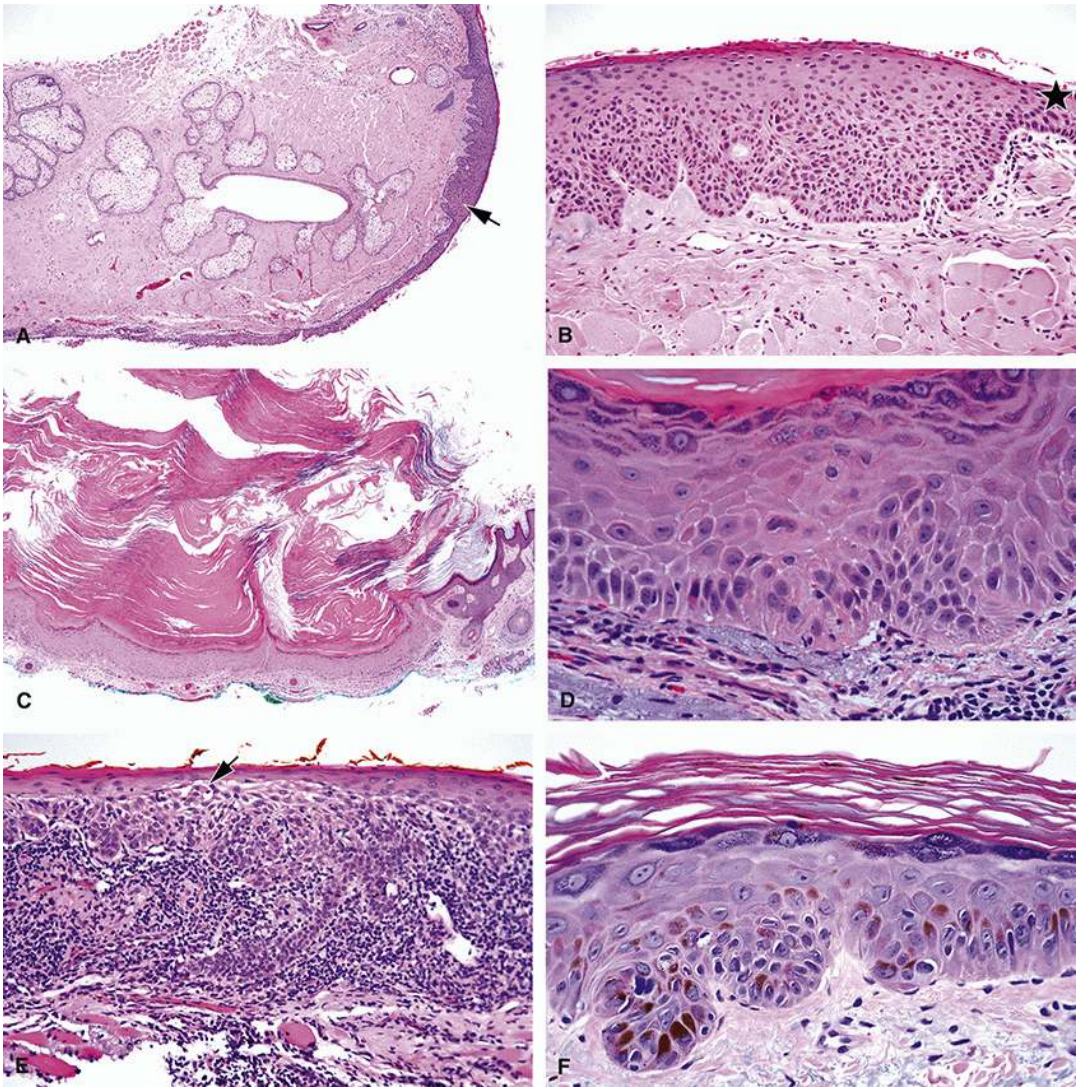

FIGURE 46.3 A and B, An area of hypertrophic actinic keratosis (AK) arises abruptly at the eyelid margin (arrow). At higher magnification (B), the hypertrophic AK has acanthosis with dysplastic disorganized keratinocytes in the lower half of the epidermis. Normal eyelid epidermis is at the right of the photomicrograph (★). C and D, This eyelid hypertrophic AK has mild to moderate acanthosis and profound hyperkeratosis. The patient had a cutaneous horn clinically, but the superficial portion of the hyperkeratosis dislodged during specimen handling. Dysplastic keratinocytes are evident in the basal epidermis when viewed at higher magnification (D). E, This eyelid lichenoid AK has dysplastic keratinocytes in the basal half of the epidermis, irregular acanthosis, vacuolar change of occasional basal cells, an apoptotic keratinocyte with bright pink cytoplasm near the surface of the epidermis (arrow), parakeratosis, and a band-like infiltrate of mononuclear leukocytes in the superficial dermis. F, Melanin accumulation in the dysplastic basal keratinocytes distinguishes pigmented AK.

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CHAPTER 47

Amyloidosis

Key Points

- Amyloidosis is a heterogeneous group of disorders defined by the extracellular deposition of insoluble misfolded proteinaceous fibrils that have undergone conformational changes
- Amyloidosis may be localized, systemic, or hereditary
- There are four major types of systemic amyloidosis; systemic amyloid light-chain (AL) amyloidosis is the most common type seen in 65% of patients with systemic amyloidosis
- Localized disease results from the proliferation of B cells or plasma cells and is the most common type seen in the eyelid skin
- Eyelid lesions present as salmon-like or friable yellowish deposits with spontaneous bleeding that can also infiltrate the tarsus and conjunctiva
- Surgical excision or debulking is a common treatment, but this is technically challenging and roughly 50% of patients require a reoperation
- The prognosis of systemic amyloidosis varies according to the type, but it continues to largely be a fatal disease

Amyloidosis is not a single disease. It is a generic term for an extremely heterogeneous group of disorders that are collectively defined by the extracellular deposition of insoluble misfolded proteinaceous fibrils that have undergone conformational changes to form β-pleated sheets, resulting in progressive organ damage.[1,2,3,4,5,6,7,8,9] Although the condition has been known from necropsy reports for hundreds of years, the enigmatic term amyloid was only coined during the 19th century to describe the lardlike or starch-like nature of the disease.[1,2,8]

Etiology and Pathogenesis

To understand the pathogenesis of amyloidosis, it is important to appreciate the process of protein folding, which is a physical process by which a primary protein structure (a linear amino acid sequence or chain) that is usually biologically nonfunctional acquires a three-dimensional geometrical form. This structural modification helps the protein to perform its biological functions in a reproducible manner. In nature, those secondary or folded protein structures normally occur in two forms that may coexist in a dynamic equilibrium, α-helices and β-strands.[10] The α-helix is a tightly coiled spiral rodlike structure, while the native β-strands are planar, almost fully extended stretches of amino acids arranged in a zigzag form, and they may align with each other to form β-sheets in a parallel or antiparallel fashion.[10]

Any disruption of this delicate process of protein homeostasis can cause protein misfolding and/or abnormal aggregation. The amyloidoses are a remarkably diverse group of disorders with diverse pathogenetic or amyloidogenic events that may be quite variable and may involve several overlapping mechanisms.[11] The predisposing factors can be summarily grouped into five recurring themes: (1) genetic mutations, (2) intrinsic amyloidogenic tendency, (3) increased concentration of amyloid proteins, (4) altered proteolytic activity, or (5) pharmaceutical amyloidosis.[11,12,13,14]

A plethora of genetic mutations (hereditary or de novo) can predispose to protein misfolding or protein overproduction, including abnormalities in the SNCA gene, the TTR gene, and the GSN gene.[11,13,14] However, several endogenous proteins (transthyretin [TTR]; atrial natriuretic factor; apolipoproteins A-I, A-IV, and E; and serum amyloid protein) have an intrinsic amyloidogenic tendency, or the innate ability to fold into an abnormal structure, causing systemic amyloidosis in the elderly without any apparent genetic predisposition.[11] A persistently high concentration of amyloidogenic proteins may be observed in chronic inflammatory conditions due to the overproduction of proteins or undersecretion of the protein in question in end-stage renal disease.[2] Altered

proteolytic activity is another plausible amyloidogenic mechanism. The quintessential example is Alzheimer disease, where amyloid-β precursor protein forms neuritic plaques, although the exact relation between amyloidosis and Alzheimer, whether it is a causal, accidental, or comorbid association, is hotly debated nowadays.[15] Pharmaceutical amyloidosis is rare. Some exogenous proteins (insulin and enfuvirtide) can deposit in tissues causing localized amyloidosis at the sites of injection.[12]

Regardless of the predisposing cause, the underlying molecular events that occur in patients with amyloidosis are essentially the same. β-pleated sheets predominate and are produced in excess of α-helices, thereby breaking the normal dynamic equilibrium in favor of β-sheets. This alters protein dynamics in the tissues involved, making them inherently unstable, which in turn increases the propensity for misfolding and aggregation.[16] β-pleated proteins congregate with each other in a highly ordered fashion to form cross-β-sheets of amyloid fibrils in vivo, which are structurally distinct from the naturally occurring or the native β-sheets.[16,17,18] *(Print pagebreak 309)* These abnormal dysfunctional proteins aggregate into structural polymers, and automatically become resistant to proteolysis, thereby losing their solubility. They subsequently accumulate extracellularly in excessive amounts as amyloid deposits, ultimately causing structural and functional tissue damage.[2,11,16,19] It should be noted that although the abovementioned processes of abnormal protein misfolding and disequilibrium are indeed the predominant underlying events in amyloidosis, they are not the only ones. An overabundance or excessive aggregation of normal reactant proteins may also cause amyloidosis (AA amyloidosis).[19]

As of April 2022, 36 different proteins are known to misfold into β-pleated sheets, and the list of these proteins is updated continuously by the International Society of Amyloidosis Nomenclature Committee. At least about 15 of these misfolded proteins cause systemic amyloidosis.[2,3,4,8,11,12,19,20]

Amyloidosis may be classified into localized, systemic, or hereditary types. There are four major types of systemic amyloidosis.[21] Systemic amyloid light-chain (AL) amyloidosis develops when an abnormal clone of plasma cells in the bone marrow produces abnormal κ or λ immunoglobulin light chains. AL amyloidosis is referred to as immunoglobulin light-chain amyloidosis, although it was previously referred to in the literature as primary systemic amyloidosis.[19,21,22] It may develop spontaneously, hence its older designation as the primary type. However, it is more commonly associated with, or secondary to, other blood dyscrasias such as multiple myeloma and Waldenström macroglobulinemia.[21,23] This is the most commonly observed type of systemic amyloidosis in clinical practice and accounts for 65% of patients.[23] The heart and kidney are the most commonly affected sites, although every organ in the body except the brain can be involved.[9,19]

Reactive systemic amyloidosis (AA amyloidosis) designates the deposition of serum amyloid A (SAA) protein, a nonimmunoglobulin protein that is an acute-phase reactant. Reactive systemic amyloidosis is usually secondary to chronic inflammatory conditions like autoimmune diseases (rheumatoid arthritis), inflammatory bowel diseases (Crohn disease), chronic infections, familial Mediterranean fever, or skin diseases (discoid lupus erythematosus, leprosy, or cutaneous tuberculosis). The liver and the kidney are the most commonly affected organs, and it was previously referred to in the literature as secondary amyloidosis.[1,2,3,4,5,7,11,16,19,21,24] The two remaining types of systemic amyloidosis that may be observed in clinical practice are dialysis-related amyloidosis (Aβ2M amyloidosis) and ATTR amyloidosis, which is caused by a mutation of the precursor TTR protein, and preferentially involves the heart or causes polyneuropathy.[19,21,24]

Localized disease is usually caused by the clonal deposition of κ or λ light chains resulting from the local or in situ monoclonal proliferation of B cells or plasma cells.[21,25,26] Localized amyloidosis causes detectable nodular masses within a single organ like the larynx, lungs, liver, tongue, or skin.[26] It is referred to in the literature as localized AL amyloidosis. The AL type is the type most commonly encountered in the eyelid skin,[6] and curiously, even though it shares the same amyloid deposit subtype with systemic AL amyloidosis, it is not routinely associated with hematologic dyscrasias.[16,21] Proteomic analysis has identified both heavy and light chains in localized AL amyloid deposits, while only light chains deposit in systemic AL amyloidosis.[27] Thus, proteomic analysis has the potential for assessing the risk of systemic disease.

Clinical Presentation

The nomenclature of the various types of amyloidoses (AL, AR, ATTR, AGel, Aβ, etc) is based on the type of the soluble protein precursor. When an amyloid deposition is not restricted to a particular organ and is identified in at least two different sites of the body, the disease is labeled systemic amyloidosis.[20]

Amyloidosis is a rare disease with an estimated overall global incidence that varies between 5 and 12.8 cases/million population per year.[1,2,28] The overall incidence of AA amyloidosis has sharply declined in the developed world, although the incidence is still high in developing countries. This is attributable to advances in the treatment of the underlying chronic or inflammatory conditions.[28] However, the incidence of AL amyloidosis has risen from 9.7 to 14 cases/million population per year in the period between 2007 and 2015.[29] Adnexal and orbital amyloidosis is rare[21] and accounts for only 4% of head and neck amyloidosis.[30]

Amyloidosis is predominantly a disease of mid-to-late life (mean age, 57 ± 17 years), but it can occur in children.[2,21] As a general

rule, unilateral adnexal involvement is more suggestive of localized disease, while bilateral adnexal disease should alert the clinician to the possibility of a systemic association.[7,21,24] The presenting complaint is usually either ptosis or a change in the consistency of the eyelids in the form of a swollen eyelid, a thickened bumpy feel, or a frank eyelid deformity (Figure 47.1). Patients with conjunctival amyloidosis or lid margin disease may present with tearing, discomfort, or a foreign body sensation.[7,24,31]

Cutaneous amyloid deposits in the eyelids are rare, which makes the condition notoriously challenging to diagnose, but when it occurs, eyelid involvement can either be an isolated finding or part of systemic disease.[6,20,24] The hallmark of eyelid disease is spontaneous bleeding around the periocular region. Amyloid tends to deposit within the walls of blood and lymphatic vessels in the skin, causing blood vessel fragility.[16] Eyelid bleeding usually occurs following minimal trauma like rubbing, or even spontaneously without a traumatic event (Figure 47.2A).[32,33] Although cutaneous hemorrhages may be observed elsewhere in the body, there is a particular affinity for this process to occur around the eyes with petechiae and ecchymosis causing this classic sign, which is frequently referred to in the literature as “raccoon eyes” (periorbital purpura). Whenever present, *(Print pagebreak 310) (Print pagebreak 311)* this alarming sign should alert the clinician to the possibility of undiagnosed systemic amyloidosis.[16] Periorbital bleeding associated with ocular adnexal amyloidosis may occur secondary to multiple myeloma (AL amyloidosis), TTR amyloidosis, or AA amyloidosis presenting with renal disease,[34] or after general anesthesia, and following surgical procedures elsewhere in the body (such as diagnostic proctoscopy), in patients with AL amyloidosis.[34] It should be noted that this striking clinical sign is a late, albeit sinister, manifestation of systemic amyloidosis, but it is relatively uncommon.[7]

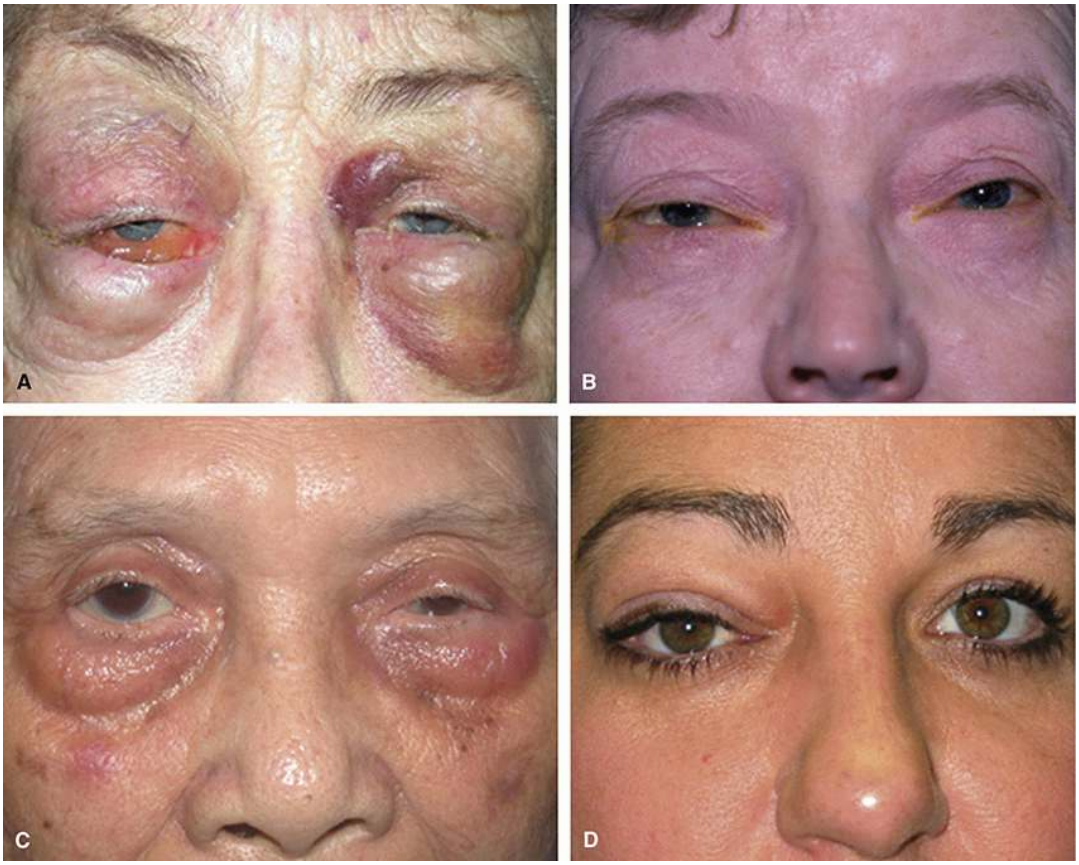

FIGURE 47.1 A-D, Periorbital amyloidosis cases with chronic eyelid edema and mechanical ptosis.

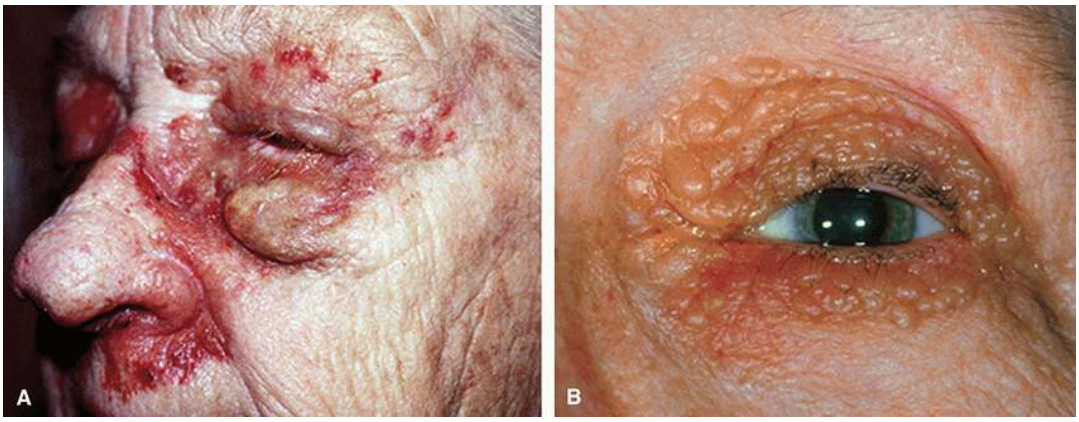

FIGURE 47.2 A, Racoon eyes from spontaneous hemorrhage in bilateral periorbital amyloidosis. B, Upper and lower eyelid amyloidosis with numerous small confluent papulonodular masses.

More commonly, eyelid amyloidosis presents with bilateral, symmetric, and variably sized palpable waxy cutaneous papulonodular masses (Figure 47.2B), which are usually confluent, and may result in ptosis if they involve upper eyelid tissues.[21,35] Hemorrhagic or nonhemorrhagic blisters, as well as noduloulcerative lesions, have also been described on the skin surface and the eyelid margin.[21,31,36] Eyelid amyloidosis may also rarely manifest with chronic eyelid edema and may occasionally cause madarosis (Figure 47.3).[21,37,38,39] As a general rule, the conjunctiva is usually spared if the eyelid skin is involved.[16,33]

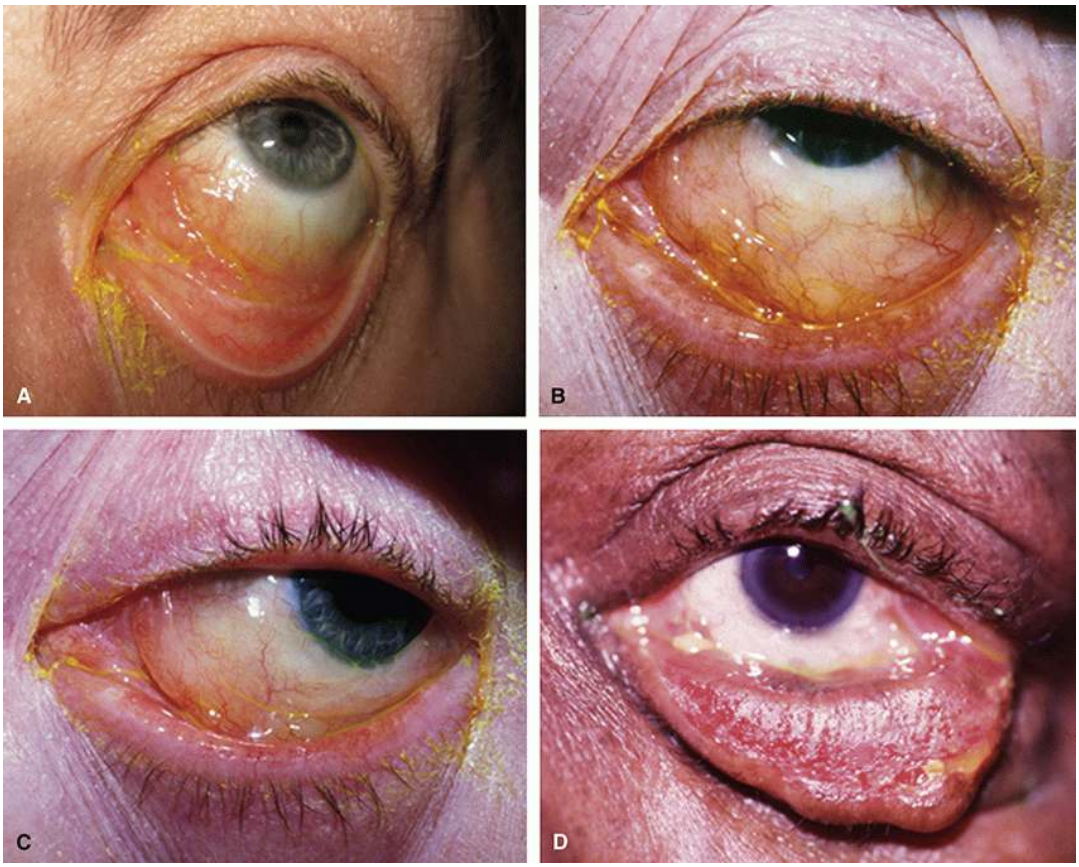

FIGURE 47.3 A-D, Conjunctival amyloid with salmon patch infiltrations, subconjunctival masses, erythema, madarosis, and mechanical ectropion. (A, Courtersy of Dr. Bita Esmaili.)

Although eyelid amyloid deposits have been considered to be pathognomonic of systemic amyloidosis,[7,36,40] there are frequent reports in the literature of the contrary, where patients with eyelid amyloidosis have no apparent systemic involvement even after repeated and extensive testing, and consequently, several authors have recently challenged this notion.[7,21,31,36,40] It is not entirely implausible that the aforementioned classic dictum of an alleged association between systemic amyloidosis and eyelid disease stems from the clinical observation of raccoon eyes, which is one of the defining signs of systemic amyloidosis.[16] However, this dictum may not necessarily apply to the more common presentation of amyloid eyelid masses or nodules, which is more commonly observed in clinical practice.[7]

Salmon-like patches or friable yellowish deposits of amyloid can also infiltrate the tarsus or the conjunctiva, amid a conjunctival vasculature that is typically engorged.[7,20,21] Amyloid may also infiltrate the levator and/or the orbicularis *(Print pagebreak 312)* muscles.[21,24,31] Therefore, ptosis in patients with amyloidosis may be mechanical due to involvement of the skin, tarsus, levator aponeurosis, Müller muscle, or palpebral conjunctiva. Alternatively, it may be myopathic due to infiltration of the levator muscle in the orbit.[21] Recurrent episodes of hyposphagma (subconjunctival hemorrhages) are a frequent symptom in patients with conjunctival amyloidosis.[7,20,21]

In a series of 24 patients with orbital and adnexal amyloidosis, the conjunctiva was exclusively involved in 56.2% of patients, and none had evidence of systemic amyloidosis.[21] Conjunctival amyloid may be unilateral or bilateral,[21] and typically involves the palpebral conjunctiva, the fornices (predominantly the superior fornix), and rarely the bulbar conjunctiva.[21,24,31] A classic dictum in the literature is that the conjunctiva is usually spared if the eyelid skin is involved, and vice versa,[16,31,33] but there are exceptions, and simultaneous involvement of both has been observed.[31,40] One study observed amyloid material infiltrating all tissue planes in the eyelid starting from the eyelid skin and extending to the subconjunctival plane.[41]

Amyloid may also infiltrate the lacrimal glands, extraocular muscles, and the orbit (amyloidoma). Fortunately, orbital hemorrhage, in contrast to eyelid bleeding, is rare in the setting of amyloidosis.[7,21,34]

A detailed discussion of the ocular abnormalities in patients with amyloidosis is beyond the scope of this textbook but include vitreous opacities, chronic open-angle glaucoma, neovascular glaucoma, keratoconjunctivitis sicca, corneal stromal deposits (lattice lines), neurotrophic keratitis, cataracts or lens capsule opacities, retinal vascular changes, or irregular pupils.[7]

If suspicious amyloid deposits are observed by the ophthalmologist elsewhere in the body (around the mouth, on the tongue, or in mucocutaneous junctions), or if systemic amyloidosis is suspected from history or clinical observation, prompt referral to an internist is warranted to undergo a thorough workup to determine if the patient has systemic or localized amyloidosis.[7] The management of amyloidosis is a multidisciplinary task, and all patients should routinely be referred to an internist. Systemic amyloidosis may involve multiple organs, including the heart, kidneys, liver, spleen, autonomic or peripheral nervous system, the gastrointestinal tract, joints, bones, periarticular tissue, or the skin.[2,7,19,42] Cutaneous amyloidosis (beyond the eyelids) takes several forms including macular amyloidosis, lichen amyloidosis, and nodular amyloidosis, which by far is the rarest form.[40,43]

The proper identification of the amyloid proteins and their subtypes is essential because treatment is disease specific.[6] The first step in the diagnosis of amyloidosis is histological confirmation, as discussed in detail in the histopathology section of this chapter. The second step in the diagnosis of amyloidosis is determining the amyloid protein subtype, with immunohistochemistry and mass spectrometry being the two most widely used methods.[44,45] Immunofluorescence requires fresh tissue sampling and is not routinely used.[6] Although immunohistochemistry may be more readily available, mass spectrometry offers more accuracy (up to 100%) in protein subtype identification.[6]

Additional investigations may be needed to rule out a systemic association, and these should include plasma protein electrophoresis, urine protein collection, bone marrow biopsy, or a specific organ biopsy (rectal, visceral, or a biopsy from the subcutaneous abdominal fat).[2,19] Radiolabeled serum amyloid P (SAP) scintigraphy is a new, quantitative, and noninvasive method for imaging amyloid deposits in patients with systemic amyloidosis, but is not widely available.[2,23] The scintigraphy test is based on the observation that the amyloid fibril deposits in systemic amyloidosis, regardless of the protein subtype, always contain the nonfibrillar normal plasma protein SAP.[23]

Differential Diagnosis

Because spontaneous bleeding is a frequent presenting sign of adnexal amyloidosis, it is worth considering the condition in the differential diagnosis of nontraumatic orbital/adnexal hemorrhage. The list of simulating conditions should include vascular lesions, bleeding disorders, orbital infections or inflammations, other neoplastic conditions, or the use of anticoagulants.[34]

It is important to exclude amyloidosis in patients with unexplained ptosis. Patients with localized amyloidosis may present with a long history of ptosis that has persisted for months or even years and may have been misdiagnosed as myasthenia gravis, involutional ptosis, or dermatochalasis.[24,46] Amyloidosis can also rarely masquerade as a chalazion or as chronic blepharitis. In these patients, a known history of blood dyscrasias may help clinch the diagnosis.[24,47] Because some patients with eyelid amyloidosis may present with madarosis, other causes of eyelash loss may need to be excluded.[38,39]

Because of the heterogeneous nature of cutaneous eyelid lesions in amyloidosis, and their relatively slow growth, cutaneous amyloidosis should be considered in the differential diagnosis in any patient with a slowly growing or chronic eyelid lesion, particularly if these lesions are multiple like milia, or lichen planus.[48] One differentiating sign that may confirm the diagnosis of amyloidosis is the presence of petechiae in and around the lesions, although this sign might not be of much help in lichen planus lesions because they are usually erythematous.[48]

The presence of an amyloid deposit in the conjunctival fornix may be confused with a lymphoproliferative disorder or conjunctival mucosa-associated lymphoid tissue lymphoma, and a diagnostic biopsy may be needed to differentiate both conditions.[7,20] When adnexal amyloidosis presents with tarsal conjunctival thickening, giant conjunctival papillae, diffuse thickening, or telangiectatic vessels on the eyelid margin, rosacea should be considered in the differential diagnosis.[20,41] Patients with amyloidosis may rarely present with chronic eyelid edema; therefore, the diagnosis should be considered in patients suffering from persistent eyelid edema of unknown etiology.[37]

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Treatment

The treatment of periocular amyloidosis is controversial and complex, particularly when the disease is associated with

systemic conditions that are rapidly fatal like multiple myeloma, or when vital organs are already critically damaged.[21,33] In such scenarios, observation is preferred. Topical lubricants or a bandage contact lens may provide the critically ill patient with ocular comfort and temporary relief from symptoms, and it should not be underplayed as a therapeutic option.[24,31] These options may also be indicated in patients with nonprogressive localized disease and in patients with advanced systemic disease.

Surgery is indicated to improve cosmesis in patients with severe cosmetic disfigurement or to address ptosis in patients with a significant obscuration of the visual axis.[21,33] If the decision is to proceed with surgery, surgical debulking may be tried, but local recurrences are not infrequent, and the procedure is technically challenging. Respecting tissue planes, as well as the preservation of normal tissue, may be difficult as the amyloid deposits are friable and liable to bleed.[24,40] The use of a surgical curette or scoop, as well as the use of microdiathermy, may help the surgeon respect tissue planes.[24] Alternatively, wide local excision may be tried, which may or may not be followed by closure of the resultant defect with a full-thickness skin graft.[33,41] For conjunctival lesions, debulking or simple excision of the conjunctival or suborbicularis amyloid deposits with a spooned curette have been advocated.[33] Orbital radiotherapy may be used postoperatively to halt progression and reduce recurrences.[25] Reported doses are in the range of 18 to 30 Gy, but this modality is more commonly employed in patients with orbital amyloidosis rather than eyelid or conjunctival amyloidosis.[21] The mechanism by which radiotherapy works is by ablation of the local B-cell populations that produce the amyloidogenic monoclonal immunoglobulin light chains, and this may halt further amyloid deposition. However, this mechanism of action implies that radiation alone (without debulking) would not be effective because it would not eradicate the amyloid already deposited.[25] Liquid nitrogen cryotherapy is another alternative to surgery, which was reported once in a case series of conjunctival rather than for eyelid amyloidosis and was associated with a recurrence rate of 50%.[49] Of note is that patients with localized amyloidosis do not require systemic therapy.[26]

In contrast to the management of localized amyloidosis, which has not appreciably progressed in recent years, therapeutic options to address systemic amyloidosis have advanced tremendously.[9,24] The current therapeutic philosophy for the management of systemic amyloidosis is entirely dependent upon the identification of the misfolded fibril protein and reducing its abundance to effect regression of amyloid deposits, prevention or recovery of organ failure, and improving patient survival. In patients with AL amyloidosis, cytotoxic chemotherapeutic agents are frequently employed to suppress pathogenic cell clones, but the dysfunction of amyloid-infiltrated organs often limits their effectiveness.[2,6,23] Other recent therapeutic options that have shown promising results include high-dose melphalan, steroids, thalidomide, bortezomib, or autologous stem cell transplantation.[9,29]

In patients with reactive systemic amyloidosis (AA amyloidosis), the key to suppressing the proliferation of amyloid deposits in tissues is to control the underlying inflammatory condition like Crohn disease or rheumatoid arthritis, which reduces the concentration of the SAA protein.[9,21] However, because 95% of TTR is synthesized in the liver, orthotopic liver transplantation was considered the gold standard for the management of ATTR amyloidosis before the advent of newer and promising therapeutic agents. These novel drugs either specifically inhibit the production of TTR (inotersen and patisiran) or act as kinetic stabilizers of TTR (tafamidis and diflunisal).[19,23,50]

Prognosis

Without intervention, the natural history of isolated adnexal amyloidosis is that it either remains static or accumulates very slowly.[25] Because of the variable clinical presentations, adnexal amyloidosis may pose a unique diagnostic challenge to ophthalmologists, and the correct diagnosis may be missed for years, a delay that may cause serious morbidity if a systemic association is missed.[21,37] The presence of the characteristic eyelid finding (raccoon eyes) in a patient known to have multiple myeloma is virtually pathognomonic of AL amyloidosis and is a poor prognostic sign. Raccoon eyes is a late manifestation of the disease and carries a mean survival of 2 years, and 20% of patients die within 6 months of diagnosis.[16,33] However, an accidental discovery of adnexal amyloidosis should prompt an initial and thorough investigation to rule out the presence of systemic disease.[24]

Surgical debulking of localized adnexal amyloidosis is technically challenging, is fraught with recurrences, and roughly 50% of patients will require reoperation.[24] Repeat surgery is usually more challenging than the initial procedure and may be associated with considerable morbidity.[24] Similarly, ptosis surgery in the setting of amyloidosis does not fare better, as reoperations are needed in up to 40% of patients.[24]

However, the prognosis of systemic amyloidosis varies significantly according to the type of amyloid subtype, the organotropic characteristics of the protein subtype in question, and the severity of involvement of vital organs.[2,18] In general, systemic amyloidosis continues to be a fatal disease and accounts for about 0.5 to 1.0/1000 deaths per year, most of whom (80%) die from AL amyloidosis.[51]

Histopathology

Amyloid appears as amorphous eosinophilic deposits in histological sections stained with hematoxylin and eosin.[52] The deposits are often irregularly shaped with clefts and scattered intervening fibroblasts, and they may form concentric deposits in the walls of blood vessels (Figure 47.4A). Amyloid also *(Print pagebreak 314) (Print pagebreak 315)* forms small or large nodules, with those in the eyelid and conjunctiva tending to be small nodules (Figure 47.4B).[53,54] Large masses of amyloid may develop in the orbit and extend into the eyelids; these large deposits have been termed "amyloid tumors" or "amyloidomas."[55,56] Eyelid amyloid deposits may be observed in the conjunctiva (Figure 47.4A), tarsus, orbicularis muscle, dermis (Figure 47.4B), and/or Müller muscle (Figure 47.5). On rare occasions, we have seen amyloid confined to the papillary dermis without vascular involvement, similar to lichen amyloidosus and macular amyloidosis occurring elsewhere in the skin (Figure 47.4C).[57] Scattered lymphocytes and plasma cells may infiltrate the amyloid, and multinucleated giant cells may be present (Figure 47.4D).[54] If the lymphoplasmacytic infiltrate is prominent, then immunohistochemical and/or molecular studies are warranted to determine if extranodal lymphoma is present.[58] Osseous metaplasia is a rare occurrence in eyelid amyloidosis.[20] In our experience, it is more common, though still rare, in orbital amyloidomas. Small foci of amyloid may occur as an incidental finding with cutaneous tumors,[43] most commonly basal cell carcinomas.[59,60]

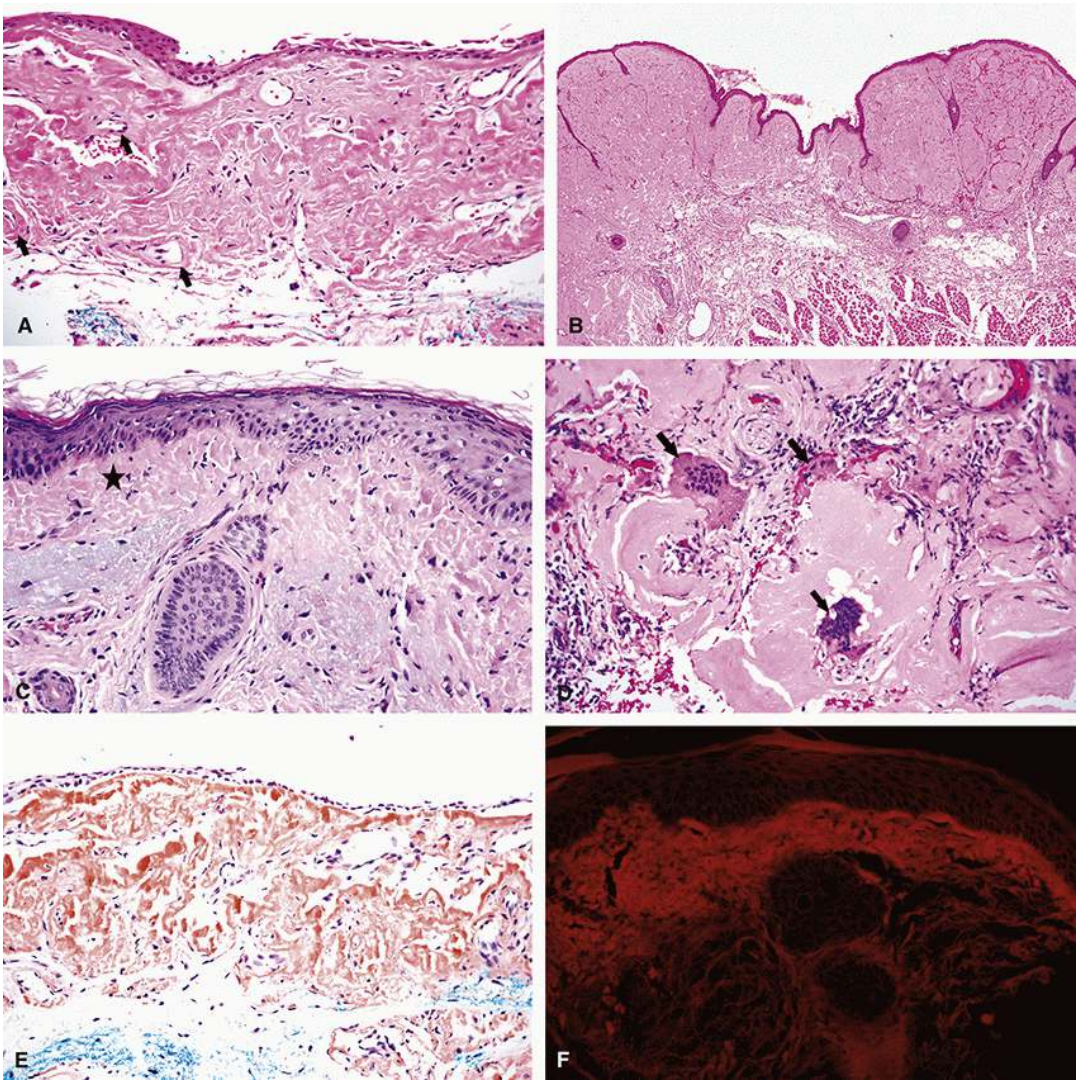

FIGURE 47.4 A, Amyloidosis of the tarsal conjunctiva usually has irregularly shaped, amorphous, eosinophilic deposits in the substantia propria with clefts and scattered intervening fibroblasts. Amyloid is also within the walls of blood vessels (arrows; hematoxylin and eosin). B, In the eyelid dermis, amyloid often forms small nodules that may become confluent (hematoxylin and eosin). C, On rare occasions, the eyelid may have amyloid confined to the papillary dermis (★) without vascular involvement, similar to lichen amyloidosis and macular amyloidosis elsewhere in the body. Actinic elastosis is below the band of amyloid that abuts the epidermis (hematoxylin and eosin). D, Lymphocytes, plasma cells, and foreign body-type multinucleated giant cells (arrows) may infiltrate the amyloid deposits (hematoxylin and eosin). E, Amyloid stains various shades of red, when viewed with unpolarized light in sections

stained with Congo red at an alkaline pH. The intensity of staining and color are influenced by pH, length of fixation in formaldehyde-containing solutions, the thickness of the cut sections, and length of storage of cut paraffin sections (Congo red). This is the same case of conjunctival amyloid as shown in Figure 47.4A. F, In sections stained with Congo red, amyloid appears bright red against a less intense red background when viewed using fluorescence microscopy with a tetramethylrhodamine isothiocyanate or Texas Red filter set. The use of fluorescence microscopy is beneficial for confirming the diagnosis of amyloid in cases that are equivocal using polarization microscopy and those with only small amounts of amyloid. This is the same case of eyelid dermal amyloid shown in Figure 47.4C.

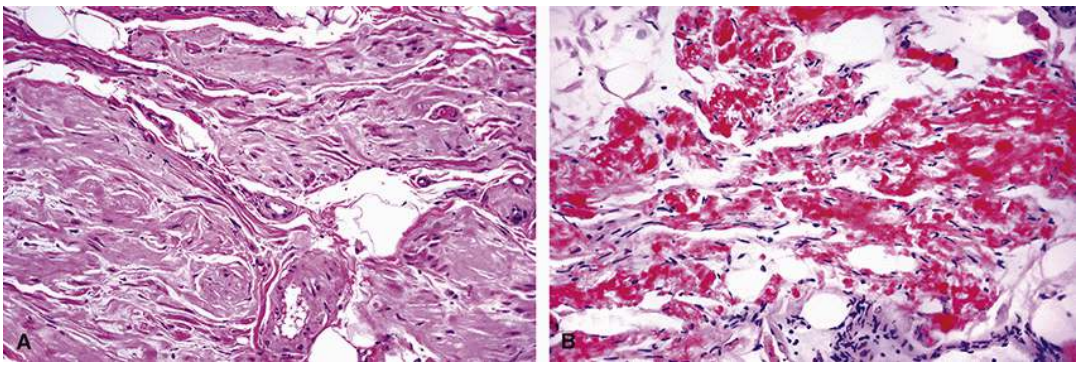

FIGURE 47.5 Ptosis developed in a man with an orbital amyloidoma associated with a localized plasma cell dyscrasia. A, This biopsy of Müller muscle shows envelopment of the spindle-shaped smooth muscle fibers by amorphous eosinophilic amyloid. B, The amyloid stained red using Congo red. It was birefringent and dichroic using polarization microscopy, confirming its identity as amyloid.

Confirmation that an amorphous eosinophilic deposit is amyloid relies on histochemical stains such as Congo red, thioflavin T, thioflavin S, Sirius red, crystal violet, or immunofluorescent staining with newer dyes such as amino naphthalenyl-2-cyano-acrylate derivatives.[52,61,62,63] Congo red is the most often employed stain and is considered the "gold standard" for identifying amyloid.[52,64] Congo red, an aniline dye developed in the 1880s for the textile industry, was first reported as a histochemical pH indicator in 1886.[64] Congo red's ability to bind amyloid was published in 1922[64] and causes amyloid in histological sections to stain various shades of red (including orange) when viewed with unpolarized light in sections stained at an alkaline pH (Figure 47.4E).[65] The intensity of staining and color is influenced by pH, length of fixation in formaldehyde-containing solutions, thickness of the cut sections,[66] and length of storage of cut paraffin sections.[52,65,66]

Congo red stain is not specific for amyloid,[52,67] and identification of a deposit as amyloid relies on the birefringence of the Congo red deposits when viewed using polarized light or characteristic red fluorescence when viewed using a fluorescent microscope.[65,66,67,68,69] The birefringence of amyloid when observed with crossed polarizer and analyzer filters causes it to appear bright against a dark background (see "birefringence" in Chapter 5, "Histopathologic terminology," for a photomicrograph of amyloid viewed with crossed polarizer and analyzer).[65,69] When viewed with crossed polarizer and analyzer, the color of amyloid is typically described as "apple green,"[52] though in practice, it is unusual to see only green.[65,69] In an accurately crossed position, if the color is green initially, then it will progress through yellow, orange, and bright red to dull red when the polarizer is turned one direction; when turned the other direction, the initial green progresses through light green or blue/green, bright white, and then "a neutral colorless appearance."[65] Fluorescence microscopy with a fluorescein isothiocyanate filter set causes amyloid to be bright yellow-orange against a dark green background[66] and bright red against a less intense red background (Figure 47.4F) using a tetramethylrhodamine isothiocyanate[66] or Texas Red[70] filter set. The use of fluorescence microscopy is particularly useful for confirming the diagnosis of amyloid in cases that are equivocal using polarization microscopy and those with only small amounts of amyloid.[66,70]

The histological differential diagnosis for amorphous eosinophilic deposits in the eyelid is colloid milium and lipoid proteinosis. Colloid milium is rare in the eyelid[71,72] and conjunctiva,[73,74] and it may be difficult to distinguish from amyloidosis since the deposits may stain positively and exhibit birefringence using Congo red stain,[75,76] though they are more commonly negative in paraffin sections.[74] The deposits in colloid milium have large clefts, and skin deposits *(Print pagebreak 316)* are separated from the epidermis by a thin layer of collagen (grenz zone).[43,57] Transmission electron microscopy may be required to differentiate colloid milium from amyloidosis. Lipoid proteinosis, a rare autosomal recessive disease resulting in deposition of amorphous eosinophilic material in the walls of small blood vessels, around eccrine sweat glands, and in the papillary dermis,[77] is differentiated from amyloidosis by the lack of Congo red staining of the deposits.[78,79] Beaded papules along the eyelid margins are a characteristic finding in lipoid proteinosis.[77,78,79,80]

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CHAPTER 48

Angioedema

Key Points

- Angioedema is an allergenic or nonallergenic, abrupt, short-lived inflammatory swelling of the reticular dermis, subcutaneous tissue, and mucous membranes
- It can occur either alone, may be associated with urticaria, or with symptoms of anaphylaxis
- It is classified broadly into hypersensitivity (histaminergic angioedema) and non-hypersensitivity (nonhistaminergic angioedema) types
- Hypersensitivity angioedema can be caused by dietary products, medications, or insect venoms
- Non-hypersensitivity angioedema may be hereditary or acquired, attributed to an abnormal complement response due to a deficiency or malfunction of complement 1 esterase inhibitor
- Angioedema presents with rapid onset of moderate to severe, nonpitting, erythematous, or skin-colored swelling
- Treatment can be with cold compresses if mild or corticosteroids if more severe
- Symptoms generally subside in 24 hours, but rarely can result in anaphylaxis

Angioedema refers to an allergenic or nonallergenic, abrupt, short-lived inflammatory swelling of the reticular dermis, subcutaneous tissue, and mucous membranes of the face and genitalia, and may be associated with a similar process in the upper respiratory tract or the gastrointestinal tract.[1,2,3,4,5,6,7,8,9,10] Angioedema may occur either alone or may be associated with urticaria, or with symptoms of anaphylaxis.[5] The terms angioneurotic edema and Quincke edema are synonymous with the term angioedema.

Etiology and Pathogenesis

Angioedema can be classified into hereditary and acquired forms. Three types of autosomal dominant hereditary angioedema (HAE) exist (types I, II, and III), and two acquired types exist (hypersensitivity and non-hypersensitivity angioedema).[5,10] However, from an etiopathogenic point of view, angioedema is better classified broadly into hypersensitivity (histaminergic angioedema) and non-hypersensitivity (nonhistaminergic angioedema) types, the former being mediated by histamine release while the latter is mediated by bradykinin release.[1,5,6] Other causes of angioedema that cannot strictly be classified into either category include idiopathic angioedema and pseudoallergic angioedema. The latter is associated with the use of nonsteroidal anti-inflammatory drugs and occurs due to the inhibition of cyclooxygenase 1 enzyme.[5,6,7]

The causes of hypersensitivity angioedema are numerous and include dietary or therapeutic ingestants, inhalant medications, parenterally administered drugs, and insect venoms.[1,10] The list of foods includes peanuts, shellfish, milk, and eggs, while the list of drugs includes penicillin and sulfa drugs.[5] This mast cell disease, mediated by histamine release, causes an increase in endothelial permeability with extravasation of intravascular fluid into the interstitial tissues, resulting in edema.[4] Sensitized individuals have circulating and cell-bound IgE to the particular sensitizing agent. On reexposure, patients undergo an immediate hypersensitivity (type I) reaction with the release of several vasoactive substances, including histamine and serotonin.[1]

Patients with non-hypersensitivity angioedema may be suffering from a hereditary (HAE, 11q12) or an acquired form of angioedema (AAE). Both conditions are attributed to an abnormal complement response that develops due to a hereditary or acquired deficiency or malfunction of complement 1 esterase inhibitor (C1-INH). Both are mediated by bradykinin and not histamine release.[5] The list of acquired causes of C1-INH deficiency includes lymphoproliferative disorders (lymphoma, monoclonal gammopathies) and some autoimmune tissue diseases.[5,8] Bradykinin release causes a rapid increase in the vascular permeability of submucosal or subcutaneous capillaries and postcapillary venules resulting in localized plasma extravasation, a situation that is not dissimilar to the pathogenic events observed with hypersensitivity angioedema.[5]

Clinical Presentation

Most patients with angioedema describe a tingling or burning sensation. However, itching is not a typical symptom, and some patients may even be entirely asymptomatic except for the edema.[4] Patients who present to the ophthalmologist with an alarming upper and lower eyelid non-hypersensitivity angioedema may be suffering from HAE or AAE. Both conditions are attributed to an abnormal complement response that develops due to a hereditary or acquired deficiency or malfunction of C1-INH. A history of a known allergic reaction to food or medications may be elicited from the patient.[5] The acute picture typically begins either immediately or 1 to *(Print pagebreak 319)* 2 days after an allergenic event has taken place.[1,3] Alternatively, a history of recurrent, episodic, nonpitting, nonpruritic angioedema or a positive family history may be obtained from patients with HAE.[2] Patients should be asked explicitly about lip or tongue swelling, abdominal pain, and difficulty breathing or swallowing.[5] The edema is usually moderate to severe and nonpitting, and can be erythematous or skin colored (Figure 48.1). Because the edema is nongravitational and posturally independent, it typically involves both the upper and lower eyelids.[1,5] Angioedema may or may not be associated with urticarial wheals, but desquamation of the skin is unusual unless rubbing occurs. The ophthalmic examination will usually reveal no ocular abnormality.[3,5,6,10]

Acute histaminergic angioedema may be localized to the eyelids, but it may also be accompanied by signs of anaphylaxis with acute dyspnea (due to bronchospasm) or stridor (due to laryngeal edema).[1,5] Signs and symptoms of shock may also be observed, but fever is absent. Patients may also complain of abdominal pain and vomiting, especially if the offending allergen was ingested.[5] Therefore, even if the patient's sole complaint is eyelid swelling, referral to a dermatologist or an internist is warranted to rule out any other allergenic foci in the body. Alternatively, if systemic manifestations of anaphylaxis are already present, immediate referral to an emergency care department is warranted.

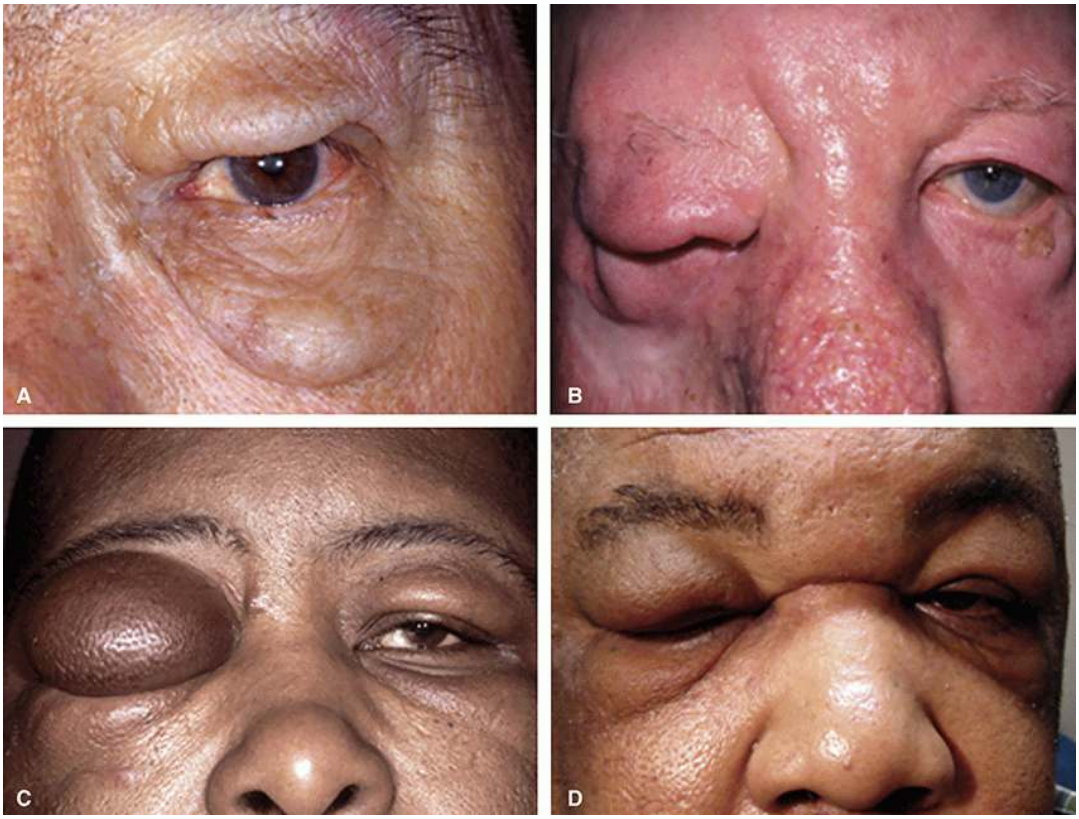

FIGURE 48.1 A-D, Clinical presentations of eyelid angioedema.

Laboratory workup may show elevated serum levels of IgE together with eosinophilia in patients with allergenic angioedema. Patch testing may be undertaken if the diagnosis is in doubt; however, it should be postponed for 3 weeks after cessation of treatment if the patient presents while they are already on immunosuppressive therapy.[3] Evaluation of complement proteins in patients with HAE may show a low complement 4 level, a normal C1q level, and a low (<50%) level of C1-INH, while patients with AAE will have a low C1q level.[2,5,10]

Differential Diagnosis

It must be emphasized that not all eyelid swellings encountered in clinical practice are angioedema, and the list of etiologic causes of pseudoangioedema is extensive.[4,11,12,13,14] Common causes of edema can generally be categorized into (1) inflammatory causes, including allergic contact dermatitis, *(Print pagebreak 320)* thyroid orbitopathy, idiopathic orbital inflammation, blepharochalasis, sarcoidosis, lupus erythematosus, or granulomatosis with polyangiitis; (2) infectious causes, including sinusitis, preseptal cellulitis, chronic canaliculitis, dacryocystitis, herpetic blepharitis (simplex or zoster), and recently SARS-CoV-2 (COVID-19); (3) neoplastic causes, such as lymphoma, sebaceous carcinoma with pagetoid spread (masquerade syndrome), meningioma of the greater wing of the sphenoid, or metastatic eyelid lesions; and (4) miscellaneous conditions, like lymphedema, Ascher syndrome, floppy eyelid syndrome, or amyloidosis.[11,12]

It is important to recognize the difference between angioedema, urticaria, allergic contact dermatitis, and lymphedema, four terms that are frequently confused by clinicians.[1,2] Contact dermatitis is a type IV allergic or inflammatory eczematoid reaction of the skin that is triggered by and is localized to areas of the eyelid skin exposed to direct contact with allergens, including chemicals like cosmetics, lotions, creams, or topical ophthalmic preparations.[1,3,4,15] Clinically, these patients suffer from a red, scaly, itchy rash in the involved areas, and the condition may be acute or chronic.[3] Acute contact dermatitis may be misdiagnosed as angioedema, as it can also cause severe swelling of the facial and periorbital skin. Acute urticaria is defined as an immediate type I hypersensitivity allergic reaction of the skin with localized or generalized release of vasoactive substances such as histamine or serotonin, is characterized by the presence of wheals (elevated discrete areas of edema), with erythematous borders and a pale center, and is usually accompanied by intense itching.[1] From a pathophysiologic point of view, urticaria is indistinguishable from angioedema except that urticaria rarely involves mucous membranes and is circumscribed to the papillary dermis and middermal layers of the skin.[5] Eyelid lymphedema is defined as tissue edema that ensues when lymphatic drainage is impaired, leading to the accumulation of protein-rich fluid in the interstitial tissues.[16] Lymphedema has a more chronic course, may be pitting or nonpitting, has a tendency to involve gravitational areas which contrasts with angioedema, and is specifically associated with a history of trauma, surgery, rosacea, or Melkersson-Rosenthal syndrome or orofacial granulomatosis.

Major causes of pseudoangioedema that are important to identify in the periocular region include preseptal and orbital cellulitis, and idiopathic orbital inflammation. Preseptal cellulitis is characterized by acute painful eyelid erythema and edema, is commonly associated with fever, lasts longer than angioedema, and is usually infectious in origin. Idiopathic orbital inflammation (previously known as orbital pseudotumor) is a benign, noninfective, nonspecific, inflammatory condition of the orbit that may have an acute, subacute, or chronic onset and may present with a wide variety of features including pain, eyelid edema, proptosis, conjunctival chemosis, with or without limitation of ocular motility.[17,18] Other causes of eyelid edema that should be excluded include herpes simplex blepharitis (Chapter 67) or the acute stage of hordeolum (Chapter 55).

Although the specifics that differentiate hypersensitivity from non-hypersensitivity angioedema are beyond the scope of this textbook, it is important to understand that histaminergic angioedema could be associated with urticarial wheals and pruritus, while both features, as well as other symptoms and signs of type I hypersensitivity reactions, are absent in bradykinin-mediated angioedema, including angioedema caused by ACE inhibitors.[5,6]

Treatment

In patients with mild angioedema, cold compresses may suffice. However, in more severe histaminergic angioedema, patients should be started on oral corticosteroids (methylprednisolone 60 mg/day), with rapid taper every 3 days if clinical improvement is observed.[3] Pheniramine maleate, an H1 receptor antagonist, or one of its derivatives may be prescribed in an oral form (50 mg tablets, two-three times daily for 5 days).[3]

In patients with anaphylaxis, the priority should be to safeguard the airway and place an intravenous line. To reduce the edema, subcutaneous or intramuscular adrenaline or intravenous or intramuscular pheniramine maleate (50 mg twice daily for 5 days) should be given alone or in combination with intravenous hydrocortisone (200 mg) or methylprednisolone (40 mg) to reduce recurrences.[3,5]

The treatment of the hereditary and acquired forms of C1 esterase inhibitor deficiency (HAE, AAE) are beyond the scope of interest of oculoplastic surgeons but suffice it to say that the therapeutic measures that work are quite distinct from the medications used for the treatment of hypersensitivity angioedema.[5,8,19] A summary of newly developed targeted therapies is provided elsewhere[9] and includes intravenous human plasma C1-INH and direct or indirect inhibitors of bradykinin release like ecallantide or icatibant, antifibrinolytics like tranexamic acid (off-label use), fresh frozen plasma, and recombinant complement C1-INH.[9] In patients with angioedema related to the use of ACE inhibitors, the offending agent should be promptly halted.[5] In patients with AAE, the most appropriate form of therapy is the recognition and management of the underlying malignancy.[9]

Prognosis

In milder cases of allergenic angioedema, the eyelid swelling normally subsides within 24 hours, and the clinician should reassure these patients that this seemingly alarming swelling is only temporarily debilitating and does not lead to tissue destruction. Once the acute attack subsides, a return to normal anatomy and function is usual, although patients should be on the lookout for early relapses, which are quite possible.[1,5]

In more severe histaminergic angioedema associated with anaphylaxis, the disease may prove fatal if not properly *(Print pagebreak 321)* managed.[5] In addition, proper recognition of HAE/AAE and ACE inhibitor-induced angioedema is of paramount importance as they do not respond to antihistamines or corticosteroids and may prove fatal due to laryngeal edema if the diagnosis is missed and the disease is not properly treated.[9]

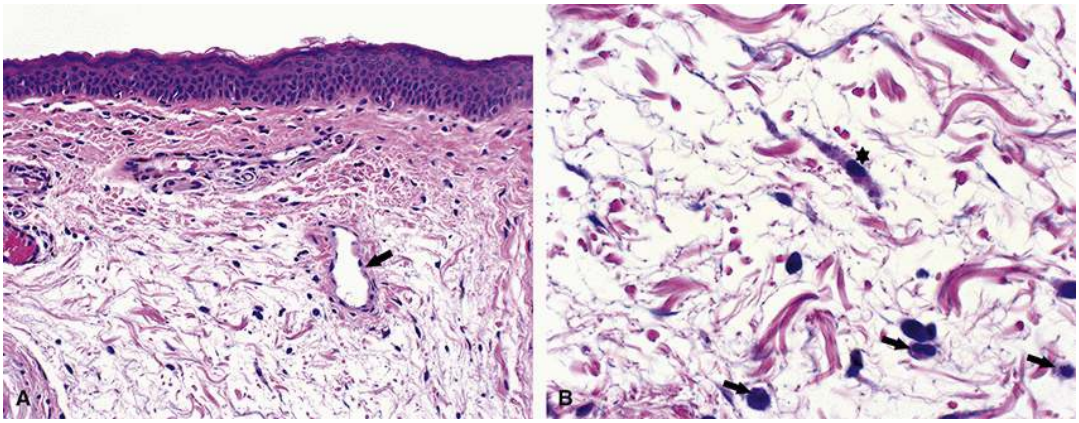

FIGURE 48.2 A, Angioedema of the eyelid has pallor of the deep dermis due to the accumulation of extracellular edema fluid with separation of collagen bundles. A dilated venule is present (arrow) (hematoxylin and eosin). B, The collagen bundles are spaced widely apart due to the accumulation of edema fluid. Mast cells (arrows) and a plump reactive fibroblast (★) are evident at higher magnification. Enlarged fibroblasts are more prominent in chronic than acute angioedema.

Histopathology

Angioedema results in edema of the deep dermis and/or subcutaneous tissue and manifests in histological sections by tissue pallor and separation of collagen bundles (Figure 48.2A and B).[20] There is marked dilation of venules, perivascular accumulation of mononuclear leukocytes, and degranulation of mast cells.[20] Urticaria has tissue edema that may be accompanied by neutrophilic vasculitis; a perivascular infiltrate of neutrophils, eosinophils, and mononuclear cells; or sparse perivascular lymphocytes.[21,22,23] Acute urticaria may also have blunting and widening of rete pegs and usually lacks perivascular inflammatory cells.[23]

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CHAPTER 49

Angiofibroma

Key Points

- Angiofibromas are cutaneous vascular neoplasms characterized by the presence of single or multiple small (1-3 mm) dome-shaped telangiectatic, translucent, skin-colored, or reddish papules
- Single lesions are extremely rare in the periocular region
- Multiple lesions generally occupy the butterfly region of the midface, may involve the eyelids, and are associated with three genetic disorders: tuberous sclerosis complex (TSC), multiple endocrine neoplasia type 1 (MEN1), and the Birt-Hogg-Dubé (BHD) syndrome
- These three syndromes have overlapping cutaneous and systemic features and should be primarily differentiated from each other
- Multiple angiofibromas should also be differentiated from acne vulgaris, dermal neurofibromas, acrochordons, and intradermal melanocytic nevi
- Treatment is usually carried out with the use of ablative or vascular lasers, surgical excision, or medical treatment with topical mTOR inhibitors like rapamycin, but recurrences are common
- Angiofibromas are benign lesions with no potential for malignant transformation, although the presence of angiofibromas in the setting of MEN1 may be an indictor the patient could be suffering from an internal malignancy

Angiofibromas are cutaneous vascular neoplasms characterized by the presence of small telangiectatic dome-shaped dermal papules that are hallmarked histologically by dermal fibrous tissue and blood vessels.[1,2,3,4,5,6] Angiofibromas exhibit broad phenotypic heterogeneity as there are several distinct clinical forms described in the literature, but they all have a shared histologic identity.[1,2,3,4] When cutaneous angiofibromas are observed in the face, they are also alternatively termed fibrous papule if the lesion is solitary or adenoma sebaceum when multiple. Although the term adenoma sebaceum is very popular in the ophthalmic literature, it is a misnomer because angiofibromas are neither adenomatous (benign tumors of glandular origin) nor of sebaceous derivation. Other alternative synonyms (pearly penile papules, periungual angiofibromas, and oral fibromas) are region-specific medical terms that are not used to describe facial angiofibromas.[1]

Angiofibromas may occur in three different varieties: (1) as a solitary nonhereditary form, (2) as multiple nonhereditary lesions, or (3) as multiple hereditary lesions. This later variety, which is the type commonly observed in the periocular region, is associated with several genetic disorders like tuberous sclerosis complex (TSC, previously termed tuberous sclerosis), multiple endocrine neoplasia type 1 (MEN1), or the Birt-Hogg-Dubé (BHD) syndrome.[2]

Etiology and Pathogenesis

What stimulates the dermis to produce a solitary fibrous papule is unknown, but the genetics of the three associated syndromes, particularly TSC, is well researched. TSC is a multisystem genetic disorder characterized by hamartoma formation in many organs, particularly the skin, brain, eyes, kidneys, and heart. This results in the classic triad of intellectual disability, seizures, and angiofibromas of the face.[5,6] There are two tumor suppressor genes (*TSC1* and *TSC2*) that are associated with the development of TSC.[6] Although the mutations in *TSC2* are more commonly spontaneous, they may be inherited from a parent in about 30% of patients, and it was calculated that any child with a TSC parent has a 50% chance of developing the condition.[5] *TSC1* encodes for hamartin, while *TSC2* encodes for tuberin.[6] Both of these molecules are physically associated in vivo, suggesting that they function in the same complex (hamartin-tuberin complex) rather than in separate pathways.[2]

When mutations occur in either of these genes, the function of this complex will be affected, resulting in abnormal hyperactivation

of the mTOR pathway (the signal transduction pathway of the mammalian target of rapamycin), which would lead to the development of TSC.[6] Compared to normal skin in the same individuals, abnormal mTOR pathway activation results in a 12-to 23-fold overexpression of epiregulin in areas of the skin harboring angiofibromas.[7] Epiregulin is an epidermal growth factor that stimulates dermal/epidermal fibroblast proliferation so that they are produced at a faster rate.[7] The vascular component of angiofibromas results from the increased expression of angiogenic factors such as vascular endothelial growth factor (VEGF).[1,5,6,7]

MEN1 is a familial cancer syndrome with parathyroid, pancreatic, pituitary, and cutaneous findings and is caused by mutations of the *MEN1* gene, which codes for the production of a protein called menin.[8] The disease is most commonly inherited as an autosomal dominant trait in 80% of *(Print pagebreak 324)* cases, but it may also occur sporadically in the sporadic form of the disease.[9]

BHD syndrome is an uncommon autosomal dominant genetic condition first described in 1997 and is caused by a mutation of the *BHD* gene. Dermatologically, the syndrome is hallmarked by a triad of multiple trichodiscomas, fibrofolliculomas, or acrochordons, but solitary as well as multiple facial angiofibromas have also been reported.[2,10] However, these characteristic cutaneous lesions are rarely reported in the eyelids.[11,12] From a pathophysiological point of view, BHD syndrome is associated with abnormal activation of the mTOR pathway, but in contrast to TSC, suppression of the pathway rather than hyperactivation is observed. This finding is interesting and represents a paradigm shift in the understanding of the pathogenesis of genetic neoplastic diseases because there is a significant clinical overlap between BHD syndrome and TSC.[3] This finding suggests that an abnormally high as well as an abnormally low level of activity within the same pathway can result in the same clinical phenotype.[13]

Clinical Presentation

The solitary nonhereditary form of angiofibroma commonly involves the nose (fibrous papule) and has only been reported in the eyelids once,[14] while the multiple nonhereditary type which commonly involves the penis has not been reported in the periocular region. The multiple hereditary type associated with tuberous sclerosis, and less commonly MEN1 and BHD syndrome, is the type that is more often observed in the periorbital region. Recent studies suggest that the frequency of TSC varies between 1/6000 and 1/10,000 live births.[6,15] The prevalence of MEN1 is estimated to be between 1/10,000 and 1/100,000 individuals,[16] while the incidence and prevalence of the BHD syndrome are unknown, but the consensus is that it is more common than was previously thought.[11]

Angiofibromas often present as small skin-colored or reddish, waxy-looking, dome-shaped papules that may be single or multiple and may or may not have overlying telangiectatic vessels (Figure 49.1A-C).[17] The multiple hereditary angiofibroma is the type most commonly encountered in the periocular region, but massive lesions are occasionally seen (Figure 49.1D). In patients with the TSC, the genetic disorder most commonly associated with angiofibromas, cutaneous lesions are found in 60% to 70% of patients, and angiofibromas are among the commonest types of skin lesions encountered in these patients. It is unusual to observe disease onset at birth, as it more commonly starts between the age of 3 and 10 years, but the condition usually exacerbates at puberty and then plateaus. TSC is characterized by the presence of bilateral (rarely, unilateral), firm, discrete, reddish-brown, pink, or skin-colored telangiectatic papules, which average in size between 1 and 3 mm in diameter or even larger, that are symmetrically distributed in the butterfly region of the face (cheeks and nasolabial folds), but similar lesions may be scattered in the lower eyelids (39% of TSC patients) as well as the chin.[2,5,17,18] The lesions are numerous, conspicuous, and they may occasionally form a large cauliflower-like mass if they coalesce together.[5] Eyelash poliosis may also be observed in TSC patients and may even be the presenting sign of the disease.[18,19,20]

Other cutaneous findings that may be associated with TSC outside the midface region include the presence of firm fibromatous plaques (forehead), periungual fibromas, or Koenen tumors (toenails or fingernails), shagreen patch (lumbosacral region), as well as white hypopigmented ash-leaf macules (trunks and limbs).[2] Of note is that histologically, most of these lesions are essentially angiofibromas.[2] Ocular findings include retinal hamartomas (44%), punched-out areas of retinal depigmentation (39%), nonparalytic strabismus (5%), colobomas of the iris, lens, or choroid (3%), and rarely papilledema or sectoral iris depigmentation.[18] Systemic findings include seizures, learning difficulties, mild intellectual disability, gross behavioral disturbances, and cardiac and renal anomalies. There are major and minor criteria for the diagnosis of TSC, and the diagnosis either requires positive TSC 1 or 2 testing, or the presence of two major or one major and two or more minor criteria.[2] Major criteria include three or more hypomelanotic macules, two or more periungual fibromas, three or more angiofibromas, a fibrous cephalic plaque, shagreen patch, retinal hamartomas, cortical dysplasia, subependymal nodules, subependymal giant cell astrocytoma, cardiac rhabdomyoma, lymphangioleiomyomatosis, and angiomyolipomas. The minor criteria are confetti-like macules, three or more dental enamel pits, retinal achromic patch, two or more intraoral fibromas, multiple renal cysts, and nonrenal hamartomas.[2]

Roughly 22% to 88% of patients with MEN1 have multiple facial angiofibromas, which may occasionally involve the eyelids, but they are smaller, more scattered, and less numerous than those present in TSC.[21] Other cutaneous findings include collagenomas,

lipomas, and café-au-lait macules.[8] Other systemic findings of MEN1 include gastroenteropancreatic lesions, especially parathyroid hyperplasia (95%); pancreatic islet tumors (60%-100%); Zollinger-Ellison syndrome (54%); anterior pituitary adenomas (15%-50%); adrenal adenomas (30%); insulinoma (21%); glucagonoma (3%); carcinoid tumors located in the bronchi, gastrointestinal tract, pancreas, or thymus (3%); and VIPoma (vasoactive intestinal peptide) in 1% of patients.[8,21]

Differential Diagnosis

Because solitary angiofibromas are extremely rare in the eyelids,[14] their presence may pose a serious diagnostic challenge. When a single lesion is encountered, it could initially be confused with pyogenic granuloma or more aggressive conditions like basal cell carcinoma until the results of the histopathology are confirmed.[2]

However, the presentation of multiple angiofibromas is distinctive and hard to miss particularly in association with *(Print pagebreak 325)* TSC. Nevertheless, the mere presence of multiple angiofibromas of the face may still pose a diagnostic dilemma and should not automatically translate to a diagnosis of TSC. This is because all three hereditary conditions associated with facial angiofibromas (TSC, MEN1, and BHD syndrome) have overlapping mucocutaneous and systemic features that may require a thorough systemic and dermatologic evaluation if the diagnosis is in doubt.[2,10,11] BHD syndrome and TSC, in particular, have significant overlap both in their systemic and cutaneous features. Facial angiofibromas, Koenen tumors, pulmonary cysts, renal cysts, and renal cancers have been described in both conditions.[3]

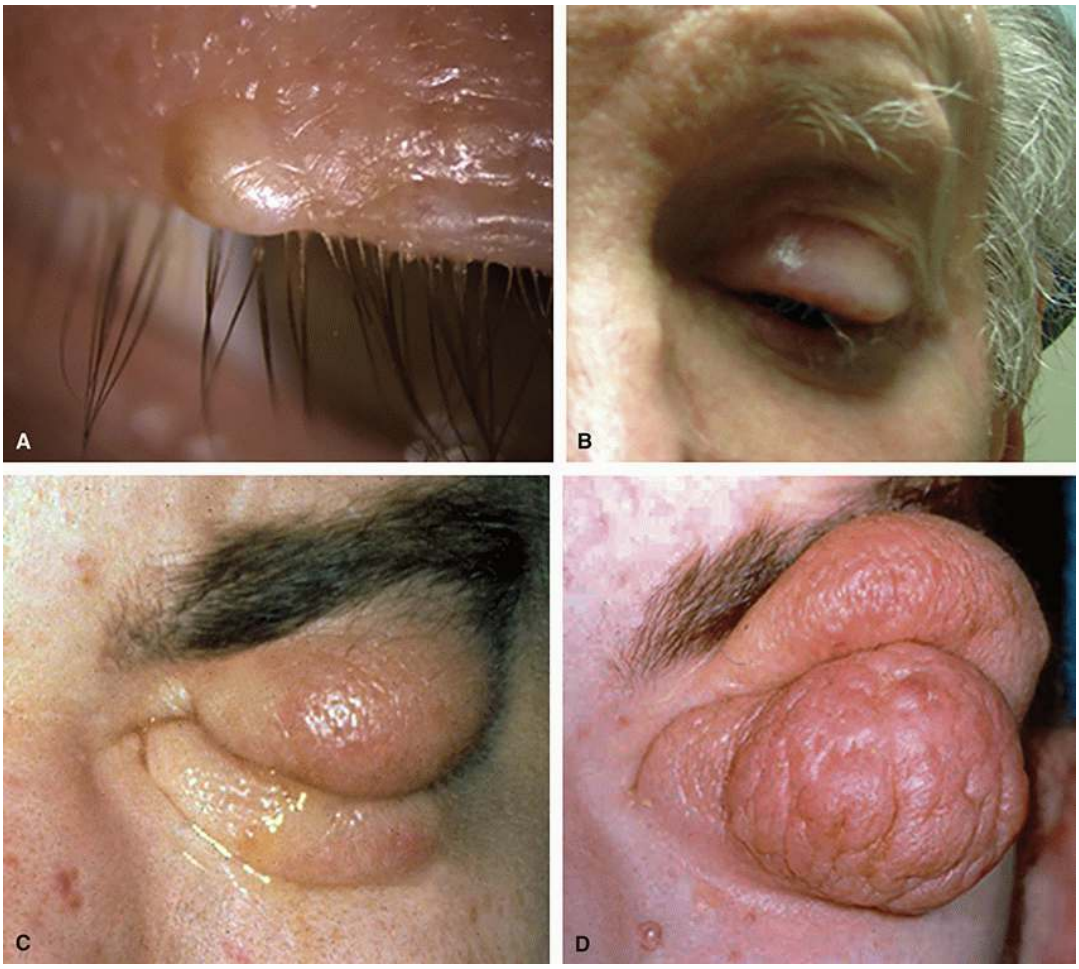

FIGURE 49.1 A, Solitary nonhereditary angiofibroma near the eyelid margin. (Courtesy of Dr. Norman Charles.) B, Angiofibroma involving the upper eyelid. C, Angiofibromas of the upper and lower eyelids. (Courtesy of Dr. Richard Anderson.) D, Massive pedunculated angiofibromas involving upper and lower eyelids. (Courtesy of Dr. David Jordan.)

When multiple angiofibromas are observed in the face, other entities that should be ruled out include acne vulgaris, dermal neurofibromas, acrochordons, or intradermal melanocytic nevi.[1] Because the age at presentation may be similar and because of the clinical mimicry, acne vulgaris, in particular, may be difficult to differentiate from multiple angiofibromas. However, the overlying telangiectasia associated with angiofibromas, as well as the lack of comedones and pustules, may help exclude acne lesions.[5]

Giant cell angiofibroma is a morphologically distinct entity that occasionally may be encountered in the periorbital region or within the orbit. It is characterized histologically by the presence of bloodless ectatic pseudovascular spaces and CD34+ spindle cells. This

entity is currently considered a variant of solitary fibrous tumors,[14,22,23] which is discussed in a separate chapter (see Chapter 116).

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Treatment

Solitary angiofibromas are benign lesions that require no treatment unless they represent a cosmetic concern or to rule out a malignant process. The latter may be a relevant indication owing to the rarity of the condition in the periocular region especially if the lesion raises clinical suspicion.

The mainstay of therapy for multiple angiofibromas is ablative or surgical, but medical treatment using mTOR inhibitors, or topical or oral beta-blockers can treat these lesions nonaggressively.[1,2] Invasive options include shave excision, dermabrasion, cryotherapy, electrodessication, radiofrequency ablation, or lasers. Ablative CO_2 laser resurfacing addresses the nodular or papular lesions and could be used alone or in combination with vascular lasers like the pulsed dye vascular laser (wavelength 595 nm) to reduce redness by addressing the residual elements.[4] Alternatively, combination treatments can also be achieved with CO_2 laser resurfacing followed by the use of topical timolol or rapamycin.[1,24] Ablative or surgical options can result in scarring, postinflammatory hyperpigmentation, or persistent erythema, and recurrence has been reported in up to 80% of patients.[1,2,4]

The introduction of topical rapamycin was undeniably a turning point in the treatment of facial angiofibromas, although many open questions still linger regarding their tolerability, development of resistance, and toxicological challenges that still need to be addressed.[24,25,26] The drug acts by binding to mTOR and downregulating its activity, thereby decreasing cellular proliferation.[1] Rapamycin is also hypothesized to decrease VEGF production by downregulating VEGF-stimulated endothelial cell proliferation, but maintenance therapy may be required.[1] Reported side effects from the use of rapamycin are mild and include minimal irritation and/or erythema; however, the lack of standardized formulations (0.1%-1%), problems with insurance coverage, and the fact that it is more effective in smaller lesions (<4 mm) limit its widespread availability and use.[1,2,5,24] Ablative laser pretreatment before topical rapamycin application therapy may be more effective for larger lesions and may help decrease the overall dosage of rapamycin, thereby reducing the financial burden on the patients who pay from their own pockets.[1]

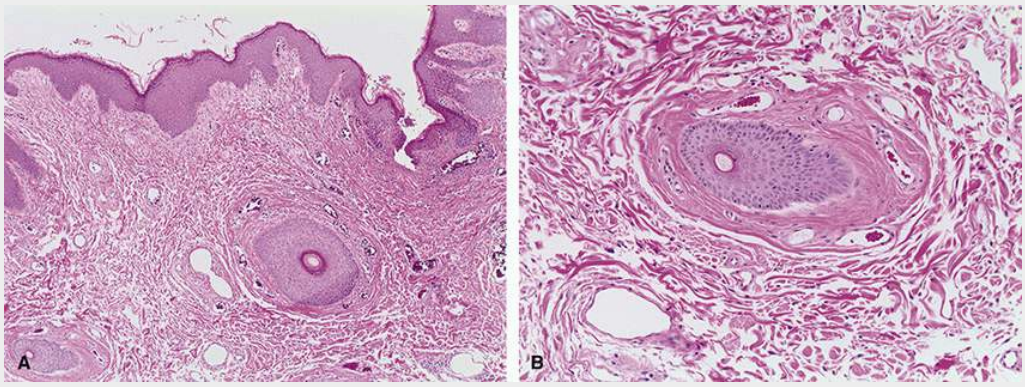

FIGURE 49.2 A, Angiofibroma with a papillomatous appearance from the lateral left upper eyelid of a teenager with tuberous sclerosis complex. The dermis is fibrotic with prominent dilated blood vessels. Concentric fibrosis surrounds hair follicles, and sebaceous glands are absent. B, A common feature in angiofibromas is concentric lamella of hyalinized fibrous tissue surrounding hair follicles. Many dilated vessels are evident in the fibrotic dermis.

Prognosis

Angiofibroma lesions persist indefinitely and may increase in number in the setting of genetic disorders like TSC. Also, they may be associated with disfigurement, bleeding, pruritus, and multiple recurrences following treatment, which may lead to significant psychosocial consequences.[24] Nevertheless, they are benign lesions with no malignant potential.[2]

Although angiofibromas are completely benign, some of the conditions linked with them, particularly MEN1, are not. The mere presence of these lesions is considered one of the cutaneous markers of internal malignancy[8] and should alert the clinician that the patient may have an underlying malignant process that could metastasize. MEN1 should, therefore, be excluded before rushing to an

alternative diagnosis. Indeed, metastasis from malignant pancreatic neuroendocrine tumors or thymic carcinoid tumors is a common cause of mortality in MEN1 patients.[8,27]

Histopathology

The histological appearance of cutaneous angiofibromas in TSC[28,29,30] is identical to solitary melanocytic angiofibromas[29] and similar to fibrous papule of the nose.[30,31] The consistent finding in angiofibromas of the TSC is dermal fibroblastic proliferation, fibrosis with coarse collagen bundles, and vascular proliferation with prominent dilated blood vessels and lymphatics (Figure 49.2).[28,29,30,32] Dermal fibroblasts may have a spindle or stellate configuration.[28,29,32] Dermal fibrosis *(Print pagebreak 327)* may result in a dome-shaped, pedunculated, or papillomatous configuration.[28] Hyalinized fibrous tissue often surrounds blood vessels and adnexal structures concentrically (Figure 49.2B), leading to atrophy of hair follicles and sebaceous glands.[28,29,32] As noted in the introduction, "*adenoma sebaceum*" is a misnomer since sebaceous glands are usually "*compressed, atrophic, or absent as a result of the expanding connective tissue and angiomatous elements*."[28] The fibrotic dermis completely lacks elastic fibers, in contrast to the subjacent dermis.[28] The epidermis of tuberous sclerosis angiofibromas may be normal[32] or may have a prominent granular cell layer, hyperkeratosis, and scattered atrophic or flattened rete ridges.[29]

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CHAPTER 50

Arteriovenous Malformations

Key Points

- Arteriovenous malformations (AVMs) are complex developmental anomalies of small abnormal arteriovenous connections that bypass the high-resistance vascular capillary bed
- They occur principally in the head, neck, and brain, and 79% are evident at birth, or are noted in childhood or puberty
- They are progressive high-flow lesions that can progress from areas of small cutaneous blush to lesions that are painful, ulcerated, and associated with by cardiac failure
- Treatment paradigm involves endovascular embolization followed by surgical resection and reconstruction as needed
- The prognosis for AVM is generally favorable; however, if they are not managed appropriately, they can recur more aggressively

According to the International Society for the Study of Vascular Anomalies (ISSVA), an arteriovenous malformation (AVM) is defined as a high-flow direct communication between arteries and veins without the normal intervening high-resistance capillary bed.[1,2,3,4,5,6,7,8] AVMs are extremely rare vascular malformations that are associated with high morbidity, limited treatment options, and, unfortunately, the lack of standardized therapeutic guidelines.[1,2,3,4,5,6]

A distinction should be made between a congenital AVM and a congenital arteriovenous fistula (AVF) as there is some confusion in the oculoplastic literature between both conditions. An AVM (congenital or sporadic) is a high-flow communication between arteries and veins with an intervening abnormal capillary nidus devoid of autoregulation, which bypasses the normal high-resistance capillary bed.[6] An AVF (traumatic, spontaneous, or less commonly congenital), however, is a direct arteriovenous connection without the characteristic nidus, which is typical of a congenital AVM.[6] To the best of our knowledge, a congenital orbital AVF has never been documented in the literature.

Etiology and Pathogenesis

Unlike AVFs, which are typically acquired lesions and usually characterized by one or a few large AV shunts, AVMs are complex developmental anomalies composed of a myriad of small abnormal arteriovenous connections that bypass the normally controlled, high-resistance vascular capillary bed that is replaced by a nidus of abnormal intervening capillaries.[9,10] This capillary nidus may be primary or may reflect secondary capillary hypoplasia. But for unknown reasons, some pure eyelid AVMs do not show this capillary nidus.[10]

The origin of AVMs is not well established, but they are generally believed to be heritable. Several somatic mutations in the *RASA1* gene, which regulates the RAS/MAPK pathway, have been implicated in AVMs as well as in the autosomal-dominant capillary malformation-AVM syndrome.[3,6,10,11] However, this genetic origin is contested by some authors who believe these lesions are acquired. This point of view reflects the frequent clinical observation of adult-onset AVMs, as well as the severity of these defects when they manifest clinically. According to this hypothesis, if AVMs were transmitted genetically, they should have resulted in early embryonic lethality.[1,2,6,7,12,13,14] It should be noted that the concept of an acquired vascular malformation developing much later in life is not unheard of and is well documented not just in AVMs but to a lesser extent in acquired port-wine stains (the so-called Fegeler syndrome) as well.[6] An interesting conciliatory concept was proposed recently to explain the development of spontaneous acquired AVMs later in life.[6] According to this theory, spontaneous AVMs are true developmental lesions that are initially quiescent. Their adult vascular remodeling may require interaction between genetic susceptibility involving downstream alterations in the RAS-MAPK pathway and an environmental second hit (hypoxia, hormonal influences, trauma, radiation, etc). This second hit acts as a “revealing trigger” and is required to initiate the development of an AVM through the loss of angiogenic suppressor mechanisms and upregulation and activation of angiogenesis, which results in abnormal vessel formation and sprouting later in life.[6]

Clinical Presentation

AVMs occur principally in the head, neck, and brain.[12,13,14,15,16,17,18] Head and neck AVMs are evident at birth in 59% of patients and are noted in childhood or puberty in another 20% of individuals.[16] AVMs may remain asymptomatic until puberty or adulthood when they grow and start to manifest clinically.[12,13,14,15,16,17] Pure preseptal eyelid AVMs are rare, and orbital cutaneous lesions are far more common (Figure 50.1). Fewer than 20 cases of pure palpebral AVMs have been described in the literature.[10,13,14,15,16] Eyelid AVMs more commonly involve the upper eyelids; however, the significance of this observation is unknown.[10]

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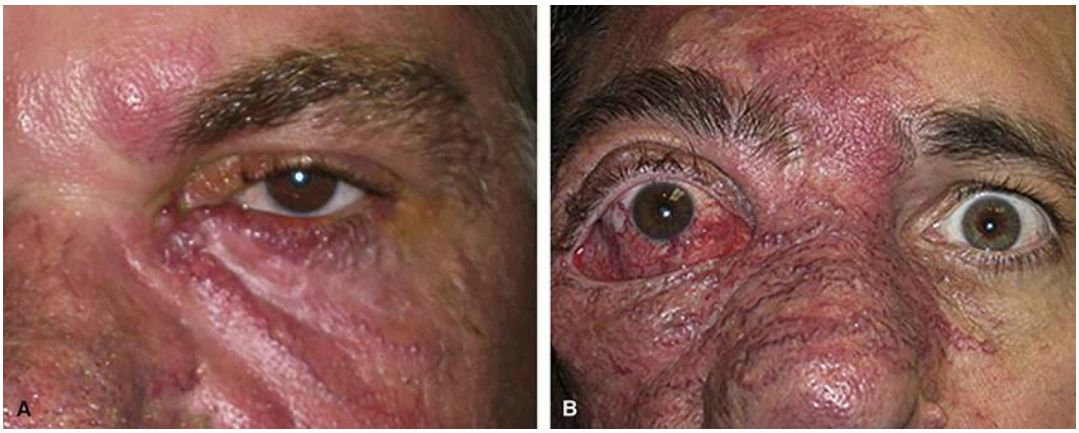

FIGURE 50.1 A and B, Arteriovenous malformations involving the eyelids and face. (B, Courtesy of Dr. Jeffrey Nerad.)

AVMs are exceedingly uncommon heterogeneous lesions that have been described in a multitude of subclassification systems in the literature, despite the absence of any clear differences in treatment options.[6] The Schöbinger severity scoring system is concerned with the prognostication or natural progression of AVMs and is divided into four stages or grades that include stage I, the quiescent stage with pink or blue dot lesions, a red flag sign that may occasionally be encountered in the periorbital region (Figure 50.2A); stage II, the expansive stage characterized by pulsatile, expansive lesions, with engorged draining veins; stage III, similar to stage II but includes necrosis, infection, or hemorrhage (Figure 50.2C and D); and stage IV, the decompensated stage of stage III with the addition of cardiac failure.[6,14] From an oculoplastic perspective, Warier and associates classified orbital AVMs based on location into (1) purely orbital AVM; (2) orbital and periorbital AVM; and (3) orbital with retinal or cerebral AVM (Wyburn-Mason syndrome).[7] Other rheologic subclassification systems that are primarily concerned with brain AVMs were proposed to effectively treat those complex lesions. The most favored ones are the Houbert, the Cho-Do, and the Yakes AVM classification systems, but these may be difficult to adapt to the periorbital region.

Most eyelid lesions present to the clinician as Schöbinger stage II AVMs. As patients progress from stage I, they usually present with an eyelid swelling, which may be significant enough to obscure the visual axis (Figure 50.2C). These lesions may also result in diplopia due to orbital involvement in orbitocutaneous AVMs.[6] The mass is usually warm and painless, may swell acutely with exercise, and can be associated with a palpable bruit or pulsation, as well as proptosis in orbitocutaneous lesions.[6,7,10] Pulsations may occasionally be absent due to thrombotic episodes within the lesion.[10] Engorged dilated, nonpulsatile vessels are observed on the surface of the eyelid surrounding the lesion. These blood vessels typically disappear with digital compression.[10]

Destructive changes are the hallmark of stage III, and pain is usually significant (Figure 50.2D). Stage III patients also suffer from spontaneous bleeding or infection,[5] as well as dystrophic skin changes in the form of discoloration and/or skin ulceration. Episcleral vessels are usually congested, and the intraocular pressure may be elevated.[18] Stage IV lesions are marked by flow steal syndrome, chronic fatigue, or high-output cardiac failure, but to the best of our knowledge, this stage has not been reported in eyelid AVMs. Eyelid AVMs may occur in isolation, may be associated with hemifacial AVMs, or with other vascular malformations in the central nervous system as in Wyburn-Mason syndrome, which may also be associated with retinal and cerebral AVMs.[7,19]

Diagnostic imaging plays a pivotal role in the proper diagnosis of AVMs. A Doppler ultrasound may demonstrate a soft-tissue structure with exuberant arterial flow together with venous shunting.[10] Magnetic resonance imaging (MRI) and MR angiography (MRA) represent the best diagnostic tools to demonstrate the feeding vessels and draining veins, but they may be inconclusive in small eyelid AVMs.[10,20] MRI with or without contrast will typically show the characteristic flow voids because of high flow in the vessels supplying the lesion.[5] MRI will also show an intermediate signal on T1 and a hyperintense signal on T2.[2] Recently, it has

been shown that the addition of dynamic MRI imaging with DWI (diffusion-weighted imaging), coupled with ADC (apparent diffusion coefficient; the so-called DWI-ADC protocol), as well as TRICKS-MRA (time-resolved imaging of contrast kinetics sequences), is invaluable in defining the unique flow dynamics of AVMs.[5] TRICKS-MRA is a recently introduced technique that improves temporal resolution and facilitates obtaining dynamic images during the arterial, capillary, and venous phases.[20]

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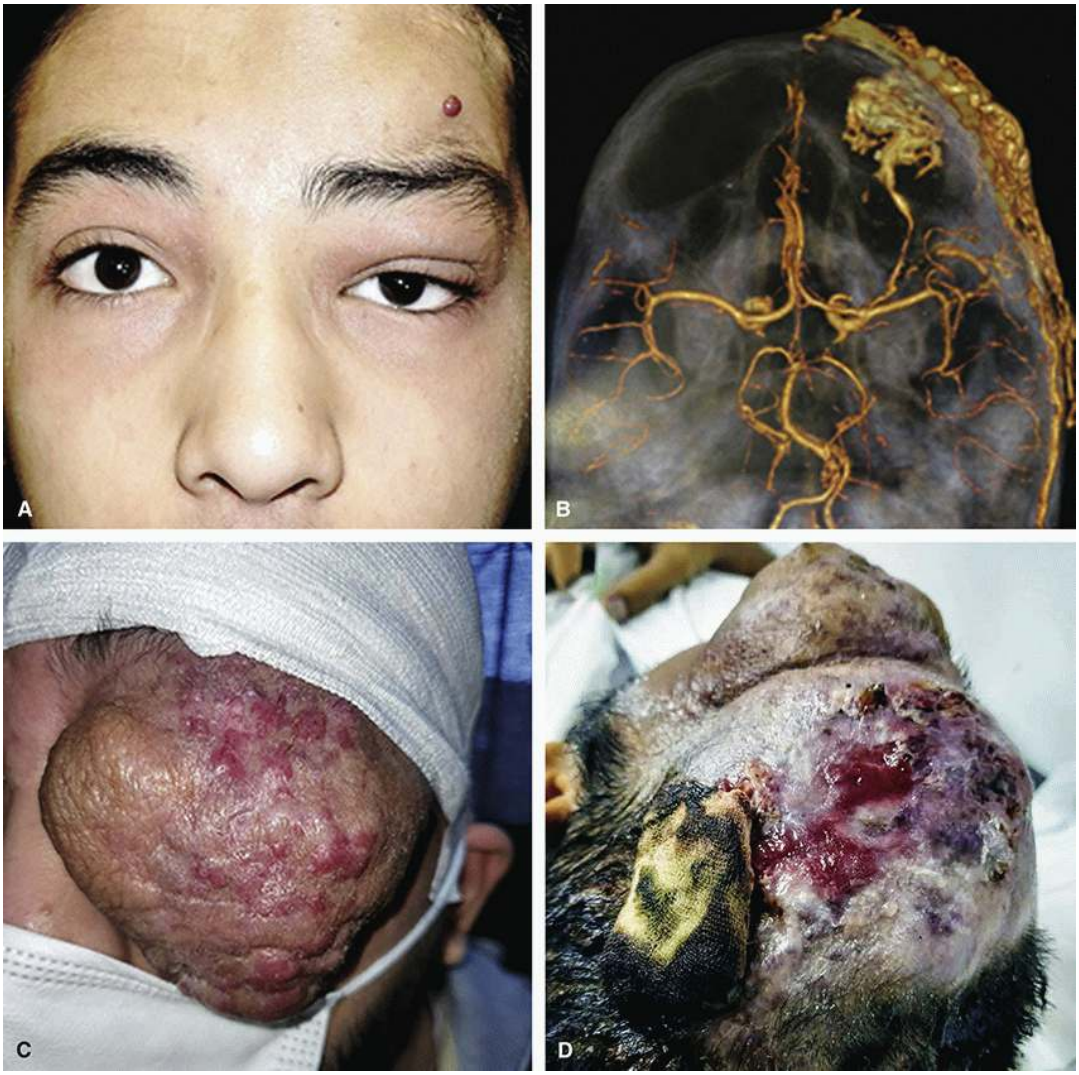

FIGURE 50.2 A, Progression of an arteriovenous malformation of the left orbit and eyelid from Schöbinger stage I in 2013. B, Brain CT-angiography (December 2013) with an arterial feeder from the external carotid artery and a feeder from the ophthalmic artery. C and D, The same patient (August 2021) with progression to Schöbinger stage III following multiple procedures.

Differential Diagnosis

Misdiagnosis of an AVM may lead to catastrophic consequences.[2] Interestingly, the most common lesion that is confused with a small AVM is a hordeolum or chalazion, and warm compresses together with a topical antibiotic steroid ointment are sometimes prescribed by the ophthalmologist without any therapeutic benefit. Misdiagnosis of an AVM as a chalazion may lead to serious consequences if surgery for chalazion excision is undertaken.[10]

The differential diagnosis for a palpebral AVM in neonates includes infantile or congenital hemangiomas as they may clinically be indistinguishable, while in adults, an AVM may be confused with distensible venous malformations. A Valsalva maneuver in the prone position can help exclude a venous malformation, although an MRI/MRA will still be required in all cases to help confirm the diagnosis.[18,19]

The distinction between palpebral AVMs and AVF should not be difficult but is still tremendously important because the therapeutic approaches are very different.[18,19] *(Print pagebreak 331)* AVFs are direct connections between feeding arteries and

draining veins, and they usually occur in association with trauma.[18,19] Only on very rare occasions do they present as a pulsatile eyelid mass,[21] which makes the distinction easy in most cases. AVFs are generally less aggressive than AVMs, and treatment is usually straightforward with a single session of endovascular embolization.

Treatment

Every effort should be made to eradicate the AVM and its nidus. To achieve this aim, close cooperation between the surgeon and the neuroradiologist is of utmost importance.[5,18] Currently, the treatment paradigm involves endovascular embolization followed by surgical resection, with an immediate or delayed reconstruction of the resultant eyelid defect.[18] Embolization of the feeder vessels under angiographic guidance using coils, *n*-BCA glue, Onyx, or precipitating hydrophobic injectable liquid followed by surgical resection is generally recommended.[18,19] A less commonly applied modality is intralesional sclerotherapy with bleomycin or other sclerosants.[6,15,18]

Preoperative embolization helps to reduce the flow dynamics within and outside of the lesion, thus minimizing blood loss during the subsequent stage of surgical debulking. Surgical debulking of the embolized lesion should preferably be carried out within a 72-hour window after embolization.[7,18] The reason behind this early debulking is twofold. First, embolization causes chronic tissue edema and moderate to severe inflammation that may persist for weeks, thus resulting in an unnecessary surgical delay. Second, this delay may, in turn, result in the recruitment of collateral blood vessels and a recurrence of the AVM.[7,18] Intraoperatively, any residual feeder vessels are cauterized or ligated.[6] Surgical debulking may be guided by intraoperative stereotactic navigation,[18] and hemostasis should be pursued meticulously with cautery. Small superficial lesions that lack a prominent large feeding artery may be amenable to surgical excision under strict hemostatic control without preoperative embolization.[10]

Surgical reconstruction of any residual defect after excising the eyelid lesion is usually carried out with standard reconstructive procedures. However, the timing of surgical reconstruction is controversial. Reconstruction is often deferred to a later date, but delayed reconstruction may result in prolonged periods of visual deprivation if the visual axis is obstructed. In addition, extensive scarring may have already developed by the time reconstructive efforts have begun, particularly in the levator muscle, which might negatively impact the final cosmetic outcome.[18] Furthermore, it is theorized that the earlier use of well-vascularized tissue flaps overlying the eyelid defect might help improve local ischemia, thus preventing re-recruitment of blood vessels and ultimately reducing AVM recurrence.[18] Ptosis is repaired at the same session. Although the levator muscle may show fatty degeneration or scarring from prior embolization or sclerotherapy, it rarely bleeds, particularly if reconstruction

is undertaken early.[18] Because AVMs have a rapid blood flow, these lesions are not typical candidates for percutaneous sclerotherapy as the sole therapeutic approach, but it may be attempted in selected cases where a single draining vein is associated with the lesion. In such a scenario, direct transcutaneous delivery of the sclerosing agent may be tried, provided the lesion is small enough to allow direct compression during the injection to minimize the flow through the draining vein.[15,22] However, it should be stressed that embolization and excision are not only more effective than sclerotherapy but also a far safer option in the closed confines of the orbit. The potential to develop orbital compartment syndrome with loss of vision to a no perception of light level following sclerotherapy in the closed confines of the orbit should not be underestimated.

Prognosis

Despite its occasional deceptively benign clinical appearance, AVMs, in general, behave more aggressively than other vascular malformations. If not managed appropriately and carefully, improper treatment may result in more aggressive behavior and accelerated progression of the AVM (Figure 50.2).[5] It should be clearly explained to the patient that not all AVMs can be cured without impairing functionality or sacrificing esthetically relevant structures.[5] Patients should be given a choice whether to proceed with embolization and surgery or defer treatment altogether. AVMs may harbor unfilled or unrecruited mature vessels adjacent to the angiographically visible nidus. Following nidus resection or embolization of the AVM, these vessels that are normally poorly solicited in untreated AVMs may become recruited following resection of the nidus resulting in recurrence and/or progression.[23] Therefore, it should be made clear to the patient that in light of the attendant risks, which include massive bleeding, central retinal artery occlusion, skin necrosis, and recurrence or progression, therapeutic abstention may be the best available option for quiescent lesions or when the sole presenting complaint is only mild aesthetic impairment.[5,15,19] However, for patients with lesions that possess an unusual or uncontrollable growth pattern, or lesions that bleed profusely and repeatedly, surgery may a better alternative.[19]

Histopathology

AVMs of the soft tissue, brain, and orbit are composed of a varying proportion of large arteries and veins (Figure 50.3A and B).[24,25,26] The proportion of arteries and veins may differ from one area to another within the lesion,[24] and the arteries may be tortuous with focal loss, duplication, and distortion of the internal elastic lamina.[24,25,26,27] Elastic stain is particularly useful for demonstrating the internal elastic lamina of the arteries.[28] Visualizing communications between the arteries and veins may require step sections, and the veins may have secondary hypertensive changes manifest as thickened and *(Print pagebreak 332)* muscularized walls.[24] AVMs usually have a small vessel component of capillaries, venules, or indeterminate types.[24,27] A capillary component was a prominent feature of an orbital AVM reported by Howard, Jakobiec, and Michelsen.[26] Only capillary-sized vessels were seen in an eyelid AVM that reported histological examination.[10]

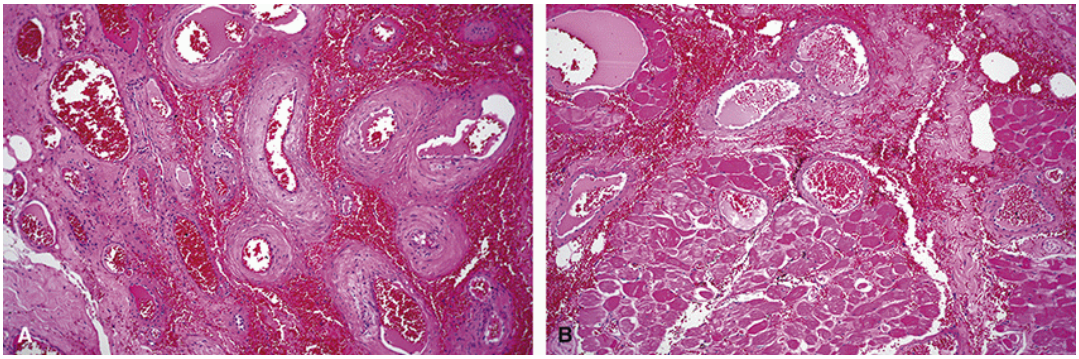

FIGURE 50.3 A, Arteriovenous malformation of the left upper eyelid composed of thick-walled arteries (on right) and thin-walled veins (on left). The proportion of arteries and veins varies from one region of a malformation to another (hematoxylin and eosin). B, Lesion extending through the orbicularis muscle (hematoxylin and eosin).

The histopathologic differential diagnosis of cutaneous AVMs includes other acquired benign vascular tumors such as venous spiders, angiokeratomas, cherry hemangiomas, cavernous hemangiomas, and pyogenic granulomas (lobular capillary hemangioma).[29,30,31] Venous spiders feature a central artery that arborizes into delicate arterial branches and then into capillaries.[30] Angiokeratomas have hyperkeratosis, acanthosis, and intraepidermal vascular spaces, features that are lacking in AVMs.[30] Cherry hemangiomas may have dilated capillaries, but thick-walled vessels are lacking.[32] Cavernous venous malformations (cavernous hemangioma) consist of thin-walled vessels in the dermis and lack thick-walled vessels,[33] but these lesions have been reclassified as venous malformations by the ISSVA (see Chapter 54). Pyogenic granulomas are easily distinguished from AVMs by a resemblance to granulation tissue with capillary proliferation, edematous or myxoid stroma, inflammation, and absence of thick-walled vessels.[30]

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CHAPTER 51

Arthropod Bites and Stings

Key Points

- The classes of arthropods that are medically significant to humans include centipedes, millipedes, spiders, mites, and insects
- The pathophysiologic mechanisms causing clinical symptoms from arthropod bites and stings include mechanical injury to the bite site and/or an immune response to saliva or injected toxins
- Ophthalmic manifestations from arthropod bites or stings can include eyelid and periorbital pain, erythema, edema, pruritus, and occasionally eyelid necrosis, reactive blepharospasm, and rarely orbital inflammatory syndrome
- Most arthropod bite and sting symptoms are short-lived and are managed with supportive measures consisting of acetaminophen or NSAIDs for pain, wound cleansing with soap and water, ice compresses, and elevation for significant edema
- Anaphylaxis is a rare complication that must be managed immediately with intramuscular epinephrine, recumbent posture, and adjunct measures such as IV fluids and oxygen
- If hairs or stingers are left behind, they are removed manually
- The greatest concern with arthropod bites is the transmission of infectious viral or bacterial diseases

Although the term "*bite*" is commonly used in the literature, it applies to both bites and stings inflicted by arthropods. Arthropods are members of the phylum Arthropoda, the largest phylum in the animal kingdom. About 80% of all known species of animals are members of this phylum.[1] This group includes five subphyla and a total of 16 classes that together contain the insects, centipedes, millipedes, spiders, scorpions, mites, ticks, lobsters, crabs, crayfish, and the extinct trilobites. Insects represent the largest class and include such common groups as ants, bees, wasps, fleas, mosquitoes, bedbugs, caterpillars, and lice. Arthropods live in every ecological habitat on the planet, from aquatic to terrestrial, and even airborne, and exhibit a very wide variety of adaptations. The distinguishing feature of arthropods is the presence of a jointed exoskeleton composed of chitin bound to protein. Key characteristics shared by all arthropods are jointed appendages from which the name arthropod ("*jointed feet*") is derived, and a segmented body, typically consisting of a head, thorax, and abdomen, though in some cases the head and thorax are fused into one segment. About one million arthropod species have been described, of which most are insects. This number, however, is likely only a fraction of the total, and global arthropod species have been estimated to be 5 to 10 million species.[2]

The classes of arthropods that are medically significant include centipedes, millipedes, spiders, mites, and insects, which represent more than half of all living organisms, and all of them can have a clinical impact on humans.[1] The incidence of arthropod bites and stings in the United States is difficult to quantify because most produce only minor symptoms that go unreported. The American Association of Poison Control Centers reported 28,087 cases of arthropod exposures in 2015, which, because of underreporting, likely represents only a small percentage of arthropod encounters.[1] There is no race, age, or gender predilection.

The most important concept in reducing the occurrence of arthropod bites and stings is prevention. Most available methods for prevention focus on mosquitoes and ticks, which transmit most cases of vector-borne pathogens to humans. Bite avoidance generally involves the use of insect repellents, but these do not affect bees, spiders, fleas, ants, or lice.[1] Protective clothing is another method that can be used in selective environments.

Etiology and Pathogenesis

Several pathophysiologic mechanisms cause the clinical symptoms seen with arthropod bites and stings. Mechanical injury during the bite or sting results in local pain and swelling. Even when other symptoms are minimal, breakage of the skin can serve as a

portal of entry for bacteria and viruses that can result in a secondary infection. Arthropod saliva often aids in digestion and inhibition of blood coagulation. It may also increase blood flow to the region and anesthetize the bite site. Most responses to insect bites and stings result from the victim's immune response to these secretions.[1] Some insects, such as bees, inject venom through a stinger that can cause allergic reactions in the skin, the respiratory tract, the cardiovascular system, and the gastrointestinal system. These are due to the presence of multiple protein allergens that possess enzymatic activity. Arthropods can also transmit pathogenic microorganisms to their vertebrate host through a bite or with contaminated feces. These, in turn, can cause a vector-borne disease.[3]

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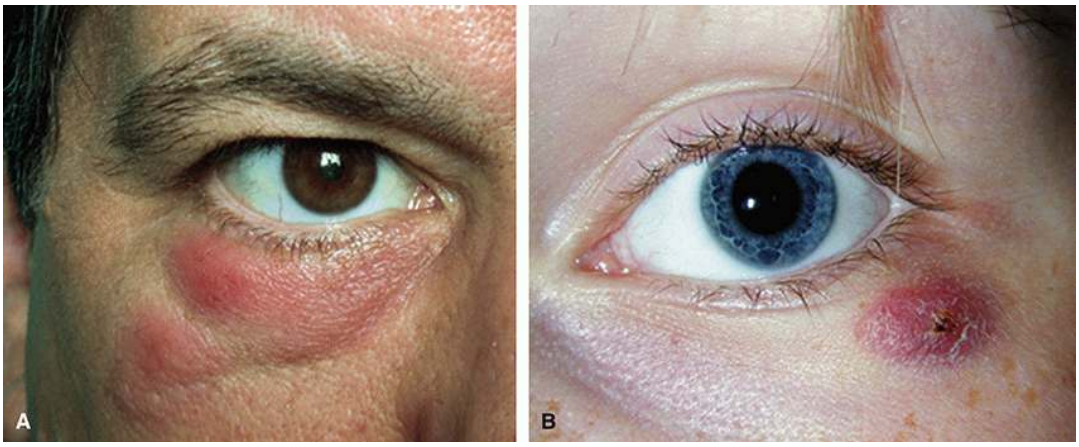

FIGURE 51.1 A and B, Nonspecific insect bites with local erythema and edema of the lower eyelids. A, (Courtesy of Dr. Robert A. Goldberg.)

Clinical Characteristics

Arthropod bites and stings typically cause cutaneous traumatic injury or local inflammatory and hypersensitivity reactions to the arthropod saliva or stinger venom. Clinically, bites and stings typically manifest as erythematous and edematous papules and urticaria. When associated with toxic venom, significant allergic and systemic reactions can follow, including autonomic instability, neurotoxicity, angioedema, anaphylaxis, organ failure, or circulatory collapse.[1] Arthropod bites can also serve as vectors for bacterial, viral, and protozoal diseases.

Ophthalmic manifestations from arthropod bites or stings are varied, depending on the type of organism and the location of the injury. Stings and bites to the eyelids and periorbital skin are usually associated with pain, erythema, edema, and pruritus (Figure 51.1).[4,5,6] Eyelid necrosis,[7] reactive blepharospasm,[8] and orbital inflammatory syndrome[9] have all been associated with ocular or eyelid insect bites and stings. Conjunctival arthropod bites and stings are uncommon but have been described from bee stings, wasps, and ants. Symptoms include pain, chemosis, hyperemia, epiphora, photophobia, and foreign body sensation.[10,11,12,13]

Centipede bites inject a venom containing histamine, serotonin, enzymes, acid, alkaline phosphatase, and naphthylamidase.[1] Contact with skin most commonly results in intense localized pain, erythema, and edema that produces two hemorrhagic punctures accompanied by pain.[14,15] Millipedes inflict damage through the secretion of a toxic liquid from glands on the sides of their body segments. These secretions contain hydrogen cyanide, organic acids, cresol, phenol, benzoquinones, and hydroquinones.[1] The toxin produces a localized caustic effect resulting in intense burning accompanied by erythema and occasionally vesicle formation.[16]

Caterpillars contain tiny hairs (setae) covered by microscopic barbs or spines on their body.[17] The setae can blow in the wind and land on the skin, in the eyes, and on clothing, sometimes causing allergic reactions.[16] Several caterpillar species contain a toxin and can cause poisoning. When the setae or spines contact human skin, they can cause pain, pruritus, and hemorrhagic purpuric papules at the site of contact. When they land on the eyelids or conjunctiva (Figure 51.2), setae can result in severe ocular surface inflammation.[18,19,20,21,22,23] Rarely, they may become impacted in the meibomian gland orifices (Figure 51.3),[24] or even penetrate the cornea (Figure 51.4) or extend through it into the anterior chamber.[25] Iritis, vitritis, and papillitis are uncommon but well-documented ocular complications from caterpillar hairs.[20,21,26,27]

Spiders are carnivorous arthropods that use venom to immobilize their prey. The two spiders with the greatest potential to cause significant morbidity in humans in the *(Print pagebreak 336)* United States are the brown recluse (*Loxosceles reclusa*) and black widow (*Latrodectus mactans*).[28] Brown recluse spiders have a yellow to brown cephalothorax and a tan abdomen and possess a violin-shaped marking on their dorsal cephalothorax. They are found predominantly in the South and the Central United States, where they reside in dark, dry places. They usually bite on the extremities when disturbed and bites often cause a small painless,

erythematous lesion. Brown recluse venom contains hemolytic enzymes that can cause ischemia with extensive tissue destruction and full-thickness skin necrosis (Figure 51.5).[14,29,30] Black widow spiders are dark brown or black with a rounded, shiny abdomen and have a red or orange hourglass on the ventral surface of their abdomen. With a bite, there is usually a dull ache or numbness at the puncture site and two puncture wounds are surrounded by erythema that may appear within 60 minutes. Black widow venom contains the potent neurotoxin, alpha-latrotoxin, which causes the release of excessive amounts of neurotransmitters, including acetylcholine, norepinephrine, glutamate, and dopamine from presynaptic nerve terminals. It can cause significant muscle pain, diaphoresis, tachycardia, flushing, hypertension, ptosis, nausea, vomiting, dyspnea, and rarely death.[1,31] Unlike the brown recluse, the venom of the black widow does not cause local necrosis.

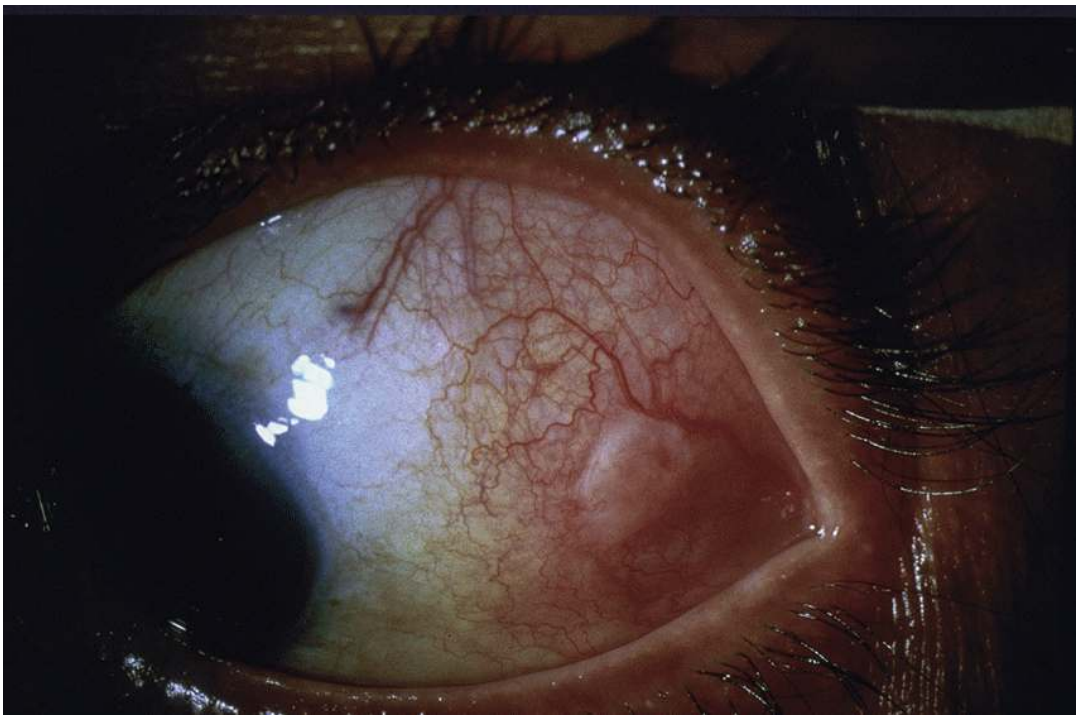

FIGURE 51.2 A conjunctival granuloma (ophthalmia nodosa) resulted from the hair of a woolly bear caterpillar, the larval form of the isabella tiger moth (*Pyrrharctia isabella*).

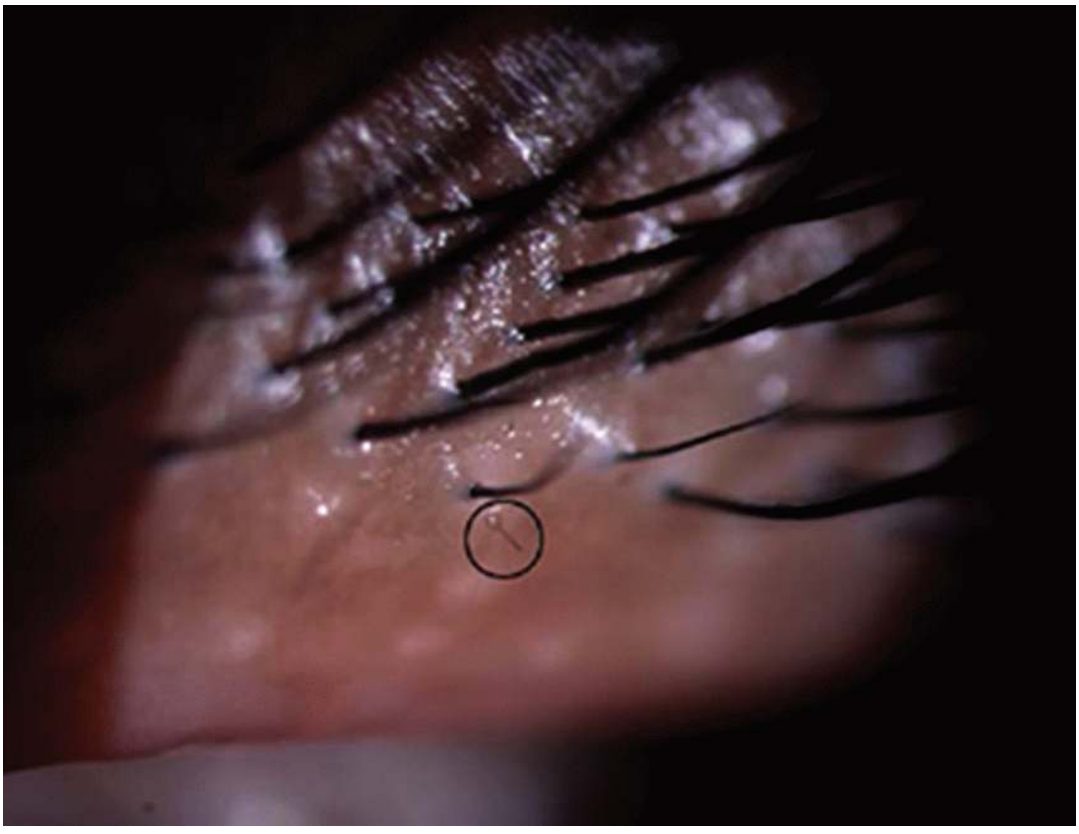

FIGURE 51.3 Caterpillar hair in a meibomian gland orifice. (Reprinted with license from Wolters Kluwer: Rajagopalan J, Joy A, Yadalla D. A rare hideout for caterpillar hairs. *Ophthalmic Plast Reconstr Surg* . 2020;36(4):e93-e94; Figure 2.)

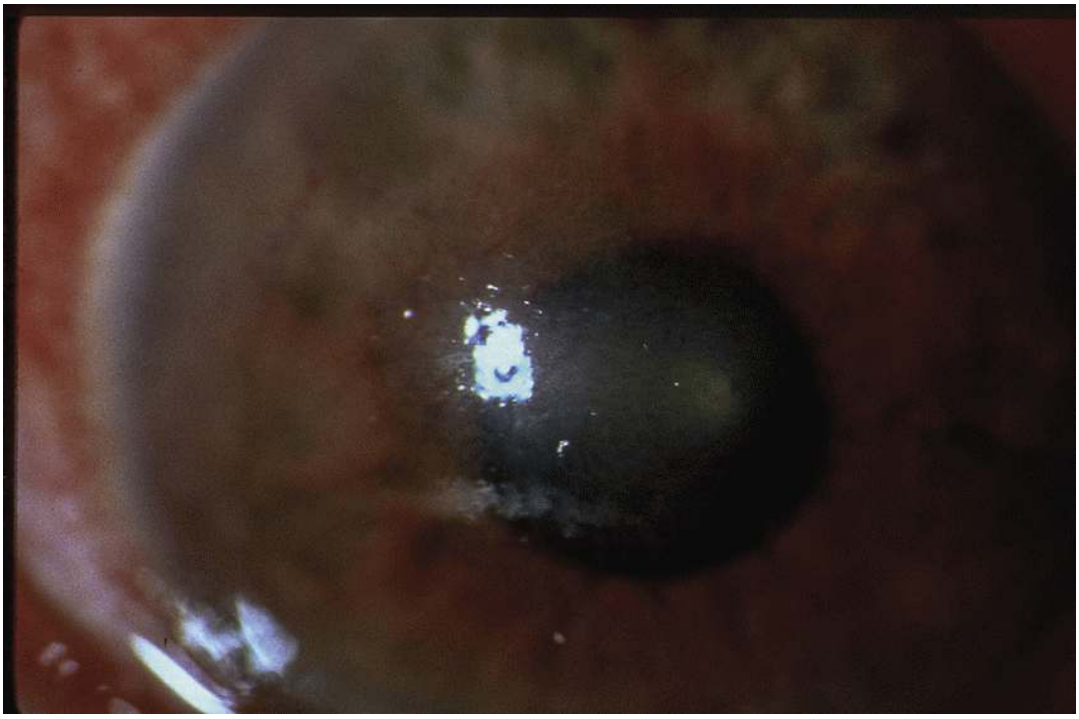

FIGURE 51.4 A woolly bear caterpillar hair penetrated into the cornea; this is the same patient shown in Figure 51.3.

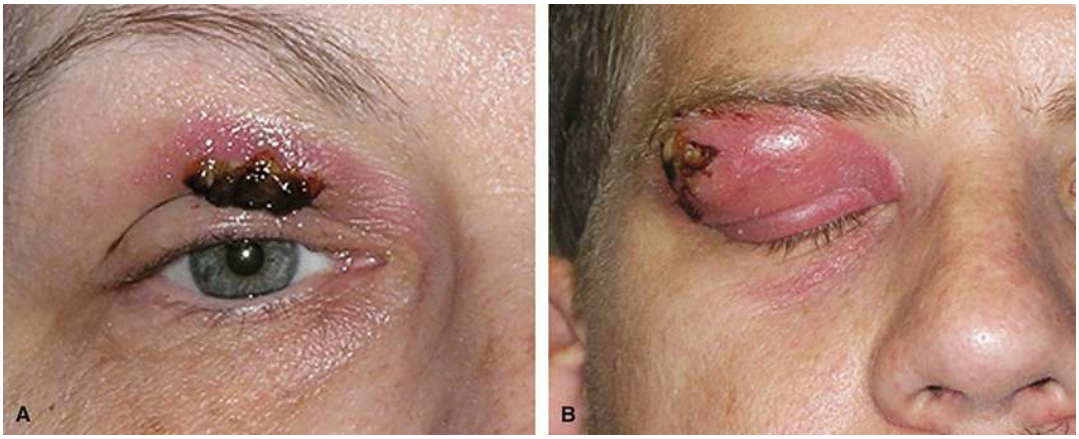

FIGURE 51.5 A and B, Spider bite lesions with edema, erythema, and focal tissue necrosis. (Courtesy of Dr. Charles Soparkar.)

Wasps, bees, yellow jackets, hornets, and fire ants are included in the insect order of Hymenoptera. They all have a stinger that can deliver venom containing bradykinin, acetylcholine, histamine, and serotonin that are responsible for most of the clinical toxicity.[1] Local reaction to stings typically presents with the immediate onset of pain, erythema, and edema. Severe reactions can occur with pruritus, facial flushing, and urticaria progressing to respiratory distress, angioedema, vomiting, abdominal cramping, and syncope. Some honeybees and bumblebees possess a stinger with curved barbs that remain in the injection site following a sting. Wasps and yellow jackets do not lose their stinger during the sting so they can sting multiple times. Ocular bee *(Print pagebreak 337)* stings most often involve the cornea, and less frequently the conjunctiva or the eyelid.[12,32,33,34] Symptoms are usually mild but rarely can result in severe visual symptoms including intraocular inflammation, marked loss of vision, and optic neuritis.[35,36,37,38] Rare cases of anaphylaxis, renal failure, and death have been reported.[39]

Mosquitoes are members of the fly family and live in grass and bushes located close to areas where humans live and work. They are considered the deadliest animals on Earth because they harbor and can transmit a highly diverse microbiota, including bacteria, fungi, and viruses.[40] Male mosquitos do not bite humans, but females do. They have a long tubular proboscis for biting to feed on blood. During the bite, saliva is injected while siphoning the blood. The saliva contains proteins that cause an allergic reaction in most individuals.[41] The most common symptoms are urticarial wheals and pruritus. The greatest danger from mosquitos is their

ability to transmit several serious diseases including malaria, filariasis, yellow fever, dengue fever, West Nile virus, Zika virus, and chikungunya.[42,43]

Fleas are ectoparasites that feed on mammals and birds. They do not have wings but jump from one organism to another. The life cycle of the flea consists of egg, larva, pupa, and biting adult, and the adult flea feeds on blood. Fleas can transmit several infections such as rickettsiosis, bartonellosis, typhus, and tungiasis.[44,45] Flea bites typically present as erythematous papules, or urticarial vesicles or bullae, sometimes with a hemorrhagic center and associated with severe pruritus. Scratching can result in secondary bacterial infection. A case of orbital inflammatory disease from a flea beneath the eyelid was reported.[9]

Ticks feed by cutting a hole in the epidermis and injecting an anticoagulant agent to inhibit platelet aggregation.[1] Tick bites are usually painless, presenting as an erythematous papule or a pruritic urticarial rash. The most important possible consequence of tick bites is their ability to serve as vectors for diseases such as Rocky Mountain spotted fever, endemic typhus, Q-fever, hemorrhagic fever, Lyme disease, relapsing fever, babesiosis, ehrlichiosis, and tularemia.[46]

Lice are parasitic insects that also feed on human blood, injecting their saliva into the skin. Three types of lice feed on humans: the head louse, the body louse, and the pubic or crab louse (*Pthirus pubis*). Head and pubic lice do not transmit disease, but body lice can transmit typhus and louse-borne relapsing fever.[1] Head lice occur most frequently in younger children, and because these insects are unable to hop, jump, or fly, they are spread through direct head-to-head contact. Transmission on environmental surfaces such as combs and towels is less common since lice do not survive off the scalp for more than about 1 day.[47] They are typically seen on the head, eyebrows, and eyelashes and exist as adults, nymphs, and eggs (or nits) clinging to hair shafts. Symptoms can result from hypersensitivity reactions manifesting as diffuse eczematous dermatitis or diffuse skin-colored papules.[48,49] Secondary bacterial infection with regional lymphadenopathy can complicate the clinical picture.[50] Pubic lice are generally limited to areas with short hair, such as pubic hair, but may occasionally be found on eyelashes, eyebrows, and axillary and beard hair.[1] Transmission is usually through sexual contact and occurs most frequently in adults. Body lice live and lay their eggs in seams of clothing or bedding, moving to the skin only to feed. They produce more severe pruritus from an allergic response to the lice saliva.

The human bedbug is a small parasitic insect that feeds on blood and has a worldwide distribution.[1] They use a small tubelike proboscis to pierce the skin.[16] In most cases, symptoms occur either immediately or may progress over several days. Symptoms can include burning pain, local inflammation, pruritus, red papules, and spots of blood, but most symptoms typically resolve after 1 to 2 weeks. Systemic reactions may include asthma, angioedema, generalized urticaria, iron deficiency anemia, and, rarely, anaphylaxis.[51]

Differential Diagnosis

The differential diagnosis for arthropod bites and stings is extensive. It should include contact dermatitis, erythema multiforme, bullous diseases, cutaneous drug eruptions, dermatitis herpetiformis, tinea, eczema, vasculitis, pityriasis, viral exanthem, cellulitis, abscess, impetigo, folliculitis, erysipelas, and necrotizing fasciitis, among others.[14,52] Necrotic ulcers from a brown recluse bite can be confused with staphylococcus or streptococcus skin infection, fungal infections, necrotizing fasciitis, pyoderma gangrenosum, diabetic ulcers, leishmaniasis, and sporotrichosis.[52]

Treatment

Most arthropod bite and sting symptoms, such as those from millipedes, bedbugs, mosquitos, and fleas, are short-lived and can be managed with supportive measures consisting of acetaminophen or nonsteroidal anti-inflammatory drugs for pain, local wound cleansing with soap and water, ice compresses, and elevation of the area if there is significant edema. Pruritus is treated with antipruritic creams, antihistamines, or topical corticosteroids. If a secondary infection is present, appropriate antibiotics should be started. Evaluation for vector-borne diseases and initiation of appropriate antimicrobial therapy should be considered when indicated.

Treatment of caterpillar-induced cutaneous reactions is the same, but if hairs or spines are present on the skin, they can be removed with adhesive tape. Treatment of acute conjunctival reaction to caterpillar hairs is irrigation and manual removal of hairs, along with topical antibiotics and corticosteroids.[26] If the patient develops chronic keratoconjunctivitis, then a careful search for previously undetected hairs should be undertaken, along with their removal.[26] If conjunctival nodules result from hairs that penetrate the conjunctival epithelium, then excision is required to prevent the hairs from migrating into the eye.[26] Corneal hairs should also be removed if they are located deeply and appear to be migrating toward the interior of the eye. Iritis is treated with topical *(Print pagebreak 338)* steroids, while vitritis and papillitis require oral or periocular steroids with consideration of vitrectomy if the ocular inflammation does not respond to steroids.[26] Intraocular inflammation from caterpillar hairs penetrating to the inside of the eye may rarely require enucleation for relief of pain.[20,27]

Head lice infestation treatment is with pediculicides such as pyrethrins and permethrin 1% lotion. Nits should be removed from hair with a fine comb. Since most treatments do not entirely eradicate the eggs, retreatment is usually necessary seven to 10 days later. For body lice, showering and regular laundering of clothing in hot water will often eradicate the infestation. Antibiotics may be required for secondary infections.[16] For Hymenoptera that lose their stinger during the sting, the stinger should be removed manually.[53]
In venom-allergic patients, immunotherapy can be a very effective approach, conferring long-term protection in over 98% of cases against future stings in patients with a history of anaphylaxis.[54]

Treatment of brown recluse envenomation consists of routine wound care, evaluation of tetanus status, and the local application of ice, which may decrease the activity of damaging enzymes found in the venom. In cases where necrotic ulceration occurs, early surgical excision is not recommended because it can result in recurrent wound breakdown, delayed healing, and scarring.[53]

Ticks should be removed with fine-tipped forceps and the bite is treated with routine wound care. Treatment of bedbug bites consists primarily of symptomatic care with the use of topical glucocorticoids and systemic antihistamines to control pruritus.[15] Secondary infections should be treated with the appropriate antibiotics. Elimination of infestations can be difficult and often requires a combination of professionally applied insecticide and nonchemical controls.

Anaphylaxis is a rare complication, but when present must be managed immediately with intramuscular epinephrine, recumbent posture, and supportive measures such as IV fluids and oxygen.[54] Adjunctive treatments such as systemic corticosteroids, albuterol, and antihistamines can be utilized.

Although numerous diseases are transmitted by arthropod vectors, for many of these diseases, effective vaccines are still not available so that prevention is the main strategy. The “Global Vector Control Response 2017 to 2030” was approved by the World Health Organization in 2017 and provides strategic guidance to countries and development partners for urgent strengthening of vector control as an approach to preventing disease and responding to outbreaks.[55]

Prognosis

Most arthropod bites and stings cause only mild, uncomplicated localized cutaneous reactions. The prognosis is usually favorable with symptomatic treatment and supportive care alone. A worse prognosis can be seen in children, the elderly, or individuals with significant underlying cardiovascular disease.[1]

Significant complications are rare and a small number of cases may be fatal secondary to the development of anaphylaxis. The US Centers for Disease Control and Prevention estimates an annual rate of 90 to 100 deaths from insect venom anaphylaxis,[56] and bees, wasps, and imported fire ants are responsible for the majority of cases.[57,58] Risk factors for increased severity include older age, preexisting cardiovascular disease, treatment with beta-adrenergic blockage or ACE inhibitors, and honeybee stings.[59] Acute kidney injury can occur due to intravascular hemolysis, arterial hypotension, rhabdomyolysis, hypotension, and direct toxicity of the venom components to the renal tubules.[60,61] Rare mosquito bites can result in fever, hemorrhagic bullae, eschars, and healing with scar formation.[62] Cases of monoparesis and transient visual loss following multiple bee stings have also been reported and can involve both the anterior and posterior circulation territories to the brain.[63]

The greatest concern with arthropod bites is the transmission of infectious diseases. The prognosis for these arthropod-borne infections depends on the specific organism transmitted.

Histopathology

The histological appearance of an insect bite depends on the arthropod species, the time between the bite and biopsy, and the degree of sensitivity of the individual.[64] Goldman, Rockwell, and Richfield examined the histopathological response over time to bites by *Aedes aegypti* (yellow fever mosquito), *Anopheles quadrimaculatus* (common malaria mosquito), *Xenopsylla cheopis* (oriental/tropical rat flea), *Cimex lectularius* (common bedbug), *Pediculus humanus* (head and body louse), *Amblyomma americanum* (lone star tick), and *E. alfreddugesi* (common chigger).[64] Thirty minutes after an *A. aegypti* bite in subjects with a moderate clinical reaction, there was edema of the superficial dermis and “the beginning of a perivascular infiltrate of polymorphonuclear leukocytes, eosinophils, lymphocytes, and plasma cells.”[64] After 6 hours, there was increased edema and perivascular inflammation, with spread of the inflammation. At 24 hours, the edema decreased, but the inflammatory infiltrate increased and was composed of lymphocytes and eosinophils.[64] Mild edema persisted after 48 hours, but the inflammatory infiltrate had diminished, and there was an increased percentage of lymphocytes and macrophages.[64] Edema had subsided after 5 days, and there were only a few

lymphocytes.[64] In a subject with a macular reaction to *A. aegypti* after 1 day, there was only a slight perivascular infiltrate composed mainly of lymphocytes and occasional eosinophils and neutrophils.[64] A 3-day-old papulovesicular mosquito bite reaction exhibited marked subepidermal edema, vesicle formation, and a dense perivascular infiltrate composed predominantly of lymphocytes.[64] Three days after an *A. quadrimaculatus* bite in a sensitive patient with clinical reactions up to 15 cm in diameter, there was a dense infiltrate of numerous eosinophils, polymorphonuclear leukocytes, lymphocytes, macrophages, and *(Print pagebreak 339)* an occasional plasma cell extending into the subcutaneous adipose tissue. These studies with mosquitos demonstrate the variability in the bite reaction among individuals having different clinical responses. In general, severe clinical reactions have more marked epidermal and dermal edema, a denser and more extensive inflammatory infiltrate, and a greater proportion of eosinophils and neutrophils than seen in patients with milder clinical reactions.[64]

The head and body louse (*P. humanus*) feeds longer than a mosquito, but the histological response to a bite again depends on the sensitivity of the individual being bitten.[64] People lacking a clinical reaction have only a "*small*" perivascular infiltrate of lymphocytes with occasional neutrophils and eosinophils; the neutrophils and eosinophils disappear within 2 days.[64] People with a moderate clinical response to louse bites have a histological appearance resembling mosquito bites in moderately sensitive people.[64] Scanning electron microscopy may assist in confirming a diagnosis of pubic louse (*P. pubis*) infection (Figure 51.6).[65]

Flea bites (*X. cheopis*) in sensitive individuals feature the same histological progression as seen following mosquito and louse bites, while bites in nonsensitive people resemble those following louse bites in people lacking visible clinical reactions.[64] Bedbug bites (*C. lectularius*) may have a histological reaction pattern similar to that produced by mosquito bites,[64] or there may be a bullous response.[66] People developing a bullous response have prominent edema, a paucicellular inflammatory infiltrate, and mast cell degranulation 30 minutes after a bite.[66] An inflammatory vasculopathy with a mixed cellular infiltrate of neutrophils, macrophages, and lymphocytes was seen after 6 hours, and this progressed to a neutrophil-predominant leukocytoclastic vasculitis by 12 hours.[66] There was a necrotizing eosinophil-rich vasculitis at 24 hours with stellate collagen necrosis ("*necrobiosis*") and eosinophil granules encrusting degenerating collagen fibers.[66] The reaction at 24 hours resembled that in Churg-Strauss syndrome,[66] and it may also be seen in Sweet syndrome (acute febrile neutrophilic dermatosis).[67] Flea and bedbug bites may also produce papular urticaria,[68] and the histological response is duplicated by injection of flea or bedbug antigen.[69] Following antigen injection, there is a moderate to heavy perivascular and periappendiceal infiltrate of lymphocytes with a large number of eosinophils, chiefly in the middle and lower thirds of the dermis and sometimes extending into the subcutis.[69] Focal necrobiosis (collagen necrosis) may occur in the lower third of the dermis.[69] Involuting papular lesions have a sparse inflammatory infiltrate and lack eosinophils.[69]

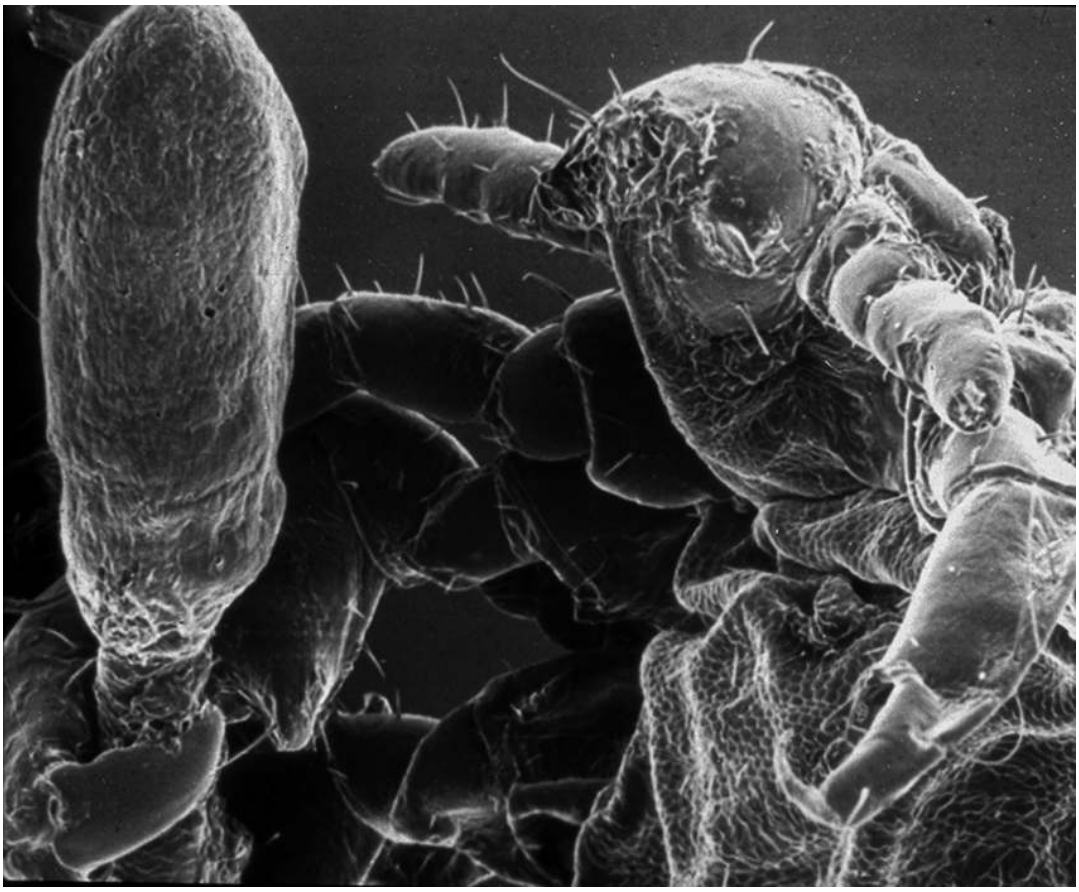

FIGURE 51.6 Scanning electron micrograph of a pubic louse (*Pthirus pubis*) attached to a plucked eyelash.

Chigger bites (*E. alfreddugesi*) display marked intraepidermal edema with central bullous formation and a heavy perivascular lymphocytic infiltrate that may persist for some days.[64,70] Parakeratosis is present at the point of epidermal piercing by the pointed mandibular claws.[70] Edema begins in the dermis as spastic ischemia, followed by active hyperemia, capillary hemorrhage, and serous exudation that extends upward into the epidermis.[70] Involution begins about the third day, is very slow, and results in resorption of vesicle fluid, cellular debris, and hemorrhage.[70] Dermal fibrosis invariably results.[70]

Goldman and coworkers noted moderate intraepidermal edema, a small intraepidermal vesicle, and marked dermal edema with a prominent perivascular infiltrate of lymphocytes and macrophages in 4-day-old lone star tick bites (*A. americanum*).[64] A 2-week-old *A. americanum* bite had coagulative necrosis of the epidermis and papillary dermis, along with a dense infiltrate of neutrophils, lymphocytes, plasma cells, macrophages, and "*a considerable admixture of eosinophils*" in the papillary and reticular dermis and extending into the subcutaneous adipose tissue (Figure 51.7A and B).[71] Acute bites (1 month or less) from the American dog tick, *Dermacentor variabilis*, display a bloody crust over disintegrating epidermis containing hemorrhage and eosinophils.[72] The papillary dermis has a few eosinophils and dilated blood vessels surrounded by a few lymphocytes, while the deeper dermis has only edema.[72] Subacute lesions of several months duration have intact epidermis with flattening of the rete pegs, "*practically normal*" papillary dermis, and the reticular dermis and subcutaneous fat have a dense infiltrate of lymphocytes, neutrophils, fibroblasts, eosinophils, and large lymphocytes, which is most pronounced around blood vessels.[72] Eosinophils were less numerous in subacute than acute tick bites (Figure 51.7C), and there were fewer eosinophils than mast cells.[72] Chronic *D. variabilis* bites, those of a year or more in duration, had flattened epidermis overlying dense dermal fibrosis with numerous mast cells, occasional Langerhans giant cells, a few lymphocytes, and several eosinophils.[72] Tick bites may also produce eosinophilic cellulitis mimicking Wells syndrome.[73] Tick identification, should it be necessary, relies on tick shape, size, and color, along with the appearance of the mouthparts (capitulum), dorsal shield (scutum), and posterior abdominal markings (festoons).[74]

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Guinea pigs bitten by brown recluse (*L. reclusa*) spiders develop dermal, subcutaneous, and superficial muscle hemorrhage along with dilated and thrombosed capillaries and slight leukocyte infiltration 2 hours after a bite.[75] After 24 hours, the bite site had necrotic epidermis, the hair follicles were disintegrating, capillaries were thrombosed, and there was a marked leukocytic infiltrate in the hemorrhagic zone.[75] Three days after a bite, guinea pigs had skin ulceration overlying a large dermal and subcutaneous abscess surrounded by dense inflammation and peripheral fibroblastic proliferation.[75] After 13 days, the bite abscess had ruptured through the skin surface, and the wound was becoming scarred.[75] The composition of the leukocytic infiltrate was not described in the guinea pig studies by Atkins and colleagues.[75] Injection of brown recluse spider venom into the rabbit eyelid demonstrated a similar development of lesions with progressive dermal capillary thrombosis, influx of leukocytes with abscess formation and zonal necrosis, progression to full-thickness eyelid necrosis by day 4, granulation tissue at 17 days, and organized collagen and regenerated epithelium by 31 days.[30] Human bites by the brown recluse have been examined only rarely with "*early*" lesions featuring hemorrhage, dermal-epidermal separation, and a moderate inflammatory infiltrate.[29] We are not aware of reports of histopathological findings following black widow spider bites.

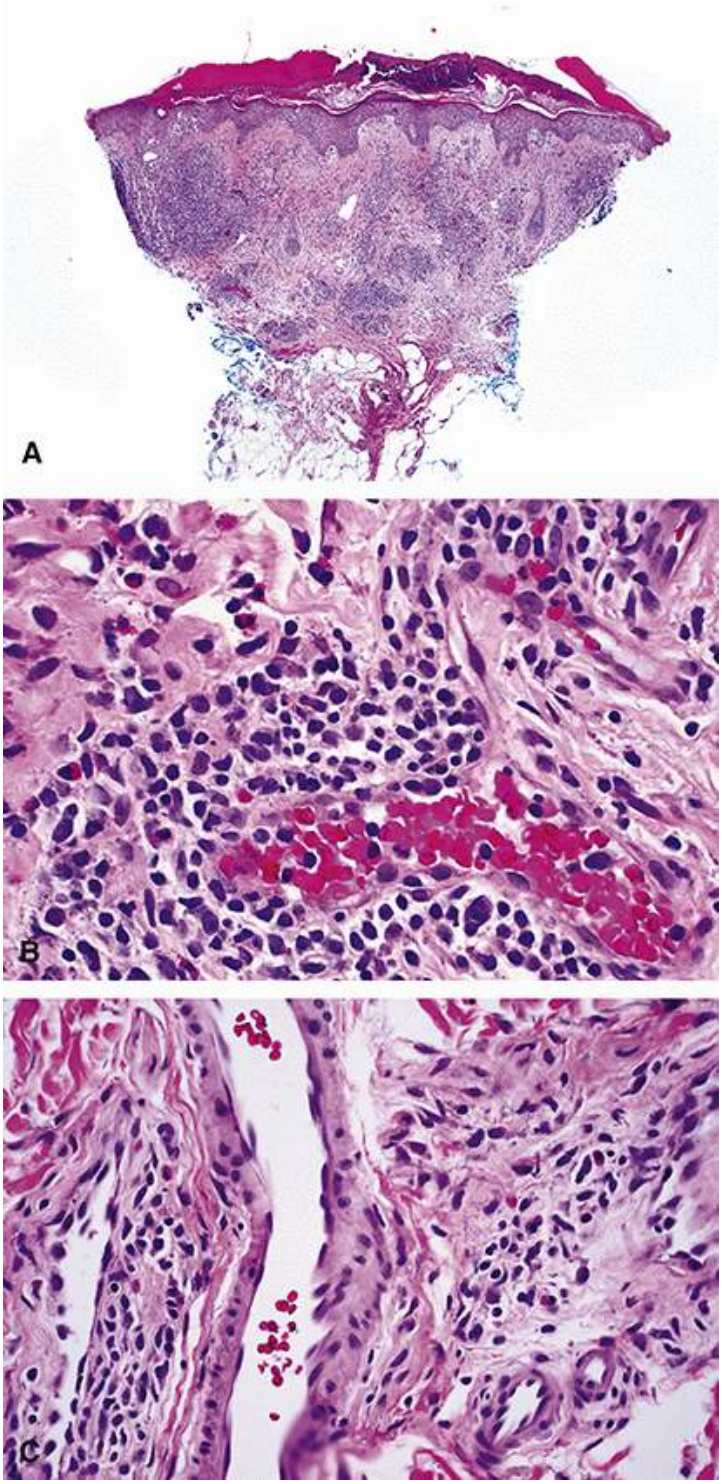

FIGURE 51.7 A, This biopsy 1.5 weeks following a tick bite shows a prominent perivascular inflammatory infiltrate. The epidermis has spongiosis with an overlying serum crust. B, At higher magnification, the 1.5-week-old tick bite has eosinophils mixed with macrophages and lymphocytes. C, The perivascular inflammation may persist for a long time, as shown in this biopsy several months following an insect bite. These vessels in the deep dermis have a mild perivascular infiltrate of macrophages, lymphocytes, and eosinophils.

The histopathology of caterpillar hair dermatitis has been studied by applying setae from the larvae of European brown-tail moths (*Euproctis chrysorrhoea*) to the skin of human volunteers.[76] After 1 hour, there is disruption of the epidermal horn layer, lysis of underlying epidermal cells, formation of small intraepidermal bullae, and superficial dermal edema with beginning mononuclear and neutrophilic inflammation, sometimes with a few eosinophils.[76] Intraepidermal bullae containing neutrophils develop by 5 hours, spongiosus develops, and there is increasing superficial dermal perivascular mononuclear inflammation, though neutrophils and eosinophils may be present.[76] By 48 hours, there is increased spongiosus, extensive intraepidermal bullae with invading neutrophils and eosinophils, and a predominantly mononuclear infiltrate in the dermis.[76] Conjunctival lesions (ophthalmia nodosa) have been examined after nodules develop clinically and feature granulomas with a caterpillar hair sometimes visible within the center (Figure

51.8).[18,20,23,26,27] *(Print pagebreak 341)* Granulomas may also form within the eye if the hairs penetrate internally.[20,27] Tarantula hairs may result in a similar clinical and histopathological ophthalmia nodosa.[77,78]

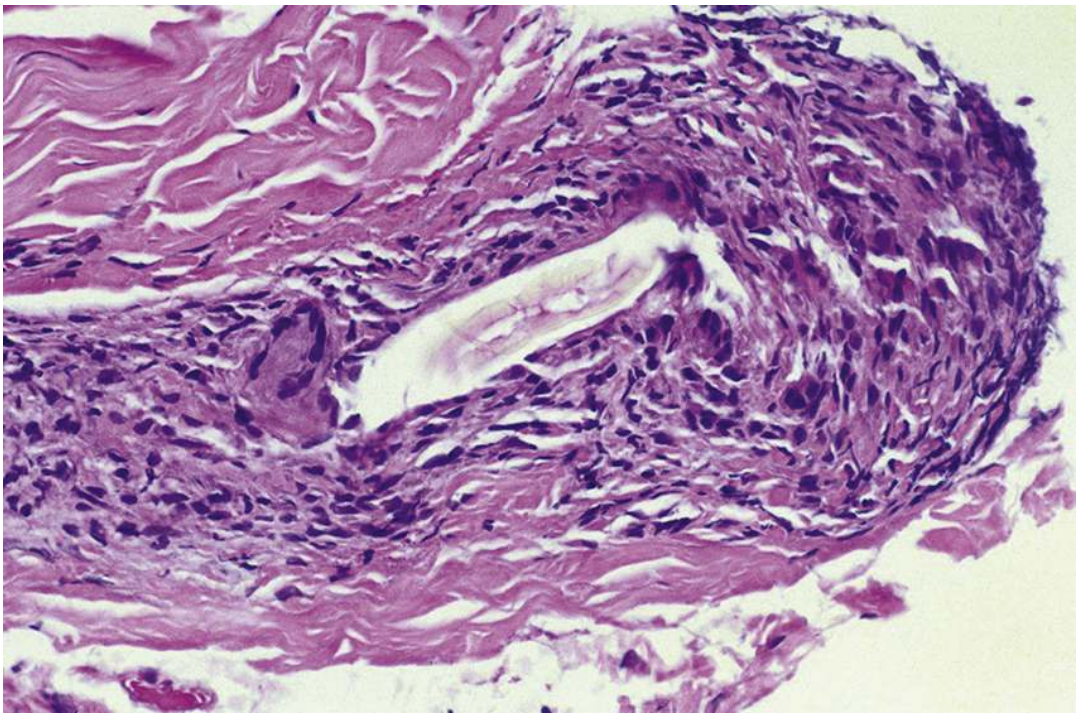

FIGURE 51.8 Ophthalmia nodosa features granulomas surrounding caterpillar hairs, as shown in this nodule removed from the anterior episclera of the patient shown in Figure 51.2.

Bee and wasp stings are rarely examined histopathologically unless the stinger is retained.[79] Retained stingers may elicit epidermal necrosis, epidermal pseudoepitheliomatous hyperplasia, and an intense dermal lymphohistiocytic and eosinophilic infiltrate.[79]

Eosinophils are considered to be a "*constant feature to the inflammatory infiltrate in insect bite reactions*,"[80] though this is not always the case, as seen from the experimental studies presented above. If eosinophils are present, then the main differential diagnosis is other dermal hypersensitivity reactions, including drug reactions, idiopathic urticaria, and eczematous dermatitis with urticarial features.[81]

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CHAPTER 52

Atopic Dermatitis

Key Points

- Atopic dermatitis is a chronic inflammatory skin condition characterized by the presence of chronic, eczematous, or scaly lesions with remissions and exacerbations
- Patients may have a history of other atopic diseases like allergic rhinitis or asthma
- Atopic dermatitis is a complex heterogeneous inflammatory disease with type I and IV allergies complicated by genetic, immunologic, and environmental factors
- Onset is usually within the first 2 years of life, and approximately 85% are afflicted before the age of 5 years
- The disease is characterized by relapsing pruritic dermatitis, with eczematous eruptions, often accompanied by diffuse and symmetrical erythema
- Patients may have associated atopic keratoconjunctivitis, presenting with chronic ocular burning, itching, and redness, as well as papillary conjunctivitis, symblepharon, corneal vascularization, stromal scarring, corneal opacification, keratoconus, or cataracts
- General treatment includes lid hygiene, and avoidance of specific or nonspecific provoking environmental factors
- Low potency topical steroids and oral antihistamines are effective in resolving symptoms

Atopic dermatitis (eczema, atopic eczema) is defined as a chronic inflammatory skin condition characterized by the presence of eczematous or scaly lesions with an itch, which usually follows a chronic course of remissions and exacerbations in patients who may have a history of other atopic diseases like allergic rhinitis or asthma.[1,2,3,4,5,6,7,8,9,10,11,12,13]

Etiology and Pathogenesis

Atopic dermatitis is a complex heterogeneous inflammatory disease with type I and IV allergies intertwined in a complicated manner, and the etiology may be multifactorial (genetic, immunologic, and environmental).[14,15] There are two competing theories to explain the etiology. The most commonly accepted theory is that the disease occurs because of an intrinsic genetic defect in the epidermal barrier.[2] Filaggrin is a key protein that controls the terminal differentiation and formation of the epidermis, as well as maintenance of the skin barrier.[2] A genetic defect in this protein disrupts the epidermis, which allows allergens or irritants to penetrate the epidermal barrier easily.[16] This event facilitates contact between immune cells in the dermis and antigens from the external environment, thus inducing a secondary immunologic reaction. This hypothesis is dubbed the outside-to-inside hypothesis and is the most accepted theory.[1,2] Atopy leads to intense itching and scratching, which in turn can lead to further disruption and inflammation of the epidermal skin barrier. This results in a vicious cycle that has been dubbed the itch-scratch cycle.[1] That said, it should be noted that the genetic origin of atopic dermatitis is complex and poorly understood. Multiple alleles at several susceptibility loci, including 3q21, 1q21, 17q25, and others, have been proposed recently and are summarized elsewhere.[17] Genetic defects in the filaggrin protein are also implicated in other forms of atopy like allergic rhinitis and asthma.[16,18]

An alternative theory that was more popular in the past is the so-called inside-to-outside hypothesis.[2,19,20] This theory postulates that cutaneous inflammation precedes barrier impairment and that immunological aberrations are a primary event in the initial development of atopic dermatitis. Regardless of the correct theory, the ultimate pathogenetic event is a leaky epidermal barrier or skin barrier insufficiency.[16]

It is difficult to attribute the global increase in the prevalence rates of atopic dermatitis to genetic or immunologic factors alone; in fact, both theories require a trigger factor.[19] Environmental exposure to various agents may trigger initiation or flare-up of the disease in predisposed individuals.[16,19] These factors may occur due to in utero or early life exposure to various environmental and

climatic irritants or pollutants.[19]

Clinical Presentation

The hallmark of the disease is early-onset, chronic relapsing pruritic dermatitis, with eczematous eruptions that are often accompanied by diffuse and symmetrical erythema.[14,16] Atopic dermatitis is a common chronic disease affecting approximately 10% to 20% of the general population, and the prevalence is steadily increasing, at least in developing countries.[2] About 40% of patients have a history of other atopic diseases such as allergic rhinitis or asthma, and the disease is more frequent in females.[4,21] Because of the strong genetic component, the onset of atopic dermatitis usually occurs within the first 2 years of life, and approximately 85% are *(Print pagebreak 344)* afflicted with the disease before the age of 5 years, although the incidence and prevalence increase with advancing age.[12,16]

A major obstacle in diagnosing atopic dermatitis is the clinical overlap with other dermatologic problems, as well as the lack of definitive biomarkers and histological findings for the disease. Therefore, the diagnosis has to be based on clinical findings, including the characteristic morphologies, age-dependent distribution, and associated clinical signs.[3] The diagnostic criteria of atopic dermatitis have been laid out by Hanifin and Rajka in 1980 and included major and minor criteria.[7,8] At least three of the major and minor criteria should be present to establish the diagnosis. Major criteria include (1) pruritus; (2) typical morphology and distribution of the lesions (facial and extensor involvement in infants and children or flexural lichenification in adults); (3) chronic or chronic relapsing dermatitis; or (4) personal or family history of other atopic diseases (asthma, allergic rhinitis).[7,8] Minor criteria include cataracts, cheilitis, eczema, blepharoconjunctivitis, facial pallor or erythema, food intolerance, nonallergenic hand dermatitis, ichthyosis, elevated IgE, a predisposition to recurrent cutaneous infections (staphylococcal blepharitis, etc), Dennie-Morgan lines (prominent infraorbital lines, creases, or folds), itching when sweating, keratoconus, periorbital hyperpigmentation (allergic shiners), nipple dermatitis, palmar hyperlinearity, pityriasis alba (children), white dermographism, wool intolerance, or xerosis.[7] A detailed discussion of alternative diagnostic standards including the criteria laid out by the American Academy of Dermatology and the Japanese Dermatological Association is beyond the scope of this chapter and is discussed elsewhere in the literature.[14,22]

Eyelid changes may begin with spongiotic dermatitis consisting of red, pruritic, inflamed areas of cracked skin with fluid accumulation (Figure 52.1A) and then evolve to broad areas of erythematous, edematous, indurated, or weeping eczematous lesions (Figure 52.1B). Pruritus often leads to chronic rubbing, and as a result, the eyelid skin becomes violaceous early on (Figure 52.2), and with time, this violaceous hue evolves into periorbital hyperpigmentation, which is a common characteristic of the disease. Coalescent papules, fissures, and fine scaling may also be observed. As the condition progresses into chronicity, thickening and accentuation of normal skin lines (lichenification) are observed. This thickening occurs more frequently in the medial part of the upper or lower eyelids (Figure 52.3).[13] Alternatively, periocular skin atrophy or hypopigmentation may be concomitantly observed if corticosteroid ointment was chronically applied in the past.[13]

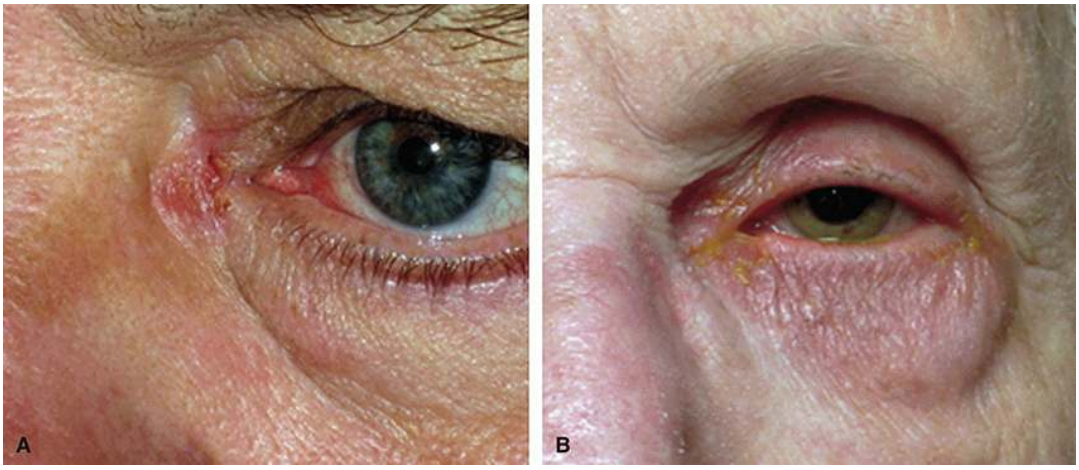

FIGURE 52.1 A, Spongiotic dermatitis with a small medial patch of an inflammatory rash with cracked skin and fluid. B, Atopic dermatitis with eyelid edema and erythema.

Gradually, eversion or stenosis of the lacrimal puncta may occur, and frank ectropion may be seen in severe cases, as well as the loss of eyelashes. Infectious complications are common, and it has been shown that a significant proportion of patients with atopic dermatitis show bacterial colonization in the conjunctival sac and on the eyelid margins.[23] This secondary bacterial infection is commonly attributed to the colonization of the eczematous skin with *Staphylococcus aureus* and usually leads to chronic anterior blepharitis, which may make the diagnosis difficult. Also, bacterial infection may lead to skin ulceration with serous exudation.[13]

Patients with atopic dermatitis may have associated atopic keratoconjunctivitis, typically presenting with symptoms of chronic ocular irritation (burning, itching, and redness), which may be exacerbated during cold damp weather. These patients usually manifest with diffuse conjunctival injection and superficial punctate corneal epitheliopathy that may be attributed to chronic eye rubbing.[13] Other clinical signs include chronic nonspecific papillary conjunctivitis, giant papillary conjunctivitis, symblepharon, corneal *(Print pagebreak 345)* vascularization, corneal pannus, stromal scarring, corneal opacification, keratoconus, or cataracts.[6,13,24,25,26,27,28,29,30,31] The prevalence of cataracts (particularly anterior or posterior subcapsular cataracts) in patients with atopic dermatitis is increased compared with the general population (8%-17%).[24,25,26,27,28,29,30,31] The mechanisms behind cataract formation remain elusive; however, a mechanical cause due to repetitive local rubbing and scratching or oxidative stress may be responsible.[27] Anterior subcapsular cataract appears to be more specific to the disease, but posterior subcapsular cataract is also very common.[27]

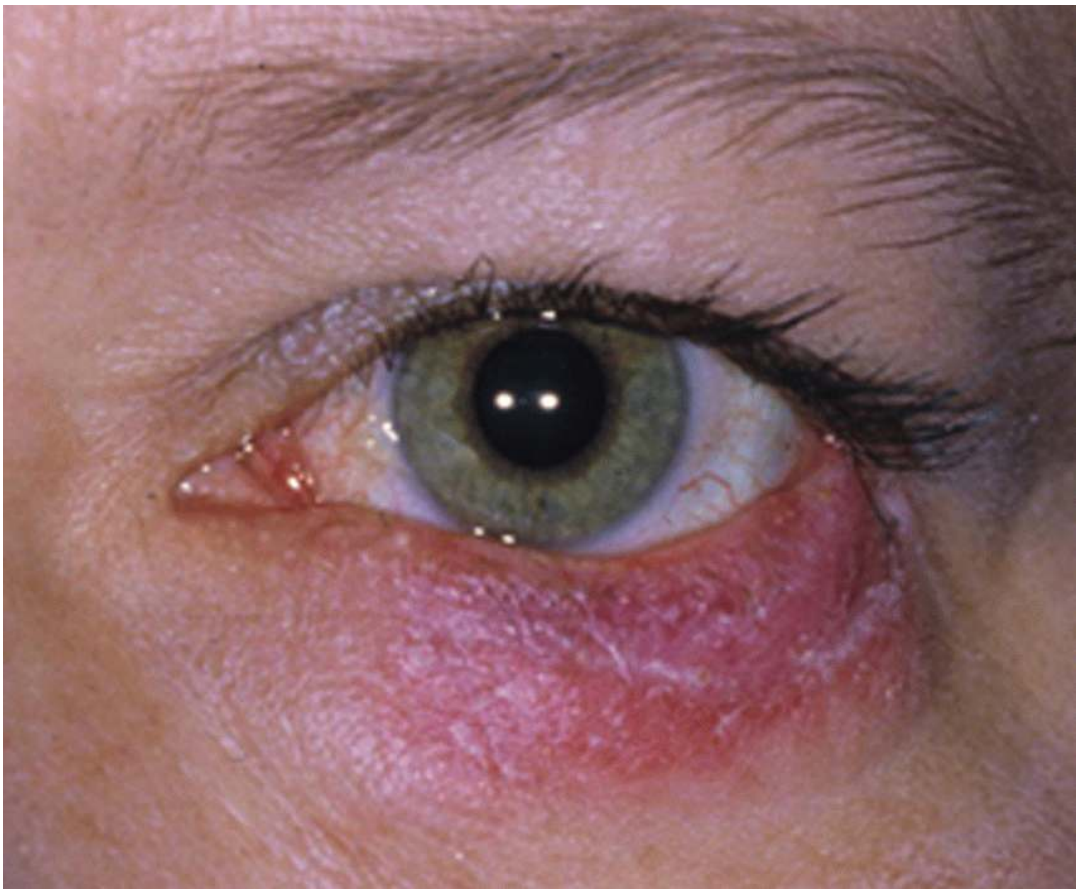

FIGURE 52.2 Eyelid thickening with violaceous coloration.

Elsewhere in the body, atopic dermatitis patients manifest uniquely different features according to their age. In infancy, exudative erythema, papules, exfoliative scales, and crusts are commonly observed in the face. These lesions extend from the forehead down to the cheeks and laterally to the skin in front of the ears and are frequently associated with traces of itch-induced scratching. After the age of 2 to 3 years, erosions, lichenification, and pigmentary skin changes develop, particularly on the face and flexural surface of the extremities. In adults, the rash may be bright red, edematous, and oozing, or more chronic appearing with lichenified and hyperpigmented patches, or it may present as a mixture of both. While various signs characterize the respective age groups, the general and shared feature irrespective of age is recurrent pruritic eczematous lesions.

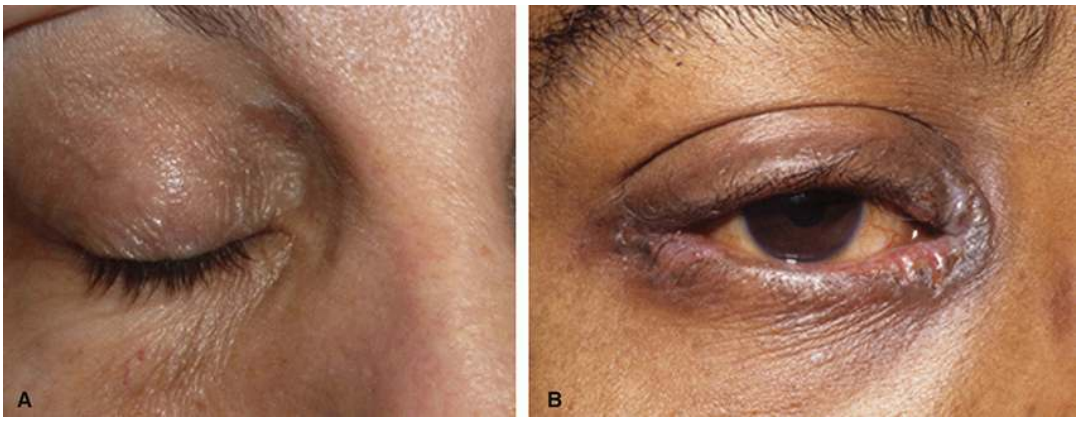

FIGURE 52.3 A and B, Medial eyelid thickening and lichenification.

Differential Diagnosis

Several skin conditions can result in periocular dermatitis. To distinguish the different subtypes, patients often require a detailed workup as well as formal allergy testing. Clinicians should have a low threshold for referral of patients with periocular dermatitis to a dermatologist or an allergy specialist.[4] Because the eyelid skin is very thin (0.5 mm) compared to the skin in the rest of the face (2.0 mm), the eyelid is susceptible to other types of dermatitis, particularly contact dermatitis, which is more common than atopic disease of the eyelids.[4] It usually results from skin contact with exogenous substances, and two major forms have to be distinguished (allergic and irritant).[4,32,33,34,35] Allergic contact dermatitis is less common than irritant contact dermatitis; it usually develops as a type IV hypersensitivity reaction elicited upon reapplication of a chemical to the skin after previous immunological sensitization to allergenic chemicals like cosmetics, lotions, creams, or topical ophthalmic preparations.[36] The allergenic components in topical eye drops and ointments include either the preservative or the active ingredient, but it is not always possible to determine whether the offending agent is the active ingredient or the preservative except with patch testing.[32,33,34,35,36] Topical antibiotics usually top the list of offending allergens with tobramycin as the most common allergenic agent, followed by preservatives or nonactive ingredients. Corticosteroids and mydriatics come next. Interestingly, antiglaucoma medications are at the bottom of the list.[36]

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The second form of contact dermatitis that may be confused with atopy is irritant contact dermatitis. Irritant contact dermatitis is a frequently overlooked cause of periocular dermatitis, which is four times more common around the eyes than allergic dermatitis.[32,33,34,35,36] Irritant dermatitis is a localized dose-dependent, nonallergic toxic effect typically resulting from the prolonged contact or chronic use of irritants such as topical eye drops, particularly antiglaucoma medications.[32,33,34,35,36]

Patients with allergic or irritant contact dermatitis are predominantly females, and the disease has a bimodal presentation with peaks around the ages of 20 and 60 years. This bimodal presentation pattern is probably related to the use of cosmetics in younger individuals and glaucoma medications in the older age group. In contrast to atopic dermatitis, contact dermatitis rarely occurs in children. Itching and burning are symptoms that are shared between atopic and contact dermatitis. However, the intense signs of ocular inflammation and scarring are usually absent in patients with allergenic contact dermatitis, although it may rarely be observed in patients with irritant contact dermatitis.[37] A careful history, including family history and patch testing, can be very helpful in separating those patients with allergic contact dermatitis from those with atopic disease.

Atopic dermatitis and angioedema are distinct clinical entities, yet they are frequently confused. Like angioedema, contact dermatitis can also result in dramatic facial and/or eyelid swelling, but clinical signs, such as erythema, severe itching, or burning, are more indicative of contact dermatitis. Also, resolution of contact dermatitis may cause skin peeling, a sign which is typically absent in angioedema.[38]

Other important skin diseases that may manifest in the periocular region and need to be differentiated from atopic dermatitis include common conditions like seborrheic dermatitis, rosacea, and, to a lesser extent, psoriasis.[5] Seborrheic dermatitis is a chronic relapsing skin disease affecting the sebaceous gland-rich body areas, including the scalp and face.[16] It is postulated that a lipophilic yeast of the genus *Malassezia* that feeds on lipids in the skin may contribute to seborrheic dermatitis with accompanying blepharitis.[39,40] Patients with seborrheic blepharitis are generally older than patients with atopic disease, and the disease does not have a gender predilection.[41,42] The disease is characterized by the presence of irregularly shaped yellowish greasy scales in the anterior eyelid. Seborrheic blepharitis is more commonly observed around the eyelashes, which may help clinch the diagnosis. Ocular conditions associated with seborrheic blepharitis include keratoconjunctivitis sicca (30%) or corneal erosions (15%). Almost 95% of

patients with seborrheic blepharitis also have an associated seborrheic dermatitis involving the eyebrows and/or the scalp.[42,43,44] Rosacea is a chronic inflammatory skin condition affecting approximately 10% of adults and is a frequent cause of periocular dermatitis. It is characterized by facial erythema, papules, pustules, telangiectasia, sebaceous gland hyperplasia, and meibomian gland dysfunction, and in severe cases, it may result in lymphedema (Morbihan disease).[45,46,47]

Treatment

General measures, including attention to lid hygiene, avoidance of specific or nonspecific provoking environmental or climatic predisposing factors, maintenance of skin hydration, and cooling of the inflamed skin, may help break the itch-scratch cycle.[4,48] Systemic treatment most often consists of a combination of oral antihistamines, oral steroids, or systemic antibiotics (if there is a secondary bacterial infection), coupled with a topical application of corticosteroids (loteprednol etabonate ophthalmic ointment, hydrocortisone cream, fluorometholone 0.1% ophthalmic ointment), emollients (petrolatum products like Vaseline or Aquaphor), steroid/antibiotic combination (dexamethasone/neomycin/polymyxin B ophthalmic ointment, tobramycin/dexamethasone ointment), topical calcineurin inhibitors (TCIs) (tacrolimus or pimecrolimus), or hydroxypropyl methylcellulose gel, or any combination of the above.[4,48]

Patients treated with a combination of low potency topical steroids together with oral antihistamines are four times more likely to experience a cure in comparison to patients treated with topical steroids alone.[4] This combination is effective because it breaks the itch-scratch cycle. Antihistamines reduce the itch, while steroids modulate the inflammatory component.[1,4,5] Of note is that the prolonged application of topical steroids may not only result in local atrophic skin changes (skin thinning, hypopigmentation, and telangiectasia), or increased staphylococcal colonization in the skin, but may be associated with the development of cataract and glaucoma.[31,49,50,51] It is not entirely clear how the careful topical application of corticosteroids on the eyelid skin can cause glaucoma or even cataracts.[31] Systemic absorption through the skin is unlikely, and more logical explanations include an inadvertent spill over the lid margin during application, or via sweating if the cream is applied to the upper eyelid.[31]

As was mentioned earlier, cataracts are more common in patients with atopic dermatitis. If a cataract develops during therapy with steroids, it may be challenging to decide whether the cataract resulted from the local steroid therapy or from the disease itself because the incidence of cataracts in corticosteroid-naïve patients is no different from atopic dermatitis patients receiving topical steroids.[27,31] A more recent study has refuted the possibility that glaucoma or cataracts develop after prolonged use of weak topical steroids on the eyelid skin.[31] The bottom line is that the careful periorbital application of weaker steroid ointments (class III and IV steroids) is generally safe.[31,48,52] The use of a steroid/antibiotic combination does not appear to offer any therapeutic advantage over the use of topical steroids alone, neither in the periocular region nor elsewhere in the body.[4,53,54] Furthermore, tobramycin itself, an active ingredient that is used almost exclusively in ophthalmic preparations, has been implicated in allergic contact dermatitis, and therefore its use may complicate the picture.[4,36,55]

TCIs like tacrolimus 0.03% (Protopic), or pimecrolimus, are also prescribed for eyelid eczema as a nonsteroidal *(Print pagebreak 347)* alternative to topical steroids.[13] TCIs are hydrophobic macrolide lactones that were initially developed for the prevention of organ transplant rejection. The anti-inflammatory effect of TCIs is attributed to the reduction in the population of local dendritic epidermal cells, the reduction of epidermal cytokine expression, and blockage or downregulation of T-lymphocyte activation.[13,56,57] Tacrolimus is topically applied to the affected eyelid skin of both eyes twice a day for 6 weeks or even longer until symptoms and signs are brought under control. Later, tacrolimus can also be used for long-term twice-weekly maintenance treatment indefinitely, provided that patients are careful not to apply the medication on the ocular surface.[13] Because they do not interfere with collagen metabolism, TCIs do not cause skin thinning, atrophy, discoloration, or telangiectasia, complications that are associated with prolonged topical application of corticosteroids. However, TCIs can result in photosensitivity, so they are best applied in the evening. Other side effects include a transient burning and stinging sensation when first put on, but this usually subsides after a few days as the dermatitis improves; therefore, patients will need reassurance to go on with the treatment despite the initial burning sensation.[13,58] A higher concentration of tacrolimus is commercially available (0.1%), and its efficacy is comparable to topical steroids in nonophthalmic locations, although the periocular use of this higher concentration may be associated with reactivation of herpetic blepharitis/keratitis.[13,59] The management of contact dermatitis is discussed in Chapter 16.

Prognosis

Functionally and cosmetically, atopic dermatitis can be disabling for the patient,[48,60] and affected individuals should be counseled

that although the disease is usually mild and can be managed with supportive measures alone, it is a genetically fixed disease that remains with the patient throughout their life. The disease cannot be eradicated, regardless of whether the patient is currently showing symptoms or not.[48] Also, vision-threatening complications can pose a challenging therapeutic problem. Therefore, there has been a recent paradigm shift in the management of atopic dermatitis. The previous therapeutic approach focused solely on the control of exacerbations, while the current therapeutic strategy has shifted to a proactive approach where maintenance therapy in the form of low-dose topical medications is used almost indefinitely to prevent flare-ups after stabilization of acute disease.[48]

An unusual problem with eyelid eczema is related to the patient's, as well as the physician's, perception of topical steroids (steroid phobia).[31,52,58,61] Some physicians may succumb to pressure from the patient, thereby undertreating the condition. This hesitancy or reluctance on the side of the clinician to use topical steroids on the eyelid skin for prolonged periods for fear of a rise in intraocular pressure could result in serious ocular complications.[31,61] Interestingly, a pervasive myth among nonophthalmologists is that the application of topical steroids anywhere in the body even beyond the periocular region is associated with the development of cataract and glaucoma.[52]

Patients should be assured that except in steroid responders, or patients with a positive family history of glaucoma, the careful use of low potency steroid ointment preparations on the eyelids is safe.[31] Alternatively, if the patient is still concerned about the use of steroids, tacrolimus may be used, but the take-home message is that every measure should be taken to control this chronic disease because this steroid phobia may have a detrimental effect on management outcomes and may lead to serious ocular complications.

Histopathology

Biopsies are rarely performed for the diagnosis of atopic dermatitis since the diagnosis is clinical, and the histopathological findings are nonspecific. Most of our knowledge of the histopathology of atopic dermatitis stems from studies performed 3 to 6 decades ago.[62,63]

Prose and Sedlis conducted the most extensive histopathological study of atopic dermatitis using 86 biopsies from 71 infants and children ranging in age from 6 weeks to 11 years.[64] Most biopsies of diseased skin were from the extremities, though there were seven each from the scalp and face, and an occasional specimen was from the trunk. Younger patients tended to have more acute lesions manifest clinically as erythematous, edematous, scaling, and crusted areas of skin. Older patients usually had more chronic lesions with erythematous and lichenified patches. The subjects varied in the clinical severity of their acute and chronic lesions, and this variability was reflected in the histological findings. Prose and Sedlis[64] made these generalizations:

1. The epidermis was hyperkeratotic or more frequently parakeratotic, sometimes with alternating zones of hyperkeratosis and parakeratosis. Pilo-sebaceous orifices often had increased amounts of keratin (Figure 52.4A).

2. The granular cell layer was usually prominent, but it was often narrow or absent beneath an infected crust or overlying a severely edematous corium.

3. The stratum spinosum was acanthotic, usually more pronounced in the rete ridges than in the suprapapillary zones, and the rete ridges tended to extend into the dermis to a uniform depth in individual specimens. Rete ridges are occasionally fused into plates (Figure 52.4A). Exaggerated acanthosis sometimes resembled that in psoriasis.

4. Sweat pores were frequently slit-like and surrounded by compact keratin.

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5. Occasional biopsies had focal separations of the basal cell layer from the edematous dermis. When spongiosis was present, it was more prominent in the lower epidermis. Vesicles were rare; when present, they were small, usually beneath the stratum corneum, and contained epidermal cells and rare mononuclear cells.

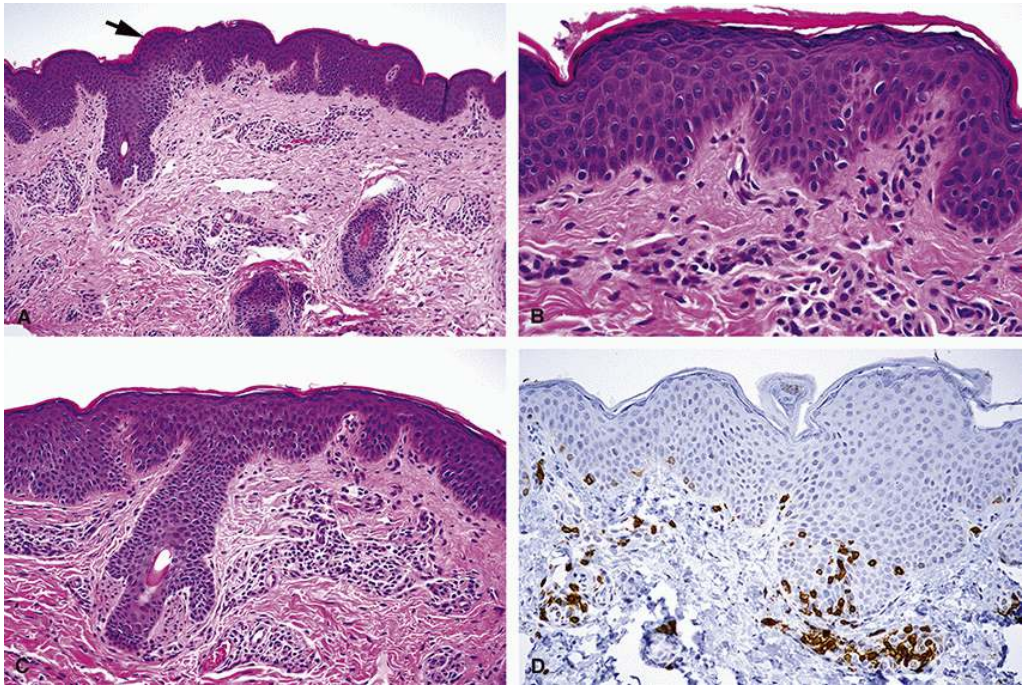

FIGURE 52.4 This eyelid biopsy was from a 5-year-old boy with an approximately 1-year history of photosensitivity and atopic dermatitis. His arms and legs had eczematous, scaly, erythematous patches, and thin plaques, and his upper and lower eyelids were thickened and erythematous. A, There are focal parakeratosis adjacent to a follicular orifice (arrow), acanthosis with occasional fusion of elongated rete ridges to form plates, perivascular mononuclear leukocytes, and lymphangiectasia. The papillary dermis appears more dense than usual (fibrotic), though this is subjective. B, Scattered mononuclear cells (cells with darker nuclei and a surrounding clear zone) infiltrated the epidermis. Mononuclear leukocytes (lymphocytes and macrophages) surround blood vessels in the superficial dermis. C, The infiltrate around blood vessels in the papillary and superficial reticular dermis was occasionally prominent. The small vessels have prominent endothelial cells. D, An immunohistochemical stain using antibodies to CD3 highlights T lymphocytes around dermal blood vessels and infiltrating the epidermis. Macrophages accounted for the other perivascular mononuclear cells, as evidenced using staining with antibodies to CD68 (image not shown). Only rare B lymphocytes were seen using antibodies to CD20 (image not shown).

6. Exocytosis was not prominent, and migrating cells were mainly mononuclear cells (Figure 52.4B). If there was an infected crust, then neutrophils were seen.

7. Small blood vessels in the upper and mid dermis were prominent due to swollen endothelial cells, perivascular edema, and perivascular mononuclear leukocytes (Figure 52.4C). Neutrophils and eosinophils were rare. Lymphangiectasia was common.

8. Mast cells and eosinophils were most numerous in biopsies of chronic, moderate to severe atopic dermatitis with a predilection for being perivascular.

9. Sebaceous glands were normal in minimally diseased skin, while they were small in moderately severe eruptions.

Studies after that of Prose and Sedlis examined fewer biopsies. Ofuji and Uehara examined 38 biopsies of follicular papules that usually arose on the lateral parts of the trunk in patients with atopic dermatitis.[65] All of the specimens had follicles filled with hyperkeratotic, partly parakeratotic material, with varying degrees of spongiosis and exocytosis of mononuclear leukocytes at the upper external root sheaths. Ofuji and Uehara postulated that the follicular papules represent the first visible eruption of atopic dermatitis before superimposed secondary changes occur.[65] Mihm and coworkers examined 1-µm-thick plastic sections from four acute vesicular lesions and five lichenified plaques.[66] Their histological findings were similar to those of Prose and Sedlis using paraffin sections, with lichenified lesions having the *(Print pagebreak 349)* most acanthosis, minimal spongiosis, and papillary dermal thickening by an infiltrate of macrophages, lymphocytes, and mast cells. More recently, Hurwitz and DeTrana examined 16 biopsies from eight adult patients with well-established atopic dermatitis.[67] Biopsies were from early eruptive or evolving (24-to 48-hour-old) erythematous, dome-shaped papules, discrete red-brown lichenoid papules, or late well-established (1-to 2-week-old) ashen, lichenified plaques. They concluded that atopic dermatitis "begins with a perivascular spongiotic dermatitis, evolves into a psoriasiform microvesicular spongiotic dermatitis, which is sometimes lichenoid, and eventually concludes as psoriasiform dermatitis."[67] Immunopathological studies have shown that the dermal lymphocytes are predominantly T lymphocytes (Figure

52.4D), mostly CD4+ (helper/inducer) cells.[62] The number of epidermal Langerhans cells is increased in chronic lichenified plaques to a greater degree than in acute erythematous plaques.[62]

As we noted in the first paragraph of this section, the histopathological findings of atopic dermatitis are nonspecific. Dermatopathologists classify atopic dermatitis as an eczematous or spongiotic dermatitis, and the histological features overlap with those of seborrheic dermatitis, autosensitization (Id) reaction, allergic contact dermatitis, and irritant contact dermatitis.[68]

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CHAPTER 53

Blepharitis

Key Points

- Blepharitis is a common chronic inflammatory condition that affects the eyelid margin
- It can be classified etiologically into infectious and noninfectious types, and anatomically into anterior and posterior blepharitis
- Staphylococcal blepharitis is due to bacterial colonization of the anterior lid margin, mostly by *Staphylococcus aureus*
- Seborrheic blepharitis is not well understood, but risk factors can include hormonal influences, a weakened immune system, and lipophilic yeast infections, HIV/hepatitis C infection, Parkinson disease, Down syndrome, and chronic alcohol pancreatitis
- *Demodex* mites are a major cause of anterior and posterior blepharitis
- Clinical symptoms include burning, itching, gritty or foreign body sensation, crusting, and redness or irritation of the lid margins
- With chronicity, patients may develop notching and thickening of the lid margin, trichiasis, thinning or loss of the eyelashes, papillary conjunctivitis, punctate epithelial keratitis, marginal corneal infiltrates, or phlyctenular keratitis
- Lid hygiene with warm compresses and shampoo scrubs provides symptomatic relief
- When bacterial overgrowth is suspected, topical antibiotic ointments are recommended
- Blepharitis is a chronic condition with no permanent cure

The term blepharitis is a generic term that is used in clinical practice to indicate the presence of chronic inflammatory changes that affect the eyelid margin rather than the entire eyelid as the term blepharitis might specifically imply.[1,2,3,4,5,6,7,8,9,10,11,12] In this regard, the term marginal blepharitis would be more accurate, yet it is less commonly used in the literature.[5] Blepharitis is a common cause of chronic ocular irritation; however, this supposedly mild and benign condition frequently represents a diagnostic as well as a therapeutic dilemma.[1,2,3,4,5,6,7,8,9,10,11,12]

Etiology and Pathogenesis

Because of the complex and incompletely understood nature of the disease, and because of its heterogeneous and occasionally overlapping presentation, attempts to classify blepharitis have been difficult.[12] In general, blepharitis can be classified etiologically into infectious and noninfectious, or anatomically into anterior and posterior blepharitis,[1,2,3,4,5,6,7,8,9,10,11,12] although more elaborate classification schemes that subdivide blepharitis into multiple categories have been proposed.[1,4] Numerous subclassification systems were also proposed for meibomian gland dysfunction (MGD), but the most common is to categorize the condition into obstructive, hyposecretory, and hypersecretory forms.[9,13]

In an attempt to simplify the diagnostic and therapeutic process of blepharitis, the American Academy of Ophthalmology adopted an anatomical model whereby blepharitis was classified into anterior (seborrheic and staphylococcal) and posterior blepharitis (MGD).[9] A modified version of this classification scheme is adopted in this chapter, whereby demodicosis is discussed separately in addition to the three main blepharitis subcategories outlined above.[1,9,10]

Staphylococcal blepharitis occurs due to bacterial colonization of the anterior lid margin, mostly by *Staphylococcus aureus*. Other isolates include coagulase-negative staphylococcus (CoNS), *Staphylococcus epidermidis*, *Propionibacterium acnes*, and *Corynebacterium.*[1,4] Although *S. aureus,* and the less virulent commensals CoNS and *S. epidermidis,* may be isolated from the

eyelid margin of normal healthy patients without blepharitis,[11,14] blepharitis patients have a more heavily colonized lid surface than normal controls.[15] Yet despite this heavy load, it is not entirely clear whether the morbidity of staphylococcal blepharitis occurs due to a direct infection by *S. aureus,* a cell-mediated immunologic allergic response to *S. aureus,* or indirectly as a reaction to the exotoxin produced by the organism rather than the organism itself.[4,11]

The exact cause of seborrheic blepharitis is also not well understood. The etiology might be inferred indirectly from studying the multifactorial etiology of seborrheic dermatitis, which is a chronic relapsing skin disease affecting the sebaceous gland-rich body areas including the scalp and face.[16] Hormonal influences, a weakened immune system, and lipophilic yeasts of the genus *Malassezia* (former *Pityrosporum*) that feed on lipids in the skin may all contribute to seborrheic dermatitis with accompanying blepharitis.[16,17] Other risk factors for seborrheic dermatitis include HIV/hepatitis C infection, Parkinson disease, Down syndrome, and chronic alcohol pancreatitis.[16,18] It appears that *Malassezia* plays a definitive role in the etiology of seborrheic dermatitis/blepharitis, but the exact etiopathogenetic events are not known.[16,18] The yeast genes are switched on to produce *(Print pagebreak 352)* different irritants or metabolites like malassezin, which may activate an inflammatory pathway eventually leading to the typical clinical signs of the condition.[16,18] Of all the *Malassezia* species recognized so far, *Malassezia restricta* and *Malassezia globosa* are the most common isolates in seborrheic dermatitis.[16]

Although the terms posterior blepharitis and MGD are used synonymously in the literature, they are not unequivocally interchangeable, as other rare causes of posterior blepharitis can occasionally be observed including infectious or allergic conjunctivitis as well as congenital absence of the meibomian glands.[5,12] Meibomian gland agenesis is observed in association with the exceedingly rare anhidrotic ectodermal dysplasia.[12] The ectodysplasin A (*EDA*) gene responsible for the disease controls the development of sebaceous glands throughout the body, including the meibomian glands. The gene expresses the EDA protein, which is detected in tears and helps in maintaining the ocular surface.[12,19,20]

It is the acquired form of MGD that is far more commonly observed in clinical practice.[21] The exact cause of acquired MGD is largely unknown. Recent research has provided direct evidence supporting the hypothesis that altered lipid composition of meibomian secretions as well as oxidative stress play a crucial role in the development and/or exacerbation of MGD.[20,22,23] What exactly changes the lipid composition of meibum is largely unknown, but the biochemical alteration that ensues leads to thickening of the secretions, plugging of the glands, and pouting of the meibomian orifices.[1,22,24] However, oxidative stress results in a chronic accumulation of reactive oxygen species, which is hypothesized to promote inflammation through the release of proinflammatory cytokines.[1,22,23]

Although the underlying pathogenetic events are hypothetical, there are several established local and systemic risk factors that may influence the structure and function of the meibomian glands.[12,25,26] Aging is a major factor influencing the dynamics of meibomian function. The critical etiologic role of aging is probably related either to the buildup of reactive oxygen species or due to an age-related decline in androgen level because androgen is a potent regulator of sebaceous gland function.[26,27,28,29,30] Likewise, androgen deficiency is also implicated in MGD associated with conditions like menopause, antiandrogen treatment, complete androgen insensitivity syndrome, and Sjögren syndrome (SS).[26,27,28,29,30] Of note is that patients with SS do not only suffer from evaporative tear deficiency, but they suffer from MGD as well. Rosacea is also an important risk factor in posterior (90% of rosacea patients) as well as in anterior blepharitis (50%).[12] Demodicosis is also a suspected but unconfirmed risk factor for MGD.[12] Medications including 13-*cis* retinoic acid, postmenopausal hormone therapy, antihistamines, and antidepressants may all be associated with MGD.[12]

An often overlooked cause of MGD is facial nerve palsy.[31] The muscle of Riolan plays a direct role in the expression of meibomian gland secretions, and its paralysis is implicated as the cause of this entity.[31,32] Environmental factors (geographic location, temperature, and humidity), as well as contact lens wear, may also play a role in MGD pathogenesis.[12] Other possible associations include chronic graft-versus-host disease after hematopoietic stem cell transplantation and the S-1 combination chemotherapy regimen, which causes irreversible destruction of the meibomian glands.[20,33]

The role of *Demodex* mites is well established as a separate entity causing either anterior blepharitis (*Demodex folliculorum*) or posterior blepharitis (*Demodex brevis*). As its name implies, *D. folliculorum* is a microscopic obligate hair follicle mite that together with *D. brevis* favorably inhabits the eyelids.[34,35] *Demodex* spp. are generally considered nonpathogenic parasites that can normally exist in asymptomatic individuals and can only induce signs and symptoms in immune-deprived patients.[34,35] The exact etiopathogenic events underlying *Demodex* blepharitis are not exactly known, but there are theories. The most plausible theory is a direct infestation by the *Demodex* mite, which lives on the skin of the eyelid causing direct damage by consuming epithelial cells and inducing microabrasions that result in epithelial hyperplasia and reactive hyperkeratinization around the base of the lashes.[35,36] Also, their debris and excretory waste may elicit a host inflammatory response via a delayed hypersensitivity reaction. Both mechanisms ultimately cause chronic blepharitis, conjunctival inflammation, and MGD.[35,36] An alternative theory is that the parasite simply acts as a carrier host for the symbiotic gram-negative bacterium *Bacillus oleronius*, which grows in the *Demodex* intestine. It is excreted by the parasite releasing several proteins, which in turn stimulate an inflammatory response in infected patients.[35,36] It is not entirely implausible that both the *Demodex* spp. and *B. oleronius* function as copathogens in the development

or exacerbation of blepharitis.[35,36] Of note is that some authors deny the pathogenic role of *Demodex* mites in blepharitis considering the mites to be innocuous saprophytes of the skin.[34]

Clinical Presentation

Because of its definitional uncertainty and the ubiquity of the condition, accurate data about the prevalence of blepharitis are largely lacking or inconsistent.[3,9,20] The condition is very common, as blepharitis is frequently observed by optometrists and ophthalmologists alike (47% and 37% of their practice, respectively).[3] Posterior blepharitis may be twice as common as anterior blepharitis (12% vs 24%),[3,37] and asymptomatic MGD may be far more common than symptomatic MGD (18% vs 29.5%).[38] The prevalence data available for MGD are also inconsistent and vary between 3.5% and 70%, again because of the lack of standardization between clinical trials,[3,12,20] but the striking trend is that MGD is generally more common in Asians than in Caucasians.[12,20] The prevalence increases markedly with age, rising from 0% for subjects younger than 10 years to 67.2% for those older than 60 years.[22]

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Blepharitis patients complain of a burning, itching, gritty or foreign body sensation, crusting and redness or irritation of the lid margins, and occasionally gluing of the lashes upon waking.[1,3] Because these symptoms are shared by both types of blepharitis as well as patients with dry eye disease, it is difficult to establish a diagnosis based on symptomatology alone.[1,12] Patient history may still help if there is an underlying skin condition.[15,39] A history of seborrheic dermatitis, atopic eczema, or rosacea may suggest the coexistence of seborrheic blepharitis, staphylococcal blepharitis, or MGD, respectively.[1,15,39] Blepharitis may also amplify the symptoms of coexisting ocular surface disease, including dry eye disease or allergy.[9] Although patients with posterior blepharitis may be more symptomatic than anterior blepharitis, some patients with overt clinical signs of MGD may be entirely asymptomatic.[1,5]

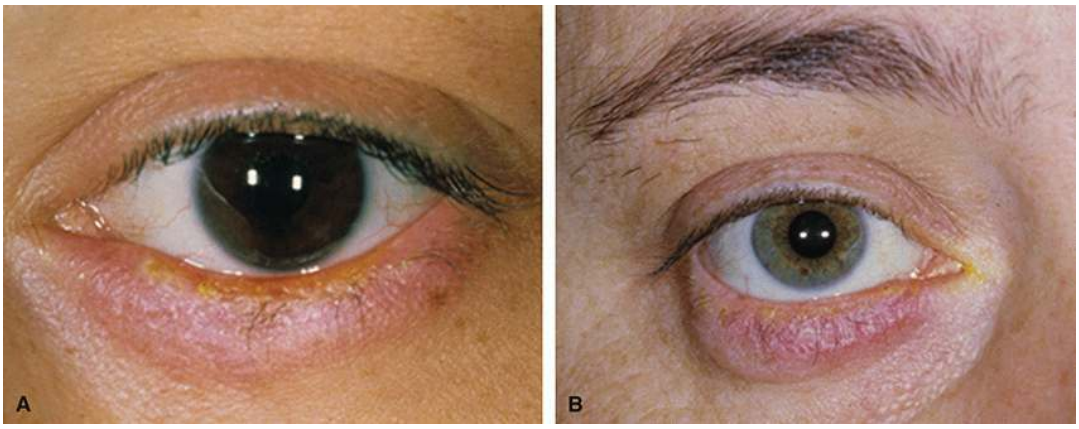

FIGURE 53.1 A and B, Blepharitis of the lower eyelids manifest as erythema and madarosis.

FIGURE 53.2 A, Severe chronic blepharitis with thickening of the eyelid margins. B, Secondary blepharospasm from severe blepharitis and corneal irritation.

In clinical practice, pure subcategories of blepharitis are the exception rather than the rule, and clinical features may overlap.[3,4,9] Demographic data and a thorough slit-lamp examination may help establish a specific diagnosis.[9] Staphylococcal blepharitis is

more common in younger females and is typically characterized by erythema, scaling, and crusting of the lid margin (Figure 53.1).[1] Brittle fibrinous circular scales can be observed encircling the base of the lashes and are termed collarettes.[1] The eyelids typically show more signs of inflammation than other types of blepharitis, and although it is generally a chronic condition, it may on occasion present in an acute fashion, or as an acute exacerbation on top of the classic chronic form.[1,4,15] Because of this chronicity, these patients may also develop notching and thickening of the lid margin, trichiasis, thinning, or loss of the eyelashes (Figure 53.2A).[1,4] In severe cases, they may suffer *(Print pagebreak 354)* from papillary conjunctivitis, punctate epithelial keratitis, marginal corneal infiltrates, or phlyctenular keratitis possibly due to the release of bacterial toxins (staphylococcal hypersensitivity syndrome).[1,15] Secondary blepharospasm may be a prominent feature (Figure 53.2B). Patients with staphylococcal blepharitis do not typically present with other dermatologic findings,[1,4] although patients with chronic atopy have an increased susceptibility to the development of staphylococcal blepharitis.[1]

However, seborrheic blepharitis patients are generally older, but the disease does not have a gender predilection.[1,15] These patients have irregularly shaped yellowish greasy scales in the anterior eyelid, but the eyelid is less inflamed than staphylococcal blepharitis unless there is an associated superinfection. Ocular conditions associated with seborrheic blepharitis include keratoconjunctivitis sicca (30%) or corneal erosions (15%).[1,4,9] Almost 95% of patients with seborrheic blepharitis also have an associated seborrheic dermatitis involving the eyebrows and/or the scalp.[1,4,9]

Patients with MGD are also older and have a prolonged history of ocular symptoms that may span up to 10 years or more.[9] Between 25% and 40% of MGD patients have aqueous tear deficiency, and 51% have rosacea.[1,4,9] The most important early sign of MGD is plugging (Figure 53.3A) characterized by capping followed by pouting of the meibomian glands, whereby the orifice becomes elevated above the surface of the lid.[7] This early sign is followed by retroplacement of the meibomian orifices behind the mucocutaneous junction. Eversion of the eyelid is important to assess meibomian gland dropout and partial glands. Both are important clinical signs in the assessment of MGD.[40] A gland dropout is defined as complete gland loss from orifice to the fornix, while a partial gland is defined as glands with a partial loss between orifice and fornix.[40] Telangiectasia and increased vascularity of the posterior lid margin are major diagnostic signs, although they may be observed as a normal variation in the elderly.[1,5,20,40] The tear film is contaminated with debris, an observation that is attributable to an alteration in the color, nature, and distribution of meibum.[7,23] Normally meibum is a clear colorless fluid that spreads evenly on the ocular surface, but abnormal secretion is either white, yellow, or yellowish-white in color.[23] In addition, while normal meibum tends to be oily and evenly distributed, abnormal meibomian secretion tends to be more viscous and ranges from a cloudy turbid fluid to a granular substance with a "*toothpaste-like consistency*" (Figure 53.3B).[1,23] Those secretions can be expressed from the glands as a plug or a curled thread. Alternatively, they can assume a nonexpressible form (meibomian foam), which is a frothy accumulation in the medial canthal region, possibly attributable to the presence of soaps in the tear film.[1] Other eyelid changes that may be observed in MGD include rounding, notching, or a frank irregularity of the lid contour. Consequently, secondary changes involving the anterior lid margin may occur, including loss of eyelashes or hyperkeratinization of the mucocutaneous junction.[1] MGD patients are also predisposed to develop chalazia. Several grading scales for the diagnosis of MGD have been proposed[41,42,43,44,45]; however, the majority is too complicated to be incorporated in everyday clinical practice, and the reliability of most of these grading scales is unverified.[40] If *Demodex* blepharitis is suspected, a slit-lamp examination may or may not show the cylindrical dandruff scales, which are characteristic of *D. folliculorum*.[1,35]

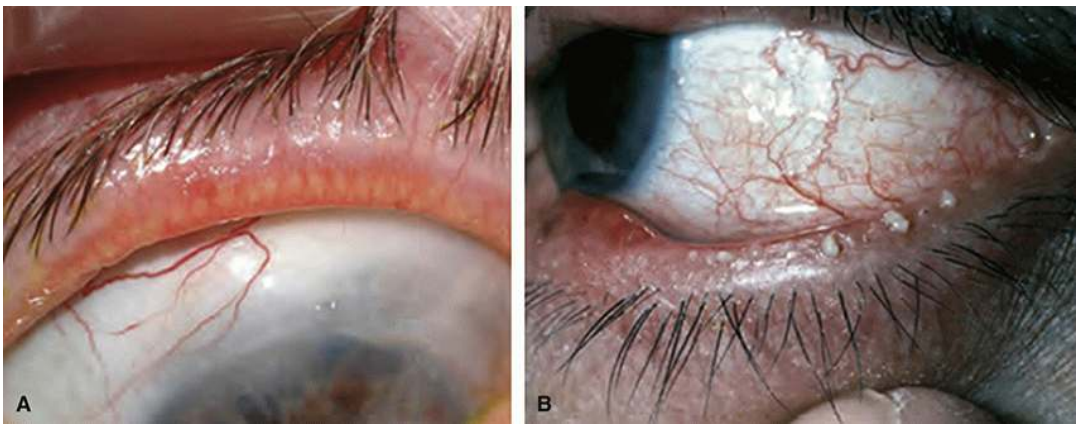

FIGURE 53.3 A, Marginal blepharitis with meibomian gland plugging. B, Thickened and ropy meibomian gland secretions from blepharitis. (A and B, reprinted with license from Wolters Kluwer, Duncan K, Jeng B. Medical management of blepharitis. *Curr Opin Ophthalmol*. 2015;26:289-294; Figure 1.)

Because patients with blepharitis may have aqueous-deficient or evaporative dry eyes, routine assessment of dry eye disease should be carried out in all patients to rule out an associated aqueous-deficient dry eye in case of anterior blepharitis or MGD-related evaporative dry eye disease in case of posterior blepharitis. Evaluation should include tear meniscus height, blink rate, tear breakup

time, fluorescein staining, and the Schirmer test.[9,15,20,44]

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A slit-lamp examination generally is sufficient to establish the diagnosis of blepharitis,[9,15] but ancillary diagnostic tools that may aid in the diagnosis may occasionally be needed. These include microbiologic cultures of the eyelid and conjunctiva, a biopsy from the eyelid tissue to exclude malignancy, or lash epilation for microscopic detection and counting of *Demodex* eggs, and adult mites if a *Demodex* infestation is suspected.[9,15,20,35] Randomly choosing an eyelash will result in a low diagnostic yield, and it is vital to epilate a lash that harbors cylindrical dandruff, which is then placed between two glass slides. A fluorescein drop is added, which dissolves the dandruff and unmasks the organism thus improving the diagnostic yield.[46] Dynamic meibomian gland imaging techniques were recently introduced including noncontact infrared meibography, the LipiView interferometer, and in vivo confocal microscopy.[20] These diagnostic aids may help to not only establish the diagnosis but also monitor treatment progress.[20]

Differential Diagnosis

The symptoms of blepharitis are strictly bilateral; therefore, any unilateral presentation should arouse suspicion of an alternative diagnosis. If unilateral disease is associated with loss of eyelashes or an unusual resistance to therapy, this should alert the clinician to the possibility of diseases masquerading as blepharitis, particularly sebaceous cell carcinoma.[1,47] If blepharitis is resistant to therapy and is associated with cicatricial changes like fornix foreshortening or symblepharon formation, cicatrizing diseases of the conjunctiva should be ruled out.[9,15] Discoid lupus and ulcerative basal cell carcinoma may also infiltrate the eyelid margin and may be mistaken for a localized form of blepharitis.[48,49]

Other rarer causes of blepharitis that should also be excluded are herpes simplex blepharitis, zoster-related blepharitis, and phthiriasis palpebrarum.[15] Both primary ocular herpes simplex virus (HSV) infection and herpes zoster ophthalmicus (HZO) are unilateral and acute and may involve any part of the cutaneous surface of the eyelid rather than the lid margin alone, as opposed to the far more common anterior/posterior blepharitis, which is bilateral and chronic and predominantly involves the eyelid margin. HSV mostly presents in children or young adults, while HZO is a disease of the elderly.[50,51,52,53,54] HSV presents with acute follicular conjunctivitis, preauricular lymphadenopathy, vesicular or ulcerative eruptions on the eyelid skin, and punctate keratitis,[50,51,52,53] while HZO is preceded by a prodromal phase of influenza-like illness followed by the characteristic dermatomal pain and rash, which are not circumscribed to the eyelid.[54] Phthiriasis palpebrarum is caused by *Phthirus pubis* (crab or pubic louse) and is characterized by hyperemia and excoriation of the lid margin with dark brown scales, which are interspersed between the lashes and are indicative of louse feces. Small, translucent oval eggs (nits) or even moving lice may be observed adherent to the lashes.[55]

Treatment

Blepharitis is one of the commonest ocular pathologies, yet there are currently no medications approved by the United States Food and Drug Administration for the treatment of blepharitis, and a consensus for treatment is lacking.[56] Nevertheless, several basic principles may direct the clinician. The most important point to remember is that mixed disease (anterior plus posterior) is not infrequent, and combination therapy that addresses both components are usually required.[9,15] It should also be remembered that anterior blepharitis is not always a chronic disease, and it can occasionally present acutely. Another basic tenet of treatment is that long-term commitment to eyelid hygiene is of paramount importance to control both anterior and posterior components of this relentless disease.[9,15] Of note is that both types of blepharitis are commonly associated with dry eye disease; therefore, frequent artificial tear use can aid in symptomatic relief and complement therapy.[15] It is vital to control blepharitis before embarking on cataract surgery because the same constellation of ocular surface pathogens that cause blepharitis are also implicated in postoperative endophthalmitis.[9,15]

Lid hygiene provides symptomatic relief for anterior as well as posterior blepharitis.[57] The process of lid hygiene begins with proper patient education about the know-how of cleansing the eyelid margin with warm compresses followed by rubbing the base of the eyelashes with mild shampoo or medicated eyelid scrubs. Warm compresses help liquefy debris, which paves the way for easier subsequent removal of this debris with scrubs or shampoo. Medicated scrubs serve the additional purpose of reducing bacterial colonization, thus restoring ocular health.[15,48] Using a cotton swab dipped in shampoo, the eyelid margin is carefully rubbed from side to side to remove crusting. Vertical digital eyelid massage should also be performed in tandem to express meibomian secretions in patients with concomitant posterior disease.[9] Initially, this cycle of warm compresses/eyelid scrubbing/vertical massage should be repeated frequently, but the frequency and duration can be significantly reduced later. During acute flare-ups of anterior blepharitis, the use of makeup and contact lens wear should be discontinued.[15] In patients with seborrheic dermatitis, referral to a dermatologist should be considered.[15]

When bacterial overgrowth is suspected, pharmacologic therapy of anterior blepharitis should include the application of

topical antibiotic ointments such as bacitracin or erythromycin, which might provide some symptomatic relief.[15,48,57] Ointment is used rather than eye drops to maximize contact time with the eyelid margin, but their use should be restricted to brief periods to reduce toxicity and minimize resistance.[15,48] Alternatively, topical 1% azithromycin eye drops (a macrolide antibiotic) is a potent immunomodulator that possesses both anti-inflammatory and anti-infective properties and has an exceptional affinity *(Print pagebreak 356)* for tissue and a long half-life, which makes it an attractive option in anterior blepharitis.[15,58] Its use significantly decreases the microbial load and reduces the release of proinflammatory cytokines, an effect that is sustained during the treatment course and a few weeks after treatment.[20] An antibiotic-corticosteroid combination or steroid eye drops alone may be used briefly in patients with the staphylococcal hypersensitivity syndrome.[48]

In patients with MGD, a staged approach that begins with eyelid hygiene is recommended, but if mechanical methods (warm compresses and vertical eyelid massage) fail to control MGD, topical followed by oral antibiotic therapy should be considered.[15,20,56,59] Once again, the use of the topical 1% azithromycin eye drops has proven beneficial.[20] Alternatively, some studies showed that topical tobramycin/dexamethasone ointment may be superior to azithromycin alone.[9,60] Other newer topical agents that have shown promising results in MGD include topical cyclosporine, diquafosol ophthalmic solution 3% (a $P2Y_2$ receptor agonist), maxacalcitol ointment (vitamin D_3 analog), and tacrolimus ointment.[20,56,61,62,63]

Oral antibiotics with antimicrobial and anti-inflammatory properties have been advocated in cases of MGD associated with rosacea or in patients with severe, recurrent, or refractory MGD.[9,15,59,60,64] In these patients, oral tetracycline derivatives like doxycycline (1-month course, 200 mg/d) or oral azithromycin (5-day course, 500 mg on day 1 and then 250 mg/d) should be prescribed, but several other antibiotics and different regimens exist, which underlies our poor understanding of the disease.[9,15,59,60,64] Long-term oral tetracycline therapy may also be beneficial in staphylococcal anterior blepharitis and *Demodex* blepharitis.[15] Other oral forms of therapy include dietary supplementation with omega-3 fatty acids (one or two 1000-mg capsules, TID for 1 year), but the results are conflicting.[9,65,66]

Various novel in-office interventional procedures for patients with obstructive MGD have been introduced recen tly.[9,20,56,59] Maskin and associates reported the successful use of small stainless steel probes as a method for the mechanical opening of obstructed meibomian gland orifices.[67,68] Other novel approaches that utilize heat to improve lipid mobilization from within the meibomian glands in obstructive MGD include the LipiFlow system and intense pulsed light (IPL).[20] The LipiFlow system allows heat to be applied to the palpebral surfaces concurrent with direct pulsed compression of the eyelids, thereby expressing the secretions of the meibomian glands.[69] IPL is a noncoherent polychromatic light source with a broad wavelength spectrum of 500 to 1200 nm that reportedly improves meibomian gland function with a secondary improvement of dry eye symptoms.[9] The mechanism by which IPL works is incompletely understood, but proposed mechanisms include heat transfer, which softens the meibum and aids expression, or thrombosis of the vasculature surrounding the meibomian glands, which could play a role in diminishing the local release of inflammatory mediators.[70] At the time of writing of this chapter, these newer modalities have not yet been subjected to rigorous research.

D. folliculorum is resistant to common antiseptic solutions as well as antimicrobials and can be exterminated by tea tree oil (TTO) in a dose-dependent fashion.[35] A daily lid scrub with 50% TTO is effective in eradicating ocular *Demodex* infestation in vivo because TTO not only cleans cylindrical dandruff from the lash root but the oil also stimulates embedded mites to migrate out to the skin. Because TTO may also exert an antibacterial action, its therapeutic benefit may also be attributed to the eradication of *B. oleronius* in *Demodex* mites' intestines.[35] Alternatively, the infestation could be controlled by rubbing cotton swabs dipped in ether or 2% yellow mercury oxide ointment or both.[71,72]

Prognosis

The chronic nature of blepharitis, and the frequent association with, or exacerbation of other ocular surface diseases makes blepharitis difficult to manage and causes a substantial negative impact on the patient's quality of life. This is compounded by the fact that strong evidence is lacking to support the beneficial use of any of the newer treatment modalities or older commercial products that are marketed to consumers or prescribed to patients without substantial evidence of therapeutic effectiveness.[57] Therefore, it should clearly be explained to the patient that blepharitis is a chronic condition and no permanent cure exists so far, that they should learn to live with blepharitis until a definitive cure is available,[9] and that keeping symptoms in check is dependent on patient compliance with a treatment regimen.[9]

Histopathology

Eyelid biopsies are not usually performed for blepharitis unless it is unilateral, not responsive to therapy, and therefore suspicious for a cutaneous malignancy.[73] Eyelid inflammatory dermatoses are classified by their reaction pattern, similar to the schema used

for other body sites.[74,75] In our experience, the most common reaction pattern is spongiotic dermatitis (Figures 53.4 and 53.5)[76,77,78] due to eyelid involvement with seborrheic dermatitis,[79,80,81] atopic dermatitis,[79] and allergic and irritant contact dermatitis.[79] Other reaction patterns such as interface dermatitis,[82,83,84] lichen planus-like keratosis (Figure 53.6),[85,86] granulomatous dermatitis,[87] and psoriasiform dermatitis[88] are much less common in eyelid biopsies, in our experience.

The spongiotic reaction pattern features intraepidermal edema with subsequent epidermal changes that vary over time.[76] Acute spongiotic dermatitis, which is not often biopsied, has a normal-appearing stratum corneum (horny layer), epidermal spongiosis (manifest as separation *(Print pagebreak 357)* of keratinocytes) ranging from minimal to formation of microvesicles, edema of the papillary dermis, and superficial perivascular inflammation with lymphocytes, macrophages, and often eosinophils.[76] The inflammation may extend into the mid dermis, there may be a lichenoid pattern, and inflammatory cells often extend into the overlying epidermis.[76] Subacute spongiotic dermatitis (Figure 53.4) has variable acanthosis, parakeratosis, spongiosis, and inflammation similar to acute spongiotic dermatitis, often with admixed eosinophils.[76] Dermal edema is usually less than that in acute spongiotic dermatitis.[76] Chronic spongiotic dermatitis has minimal spongiosis, more prominent reactive epidermal changes (compact hyperkeratosis, variable parakeratosis, and acanthosis), superficial perivascular lymphocytes often with admixed eosinophils, and varying degrees of superficial dermal fibrosis.[76] The degree of epidermal acanthosis may create a psoriasiform pattern,[76] including in patients with longstanding seborrheic dermatitis.[80,81,89] The spongiotic reaction pattern is characteristic of seborrheic dermatitis, but it is also seen in many other conditions, including atopic dermatitis, allergic and irritant contact dermatitis, nummular dermatitis, and id reactions.[76,77,78]

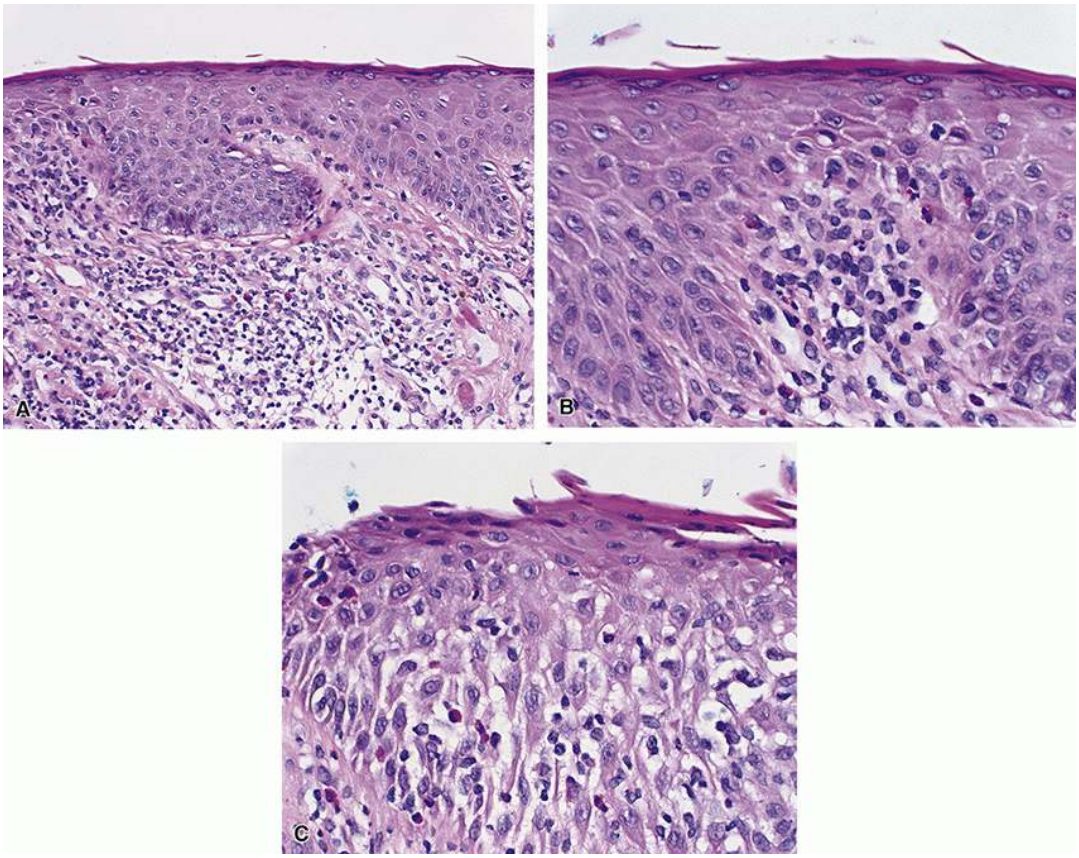

FIGURE 53.4 This left medial canthus eyelid margin biopsy with subacute spongiotic dermatitis was performed because of thickening and induration for the prior 18 months, refractory to topical antibiotic and corticosteroid steroid therapy. A, The epidermis is acanthotic with a thin layer of parakeratosis. The papillary dermis is focally edematous and has an infiltrate of lymphocytes, macrophages, and occasional eosinophils. B, In this area, the papillary dermal inflammation is mostly macrophages with fewer lymphocytes and eosinophils. C, There were a few areas with prominent spongiosis. There are lymphocytes and eosinophils within the spongiotic epidermis (exocytosis).

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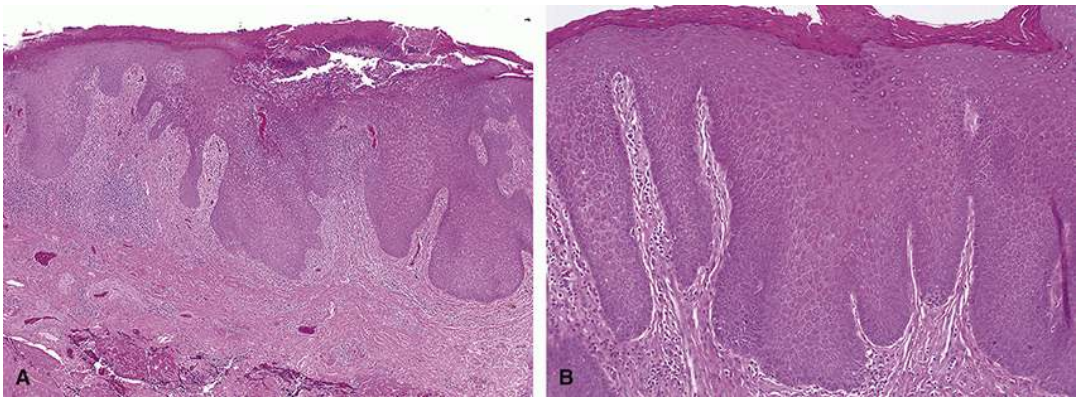

FIGURE 53.5 A man in his early 60s had bilateral thickening of his eyelid skin with erythema and pruritus. The eyelid abnormalities developed over 6 years, during which he was using various types of eye drops for treating glaucoma. A, The left lower eyelid has psoriasiform dermatitis with acanthosis, parakeratosis, and chronic dermal inflammation. The surface has focal excoriation. B, A biopsy of the right lateral canthus has psoriasiform dermatitis similar to that in the left lower eyelid. Subsequent patch testing indicated that his blepharitis was most compatible with chronic allergic contact dermatitis.

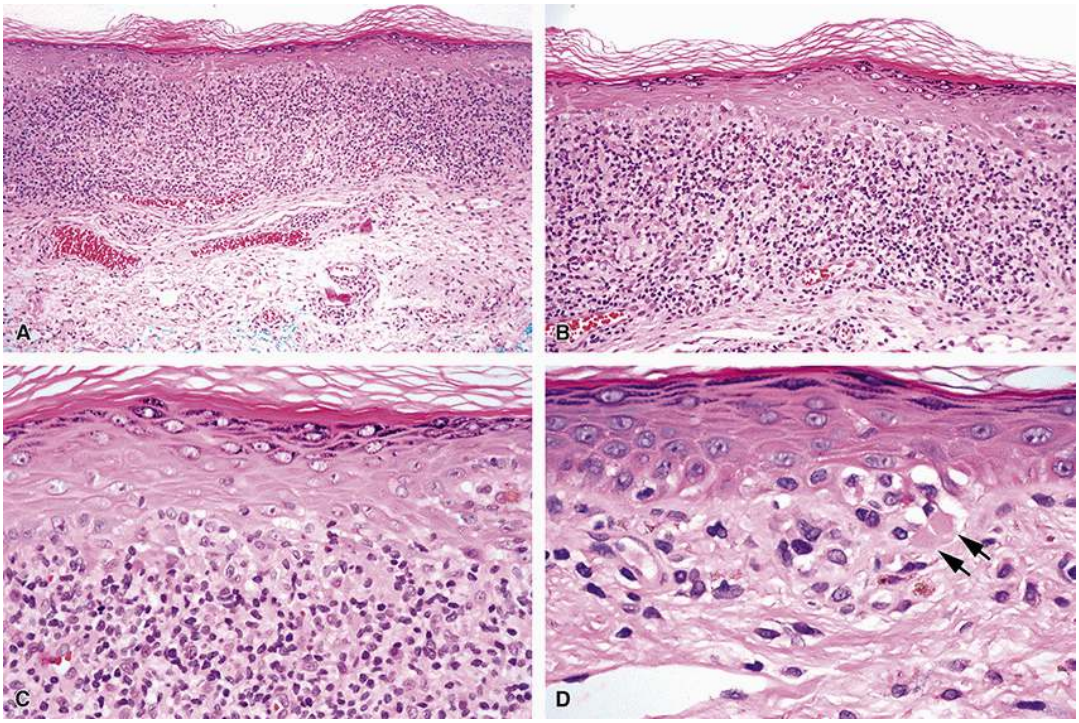

FIGURE 53.6 This example of lichen planus-like keratosis was from the left upper eyelid of a man in his late 40s who developed a white lesion that was clinically suspicious for malignancy. A, A dense band of chronic inflammatory cells (lichenoid infiltrate) is in the dermis abutting the epidermis. B, The epidermis is atrophic with hyperkeratosis and hypergranulosis. C, The lichenoid dermal inflammatory infiltrate contains lymphocytes and macrophages without many plasma cells. The keratinocytes lack cytological atypia. D, The epidermis had scattered necrotic keratinocytes (colloid bodies) in the basal epidermis and adjacent papillary dermis (arrows). Lichen planus-like keratosis is a common benign skin condition that is most often biopsied to exclude a cutaneous malignancy.[85,86]

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CHAPTER 54

Cavernous Venous Malformations

Key Points

- Cavernous venous malformations, previously called cavernous hemangiomas, are rarely observed in the eyelids
- They are low flow developmental venous malformations and not true tumors, and the exact pathogenesis remains elusive to this day
- Growth results from relative stasis of vascular elements and repeated bouts of thrombus formation, followed by recanalization with endothelial cell proliferation to line the newly formed spaces
- In the eyelid, CVM can be located subcutaneously, are not encapsulated, and tend to adhere to the dermis
- Alternatively, they may arise from the palpebral conjunctiva, usually in the caruncle
- Eyelid CVMs were thought in the past to be associated with the blue rubber bleb nevus syndrome or sinusoidal hemangioma
- Surgical excision is the preferred method of treatment
- Surgical excision is both curative and safe with very few recurrences

Cavernous venous malformations (CVMs), previously called cavernous hemangiomas, are the most common primary lesions in the orbit in adults, but they are rarely observed in the eyelids or on the ocular surface.[1,2,3,4,5,6,7,8,9]

Because their endothelium lacks a proliferative potential, CVMs are currently considered low flow developmental venous malformations and are not true tumors.[3,4] Although the term cavernous hemangioma is deeply entrenched in the ophthalmic literature and remains heavily used up to the present day,[8] the suffix *oma* is incorrect and should not be used in clinical practice.[1,3,4,5,6] However, taking a radical approach in the opposite direction and referring to CVMs simply as venous malformations,[9] instead of the traditional term cavernous hemangioma, may be misleading as well. The term "*venous malformation*" is a generic collective term that is currently recommended by the International Society for the Study of Vascular Anomalies (ISSVA) to describe venous anomalies in general.[7] Adopting this simplistic approach does not differentiate between distensible venous malformations, referred to in the ISSVA classification as common venous malformations, and CVMs of the orbit.[7] This approach is based on a misinterpretation of the ISSVA classification, which does not include the term "cavernous" in its orbital context.[7,10] Nevertheless, the term "cavernous" is still repeatedly used by ISSVA in relation to cerebral CVM. Therefore, we believe that what should be discarded is the term "hemangioma" only, whereas the discerning nomenclature "cavernous" should be retained for now because discarding it may add to the confusion rather than reduce it.[10] To solve this dilemma, it was recently proposed to subclassify orbital venous malformations (OVMs) into three[3] or five[10] distinct types. Cavernous hemangiomas are termed orbital venous malformation type 1 (OVM1), while orbital varices are referred to as OVM2. OVM3 is a more extensive version of OVM2 with widespread communication between the orbital and intracranial venous systems,[3] OVM4 is glomuvenous malformation (glomus tumor), and OVM5 is intraosseous VM.[10] As a trade-off, until a formal classification that takes into consideration the unique spectrum of all periocular vascular anomalies is adopted, the term CVM will be used in this chapter while the term distensible venous malformations will be used in the chapter about eyelid varices (see Chapter 60).

Etiology and Pathogenesis

Despite the numerous articles that have been published about CVMs in the literature, research has not been very active regarding the origins and pathogenesis of these curious lesions, and surprisingly very little is known about their etiology.[10,11] Unfortunately, the question that was raised in the 1980s "What is cavernous hemangioma of the orbit?"[12]—still lingers unanswered in early 2022.[10] The growing consensus in the past 2 decades, which is frequently quoted and inadequately explained, maintains that (1) CVMs are

slow flow malformations and not tumors; (2) they are exclusively venous malformations (akin to a PUIG type I pure venous malformation); therefore, they should fall under the ISSVA category of venous malformations; and (3) their growth is attributed to ectasia and hypertrophy rather than endothelial proliferation, which is attributable to local hormonal changes or local hemodynamic disturbances resulting from the sluggish blood flow and ischemia or hypoxia.[1,10,11,12,13,14,15,16,17,18,19,20] Although a great deal of evidence *(Print pagebreak 362)* exists in support of the scientific idea that CVMs are relatively stable venous malformations, and not true tumors, there are considerable clinical differences between vascular malformations and orbital CVMs, which might challenge the current consensus that CVM is a true malformation. There is no overlap in the age of presentation between CVM and vascular malformations as the onset of CVM is typically much later (around the 5th decade). Their growth pattern is also different as malformations generally grow commensurately with the growth of the child and, by definition, should not regress or involute, while orbital CVM may present suddenly, may have a variable growth pattern, and may even reduce in size postmenopause.[10] The confusion is buttressed even further by their vastly dissimilar prognosis. While CVM rarely recurs even after incomplete excision, recurrences or rather recrudescences are the rule rather than the exception in malformations.[10]

Moreover, numerous histopathological studies have demonstrated that orbital CVMs are not that static and may potentially have a low proliferative capacity, as they express several immunohistochemical vascular enhancers like vascular endothelial growth factor A (VEGFA) and its receptor VEGFr2 in 27% to 100% of the lesions.[19,20,21] However, the current consensus or counterargument is that the overexpression of those proangiogenic regulators or vascular enhancers by orbital CVM is simply a secondary effect of ischemia and recurrent bouts of thrombosis, which might stimulate mitotic activity resulting in the vascular remodeling observed in CVM. According to that scenario, VEGF is not a "true engine of growth"[17]; nevertheless, what these results merely suggest is that VEGF, which is a major effector and promoter of endothelial cell proliferation and differentiation, is somehow involved in the growth of CVM, and perhaps more research is needed in this area to clarify its exact role.[20] Furthermore, the purely venous nature of CVM is not firmly established either, and over the years, the thought of an arterial contribution to CVM has repeatedly been entertained in the oculoplastic literature.[14,18,22]

The abovementioned cellular and molecular arguments may only help to describe the progression or growth of CVM, but they fail to explain the initial events that triggered their genesis in the first place. Despite its presentation in adult life, an underlying genetic defect cannot be entirely ruled out, though none has ever been found, and most of the evidence supporting a genetic origin is circumstantial at best.[10,23] It is remotely possible that a CVM may arise from a preexisting collapsed congenital vascular malformation, which could have possibly originated from a not-yet-identified primitive multipotential endothelial analog. According to this hypothesis, these vessels that have remained dormant for decades may abruptly become dilated later in life due to local hemodynamic disturbances or hormonal effects. However, because no convincing case of orbital CVM has ever been documented in the first 2 decades of life, this theory is highly unlikely.[12,18] Alternatively, it is not entirely implausible to propose that CVMs could arise independently in adult life as totally de novo lesions without the presence of any preexisting quiescent vascular defect.[12]

All these ideas are entirely speculative, and a detailed discussion is beyond the scope of this chapter and should be sought elsewhere.[10] It remains to be seen whether any of these concepts can be extrapolated to CVM pathogenesis or the current dogma will hold. The bottom line is that CVMs are neither tumors in the usual sense of the word nor do they perfectly fit the description of an OVM; therefore, their exact nosologic position warrants a further reevaluation in the future.

Clinical Presentation

Although orbital CVMs are one of the more common orbital lesions encountered in clinical practice, true palpebral or conjunctival CVMs are extremely rare.[24,25] In an extensive literature search (October 2021), we found very few convincing cases of histopathologically proven conjunctival CVMs on Pubmed/Medline and even fewer cases of eyelid CVM. In their detailed textbook on eyelid, conjunctival and orbital tumors, Shields and Shields documented four cases of conjunctival CVM but no cases of eyelid CVM.[24]

No age or sex predilection is known probably because of the rarity of these lesions, but they seldom appear before puberty. Three different presentations may be observed. The first is a soft bluish compressible mass located subcutaneously.[25,26,27] According to some authors, palpebral CVMs are usually not encapsulated and tend to adhere to the dermis.[25] A CVM does not increase in size with a Valsalva maneuver, and no bruits are heard on auscultation.[26] In the very rare situation when a CVM involves the upper eyelid, it may cause blepharoptosis (Figure 54.1) or even keratoconus.[26]

Alternatively, a CVM may arise from the palpebral conjunctiva, usually in the vicinity of the caruncle (Figure 54.2), and may cause recurrent bouts of bloody tears.[2,24,25] These lesions may be observed protruding through the palpebral aperture or may be concealed beneath the eyelid where they can easily be detected upon eyelid eversion.[2,24,25]

A third and far more common presentation that cannot be technically considered palpebral CVM is when an anteriorly located orbital CVM that is closely positioned to the eyelid simply protrudes into the eyelid skin and presents as a subcutaneous mass that assumes the color of the skin and could be misdiagnosed as unilateral fat prolapse or steatorrhea (Figure 54.3).[28]

In the past, cardiovascular and dermatologic examinations were routinely carried out in patients with CVM *(Print pagebreak 363)* to rule out any syndromic association because some eyelid CVMs were presumed to be associated with the blue rubber bleb nevus syndrome (bean syndrome, or BRBN syndrome) where the gastrointestinal tract may also be involved, resulting in gastrointestinal bleeding and anemia.[25,29,30] This association is no longer valid. After a closer look at the frequently cited case reports where CVM was described in association with BRBN syndrome, several authors have pointed out that the overwhelming majority of these cases are common venous malformations that were misdiagnosed as CVM.[31,32] Similarly, it was presumed in the past that sinusoidal hemangioma is a variant of CVM. In patients with a sinusoidal hemangioma, the lesion is usually larger, darker blue, compressible, and multiloculated and may extend to the cheek.[25] However, the latest iteration of the ISSVA classification lists sinusoidal hemangioma separately under the subheading of "*provisionally unclassified vascular anomalies*" and not as a venous malformation.[7]

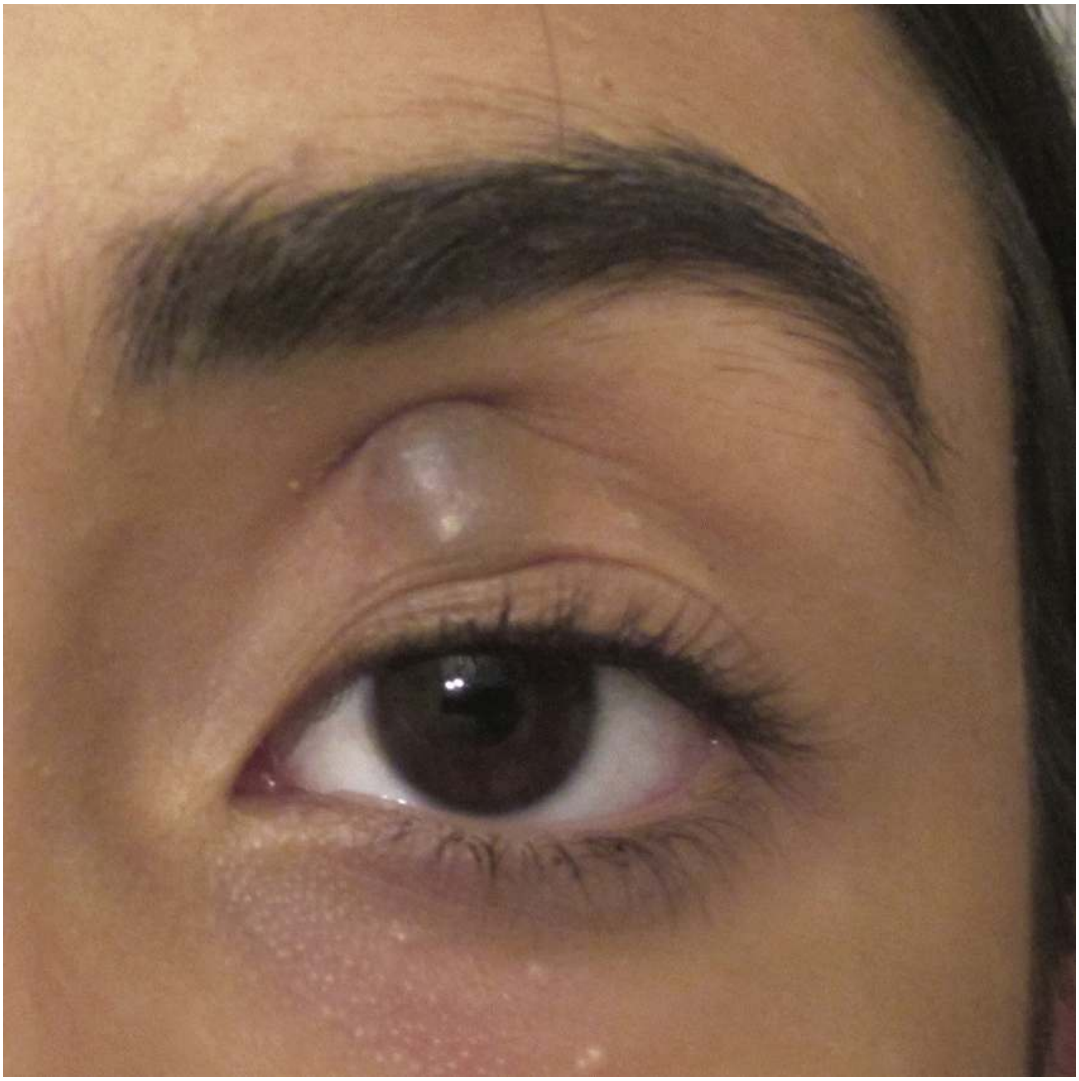

FIGURE 54.1 Cavernous venous malformation of the eyelid. (Courtesy of Dr Mohsen Kashkouli.)

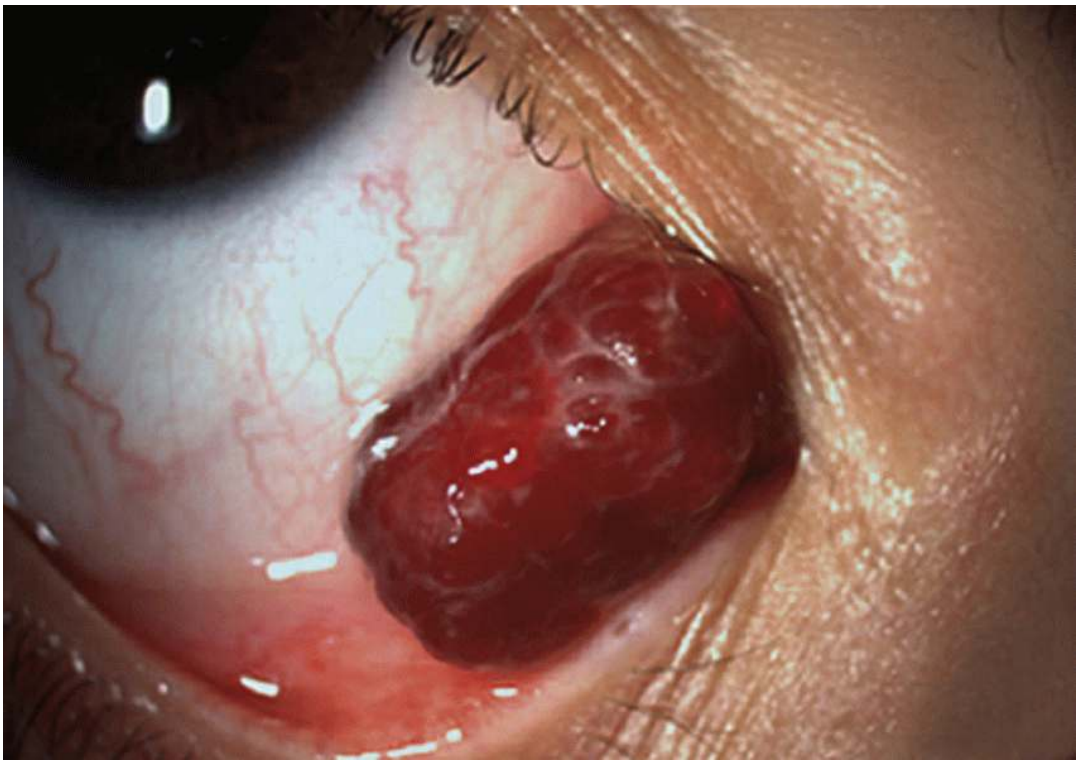

FIGURE 54.2 Cavernous venous malformation of the conjunctiva. (Reprinted with permission from Yazici B, Ucan G, Adim SB. Cavernous hemangioma of the conjunctiva: case report. *Ophthalmic Plast Reconstr Surg*. 2011;27:e27-e28.)

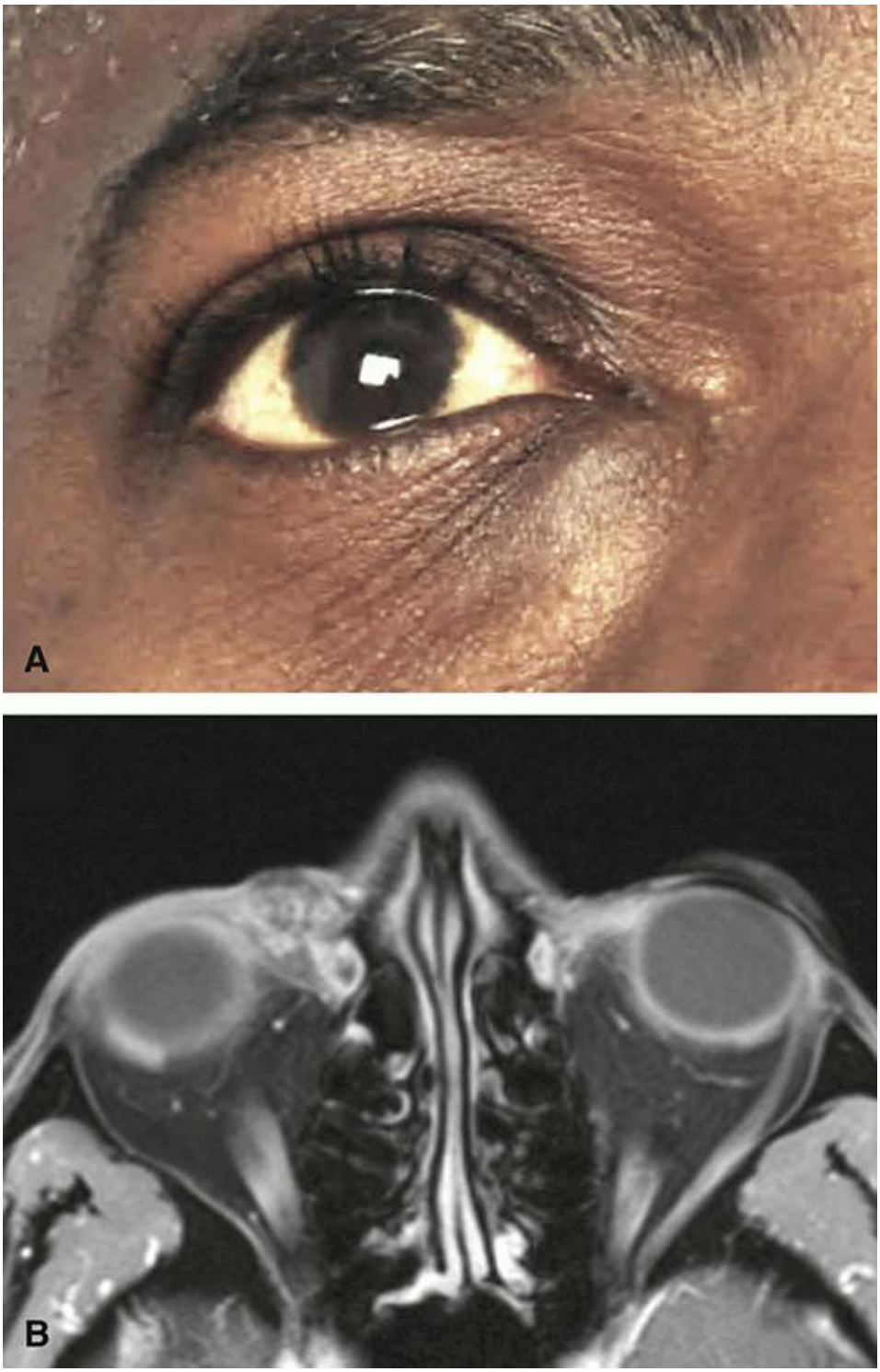

FIGURE 54.3 A, An anteriorly located orbital cavernous venous malformation that protrudes through the eyelid skin. B, Axial CT scan of the right orbit showing the anteromedial CVM. (A and B, Courtesy of Dr Daniel Rootman.)

Differential Diagnosis

Several vascular anomalies like arteriovenous malformation (AVM) and eyelid varices need to be differentiated from eyelid CVM because the management in each case *(Print pagebreak 364)* is entirely different and an error in diagnosis may prove catastrophic. AVMs occur principally in the head, neck, and brain. In contrast to CVMs, they are evident at birth in 59% of patients, but they may remain asymptomatic until puberty or adulthood when they grow and start to manifest clinically. Pure preseptal eyelid AVMs are rare, and orbital cutaneous lesions are far more common (see Chapter 50). Distensible venous malformations (varices) present as a unilateral, nontender, well-circumscribed, soft, compressible subcutaneous mass that may or may not enlarge with a Valsalva maneuver (see Chapter 60). In either case (AVMs and varices), the distinction should not be difficult clinically; nevertheless, a radiologic workup is mandatory.

A glomuvenous malformation (glomus tumor) also needs to be differentiated from an eyelid CVM. In patients with glomuvenous malformations, the lesions generally present as slow-growing, solitary or multiple, bluish to violaceous plaque-like, soft, spongy, or firm nodular lesions. Whereas solitary lesions appear in adults, multiple tumors arise more commonly in childhood and may be familial (see Chapter 64).[33]

CVMs of the eyelid should not be confused with senile cherry angiomas (Campbell de Morgan spots), which are usually small (0.5-5 mm), solitary acquired reddish papules.[24] These lesions, which are frequently observed in the elderly population, are benign with distinct histopathologic characteristics but are not yet listed in the latest ISSVA classification update.[7] They move with movement of the skin and may bleed after trauma, but usually are inconsequential and require no treatment.[24]

Reactive lesions like lobular capillary hemangioma (pyogenic granuloma) may be confused with conjunctival CVM because they have a predilection for the palpebral conjunctiva; however, they may also be observed on the surface of the eyelids as sessile broad-based lesions and could also pose a diagnostic problem with eyelid CVM. A history of minor trauma to the cutaneous surface of the eyelids or prior chalazion excision in cases with pyogenic granuloma of the palpebral conjunctiva should be obtained from the patient to establish the diagnosis (see Chapter 107).[21]

Treatment

Surgical excision is usually the preferred method of treatment both for palpebral and conjunctival CVM.[2]

Prognosis

Surgical excision is both curative and safe. Similar to their orbital counterpart, extensive bleeding is unusual, and recurrences are extremely rare.[17]

Histopathology

In general, cutaneous venous malformations are benign lesions composed of irregular venous channels of varying caliber, lined by flattened endothelium, with scant mural smooth muscle,[34] or smooth muscle that is focally absent or less than expected for the vessel diameter.[35] Lesions are typically located in the deep dermis or subcutaneous tissue but may occur at any level of the skin.[34] The vascular channels may be juxtaposed, in clusters, or randomly distributed,[35] and they "*may dissect through and around normal soft-tissue structures.*"[34] The dilated slow flow blood channels often thrombose and may undergo organization and recanalization or development of papillary endothelial hyperplasia or phleboliths.[34,35] In our experience, venous malformations of the eyelid are rare and may be noted at birth (Figure 54.4) or later in life (Figure 54.5).

The so-called cavernous hemangiomas in the older dermatology[36,37,38] and ophthalmology[39,40] literature feature large, dilated, endothelium-lined, blood-filled spaces in the dermis and subcutaneous tissue. Fibrous stroma separates the vascular spaces and may have focal chronic inflammation.[40] Eyelid CVMs are usually well circumscribed but not encapsulated.[40] Many of the so-called eyelid cavernous hemangiomas in the older literature likely represented involuting infantile hemangiomas (Figure 54.6A and B)[41] or cherry (senile) angiomas (Figure 54.6C and D), though some lesions do resemble orbital CVM (Figure 54.6E and F). Histological features that help distinguish an involuting capillary hemangioma from a CVM are a lobular architecture, more variably sized vascular channels, lack of vessels with mural smooth muscle, and sometimes residual capillaries. Cherry angiomas occur in early adulthood, increase in frequency with age, and have dilated capillary and postcapillary venules in the papillary dermis.[42,43] Fully developed cherry angiomas have a loss of epidermal rete ridges with the formation of a collarette of epidermis resulting in a polypoidal lesion.[42] Based on current morphological criteria, some lesions classified in the past as a cavernous hemangioma defy ready classification as a venous malformation or even any other entity listed in ISSVA 2018.[44]

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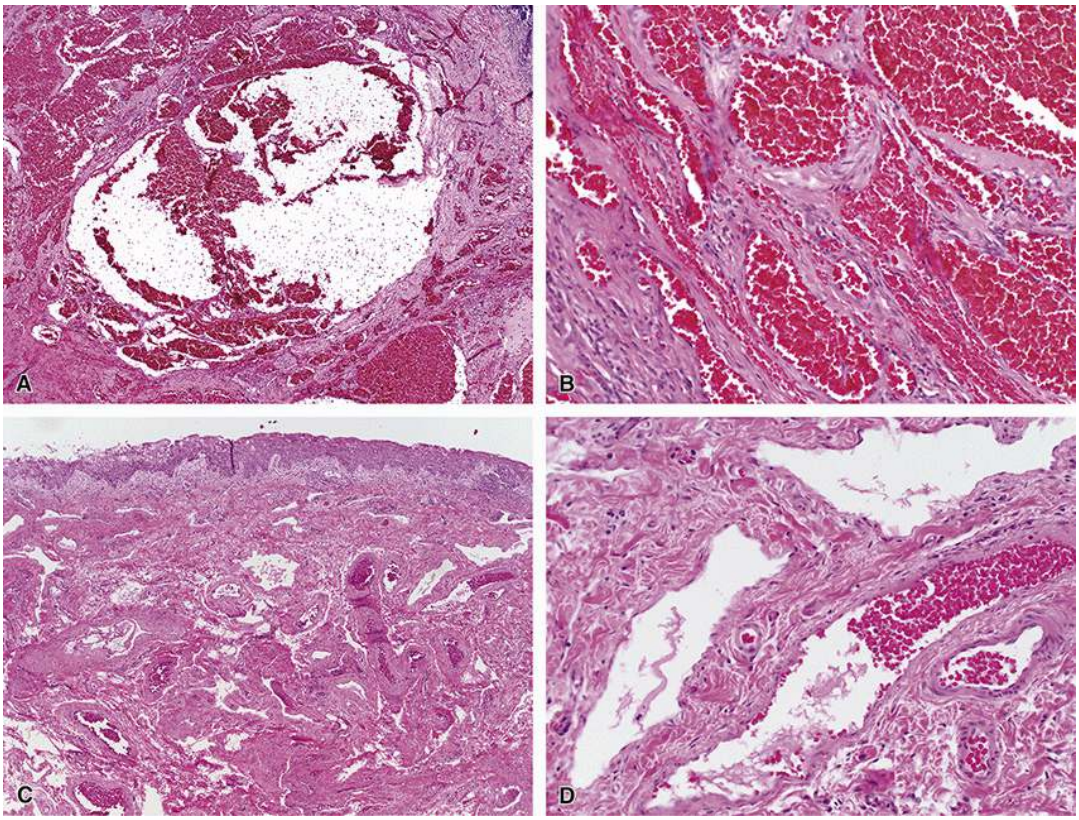

FIGURE 54.4 This cavernous venous and lymphatic malformation, excised at the age of 3 years, was noted at birth and involved the left anterior orbit and left upper eyelid. A, The orbital component of the malformation is a venous malformation with vessels having marked variability in caliber. B, The orbital venous malformation has marked variability in vessel wall thickness, with some having mural smooth muscle. C, The vascular malformation infiltrated into the eyelid beneath the conjunctiva and had numerous irregularly-shaped dilated vascular channels. D, The vessels vary in size and wall thickness, with only some having smooth muscle in their wall. Two lymphatics have thin walls and lumens with lightly eosinophilic material devoid of erythrocytes.

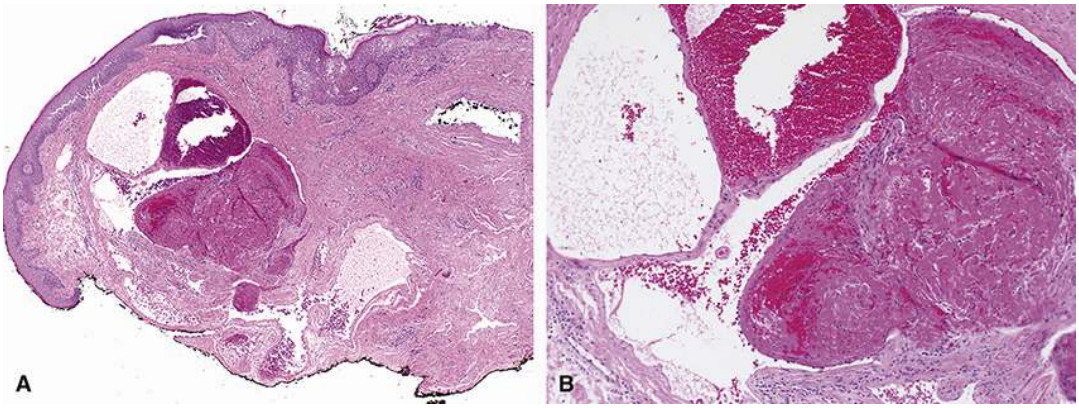

FIGURE 54.5 This cavernous venous malformation of the lateral right upper eyelid was present for 15 years before excision in the patient's middle 40s due to enlargement over 3 years. A, Large malformed venous channels are in the dermis. Thrombus is within a large vessel and two smaller vessels beneath it. The black ink at the specimen base was for orienting the tissue during embedding in paraffin. B, The thrombus is organizing, as reflected by the ingrowth of spindle cells and capillaries.

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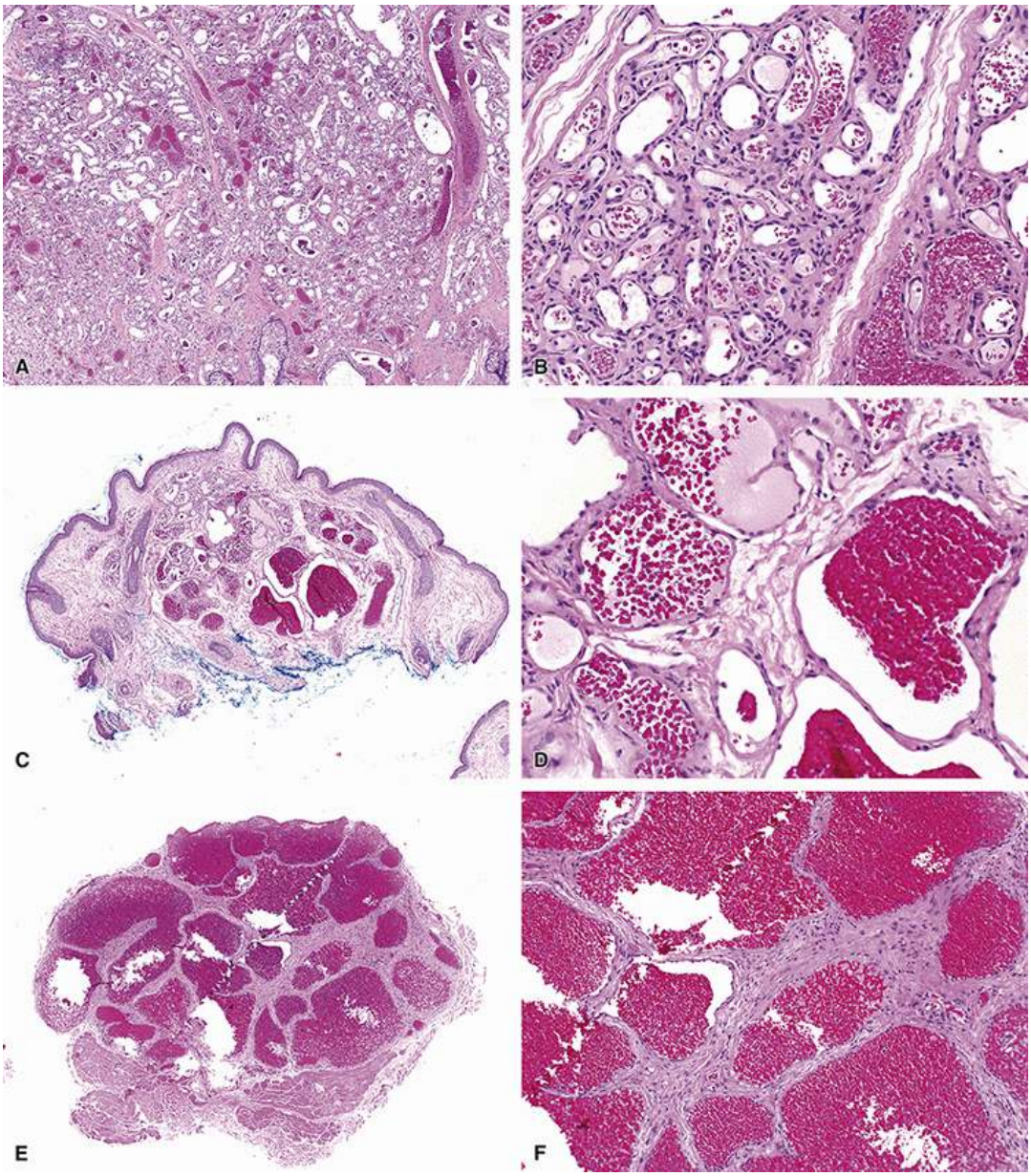

FIGURE 54.6 A and B, This involuting capillary hemangioma involved the left upper eyelid and anterior orbit of a young boy. It was present since birth and excised at age 6 years due to thickened eyelid with reduced mobility. A, At low magnification, there are lobules of dilated vascular spaces. Meibomian glands are at the bottom of the photomicrograph. B, At high magnification, the involuting capillary hemangioma has dilated and normal caliber capillaries, which help distinguish this lesion from a cavernous malformation. C and D, This cherry angioma was removed from the left upper eyelid of a woman in her early 60s. C, It consists of a circumscribed collection of dilated vessels in the superficial dermis. D, At higher magnification, the thin-walled vessels are compatible with dilated capillaries and postcapillary venules. E and F, This cavernous vascular lesion was removed from the right upper eyelid of a woman in her late 40s. The lesion felt cystic, was blue, and had been present for 1.5 years with a slow increase in size. E, The lesion was well circumscribed and completely excised. Orbicularis oculi muscle is at the base of the lesion composed of markedly distended blood vessels separated by fibrous septa. F, At high magnification, the vessels are lined by flat endothelium and lack mural smooth muscle. Dense fibrous tissue separates the vascular channels. This lesion has a histological appearance identical to orbital cavernous hemangiomas/malformations.

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CHAPTER 55

Chalazion and Hordeolum

Key Points

- Hordeolum is a common painful infection of the eyelid margin
- It is usually caused by a staphylococcal infection and presents as a red swollen furuncle with an acute onset
- A chalazion is a granulomatous foreign body reaction that may develop secondary to a sterile noninfectious obstruction of sebaceous gland ducts and can develop from a chronic hordeolum
- Predisposing factors include poor lid hygiene, chronic staphylococcal blepharitis, demodicosis, meibomian gland dysfunction, and rosacea
- Rosacea is common in patients with chalazia
- Acute hordeola generally present as diffusely inflamed abscess, with localized tenderness, and edema centered around an eyelash and usually pointing anteriorly onto the eyelid skin
- Chalazion forms a thin fibrous nodule that appears as a fleshy mass on the tarsal conjunctiva or may protrude through the skin if it originates from an external hordeolum
- Treatment of acute hordeolum is generally conservative with warm compresses, lid scrubs, and topical antibiotics
- Chalazia can be managed with intralesional steroid injections or incision and curettage
- Chalazia generally resolve medically or surgically, and in some cases may undergo spontaneous resolution

Hordeolum is a common painful inflammation of the eyelid margin that usually presents as a red swollen furuncle with an acute onset and is usually caused by a staphylococcal infection. An acute hordeolum can arise from the meibomian glands (internal hordeolum) or the Zeis/Moll glands (external hordeolum or stye).[1,2,3,4,5,6,7,8,9,10,11,12,13] The lesion either drains on its own with spontaneous resolution or can become chronic and evolve into a chalazion, which is a common lipogranulomatous inflammation of the meibomian glands of the eyelid.[1,2,3,4,5,6,7,8,9,10,11,12,13]

In clinical practice, the terms chalazion, hordeolum, and stye are often used interchangeably in the vernacular, although the three entities differ in their anatomical location (stye vs chalazion), their evolutionary stage (hordeolum vs chalazion), as well as the underlying pathogenetic event. A hordeolum is an abscess (acute pyoderma), while a chalazion is fundamentally a granulomatous foreign body reaction.[13,14]

Etiology and Pathogenesis

A hordeolum is an acute focal inflammation of the eyelid, which develops due to microbial infection (usually *Staphylococcus aureus*) of the meibomian or Zeis glands.[14] Pus forms within the lumen of the infected gland, and thus an acute hordeolum is formed. When an acute hordeolum involves the Zeis gland (external hordeolum), the abscess is centered in the pilosebaceous unit around an eyelash.[10]

The etiopathogenetic events leading to the development of a chalazion may be of infectious origin if it evolves from an unresolved hordeolum, or it may develop secondary to a sterile noninfectious obstruction of sebaceous gland ducts, which may or may not be complicated by a secondary infection on top.[14,15] Either way, blockage of a meibomian gland duct results in rupture of the gland with the release of sebaceous contents into the tarsus and the surrounding tissues. This initiates an inflammatory, granulomatous, or foreign body reaction to the inspissated lipid secretions of the meibomian or Zeis glands.[14,16,17] With time, the inflammatory process is then walled off, resulting in a cyst-like lesion.[13,14]

Predisposing factors for the development of single, multiple, or recurrent hordeola and chalazia are manifold. Poor lid hygiene as well as chronic staphylococcal blepharitis, demodicosis, meibomian gland dysfunction (MGD), and rosacea play a definite role.[1,3,14,18,19,20,21] Other associated risk factors include young age, female sex, urban living, gastritis, anxiety, irritable bowel syndrome, chronic constipation, anemia, poor nutrition, IgM deficiency, viral conjunctivitis, and menstrual abnormalities or menstruation itself due to their impact on lipid metabolism.[21,22,23,24,25,26] Diabetes, hypothyroidism, and obesity are also possible risk factors due to the reduction of androgen levels.[24]

Rosacea is common in patients with chalazia and is even twice as common as in patients with recurrent chalazia.[27] In a series of 51 patients scheduled for chalazion excision, 55% had rosacea, compared with only 12% in a control group without chalazia.[27] Two *Demodex* species (*Demodex folliculorum* and *Demodex brevis*) frequently inhabit the eyelids including the eyelash follicle (*D. folliculorum*) and the meibomian glands (*D. brevis*).[18,19,20] Both species frequently coexist and demodicosis should be ruled out in children as well as adults with recurrent chalazia.[18,19,20] A recent study demonstrated a high prevalence of *D. brevis* infestation in patients with recurrent chalazia.[19] The same study also showed that the prevalence of demodicosis in patients with chalazia is far more common than the prevalence of chronic blepharitis *(Print pagebreak 369)* (69.2% vs 19.78%).[19] It is not clear whether *D. brevis* causes chalazia by direct mechanical blockage of the meibomian gland orifices or indirectly by acting as a vector to bring in symbiotic bacteria like *Bacillus oleronius* or *S. aureus*.[18,19] Although chalazia are not strictly considered within the context of MGD,[28,29,30] the presence of MGD predisposes to the development of chalazia, and chalazion is listed or labeled by the international workshop on MGD as a comorbidity, localized MGD, or plus disease.[28,29,30]

Clinical Presentation

The incidence and prevalence rates of hordeolum are largely unknown.[1,3,7] The condition is ubiquitous and most cases resolve on their own. In addition, people with hordeolum do not seek professional medical treatment often preferring to rely on home remedies, and even when they do, patients usually present to a general practitioner, so that hordeolum/chalazion cases are seldom reported. A recent study that sought to determine the epidemiology of eye-related emergency department visits on a national level in the United States between 2006 and 2011 showed that 3.8% of the visits were due to an acute hordeolum.[31] Hordeola and chalazia are not limited to any age, race, or sex, although they may be more common in younger females. Chalazia also generally cluster around puberty, pregnancy, and menopause possibly due to hormonal influences on sebaceous secretion.[1,24]

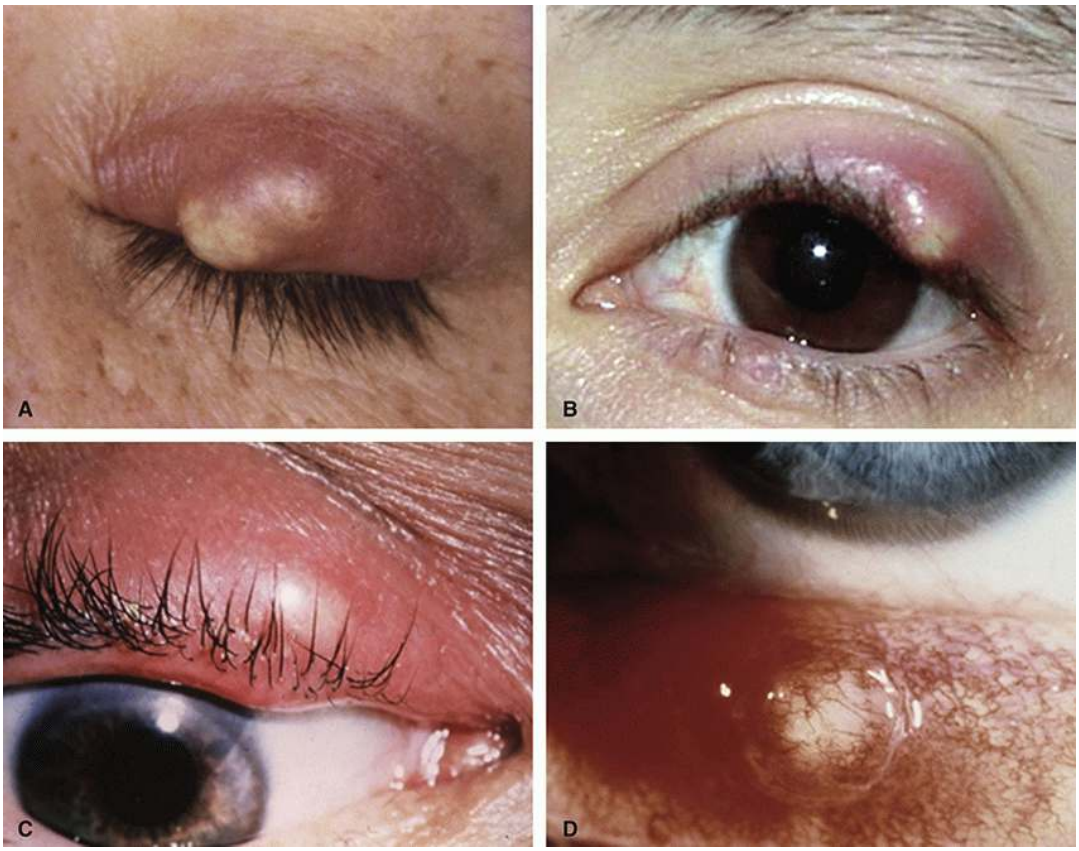

FIGURE 55.1 A-D, Acute hordeolum of the eyelid pointing to the skin.

The course of an acute hordeolum is relatively short and mostly self-limited but with an explosive onset.[1] Patients typically present

with a variable degree of acute pain (slight to severe), irritation, and swelling. Cases with an acute external hordeolum typically experience a greater degree of pain and tenderness compared to an acute internal hordeolum.

The natural history of an acute hordeolum generally spans 1 to 2 weeks, beginning with an initial phase whereby the eyelid is diffusely inflamed, with localized tenderness over the inflamed gland. Edema may be enormous and may spread to the other ipsilateral eyelid.[14] In acute external hordeolum, the abscess is centered around an eyelash and usually points anteriorly onto the eyelid skin (Figure 55.1). In *(Print pagebreak 370)* a case of an acute internal hordeolum, dilation of the orifice of the involved meibomian gland can be observed, which on closer inspection will show that it is filled with inspissated secretion or purulent material that can be expressed with gentle pressure on the eyelid against the globe.[1,3,13] In some cases of acute hordeolum, the infection can progress to preseptal cellulitis, but rarely if ever does it penetrate the orbital septum resulting in orbital cellulitis.[1,3,32,33,34]

The acute phase ends with either complete resolution or the development of a chalazion. On rare occasions, residual inflammatory signs may persist for weeks simulating an acute lesion, although the pain and tenderness are absent.[13] In cases of a nonresolving external hordeolum, a crust overlying the lesion may persist for weeks.[13]

If spontaneous resolution does not occur, an acute internal hordeolum can become chronic and develop into a chalazion forming a thin fibrous sac or a firm or even a hard nodule that may appear to bulge on the skin surface or form a fleshy mass on the tarsal conjunctiva (Figure 55.2). A chalazion may also protrude through the skin if it has originated from an external hordeolum or if an internal hordeolum ruptures anteriorly.[3,30,35,36] Large untreated chalazia can lead to destruction of the acini of the involved meibomian gland and may rupture through the tarsus leading to the development of a pyogenic granuloma. An alternative presentation of a chalazion is a more chronic onset where patients present insidiously with a firm, painless nodule beneath the skin without a history of acute onset. This form of presentation is not uncommon and both forms may be observed in the same patient at different times or even simultaneously.[17]

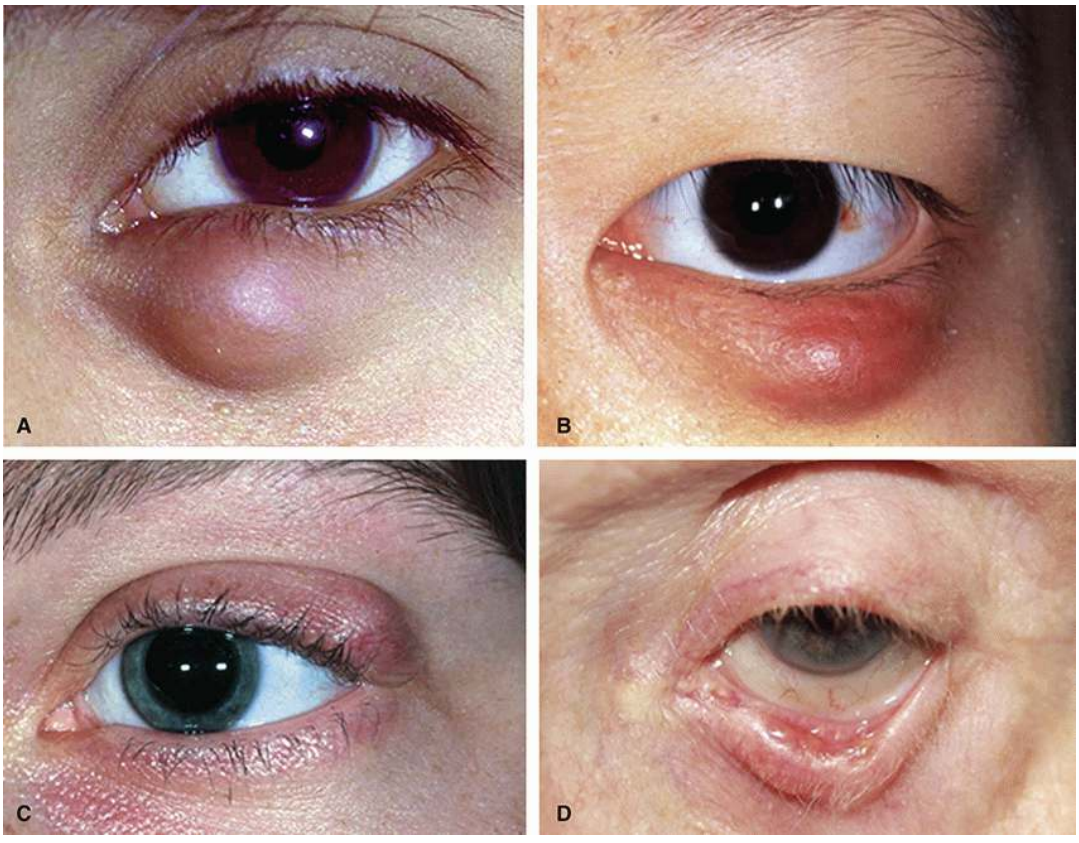

FIGURE 55.2 A-D, Chronic chalazion forming an anterior subcutaneous bulge or pointing posteriorly.

Eyelid comorbidities that may be observed in patients with hordeolum or chalazion include conjunctival scaring from a prior chalazion excision, diffuse meibomian gland disease, and a papillary reaction with hyperemia of the palpebral and tarsal conjunctiva.[35] Hordeola/chalazia rarely if ever threaten vision, although there have been occasional reports of large neglected chalazia resulting in amblyopia due to mechanical ptosis, hypermetropia, or induced astigmatism.[15,30]

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Differential Diagnosis

An acute hordeolum should be differentiated from preseptal or orbital cellulitis.[14] The inflammatory process in acute hordeolum is caused by local lymphatic congestion and can be differentiated from more ominous infectious processes by the nature of the pain, which is localized in patients with acute hordeola but may be of a more diffuse and intense nature in preseptal/orbital cellulitis. The absence of tense erythema and leukocytosis may also help clinch the diagnosis.[14]

When associated with other nodules in the face, chalazia may be confused with a new entity of unknown etiology called idiopathic facial aseptic granuloma (IFAG).[37,38,39,40] IFAG appears to be a granulomatous reaction circumscribed to the skin of the midface,[38] and, in contrast to chalazia, the inflammation does not involve the meibomian glands.[38,39] These lesions usually present as asymptomatic erythematous subepidermal eyelid nodules in the cheek and/or the eyelid and should not be difficult to differentiate from chalazia. However, when they are confined to the eyelid without accompanying lesions in the midface, the distinction is difficult. It is imperative to differentiate both conditions because IFAG responds well to oral clarithromycin and surgical excision is unwarranted.[38,39] Although some authorities consider IFAG to belong to the spectrum of rosacea,[41] many differences exist, the details of which are beyond the scope of this chapter. Suffice to say that if clinical suspicion arises, referral to a dermatologist is indicated.[38,39,40,41] A zinc deficiency should be suspected in the pediatric population if hordeola are associated with a perioral rash. This condition typically occurs in children with food allergies with subsequent restrictions of the dietary intake of foods rich in zinc.[7]

It is not uncommon for other benign, premalignant, and malignant eyelid conditions to masquerade as a chalazion. One study showed that in 6.4% of lesions labeled as chalazion, an alternative diagnosis was found on histopathological examination. Most of the lesions were benign and only 0.2% were malignant.[42] When atypical clinical findings are observed, submission of the curetted contents for histopathology is indicated.[43,44] A quintessential example is sebaceous carcinoma (SbC) because its clinical appearance is seldom pathognomonic and 20% of patients are misdiagnosed initially as a chalazion.[45,46] When a chalazion is recurrent in the same location and it is associated with persistent unexplained redness, localized madarosis, or lid thickening and telangiectasia, SbC should be suspected.[45,46,47] SbC often originates in the meibomian glands of the upper eyelid but it should not be ruled out if a suspicious lesion arises in the lower eyelid, or if the lesion presents anteriorly associated with cilia because SbC may also arise from a Zeis gland.[48]

The clinical features of an intratarsal keratinous cyst (IKC) can closely resemble a chalazion, although there are some distinguishing features. Chalazia are frequently surrounded by inflammation, while an IKC is not. The margins of chalazia are indistinct, while on eversion of the eyelid, the margins of IKC are well defined. Therapeutically, it is of paramount importance to distinguish IKC from a chalazion because IKC requires complete excision and will recur if it is treated as a chalazion with incision and curettage (I&C).[49]

Other rare benign and malignant lesions that may be confused with a chalazion include pilomatrixoma, steatocystoma, hemangioendothelioma, infantile hemangioma, epidermal inclusion cysts, tuberculosis, basal cell carcinoma, seborrheic keratosis, intradermal nevus, amyloidosis, Merkel cell carcinoma, desmoplastic malignant melanoma, microcystic adnexal carcinoma, neurilemoma, benign reactive conjunctival lymphoid hyperplasia, or localized eyelid rhabdomyosarcoma.[49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64]

Treatment

In patients with an acute hordeolum, the initial management is conservative.[1,2,3,5,43,65,66] This consists of the application of warm compresses several times a day (5-10 minutes each) followed by eyelid massage, lid scrubs, and topical antibiotics.[1,3] The application of warm or hot compresses may facilitate drainage by clearing debris from the lid margin, softening the granuloma, and widening the gland orifices to facilitate drainage, which paves the way for eyelid massage to physically express secretions from the infected glands.[13,35] Nicking the capsule at the mouth of the occluded orifice or epilation of the involved eyelash in cases of external hordeolum may accelerate the resolution of infection; however, forceful rupture should not be attempted in acute hordeolum to avoid further dissemination of the infection.[1,3,14,35]

Because hordeolum is an acute suppurative inflammation of the meibomian glands, using topical and systemic antibiotics to help reduce the bacterial load would seem appropriate.[1,3,38,67] However, while the use of topical antibiotics is usually recommended,[1,3,65] the routine use of systemic antibiotics is not yet supported by clinical evidence.[67] In general, systemic antibiotics are reserved for cases where topical antibiotics fail, or when the hordeolum is complicated by the presence of preseptal cellulitis.[1,3,38] The judicious use of topical steroids may also help reduce the inflammation.[1,3,35]

Conservative measures are not always effective, and the reported resolution rates vary between 18% and 71%.[38,43,44,66] The actual cure rate with conservative measures may be higher than the published data because patients who are cured tend to drop

out of clinical trials.[43,44] Additionally, some of the published studies do not restrict the application of conservative measures to acute cases, and because of the granulomatous nature of chronic chalazia, they would not be expected to resolve with topical therapy.

The indications for treating chalazia include failure of conservative measures, long-standing lesions (delayed presentation >2 months after onset), cosmetically disfiguring lesions, persistent pain or discomfort from the lesion, clinical suspicion as of the true nature of a chalazion, lesions protruding through the skin, and chalazia causing mechanical ptosis particularly in children where it is potentially *(Print pagebreak 372)* amblyogenic due to induced astigmatism or visual obstruction.[35] Smaller lesions tend to disappear spontaneously, even after prolonged periods, and may be left untreated.[68]

Treatment options for chalazia include I&C of contents or the intralesional injection of steroids.[32,43,69] The decision to adopt either route depends upon several factors, including the preference of the surgeon and the patient. Intralesional injections may be preferred when chalazia are close to the lacrimal system or the lid margin or when the I&C is refused by an anxious patient or their parents. However, I&C is more effective than intralesional steroid injections, leading to a complete cure in up to 100% of cases.[17,44,70] Hard chalazia, chronic lesions lasting >8.5 months, lesions >11 mm, and patients older than 35 years are more likely to benefit from I&C.[14,17,43,70] Advocates of I&C argue that besides being a more definitive form of therapy that does not need to be repeated to achieve a complete cure, it is also less painful, and there is no risk for embolization of the ocular vasculature. However, opponents of surgery argue that injections neither require an operating room, postoperative patching, an antibiotic prescription, or days off from work, which makes injections the more economically feasible option.[17,70,71,72]

Because a chalazion is essentially an inflammatory granulomatous reaction, the use of intralesional steroid injections is warranted, and clinical level I and II studies do support their use.[28,73,74,75,76] The procedure usually requires sedation or general anesthesia in the pediatric age group,[32] but adults only require topical anesthetic eye drops.[17,70] Between 0.1 and 0.2 mL of Kenacort-A (triamcinolone acetonide, 10-40 mg/mL) is injected directly into the lesion via a conjunctival or skin approach.[17,70] No patch is used at the end of the procedure but patients are instructed to do regular massage at home.[44,70,73] Intralesional steroids are contraindicated in darkly pigmented individuals,[15] but the use of the conjunctival route rather than the transcutaneous route for injection can reduce the incidence of depigmentation.[14,77,78,79] Reported success rates vary from 76% to 93%, but the procedure may have to be repeated within a month to achieve a cure.[14,44] The reported need for a second injection varies in the literature, but the rate may be up to 50%, and in some patients, multiple injections up to seven time may be required.[73,76,80]

For I&C, the eyelid skin is injected with 1 mL of bupivacaine 0.25% with epinephrine 1:200,000. If general anesthesia is required in a child, a local anesthetic injection should be given as well to achieve intraoperative hemostasis and to reduce postoperative pain. Briefly, a chalazion clamp is placed over the lesion, the eyelid is everted, and a scalpel blade is used to make an initial vertical tarsal incision parallel to the meibomian glands, which may or may not be followed by a horizontal cut into the tarsus to create a cross-shaped incision in the chalazion. However, horizontal cuts may cause scarring of the meibomian ducts.[14] A chalazion curette is used to scrape out the contents of the cyst, and the fibrous capsule around the chalazion is excised with scissors. The clamp is slowly loosened, any bleeding points are lightly cauterized, and the eye is patched.[70] In situations where a chalazion presents with a subcutaneous mass, a additional skin incision may be required to evacuate the contents. In contrast to the tarsal incision, the cutaneous incision should be parallel to the lid margin and as close as safely possible to the eyelashes to minimize visible scarring.[14]

In patients with recurrent chalazia, the management of associated blepharitis in children or MGD in adults is essential.[32,35] Also, maintaining lid hygiene with hot compresses using commercially available lid scrub products, or with unscented nonirritating soap, may also help reduce recurrences particularly in children.[32,35] If these measures fail, some form of systemic anti-inflammatory medications may be required, including either low-dose oral tetracycline or doxycycline, which have a dual mechanism of action to reduce inflammation due to their matrix metalloproteinase inhibitor properties, as well as to fend off infection.[32,81] Dietary supplements including omega-3, flaxseed oil, or other fish oil preparations rich in docosahexaenoic acid and eicosapentaenoic acid may also help regulate meibomian gland secretion and reduce inflammation.[32,35,67] Newer alternative methods for the management of hordeola and chalazia include acupuncture for acute hordeolum or photobiomodulation with low light level therapy or intense pulse light therapy for chalazia.[82,83] But there is no ample scientific evidence to support either intervention, and further research is needed to support their use.

Prognosis

Chalazia generally resolve medically or surgically without any effect on vision except in the very rare situation in pediatric patients where an oversized chalazion is neglected. Even for lesions left untreated for 6 months[68] to up to 5 years,[36,66,68] some authors

report an overall spontaneous cure rate of 25% to 43%.

An issue of significant concern is the problem of recurrence. Recurrent chalazia are more frequently observed in the pediatric population (17%-25%) than in adults.[18,19,24,25] When recurrences occur in the same location, SbC must be ruled out. However, if multiple recurrences occur within a short period in different locations, an underlying systemic condition, such as rosacea or local demodicosis, should be ruled out, although the far more common cause of recurrent chalazia is improper eyelid hygiene.[35]

Histopathology

An external hordeolum exhibits purulent infection of the hair follicle and its associated sebaceous glands, with cellulitis of the adjacent connective tissue.[84] Internal hordeola feature severe suppurative inflammation of one or more meibomian glands.[85,86] The abscess may "*open through the gland duct or onto the conjunctival surface*."[85] Internal hordeola may spread to the surrounding tarsus causing tarsal necrosis[85] or into the orbicularis muscle.[86]

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A chalazion is a localized noninfectious lipogranulomatous reaction[84,85,87,88] to lipids released from eyelid sebaceous glands (either the meibomian glands or the glands of Zeiss). Superficial chalazia derive from the glands of Zeis and deep chalazia from meibomian glands. Obstruction of sebaceous gland ducts results in a granulomatous response surrounding vacuoles that remain when lipid dissolves during histological processing (Figures 55.3 and 55.4). Epithelioid cells, foreign body giant cells, Langhans giant cells, neutrophils, lymphocytes, and plasma cells are present in the lipogranulomas, which often become confluent.[16,84,85,86,88] The giant cells may contain asteroid bodies (Figure 55.4D) and Schaumann bodies,[86] though these are rare in our experience. The number of multinucleated giant cells is highly variable, and they may not be apparent in older chalazia. Neutrophils may be prominent in some lesions,[16,84] while increasing fibrosis occurs in more chronic chalazia (Figure 55.5).[84] Histochemical stains for microorganisms are not indicated when the clinical diagnosis is a chalazion, and the histological features are compatible with that diagnosis. Chalazia arising from the meibomian glands may rupture into the conjunctival substantia propria or involve the dermis. Chalazia developing from a gland of Zeiss usually remain localized to the eyelid margin.

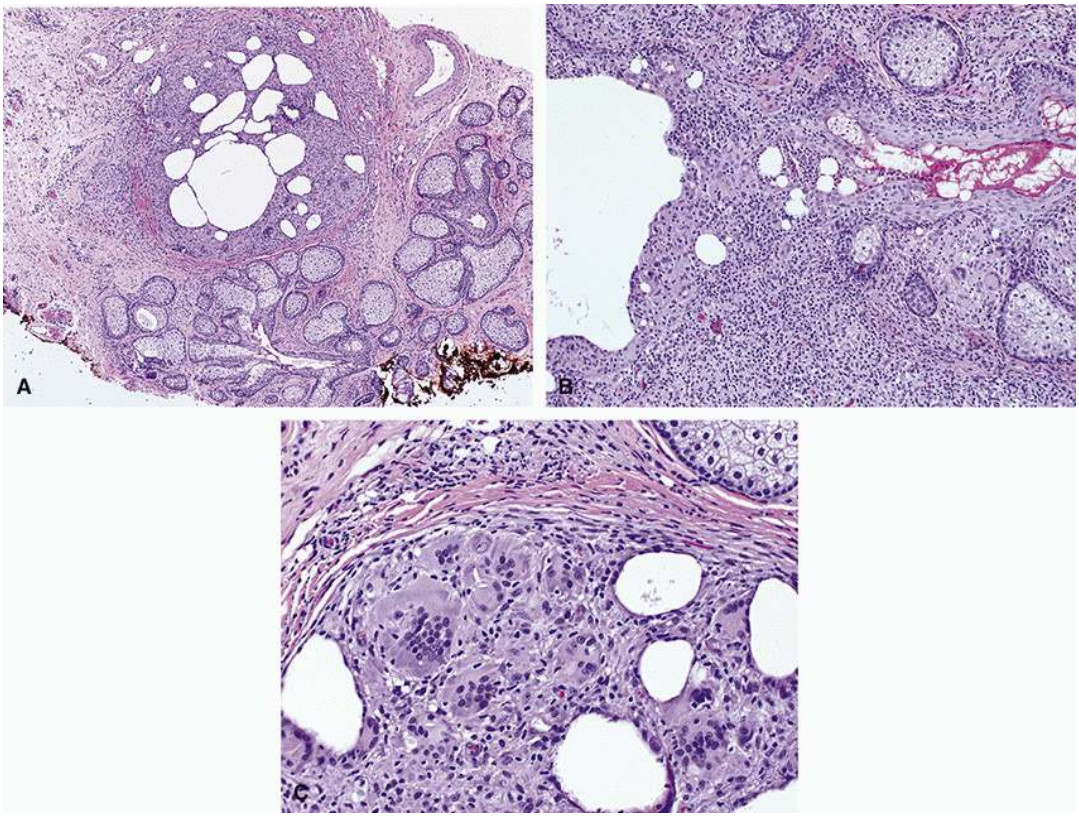

FIGURE 55.3 A, Deep chalazion featuring a lipogranuloma with many large vacuoles of dissolved lipid in the connective tissue adjacent to the tarsal meibomian glands. B, In a histological section adjacent to that in (A), the lipogranulomatous inflammation is in continuity with a meibomian duct, and lipogranulomatous inflammation has replaced the glands that would normally be present in this area. The inflammatory infiltrate contains many epithelioid cells, a few multinucleated giant cells, and lymphocytes and plasma cells. C, Foreign body giant cells, such as those in this photomicrograph, are the most common multinucleated giant cells seen in chalazia. Giant cells engulf the lipid

droplets.

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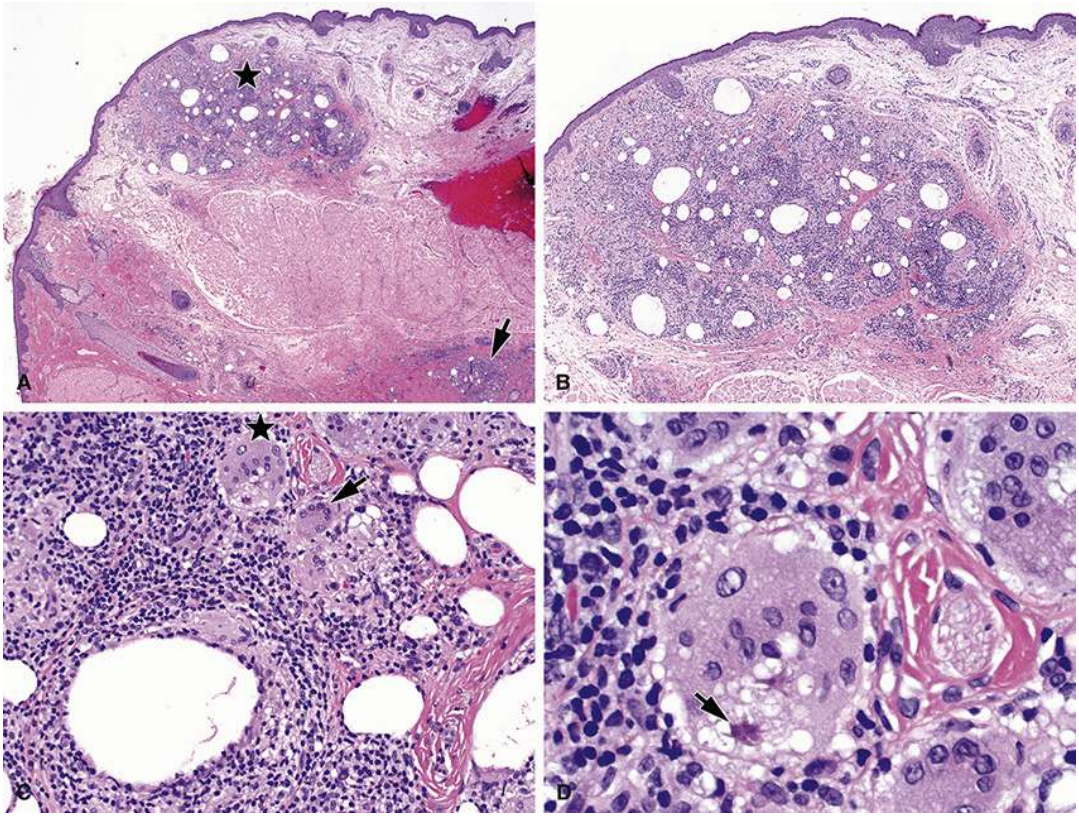

FIGURE 55.4 This full-thickness left upper eyelid resection was from an older woman with multiple recurrences of chalazia. A, The eyelid had both a superficial chalazion arising from glands of Zeiss (★) and a deep chalazion arising from meibomian glands (arrow). B, The superficial chalazion has abundant variably-sized vacuoles of dissolved lipid surrounded by lipogranulomatous inflammation. C, The lipogranulomatous response features epithelioid cells with light pink cytoplasm, Langhans (arrow), and foreign body (★) giant cells, dissolved lipid droplets, and interspersed lymphocytes, plasma cells, and macrophages. D, This multinucleated foreign body giant cell contains dissolved lipid droplets and a prominent asteroid body (arrow). Asteroid bodies are stellate or star-shaped eosinophilic cytoplasmic inclusions within multinucleated giant cells. In our experience, they are seen uncommonly in chalazia.

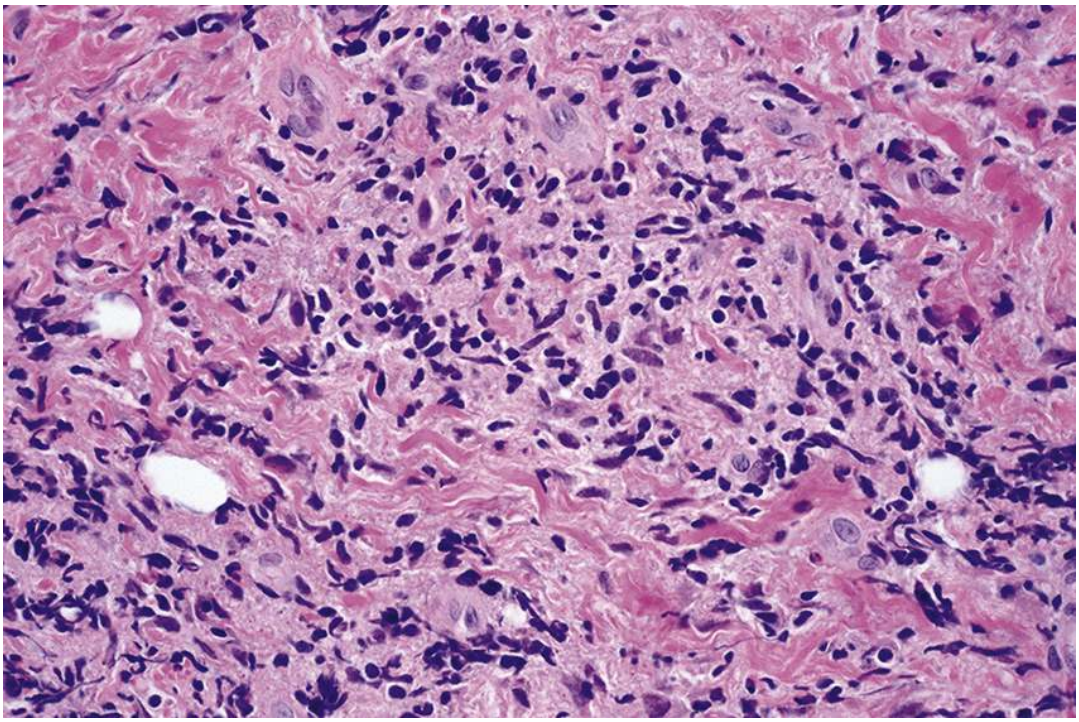

FIGURE 55.5 This chronic chalazion has ill-defined granulomas with prominent fibrosis and absent giant cells.

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CHAPTER 56

Comedones

Key Points

- A comedo is a skin condition that occurs when a dilated pilosebaceous orifice is clogged by a keratotic plug and sebum
- They may be open (blackheads) or closed (whiteheads)
- Comedones in the periocular region are either single lesions (dilated pore of Winer/single giant comedo) or multiple lesions (nevus comedonicus and Favre-Racouchot syndrome)
- Nevus comedonicus is an adnexal hamartoma associated with a somatic mutation in the *NEK9* gene
- Smoking and excessive sun exposure are the predisposing factors leading to the development of Favre-Racouchot syndrome
- Nevus comedonicus is extremely rare, while the Favre-Racouchot syndrome is fairly common
- A dilated pore of Winer is considered a solitary form of nevus comedonicus that is architecturally simpler
- Most cases of nevus comedonicus are observed at birth, or before the age of 10 years, while the presentation of Favre-Racouchot syndrome is delayed (middle-age to elderly in males)
- Favre-Racouchot syndrome is hallmarked by signs of severe actinic damage to the skin, while the characteristic finding in nevus comedonicus is that the lesions are grouped in a linear pattern along Blaschko lines
- The main indication for surgery is cosmetic rehabilitation
- Simple curettage with a comedo extractor may lead to recurrence; complete excision of the infundibular lining is definitive

A comedo (plural, comedones) is a skin condition that occurs when a dilated pilosebaceous orifice is clogged by a keratotic plug and sebum. It manifests clinically as a small pit with a raised edge and a crater filled with keratin.[1,2,3,4,5,6,7,8,9,10] Follicular retention cysts occur as a result of plugging of the follicular orifices. If these open directly into the surface of the skin, they are called open comedones or blackheads; but if they have a blocked or sealed outer surface, they are termed closed comedones or whiteheads.[1,2,3,4,5,6,7,8,9,10]

Comedones are a type of skin lesion, not a single disease entity.[10] Their presence is a manifestation of several dermatologic conditions including acne vulgaris, comedonal acne, hidradenitis suppurativa, discoid lupus erythematosus, seborrheic keratosis, nevus comedonicus (NC), epidermal inclusion cysts, Favre-Racouchot syndrome (FRS), chloracne, and the dilated pore of Winer.[1,2,3,4,5,6,7,8,9,10,11,12,13,14,15] Although a comedo is the primary lesion of acne vulgaris and is central in the pathogenesis of this adolescent disease, acne vulgaris tends to spare the eyelids.[11,13] However, comedones may still be observed in the periocular region, more commonly as multiple lesions (NC or FRS), or rarely as a single lesion (dilated pore of Winer/giant comedo).

During the final decade of the 19th century (1895-1896), NC was independently described by three different researchers (Kofmann, Selhorst, and Thibierge), and it was originally known as comedo-nevus, a term which is still occasionally encountered in the literature.[8,14] FRS is known by several alternative names, such as senile comedones, giant comedones, solar comedones, or more accurately nodular cutaneous elastosis with cysts and comedones.[7] It was first described in 1932 by Favre and later reviewed in detail by Favre and Racouchot in 1951.[7] The syndrome is a ubiquitous condition, far more common than NC, and classically involves the periorbital region. Nevertheless, the condition is not widely recognized by ophthalmologists.[12] The dilated pore of Winer was described for the first time in 1954.[15]

Another confusing term frequently encountered in the literature is giant comedones. This is a descriptive term that is simply related

to the size of a comedo lesion and merely denotes that a comedo is exceptionally large. It has no specific histopathologic significance and can be associated with multiple dermatologic diseases. In the periocular region, the term is frequently used to describe the dilated pore of Winer, and less frequently the macrocomedones in FRS.

Etiology and Pathogenesis

The microcomedone theory has been the cornerstone of comedogenesis.[11] Because comedones are central to the evolution of acne vulgaris, comedo lesions have been extensively studied in that setting, but it is not entirely implausible to propose that the pathogenetic events during comedogenesis are essentially the same, regardless of whether the final disease is seen with acne vulgaris or any of the other entities observed in the periocular region.[11] A comedo is essentially a disorder of the pilosebaceous unit, and this theory maintains that due to hormonal and other factors, the elemental step in comedogenesis is excessive production *(Print pagebreak 378)* of keratin.[11] The initial keratinizing process usually involves the superficial infundibular region of the hair follicle where follicular hyperkeratinization can plug the orifice. Those keratotic plugs later cause back pressure which may result in the development of cystic dilations, or secondary epidermal inclusion cysts in the "downstream portion of the follicle."[4,9] Of note these intrafollicular retention cysts are not just a collection of keratin, but also contain sebum and occasionally bacteria.[4,11]

NC is an uncommon skin lesion characterized by the aggregation of dilated follicular orifices filled with keratinous material (comedones). There are approximately 200 reported cases in the literature, but the exact etiology is unknown.[4,16] It is either categorized as a congenital hair follicle deformity (a hamartomatous malformation caused by an imperfect development of the folliculosebaceous unit) or as an epidermal nevus involving the hair follicle.[4,6] Genetic evidence is more in favor of an adnexal hamartomatous origin because the somatic mutation that has been observed in association with NC occurs in the *NEK9* gene, a gene that is believed to be involved in follicular homeostasis.[6,13] The epithelial-lined invaginations which are destined to form mature terminal hairs and sebaceous glands are incapable of performing such a task, and instead accumulate a soft cornified ostial product resulting in a comedo-like plug.[6,13,14] Abnormalities in FGFR2 signaling have also been implicated in comedogenesis in NC patients, as well as in the subsequent inflammation that frequently occurs with these lesions. Mouse models have demonstrated that FGFR2 is also necessary for skin and hair follicle homeostasis and in the regulation of cutaneous inflammation.[13,17]

Several theories have been put forward in trying to elucidate the etiology of FRS. Possible predisposing causes include extensive sun exposure and ultraviolet damage (UV-B, or UV-A 1), smoking, radiation therapy, and topical or systemic steroids.[4,12]

The exact pathogenesis of a dilated pore of Winer is controversial. Whether it represents a variant of an infundibular cyst that has ruptured with ensuing inflammation, followed by induction of scar tissue formation and fibrosis, or whether it is a true neoplasm (infundibuloma) remains to be determined.[8,15] Nevertheless, the dilated pore of Winer is considered by some authorities to be an architecturally simpler, solitary form of NC, with a single, large dilated infundibulum filled with keratin.[4,15]

Clinical Presentation

In patients with NC, half of the cases are congenital while the other half develops the disease before the age of 10 years. Acquired NC cases have rarely been reported in association with trauma, irritation, or systemic disease. Nevertheless, the clinical presentation of congenital NC may be delayed because of the benign nonprogressive nature of these lesions.[2,4] On the other hand, FRS arises in middle-aged or elderly individuals.

While NC is a rare condition with a prevalence of 1/45,000 to 1/100,000,[18] FRS is far more common. It has an overall prevalence of 1.4% in adults aged between 25 and 74 years, a 6% prevalence in patients aged between 40 and 60 years, and a prevalence of 2.5% among agricultural workers regardless of age.[12,19,20]

There is no racial predilection for all three comedo conditions. FRS is common in males because of obvious occupational reasons, while the dilated pore of Winer is more common in females.[7,15] Except for a chronic history of sun exposure or smoking in patients with FRS, the history is generally unremarkable, although some patients may report that the lesions itch or cause discomfort.[7] NC is predominantly a unilateral condition, but bilateral cases have been described. FRS is usually distributed bilaterally, although the distribution may be asymmetric if one side of the face is asymmetrically exposed to the sun.[7,8,12] Comedones may either be of the open variety (blackheads) which are creamy papules or cysts with a central or eccentric crater filled with gray or black material which can be easily expressed or extracted, or the closed variety (whiteheads) which are skin-colored papules that cannot be expressed or extracted and need to be punctured to remove the contents.[1,2,3,4,5,6,7,8,9,10]

The typical appearance of comedones in patients with FRS is the presence of bilateral discrete follicular orifices plugged by keratotic material, which usually occur in groups or clusters of variably sized nodules with an elevated margin and an eccentric opening or pore predominantly filled with black material (blackheads).[12,21] The disease has a predilection for the lateral canthal region, and the lesions are usually clustered in the lateral part of the upper or lower eyelids,[21] but the malar eminence is usually

involved as well. Any part of the eyelid, as well as the infrabrow region, may be involved, and not just the lateral part (Figure 56.1). The surrounding skin usually shows classic unmistakable signs of severe actinic damage such as yellowish skin discoloration and severe wrinkling.[4,12]

The comedones in patients with NC are usually unilateral, and they are arranged in a linear array (linear streaks) composed of clusters of dilated follicular ostia containing pigmented, cornified material (open or closed comedones). These linear arrays generally follow Blaschko lines which are the lines that are thought to map the pattern of migration of epidermal cells during fetal development. Lesions also commonly involve the malar and temporal areas (Figure 56.2).[3,4,14] Because the condition is usually congenital, the typical age of presentation in patients with NC is in the first decade of life. However, in most published case reports of eyelid NC, the presentation was in the seventh or eighth decades, the condition was mostly bilateral, and the lesions did not display a clean-cut grouped linear configuration observed elsewhere in the body.[4,22,23] Although the diagnosis of NC was confirmed clinically and histopathologically in one of these cases,[4] the attendant figures in the other case reports possibly suggest an alternative diagnosis of FRS.[22,23,24]

(Print pagebreak 379)

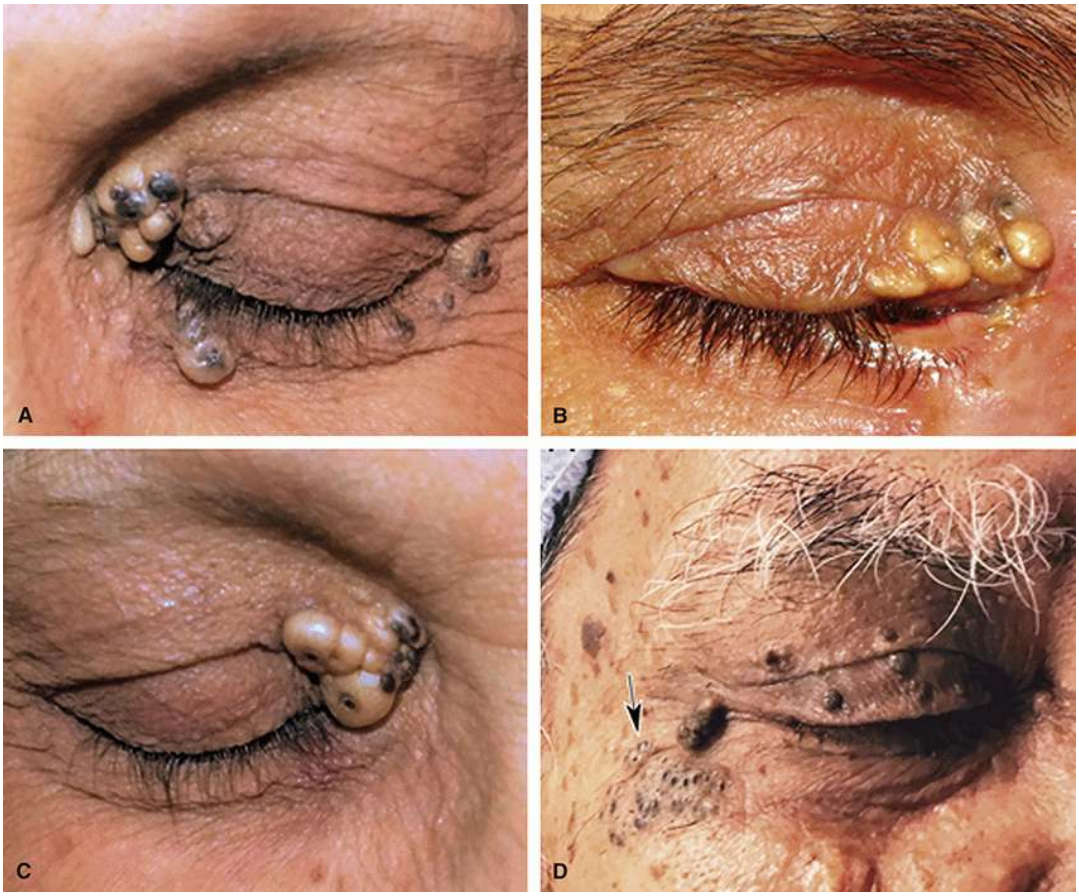

FIGURE 56.1 Favre-Racouchot syndrome. A, Large comedones involving the medial and lateral canthal regions. B and C, Medial canthal comedones. D, Dark comedones in the lateral canthal region.

Although FRS is a ubiquitous condition that predominantly affects the periocular region, it is underappreciated in the ophthalmic literature, and some patients with FRS may be misdiagnosed as NC. Both FRS and NC can easily be differentiated from each other by the age of onset, the typical arrangement of NC lesions in a linear streak pattern, which in its classical form has a striking appearance,[25] and by the physical appearance of the facial skin in patients with FRS.[4] As previously noted, the actinic skin damage in patients with FRS is so severe that the skin acquires a yellowish hue and may become variably hyperpigmented, with multiple nodules and extensive wrinkling.[4] Ptosis and ectropion may be observed when the eyelid comedones are large and/or multiple.[22]

A solitary giant or macrocomedo is better classified as a dilated pore of Winer.[3,4,15] A dilated pore usually occurs as a single white creamy papular or cystic, markedly dilated giant comedo, with sharply defined margins and a central black core (blackhead) which usually involves the thicker skin of the face, but is less commonly observed in the periocular region (Figure 56.3).[5,26,27,28] When the keratin contents are expressed from the dilated pore, a residual groove or a pit-like structure is observed on the skin.[5,27,28] The rarity of the condition in the periocular region may be attributed to the thinness of the eyelid skin.[26]

The general physical and ocular examination in patients with a dilated pore and FRS are usually normal, which contrasts with patients with NC where local and systemic associations (usually hereditary) have been reported. Local ocular conditions that may be observed with NC include congenital cataracts.[2,29] Because NC is extremely rare and because its co-occurrence with cataracts is even rarer, it is unclear at the present moment whether there is a causal association between both conditions or whether this is an accidental *(Print pagebreak 380)* finding. The frequently cited temporal developmental association between the hair follicle and the lens anlagen[4,29] is an unlikely explanation, because lens development (week 5, 31-35 days, 5-7 mm stage) precedes the very first indication of eyelid development (week 6, 37-42 days, 8-11 mm stage). Furthermore, eyelash follicle anlagen are not observed until much later during week 11.[30] Therefore, the claim that a shared genetic hit has affected both tissue anlagen at the same time is difficult to fathom.[4,29]

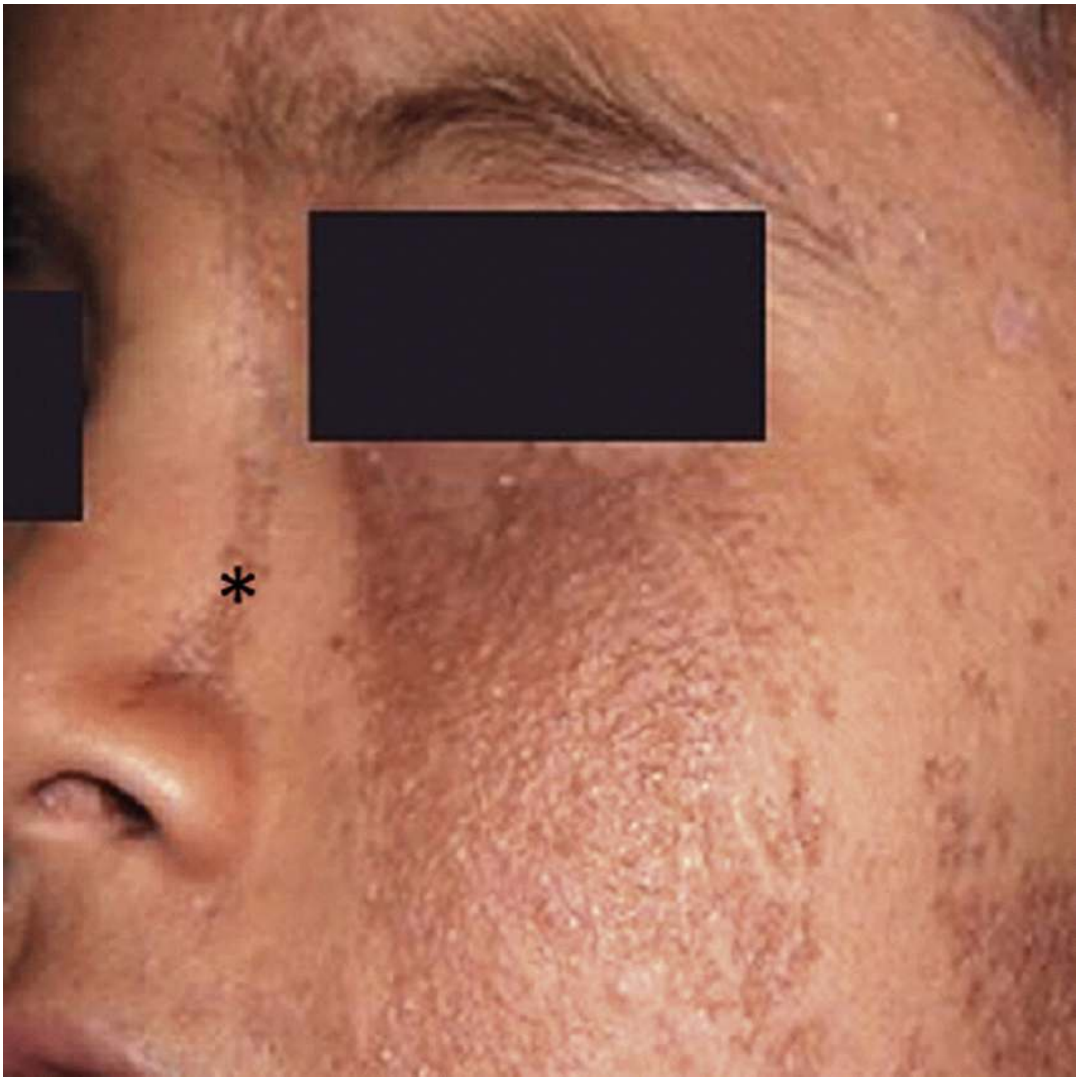

FIGURE 56.2 Nevus comedonicus with unilateral comedones arranged in linear streaks which follow Blaschko lines (asterisk). (Reprinted from Pavithra S, et al. Nevus comedonicus syndrome. *Indian J Dermatol*. 2011; 56(2):771-772. © Indian Journal of Dermatology. CC BY-SA 3.0.)

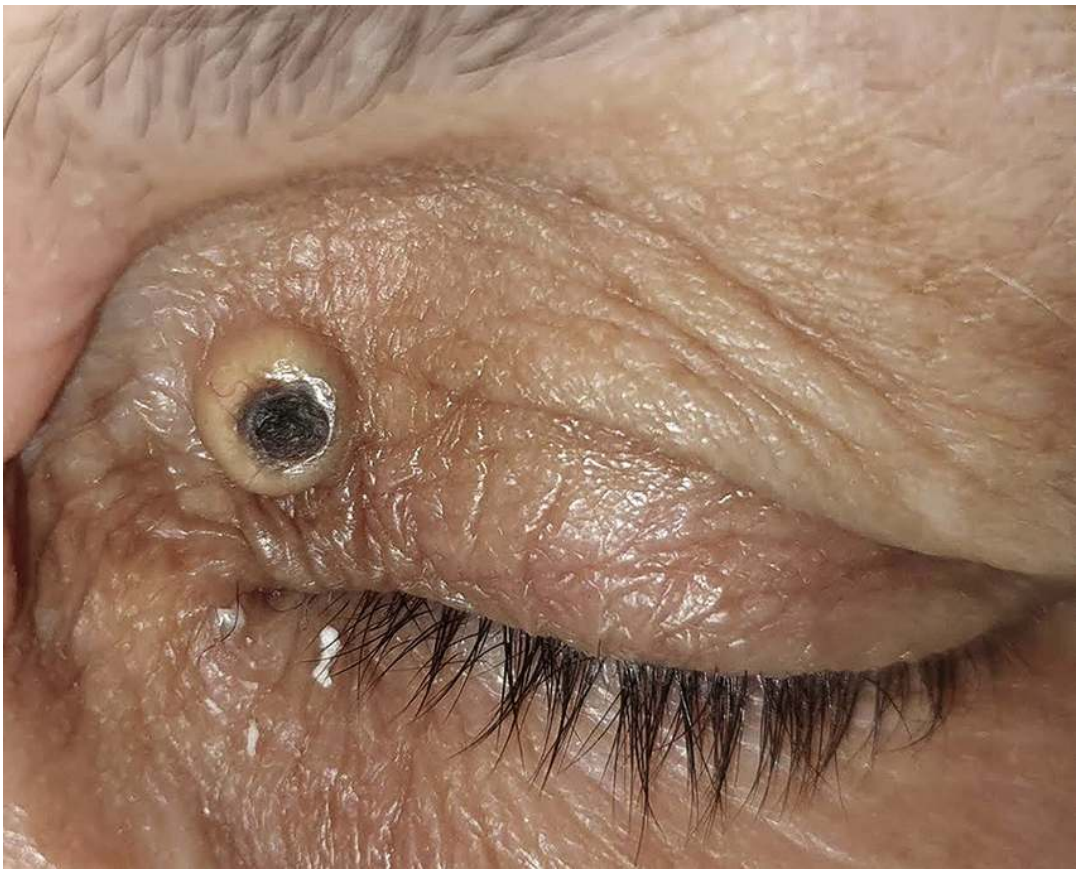

FIGURE 56.3 A solitary giant or macrocomedo (dilated pore of Winer) presenting as a single white, markedly dilated giant comedo, with sharply defined margins and a central black core (blackhead).

Systemic associations, sometimes referred to as nevus comedonicus syndrome, include vascular abnormalities (Sturge-Weber syndrome, extensive vascular nevi, Alagille syndrome), cerebral anomalies (brain dysgenesis, microcephaly), skeletal abnormalities (spinal dysraphism, syndactyly, adactyly, polydactyly, clinodactyly), and endocrine disorders (hypothyroidism), as well as other skin lesions such as depigmented hairs, Becker nevus, epidermal nevus, basal cell carcinoma (BCC), squamous cell carcinoma, or nevus sebaceus of Jadassohn. It should be noted that some of these syndromic associations overlap with the syndromic associations of an epidermal nevus,[4] which led some authors to suggest that NC is nothing more than an epidermal nevus that affects the folliculosebaceous unit.[14]

Differential Diagnosis

Many cutaneous lesions present with comedones and should be differentiated from FRS and NC, but most of these entities are not frequently observed in the periocular region. Because of the peculiar clinical appearance of comedones, the diagnosis is usually a spot diagnosis and can easily be made with little difficulty. The main problem does not lie in diagnosing a comedo as such, but in discerning NC from the FRS.

Entities that may be considered in the differential diagnosis include cutaneous keratinous cysts, sebaceous cysts, seborrheic keratosis, acanthosis nigricans, or trichoadenoma.[4,5,26] Cutaneous cysts in the periorbital region can originate from dermal adnexal elements such as sweat glands or hair follicles. Several types of keratinous cysts, such as epidermal inclusion cyst, epidermoid cyst, trichilemmal cyst, and hybrid cysts, can only be distinguished histopathologically and are difficult to differentiate by clinical examination alone.

A solitary comedo (dilated pore of Winer) should always be differentiated from pilar sheath acanthoma (infundibuloisthmicoma), trichoadenoma which is a benign and rare cutaneous tumor of the hair follicle that can simulate a comedo head, as well as a trichoepithelioma. A more important entity to consider in the periocular region is a large-pore BCC.[3,19]

Treatment

In patients with FRS, treatment is generally recommended for esthetic reasons.[12] When discussing therapeutic options, three main components should be addressed: (1) the presence of large disfiguring open comedones, (2) secondary bacterial infection which may complicate those lesions, and (3) the photodamaged skin surrounding the lesion.[6,12]

Because topical retinoids inhibit comedogenesis, and because they provide the extra benefit of addressing photodamaged skin, they are the mainstay of therapy for FRS.[12,31] Of note is that these agents are not very effective in larger or deeper lesions[12] and may cause severe irritation to the thin skin of the eyelid. They are better tolerated in areas *(Print pagebreak 381)* with thick skin like the infrabrow region or in the malar area.[12,31] Therefore, in the eyelid skin, surgical excision of the comedones may be considered the mainstay of therapy, although aggressive treatment or major reconstruction is not advised because comedones are essentially benign conditions.

The most common approach is the expression of the comedones with a comedo extractor. This simple evacuation/curettage procedure of the keratin plug may not be an adequate approach because the lesion may recur due to the residual infundibular lining, or it may develop a secondary infection. Furthermore, the chance for histologic confirmation of the benign nature of the condition is lost.[12] A comedo extractor or expressor is a metal instrument with a small cup-shaped end and a smaller hole in the center, which is frequently used by dermatologists. Therefore complete surgical excision of the infundibular lining coupled with expression of the contents is preferable.[12] Cosmetic treatment for the postinflammatory scarring might also be required. In some cases, it might be necessary to address associated complications such as secondary infection or abscess formation with the use of antibiotics.[6,12] Other treatment options include systemic retinoids combined with topical retinoids, steroids for their anti-inflammatory action, salicylic acid, or 12% ammonium lactate.[6,12] Referral to dermatology may be indicated to assess and address the photodamaged skin.

In patients with a solitary giant comedo/dilated pore, complete excision of the lesion is indicated for histopathologic confirmation.[27] NC is more difficult to remove than the comedones associated with FRS or the dilated pore of Winer because the majority of these lesions are resistant to almost any type of medical treatment. Complete surgical excision may not be practical as it may require a skin graft or even tissue expanders.[2,4,12,32] Manual comedo extraction, dermabrasion, or the use of keratolytic agents may help, but they are of limited therapeutic value.[2]

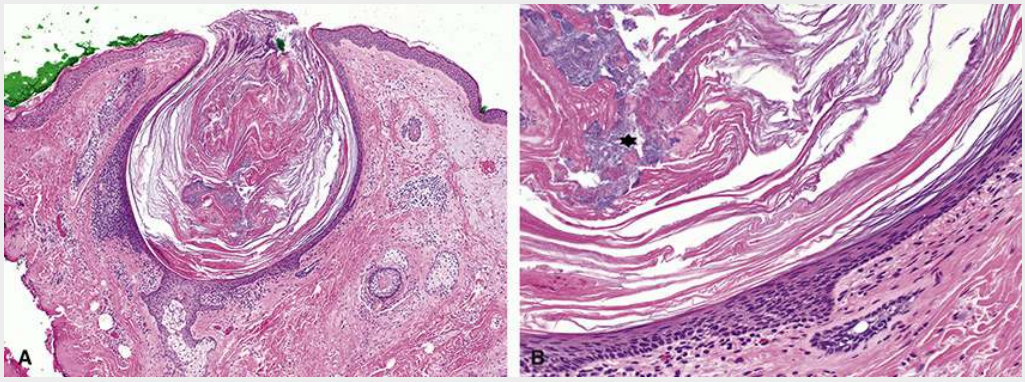

FIGURE 56.4 A, This open comedone shows a follicular infundibulum distended by keratin, which protrudes from the orifice. Green ink was used for orientation and is present on the epidermal surface. B, The comedone is lined by stratified squamous epithelium having an inconspicuous granular cell layer. Colonies of *Cutibacterium acnes* are present among the keratin and appear as basophilic particles (★).

Prognosis

From a medical and functional perspective, comedones are inconsequential benign conditions, but surgery which is generally indicated for cosmetic reasons is still preferred because spontaneous resolution has not been described, and because if left untreated, patients (particularly those with NC) may show signs of residual scarring due to recurrent episodes of rupture and inflammation.[2,6,14]

Histopathology

Comedones begin in the infrainfundibulum of sebaceous follicles, which accounts for the deeper four-fifths of the sebaceous follicle infundibulum; it is lined by stratified squamous epithelium having an inconspicuous granular cell layer and a layer of two or three horn cells that have indistinct outlines and stain weakly with eosin.[33] The initial phase of comedone formation manifests

histologically as a more prominent granular cell layer and more distinct and cohesive horny cells that form a dense eosinophilic horn.[33] Microcolonies of *Cutibacterium acnes* are evident at this stage.[33] A microcomedone forms when sufficient horn cells stick together to impact the infundibulum and distend the lumen. A closed comedone results when horn cell (keratin) accumulation distends the lumen to about 1 mm.[33] The pore of closed comedones is challenging to see without serial histological sections due to its microscopic size.[33] An open comedone is formed as more keratin accumulates, the epithelial lining thins to three or four layers, and the pore dilates with protrusion of keratin through the orifice (Figure 56.4A).[33] Colonies of *C. acnes* increase as comedones progress through their development (Figure 56.4B).[33] One or two hairs are typically found in closed comedones, while the number of hairs in open comedones is directly proportional to their size, with as many as 16 in large comedones.[33] Comedone *(Print pagebreak 382)* rupture releases lipids and keratin, inciting inflammation in the perifollicular dermis.[34] Comedone rupture may result from distention or dermal lymphocytes infiltrating and disrupting the duct wall with subsequent neutrophil accrual.[35] The histological appearance of closed and open comedones in Favre-Racouchot disease is the same as in acne vulgaris.[36]

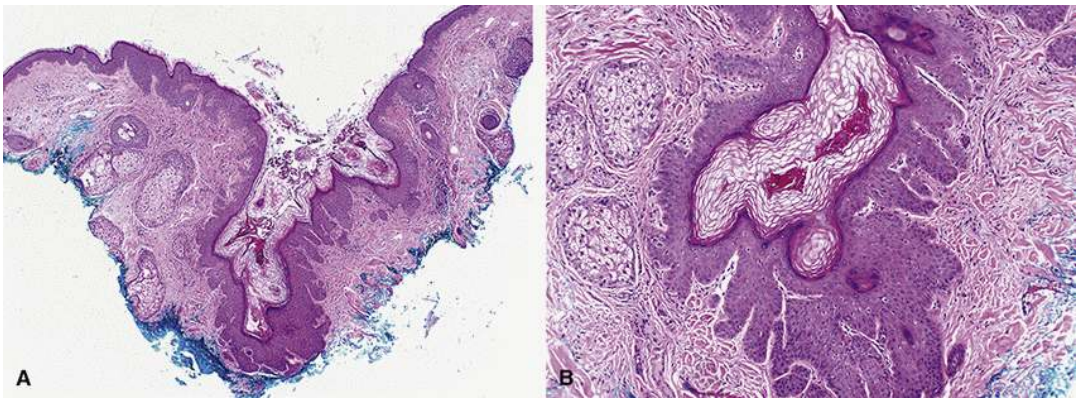

FIGURE 56.5 A, A dilated pore of Winer histologically appears as a keratin-plugged, cystically dilated hair follicle. Acanthotic stratified squamous epithelium lines the dilated pore and forms irregular projections into the adjacent dermis. B, Lamellae of keratin occupy the cystically dilated hair follicle. Irregular budding of the epithelium into the adjacent dermis is characteristic of dilated pores.

A dilated pore of Winer presents clinically as a large comedone and histologically appears as a keratin-plugged, cystically dilated hair follicle (Figure 56.5A).[37] Acanthotic stratified squamous epithelium lines the dilated pore and forms irregular projections into the adjacent dermis (Figure 56.5B).[37]

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CHAPTER 57

Cutaneous Horn

Key Points

- A cutaneous horn is a firm, variably pigmented, conical projection composed of compacted keratin
- They may arise on top of benign, premalignant, or malignant skin lesions
- The pathogenesis is unknown but is related to an abnormality in the spinous layer of the epidermis resulting in excessive production and accumulation of keratin
- They usually appear as a solitary, hard, conical, white, brown, gray, or yellow mass clinically obscuring the underlying pathology
- The recommended treatment is excisional biopsy along with wide local excision of the base of the lesion
- Prognosis depends upon the underlying lesion, especially when malignant, and the presence of the horn is not a predictor of the malignant potential of the lesion

A cutaneous horn, or keratin horn (cornu cutaneum), is a firm to hard, variably pigmented, conical projection that arises from the surface of the eyelid skin and is composed of compacted keratin.[1,2,3,4,5,6,7,8] They earned their name due to their similarity with animal horns, although in contrast to their animal counterpart, human cutaneous horns do not possess a bony core.[8] To earn its designation as a horn, the height of the horn should exceed at least one-half of its greatest diameter.[2] These lesions may arise on top of benign, premalignant, or malignant skin conditions; accordingly, a cutaneous horn is not a distinct pathologic diagnosis or entity but rather a morphologic description.[4]

Etiology and Pathogenesis

The exact causes leading to the development of a cutaneous horn are still unknown, but radiation damage, chronic sun exposure, xeroderma pigmentosa, chronic skin irritation, or a human papilloma virus-2 infection are possible risk factors.[4,8] Other possibly associated conditions include a history of a skin malignancy elsewhere in the body or a history of systemic malignancies like renal cell carcinoma or Paget disease of the breast.[1] Regardless of the exact predisposing factors, a cutaneous horn results when an abnormality in the spinous layer of the epidermis results in excessive production and accumulation of keratin.[4]

Clinical Presentation

Cutaneous horns may affect any race, age, or sex and can occur anywhere in the body. However, they are more common on sun-exposed areas of elderly fair-skinned men older than 50 years.[4,5,6] On the eyelids, cutaneous horns rarely exceed several millimeters in length (height), although elsewhere in the body they may reach up to several centimeters.[1,3] They have a predilection for the face, ears, the dorsum of the hands, or the penis, but eyelid involvement is infrequent, representing a mere 4% of all surgically excised eyelid neoplasms in one recent study that spanned 10 years.[6] To the best of our knowledge, only three case series about cutaneous horns exist in the literature, which also underlies the rarity of the condition.[1,4,6] The mean age at presentation is during the seventh decade, but females may present at an earlier age (6th decade). The condition is rare before the age of 40 years, but cases have been reported in the eyelids as early as 6 years of age.[5,6]

Cutaneous horns are usually solitary but rarely may be multiple, particularly in patients with compromised immunity.[1,4] The upper eyelid is more commonly involved than the lower, and the lateral canthus may be involved as well. Lesions involving the eyelid margin are rare.[6] Eyelid cutaneous horns average between 0.7 and 0.8 mm in height, but can be larger and rarely exceed 2 cm.[4,6] Cutaneous horns are typically conical in shape but may take many other forms such as pipe-shaped, cylindrical, lobulated, pointed, or trident or they can have an incurved form (Figure 57.1).[4,6] The outer surface of a cutaneous horn may be papillomatous,

irregular, verrucous, or smooth and its color may be white, brown, gray, yellow, or tan (Figure 57.2).[4] The majority of underlying conditions are benign, but premalignant and malignant lesions combined represent between 25% and 36% of the examined specimens.[1,6] Although cutaneous horns predominantly involve the eyelids, other rare periocular locations such as the surface of the globe, the skin overlying the lacrimal sac, and the brow are reported.[4,8,9]

Differential Diagnosis

The clinical diagnosis of a keratin horn is straightforward, but the real challenge is establishing the nature of the underlying lesion. Cutaneous horns may be associated with many different pathologic conditions. Benign lesions include seborrheic keratosis, trichilemmoma, verruca vulgaris, squamous *(Print pagebreak 385)* papilloma, inverted follicular keratosis, chalazia, pilomatricoma, lichen simplex chronicus, angiokeratoma, pyogenic granuloma, nevus sebaceus of Jadassohn, pseudoepitheliomatous hyperplasia, epidermal cyst, or even a dermoid cyst.[1,3,4,6] Premalignant conditions include actinic keratosis, radiodermatitis, keratoacanthoma, or Bowen disease (squamous cell carcinoma in situ),[1,4,6,7] whereas underlying malignant conditions include squamous cell carcinoma, basal cell carcinoma, sebaceous carcinoma, or malignant melanoma.[1,4,6,10,11,12,13] Squamous cell carcinoma is by far the most common malignant entity associated with a cutaneous horn.[1]

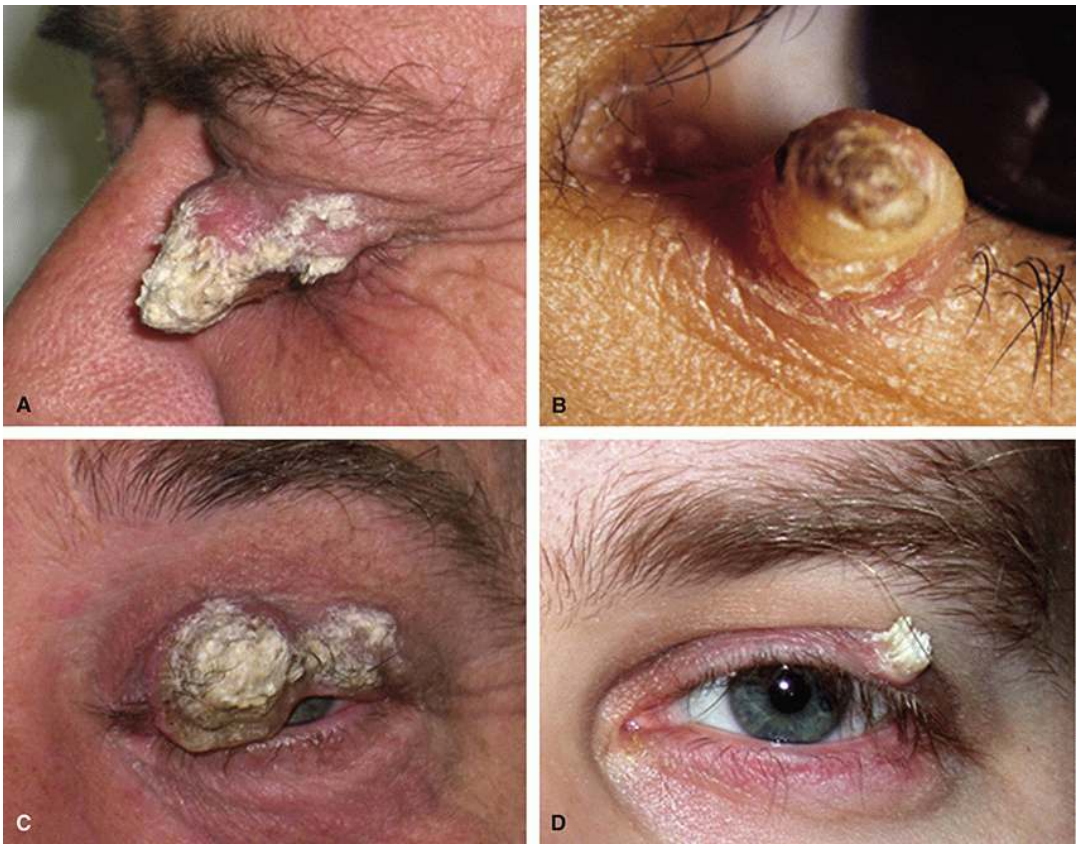

FIGURE 57.1 Various shapes of eyelid cutaneous horns. A, Conical horn. B, Nodular shape overlying the lacrimal punctum. C, Multiple lobular cutaneous horns. D, Filiform horn. (Courtesy of Dr. Charles Soparkar.)

Of note is that any eyelid skin lesion with an overlying hematic or fibrinous crust may simulate a cutaneous horn, and it may difficult to establish a diagnosis on clinical grounds alone, therefore histopathology is always required.[8]

Treatment

In the past, the standard treatment of cutaneous horns was scraping of the lesion, followed by cautery or cryotherapy of the base. However, because the risk of an associated malignancy is real and there are no defining features in the horn that can predict the malignant potential of the underlying lesion, the practice of scraping and cryotherapy should be avoided.[1] Currently, the recommended treatment is excisional biopsy of the horn along with wide local excision of the base of the lesion with a tumor-free margin of at least 3 mm.[6] Both the lesion and its base should be submitted to histopathology because the horn itself is usually benign as it is composed of dead keratin, but the relevant pathology lies in the base of the horn, where the underlying disease exists.[5,6]

(Print pagebreak 386)

FIGURE 57.2 The spectrum of surface characteristics of eyelid cutaneous horns. A, Rugose surface. B, Crusted surface. (Courtesy of Dr. Robert Goldberg.) C, Pigmented horn. (Courtesy of Dr. Charles Soparkar.) D, Irregular keratinous horn. (Courtesy of Dr. Robert Goldberg.)

Prognosis

There are no peculiar clinical features that readily and reliably distinguish between an underlying benign, premalignant, or a malignant condition,[1,8] although there are some suggestive ominous signs that may be indicators of malignancy. These include a wide basal diameter, a low height-to-base ratio, an older age at presentation, bleeding, significant pain or tenderness, and lesions with a large, or red erythematous base.[1,3,4,6] It appears that the diameter of the base of the lesion is more predictive of malignancy than the height of the cutaneous horn.[6] It should be noted that when a cutaneous horn is associated with an underlying malignant condition like squamous cell carcinoma, the mere presence of the horn is not a negative or positive predictor of the malignant potential of the lesion, although in general, keratin horns may be more prevalent in patients with well-differentiated squamous cell carcinomas.[14]

Histopathology

Cutaneous horns have a layer of amorphous or lamellated keratin over an epidermal abnormality from which the horn arises (Figures 57.3 and 57.4).[3] The nature of the underlying epidermal abnormalities is shown in Table 57.1, which summarizes the histopathological data from the three published series of eyelid cutaneous horns.[1,4,6] Benign lesions are more frequent causes of cutaneous horns of the eyelid (69.8%) than premalignant lesions (19.8%), while malignant lesions are the least common (10.5%). The most common benign eyelid lesions giving rise to a cutaneous horn were seborrheic keratosis (Figure 57.2), *(Print pagebreak 387) (Print pagebreak 388)* followed closely by squamous papillomas (acrochordons) and epidermal hyperplasia (defined by Mencia-Gutiérrez and coworkers as thickened epidermis without cellular atypia[6]). Actinic keratoses and squamous cell carcinomas are the predominant premalignant and malignant lesions. The histopathological features of the underlying epidermal lesions and their differential diagnoses are given in their respective chapters.

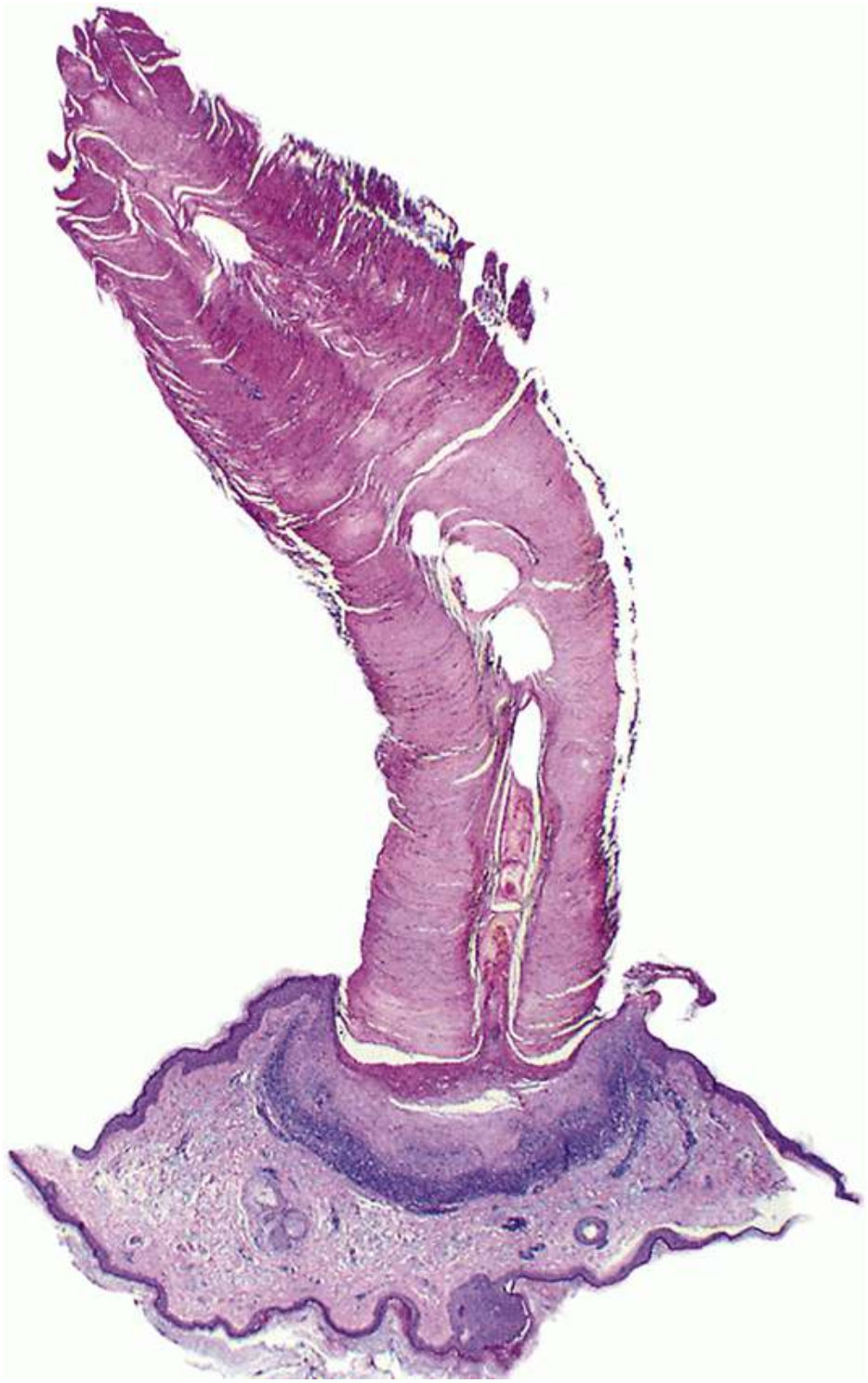

FIGURE 57.3 This cutaneous horn shows a layer of amorphous or lamellated keratin arising over an actinic keratosis.

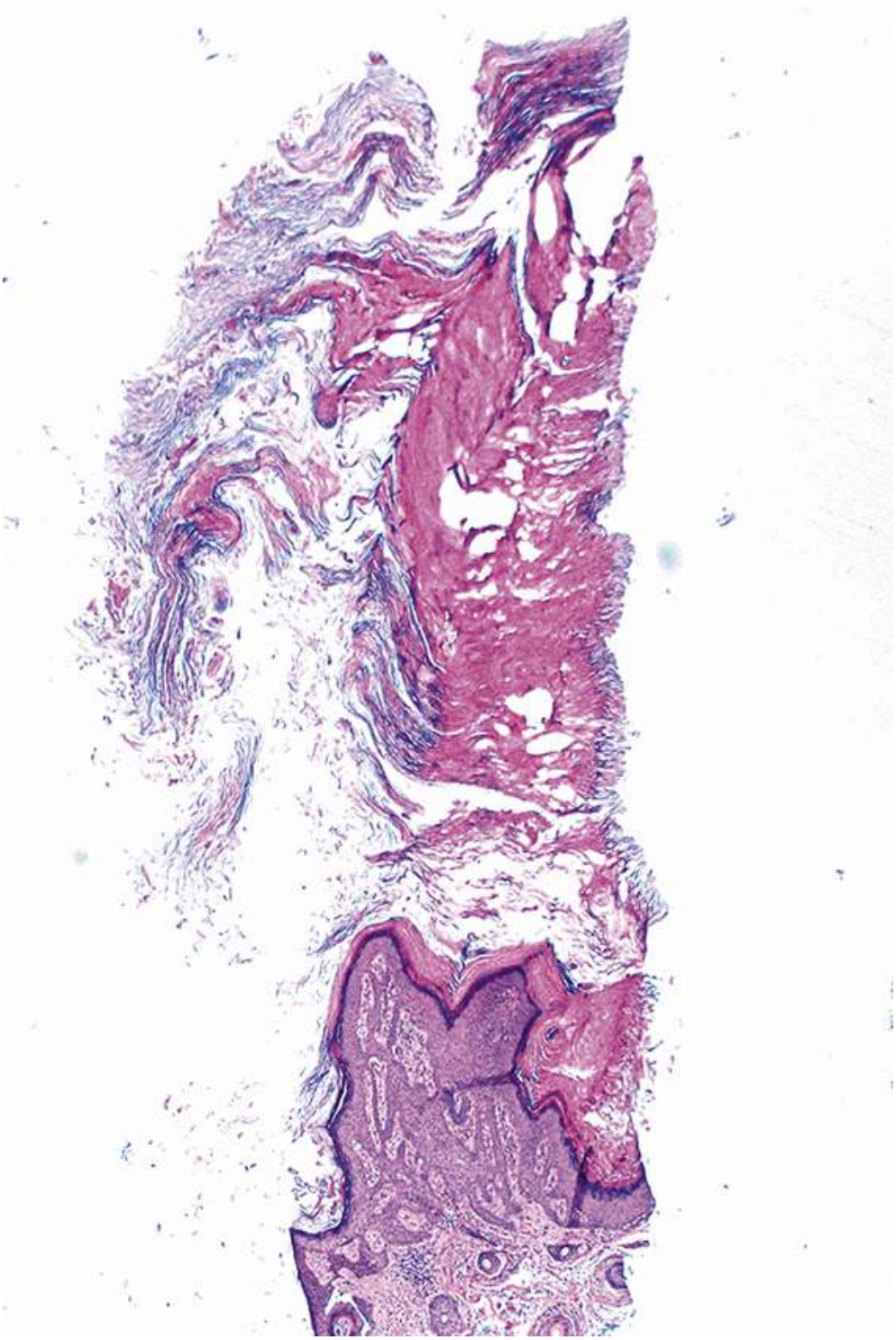

FIGURE 57.4 Cutaneous horn formed over a hyperkeratotic seborrheic keratosis on the right upper eyelid.

TABLE 57.1 Histopathology of Epidermal Abnormalities Associated With Cutaneous Horns

	Mencia-Gutierrez et al[6]	Tambe et al[1]	Pointdujour-lim et al[4]	n	%
Benign					
Seborrheic keratosis	11	6	1	18	20.9
Squamous papilloma	5	8	0	13	15.1
Epidermal hyperplasia	10	1	0	11	12.8
Verruca vulgaris	8	0	0	8	9.3

Inverted follicular keratosis	1	1	2	4	4.7
Chalazion	1	0	0	1	1.2
Pilomatricoma	1	0	0	1	1.2
Dermoid cyst	1	0	0	1	1.2
Pseudoepitheliomatous hyperplasia	0	0	1	1	1.2
Trichilemmoma	0	0	1	1	1.2
Nevus sebaceus of Jadassohn	0	0	1	1	1.2
Premalignant					
Actinic keratosis	5	6	4	15	17.4
Squamous cell carcinoma in situ	0	1	0	1	1.2
Radiodermatitis	1	0	0	1	1.2
Malignant					
Squamous cell carcinoma	2	1	2	5	5.8
Basal cell carcinoma	2	1	0	3	3.5
Sebaceous carcinoma	0	0	1	1	1.2

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CHAPTER 58

Dermoid Cyst

Key Points

- Dermoid cysts are a common developmental cystic choristoma
- Approximately 7% occur in the head and neck most commonly in the periorbital region
- Ninety percent or more of periorbital cases present as a slow-growing, painless, subcutaneous mass in the lateral upper eyelid
- They are rarely reported in the orbit, tarsus, and caruncle
- Rupture of the cyst wall can be from trauma, but more often it is spontaneous, causing intense inflammatory sequelae manifesting as local pain, edema, and erythema
- Dermoid cysts can arise embryologically from sequestration of dermal and epidermal elements along fetal lines of bone closure or facial fusion lines
- Surgical excision with complete removal of the cystic wall without rupture is the gold standard for treatment of a dermoid cyst
- The prognosis following surgical excision of periorbital and orbital dermoid cysts generally is excellent

Dermoid cysts are common cystic lesions that represent a developmental choristoma. They are congenital lesions that enlarge very slowly as they accumulate sebum and keratin. Dermoid cysts can be found in any part of the body. Approximately 7% occur in the head and neck,[1] with the most commonly reported locations being periorbital, nasal, submental, neck, and suprasternal.[2,3,4,5] In a study of the incidence and clinical characteristics of periocular dermoid cysts diagnosed among a population-based cohort of children older than 20 years of age, 54 cases were diagnosed yielding a birth incidence of 1 in 638 live births.[6] The mean age at diagnosis was 15 months (range 1-60 months), and 50% of patients were diagnosed by the age of 1 year. There was no gender predilection. The clinical presentation was a periocular mass, without inflammation or erythema.

In a large series of orbital and periorbital dermoid cysts, Shields et al[5] proposed a classification that included soft-tissue orbital lesions that were mostly of conjunctival origin, sutural dermoids that extended into bony sutures and were immobile, and juxtasutural dermoids near but not into bony sutures. Most of the superficial periorbital lesions were of the latter type. When dermoid cysts are associated with or near periorbital bony sutures, most show growth outward into the eyelid where they present as a palpable mass and are typically noted early in young children. More rarely they may extend inward into the orbit in which case they tend to present later in life, in teens or young adults.

Orbital and periorbital dermoids together represent 35% to 47% of orbital pediatric lesions and 89% of all orbital cystic lesions.[7] In most patients, they present with a prominent extra orbital component, and in 90% to 99% of cases, presentation is with a slow-growing, painless, subcutaneous mass in the eyelid.[4,5,8] Lesions most often occur superotemporally, associated with the frontozygomatic suture at the superolateral orbital rim in 55% to 75% of cases,[4,6,8,9] and less frequently in a superomedial periorbital location within the frontoethmoid or frontonasal sutures. Cysts located deep in the orbit are uncommon, seen in 0.5% to 10% of cases,[5,8] and may present with proptosis, optic nerve compression, or restriction of eye movements.[5,10] In very rare cases, a dermoid cyst can be located within an orbital extraocular muscle and when large can cause visual compromise.[11,12,13] There are also reports of dermoid cysts involving the lacrimal gland and the caruncle.[14,15] A case of tarsal dermoid has also been described.[16]

Rupture of the cyst wall can occur as a result of trauma or can be spontaneous. Cyst rupture can cause intense inflammatory sequelae manifesting as local pain, edema, and erythema.[17] Since most periorbital dermoids are superotemporal, a ruptured cyst may present with a clinical picture of preseptal cellulitis or dacryoadenitis.[18] Very rarely, a dermoid cyst can present with chronic osteomyelitis or with inflammatory symptoms due to bony involvement adjacent to cyst leakage.[19] Clinical or histologic evidence

of spontaneous cyst rupture was identified in a series of 86 cases by Siah et al[17] In that series, the median patient age was 5.5 years (range, 1-63 years). Clinical evidence of rupture was identified in 29 cases (33.7%), and of these, 2 (6.9%) ruptured spontaneously before presentation, and 27 (93.1%) ruptured during surgery. The remaining 57 cases (66.3%) had histologic evidence of subclinical spontaneous rupture. This was consistent with an earlier study by Lane et al[20] who reported that 75% of 40 orbital dermoid cysts had histologic evidence of rupture and inflammation, and Shields et al[5] who reported chronic granulomatous inflammation in the walls of 34% of 197 dermoid cysts.

Imaging of superficial dermoid cysts presenting as a cystic superotemporal eyelid mass, especially when they are mobile, is usually not necessary to make the diagnosis. In *(Print pagebreak 390)* a radiological review of 70 patients with a diagnosis of lateral dermoid cysts, Sathananthan et al[21] showed that in cases where the lesion is both superficial and mobile in all directions, a scan is not required. However, when the cyst is fixed to the underlying bone, and because of the rare occurrence of the cyst extending through a bony suture with a dumbbell configuration and simultaneous masses in the orbit or intracranial compartment, neuroimaging is recommended before any surgical intervention. On computed tomography, a dermoid cyst appears as a round to oval, well-defined cystic lesion.[8,22] The cyst is almost always extraconal and has a cystic center generally with low density in 72% of cases, is usually homogeneous, but occasionally can be heterogeneous depending on the proportions of lipid and keratin content. Denser foci within the cyst represent flecks of keratin and sebum.[8] The cyst cavity is surrounded by a thin rim of tissue density that may have areas of calcification in about 6% of cases.[23] Adjacent bone commonly shows remolding from long-standing pressure, seen in 53% of cases.[8] Contrast administration produces mild enhancement of the cyst rim, but not of the lumen. On magnetic resonance imaging (MRI) T1-weighted sequences, the cyst cavity can be isointense to hypointense to fat and hypointense to muscle because of its water content. In lesions with high fat content, the T1-WI will be hyperintense, closer to that of orbital fat. On T2-weighted sequences, the signal is isointense or hypointense with respect to vitreous and hyperintense to fat. Images may be homogeneous to heterogeneous depending upon the cyst contents. A fat-fluid level is seen in some cases, with the upper lipid layer giving a brighter signal on T1 and a lower signal on T2 relative to the lower water-keratin layer. Calcifications appear as signal voids. With gadolinium, the cyst rim shows moderate enhancement, but the lumen does not enhance. In a series of 280 orbital and periorbital dermoid cysts, Pushker et al[23] reported a fat-fluid level in 24% of cases, and 75% had bone excavation adjacent to the cyst. Of the orbital lesions, 6% were dumbbell-shaped with connection to the temporalis fossa through a defect in the lateral orbital wall.

Etiology and Pathophysiology

Congenital orbitofacial dermoid cysts are thought to derive embryologically from sequestration of dermal and epidermal elements along fetal lines of bone closure.[4,5,8,9,24] They are solitary, or occasionally multiple, hamartomatous tumors that contain fat and adnexal structures including sebaceous glands and hair and are covered by a thick dermis-like wall. In some locations, dermoid cysts may contain nails, teeth, cartilage, and bonelike structures.

It has also been proposed that craniofacial and spinal dermoid cysts develop from congenital malformations resulting from impaired formation of structures along the craniospinal axis due to the failure of surface ectoderm to separate from the neural tube during early embryonic development. This results in the ectopic inclusion of epithelial cells during closure of the neural tube and facial fusion lines.[25] These are referred to as craniospinal dysraphisms, which range in severity from clinically insignificant to lethal. Although they can occur anywhere on the face, scalp, or spinal axis, most commonly they are seen overlying the scalp, the upper lateral region of the forehead, and in the submental region.[26]

Neural tube development occurs during the second to sixth weeks of gestation through a complex process.[27,28,29,30] During primary neurulation, or formation of the brain and spinal cord, the midline notochord induces the overlying ectoderm to differentiate into neuroectoderm. The neural tube separates from the surface ectoderm in a process known as disjunction as the mesoderm migrates between these layers to form the meninges, vertebrae, skull, and paraspinal muscles. The human face develops from five prominences of mesenchyme separated by fusion lines. Union of these prominences occurs between the sixth and the eighth weeks of development and requires the disintegration of their contact with surface epithelium allowing contact of the mesenchymal cells of adjacent prominences. Failure of fusion has been the classic theory for the development of facial clefts,[31,32,33] but it has also been proposed that during this process, dermal inclusions may be trapped between the fusing prominences, particularly within the lateral eyelid fusion line, resulting in dermoid cysts.[3,26,34]

Acquired dermoid cysts in the head and neck region can result from iatrogenic or traumatic implantation of dermal cells that subsequently grow and form uniloculated cysts lined by skin, containing sebaceous glands and hair follicles. They include acquired orbital dermoid cysts of conjunctival origin,[22] dermoid cysts of mucosal origin in the mouth,[35] and dermoids of the auricle from traumatic implantation of skin.

Clinical Presentation

Clinically, superficial dermoid cysts in the eyelid slowly enlarge from the accumulation of keratin and lipid debris and may compress and excavate the adjacent bone as they enlarge.

Superficial dermoids are more readily visible clinically and present at an earlier age than deep orbital lesions. Sherman et al[36] reported that children with superficial dermoids are most often diagnosed in infancy, whereas children with deep orbital dermoids present at a mean age of 18 years.

In a recent study of 115 patients with periorbital dermoid cysts, 44.3% were males,[8] and the mean age at the time of surgery was 39.2 months with a range of 5.6 months to 16.4 years. The right eye was involved in 44.3% of the cases and the left eye in 55.7%. Most of the lesions were superficial (90.4%) and only 9.6% were deep. Similar to tumor locations in other reports, 54.8% of these lesions were superotemporal on the orbital rim, 39.1% were superonasal, 3.5% were inferotemporal, and 1.7% were inferonasal. In another larger series of 197 orbital and periorbital dermoids, Shields et al[5] found 72% to be superotemporal, 17% superonasal, 2% inferonasal, and only 0.5% were in the deep orbit (Figure 58.1). Rare facial locations can involve the nasal bones, skull base, *(Print pagebreak 391)* orbital floor, cheek, and roof of the mouth.[37,38,39] In one of the largest reported series of 280 orbital and eyelid dermoid and epidermoid cysts, Pushker et al[23] found that only 6% were noticed at birth, and 70% presented within the first year of life. Most large series found that 90% to 99% of periorbital and orbital dermoid cysts were superficial periorbital lesions.[5,8]

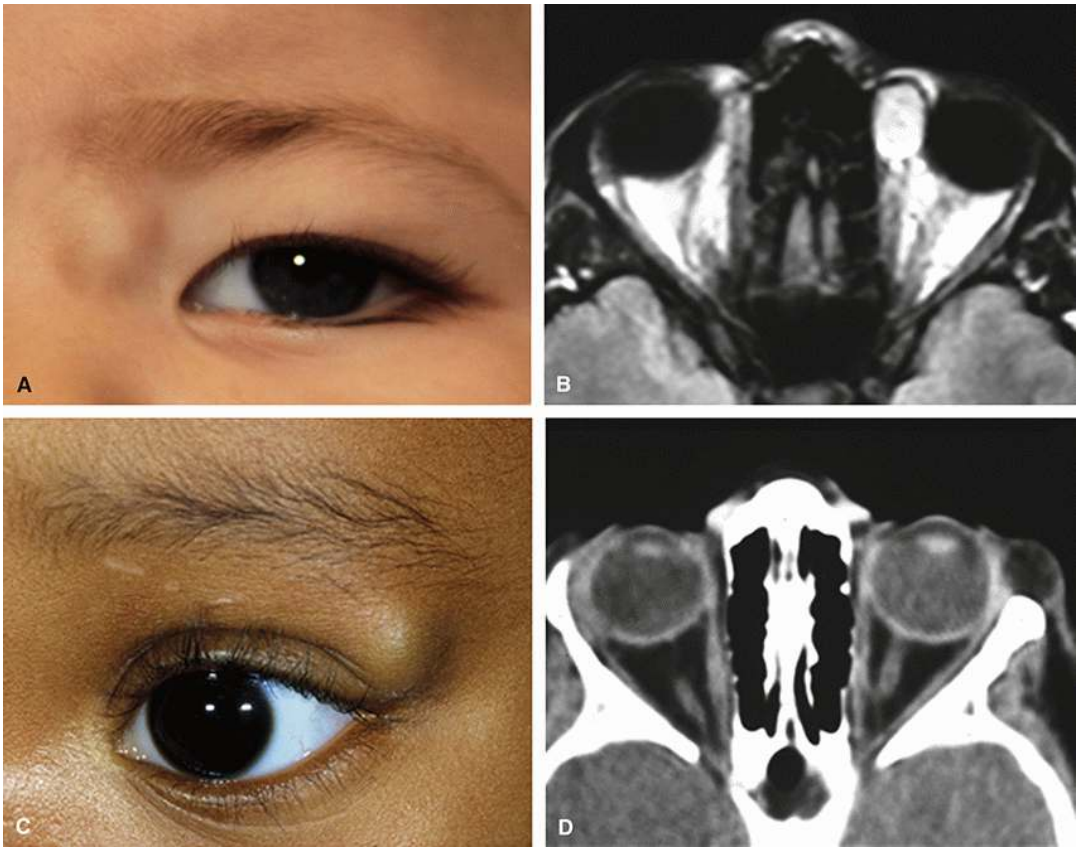

FIGURE 58.1 Major locations of periorbital dermoid cysts. A, Superomedial dermoid. B, Axial magnetic resonance scan of a medial orbital and eyelid dermoid cyst. C, Superotemporal dermoid cyst. D, Axial CT scan of a superotemporal dermoid cyst.

In the periorbital region, dermoid cysts generally manifest as a smooth, soft, slow-growing, nontender subcutaneous mass that may be fixed to the underlying bone or freely mobile (Figure 58.2). When they are large, they can result in cosmetic deformity and mechanical ptosis.[4,5,40,41,42,43] About 4% of cases can be associated with pain.[4] The average size of eyelid dermoid cysts is 1 cm but can range from 5 mm to more than 3 cm. Bone excavation is common. In a retrospective review of 145 patients with periorbital and orbital dermoid cysts, Bonavolonta et al[9] reported bone destruction in 14% of intraorbital dermoids, but less than 1% of periorbital dermoids. However, in a review of 70 patients with dermoid cysts, Sathananthan et al[21] described evidence of bone erosion in 87% and full-thickness bone defects in 34%. Other cases of transcranial and intraorbital extension of temporal dermoid cysts have been described.[4,44,45] Superficial dermoids can sometimes extend into the orbit, and rarely orbital dermoids can extend intracranially.[45,46,47]

Ghafouri et al[15] described a rare case of a caruncular dermoid cyst in an 11-year-old child presenting as a firm white medial canthal mass bound to the upper eyelid, with intermittent spontaneous bleeding.

Differential Diagnosis

The differential diagnosis of an upper eyelid dermoid cyst in a pediatric patient includes superficial eyelid lesions such as chalazion, papilloma, hemangioma, granuloma pyogenicum, and epidermoid cyst.[48] All of these are superficial in the eyelid involving the dermis or epidermis and the skin is not mobile over these lesions as it is with a subcutaneous *(Print pagebreak 392)* dermoid cyst. Other rare lesions in the differential include neurofibroma, lymphatic or venous vascular malformation, apocrine hidrocystoma, and foreign body granuloma. In the orbit, rhabdomyosarcoma and lacrimal gland tumors can cause superotemporal eyelid swelling that can simulate a dermoid. These can easily be differentiated with CT or MRI.

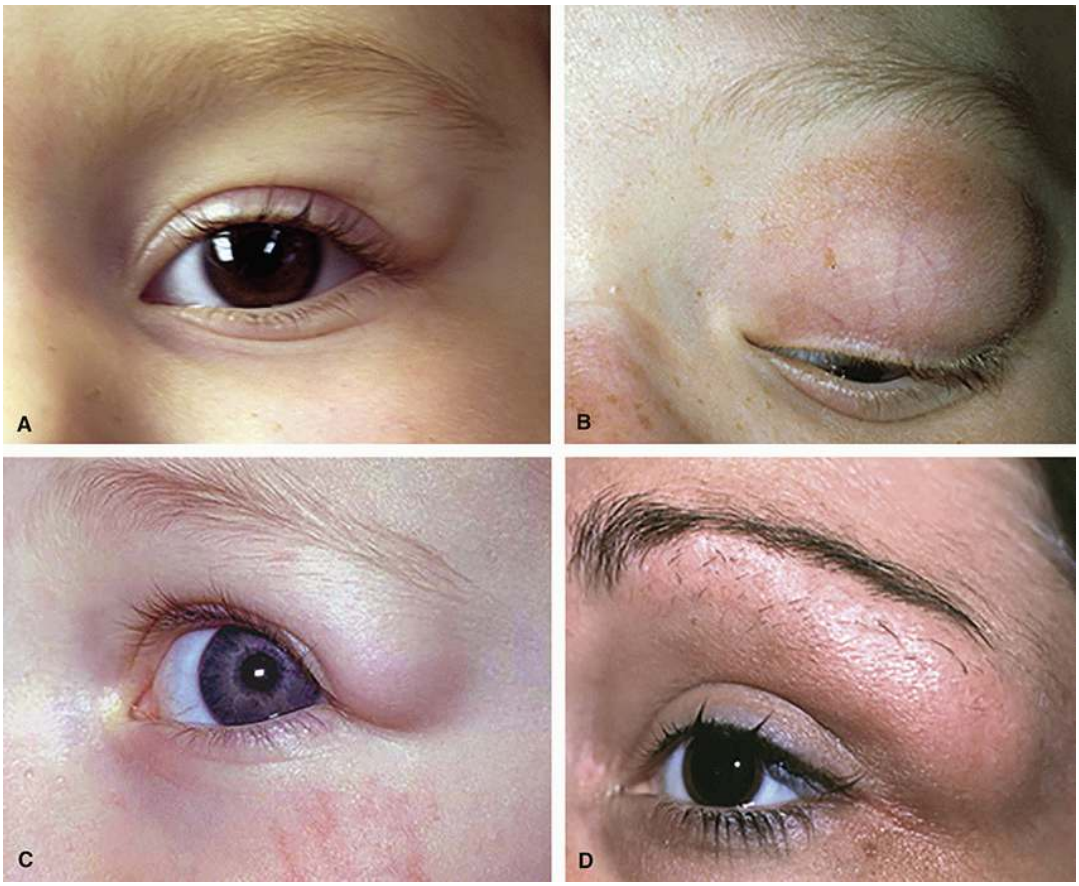

FIGURE 58.2 A-D, Superotemporal periorbital dermoid cysts.

Treatment

Surgical excision with complete removal of the cystic wall without rupture is the gold standard treatment for a dermoid cyst.[5,41] Superficial eyelid dermoids can usually be removed through an eyelid crease incision with minimal postoperative scarring.[8,49,50,51] In some locations, an incision directly over the lesion may be necessary for better access. Larger lesions, particularly in the orbit, can be decompressed by needle aspiration to reduce their size before surgical excision. Methylene blue has also been injected to identify the cyst wall and enhance complete resection.[52] For more complex cases in difficult anatomic locations such as intracranial, a multidisciplinary approach with neurosurgery or maxillofacial surgery may be required.[53,54,55]

Prognosis

The prognosis following surgical excision of periorbital and orbital dermoid cysts generally is excellent with a good cosmetic result and low recurrence rate.[56] In a series of 48 cases of periorbital dermoid cysts undergoing surgical excision by Bajric et al,[6] five (10.4%) had documented unintentional intraoperative rupture of the cyst wall, but none of these developed postoperative inflammation or cyst recurrence. Five other patients had postoperative complications including hematoma (5.6%), transient frontalis muscle weakness *(Print pagebreak 393)* (1.9%), or a prominent scar (1.9%), and 4.2% had cyst recurrence after 8 and 12 months,

respectively. In another series of 115 periorbital dermoids, Montolío-Marzo et al[8] reported that 7.8% were inadvertently ruptured during surgery without complication, and 1.6% of the cysts recurred.

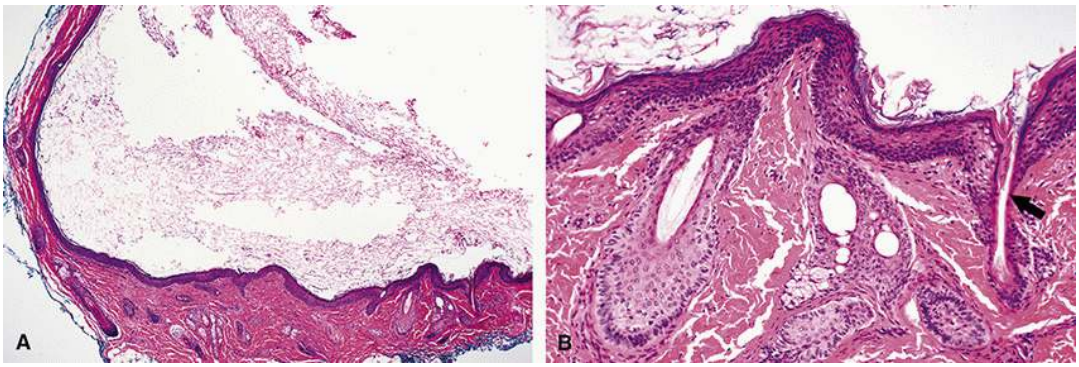

FIGURE 58.3 A, Superotemporal periocular dermoid cyst with a keratinized, stratified squamous epithelium with sebaceous glands and hair follicles. The cyst cavity contains keratin and hair shafts. B, Close-up of the cyst wall showing the keratinized, stratified squamous epithelium, keratin debris in the lumen, and multiple hair follicles, one of which (arrow) has a hair projecting through the lining epithelium.

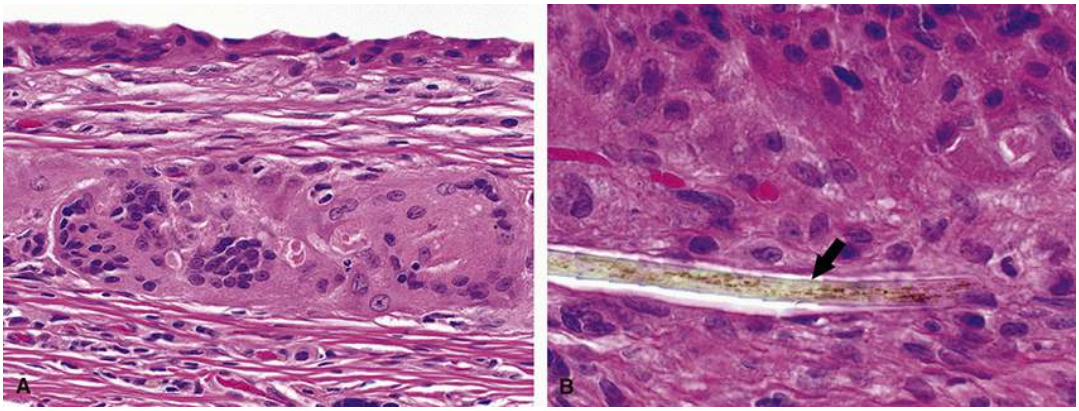

FIGURE 58.4 A, This periocular dermoid cyst had ruptured, resulting in a focal granulomatous response with lymphocytes, macrophages, and fibrosis adjacent to the granuloma. The granuloma has large foreign body giant cells, several containing eosinophilic keratin debris surrounded by a halo. B, This lesion removed from the superotemporal periocular region lacked a cyst and showed only keratin debris, hair fragments (arrow), and a granulomatous reaction.

Histopathology

Periocular dermoid cysts are usually lined by keratinized, stratified squamous epithelium, identical to that of the epidermis, with adnexal structures including sebaceous and eccrine glands and hair follicles (Figure 58.3).[5,57,58,59] Less commonly, the cyst wall may have goblet cells,[57] and Shields and coworkers[5] designated these dermoid cysts of conjunctival origin (conjunctival dermoids). The cyst cavity contains keratin, hair shafts, and sebaceous secretions. If the cyst ruptures, it incites an intense granulomatous inflammatory response (Figure 58.4).[57,58,59] Occasional specimens submitted for histopathological analysis will show only keratin debris, hair fragments, and a granulomatous reaction. Polarization microscopy will help identify the hair shafts in such cases due to their birefringence.

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CHAPTER 59

Dermatofibroma

Key Points

- Dermatofibroma is a benign, cutaneous form of fibrous histiocytoma occurring in the dermis of the skin
- The etiology remains controversial but theories include a reactive process or a neoplastic proliferation
- Dermatofibroma clinically present as dome-shaped, asymptomatic, slow-growing, nontender, firm, freely moveable reddish, yellowish, or tan cutaneous nodules
- Complete surgical excision, with a 3-mm clear margin and including subcutaneous fat, is indicated for cosmetically bothersome or symptomatic lesions
- The prognosis is excellent following surgery, and spontaneous regression has been reported in rare cases

Dermatofibroma is a commonly occurring cutaneous entity occurring in the dermis. In the past, they were referred to as benign fibrous histiocytomas of the skin, or superficial/cutaneous benign fibrous histiocytomas, or common fibrous histiocytoma. Today, the term fibrous histiocytoma refers to subcutaneous lesions, and dermatofibroma is restricted to the cutaneous form of the disease. The overall worldwide incidence is uncertain because the vast majority of patients are relatively asymptomatic. It occurs in patients of any age, with a peak in patients aged 20 to 49 years.[1,2,3] Females are affected more commonly than males, with a male-to-female ratio of 1:2 or higher.[1,3,4,5,6]

Etiology and Pathogenesis

The etiology of dermatofibroma remains controversial. There are several theories for the genesis of dermatofibromas: a reactive process and a neoplastic proliferation. Evidence exists for both of these theories.[2] Some patients report a history of local traumatic cutaneous insult such as insect bite, skin tattooing, skin injections such as tuberculin test or cosmetic filler, superficial puncture wound from thorns, or wood splinters, surgical trauma, and folliculitis, all of which argue for a reactive process. However, local trauma as a predisposing factor is inconsistent, and more commonly the lesions develop spontaneously without an inciting event.[7,8,9,10,11]

Some authors have favored a clonal or neoplastic etiology,[2] and studies have identified clonal markers in dermatofibromas supporting a neoplastic process. Clonal proliferative growth has been shown in some dermatofibromas suggesting that they may represent a neoplastic process,[12] although clonality is not necessarily indicative of a neoplastic process and can be seen in some inflammatory conditions. One study proposed that dermatofibroma tumorigenesis may be due to distorted protein kinase C activity.[13] Antibodies to factor XIIIa, which label dermal dendritic cells, are frequently positive in dermatofibroma.[14] Spindle-shaped cells stain positively for HSP47, a marker for skin fibroblasts, suggesting that skin fibroblasts may be a major constituent of dermatofibromas.[15] $CD14^+$ monocytes have been proposed as the cell of origin of dermatofibromas.[16]

Transforming growth factor beta and other fibrinogenic factors have been reported to occur in high numbers in dermatofibromas[17] and might serve as triggers of fibrosis.[18] Some evidence suggests a role for the cell surface proteoglycan, syndecan-1,[19] and fibroblast growth factor receptor 2, involved in epithelial-mesenchymal cross talk,[20] in the growth of dermatofibromas. Gene fusions have been described in dermatofibroma tumorigenesis.[21,22] *ALK* gene rearrangement and overexpression have been demonstrated in both epithelioid and atypical variants of dermatofibroma.[23,24]

It has been proposed that eyelid dermatofibroma be considered related to, but distinct from, the classic dermatofibroma. This distinction was based on the unique dermal structure of the eyelids as well as eyelid-specific histopathological findings.[25]

Clinical Characteristics

Dermatofibromas of the dermis clinically present as asymptomatic, slow-growing, nontender, firm, freely moveable reddish, yellowish, or tan cutaneous nodules (Figure 59.1).[26] Lesions usually are dome shaped, with a smooth or cystic appearance, and may have a central dimpling.[2,27,28] They usually are relatively small, less than 1 cm in diameter.[11,14,29,30] Lesions are mostly solitary but may be multiple involving the eyelid and face.[31]

Differential Diagnosis

The differential diagnosis of dermatofibroma includes a wide variety of benign cutaneous lesions.[32,33] These include acrochordon, atypical fibroxanthoma, nevus, cutaneous *(Print pagebreak 397)* melanoma, cutaneous lipoma, juvenile xanthogranuloma, neurilemmoma, leiomyoma, and pilomatrixoma. More importantly, the differential can include malignant lesions such as basal cell carcinoma, squamous cell carcinoma, keratoacanthoma, Merkel cell carcinoma, and T-cell lymphoma. It is important to distinguish benign dermatofibroma from dermatofibrosarcoma protuberans (DFSP). These two lesions have a similar appearance but DFSP is a more aggressive cutaneous neoplasm.[4,12,34] DFSP is usually larger, and more commonly involves the subcutis. Immunohistochemical staining can be very helpful in distinguishing it from benign dermatofibroma. Kaposi sarcoma may be mistaken for the aneurysmal variant of dermatofibroma. Basal cell carcinomas can mimic dermatofibroma clinically and histologically.[35,36,37,38]

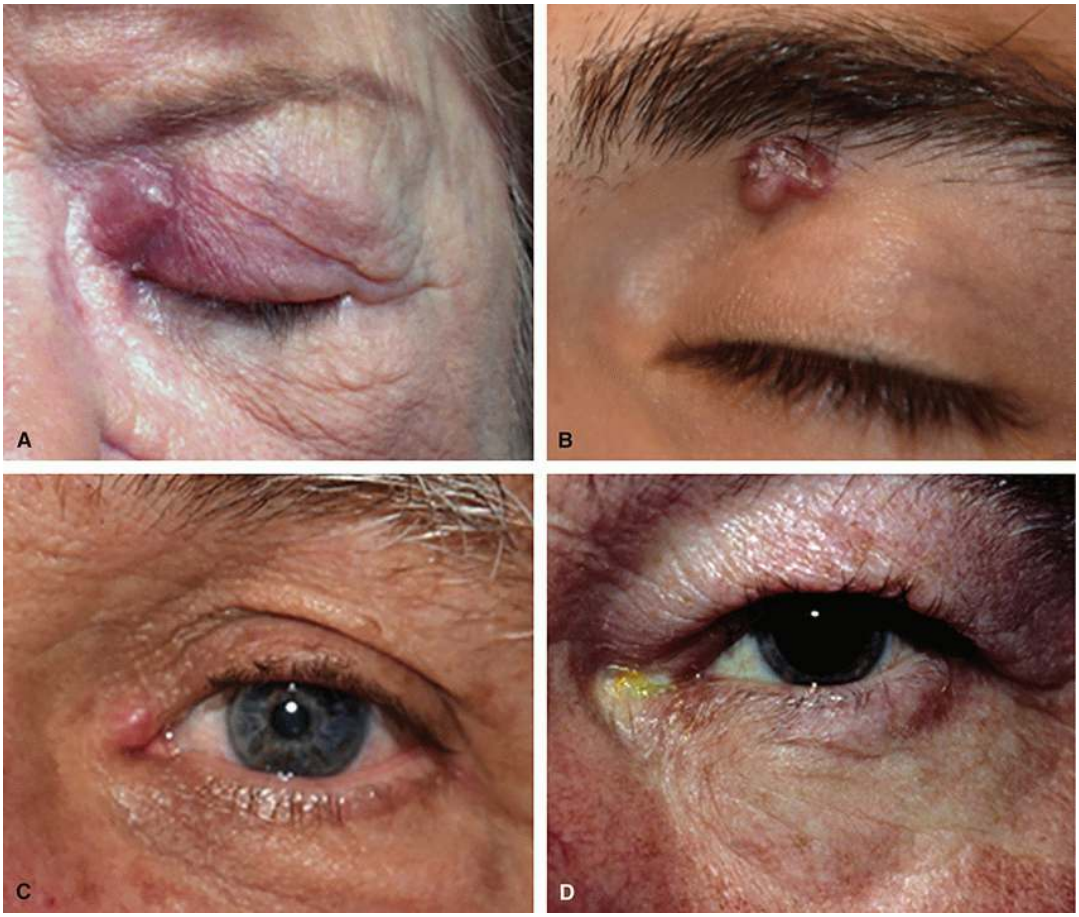

FIGURE 59.1 A-D, Dermatofibroma of the eyelid. (A, Courtesy of Dr. Robert Goldberg; B, Courtesy of Dr. Suzanne Freitag; C, Courtesy of Dr. Frederick Jakobiec.)

Treatment

For cosmetically bothersome or symptomatic lesions, or when a more aggressive subtype is suspected, complete surgical excision, with a 3-mm clear margin and including subcutaneous fat, is indicated[39] Mohs micrographic surgery has also been employed successfully.[40]

Cryosurgery has been used for improved cosmesis or to decrease symptoms. Significant clinical improvement, including visible flattening of raised dermatofibromas and lightening of pigmentation, has been reported in 80% to 90% of patients.[41,

[42] Fractionated carbon dioxide and dye laser ablation have also been reported to achieve cosmetic improvement.[31,43,44]

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Prognosis

The prognosis for patients with benign dermatofibroma is excellent. Spontaneous regression is rare but has been reported.[31]

Cellular, aneurysmal, and atypical variants of dermatofibroma are more locally recurrent and rarely can metastasize.[34,45,46,47,48] In the latter cases, lymph node and pulmonary metastases are most commonly seen.[49]

Histopathology

Dermatofibromas have a highly variable histological appearance, with the commonality being their varying combinations of fibroblast-like cells, macrophages, and coarse collagen.[50,51,52,53] In two recent studies of dermatofibromas, fibrocollagenous (common) dermatofibromas accounted for 49/122 (40%) in one study[54] and 154/192 (80%) in another.[3] Other variants in these studies were histiocytic, cellular, aneurysmal, angiomatous, sclerotic, monster, palisading, keloidal, hemosiderotic, epithelioid, lipidized, atrophic, and clear cell dermatofibromas.[3,54] Many other even rarer variants exist.[50,52]

The prototypical dermatofibroma is a poorly demarcated spindle cell proliferation centered in the mid reticular dermis with an ill-defined rounded to wedge-shaped outline, increased collagen, and a variable infiltrate of lymphocytes.[51,52] Lesions often extend into the upper cutis and may occasionally extend deeper.[51,53] A majority of dermatofibromas have overlying epidermal hyperkeratosis, acanthosis, and basal hyperpigmentation.[3,54] Early dermatofibromas have abundant plump spindle to round cells with round to elongated vesicular nuclei, inconspicuous nucleoli, and scant cytoplasm.[51,52] Collagen is often trapped at the edge of the lesions creating collagen balls.[51,52] Older lesions have more abundant collagen and fewer macrophages, and a storiform pattern may be present (Figure 59.2).

Cellular dermatofibromas, which have a higher local recurrence rate than other dermatofibromas,[55] are densely cellular with a fascicular growth pattern, eosinophilic spindle cells with tapering nuclei, a moderate number of mitotic figures (mean = 3 per 10 high-power fields), and less abundant stroma.[32] Dermatofibromas with monster cells feature cells with “huge, hyperchromatic, round, or oval nuclei having one or more prominent nucleoli” in a background otherwise typical of early dermatofibroma.[56] One example of an eyelid dermatofibroma with monster cells has been reported.[14] Other histological variants of dermatofibroma are described and illustrated in detail elsewhere[52] and have not been reported in the eyelid. Immunohistochemical stains for factor XIIIa and CD34 may assist in differentiating a dermatofibroma (factor $XIIIa^+$ and $CD34^-$) from an early DFSP ($CD34^+$ and factor $XIIIa^-$) or scar (factor $XIIIa^-$ and $CD34^-$).[28,52,57]

Abdelhakim and colleagues recently reviewed the histopathology of the 11 reported cases of eyelid dermatofibroma.[25] They noted that eyelid dermatofibromas tended to differ from those elsewhere on the body by being basophilic rather than eosinophilic, round versus longitudinal when viewed at low magnification, no layer of uninvolved papillary dermis (grenz zone[58]), nonacanthotic epidermis, a paucity of collagen trapping, and pronounced cellularity.[25] They postulated that eyelid dermatofibromas' rarity and the different histological features might be due to facial fibroblasts arising from neural crest rather than lateral plate mesoderm or the unique composition of eyelid skin, which is mostly papillary dermis with only a little reticular dermis.[25] Further studies are needed to clarify this issue, but Figure 59.3 is an example of an eosinophilic right upper eyelid dermatofibroma with acanthotic epidermis, a grenz zone, collagen trapping, and moderate cellularity.

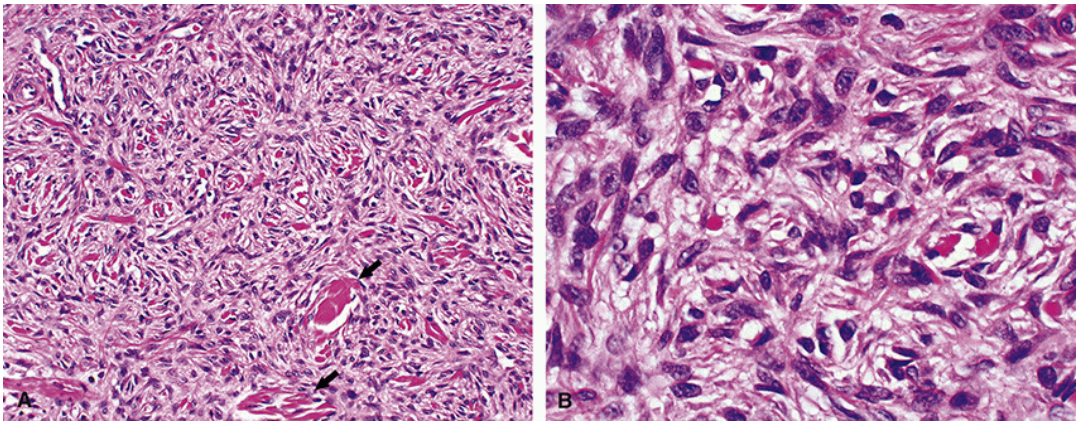

FIGURE 59.2 A and B, Dermatofibroma of the neck illustrating a hypercellular proliferation of plump spindle-shaped cells with scant cytoplasm, a prominent storiform pattern, and collagen trapping (arrows).

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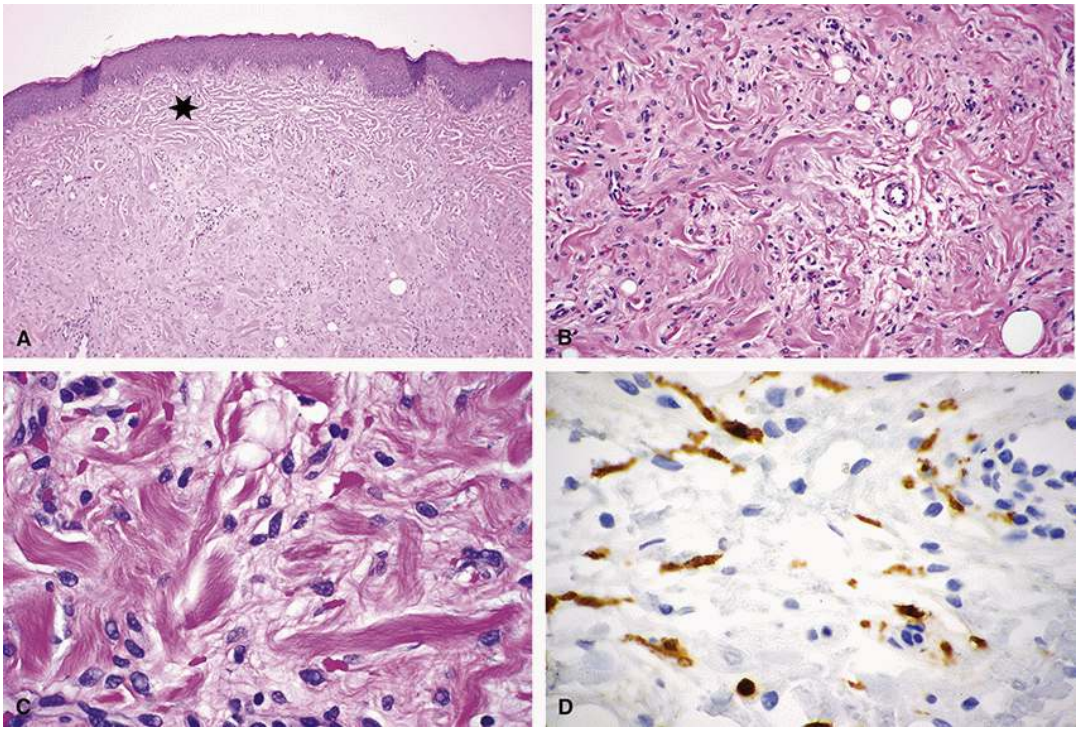

FIGURE 59.3 Dermatofibroma of the right upper eyelid in a man in his middle 50s. A-C, The tumor is composed of lightly eosinophilic cells with scant cytoplasm and oval vesicular nuclei between bundles of brightly eosinophilic collagen. The tumor is separated from irregularly, mildly acanthotic epidermis by normal papillary dermis (★ in A). The tumor cells were immunoreactive using antibodies to factor XIIIa (D) but negative for CD34 expression.

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CHAPTER 60

Distensible Venous Malformations (Varices)

Key Points

- Distensible venous malformations (DVMs) are abnormally enlarged and tortuous veins, or less commonly
- Periocular DVMs are more commonly seen in the orbit than in the eyelid
- They may develop from a congenital or acquired weakness of the involved vessel wall, obstruction of circulation, compression by a tumor, or trauma or infection that involves the vessel
- DVM presents as a unilateral, nontender, well-circumscribed, soft, compressible subcutaneous mass that often enlarges with a Valsalva maneuver
- In most cases, an eyelid DVM can safely be observed
- Symptomatic DVMs in the head and neck region are preferentially treated surgically
- Alternative therapy can include embolization with transvenous coiling or n-butyl cyanoacrylate glue or sclerotherapy using 0.75% sodium tetradecyl sulfate
- Complete surgical excision gives excellent cosmetic results, and recurrences are rare

Low-flow vascular malformations in the orbit are divided into venous malformations (VMs), lymphatic malformations, and combined venous-lymphatic malformations (VLMs).[1,2] Pure VMs include distensible and nondistensible venous malformations.[1,2] Distensible venous malformations (DVMs) are characterized by the presence of abnormally enlarged and tortuous veins, which may or may not be associated with lymphatic vessels.[1,2] The classical example of a nondistensible VM in the orbit is the cavernous venous malformation, which is discussed in Chapter 54. On the other hand, combined VLMs include two types or varieties based on hemodynamics: the distensible venous dominant (VD-VLM), and the nondistensible lymphatic dominant (LD-VLM).[2]

DVMs were previously referred to as varices, but that term is no longer used in the International Society for the Study of Vascular Anomalies 2018 classification. DVMs are abnormally enlarged and tortuous veins, which may harbor lymphatic or arterial elements.[1,2] Periocular DVMs are more commonly seen in the orbit than in the eyelid, and eyelid DVMs frequently represent an extension from the orbit, usually from the anterior feeders and portions of the superior ophthalmic vein.[3,4,5,6,7] They can also represent venous abnormalities associated with facial veins that extend to the eyelids, especially the angular vein. In some instances, facial DVM may be seen in genetic disorders such as Klippel-Trenaunay-Weber syndrome. This is a rare congenital condition usually exhibiting excessive growth of bones and soft-tissue vascular anomalies including port wine stains, hemangiomas, and varicose veins that commonly appear in the facial area,[8] and associated with additional VMs in other locations such as the legs, arms, or abdomen.[9]

DVM can be imaged with ultrasound and color Doppler,[10] which will show the dilated blood vessel, and the nonpulsatile blood flow confirms the passive or venous nature of the blood flow. Since the majority of eyelid DVMs are associated with orbital vascular anomalies, any new or spontaneous-onset of eyelid DVM should elicit orbital imaging.[6,11] Magnetic resonance venography and conventional phlebography can confirm the diagnosis and allow visualization of the location and extent of the lesion, its anatomic relations and boundaries with surrounding tissues, and the inflow and outflow vessels.[12]

Etiology and Pathogenesis

DVM may develop from a congenital or acquired weakness of the involved vessel wall, or obstruction of circulation, or both.[5,6] They can also result from compression by a tumor or an arterial aneurysm over an adjacent vein, an arteriovenous malformation, or any trauma or infection that involves the wall or lumen of the vessel.[6,13]

Clinical Characteristics

Eyelid DVMs typically present as a unilateral, nontender, well-circumscribed, soft, dark blue to brown or purple, compressible subcutaneous mass with no associated audible bruit or thrill (Figure 60.1). The lesion often enlarges with any activity that increases venous pressure, such as bending over for several minutes, or from a Valsalva maneuver with pressure exerted on the jugular vein, such as coughing, straining, and crying (Figure 60.2).[5,13] When subtle, a DVM may not enlarge significantly with Valsalva to be clinically apparent but if such scenario is encountered distensibility with Valsalva can be elicited with radiology.[2,14] They usually do not cause eyelid dysfunction, but they can be complicated by inflammation or by thrombus with hemosiderin and dystrophic calcification.[15] *(Print pagebreak 402)* If thrombosis occurs, the patient usually presents with acute pain, the lesion may be firm, less compressible, and may not enlarge with Valsalva.[2] DVM can rupture with minor trauma or vomiting, resulting in hemorrhage and ecchymosis.[16] If the eyelid lesion is an extension of an orbital varix, a deep hemorrhage can present with acute pain, proptosis, and motility restriction.[7]

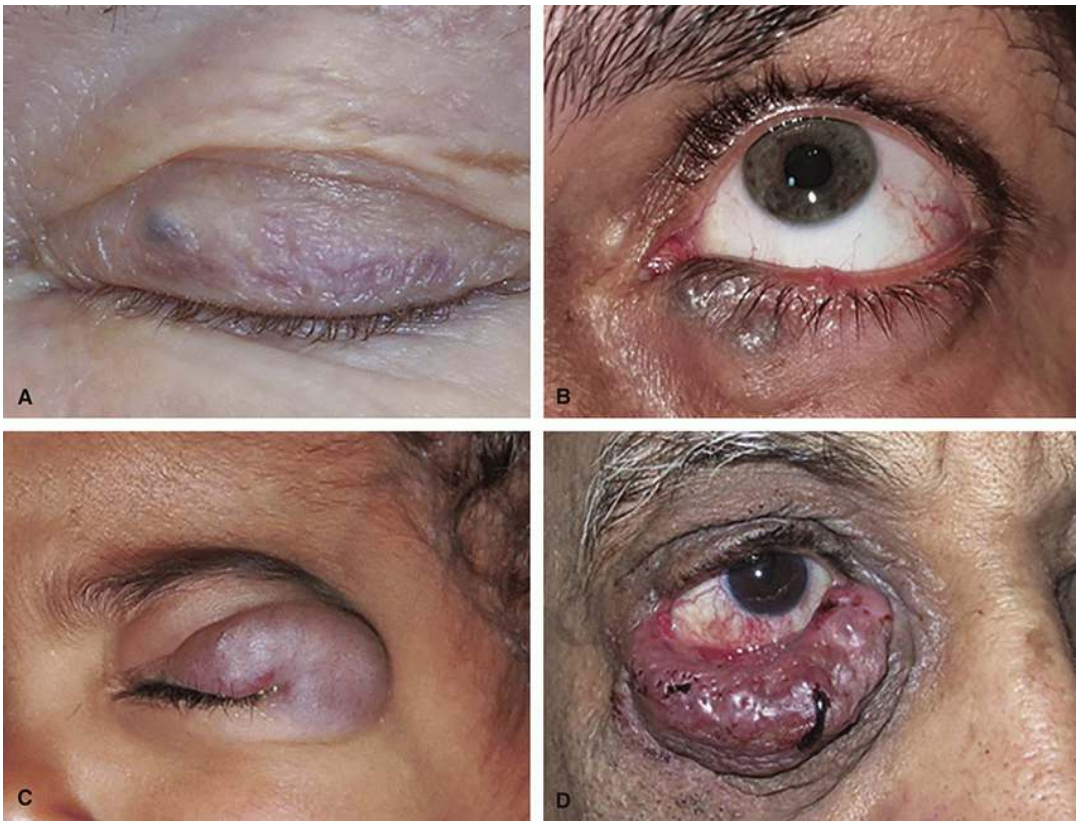

FIGURE 60.1 The spectrum of presentations of eyelid varices. A, Small varix of the upper eyelid skin. B, Multifocal varix of the lower eyelid. C, Serpentine varix of the upper eyelid and lateral canthus. D, Extensive varix involving the lower eyelid and conjunctiva.

There have been very few reported cases of DVM of the angular vein. Most present as a nontender, mobile, soft mass in the subcutaneous medial canthus or paranasal region.[6,14,17,18,19,20] An angular vein DVM is usually seen through the thin skin and 6 to 8 mm medial to the medial canthus.[21] They typically are seen just below the medial canthal tendon,[6,18,19] but can occasionally occur above the medial canthal tendon, where it may confuse the diagnosis.[14]

Conjunctival varices are uncommon, with most being anterior extensions of orbital varices, but a pure conjunctival varix is rare.[22] They present as a bluish mobile mass not fixed to the sclera (Figure 60.3).

The diagnostic workup of patients with suspected DVM should include ultrasound imaging with color Doppler assessment that will show the dilated blood vessels and the nonpulsatile blood flow.[2] These findings demonstrate the passive or venous nature of the blood flow within these lesions. In addition, computed tomography angiography, magnetic resonance venography, or direct conventional venography with or without Valsalva can confirm the diagnosis and allow visualization of the location and extent of the lesion, its anatomic relations and boundaries with surrounding tissues, and the inflow and outflow vessels.[2,3] Other advanced dynamic MRI imaging techniques that can also be ordered include DWI (diffusion weighted imaging), ADC (apparent diffusion coefficient), and TRICKS (time resolved imaging of contrast kinetics) sequences.[3] Furthermore, if a widespread communication with the intracranial circulation is suspected, a CT is necessary to show the potential bony defects, which may vary from minor bony pitting defects to extensive defects that may be associated with encephaloceles or meningoencephaloceles.[10,11] An additional sign

that may observed on CT is focal areas of calcification (phlebolith formation) from previous bouts of thrombosis.[2] Of note is that when radiology *(Print pagebreak 403)* is ordered for patients with adnexal/orbital DVMs, intracranial developmental venous anomalies may be observed as an incidental finding, which may or may not be of clinical significance.[1,2]

FIGURE 60.2 Medial upper eyelid varix before (A and C) and during (B and D) a Valsalva maneuver.

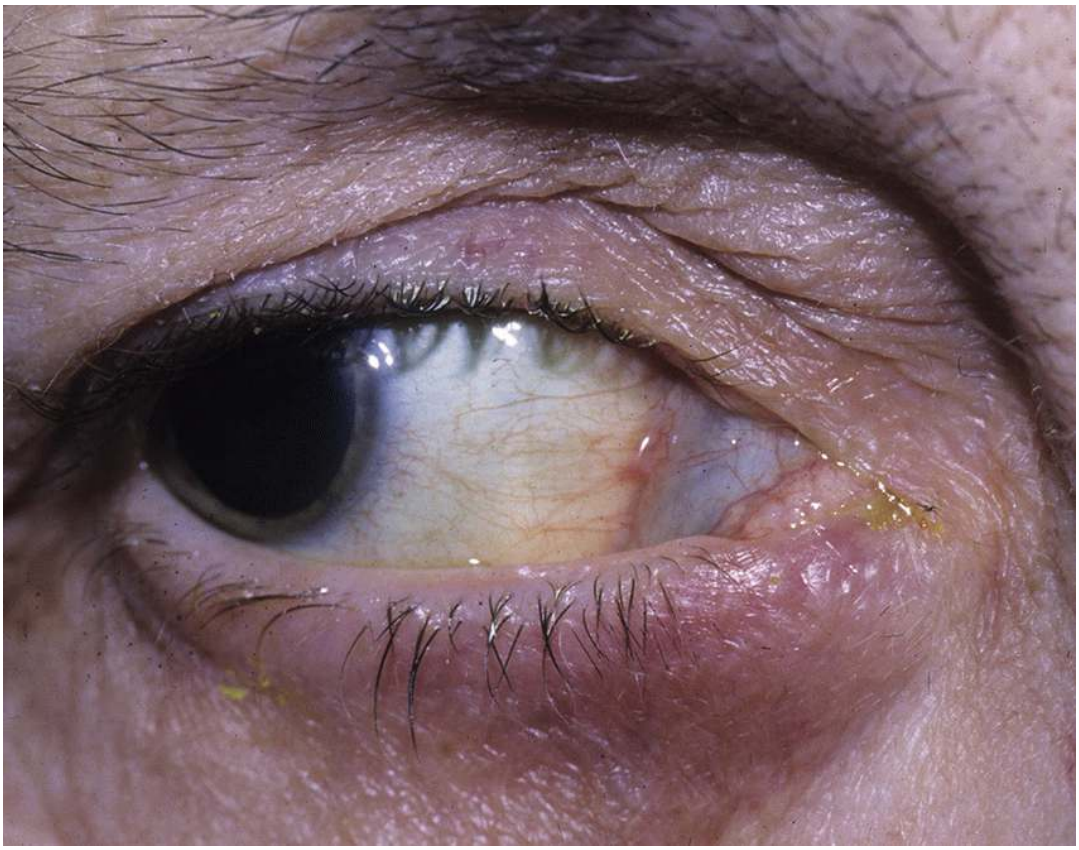

FIGURE 60.3 Medial conjunctival varix.

Differential Diagnosis

The differential diagnosis of eyelid DVM includes both capillary and cavernous hemangioma, arteriovenous malformation, and lymphangioma.[14] A mass located at the medial canthal area may also be secondary to an abscess, a diverticulum, neoplasm, or dacryolith in the lacrimal sac. Other differentials include sinus mucoceles, hemangiomas, and meningoceles. DVM with an orbital extension may mimic conditions that present with symptoms of acute proptosis, swelling, and hemorrhages, such as idiopathic orbital inflammation, acute myositis, hemangioma, or a lymphangioma.[22]

Treatment

In most cases, an eyelid DVM can safely be observed.[23] The decision to treat and the choice of treatment are dependent on the characteristics of the lesion, its location, any associated symptoms, eyelid dysfunction, or cosmetic concerns.[24] Symptomatic DVMs in the head and neck region are preferentially treated surgically. Superficial lesions in the eyelid and face are usually easily exposed and dissected. The *(Print pagebreak 404)* feeding vascular segments on either side are tied, and the dilated portion is completely excised,[6] thereby minimizing the probability of recurrence. During surgery, the patient can be placed in a recumbent position, and compression applied just distal to the dilated vein, increasing the prominence of the vessel. Surgery is especially indicated for larger and deeper DVMs that are more difficult to manage by endovascular or local transcutaneous approaches. Surgical treatment is also indicated for cases where eyeglasses may rest on the DVM causing discomfort and an increased risk of hemorrhage.[14]

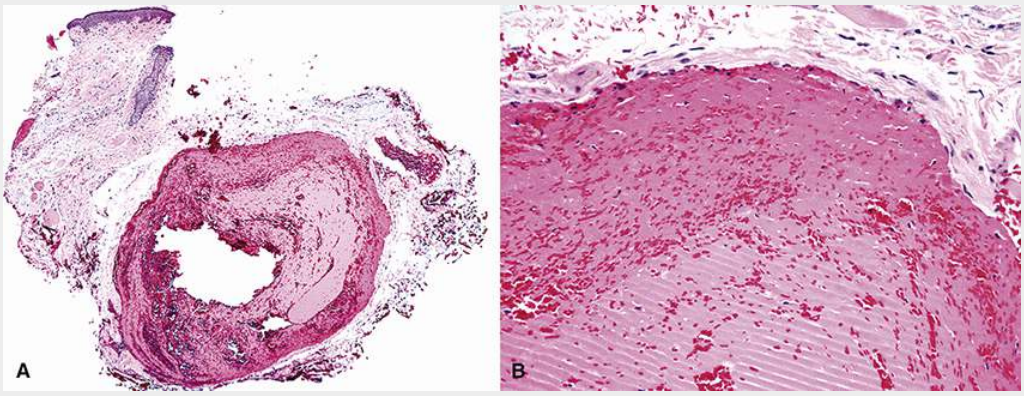

FIGURE 60.4 A, This varix from the left upper eyelid was present for several years. At low magnification, a dilated vein filled with acute thrombus is in the dermis. B, The varix wall has an endothelial lining and a thin layer of smooth muscle cells and fibrous connective tissue, features characteristic of a small muscular venule.[39]

Surgical treatment of the orbital component can be difficult, and complete excision is rarely accomplished because of poorly defined surgical margins, especially if the DVM extends into the orbital apex.[25] Embolization for the treatment of orbital DVM has been available for several decades, using transvenous coiling or n-butyl cyanoacrylate glue.[24,26,27,28,29,30]

Sclerotherapy using 0.75% sodium tetradecyl sulfate has been used in some cases and has been reported to be successful in promoting the resolution of ectatic periocular veins.[22,31] There have also been several reports describing the percutaneous injection of bleomycin,[32,33] which reportedly causes less orbital swelling and inflammation than sodium tetradecyl sulfate.

Prognosis

For DVM confined to the eyelid and face, complete surgical excision gives excellent cosmetic results, and recurrences are rare. In cases with orbital extension, spontaneous hemorrhage can be seen with sudden proptosis, motility restriction, and eyelid ecchymoses.[34] Any associated deeper orbital DVMs are more difficult to completely resect, even when surgery is combined with embolization, and recurrences are not uncommon.[28,35]

Histopathology

Varices are fusiform or saccular dilations of a vein,[36] usually associated with vessel wall thinning (Figure 60.4). There are only

scant reports of the histopathology of periocular varices,[6] and most have focused on secondary changes such as phlebolith formation due to calcification of old thrombus[37] or intravascular papillary endothelial hyperplasia development[37,38] (Chapter 74). In the case reported by Mudgil, Meyer, and Dipillo, "histologic examination disclosed an endothelial cell-lined, thin-walled, vascular structure with a large lumen, composed of smooth muscle separated by a loose network of collagen and elastic fibers."[6]

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CHAPTER 61

Erysipelas

Key Points

- Erysipelas is a nonnecrotizing bacterial infection of the superficial layers of the skin
- The most common causative organism is *Streptococcus pyogenes* (group A streptococci)
- *S. pyogenes* has a special predilection to invade the dermal lymphatics
- The main presenting symptoms are tenderness, pain, fever, and malaise
- A history of a scratch or an insect bite may be elicited from the patient
- The affected skin shows a bright red, well-defined inflamed area with a raised edge, ± bullae on the border of the lesion
- Isolated eyelid involvement is extremely rare
- Erysipelas is generally considered a nonculturable condition, and attempts to culture bacteria are usually unsuccessful
- Radiology is of no particular value in the diagnostic workup of the disease
- The condition should be differentiated from allergic contact dermatitis and necrotizing fasciitis
- Empiric antimicrobial therapy (β-lactams) should be started immediately
- If properly treated, the condition settles within a week or 2, but if it is inadequately treated, it can progress to necrotizing fasciitis

Erysipelas (St. Anthony's fire) is an acute, nonnecrotizing diffuse bacterial infection of the superficial dermis, upper subcutaneous tissue, and lymphatics, which is hallmarked by the presence of a bright red, well-defined inflamed area of the skin that resembles a rash.[1,2,3,4,5,6,7,8,9,10] Traditionally, the special predilection of this disease to involve the superficial dermis was used as a differentiating point to distinguish erysipelas from cellulitis. According to the classic definition of cellulitis, it should involve deeper tissue planes than erysipelas[1,2,3,4,5,6,7,8,9,10]; however, the current trend in the dermatology literature is to deal with both entities as a single disease rather than two distinct entities. According to this updated view, the definition of cellulitis should be expanded to include both superficial infections (erysipelas) and deeper tissue involvement (cellulitis).[1,4,9] This view is supported by the fact that the risk factors, diagnosis, and management of erysipelas are similar to those of cellulitis. In addition, the bacteriology of both conditions is similar, as streptococcal antigens are demonstrated in the dermis and subcutis in both conditions.[4] However, both entities will be described separately in this textbook, simply because the term “cellulitis” has special connotations in ophthalmic and oculoplastic literature, which brings to mind specific preseptal and orbital infectious conditions.

Etiology and Pathogenesis

Erysipelas is bacterial in origin and the most common causative organism is *Streptococcus pyogenes* (group A streptococci, GAS). Other organisms that are less frequently implicated in the pathogenesis of erysipelas include groups B, C, D, G, and F streptococci.[1,2,4,10] *Staphylococcus aureus* may rarely be isolated together with streptococcal species, but it is rarely cultured alone in erysipelas patients, and its isolation should be regarded as an occasional finding.[2]

In immunologically competent patients, erysipelas usually results from the disruption of the cutaneous barrier.[11] A small break in the skin due to an insect bite, a minor scratch, or rarely laser resurfacing allows the organism to gain access to the dermis.[4,6,12] As a species, *S. pyogenes* has a special predilection to invade the dermal lymphatics, whereby they can reach the lymph nodes and later the circulation.[13] The mechanism underlying this lymphatic tropism is unknown, but it is hypothesized that the hyaluronan capsule

of GAS plays a crucial determinant role.[13] This lymphatic affinity is probably why streptococcal life-threatening infections may be observed, even in healthy individuals.

Other predisposing factors include advancing age, obesity, smoking, edema (eg, lymphedema), a previous history of cellulitis or malignancy, and immunosuppression (diabetes, HIV, or pharmacologic).[1,2,6,8]

Clinical Presentation

Erysipelas has a special predilection for the lower extremities (70%-90%), upper extremities (12%), and to a lesser extent the face (2%-10%).[5,6,7,8] Isolated eyelid erysipelas is extremely rare, and when it is observed, it is usually due to extension from the cheeks and forehead. Any age can be affected including children, but the disease has a special predilection to involve individuals between the fourth and the sixth decades and is more common in males.[4]

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The main presenting symptoms are tenderness, pain, fever, and malaise, which vary according to the virulence of the organism.[4] A history of a scratch or an insect bite may be elicited from the patient, although in a significant proportion of patients, the portal of entry may not be obvious and no history of trauma is elicited.

The initial presentation is usually with a small, sharply defined, erythematous skin patch at the infected site, which looks like a rash but with a raised edge. If it starts in the cheek or the bridge of the nose, it may on occasion rapidly spread to involve the periorbital region, particularly the lower eyelids and the medial canthal area.[14] The relatively diffuse nature of erysipelas is simply attributed to the clinical/pathogenic nature of the predominant causative organism (GAS).[15] *S. pyogenes* remains the leading cause of both forms of diffuse cellulitis including erysipelas, in contrast to the other major skin pathogen *S. aureus*, which generally causes more localized disease (eg, abscess).[15] The erythema is irregular with tongue-like extensions along the lymphatic vessels. The clinical appearance of an elevated, erythematous, indurated area with a sharp border is very characteristic, especially when tiny vesicles or bullae are seen at the advancing margin (Figure 61.1). In addition, the area is hot, edematous, and tender to touch. This tense edema gives the skin a shiny glazed appearance.[10] In more severe cases, the skin can turn purple or black with blisters filled with fluid or blood (Figure 61.2). As the blisters rupture, raw areas of skin result. Regional lymphadenopathy usually accompanies the infection and local complications may include hemorrhagic infarction, skin ulceration, or necrosis.

Erysipelas is generally considered a nonculturable condition.[10] Attempts to culture bacteria from the bullae, from tissue biopsies, or even from needle aspiration of saline-injected sites are usually unsuccessful because bacteria are present in small numbers.[2] Imaging studies are also of no particular value in patients with erysipelas except to exclude a deeper extension of the infectious process.[1]

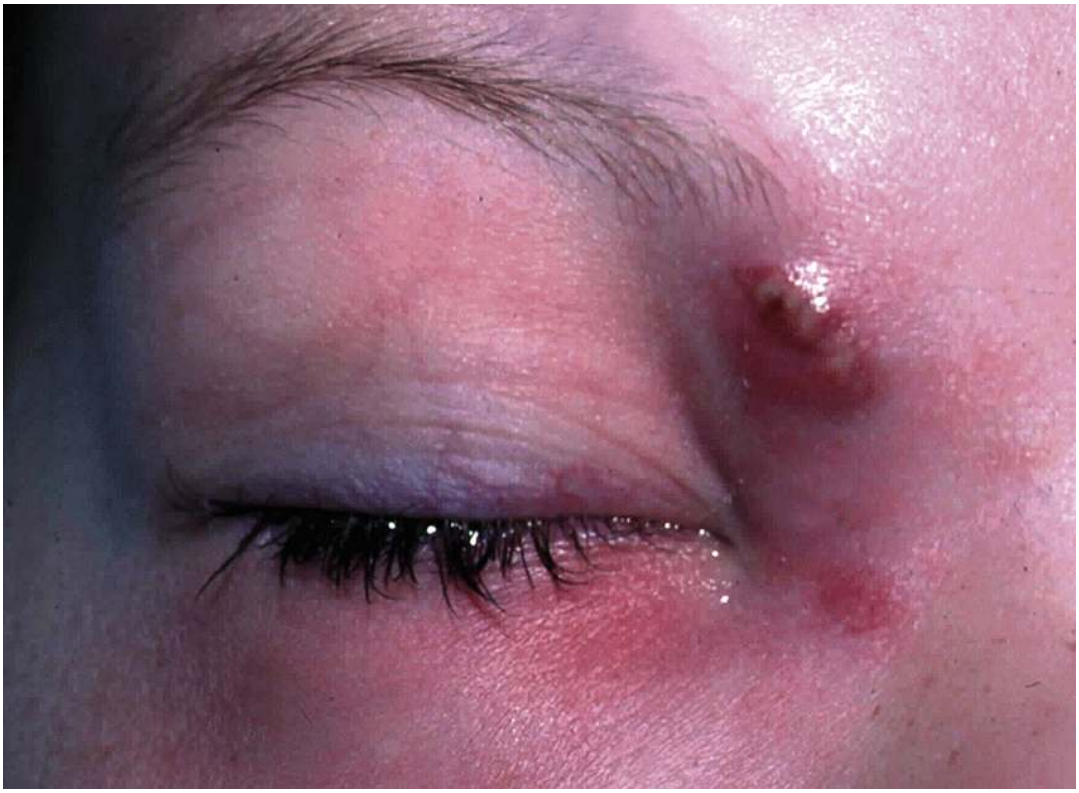

FIGURE 61.1 Mild erysipelas with areas of erythema and vesicles.

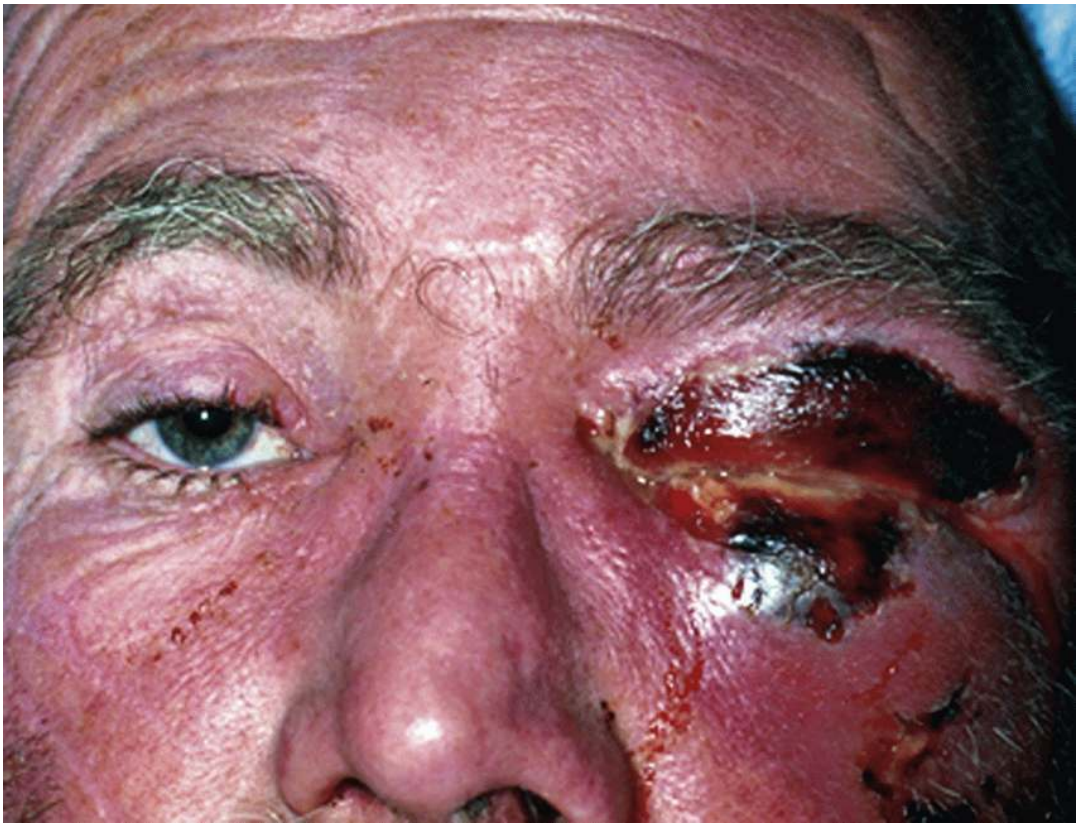

FIGURE 61.2 Severe erysipelas with black skin, ruptured bullae, and areas of raw skin. (Courtesy of Dr. John Holds.)

Differential Diagnosis

The differential diagnosis includes mucormycosis, preseptal cellulitis, contact dermatitis, necrotizing fasciitis (NF), orbital cellulitis, herpes zoster, or cutaneous T-cell lymphoma.[1,14,16,17,18,19,20,21,22,23,24,25,26,27,28] Erysipelas should also be differentiated from other cutaneous conditions that have a special predilection to involve the face like atopic eczema, seborrheic dermatitis, rosacea, heliotrope rash (dermatomyositis), and lupus pernio (sarcoidosis), but the majority of these lesions have a more chronic course and peculiar defining features that make it relatively easy to differentiate from erysipelas.[5,14,16,17,18,19,20,21,22,23,24,25,26,27,28]

Because of the peculiar clinical appearance of erysipelas, one condition that needs to be excluded is allergic contact dermatitis because the eyelid skin is very thin (0.5 mm) compared to the skin of the rest of the face (2.0 mm). This makes the eyelids particularly susceptible to contact dermatitis, which usually develops as a type IV hypersensitivity reaction elicited upon reapplication of a chemical to the skin after previous immunological sensitization. However, contact dermatitis is not associated with pain or tenderness; therefore, the presence of these symptoms together with a history of trauma should alert the clinician to the possibility that an infectious process may be going on.[16]

Another condition that also needs to be promptly excluded is NF, which is a rapidly progressive and potentially fatal bacterial infection that may also be precipitated by minor trauma, and in the periocular region may also be caused by group A *S. pyogenes*.[1,17,18,19,20,21,22,23,24,25] NF is not infrequently encountered in the periorbital region, but it originates at a deeper level than erysipelas (muscles, fascia, and subcutaneous fat) and may progress rapidly resulting in eyelid necrosis.[1,17,18,19,20,21,22,23,24,25] Of note is that when NF was initially described by Fournier in 1883, it was also known as gangrenous erysipelas or necrotizing erysipelas, which underlies the fact that *(Print pagebreak 408)* erysipelas itself may progress to NF if the condition is not properly treated.[24] Some of the older reports of isolated eyelid erysipelas may have confused the condition with NF,[3,28] and indeed during the early course of the disease, both conditions may be clinically similar, and it may be impossible to differentiate them, although NF patients have more severe pain and more significant systemic toxicity.[1,17,18,19,20,21,22,23,24,25] Laboratory investigations may help distinguish NF from erysipelas. A white blood cell count >15,400 cells/mm^3, a serum sodium level <135 mEq/L, a serum lactate level of >2.0 mmol/L, and a C-reactive protein level ≥150 mg/L are suggestive of tissue necrosis.[1,17,18,19,20,21,22,23,24,25]

Treatment

Empiric antimicrobial therapy (β-lactams) should be started immediately, to be modified later if the specific pathogen is identified.[1,2,10] This may be combined with the topical application of an antibiotic or a steroid/antibiotic ointment.[29] Treatment may be initiated with oral flucloxacillin alone. The definitive treatment for presumed streptococcal infections is intravenous benzylpenicillin 600 to 1200 mg q6 hours daily, and the parenteral regimen is reserved for more severe cases.[2] In the case of penicillin allergy, clarithromycin 500 mg twice daily or intravenous clindamycin 600 mg q8 hours has been recommended.[2]

Prognosis

If properly treated, the disease typically settles over 1 to 2 weeks, although recurrences can still be observed, which may impact the patient's quality of life.[1,2] If recurrences do occur, they may require long-term preventive antibiotic prophylaxis with a daily dose of penicillin V (500 mg-2 g daily); however, if secondary penicillin prophylaxis is stopped early, any beneficial protective effect may be lost.[2]

If erysipelas is inadequately treated, the condition may lead to the development of a subcutaneous abscess, which may spread remarkably rapidly, extending into the deep subcutaneous and fascial tissues leading to NF. Untreated erysipelas may also progress to septicemia,[4] and some streptococcal infections may be fatal, especially in infants, or if the patient is debilitated or immunosuppressed.[4] As with many streptococcal infections, recurrent infections may trigger autoimmune diseases like acute poststreptococcal glomerulonephritis, acute rheumatic fever, and rheumatic heart disease.[30] In less severe cases, long-term eyelid sequelae include lower eyelid cicatricial ectropion, upper eyelid entropion, cicatricial epicanthal folds, or persistent eyelid lymphedema.[3,6] Moreover, chronic lymphedema is not just a consequence of erysipelas, but may be a risk factor for the condition as well.[6]

Histopathology

This distinctive form of cellulitis has marked subepidermal edema[31] that may cause vesiculobullous lesions.[32,33] Beneath the marked edema zone, there is a diffuse and heavy infiltrate of neutrophils without abscess formation (Figure 61.3).[31] Neutrophils may be accentuated around blood vessels (Figure 61.3A), and there may be dilation of blood vessels and lymphatics. As the lesions heal, leukocytes diminish, and granulation tissue may form beneath the zone of subepidermal edema.[31] The streptococcal species can be identified by direct immunofluorescence staining[34] or next-generation sequencing of 16S ribosomal RNA,[35,36] if necessary.

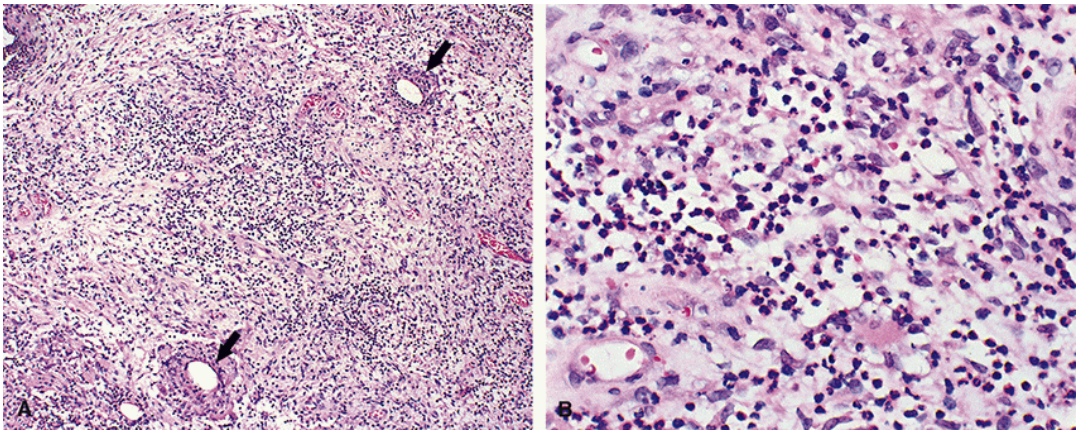

FIGURE 61.3 A, The dermis in erysipelas is edematous with a diffuse and heavy infiltrate of neutrophils, which may be accentuated around dilated blood vessels (arrows). B, Neutrophils predominate in the edematous dermis of acute erysipelas.

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CHAPTER 62

Erythema Multiforme

Key Points

- Erythema multiforme (EM) is an acute, self-limited or recurrent, immune-mediated disorder that affects the skin and mucous membranes
- Clinically, EM is classified as EM minor and EM major based on the distribution of lesions, severity of the inflamation, and extent of mucosal involvement
- EM minor is typically infectious in origin and is usually seen in young adults; mucosal lesions are rare
- In EM major, two or more mucosal sites are severely involved, most often the oral, buccal, and labial mucosa as well as the conjunctiva
- In about 90% of cases, the precipitating agent is infectious, with herpes simplex virus accounting for the majority of cases
- The most common inciting drugs are antibiotics, nonsteroidal anti-inflammatory drugs, and anticonvulsants
- Skin lesions appear as well-defined, elevated, target-shaped lesions with three concentric circles, less than 2 to 3 cm in diameter
- Treatment depends on the severity of the disease and should include management of any associated viral infection, and suspected inciting drug should be discontinued

Erythema multiforme (EM) was first described by Ferdinand von Hebra in 1860 as a benign, self-limited, symmetrical, polymorphous erythematous rash confined to the skin.[1,2] In 1922, Stevens and Johnson[3] described a severe acute febrile illness characterized as a new eruptive cutaneous disorder associated with stomatitis and ophthalmia. In 1950, Thomas[4] combined these two entities as EM and suggested a division into two forms: EM minor (von Hebra) and EM major (Stevens-Johnson syndrome [SJS]) as distinct clinical forms along the same disease spectrum.[5] Subsequently, the term SJS became considered to be a more severe form of EM.[6]

In 1956, Lyell[7] described a clinical condition characterized by extensive epidermal loss, which he termed toxic epidermal necrolysis (TEN). Later studies showed that both SJS and TEN shared many characteristics, such as similar inciting drugs, the development of epidermal necrosis in more severe cases of SJS, and atypical cutaneous and mucosal target-like lesions.[8,9,10] Subsequently, EM, SJS, and TEN were all considered to be variants along a clinical spectrum.[11]

However, in 1993, based on the distribution of lesions, morphological criteria, and inciting factors, an international consensus classification defined five related severe bullous skin conditions that included the major form of EM, as well as SJS and TEN.[12] They proposed a novel classification with EM designated as a different entity from SJS/TEN, with its own etiology, pathophysiology, and clinical course. Later, pediatric EM was characterized as a separate entity, based on epidemiological, etiological, clinical, laboratory, and treatment characteristics.[13]

In EM, children are mostly affected and the inciting factor is predominantly infectious. In SJS and TEN, adults are most commonly affected, and inciting factors are usually drug related, although in children infectious causes are more frequent.[14] Skin detachment is rare in EM but involves more than 30% of the body surface area in TEN. In EM, the typical skin lesions are raised, sharply demarcated, and target shaped with three concentric rings and are nonprogressive. In SJS and TEN, they are less well defined, flat, and atypical, with only two concentric rings around a central epidermal lesion, and may be confluent.[12] It is still unclear whether EM and SJS should be considered separate diseases or variations along a single disease spectrum. But since both have distinctive clinical characteristics, we will treat them in separate chapters in this volume.

EM is an acute, self-limited, or recurrent, immune-mediated disorder that affects the skin and mucous membranes.[15,16,17,18] It is characterized by target or iris-shaped, erythematous papules, preferentially localized on the skin of the extremities and trunk.[19,20,21] Mucous membranes can also be involved, primarily seen on the oral mucosa and less frequently, the conjunctiva.

EM occurs worldwide with an estimated prevalence rate of 0.01% to 1%,[17,22] and the disease can show a peak incidence in the spring or fall.[23] It affects patients at any age but is seen more frequently in young adults aged 20 to 40 years,[15] with only about 20% of cases occurring in children.[17,24] The condition is slightly more common in women than in men with a M:F ratio of 1.5:1.[15,25]

Clinically, EM is classified as EM minor and EM major based on the distribution of lesions, severity of the inflamation, and extent of mucosal involvement.[26,27] EM minor is typically infectious in origin and is usually seen in young adults. Skin lesions occupy less than 10% of the body surface area and have a symmetric distribution mostly on the extensor (acral) surfaces of the extremities.[15] Circular, erythematous plaques, 2 to 20 mm in size, are seen in a *(Print pagebreak 411)* concentric target-shaped pattern with three distinct rings. Mucosal lesions are uncommon. When present, they are seen only on a single mucosal area and are usually mild, occurring most often on the oral mucosa, gingiva, and palate, and on the vermilion border of the lips. The conjunctiva is very rarely involved. Occasionally, EM minor can be isolated to the oral mucosa alone, without skin involvement.[15] Both skin and mucosal lesions usually heal without scarring within 1 to 4 weeks.

In EM major, two or more mucosal sites are severely involved, most often the oral, buccal, and labial mucosa as well as the conjunctiva.[11,28] Less frequently, the floor of the mouth, palate, and gingiva are involved.[15] Typical target skin lesions occupy less than 10% of the body but are larger than in EM minor. Mild systemic symptoms, such as fever or chills, may also be seen.

Etiology and Pathophysiology

EM is an acute hypersensitivity reaction arising from immune complex mechanisms involving antigen-antibody reactions that target small blood vessels in the skin or mucosa.[15] In about 90% of cases, the precipitating agent is infectious, with herpes simplex virus (HSV) accounting for 70% to 80% of these.[29,30,31] It has been suggested that autoreactive T cells triggered by viral antigen-positive cells containing the HSV DNA polymerase gene play an important role in the development of EM.[32] Viral gene expression in the skin and recruitment of T helper 1 cells initiate an inflammatory response from upregulation of cytokines and chemokines, resulting in epidermal damage with keratinocyte lysis and apoptosis.[15,33,34]

A wide variety of other infectious agents can initiate an EM response.[15] These include Epstein-Barr virus, cytomegalovirus, varicella zoster virus, adenoviruses, enteroviruses, and coxsackievirus B5. Causative bacterial agents include *Mycoplasma pneumoniae*, *Corynebacterium diphtheria*, hemolytic streptococci, *Salmonella*, and *Pneumococcus.* [15] EM has also been associated with vaccinations, most commonly childhood vaccines of measles, mumps, and rubella, as well as human papillomavirus, pneumococcal, smallpox, polio, and rabies vaccines.[35,36]

Certain medications can also trigger EM. The most common inciting drugs are sulfonamides, penicillins, amoxicillin, ampicillin, erythromycin, tetracyclines, nonsteroidal anti-inflammatories, and anticonvulsants.[15,27] EM has been reported as a complication of imiquimod therapy, proposed as a result of the application to wounded skin with impeded barrier function that allows more systemic absorption triggering an EM response from the release of cytokines induced by imiquimod.[37,38,39,40] A case of EM induced by fluconazole in an immunocompetent patient was also reported.[41]

Some immune disorders, such as graft-versus-host disease, inflammatory bowel disease, polyarteritis nodosa, sarcoidosis, and systemic lupus erythematous, have also been associated with EM.[15] Renal and gastric carcinoma and food additives (benzoates and nitrobenzene) have rarely been reported to trigger EM.[42,43]

Genetic factors have also been implicated in the development of EM, with several human leukocyte antigen (HLA) phenotypes, such as HLA 36 and HLA 35, possibly playing a predisposing role.[30,44,45]

Clinical Presentation

The histopathologic and laboratory findings of EM are nonspecific so that the diagnosis is mainly based on the history and clinical presentation. The onset of characteristic target lesions on the skin and mucous membranes is typically acute, often preceded by an HSV infection or a history of recent drug ingestion.[15] The skin rash typically appears as well-defined, elevated, target-shaped lesions with three concentric circles, less than 2 to 3 cm in diameter. Each ring is separated by near normal skin. The peripheral ring is generally erythematous; the middle zone is often clearer, edematous, and palpable; and the center is erythematous, covered by a blister.[24] Lesions occur symmetrically on the palms and backs of the hands, the feet, and the extensor surfaces of the limbs. The trunk is often spared, but the face and ears can be involved.

The clinical behavior of EM has been divided into three subgroups that include classical or isolated EM, recurrent EM, and persistent EM.[46] In the classic group, skin lesions are symmetric, target or iris-shaped lesions characterized by three concentric erythematous rings separated by rings of near normal skin on the dorsal surfaces of hands, feet, elbows, and knees.[47] Lesions are usually asymptomatic, but occasionally can be associated with burning or itching. Spontaneous resolution without scaring usually occurs within 1 to 4 weeks, although transient hypopigmentation or hyperpigmentation may be seen.[47] Macules, papules, vesicles, bullae, and urticarial plaques can be seen, but occur less frequently (Figure 62.1). Mucosal lesions are rarely seen in EM minor, usually in the mouth or the conjunctiva.[48] In EM major, mucosal lesions are typical, involving at least two different sites, with one usually involving the oral mucosa.

Recurrent EM can be seen as repeated episodes occurring over years,[45] but an inciting factor can be identified in only 42% of these cases.[42] Prodromal symptoms such as fever, malaise, headache, cough, rhinitis, sore throat, myalgia, arthralgia, and nausea precede the eruption of cutaneous lesions by 7 to 14 days.[15]

Persistent EM is rare and is characterized by the presence of typical and atypical lesions over a protracted course lasting months to years without periods of resolution.[46,49,50,51] Lesions are often more inflammatory, necrotic or bullous than in other forms of EM (Figure 62.2),[49] and the condition can be associated with malignancy,[52] inflammatory bowel disease,[53] and some viral infections.[51]

Oral mucosal lesions presenting as diffuse erythema or superficial ulcerations occur in more than 70% of EM cases, mostly with EM major.[15,25,47,54]

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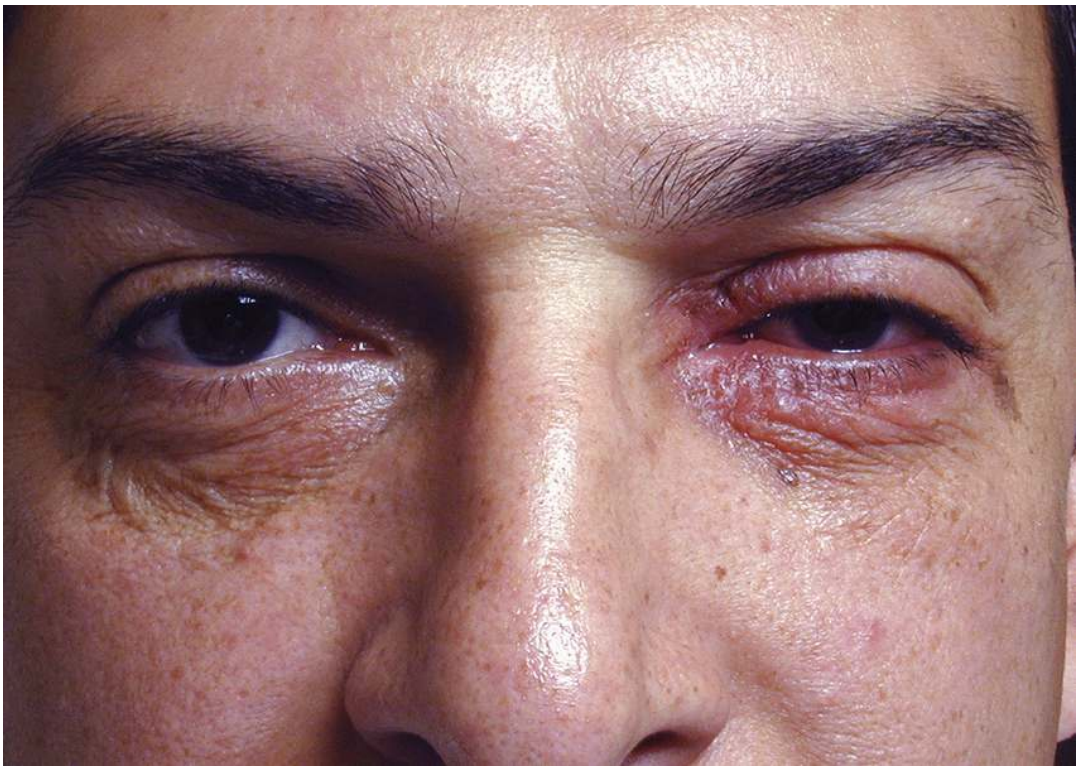

FIGURE 62.1 Diffuse macules of erythema multiforme involving the upper and lower eyelids. (Courtesy of Dr. Robert Goldberg.)

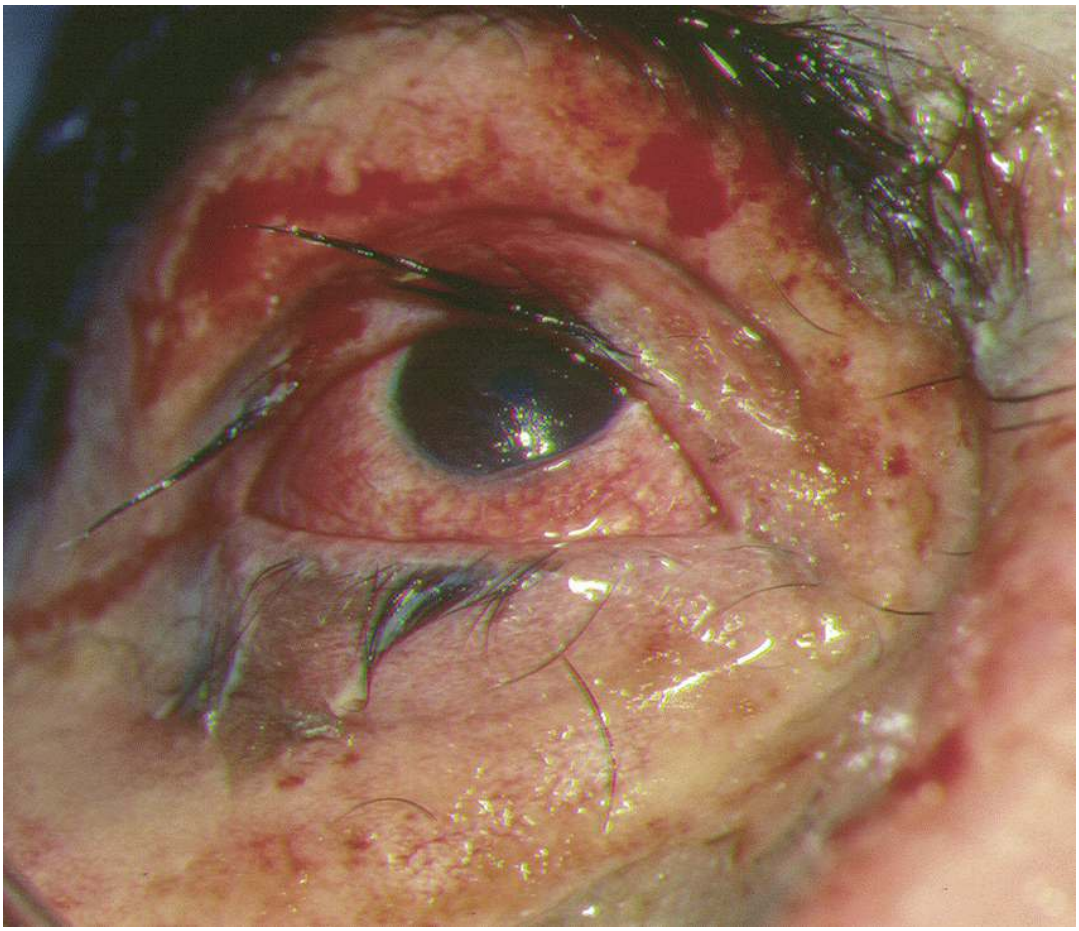

FIGURE 62.2 Persistent inflammatory erythema multiforme with areas of bullae and necrosis. (Courtesy of Dr. Charles Soparkar.)

Differential Diagnosis

The differential diagnosis of EM includes autoimmune vesiculobullous diseases, such as pemphigus vulgaris, bullous pemphigoid, or paraneoplastic pemphigus, urticaria, SJS, drug-induced eruptions, and primary herpetic gingivostomatitis.[15] Pemphigus vulgaris occurs in middle-aged individuals and presents as a chronic disease with multiple shallow, irregular, and painful cutaneous and oral ulcers proceeded by vesicles or bullae. It is characterized by periods of remission or exacerbation. Bullous pemphigoid is a chronic condition that presents with large intraoral, ocular, and other mucous membrane bullae or vesicles. Paraneoplastic pemphigus is another chronic disease characterized by progressive polymorphous skin lesions and severe mucosal and conjunctiva involvement in the presence of an underlying malignancy. Urticaria is a transient condition presenting as plaques with a central zone of normal skin or erythema. Fixed drug eruptions are associated with medication exposure. They present as single or multiple erythematous skin plaques with or without central necrosis. Mucosal involvement is uncommon. Primary herpetic gingivostomatitis is usually seen in children younger than 5 years and presents with fever and general malaise followed by multiple painful oral vesicles and ulcers. A skin rash is usually not present.

EM major can be confused with SJS. Mucosal erosions are found in both diseases, but EM is characterized by typical acral cutaneous three-ring elevated targets, whereas SJS is characterized by purpuric erythematous macules, and flat atypical targets with epidermal detachment preferentially localized on the trunk.[12] EM is predominantly due to infection, primarily with the HSV,[17,42,55] and *M. pneumoniae*,[56,57,58] whereas SJS is almost exclusively due to drug hypersensitivity.[12,59,60,61]

Treatment

The clinical course of EM is variable, and treatment varies depending upon the severity of the disease. Treatment that is appropriate for the management of any associated active viral infection should be instituted, and any drug suspected to be an inciting factor should be discontinued.[20]

Treatment of EM minor is primarily symptomatic with topical anti-inflammatory or analgesic agents. Fluocinonide 0.05% or other topical steroid agents are applied to skin lesions two to three times per day, and mouthwash containing equal parts of viscous lidocaine 2%, diphenhydramine (12.5 mg/5 mL), and an aluminum hydroxide and magnesium hydroxide mixture (Maalox) can be gargled and spit out up to four times per day.[15]

In more severe EM major with significant painful oral lesions, supportive care might include a liquid diet, intravenous fluids, electrolytes, and nutritional support. Prednisone 40 to 60 mg per day tapered over 2 to 4 weeks may be required. In some cases, systemic steroids may only partially suppress the disease, and in fact, they may even prolong the duration of attacks.[62] For cases initiated by HSV in which attacks are recurrent and severe, continuous antiviral therapy with either acyclovir, 400 mg twice daily, valacyclovir, 500 mg twice daily, or famciclovir, 250 mg twice daily, is effective.[42,63,64] For patients who fail to respond to systemic antiviral therapy, azathioprine, 100 to 150 mg/d or 2 mg/kg/d, or mycophenolate mofetil, 1 gm twice per day, have been advocated.[17] Dapsone has been used for recurrent EM with mixed results. Complete resolution was reported in 23% to 33% of cases and partial resolution in 88%.[42,55,63]

Prognosis

The prognosis for EM is mainly related to the body surface and mucosal areas involved. Spontaneous healing of skin lesions is typically seen in 2 to 3 weeks for EM minor and 4 to 6 weeks for EM major. Mucosal lesions usually take longer to heal.[19,24] *(Print pagebreak 413)* Bacterial superinfections are a potential complication of skin or mucosal lesions.[18,19] Severe conjunctival mucosal lesions can cause synechia, which can result in blindness.

Histopathology

The histological features of cutaneous and mucous membrane lesions in EM are similar[65] and depend on the lesion's age and clinical appearance.[65,66,67,68,69] The earliest changes, in erythematous macules, are a sharply delimited perivascular infiltrate of predominantly lymphocytes in the upper dermis associated with endothelial cell swelling and thickened vessel walls.[67,68] Neutrophils, eosinophils, and plasma cells may be present, or there may be only lymphocytes and macrophages.[67] Dermal edema follows the perivascular inflammatory phase,[67] and then comes intercellular edema between keratinocytes, with some biopsies having epidermal necrosis with rounded and eosinophilic necrotic keratinocytes that may be anucleate or have pyknotic nuclei.[65,68] As macules progress to papules, inflammatory cells extend into the epidermis (“exocytosis”), keratinocyte intracellular edema advances leading to vacuolar (liquefactive) degeneration (Figure 62.3A), and subepidermal and intraepidermal bullae develop (Figure 62.3A and B) along with more necrotic keratinocytes (Figure 62.3C).[67,68] Lymphocytes may surround dying keratinocytes (“satellite cell necrosis”).[66] Target lesions (also known as iris lesions) have a central zone of subepidermal separation from the epidermis with necrotic keratinocytes in the overlying epidermis.[66] The periphery of target lesions has dermal changes similar to those in the macules.[66]

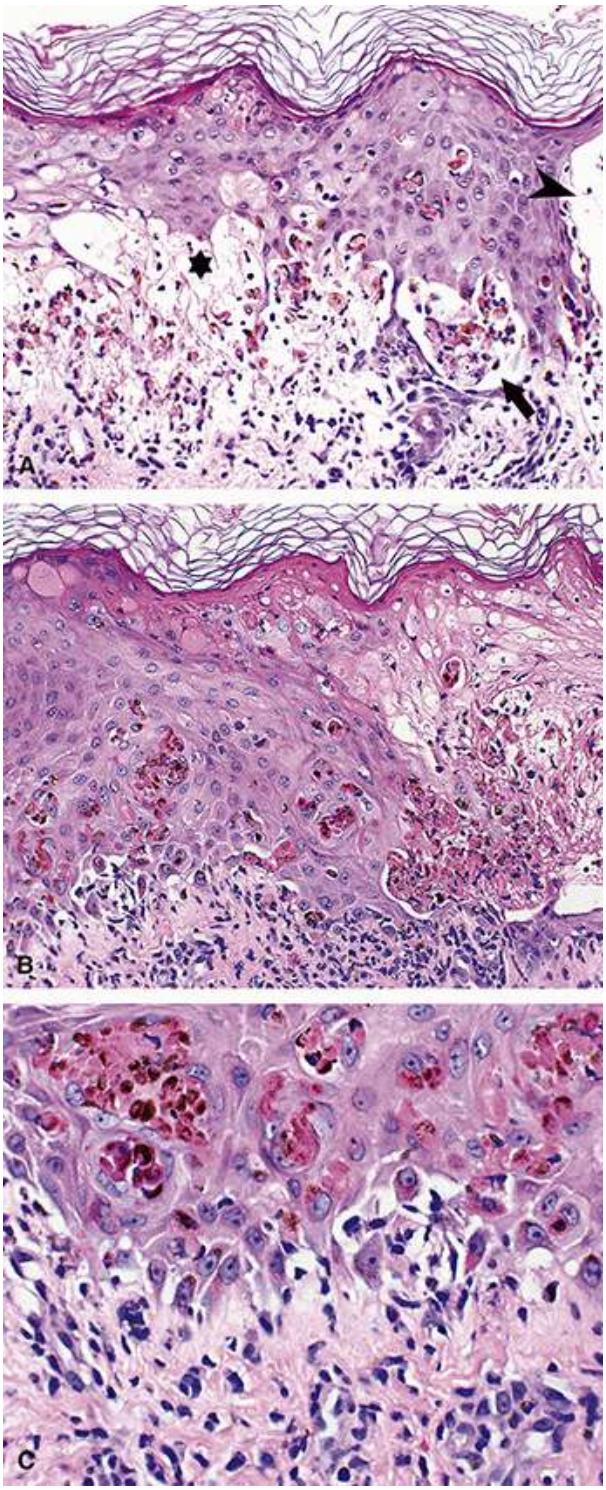

FIGURE 62.3 A, This erythema multiforme target lesion shows prominent vacuolar degeneration of basal keratinocytes (★), a small intraepidermal blister (vesicle) containing necrotic keratinocytes (arrow), and the edge of a larger intraepidermal blister (arrowhead). B, The target lesion has numerous brightly eosinophilic necrotic keratinocytes, along with an area of vacuolar degeneration occupying almost the full thickness of the epidermis. Macrophages and lymphocytes are in the papillary dermis with extension into the basal epidermis. C, Close-up view of the necrotic keratinocytes having brightly eosinophilic cytoplasm and pyknotic or absent nuclei. Melanin is in many of the necrotic cells of this black patient.

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CHAPTER 63

Fibrous Histiocytoma

Key Points

- Fibrous histiocytoma (FH) is a soft-tissue tumor characterized by a proliferation of spindle-shaped cells, usually admixed with inflammatory cells
- It is believed to originate from a primitive mesenchymal cell with differentiation into fibroblast or histiocyte-like components
- This tumor can occur in any part of the body and can be benign or malignant
- Eyelid lesions usually present as a slow-growing, firm, painless, subcutaneous, or tarsal nodular mass, ranging from 4 mm to 1.5 cm in diameter
- Rarely they can be localized to the bulbar conjunctiva where they present as slow-growing, painless, vascular, yellow to pink elevated nodules that occasionally can infiltrate the cornea
- Local surgical excision is the treatment of choice
- Radiation therapy may be helpful as an adjuvant treatment in certain settings
- Local recurrence following surgical excision of benign FH has been reported between 5% and 11%
- Rates of local recurrence for malignant fibrous histiocytoma range from 25% to 75% with a 5-year overall survival rate of 48%

Fibrous histiocytoma (FH) is a common soft-tissue tumor characterized by a proliferation of spindle-shaped cells, usually admixed with inflammatory cells.[1,2] Lesions previously included under this name can be cutaneous or subcutaneous in location. In recent years, cutaneous tumors located in the dermis are more commonly referred to as dermatofibroma.[3,4] Deeper, subcutaneous tumors of this type are termed FH. These are less common than cutaneous forms and generally are larger and better circumscribed.[2,5,6,7]

FH was first described in 1961 by Kauffman and Stout.[8] It frequently involves muscular, fibrous, and fatty tissues.[9] Ocular involvement is infrequent and primarily limited to the orbit where it represents 0.5% of all benign orbital tumors and is considered to be the most common primary mesenchymal tumor of the orbit seen in adults.[10,11] Rarely, these tumors can arise in the conjunctiva, episclera, choroid, and lacrimal sac.[12,13,14,15,16,17,18,19,20,21,22,23,24,25] Its occurrence in the eyelid is rare.[4,19,26,27,28,29,30,31,32,33,34,35,36,37]

Malignant fibrous histiocytoma (MFH) was described in 1961 by Kauffman and Stout[8] and has been considered to be the most common adult soft-tissue sarcoma.[38,39] However, major advances in immunohistochemistry during the past several decades have led to a reclassification of many tumors once included under MFH,[40] so that nearly three-fourths of tumors previously diagnosed as MFH are now considered to represent alternative diagnoses.[41] Although controversial, some studies have indicated that the most probable cells of origin for MFH may be primitive mesenchymal or fibroblastic cells, rather than histiocytic cells. As a result, MFH is now frequently referred to as pleomorphic undifferentiated sarcoma.

MFH develops in males in approximately two-thirds of cases, arising most commonly during the sixth and seventh decades of life.[42,43] It most commonly occurs in the head and neck region, trunk, extremities, and retroperitoneum, but very rarely is seen in the eyelid.[37,44,45,46,47,48] It has a high potential for local muscle, perineural, and blood vessel invasion, and to progress to distant metastasis.

Etiology and Pathogenesis

FH is a soft-tissue neoplasm with both fibrocytic and histiocytic components. The tumor was initially thought to arise from two different cell types,[8] but it is now believed to originate from a primitive mesenchymal cell with differentiation into fibroblast or histiocyte-like components.[10] This tumor can occur in any part of the body and can be benign or malignant.[8] The orbit is the most common ocular site.[10] Case reports have described the occurrence of conjunctival FHs in individuals with a history of trauma, leukemia, chemotherapy, prednisone use, radiation, rheumatoid arthritis, and xeroderma pigmentosum.[49,50] There is also an association between systemic lupus erythematosis, multiple dermatofibromas, and FH in extraocular locations.[51]

Angiomatoid FH is a rare form with intermediate biologic potential most often arising in the extremities of children and young adults. Only one case has been described in the eyelid.[33] Genetic abnormalities have been described in angiomatoid FH, associated with three characteristic gene fusions, EWSR1-CREB1, EWSR1-ATF1, and, rarely, FUS-ATF1. Angiomatoid FH is now recognized in an increasing number of sites and is known to display a variety of unusual histologic features.[52,53,54]

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For MFH, previous ionizing radiation therapy (RT) appears to be a risk factor in some cases.[55,56,57] It is the most commonly diagnosed sarcoma in patients with prior radiation exposure in the head or neck region, and patients with radiation-associated tumors in this region have a worse prognosis than those with tumors not associated with prior RT.[58,59,60,61] Genetic alterations in MFH include the p53 gene,[62] as well as H- and K-ras gene activation.[63]

Clinical Characteristics

Benign FHs involve subcutaneous tissue and generally are seen in adults older than 25 years, with a mean age of 40 years.[64] The majority occurs on the extremities, but they also rarely occur in the head and neck region. Clinically, deep FHs are usually painless, well-circumscribed, slowly enlarging encapsulated masses. Eyelid FH usually presents as a firm, painless, subcutaneous, or tarsal nodular mass, ranging from 4 mm to 1.5 cm in diameter. They are seen equally on the upper and lower eyelids, and rarely in the medial canthus.[4,26,28,32,35,65,66,67,68]

Eyelid lesions often grow slowly but can occasionally enlarge more rapidly over several weeks to months. Males are affected slightly more frequently than females, and the mean age at presentation is 37 years, with a range of 17 to 74 years. These tumors often are associated with local edema and erythema. Several cases have been localized to the bulbar conjunctiva,[14,69,70,71,72] where they present as slow-growing, painless, vascular, yellow to pink elevated nodules measuring 3 to 6 mm in diameter (Figure 63.1) Occasionally they can infiltrate the cornea.

For MFHs, the clinical presentation typically presents as a painless or painful, rapidly enlarging subcutaneous nodule that can be invasive and destructive of surrounding tissues (Figure 63.2). They are seen most commonly in the head and neck, extremities, and trunk.

Differential Diagnosis

The diagnosis of benign FH continues to be difficult and is frequently a diagnosis made through the exclusion of simulating lesions. The most important lesions in the differential diagnosis are malignant neoplasms, particularly MFH. MFH usually progresses more rapidly, is more likely to be painful, and generally affects younger males at a mean age of 26 years, compared with 47 years with a 60% male predominance for benign FH.[73] The recurrence rate for MFH is 40% with tumor-related mortality of 47%. Immunohistochemistry is important in distinguishing among these lesions.

Other lesions in the differential include xanthelasma, tuberous xanthoma, juvenile xanthogranuloma, and necrobiotic xanthogranuloma. Juvenile xanthogranuloma most commonly occurs in infants and children, while xanthelasma, *(Print pagebreak 418)* tuberous xanthoma, and necrobiotic xanthogranuloma are diseases of middle-aged and elderly patients.[74] Xanthelasmas are typically elevated, yellowish plaques, usually bilateral, and are located on the medial surfaces of the upper and lower eyelids.[74] Tuberous xanthomas appear as multiple, firm, nontender, yellowish nodules that can involve the upper and lower eyelids bilaterally.[75] Necrobiotic xanthogranuloma is characterized by indurated, nontender, dermal, or subcutaneous yellow nodules and plaques that infiltrate the eyelids and periorbital structures.[76]

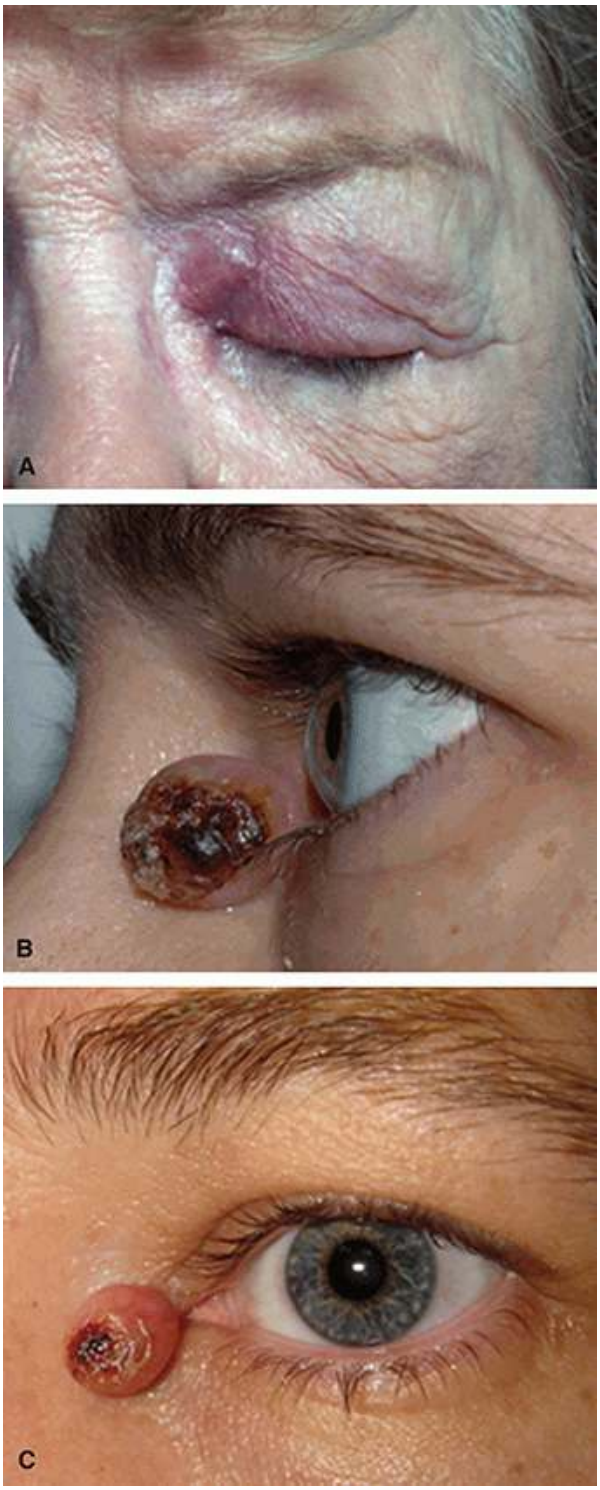

FIGURE 63.1 A-C, Nodular lesions of benign fibrous histiocytoma in the medial eyelid and medial canthus. (A, Courtesy of Dr. Robert Goldberg; B and C, Courtesy of Dr. Ramon Malhotra.)

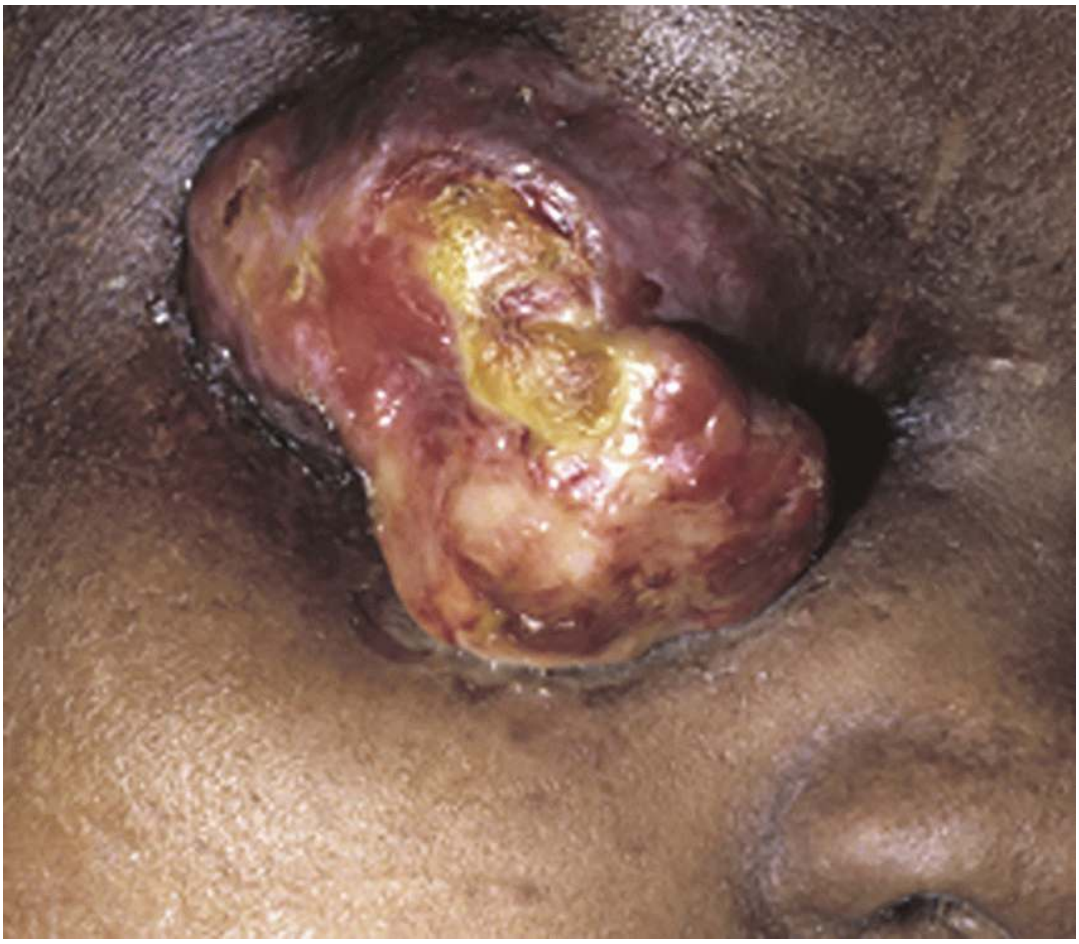

FIGURE 63.2 Malignant fibrous histiocytoma of the upper eyelid following radiation therapy for retinoblastoma as a young child.

The differential diagnosis of conjunctival FH must include neoplastic lesions such as corneal intraepithelial neoplasia, squamous cell carcinoma, amelanotic melanoma, and conjunctival lymphoma. FH can also be misdiagnosed as pterygium, chalazia, leiomyoma, or nodular episcleritis.[16]

Treatment

Local surgical excision is the treatment of choice for FH without sacrificing structures that would cause major functional or cosmetic morbidity. Complete excision is often difficult due to the complexity of eyelid structure and function so that for MFH local recurrence rates are high, reported to range from 19% to 66%.[77,78,79,80] In a large study associated with the clinical size of operative margins with recurrence rate, 86% of patients treated with resections with margins less than 3 mm experienced local recurrence, compared with 66% following wider margins greater than 3 mm. Even with more radical resection with the clearance of regional lymph nodes, adjuvant RT, and chemotherapy or immunotherapy, 27% of patients can experience recurrence.[81]

RT may be helpful as an adjuvant treatment in certain settings.[82,83] Effective RT should employ a field that includes the tumor site and 5 cm or more of peripheral tissue, at doses ranging from 50 to 65 Gy.[84,85,86] In one study of patients with MFH of the extremities undergoing excisional surgery followed by postoperative RT, the 10-year relapse-free survival was 62% and the overall survival rate was 80%.[87] Other studies have suggested that preoperative RT may provide better overall survival rates than postoperative RT.[88] Traditional chemotherapy is typically recommended only for widespread disease, but several clinical trials have not shown a significant benefit.[89,90]

Prognosis

Local recurrence following surgical excision of benign FH has been reported between 5% and 11%,[2] mostly related to incompletely

resected, poorly defined infiltrative margins.[74,91]

For MFH, rates of local recurrence range from approximately 25% to 75%. Local recurrence may be attributed to insufficient primary tumor clearance, high rates of microsatellites, and in-transit metastases. MFH arising on the head and neck seem to exhibit more aggressive behavior than those occurring in other regions of the body. For patients with head and neck tumors, a 5-year overall survival rate of 48% has been reported compared with 77% for patients with tumors arising on the trunk and extremities.[92] Distant metastases are relatively common, primarily involving the lungs.

Histopathology

FHs of the skin are now classified by the World Health Organization (WHO) as dermatofibromas,[93] and their histopathological features are presented in Chapter 59. The WHO now classifies soft-tissue FHs as deep FHs.[94] Deep FHs are typically better circumscribed (Figures 63.3 and 63.4), are more cellular, and have a more prominent storiform pattern than their cutaneous counterparts.[94,95] There may be a vascular pattern reminiscent of a hemangiopericytoma/solitary fibrous tumor with thin-walled branching vessels (Figure 63.3A).[94,95,96] Tumor cells are plump, ovoid to spindle-shaped with oval or elongated, vesicular nuclei, and eosinophilic cytoplasm.[94,96] The tumors may lack foamy histiocytes or giant cells, and hyalinized stroma is common.[94,96] CD34 was expressed in 20 of 50 tumors (40%) examined by Gleason ad Fletcher, and 12 cases had CD34 expression by more than 50% of the cells.[96] Smooth muscle actin immunostaining was positive in 15 of 40 cases (38%). Deep FHs do not express STAT6 in their nucleus; this is useful for differentiating FHs that express CD34 from solitary fibrous tumors, which are $CD34^+$ and $STAT6^+$.[97,98]

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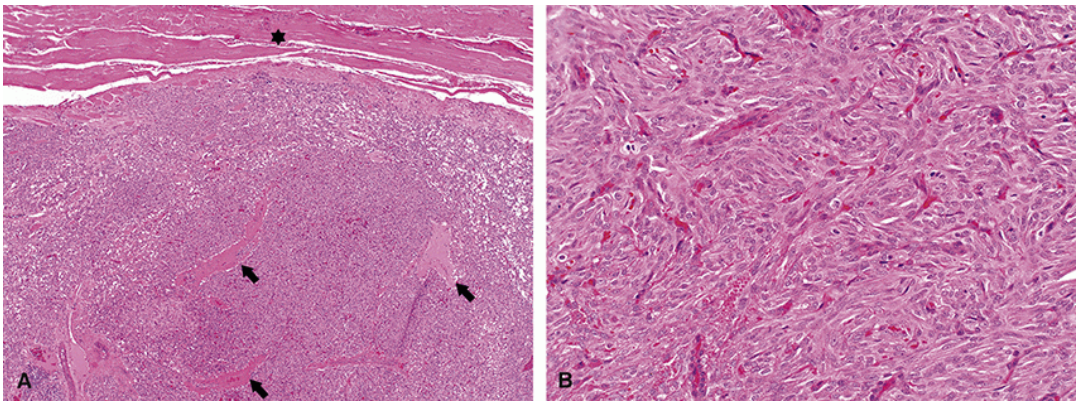

FIGURE 63.3 A, This fibrous histiocytoma arose in the left upper eyelid connective tissue between the orbicularis oculi muscle (★) and the tarsus. The tumor is circumscribed and has several large vessels (arrows) resembling those in solitary fibrous tumors. B, The plump spindle cells have a storiform configuration, which is typical in deep fibrous histiocytomas.

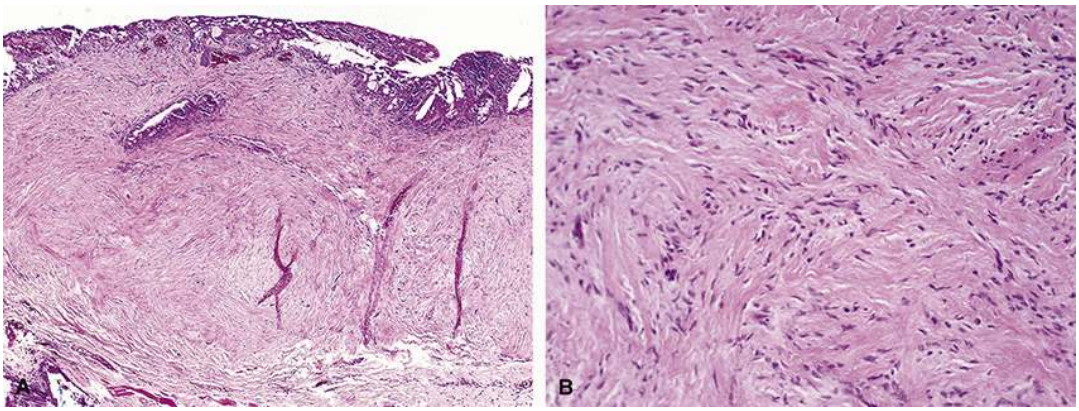

FIGURE 63.4 A, This fibrous histiocytoma arose approximately 30 years after radiation therapy for retinoblastoma as a young child. The tumor was well-circumscribed and located between the conjunctiva and the tarsus. B, The tumor cells are elongated spindle cells with pale eosinophilic cytoplasm. Though the tumor cells resemble those in solitary fibrous tumors and neurofibromas, they did not stain for either CD34 or S100 protein, thus ruling out those possibilities.

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CHAPTER 64

Glomuvenous Malformation (Glomus Tumor)

Key Points

- Glomuvenous malformation is a rare benign hamartoma of the glomus body
- The pathogenesis and genetics of sporadic GVM are poorly understood but *BRAF* or *KRAS* mutations have been identified in some cases
- On the eyelids, lesions generally present as slow-growing, solitary or multiple, bluish to violaceous plaque-like, soft, spongy to firm to nodular lesions
- Solitary lesions appear in adults, and multiple tumors arise more commonly in childhood and may be familial
- The usual treatment of GVM of the eyelid is complete surgical excision
- External beam radiotherapy, stereotactic radiosurgery, and laser ablation have been used for unresectable or incompletely resected tumors
- All reported cases of eyelid GVM have been benign, and surgical excision carries an excellent prognosis with recurrence rates reported in 10% of cases

Glomuvenous malformation (GVM), previously termed glomus tumor or glomangioma, is a rare benign hamartoma of the glomus body,[1] distinct from venous malformations, and comprising less than 2% of all soft-tissue tumors. It occurs most commonly in adults between the fourth and seventh decades of life,[2] although it has been reported even in children.[3] This tumor most frequently subcutaneously occurs in the arms (14%) and legs (13%), with less common occurrence on the trunk (3%).[2]

Terminology in the literature is rather confusing and tumors can arise from both the glomus body and the glomus cell. A glomus cell is a peripheral chemoreceptor mainly located in the carotid bodies and aortic bodies, and less commonly in other organs. They are located along some blood vessels and nerves and help the body regulate breathing. It is able to detect changes in the blood's pH, oxygen saturation, and carbon dioxide levels. Clusters of glomus cells, of which the carotid bodies and aortic bodies are the most important, are called nonchromaffin or parasympathetic paraganglia. They are also present along the vagus nerve, in the inner ears, in the lungs, and at other sites. Tumors arising from glomus cells include glomus jugulare, glomus tympanicum, and paragangliomas in other deep sites. Some publications separate tumors from glomus cells and those from the glomus body as distinct, whereas others refer to both as glomus tumors. Deep-seated GVMs arise in locations that include the mouth, trachea, esophagus, stomach, lungs, colon, vagina, penis, and bones.

The glomus body was first described by Wood in 1812.[4] It is a normal intradermal arteriovenous shunt scattered in the dermis of the skin and is most frequently found in the pulps of the fingers and toes, the tip of the nose, and pinnae of the ears. Their primary function is thought to be thermoregulation.[5] The glomus body shunts blood away from the skin surface when exposed to cold temperature, thus preventing heat loss, and allowing maximum heat flow to the skin in warm weather to allow heat to dissipate. This structure is composed of an afferent arteriole that gives rise to several preglomic arterioles, and these anastomose with venules that are surrounded by a thick sheath with an S-shaped lumen, known as a Sucquet-Hoyer canal.[6,7,8,9,10] The Sucquet-Hoyer canals are lined by endothelial cells, which are surrounded by smooth muscle cells. The glomus bodies are interspersed within the smooth muscle. Hyperplasia of any of the structures composing the glomus body, glomus cells, vasculature, and smooth muscle cells will result in a GVM.[8] Malignant and atypical GVMs have been classified into several subtypes,[11] but none of these have been reported to occur in the eyelids.

Etiology and Pathogenesis

The pathogenesis and genetics of sporadic GVM are poorly understood, and it is unclear what molecular genetic changes might be

involved in their pathogenesis. One study identified *BRAF* or *KRAS* mutations in 4/28 cases (14.3%) of GVM.[12] There is also an association of GVM with neurofibromatosis type 1,[13] and loss of NF1 results in the upregulation of signaling through the mitogen-activated protein kinase (MAPK) pathway. *KRAS* and *BRAF* mutations also signal through this pathway, suggesting a possible role of MAPK in the growth regulation of GVM.

A gene associated with a familial variant of GVM has been localized to chromosome 1p21-22 and involves truncating mutations in the glomulin gene.[14,15] In the familial autosomal dominant form, most affected family members have small multiple lesions on the body. However, occasionally one member will suffer from a more severe form of the disease, having extensive congenital lesions in a segmental *(Print pagebreak 423)* distribution. It has been proposed that such a segmental manifestation of an autosomal dominant skin disorder suggests a postzygotic mutation early in embryogenesis, with loss of heterozygosity.[16]

Clinical Presentation

Only 19 cases of GVM have been described involving the eyelids.[7,8,9,10,17,18,19,20,21,22,23] In two of these cases, similar tumors were mentioned in five additional family members, but no details were given.[8,18] They generally present as slow-growing, bluish to violaceous plaque-like to nodular lesions that often extend over large areas of the face. They may be well defined or diffuse, solitary or multiple, and discreet or confluent. On palpation, they are usually soft, spongy, and compressible, but several have been described as firm. Lesions appear highly vascular, similar to hemangiomas, but are nonpulsatile and without a bruit. Lesions may be associated with tenderness on pressure,[7,8,9,23] which may be caused by pressure on adjacent Pacinian corpuscles associated with the dilatation of the walls of the glomus body.[9] Rarely, lesions may be pigmented and confused with melanoma. Tumors may be present at birth, or appear in childhood or teens,[8,9,23] or later in adult life.[9,17]

GVMs are seen in two forms, as a solitary lesion, which is the more common type (Figure 64.1), and as multiple familial lesions.[7,8,24,25,26,27,28] Solitary lesions tend to appear in adults, are encapsulated, and have extensive numbers of glomus cells.[17] Multiple tumors arise more commonly in childhood, are generally not tender or painful, and may have a familial occurrence.[7,8] They tend not to be encapsulated and to have fewer glomus cells. Several authors have noted the familial occurrence of multiple GVM with an autosomal dominant pattern of inheritance.[26,27,28]

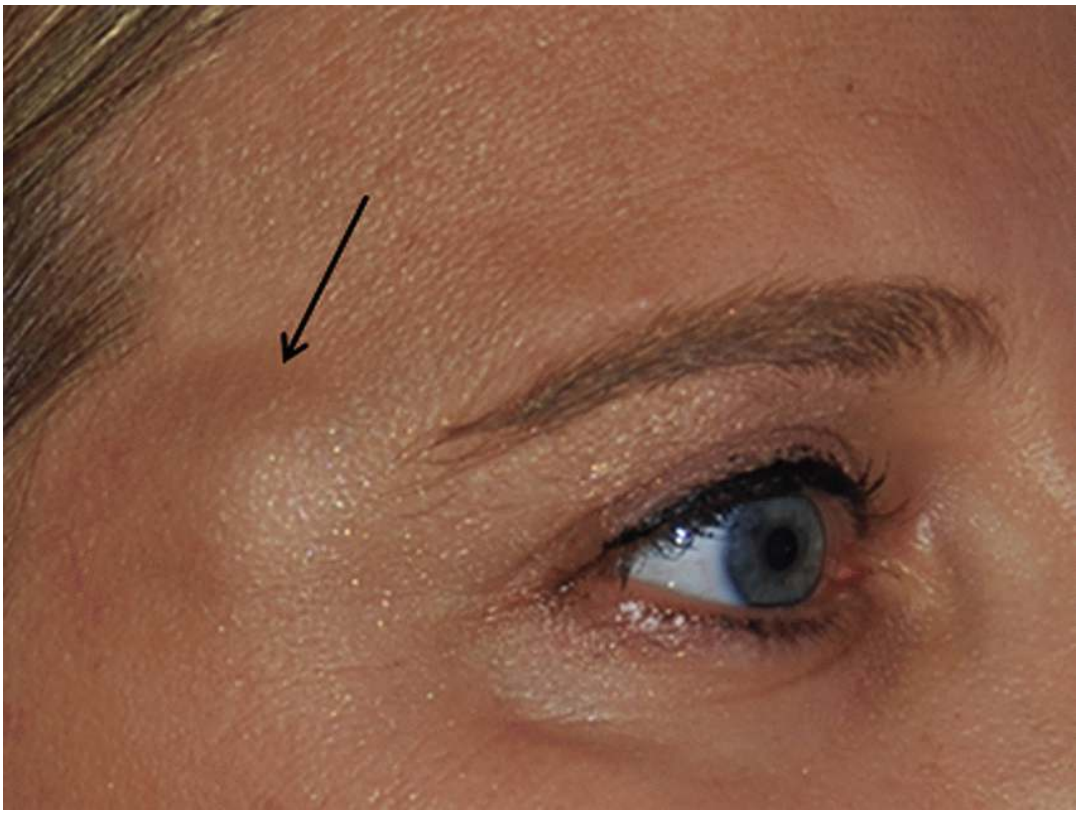

FIGURE 64.1 Solitary subcutaneous glomuvenous malformation in the lateral brow (arrow). (Courtesy of Dr. Kyle Godfrey.)

While these lesions have been reported in the orbit,[29,30,31] only one case of eyelid GVM was found at surgery to be penetrating the orbital septum, but without deep orbital invasion.[7]

Differential Diagnosis

GVMs can easily be diagnosed microscopically, but the clinical diagnosis is often difficult. A variety of solid violaceous tumors are often confused with it, including Merkel cell tumor, capillary, and cavernous hemangioma, varix, Kaposi sarcoma, pyogenic granuloma, lymphangioma, and angiosarcoma.[8]

Treatment

The usual treatment of GVM of the eyelid is complete surgical excision (Figure 64.2).[8] However, surgical removal is not always possible and depends on the tumor location, any involvement of critical vascular or neural structures, and the details of vascular supply to the tumor. More extensive facial and head and neck lesions may present significant challenges for good functional and aesthetic outcomes. In these cases, management options include surgical resection, radiotherapy, or combinations of both.[32]

Preoperative angiography and embolization have been helpful in some cases of glomus faciale and other glomus tumors.[33,34] It has been used to achieve significant preoperative tumor devascularization to decrease blood loss during surgical resection.[35] While this is not considered to be a curative treatment, it has been advocated as a beneficial preoperative surgical adjunct in selected cases.[36,37]

External beam radiotherapy (45-50 Gy) and stereotactic radiosurgery have been used for unresectable or incompletely resected tumors. Local tumor control rates of 74% *(Print pagebreak 424) (Print pagebreak 425)* to 97%, with complication rates from 4% to 20%, have been reported.[38,39,40,41,42,43,44]

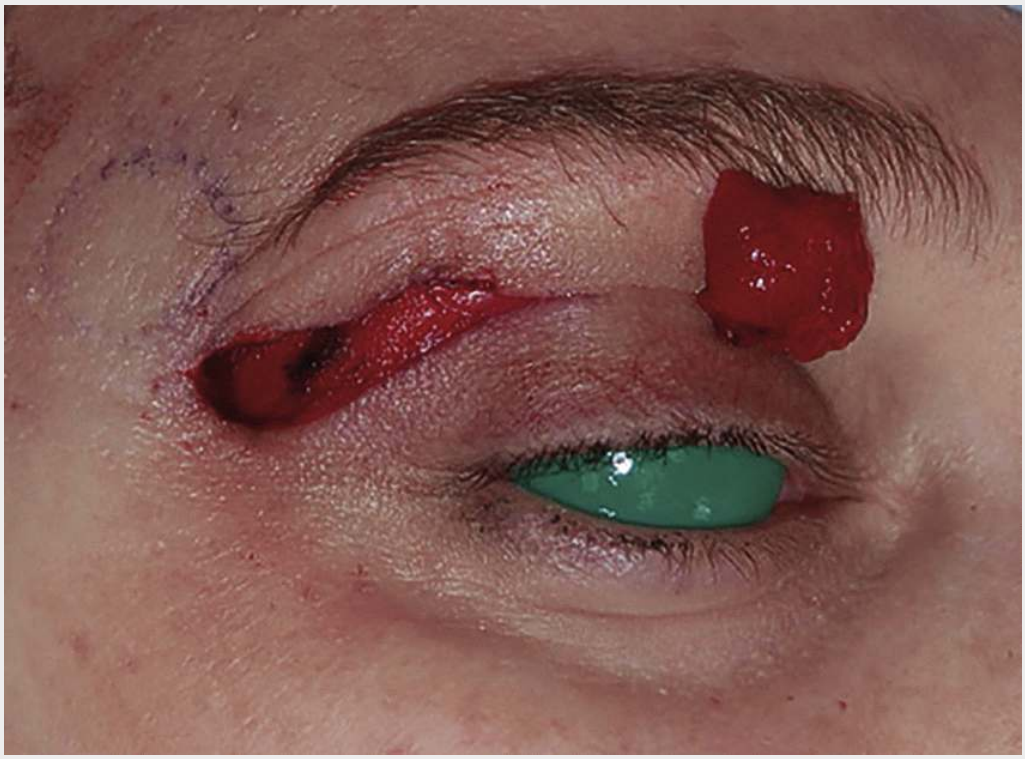

FIGURE 64.2 Surgical excision of the lesion in Figure 64.1. (Courtesy of Dr. Kyle Godfrey.)

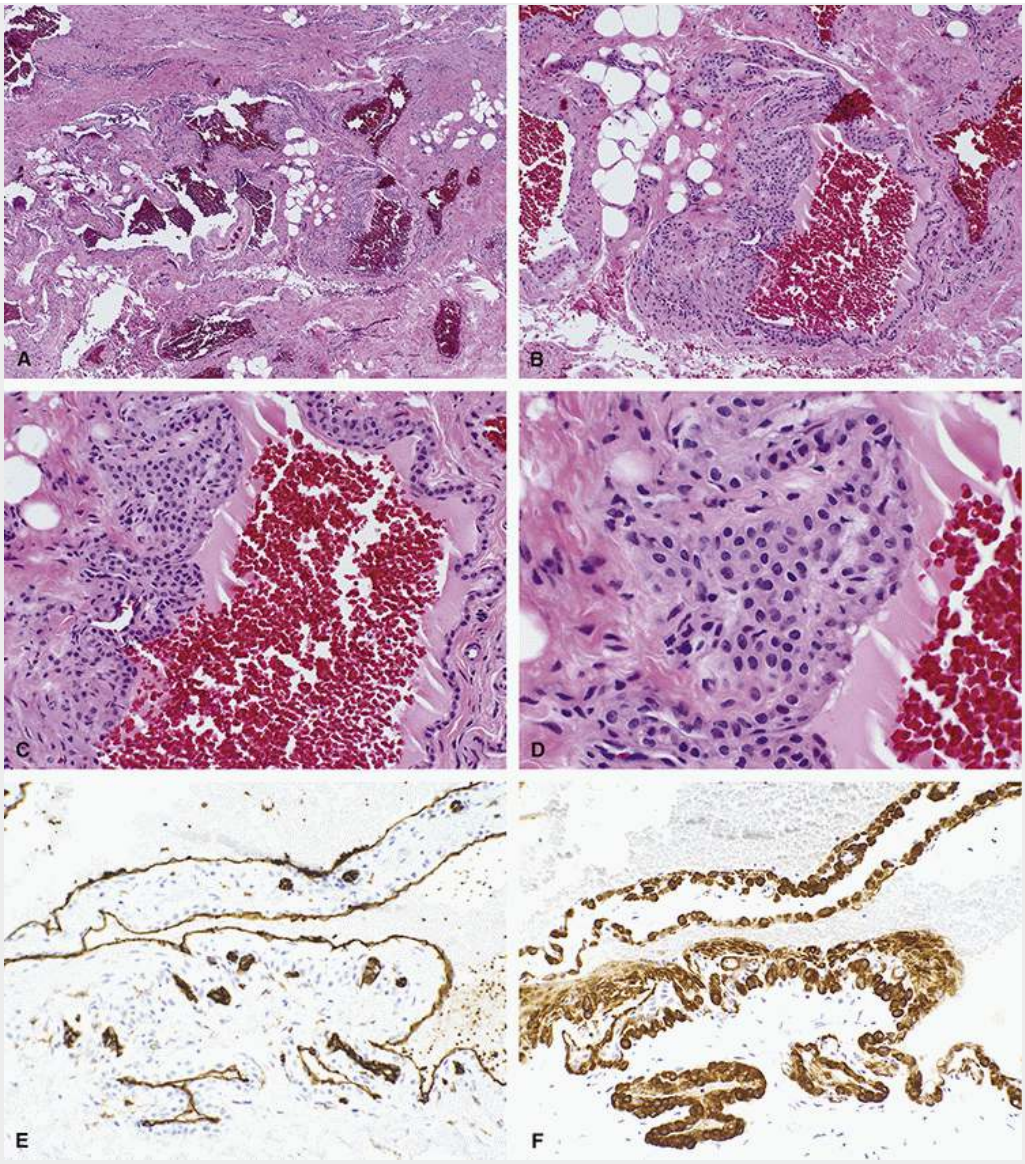

FIGURE 64.3 This glomuvenous malformation (GVM) of the eyelid was part of a larger lesion involving the face. A, At low magnification, the GVM resembles a cavernous hemangioma with interlacing, contorted, dilated blood vessels. B and C, A variably thick layer of glomus cells ensheaths the blood vessels. D, The glomus cells are uniform, large, round or cuboidal cells with a round nucleus, a rim of pale, lightly eosinophilic cytoplasm, and a distinct cell membrane that is slightly more eosinophilic than the cytoplasm. E, Immunohistochemical staining using antibodies to CD31 highlights the endothelial cells but not the glomus cells. F, The glomus cells are immunoreactive using antibodies to α-smooth muscle actin.

In a series of 17 patients, treatment with dual-wavelength PDL-Nd: YAG laser was shown to provide an excellent clinical response with a low risk of adverse events for GVMs.[45] The rationale behind sequential laser therapy was that the dual administration with pulsed dye laser allowed a greater absorption of the Nd:YAG laser due to the production of methemoglobin via hemoglobin, requiring less fluencies of the latter and therefore a decreased risk of adverse effects.

Prognosis

All reported cases of eyelid GVM have been benign, and surgical excision resulted in a cure. For most benign glomus tumors elsewhere in the body, the postsurgical recurrence rate is approximately 10%, usually associated with incomplete resection.[46] An exceptionally rare phenomenon, malignant transformation after recurrence or dedifferentiation of a benign glomus tumor has been described, but this has not been reported in the eyelid.[47]

Histopathology

The histopathology of the GVM variant of glomus tumor[48,49] was described in elegant detail in the 1920s and 1930s.[50,51,52,53] At low magnification, GVM resembles a cavernous hemangioma with interlacing, contorted, dilated blood vessels (Figure 64.3A and B).[50,51,53] The vessels are ensheathed by a variably thick layer of glomus cells (termed "epithelioid cells" in the earlier literature) that are uniform, large, round, or cuboidal cells with a round nucleus, a rim of clear or pale cytoplasm, and a distinct cell membrane best seen using Masson trichrome stain.[50,53] The blood vessels in GVM are of two types.[50,51] The first type has one or two layers of smooth muscle cells arranged circularly and separated from the endothelium by a collagenous membrane.[50,51] The circularly oriented smooth muscle cells are surrounded by "muscle cells less regularly arranged, branching, clearer, less rich in muscle fibrils, and each with a short ovoid nucleus. Proceeding peripherally, these cells are seen to pass through every gradation to typical epithelioid cells supported in a collagenous medium."[51] The second vessel type in GVM has glomus cells bordering endothelial cells without the interposition of smooth muscle cells.[50,51] Glomus cell ensheathed blood vessels are separated by connective tissue containing nonmyelinated nerve fibers that terminate around the glomus cells.[50,53] The endothelial cells in GVM can be highlighted using antibodies to CD31 (Figure 64.3E), CD34, or factor VIII-related antigen, while the glomus cells are highlighted using antibodies to α-smooth muscle actin (Figure 64.3F) and muscle-specific actin.[2] The glomus cells do not express CD31, cytokeratins, or S100 protein.[2,3]

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CHAPTER 65

Granuloma Annulare

Key Points

- Granuloma annulare is a benign dermatological condition that occurs in healthy children
- It occurs clinically as several different forms, including generalized, subcutaneous, and perforating variants
- The etiology remains unknown, but inciting triggers include local trauma, insect bites, ultraviolet light exposure, viral infections, red tattoos, and tuberculin skin tests
- GA is characterized by necrobiotic granulomas with blood vessel thickening suggesting an immunoglobulin-mediated vasculitis
- Eyelid lesions usually present as a painless, flesh to yellow-tan-colored nodule commonly in the lateral aspect of the upper eyelid and the lateral canthal region but can show a more diffuse distribution of small multiple nodules
- GA lesions are benign and often self-limited with approximately 50% of cases resolving spontaneously within 2 years
- When symptoms are present or lesions are of cosmetic concern, lesions can be treated with local surgical excision, cryotherapy, laser ablation, intralesional corticosteroids, and psoralen plus ultraviolet A (PUVA) light therapy
- The prognosis for GA is generally excellent

Granuloma annulare (GA) is a benign dermatological condition that occurs in healthy children.[1] It was first described in 1895 by Fox,[2] who referred to it as an inflammatory dermatosis. The term “granuloma annulare” was later introduced by Radcliffe Crocker in 1902.[3] Mesara et al.[4] studied deep periocular nodular lesions and in 1964 named them pseudorheumatoid nodules because they appeared pathologically identical to rheumatoid nodules. Similar lesions identified as pseudorheumatoid nodules were identified in the periorbital region of 21 patients by Rao et al. in 1975.[5] Later, in 1994, Burnstine et al.[6] referred to similar periocular lesions as GA, and since then, this has been the preferred terminology.[7]

GA is characterized by firm papules, plaques, or nodules that are usually organized in a ringlike fashion, with normal overlying skin.[8] The distribution of GA lesions in children is located on the hands or arms in 60% of cases, on the feet and legs in 20%, on both upper and lower extremities in 7%, and on the trunk or head in 5% each.[8] However, Coskey et al.[9] reported a significantly higher incidence of facial GA occurring in adults.

The skin manifestations of GA are varied due to the many variants of this disease. The localized variant accounts for about 75% of GA cases. In this form, lesions are skin colored or erythematous and occur in annular groups of papules most commonly on the dorsal hands and feet. It is typically seen in patients younger than 30 years, with a female predilection in a ratio of 2:1.[10]

Generalized GA represents 8% to 10% of GA cases and is characterized by the simultaneous occurrence of multiple widespread annular plaques.[11,12] It has been reported that this variant is more likely to occur in middle-aged or older individuals,[13] but in a retrospective study involving 54 cases of generalized GA, this disease occurred predominantly in patients younger than 10 years or older than 40 years.[14] Subcutaneous GA is more common in children and presents as firm subcutaneous nodules, more commonly on the lower legs.[15] The perforating variant of GA differs from the other variants in that lesions show a central umbilication.

In addition to the classic variants, other rare subtypes of GA have been described. These include macular, patch, or pustular forms[16,17]; a palmar distribution[18,19,20]; and a form localized in photo-exposed skin.[21,22,23] Rare subtypes have been based on their clinical appearance, anatomic location, and patient demographics. These include localized, generalized, perforating, and subcutaneous deep variants.[8,24]

Generalized GA is characterized by small, 1- to 2-mm diffuse papules on the trunk. Perforating GA most frequently presents as small papules on the hands or fingers, which may have central umbilication. Subcutaneous GA occurs almost exclusively in children

and young adults presenting as an asymptomatic subcutaneous or deep dermal nodule. They are typically located in the pretibial skin, and less commonly on the hands, scalp, and eyelids.[8,24] Most reported cases of periorbital and orbital GA are the subcutaneous variant.

Etiology and Pathogenesis

The etiology of GA remains unknown. Several inciting triggers have been recognized, which include local trauma, insect bites, ultraviolet light exposure, viral infections, red tattoos, and tuberculin skin tests.[7,8,25,26] GA has also been seen at sites of healing herpes zoster and verruca vulgaris lesions, suggesting a possible viral etiology.[6] GA developing at sites of direct local trauma possibly results from primary degeneration of the connective tissue at the site of injury that can stimulate a granulomatous inflammation, a lymphocyte-mediated immune reaction with macrophage activation, and cytokine-mediated degradation of connective tissue with increased deposition of mucin.[27]

GA is characterized by necrobiotic granulomas and biopsy specimens frequently show blood vessel thickening, suggesting *(Print pagebreak 428)* that occlusion or other events involving blood vessels may partially be responsible for the necrobiosis. In 1977, Dahl et al.[28] studied GA specimens by conventional light and immunofluorescence microscopy. In 30% of blood vessels in involved skin, they identified IgM, and in 50%, they found complement C3. IgM, C3, or fibrinogen was also observed at the dermal-epidermal junction of 8 out of 20 GA patients, and necrobiotic areas contained fibrinogen. The authors suggested that an immunoglobulin-mediated vasculitis may be involved in the pathogenesis of GA. In an earlier study by Umbert and Winkelmann in 1976,[29] deposition of fibrin and circulating macrophage migration inhibition factors were found in the granulomas and necrobiotic lesions of 11 GA patients, suggesting an etiology of delayed hypersensitivity with involvement of the clotting factors. Thornsberry et al. and Mempel et al.[30,31] studied GA biopsies and reported increased production of interleukin-2, suggesting a T helper 1 cell-mediated process. Elastic fiber degeneration was demonstrated by electron microscopy by Hanna et al.,[32] suggesting that the elastic tissue may be a target tissue in GA.

The role of ultraviolet light in the pathogenesis of GA is unclear, but generalized GA in sun-exposed areas has been described in several cases.[33,34,35]

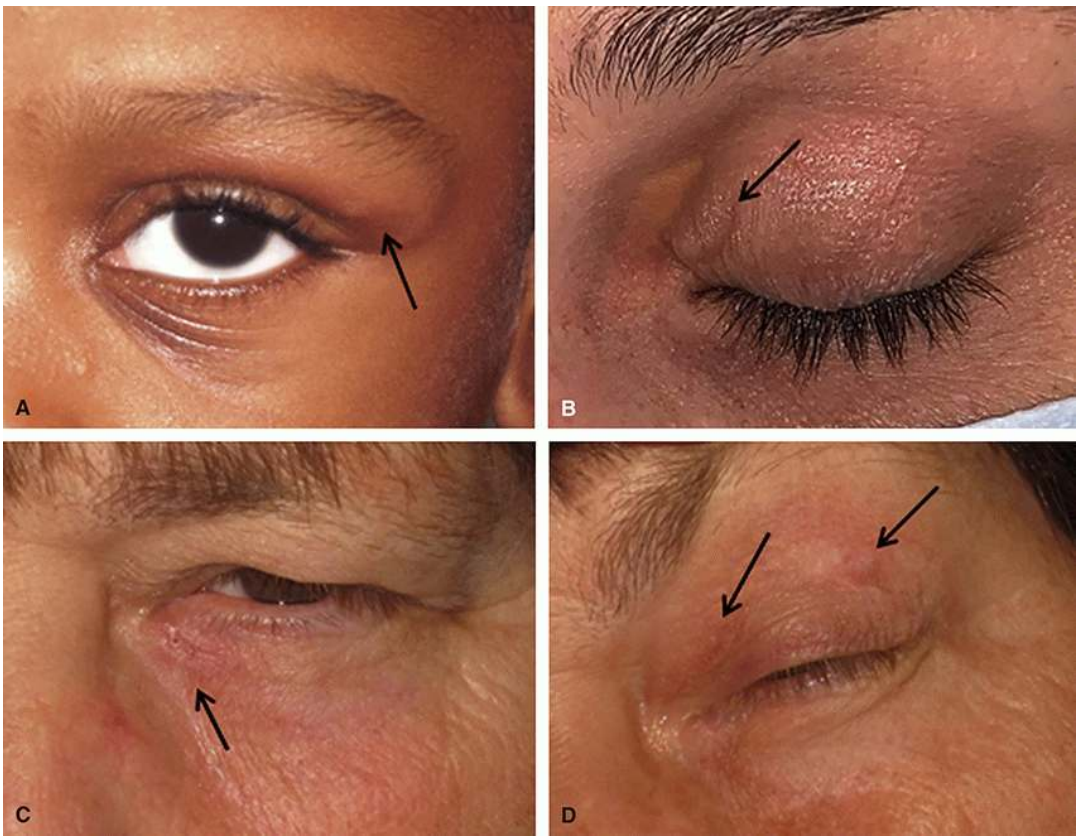

FIGURE 65.1 Granuloma annulare (GA) involving the eyelids. A, Nodular subcutaneous lesion in the lateral upper eyelid. B, GA nodule in the upper medial canthus. C and D, Small nodules of GA in the upper and lower eyelids. Arrows indicated the subcutaneous lesions.

Some systemic associations have also been reported with generalized GA, including diabetes mellitus, thyroid disease, rheumatoid

arthritis, lipid abnormalities, malignancy, human immunodeficiency virus, and hepatitis B and C.[36,37,38,39,40,41,42,43,44,45,46,47]

Clinical Characteristics

Lesions of GA most often involve the dorsal surfaces of the hands or feet, arms, legs, and trunk, and less frequently the scalp, face, and eyelids. They often present as a localized, erythematous, skin-colored, or violaceous cutaneous annular plaque, nodule, or papule with an elevated border.[48]

Fewer than 30 cases have been described involving the eyelids and periorbital region.[1,6,7,8,25,48,49,50,51,52,53,54,55,56,57,58,59,60,61] The typical presentation is as a painless, flesh to yellow-tan-colored nodule present for 3 months to 4 years. Eyelid lesions most commonly involve the lateral aspect of the upper eyelid and the lateral canthal region but can show a more diffuse distribution of small multiple nodules (Figure 65.1). Females predominate in a ratio of 3:1, and in 40% of reported cases, the patients are of African heritage. The age range is from 2 to 69 years, with a mean age at presentation of 21 years. However, two-thirds *(Print pagebreak 429)* of cases are younger than 18 years, and the median age is 11 years old. Lesions typically present as small 1 to 5 mm diameter nodules, but in rare cases can be up to 1.5 cm. In 40% of reported cases, lesions can be multiple on the same eyelid, and in 35%, they can be bilateral.

Eyelid lesions may be limited to the ocular adnexa, but similar lesions can concurrently be present on the extremities or trunk.[5,24,61] Other areas of ophthalmic involvement include the episclera,[6,62] orbit,[63] and choroid,[64] and one case was located beneath the periosteum of the orbital rim.[25] GA rarely can be associated with uveitis, retinal vasculitis, and cystoid macular edema with permanent decreased visual acuity.[65,66,67]

Differential Diagnosis

Periorbital GA can mimic many different lesions and the differential is broad because lesions do not always demonstrate the characteristic annular pattern.[68] The diagnosis usually becomes clear only after histologic examination. The most important lesions in the differential are malignant tumors, with basal cell carcinoma representing the most frequent misdiagnosis. Other lesions include eosinophilic granuloma, solitary fibrous tumor, rheumatoid nodules, systemic lupus erythematosus, sarcoidosis, tinea, nummular eczema, psoriasis, verruca vulgaris, granulomatous mycosis fungoides, chalazia, epidermal inclusion cyst, papilloma, pyogenic granuloma, nevus, pilomatrixoma, neurofibroma, and infection.[7,8,9,53,69,70,71] Basal cell carcinoma usually occurs in older adults, and typical lesions have a raised pearly border with a central cratered ulcer. Eosinophilic granuloma usually has typical although somewhat variable features. Like GA, it usually presents in the first decade of life as a tender, erythematous swelling in the superotemporal aspect of the orbit. Solitary fibrous tumor is more common in adults located in the orbit, but can occasionally be seen in the eyelid. It presents as a painless soft to hard diffuse slow-growing mass. Rheumatoid nodules are a common extra-articular manifestation of rheumatoid arthritis. They usually have a characteristic appearance as a well-defined, nontender, firm to hard, mobile subcutaneous mass. Cutaneous systemic lupus erythematosus rarely involves the periorbital skin. It is more common in middle-aged adults and presents as a pink to violaceous, unilateral erythematous swelling, mostly occurring in the upper eyelid. Sarcoidosis is a major cause of inflammatory eye disease. It can involve any ocular or periocular tissue. Eyelid lesions usually present as one or more irregular, firm subcutaneous nodules associated with multiple conjunctival granulomas, uveitis, episcleritis/scleritis, optic neuritis, and enlarged lacrimal gland. Tinea faciei is a fungal infection most often seen in children with an animal contact history. The leading organisms responsible are *Trichophyton mentagrophytes, Trichophyton verrucosum,* and *Microsporum canis*. The lesions start as a well-demarcated annular erythematous scaly patch, which progresses to a confluent thick-crusted plaque with purulent discharge over a period of days. A chalazion is a noninfectious inflammatory lesion of sebaceous glands, typically presenting as a painful, erythematous mass in the eyelid tarsus. The diagnosis is usually easily made, although some lesions may have an atypical presentation that is more diffuse with breakdown of the superficial skin or extension onto the conjunctiva.

Treatment

GA lesions are benign and often self-limited. Approximately 50% of cases resolve spontaneously within 2 years so that treatment is often not necessary.[72,73] When symptoms are present or lesions are of cosmetic concern, a number of treatment options have been used. These include local surgical excision, cryotherapy, laser ablation, intralesional corticosteroids, and psoralen plus ultraviolet A (PUVA) light therapy. However, there is no generally accepted treatment and results have yielded varying degrees of success.[24] Localized GA is most commonly treated with topical or intralesional corticosteroids.

Efficacy or optimal dosing regimen has not been established,[30,74] and steroids carry a risk of local skin atrophy and pigmentation alterations. Cryosurgery is another option and has been reported to result in the resolution of lesions with only one treatment.[75] However, there is a risk of localized pain, pigmentary changes, and scar formation during treatment. Topical

tacrolimus 1% ointment twice daily also has been reported to be successful.[50,76,77,78] Intralesional recombinant interferon gamma has been reported to be successful, but as with steroids, the optimal dosage has not been established.[79]

Phototherapy with local PUVA therapy is another option. Treatment four times a week for 17 to 40 treatments has shown partial or complete response in patients who have failed topical corticosteroids.[80,81,82]

Only a small number of reports have used laser ablation for GA.[73,83,84,85] In a series of 59 lesions in 13 patients, Passeron et al. reported >50% clearance in 56% of localized GA and 14% of generalized GA. There was a 17% recurrence rate after 6 to 12 months.[86]

Intravenous infliximab has been used successfully for generalized GA,[87,88] and adalimumab at an initial subcutaneous dose of 80 mg followed by 40 mg every 2 weeks has also resulted in positive response in several case reports.[89,90,91] Imiquimod 5% cream applied once a day for 6 to 12 weeks was reported to achieve complete resolution of GA lesions in four patients with no recurrence after a follow-up of 10 to 19 to 8 months.[92]

Prognosis

The prognosis for GA is generally excellent. It usually is self-limited over months to several years, but in about 20% of patients, lesions can recur in the same location, and in 15% to 40%, they can develop elsewhere on the body.[5,6,48]

Histopathology

There are three histological patterns of cutaneous GA: palisading granulomas, interstitial histocytes, and epithelioid (sarcoidal) nodules.[93] All patterns have normal epidermis.[34,94] *(Print pagebreak 430)* Pathological abnormalities localize to the middle and upper dermis.[93,94] Umbert and Winkelmann identified palisading granulomas in 53 of 207 (26%) cases of GA: histiocytes and lymphocytes surrounded altered collagen with their long axes perpendicular to the collagen bundles (Figure 65.2A and B).[93] Altered collagen, often termed "necrobiotic," may exhibit fragmentation of collagen bundles into fibrillary clumps; hyalinization with loss of discernible fibrillary structure in collagen bundles; basophilia with loss of distinct collagen bundle outlines accompanied by basophilic staining of the same area; sclerosis featuring densely packed collagen with little separation between individual bundles, along with a normal or decreased number of fibroblasts; and vacuolar change having clear round spaces between collagen bundles.[34] Mucin (glycosaminoglycans) may be present in the zone of abnormal collagen,[34,93,94,95,96] though its amount varies widely. The mucin is light blue in sections stained with hematoxylin and eosin, and its presence can be confirmed using Alcian blue (Figure 65.2C) or colloidal iron stains. Wood and Beerman found a "*considerable quantity*" of mucin in 13 of 25 specimens using Alcian blue stain, and occasional strands or small foci of mucin in 6 other cases.[95] When mucin is plentiful, it helps distinguish GA from rheumatoid nodules and necrobiosis lipoidica, which usually, but not always, have only slight amounts of mucin.[95] Other features that may help to distinguish the palisading granulomas in GA from those in rheumatoid nodules or necrobiosis lipoidica are delineated in the review by Muhlbauer.[94]

The infiltrative or interstitial type of GA has collections of histiocytes "*scattered between and around collagen bundles and blood vessels in the papillary and mid dermis*."[96] This was the most frequent pattern in the study by Umbert and Winkelmann, occurring in 147 of 207 (71%) cases.[93] There is minimal necrobiosis, but pericollagenous mucin is present.[93] Clinical correlation is vital for diagnosing the infiltrative/interstitial form of GA.[93] Epithelioid nodules were identified in only 7 of the 207 (3%) cases of Umbert and Winkelmann.[93] The epithelioid nodules were composed of histiocytes and "*some giant cells*"[93] and have been deemed "sarcoidal."[34,96]

Dabski and Winkelmann compared the histological findings in biopsies from 100 patients with localized and 100 patients with generalized GA, with generalized GA defined as "*involvement of at least the trunk and the upper or lower extremities.*"[34] They identified collagen changes in 79% and 53% of localized and generalized GA, respectively.[34] Most biopsies had a mixture of histological patterns, though there were differences between localized and generalized GA. Localized GA had interstitial histocytes in 75% of patients, palisading granulomas in 57%, and sarcoidal nodules in 11%.[34] Generalized GA had interstitial histiocytic infiltrates in 88% of patients, palisading granulomas in 31%, and sarcoidal nodules in 18%.[34] Despite the differences observed, Dabski and Winkelmann could not identify a pattern or feature that would allow localized and generalized GA to be diagnosed on histological grounds alone.[34]

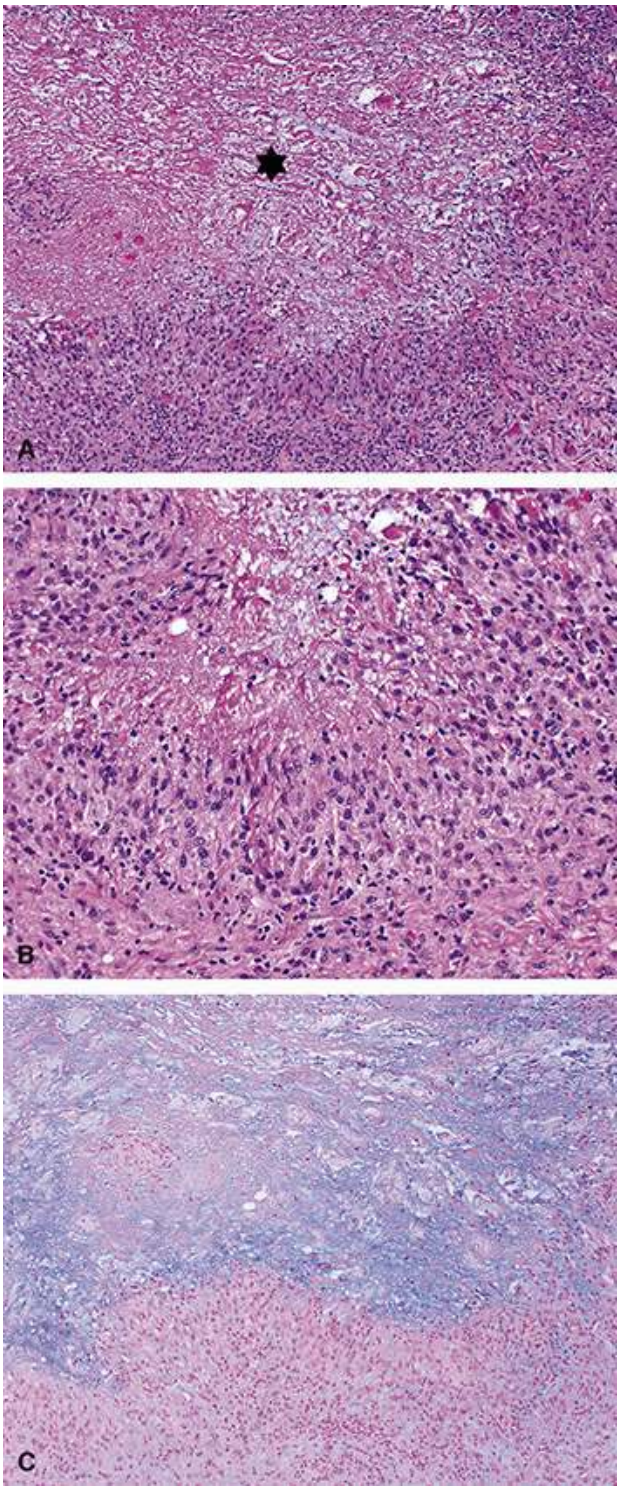

FIGURE 65.2 Granuloma annulare of the eyelid. A, A large zone of altered (necrobiotic) collagen (★) has fragmented collagen bundles, hyalinization, and basophilia. B, Palisading histiocytes and lymphocytes surround the necrobiotic collagen. The long axes of the histiocytes are perpendicular to the necrotic zone creating the palisading. C, Alcian blue stain highlights abundant mucin (glycosaminoglycan) accompanying the necrobiosis.

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CHAPTER 66

Granulomatosis With Polyangiitis

Key Points

- Granulomatosis with polyangiitis (GPA) is a chronic multisystem vasculitic autoimmune disease that is more common in older white males
- It was previously referred to as Wegener granulomatosis
- GPA is part of the spectrum of ANCA-associated vasculitis (AAV)
- c-ANCA is positive in 85% of patients with generalized disease, but the figures are lower in patients with limited disease
- Roughly 10% of patients are ANCA negative, and another 10% are p-ANCA positive
- Eyelid findings include blepharitis, edema, entropion, ectropion, retraction, necrotic lesions, or nasocutaneous fistulas
- Orbital/sinus bony destruction on radiology should raise the clinical suspicion of GPA
- Sarcoidosis and orbital IgG4-related disease should be distinguished from GPA by clinical, radiologic, and serologic findings
- The relatively high mortality of the disease is attributable to disease-related organ damage, to the development of malignancies, and as a complication of treatment regimens
- Systemic immune suppression remains the cornerstone of therapy
- Cyclophosphamide or rituximab is used for induction of remission
- GPA is a chronic disease that may require years of long-term maintenance therapy
- Rituximab, azathioprine, or methotrexate may be used for maintenance therapy

Granulomatosis with polyangiitis (GPA, formerly called Wegener granulomatosis) is a multisystem autoimmune vasculitis of the small- and medium-sized blood vessels hallmarked clinically by a triad of necrotizing granulomas of the upper and lower respiratory tracts, small vessel vasculitis, and focal necrotizing glomerulonephritis.[1,2,3,4,5,6,7,8,9,10,11,12,13,14] The disease falls under the rubric of the antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), a category of vasculitis that also includes eosinophilic granulomatosis with polyangiitis (EGPA, formerly called Churg-Strauss disease) and microscopic polyangiitis (MPA).[1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18] Following the discovery of ANCA in 1982,[15] AAV was identified as a separate entity usually characterized by ANCAs in the blood, which are directed against two main autoantigens, proteinase 3 (PR3) and myeloperoxidase (MPO).[5,6,9,14,16]

Etiology and Pathogenesis

The three main entities that constitute AAV (GPA, EGPA, and MPA) share the same underlying pathology with the involvement of small/medium-sized vessels (arteries, arterioles, venules, and veins) without the typical vessel wall immune complex depositions that hallmark primary systemic vasculitis.[5,6,7,8,9,14] GPA is a complex disease, and similar to most autoimmune diseases, the pathogenesis is multifactorial.[7] Although the exact etiology remains elusive, it has a strong underlying autoimmune diathesis, which usually develops in genetically predisposed individuals where infectious, epigenetic, and environmental factors all contribute to the full spectrum of the pauci-immune necrotizing vasculitis that is universally observed with these disease entities.[7,8,9,10,11,12,13,14] Although GPA, MPA, and to a lesser extent EGPA share fairly similar underlying etiopathogenetic events, orbital/periocular

involvement in EGPA is rare and is even rarer in MPA, which rarely if ever involves the orbit or the upper respiratory tract.[17]

The pathogenesis of GPA passes through three phases. First is the acute phase, in which an aberrant autoimmune response is generated. This phase is championed by an initiating agent, which may be infectious. This is followed by an active injury phase mediated by ANCA antibodies directed against PR3 and MPO autoantigens, the expression of which on the surface of neutrophils appears to be genetically determined. The final phase is the response-to-injury phase, which predominantly involves monocytes, macrophages, and T lymphocytes.[7]

During the acute phase, several exogenous and endogenous agents can initiate a pathological ANCA response. Microbial agents such as *Staphylococcus aureus* as well as the Ross River virus have been implicated in the pathogenesis of AAV, which is probably attributable to the molecular mimicry between these microbial peptides and ANCA autoantigens particularly PR3.[7,8] Drugs (propylthiouracil, cocaine, hydralazine, D-penicillamine, allopurinol, minocycline, and anti-TNF agents) and environmental factors (silica dust) can also trigger the development of GPA.[5,7,8,9,10,11,12,13,14]

During the active injury phase, neutrophils appear to be the major effector cells in the pathogenesis of GPA. Normally, *(Print pagebreak 434)* resting neutrophils have ANCA autoantigens (MPO and PR3) sequestered within the cell.[7] Upon exposure to an infectious or an exogenous agent, dendritic cells present the antigen to naïve T cells, which initiates a complex cascade of events that ultimately results in the priming of neutrophils, with the release of MPO and PR3 onto the surface of neutrophils as well as in the microenvironment around the cells.[14]

One of the quintessential steps in the pathogenesis of ANCA vasculitis is antigen presentation, and it is at this point in the pathogenetic cascade of AAV where genetic predisposition probably comes into play.[14] The genetic basis of GPA is undisputed and many of the genes described so far encode proteins that are involved in the immune response.[7,8,9,10,11,12,13,14,15,16] Genome-wide association studies have repeatedly provided evidence that the most convincing or strongest genetic association has been with major histocompatibility complex class II (MHC II) genes.[14,16] Susceptibility to GPA, therefore, is strongly associated with the expression of specific MHC II genotypes that are apt to present MPO or PR3 antigens to the immune system, which results in the production of ANCA.[14] Therefore, specific MHC II genetic traits correlate with certain types of ANCA autoantigens, which results in their increased membrane expression. Antibodies thus bind to the specific autoantigen presented at the surface of the cell, which ultimately directs the clinicopathologic expression of the disease.[5,7,14]

Although new associations between GPA and genetic polymorphisms continue to be reported and updated frequently in the literature, the HLA-DP locus has the strongest association with GPA.[19] Other genetic loci associated with GPA include SERPINA1 and PRTN3.[11,14] Animal models, clinical observations, and histopathologic studies have repeatedly demonstrated the central role played by ANCA antibodies in the pathogenesis of the disease.[7,8,9,10,11,12,13,14,15] The two major target antigens for ANCA autoantibodies in patients with AAV vasculitis are MPO and PR3, which are located within the granules of neutrophils, in the lysosomes of monocytes, and on the surface of neutrophils.[13] GPA is hallmarked by ANCA autoantibodies, which are more commonly directed against the PR3 and less commonly against MPO.[11] However, MPA is more commonly associated with MPO-ANCA than with PR3-ANCA.[11,12] Overall, about 10% of AAV patients are ANCA negative, a feature which is more commonly encountered in EGPA, where almost 30% to 50% of patients are ANCA negative, but the pathologic manifestations in ANCA-negative patients are similar to those of ANCA-positive patients.[7,11,12,20]

This binding of autoantibodies to primed neutrophils results in excessive activation of neutrophils.[7,14] Those activated neutrophils adhere to and penetrate vessel walls, and later undergo leukocytoclasis, a process whereby neutrophils undergo degeneration (karyorrhexis), with the formation of nuclear dust, subsequently releasing inflammatory cytokines, reactive oxygen species, and lytic enzymes in the extracellular milieu, and then the neutrophils finally disappear, to be replaced by mononuclear leukocytes including macrophages, monocytes, as well as T lymphocytes in later phases of the disease.[7,8,9,10,11,12,14,15,16,21] Furthermore, during the acute phase, the excessive activation of neutrophils by ANCAs induces the formation of neutrophil extracellular traps (NETs). The formation of NETs, which are a normal element of innate immunity, is a remarkable process by which neutrophils eject nuclear DNA impregnated with lethal antimicrobial agents into the extracellular space, creating what looks like a net trapping potential pathogens. NETs are subsequently eliminated later by an enzyme called the DNase I enzyme.[7,14] Although this is a normal physiologic process, if it exists in excessive amounts or if the NETs are insufficiently eliminated by the enzyme, NET formation in itself becomes harmful to small vessels. Interestingly, NETs are involved not only in ANCA-mediated vascular injury but also in the production of ANCAs by impairing DNase I activity; therefore, a NET-ANCA vicious cycle is accomplished, and further ANCA production is established, which contributes further to the pathogenesis of AAV.[7,14] Because ANCAs also bind to PR3 and MPO antigens on endothelial cells and other tissue sites of injury, ultimately, this entire process results not only in the apoptosis and destruction of neutrophils but also in the destruction of vessel walls and involved tissues.[5,7]

There is an ongoing debate as to whether GPA and MPA represent distinct diseases or are part of a single disease spectrum, but the consensus is that they are distinct autoimmune syndromes.[11,16] The abovementioned genetic data do support the notion that GPA does appear to be genetically distinct from MPO and other AAV-associated diseases. Confusingly, newer genetic data strongly

suggest that the HLA genomic signature of AAV vasculitides is strongly associated with ANCA specificity (PR3-ANCA vs MPO-ANCA) rather than the clinical manifestations (GPA, MPA, or EGP).[14,16] Whether this means a new classification of AAV is on the horizon remains to be determined.

Clinical Presentation

GPA has an annual incidence of 5 to 10 per million per year and a prevalence of 3/100,000.[22] The disease is more common in middle-aged white males older than 50 years, but it is rarely reported in children and the elderly.[17,23,24] Ocular/adnexal involvement is usually unilateral, but it may be bilateral in 14% to 58% of patients.[25,26,27] Ocular and adnexal disease is usually observed in up to 87% of generalized GPA patients at some point during their lifetime and may be the presenting feature of the disease in up to 16% of patients.[28,29]

The spectrum of symptoms varies from mild, nonspecific symptoms (ocular redness, eyelid swelling, epiphora, or inflamed eyelids) to more serious symptoms (painful proptosis, paralytic diplopia, or deterioration of vision). The more severe manifestations are the main presenting symptoms when the orbit is involved.[24,30,31]

GPA can be broadly classified into two distinct clinical presentations: limited (localized disease) and systemic or generalized disease.[26] It is currently unknown whether the *(Print pagebreak 435)* limited form of GPA is a subtype of generalized disease or is an entirely separate entity. Limited GPA is more common in the head and neck region including the orbit, and it also has a predilection for the upper respiratory tract, but it does not involve the kidneys. Some authors identify limited orbital/ophthalmic GPA as a separate entity that may or may not progress to generalized disease and maintain that this type is, in fact, more frequently encountered in the orbit than the generalized form.[17,23,26,31,32,33]

Ophthalmic and ocular adnexal manifestations are much more common in GPA than other ANCA-associated vasculitides like EGPA or MPA,[24] but eyelid involvement in GPA patients is relatively rare.[22] Patients with GPA may present with blepharitis with or without conjunctival chemosis, eyelid edema, ectropion, entropion trichiasis, necrotic lid lesions, and preseptal cellulitis and may rarely masquerade as a chalazion (Figure 66.1A-C).[24,26,31,34,35,36,37] The majority of patients with upper or lower eyelid edema may have an underlying orbital mass or dacryoadenitis.[31,34] Lacrimal gland enlargement may be one of the presenting features of the disease, and these patients usually present with mechanical ptosis together with an S-shaped eyelid deformity.[27] Ectropion is another early sign of the disease and usually signifies underlying bony destruction with loss of the structural bony support to the eyelids.[22] Tarsal findings include tarsoconjunctival necrosis, an early active fibrovascular proliferation of the tarsus, which may be followed by an inactive fibrous scar simulating trachomatous scarring in later stages of the disease.[28] This reparative scarring process ultimately results in symblepharon formation or frank tarsal deformities, which are the underlying cause of entropion and trichiasis that is occasionally observed in GPA patients.[28]

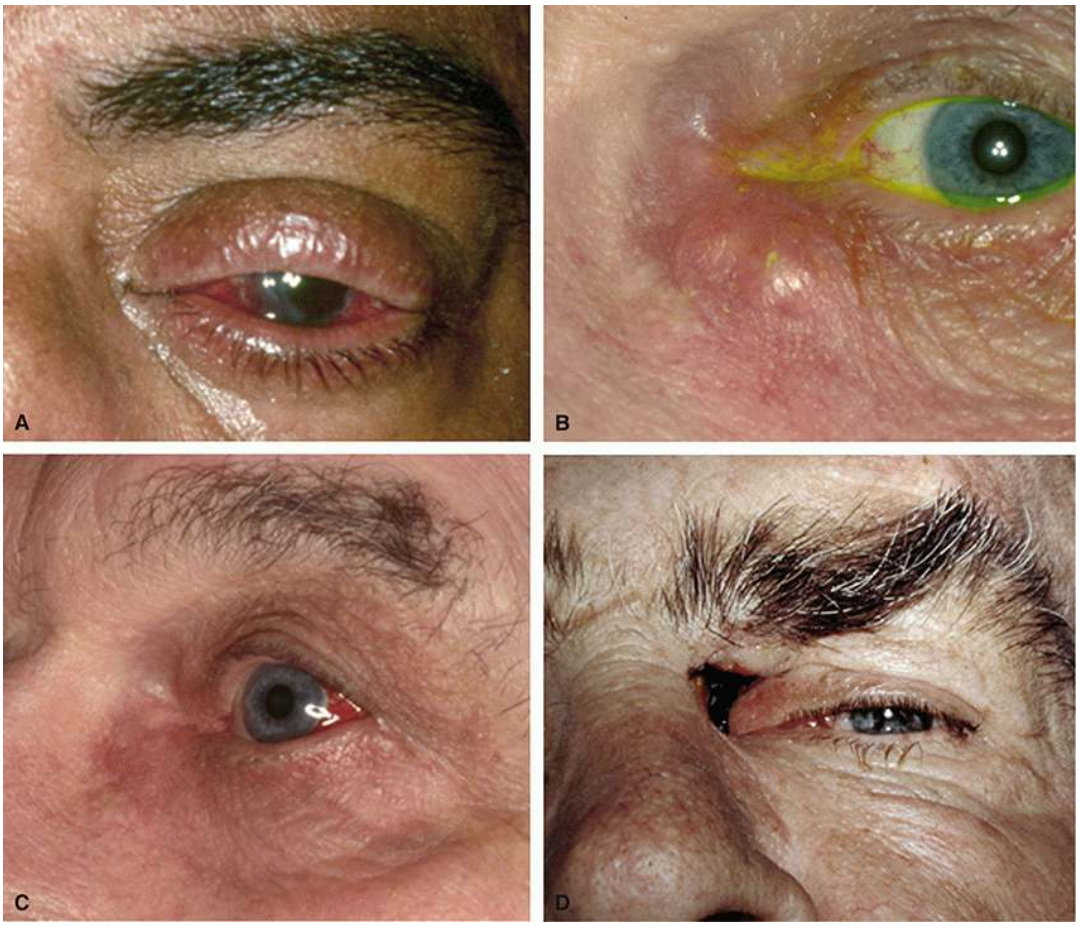

FIGURE 66.1 A-C, Granulomatosis with polyangiitis with eyelid erythema, edema, entropion, and periocular cellulitis. D, Nasocutaneous fistula in the medial canthus. (A-C, Courtesy of Dr. Charles Soparkar; D, Courtesy of Dr. Alan McNab.)

Ectropion may progress to one of the rarer cutaneous manifestations of GPA in the periocular region, that is *(Print pagebreak 436)* the development of a nasocutaneous fistula, which is more commonly observed in the medial canthal region. A nasocutaneous fistula usually develops as a result of the extensive advancement of an underlying sinus disease together with attendant bony destruction (destructive rhinosinusitis) (Figure 66.1D).[22] If a nasocutaneous fistula is still evolving, a Valsalva bubble test can be tried to support the diagnosis.[22]

Orbital involvement affects around 20% to 60% of GPA patients.[17,24] Patients may either present with orbital myositis, an orbital inflammatory disease with painful proptosis ("pseudotumor"), or an orbital infiltrating mass due to direct granulomatous orbital involvement.[24,27,30,38] Alternatively, secondary orbital involvement, extending from purulent or granulomatous inflammatory sinonasal disease, may also be observed.[23,38] This may manifest with globe displacement, eye movement restriction, or the formation of a nasoconjunctival fistula.[27] Lacrimal gland inflammatory enlargement may be acute, or chronic nonspecific, and is usually bilateral.[27] Dacryocystitis may also be observed in around 5% of patients.[27,39]

Ocular manifestations occur in around 30% of GPA patients and include conjunctivitis (52%), episcleritis (39%), marginal keratitis (7%), oculomotor nerve palsy (4%), scleritis (2%), or optic neuropathy (0.8%).[24,38,40] Of note is that scleritis usually manifests with sectoral vasodilatation of the deep scleral vessels in a typical crisscross pattern, which is not pathognomonic of the disease but may be highly suggestive.[24] Oculomotor nerve palsy is usually the result of compression by orbital tissue rather than being vasculitic in nature.[24]

Systemically, the clinical spectrum of GPA is broad. The presentation can be quite varied, ranging from a skin rash to fulminant multisystem disease, but typical features include upper respiratory tract involvement (95%), as well as renal impairment (75%).[1,26] Several disease activity scores such as the Birmingham Vasculitis Activity Score (BVAS) can act as a useful aide to record and measure disease activity, but these disease scores are complicated and require special training, so this job is beyond the context of ophthalmic practice.[1] Typical features of ear, nose, and throat manifestations in patients with GPA include nasal stuffiness and crusting or the occasional bout of epistaxis. Other features of GPA include the destruction of facial bones or soft tissues, which is highly suggestive of the disease, and if left untreated may lead to the development of a saddle-nose deformity.[22,27]

Because of the relative rarity of the condition and the nonspecific presentations, GPA usually poses a diagnostic challenge. Unfortunately, explicit diagnostic criteria are not available in the literature,[1,22] and the clue to the diagnosis may not lie in the eye or the periocular region. As a result, the diagnosis is generally based on a high index of clinical suspicion of a vasculitic condition, a positive ANCA serology, and histological evidence of necrotizing vasculitis.[22] The serological testing of ANCA is of utmost importance in the diagnosis and follow-up of GPA, as it is generally considered a sensitive and specific marker for the disease.[1,2,3,4,5,6,7,8,9,10,11,12,13,14] The two major types of ANCA have different cellular localization patterns that may be detected using indirect immunofluorescence on ethanol-fixed neutrophils.[14] Their nomenclature is prefixed (c-ANCA and p-ANCA) based on their immunofluorescence localization pattern.[17] The first fluoroscopic pattern that can be recognized is associated with diffuse cytoplasmic staining and is called c-ANCA, while the other type is associated with staining around the nucleus or perinuclear staining (p-ANCA).[14,41] Around 90% of c-ANCA is directed against PR3-ANCA, while 80% to 90% of p-ANCA is used to recognize MPO-ANCA.[17,22,41] The consensus is that c-ANCA (PR3-ANCA) is more commonly associated with GPA where it is observed in 85% of patients and is highly sensitive (91%), and specific (99%) for active disease as well, but the association is far from absolute as 5% to 10% of GPA patients are ANCA negative, and another 10% are p-ANCA positive.[22,41] However, p-ANCA (MPO-ANCA) positivity raises the possibility that the patient suffers from MPA. Of note is that in patients with limited forms of ANCA, ANCA positivity is lower than in generalized disease and varies between 32% and 67% of patients.[23,31]

Although ANCA levels are useful to monitor disease activity, they should not be used by themselves to guide treatment. The use of serial ANCA measurements as a tool to follow-up the treatment outcome during remission remains controversial,[1,14] nevertheless, a significant increase in ANCA titers, or the reappearance of ANCA, should alert the clinician to exercise a stricter control of the disease.[41] Besides ANCA, antinuclear antibodies as well as antiglomerular basement membrane antibodies should be ordered to exclude systemic lupus erythematosus and Goodpasture syndrome.[1] Other laboratory investigations include the assessment of kidney function (urea and electrolytes, with urine dip assessment, quantification of urine protein leak, and urine microscopy for red cell casts).[1]

Imaging (computed tomography) signs of sinonasal involvement that may help in establishing the diagnosis of GPA include opacification of the sinuses, sinus mucosal thickening, and bony changes, which include erosion or destruction of the sinus walls or turbinates. Destruction of the nasal septum and orbital walls may also be seen. Loss of the nasal septum is highly suggestive of GPA.[26]

Chest x-ray should be undertaken, but computerized tomography or magnetic resonance imaging may be more relevant to assess not just the chest but the brain, orbits, ear, nose, and throat structures as well.[1]

Differential Diagnosis

There are significant clinical, serologic, and histopathologic challenges that need to be addressed before a diagnosis of GPA is established; therefore, maintaining an open approach in the differential diagnosis is paramount. However, it is important not to rush to the diagnosis of GPA in any patient with vasculitis of uncertain etiology if the clinical findings and the *(Print pagebreak 437)* serological tests do not fit the typical features of GPA.[42] The diagnostic challenge is further exacerbated by the fact that the clinical manifestations of GPA can simulate many infectious, inflammatory, or neoplastic conditions.[38] Inflammatory or autoimmune diseases that may be confused with GPA are on top of the list of simulating lesions and include sarcoidosis, idiopathic dacryoadenitis, lymphoid hyperplasia, IgG4-related disease, sclerosing idiopathic orbital inflammatory disease, atypical thyroid eye disease, polyarteritis nodosa, Kawasaki disease, and very rarely CREST syndrome.[30,43,44] One differentiating feature that may help distinguish GPA from most of the abovementioned conditions is the presence of significant sinonasal pathology on imaging,[26] but in the end, a biopsy is usually required to clinch the diagnosis except in very rare situations when the clinical picture, radiologic findings, and serologic tests are strongly suggestive of a certain disorder like thyroid eye disease.[22]

Sarcoidosis in particular may cause a diagnostic dilemma. Clinical correlation with radiologic pulmonary involvement and angiotensin-converting enzyme levels can be helpful to establish the diagnosis, but only a biopsy is definitive. The presence of caseating granulomas on histopathology should raise the possibility of sarcoidosis.[43] There is considerable overlap between GPA and EGPA patients because they share the same small to medium vessel size pathology; however, in contrast to GPA, patients with EGPA typically present with a multisystem disease on a background of asthma, nasal polyposis, and peripheral blood eosinophilia, but orbital involvement is rare.[1]

Orbital IgG4-related disease should also be distinguished from GPA. The hallmark of this disease is an increase in IgG4-positive plasma cells, with reported IgG4 to IgG ratios that range from 30% to 90%.[43] Curiously, an increase in $IgG4^+$ cells or IgG4 to IgG ratios (greater than 40%) has been repeatedly reported in sinonasal or orbital/periorbital GPA biopsies, and this phenomenon may also be observed in other GPA biopsies from the head and neck region.[43,45,46] Although the significance of this finding is not yet known, this histopathological mimicry could cause a pitfall in the diagnosis of GPA. As these findings strongly suggest, an increased number of IgG4-positive plasma cells in an orbital biopsy is not enough evidence on its own to establish a diagnosis of orbital IgG4-related disease. Instead, complementary clinicopathologic information as well as additional histopathologic features of

IgG4-related disease such as the storiform fibrosis, dense lymphoplasmacytic infiltrate, and the paucity of inflammation, necrosis, microabscesses, or vasculitis may help rule out GPA.[43]

Some infectious etiologies (mycobacterial infections or invasive fungal sinusitis) should also be included in the differential diagnosis. Fungal infection is most commonly from *Aspergillus* or *Mucor* species, which can primarily involve the sinuses and secondarily invade the orbit especially in immunocompromised individuals, and it may be difficult to differentiate these infectious conditions from GPA. Several primary and secondary neoplasms, ranging from benign to malignant, need to be ruled out when considering a diagnosis of GPA, particularly orbital/adnexal lymphoma.[43]

Other causes of nasocutaneous fistulas should be excluded. The commonest cause may be iatrogenic due to thermal injury during transcanalicular laser dacryocystorhinostomy, or less commonly following external dacryocystorhinostomy. These fistulas are self-limiting and rarely require surgical intervention. Nasocutaneous fistula formation has also been reported after radiotherapy for sinonasal malignancy, following trauma to the periorbital region, frontal sinus disease, or tuberculosis.[22,47,48]

Because destruction of the nasal septum is a frequent finding in patients with GPA, other etiologies causing midline destructive lesions (previously called midline lethal granulomas) should be considered. The list includes non-Hodgkin lymphoma, foreign body, trauma, toxic agents (including cocaine), and infectious agents (fungal infections).[49]

It is important to consider the possible diagnosis of GPA in the differential diagnosis of any patient who presents with atypical lid edema.[31] Also, necrotizing fasciitis should also be excluded if the patient presents with eyelid necrosis.[36] Of note is that ANCA positivity may be found in a variety of conditions other than AAV, including inflammatory bowel diseases, other autoimmune diseases, and some infections, but the clinical significance is unclear.[41]

Treatment

In the presence of limited periocular disease, with no detectable c-ANCA levels, and no systemic disease activity, it may be difficult to recommend systemic treatment.[40] Topical corticosteroids may help reduce non-vision-threatening ocular surface inflammation.[34] Prompt referral to an ophthalmologist is mandatory for careful monitoring of the serious ocular complications that might be encountered during the disease. Orbital granulomas may not respond well to systemic chemotherapy and may require debulking or even orbital decompression.[34] Recently, the ultrasonic aspirator was successfully used to debulk an infiltrative orbital GPA mass because of limited surgical access.[50] Because of the small number of cases, the experience in treating eyelid and conjunctival GPA is limited.[40] Eyelid deformities such as ectropion, entropion, or eyelid retraction are treated according to the basic surgical principles.[34] A nasocutaneous fistula, if it occurs, is repaired with the appropriate flap.[22]

Control of systemic disease remains the cornerstone in the management of GPA.[22] From a therapeutic point of view, the traditional approach in the management of systemic AAV, particularly GPA and MPO, was to view both entities as a single group and treat them as such.[16] Treatment strategies and entry criteria for most major European and American trials have specified a general diagnosis of AAV and treated both conditions in a similar fashion.[16] There is an ongoing controversy whether both conditions (GPA & MPO) should be treated separately or not, and more recently, whether PR3-ANCA positive vasculitis and MPO-ANCA positive vasculitis should be treated as separate entities.[16]

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Treatment regimens differ depending on the stage of therapy as drugs used in the induction of remission are different from the gamut of drugs used as maintenance therapy. In the majority of patients, induction using cyclophosphamide or rituximab should be considered as a first-line measure probably in all patients with new-onset GPA to effect long-term remission.[1] Although cyclophosphamide is considered the gold standard, rituximab has been successfully tested recently in two large randomized trials (the RAVE and RITUXVAS trials), with positive results comparable to cyclophosphamide.[3,4] In both studies, a single weekly infusion of rituximab (375 mg/m^2 of body surface area) was found to be equivalent to a daily dose of cyclophosphamide (2 mg/kg) for 6 months and even proved superior for relapsing disease.[3,4] Rituximab is preferred in more severe life-threatening disease, in patients at risk of infertility, or in patients with a past history of uroepithelial malignancy, while cyclophosphamide is reserved when there is no evidence of serious organ damage.[1] In patients who present with a creatinine of >500 µmol/L, plasma exchange may be performed, or high-dose glucocorticoids may be added to the regimen.[1] In a certain subset of patients with a milder initial disease with no evidence of serious organ damage or life-threatening conditions, an alternative induction regimen composed of methotrexate or mycophenolate mofetil may be prescribed.[1]

After remission, maintenance therapy should include a shift to azathioprine or methotrexate followed by their gradual taper until complete remission is achieved. Alternatively, rituximab could be continued while the glucocorticoids are tapered until

the patient is off treatment altogether.[1] It should be noted that the MAINRITSAN trial demonstrated that rituximab 500 mg given at days 0, 14, and then every 6 months until the 18th month was more effective in remission maintenance than azathioprine.[1]

The duration of the maintenance regimen is controversial because the early cessation of therapy earlier than 1 year after commencing treatment has been associated with a higher incidence of relapse[51]; therefore, the general advice is that maintenance therapy should continue for 18 to 24 months before being gradually withdrawn. In general, attempts at reduction of glucocorticoids should be made before tapering off the main immunosuppressive remission maintenance agent.[1,51] It should be noted that changes in ANCA alone should not be used as the sole indication to effect a change in therapy. Instead, ANCA measurement should be accompanied by a regular and structured clinical assessment.[1]

Prognosis

Before the advent of systemic chemotherapy, generalized GPA was a uniformly fatal or life-threatening disease, and carried a very poor prognosis, with a mean survival of only 5 months and 82% mortality within 1 year.[17,31] However, morbidity and mortality have improved dramatically with modern immunosuppressive therapy.[17,26] The 5-year survival rate for GPA is currently estimated to be between 74% to 91%.[1,2] This relatively high rate of mortality that is still being observed is not just due to organ tissue damage inflicted by the disease itself but is also due to the complications from the therapy, and because GPA has a twofold higher predisposition to malignancies (bladder cancer, keratinocyte carcinoma, leukemia, and possibly lymphoma) than the general population.[52,53] Profound immunosuppression, an immune system dysfunction, or a longstanding immune hyperactivation may be causally associated with the higher incidence of cancer.[52]

Following the popularization of cytotoxic drugs in the management of GPA, it became a chronic disease with remissions and exacerbations. Maintenance therapy is therefore continued until complete remission is achieved.[1,54] Remission is defined as the absence of detectable disease activity using a recognized scoring tool such as BVAS.[54]

The search for the ultimate biomarker that reliably predicts GPA relapses is still elusive,[55] although evidence suggests that patients in whom the initial ANCA level was more than fourfold the normal are at greater risk of relapse.[1] The risk of relapse is also greater in patients who are PR3-ANCA (c-ANCA) positive at presentation or those who continue to remain PR3-ANCA positive even after they switch from induction to maintenance immunosuppression.[1]

Histopathology

The histopathological features of cutaneous GPA are variable.[56] Leukocytoclastic vasculitis, observed in 31%[56] to 80%[57] of biopsies, is the most common histological finding (Figure 66.2).[56,57,58,59] The cutaneous leukocytoclastic vasculitis appears similar to that considered characteristic of GPA in other organs.[56] Vasculitis involving small arteries and veins and capillaries is most common in the superficial and mid dermis, but it may involve subcutaneous vessels.[56,57] Neutrophils infiltrate and destroy the vessel wall with nuclear dust production (Figure 66.2B).[58] Fibrin thrombi form in the vessel lumen with fibrinoid material in and around the wall accompanied by erythrocyte extravasation.[56,58,59] While leukocytoclastic vasculitis is characteristic of GPA, it is also found in other cutaneous vasculitides and is thus not diagnostic of GPA.[60,61,62]

About 10% to 20% of skin biopsies in patients with GPA have palisading granulomatous inflammation surrounding degenerating (necrobiotic) collagen (Figure 66.2C and D).[56,57,58,59] The cutaneous extravascular granulomas are similar to those seen in the orbit[63] and elsewhere[64] and often have leukocytoclastic debris within them.[59] As is the case with leukocytoclastic vasculitis, palisading granulomatous dermatitis is a nonspecific finding in GPA.[65,66,67,68]

GPA skin biopsies may also exhibit lymphocytic (Figure 66.2E and F) and granulomatous (Figure 66.2G and H) vasculitis. Granulomatous vasculitis is uncommon, reported in from 0%[56] to 10% of biopsies.[58] A similar granulomatous vasculitis may be seen in other disorders, such as sarcoidosis, metastatic Crohn disease, ulcerative colitis, hepatitis *(Print pagebreak 439)* C, and postherpetic eruptions.[61] Chronic dermatitis (31% of biopsies), acute inflammation without vasculitis (9%), nonspecific ulceration (4%), erythema nodosum (2.7%), and epidermal and superficial dermal necrosis without inflammation (2.7%) were other histopathological findings in the study of 75 biopsies from 46 patients reported by Barksdale and colleagues.[56]

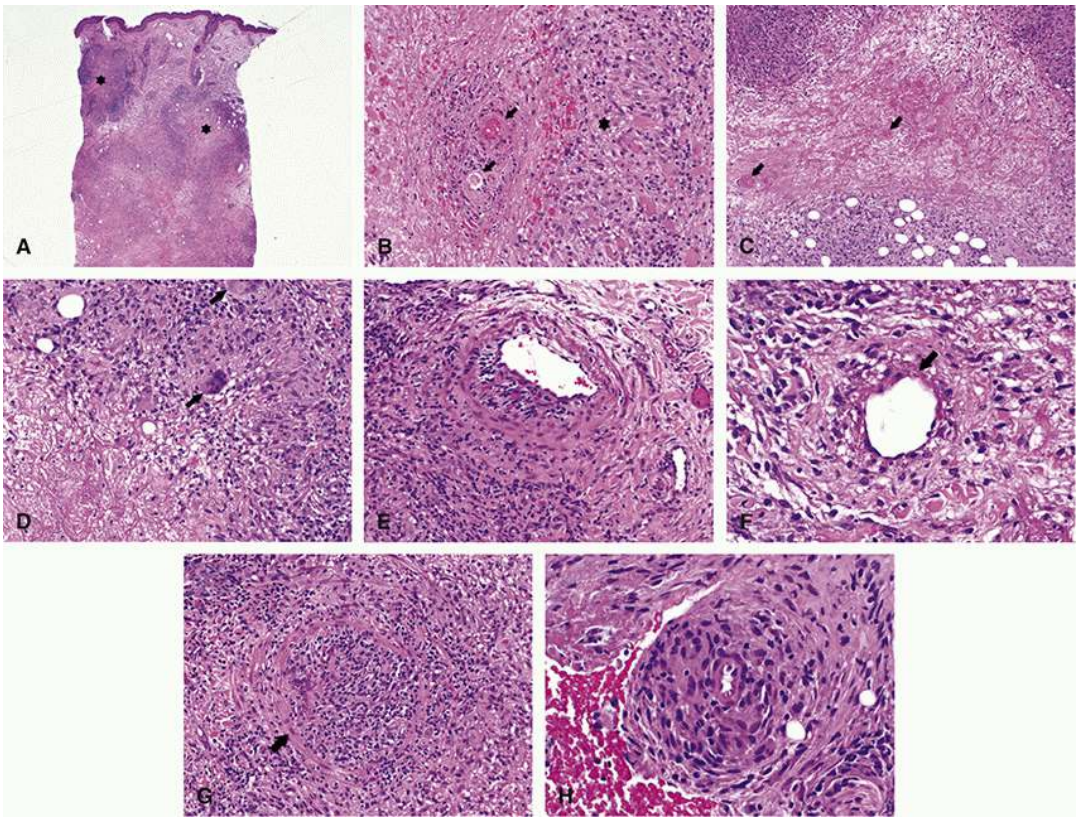

FIGURE 66.2 "Bumps" in the upper eyelid were the first manifestation of granulomatosis with polyangiitis (GPA) in this young woman. An increase in size and number of the nodules prompted this punch biopsy. A, At scanning magnification, the epidermis is normal while the superficial through deep dermis is inflamed. The most intense inflammation surrounds zones of necrosis (*). B, Palisading histiocytes (*) surround a zone of necrosis containing a small artery and vein with leukocytoclastic vasculitis (arrows). The small basophilic particles around the vessels are nuclear debris due to the disintegration of leukocytes. C, Palisading granulomatous inflammation surrounds a broad zone of collagen necrosis with several thrombosed small vessels (arrows). D, The palisading granulomatous inflammation consisted mostly of histiocytes, a lesser number of lymphocytes, and occasional multinucleated giant cells (arrows). E, This small artery has chronic lymphocytic vasculitis with lymphocytes infiltrating the tunica media and tunica intima. Lymphocytes and neovascularization expand the intima. The intimal neovascularization is indictive of chronicity. F, This small vein has lymphocytic vasculitis with fibrinoid necrosis (arrow). G, Granulomatous vasculitis is a rare finding in cutaneous GPA but is shown here involving a small artery (arrow). Lymphocytes and histiocytes disrupt the arterial wall and occlude the lumen. H, The wall of this small artery is effaced by granulomatous inflammation.

While there is no single histopathological feature diagnostic of GPA, the presence of leukocytoclastic vasculitis and/or granulomatous vasculitis together with palisading granulomatous inflammation should prompt clinical and laboratory evaluation for GPA. In Comfere, Macaron, and Gibson's study of 17 GPA patients with cutaneous manifestations, only 1 patient had a negative c-ANCA/p-ANCA at the time of cutaneous disease, and this became positive 1 year later.[59]

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CHAPTER 67

Herpes Simplex Blepharitis

Key Points

- Herpes simplex is a virus transmitted chiefly by kissing or other forms of intimate contact
- Once the primary infection is over, the HSV-1 virus ascends in a retrograde manner to the trigeminal ganglion where it is sequestered from host immune surveillance
- When reactivated, it travels along sensory neurons to target sites in the eyelids, conjunctiva, cornea, or the uveal system and retina
- Recurrences may be spontaneous or predisposed by a variety of triggers including psychological stress; fatigue; exposure to heat, sunlight, or cold; menstruation or sexual intercourse; fever; diabetes; organ transplantation; immunosuppression; or corticosteroid administration
- Presentation is with an acute onset of eyelid swelling, erythema, and tenderness that may be associated with mechanical ptosis, tearing, or conjunctival follicles
- Eyelid infection may also present as erosive blepharitis with single or multiple eyelid margin ulcers or erosions
- The blepharitis is typically fleeting but HSV keratopathy can cause corneal scarring and blindness
- Systemic and local treatment of blepharitis is indicated in isolated cases to prevent spread to the cornea and conjunctiva
- Oral acyclovir is considered the gold standard of treatment
- Healing of isolated HSV blepharitis is the rule even without treatment but severe initial eyelid involvement is associated with more frequent recurrences

The family *Herpesviridae* has more than 100 viruses, but only 8 of which routinely infect humans. The herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) belong to the α-herpesvirus subfamily. Both are ubiquitous pathogens that cause common infections with varied clinical manifestations in children as well as in adults. Although HSV-1 is a significant cause of corneal morbidity worldwide, herpetic cutaneous eyelid lesions due to HSV-1 or HSV-2 in neonates remain a minor concern.[1,2,3,4,5,6,7,8,9,10,11,12,13,14]

Etiology and Pathogenesis

HSV-1 and HSV-2 measure approximately 200 nm in diameter and contain a linear, double-stranded DNA core of approximately 150-kilo base pairs (Kbp) enclosed within a protein capsid. The DNA sequence of both HSV-1 and HSV-2 serotypes is similar but they are antigenically distinct because of a difference in the envelope proteins.[10] The majority of orofacial lesions are due to HSV-1 virus, while HSV-2 predominantly causes genital herpes. A notable exception is in neonates where exposure to HSV-2 during childbirth can result in the development of typical skin lesions during the first few days of life. It should be noted that both HSV-1 and HSV-2 are equally distributed in the trigeminal and sacral ganglia; therefore, the regional specificity of recurrent HSV infections is probably due to local host factors rather than a regional distribution of the latent virus.[12,14]

The chief mode of transmission is by kissing or other forms of intimate contact with an individual who has an active, usually recurrent, herpetic lesion, but asymptomatic patients shed the virus in the saliva as well, and accordingly are a more common source of infection.[10] Once the primary infection is over, HSV-1 ascends in a retrograde manner to the trigeminal ganglion, where the virus, which is now sequestered from host immune surveillance, safely replicates and establishes latency persisting in a dormant state for life. This predisposes the host to recurrent attacks of periodic viral reactivation. Once it is reactivated, the virus travels along sensory neurons to the target sites in the eyelids, conjunctiva, cornea, or the uveal system and retina.[10] These recurrences may

be spontaneous or predisposed by a variety of triggers including psychological stress; fatigue; exposure to heat, sunlight, or cold; menstruation; sexual intercourse; fever; diabetes; organ transplantation; immunosuppression; corticosteroid administration (oral, parenteral, topical, or even in inhaled form); and measles or HIV infection.[10,11,13,15]

Although direct viral toxicity to the eyelids is probably etiologically responsible for HSV blepharitis, the morbidity in primary HSV infections may also be immunopathogenic in origin.[7,8] After exposure to the viral antigen, there is a massive rise in the number of neutrophils (Gr-1$^+$ cells), which is the predominant infiltrating cell type and the likely source of inflammatory cytokines (IL-6, IL-10, IL-12, or IFN-γ), and therefore it could be a major effector of eyelid morbidity.[8] Shortly after that, the viral load begins to clear and CD4$^+$ T-cell count significantly increases in number. Although this immune response is essentially the same in the cornea and eyelids, it may play a different role in recurrent infections.[6] While an already primed immune system in recurrent HSV may cause an immune-mediated, potentially blinding stromal keratitis, the same immune mechanism may limit the spread of herpetic blisters in recurrent HSV, which may explain why herpetic blepharitis is an unusual occurrence in recurrent disease.[6,7,8]

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Clinical Presentation

Incidence and prevalence data about HSV blepharitis are not directly available in the literature, but the data can be inferred indirectly from epidemiologic studies concerned with corneal HSV. Between 45% and 98% of the world population is seropositive for HSV-1,[12] the majority of whom are seroconverted by adolescence, particularly in children of lower socioeconomic groups.[13] Primary infections are typically subclinical and may go unrecognized, although they may be associated with constitutional signs and symptoms. However, even in the absence of symptoms, primary infections are associated with a longer duration of viral shedding.[12]

The first presentation of ocular HSV may not necessarily represent the primary site of infection in the body.[5,13] Clinical manifestations of ocular HSV may start at any age, but it generally is a disease of the young (mean age, 34 years). HSV-related blepharoconjunctivitis is one of the presenting signs in 35% to 54% of primary (initial) ocular attacks,[5,10,11,12,13] but monosymptomatic involvement of the eyelids and conjunctiva occurs only in 21% of patients.[10] However, recurrent HSV blepharoconjunctivitis is infrequent, and the incidence was as low as 4% in some studies.[2] The disease is predominantly unilateral, but bilateral occurrence is encountered in 7.5% to 29% of patients, particularly in children or in those with atopy.[13]

Two major presentations of HSV blepharitis are observed.[16] The classic presentation is with an acute onset of eyelid swelling, erythema, and a tingling sensation with local periocular tenderness in the involved side. This inflammatory swelling may cause mechanical ptosis if the upper eyelid is involved, or it may be accompanied by a red, tearing eye and conjunctival follicles if HSV simultaneously infects the conjunctiva (Figure 67.1).[6] This is quickly followed by the appearance of a cluster of relatively large umbilicated vesicles with a yellowish content that are usually grouped together with an underlying erythematous and edematous base along the eyelashes (Figure 67.2A-C). These vesicles eventually crust and then dry out causing spontaneous unroofing of the lesions.[5,17] In rare situations, particularly in atopic patients, these infections can be quite severe and could be secondarily infected. This is especially true when it is associated with eczema, where the condition has been termed eczema herpeticum (also referred to as Kaposi varicelliform eruption).[3,5] Regional lymph nodes are usually involved, and the condition may be associated with pathognomonic follicles around the mouth or the nasal cavity.

The second and reportedly more common type of eyelid infection is intermarginal HSV blepharitis (erosive-ulcerative type),[17] which is characterized by single or multiple eyelid margin ulcers or erosions each measuring 1 to several millimeters in length. These ulcers may be associated with localized swelling and tenderness but without the characteristic cutaneous follicular lesions or the acute inflammatory signs that hallmark the more typical presentation described above.[5,16,17,18,19] The absence of cutaneous vesicular eruptions on the palpebral surface and the presence of a crust that usually covers these lesions may make the diagnosis difficult.[18] If in doubt, staining the eyelid margin with fluorescein or rose bengal may help identify the ulcers and clinch the diagnosis.[18] Whether this is a distinct clinical type of HSV blepharitis or a normal sequela of deroofing of herpetic vesicles which later coalesce is unknown.[6] Of note is that the predilection of HSV to involve the eyelid margin is not unusual, and this is the typical behavior of a virus that favors orifices and mucocutaneous junctions.[18] Both forms of presentation (large blisters/eyelid margin ulcers) discussed above are a reliable sign of clinically manifest primary HSV blepharitis, since both are rare in recurrent disease, and even when encountered, they are usually observed in a milder clinical form.[6,17] As we mentioned earlier, this is likely due to immune reactions, which would limit the extent of HSV blepharitis.[6] Other rarer eyelid presentations include acquired entropion in children, complete acquired ankyloblepharon, and punctal or canalicular scarring.[15,20,21,22,23]

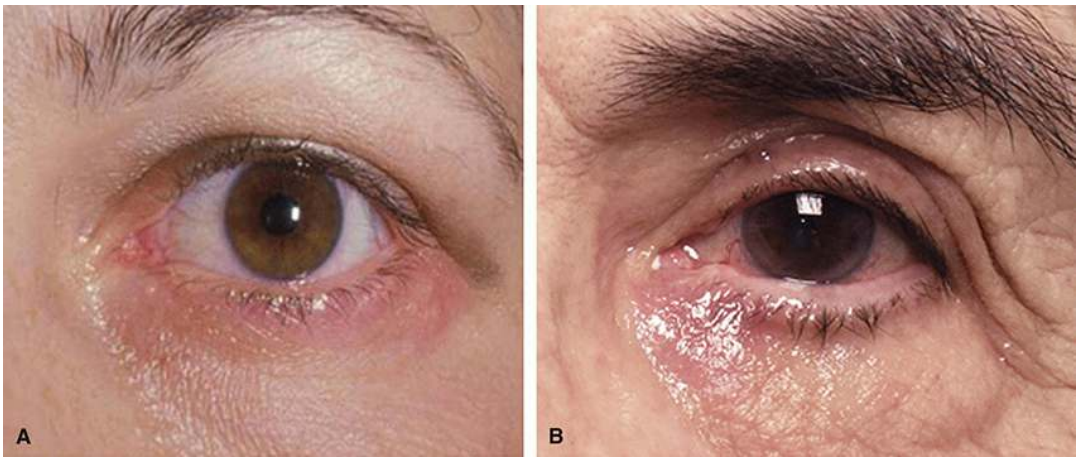

FIGURE 67.1 Early classic presentation of herpes simplex. A, Eyelid erythema and edema of the lower eyelid. B, Upper and lower eyelid swelling and erythema and blepharoconjunctivitis. (Courtesy of Dr. Robert Goldberg.)

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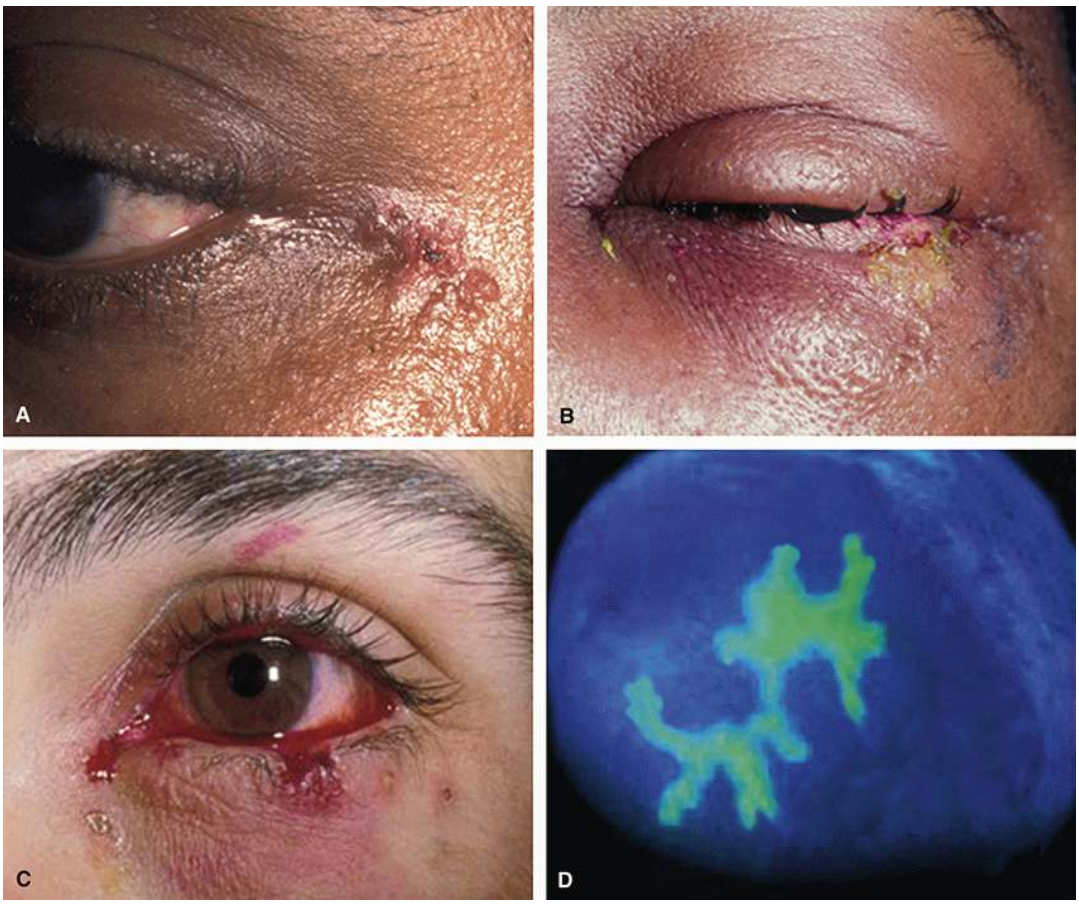

FIGURE 67.2 A-C, Herpes simplex eyelid vesicles and erosions. D, Herpetic dendritic keratitis. (A and B, Courtesy of Dr. Kenneth Cohen.)

While HSV blepharitis is typically fleeting and not of major clinical significance, HSV keratopathy is the hallmark of the disease and is a leading cause of corneal blindness.[3,4] HSV keratopathy takes many forms including epithelial disease (dendritic and geographic keratitis) (Figure 67.2D), stromal disease (stromal keratitis with or without ulceration), and endothelial disease (HSV endothelial keratitis or disciform keratitis).[13] Other rarer ocular presentations include scleritis, focal iritis, posterior uveitis, panuveitis, scleritis, trabeculitis, and glaucoma or retinitis.[17,24,25,26,27,28]

Laboratory investigations for the diagnosis of HSV are not routinely employed in clinical practice; however, if the diagnosis is in doubt, laboratory tests that could be ordered include electron microscopy, viral culture, cytological smear/Tzanck test, direct fluorescent antibody studies, tissue biopsy, or viral DNA detection by polymerase chain reaction (PCR).[12,20,29,30,31,32]

The Tzanck test is a rapid inexpensive diagnostic tool that is frequently employed by dermatologists where a smear is taken from the base of a freshly opened vesicle, stained by Papanicolaou or Giemsa stain, and examined under the light microscope. Positive smears usually show multinucleated giant cells and intranuclear eosinophilic inclusion bodies. Analysis of serum for anti-HSV antibodies may demonstrate high levels of IgM in patients with a primary infection, while elevated levels of IgG are suggestive of a nonprimary infection.[12,30,31] Herpes simplex vegetans is a rare variant of cutaneous HSV infection that can occur in immunocompromised patients (Figure 67.3). This can present as exophytic exudative or ulcerated growths that may mimic a cutaneous malignancy. These have occurred on digits, genitalia, and oral mucosa, and two cases were reported on the eyelids.[33,34] These lesions present as irregular, weeping, ulcerated, fungating masses with madarosis, and conjunctival inflammation.

Differential Diagnosis

HSV blepharitis can occasionally acquire a dermatomal distribution and may mimic herpes zoster virus lesions (zosteriform herpes simplex). If the characteristic HSV epithelial keratitis is absent, establishing the diagnosis may be difficult *(Print pagebreak 445)* and PCR may be needed to identify the specific causative virus because the Tzanck smear cannot differentiate a simplex from a zoster infection.[12,13,35,36] Patients with zosteriform herpes simplex should also be checked for HIV status.[37] Although both respond to the same antivirals, the distinction is important because the concentration of acyclovir, which is needed to inhibit the zoster virus, is 10 times more than what is needed to inhibit HSV.[37] Molluscum contagiosum typically presents with self-limiting dome-shaped papules that take 12 to 18 months to disappear. Acute inflammatory signs are generally absent in molluscum contagiosum except in HIV patients, and although central umbilication is a feature shared by both HSV and molluscum, it is more pronounced in patients with molluscum contagiosum (see Chapter 88, Figure 88.2).

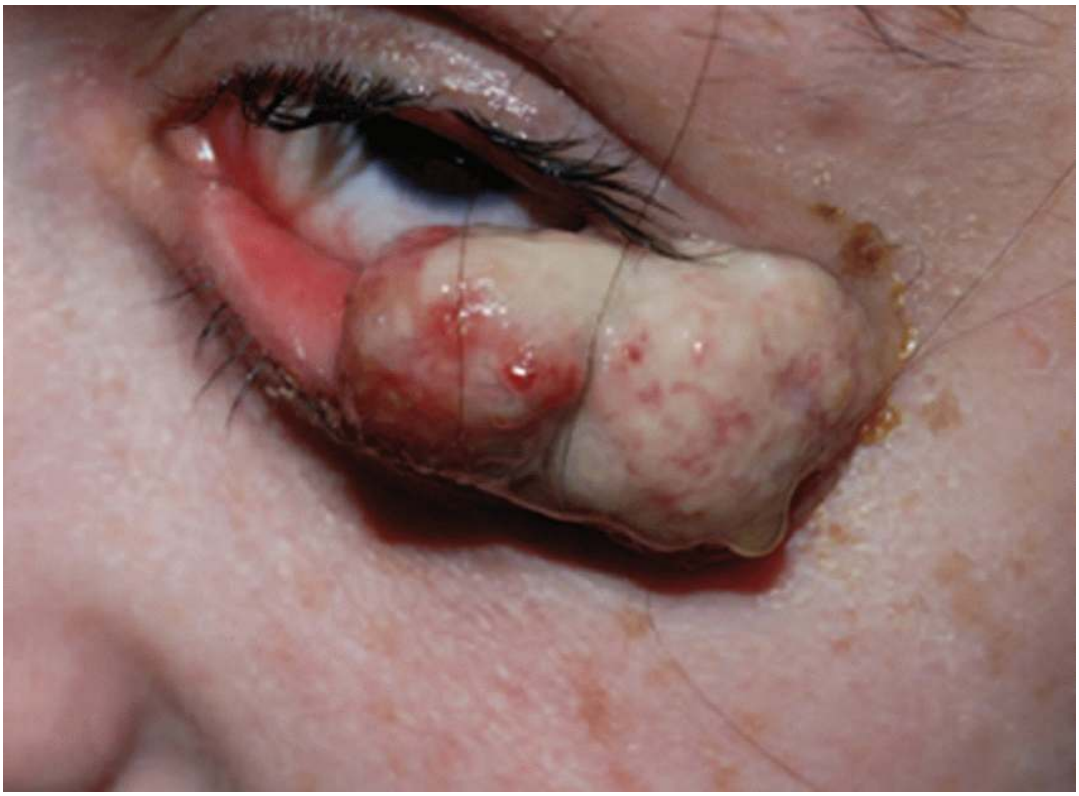

FIGURE 67.3 Herpes simplex vegetans in a patient with congenital T-cell immunodeficiency. (Reprinted with permission from Blieden LS, Chévez-Barrios P, Yen MT. Herpes simplex vegetans presenting as an eyelid mass. *Ophthalmic Plast Reconstr Surg*. 2011; 27:e58-e59.)

In neonates, the use of gentamicin ophthalmic ointment is associated with the development of cutaneous eyelid ulcers simulating intermarginal HSV. A negative PCR can help establish the diagnosis.[29]

A bacterial rash on an eczematous skin area may also be difficult to discern from eczema herpeticum, and laboratory investigations to identify the infectious agent may be needed.[17] In rare situations, HSV blepharitis may need to be differentiated from staphylococcal blepharitis if it presents acutely with folliculitis. Loss of the eyelashes, which is not infrequently observed with staphylococcal blepharitis, is never a typical sign of HSV blepharitis. In addition, the infective pustules in patients with staphylococcal blepharitis lack umbilication.[17] Because of its rarity, HSV blepharitis may also be confused with the more ubiquitous meibomian gland dysfunction (MGD), but the chronicity and delayed age of onset, in addition to the absence of umbilicated vesicular eruptions on the cutaneous surface of the eyelid, may help establish a diagnosis of MGD.[3]

Treatment

Some authorities believe that no therapy is needed in patients with monosymptomatic HSV blepharitis since these lesions usually heal spontaneously, provided that eye rubbing is avoided. Rubbing or scratching can induce a mechanical injury that can cause exogenous HSV particles from the skin lesions to force their way into the corneal surface.[17] Of note, however, is that corneal disease more commonly develops simultaneously from the endogenous spreading of the virus to the ocular surface rather than from a surface superinfection.[17]

However, systemic and local treatment in monosymptomatic blepharitis is indicated in (1) isolated severe primary HSV blepharitis to prevent the spread of HSV to the cornea and conjunctiva, (2) in atopic patients with eczema herpeticum or intermarginal HSV, (3) in AIDS patients, or (4) in children where avoidance of eye rubbing cannot be ensured.[17,18] The situation is different when HSV blepharitis is associated with ocular disease where therapy is unequivocally required, and in such situations, therapy is tailored to the specific condition at hand.[17]

There are no clinical trials documenting the efficacy of oral antivirals in monosymptomatic HSV. However, if therapy is indicated in patients with isolated eyelid disease or patients with blepharoconjunctivitis, oral acyclovir (400 mg, 3-5 times/d orally for 5-7 days) is considered the gold standard of treatment.[17] Acyclovir is well tolerated by patients, has a good safety profile, and is also available in injectable form. However, because of its poor bioavailability and short plasma half-life, frequent daily dosing is required.[12] In patients with eczema herpeticum, therapy should be initiated with a maximal dose of oral antiviral agents (acyclovir 800 mg, 5 times/d), which is later reduced to 400 mg 5 times/d for at least 2 more weeks after the onset of healing.[17]

Other alternatives include penciclovir, valacyclovir, famciclovir, foscarnet, or cidofovir. Penciclovir has a longer half-life but is much less potent. Valacyclovir is a prodrug of acyclovir, which has up to five times greater bioavailability and subsequently requires less frequent dosing, and famciclovir has pharmacokinetic properties comparable to penciclovir.[12] Foscarnet is available in injectable form only and is indicated in immunocompromised hosts if the infection is resistant to acyclovir. Cidofovir is another antiviral agent that is indicated in patients with a double resistance to acyclovir and foscarnet.[12]

The use of topical agents in the management of HSV blepharitis is supported only by anecdotal reports[15,16,18,19,23]; however, topical therapy may be indicated if there is associated conjunctivitis or epithelial keratitis. Local treatment may especially be of value in cases presenting with intermarginal HSV and in eczema herpeticum. In the intermarginal HSV subtype, local antiviral agents have unrestricted access to the viral particles through the exposed ulcer and therefore logic dictates their use.[18] Eczema herpeticum should be aggressively treated not just with antivirals but with thorough local wound care and prophylactic topical antibiotic therapy as well to prevent secondary bacterial infection.[5,15] Topical *(Print pagebreak 446)* ophthalmic preparations include acyclovir 3% eye ointment, topical trifluridine 1% solution, and ganciclovir 0.15% ophthalmic gel, while topical skin preparations include acyclovir 5% cream, docosanol 10% cream, or penciclovir 1% cream. Topical ophthalmic preparations like acyclovir 3% eye ointment (5 times/d) may be the safer option for cutaneous periocular application.[1]

Prognosis

Cellular antiviral immunity is potent in the dermis and spontaneous healing of isolated HSV blepharitis is the rule even without the use of topical or systemic antivirals, which allegedly have no impact on the healing course.[17] The type and severity of the initial eyelid involvement may have a prognostic value. Severe initial eyelid involvement is associated with more frequent recurrences.[1,10] Intermarginal HSV blepharitis is of central importance not just because its presence is pathognomonic of primary HSV but because it is prognostically important as well, as it is also a predictor of more ominous anterior segment eye disease.[6,17] Eczema herpeticum is also of prognostic importance and is considered one of the dermatological emergencies as it is associated with a mortality rate of 6% to 10% if not treated, and may rarely progress to viral encephalitis.[38]

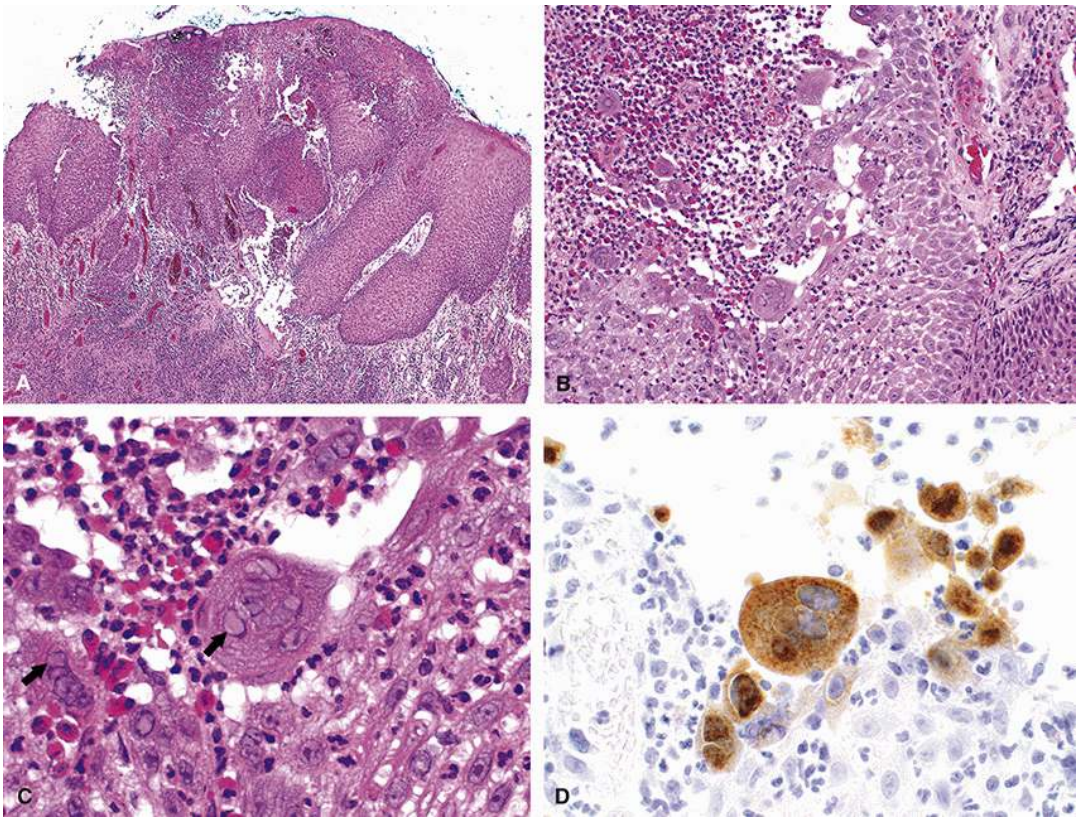

FIGURE 67.4 A, This herpes simplex virus (HSV) skin lesion preceded conjunctival and medial canthus HSV infection in a patient with HIV infection. The epidermis is ulcerated and acanthotic, and there are intraepidermal and subepidermal vesicles. The dermis has a marked infiltrate of lymphocytes, plasma cells, macrophages, and scattered eosinophils. B, The area of epidermal ulceration has infected keratinocytes mixed among numerous neutrophils. The infected cells are larger than the normal keratinocytes and have lost their cohesion with each other. C, Two enlarged, multinucleate, infected keratinocytes have eosinophilic nuclear inclusions (arrows). D, Immunohistochemical staining using antibodies specific for HSV antigen confirms the diagnosis. The infected cells are brown, while adjacent keratinocytes and inflammatory cells do not stain.

Histopathology

The histological features of skin infections by HSV (Figure 67.4), varicella, and herpes zoster virus are similar.[39,40,41,42,43] In HSV, the earliest changes are seen in the epidermal cell nuclei, which enlarge, develop a homogenous “ground glass” appearance, and have peripherally clumped chromatin.[44] Changes begin along the basal epidermal layer and progress to involve all *(Print pagebreak 447)* layers. Intraepidermal vesicles soon form secondary to ballooning and acantholysis of keratinocytes. Subepidermal vesicles may result from the destruction of the basal layer of the epidermis. Multinucleated keratinocytes are more conspicuous in lesions that have been present for several days. The histopathological clue to the diagnosis is eosinophilic nuclear inclusions, which are more common in the multinucleated cells. Diagnosis is confirmed using immunohistochemistry.[39]

In addition to the epidermal changes, HSV may infect hair follicles, sebaceous glands, and, more rarely, eccrine glands.[39,42] The histological changes of herpetic infection of dermal structures may occur in the absence of classic changes in the epidermis.[39,42] Dermal inflammation usually accompanies herpetic skin infections and may mimic lymphoma.[39,41,42]

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CHAPTER 68

Herpes Zoster Ophthalmicus

Key Points

- The varicella-zoster virus is one of the three members of the α-herpesvirus subfamily and is the etiologic agent of varicella (chickenpox) and herpes zoster (shingles)
- Virus spread is believed to occur during childhood through the respiratory tract, where viral particle replication begins in the nasopharynx
- Viremia then progresses to the skin leading to the development of chickenpox, after which a latent infection develops in sensory neurons in the dorsal root ganglia
- Once reactivation occurs, the virus can move down the neurons to the skin where it triggers a local inflammatory immune response
- Eyelid lesions appear on or near the eyelid margin in the V1 dermatome. Various stages of evolution include a preeruptive phase, an acute eruptive phase, and a chronic or relapsing phase
- Ocular disease may include conjunctival injection, chemosis, and edema, scleritis, episcleritis, limbal vasculitis, punctate epithelial keratitis, anterior uveitis, or a transient palsy of the third, fourth, or sixth cranial nerves
- Treatment begins with oral acyclovir, valacyclovir, or famciclovir
- Between 10% and 12% of patients with HZO will develop vision impairment within 6 months from corneal scarring
- Postherpetic neuralgia is a major postinfection complication

The varicella-zoster virus (VZV) is one of the three members of the α-herpesvirus subfamily[1,2,3,4,5,6,7,8,9,10,11] and is the etiologic agent of two clinically distinct diseases: varicella (chickenpox) and herpes zoster (shingles). While a primary VZV infection causes chickenpox, reactivation of the latent virus, which usually occurs in adults, causes herpes zoster, manifesting as a vesicular rash with a dermatomal distribution and acute neuritis.[1,2]

Etiology and Pathogenesis

Like other members of the alphaherpesvirus subfamily, the VZV (also termed the human herpesvirus type 3) is an enveloped virus that has double-stranded DNA, a short reproductive cycle, the potential to cause major host cell destruction during active replication, and the ability to establish lifelong latency in sensory neural ganglia.[7] Several different genotypes vary geographically.[7]

The initial virus spread is believed to occur during childhood through the respiratory tract, where viral particle replication begins in the nasopharynx. Viremia then progresses from the nasopharynx to the skin through lymphatic spread leading to the development of varicella (chickenpox), which is characterized by an initial generalized rash, after which a latent infection develops in sensory neurons in the dorsal root ganglia.[7] T cell-mediated immune mechanisms keep the VZV in check within these sensory ganglia as evidenced by the fact that once the T cell-specific immunity is below a certain level, a person is at risk for VZV reactivation.[7,8]

Although the virulence of the specific strain that primarily infects an individual may have a pathogenetic impact, local host factors play the predominant role.[8] Established predisposing factors include old age, immunosuppression, pregnancy, and HIV infection. Certain malignancies, and lymphoproliferative disorders can compromise virus-specific cellular immunity causing a reactivation and replication of the latent virus that spreads through sensory neurons causing zoster (shingles) and zoster-associated pain (ZAP).[7,11]

Herpes zoster not only develops in individuals who have already contracted the virus through community-acquired infections (wild-type varicella) but also can occur through varicella vaccination in childhood (vaccine-type VZV).[8] Herpes zoster ophthalmicus

(HZO) occurs when VZV reactivation occurs in the ophthalmic division of the trigeminal nerve (V1).[9] Once reactivation occurs, the virus can move down the neurons and satellite cells along sensory axons to the skin. Virus spread results in viremia and triggers a local inflammatory immune response in the sensory nerves and the skin.[8,9] Therefore, the pathophysiology of acute and long-term complications of adnexal as well as ocular HZO may not solely be attributable to viremia, but immune mechanisms and tissue inflammation play a role as well.[8] Reactivation of the virus occurs repeatedly throughout the patient's life, but some of these reactivations may be subclinical, which helps to boost the immune response to VZV.[9]

Clinical Presentation

The mean age of onset of chickenpox is around 4.5 years (range, 4-13 years), but the incidence has sharply declined due to routine vaccination.[12] Following a brief (24-hour) period of prodromal symptoms, the rash rapidly develops *(Print pagebreak 449)* and quickly evolves. Although ocular involvement is seen in only 4% of chickenpox patients,[13] in those with ophthalmic symptoms, eyelid manifestations predominate and are seen in 62.5% of cases.[14] The eyelid lesions usually appear on or near the lid margin and are morphologically similar to the typical varicella vesicles elsewhere in the body.[14] They may be observed in various stages of evolution (vesicle, papule, or scab) surrounded by a distinct red base. But in contrast to the rash elsewhere in the body, the eyelid lesions are usually isolated rather than grouped.[14] Eyelid lesions heal without sequelae within 2 weeks.[1,7,12] Other ocular manifestations are rare but punctal and canalicular stenosis, dacryocystitis, conjunctivitis, disciform keratitis, iridocyclitis, panuveitis, glaucoma, cataract, chorioretinitis, neuroretinitis, optic neuritis, optic atrophy, and internal ophthalmoplegia also have been reported.[12,13,14,15,16,17] Although the disease is mild and self-limiting in most cases, it can have devastating consequences in immunocompromised hosts or during pregnancy.[7,12]

Out of the one million newly diagnosed cases of herpes zoster estimated to occur annually in the United States, HZO constitutes 10% to 20%,[9,18,19,20] and for the past 2 decades, the incidence of HZO has been rising at an alarming rate (3.6% per year).[20] The cause of this trend is unknown, but it is hypothesized that mass varicella vaccinations in children may have reduced the exposure to wild-type varicella in the general population.[20] Other alternative explanations include a rise in the number of patients with immunocompromised conditions, an improvement in health-seeking behavior, and an increasingly aging population.[8,20] HZO is indiscriminate of gender and has no seasonal preference, although the incidence and severity rise with increasing age, especially in patients older than 60 years. Age is a predictor of the severity of acute pain that accompanies HZO. More importantly, postherpetic neuralgia (PHN) is estimated to develop in 36.6% and 47.5% of patients older than 60 and 70 years, respectively.[8,21] A notable exception to this rule is in patients with an HIV infection where the age of onset of HZO is usually less than 50 years, although other factors causing immunosuppression could also be associated with a younger age of onset.[22]

The clinical manifestations of HZO are divided into three phases: a preeruptive phase, an acute eruptive phase, and a chronic or relapsing phase. The preeruptive phase is characterized by neuropathic pain, which is often described by patients as burning, tingling, or shooting in nature. The pain initially is mild, then gradually rises in crescendo, and usually follows the distribution of the ophthalmic division of the trigeminal nerve (V1). The pain may or may not be accompanied by viral prodromal symptoms.[9]

Following the preeruptive phase, the rash begins to appear.[8] The skin eruptions associated with acute HZO can be highly variable in severity and extent; however, the frontal nerve, which innervates the scalp, the forehead, and the upper eyelid, is almost invariably affected in all patients.[23] It is also the site where the most severe skin lesions are observed, while skin lesions at the nasociliary dermatome are seen less frequently, in 60% of patients.[23] The two terminal branches of the nasociliary nerve, the external nasal and the infratrochlear nerves, may be involved either alone or together.[23] Hutchinson sign is the acronym given to papulovesicular lesions on the side and top of the nose due to involvement of the external nasal nerve.[8,10,23] Clinically, the acute skin rash varies from a few scattered maculovesicular skin lesions (Figure 68.1) to severe confluent, hemorrhagic bullous eruptions,[23] and new skin lesions continue to appear for 3 to 5 days. The rash of HZO evolves through the same stages as the disease elsewhere in the body, with erythema, macules, papules, and vesicles, which subsequently pustulate and crust (Figure 68.2).[8] Periorbital edema and ptosis are commonly observed, and in some patients, both eyelids are severely edematous to the extent that the palpebral fissure can hardly be opened for ocular inspection.[24] Other adnexal manifestations include punctal and canalicular stenosis or even dacryocystitis.[25,26]

Once a skin rash appears in the V1 dermatome, ocular symptoms should be expected to develop after 1 to 4 weeks. However, the term HZO is not synonymous with ocular involvement,[27,28] and only 50% of HZO patients will suffer ocular involvement.[8,27,29] Ocular disease may be acute or chronic and takes many forms. It may involve the conjunctiva (injection, chemosis, boggy edema), the sclera (scleritis, episcleritis, sclerokeratitis, or limbal vasculitis), the cornea (punctate epithelial keratitis, transient pseudodendrites, nummular anterior stromal keratitis, lipid keratopathy, and keratouveitis or endotheliitis), uveal tissue (anterior uveitis, sectoral iris atrophy), and may result in glaucoma, or a transient palsy of the third, fourth, or sixth cranial nerves.[7,8,9,30,31] The retina may also be involved, albeit rarely. Posterior segment problems include retinal perivasculitis, ischemic optic neuritis, acute retinal necrosis, or progressive outer retinal necrosis. Orbital apex syndrome and potentially blinding acute optic neuritis also have been reported.[8,27,29,32]

Ocular and adnexal chronic sequelae of HZO can persist in 30% of HZO patients, but it is seen more frequently (70%) in patients older than 80 years.[8] Patients with chronic HZO may suffer from residual ptosis, entropion, ectropion, eyelid scarring, or even eyelid necrosis with resultant lagophthalmos or permanent depigmented scars in the eyelid or on the forehead (Figure 68.3).[8,33] Most of these complications are seen rarely today and predate the acyclovir era.[24] Cicatricial eyelid changes may lead to exposure keratopathy and subsequently corneal desiccation. The picture is compounded by corneal nerve damage, which is inherent to HZO and leads to neurotrophic keratopathy, characterized by decreased corneal sensation with subsequent loss of corneal epithelial integrity, and the development of sterile epithelial defects that may become secondarily infected.[7,8] Postherpetic neuralgia is one of the chronic sequelae of HZO that may negatively affect the quality of life and could lead to serious disability. It preferentially affects the elderly and the immunocompromised, and patients often experience recurrent severe shooting and sharp pain, which may last for months.[7,8]

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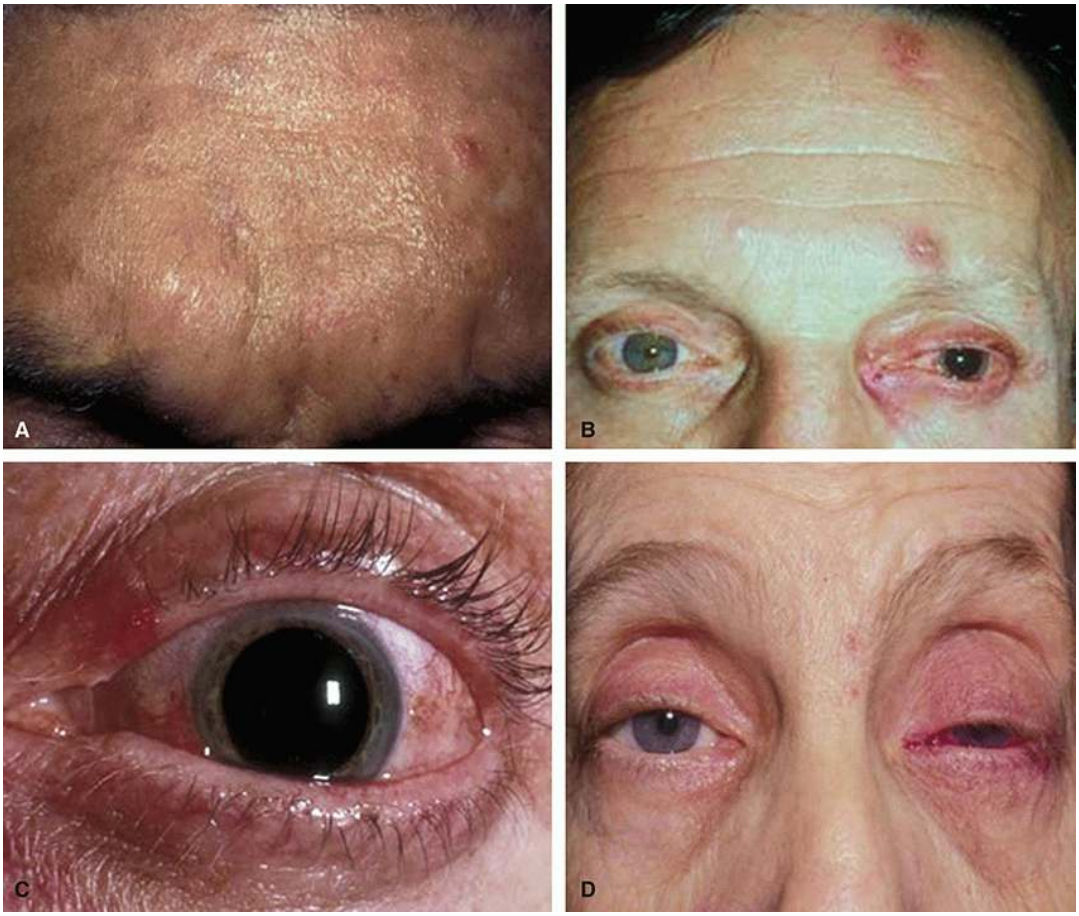

FIGURE 68.1 A-D, Early acute eruptive phase of *herpes zoster* ophthalmicus with scattered papulovesicular lesions and rash on the nose, forehead, and eyelids.

Recurrent herpes zoster is defined as the redevelopment of the characteristic vesicular rash accompanied by dermatomal pain or dysesthesia in V1, more than 3 months after the index episode.[28] It was recently estimated that the overall recurrence rates at 1, 3, and 5 years are 8%, 17%, and 25%, respectively,[28] and is counterintuitively far more common in immunocompetent patients. This suggests that recurrent disease may also be caused by an inflammatory response to the virus, rather than active viral replication.[28,29]

Occasionally, patients may suffer an acute unilateral neuropathic dermatomal pain with all the attendant complications of HZO, but the characteristic zoster rash is absent, a condition which is termed zoster sine herpete. Laboratory testing may help confirm the diagnosis.[8,34] Systemically, an affective mood disorder may follow HZO and persist for prolonged periods where patients suffer anorexia, insomnia, lassitude, severe depression, and occasionally antisocial behavior.[8]

In the presence of a strictly unilateral, unidermatomal rash of grouped vesicles on an erythematous background associated with the typical HZO pain, the clinical diagnosis of HZO is straightforward. However, laboratory testing may be needed whenever there is diagnostic uncertainty, chiefly to exclude herpes simplex.[11] Laboratory tests that are used for the diagnosis of HZV include antigen detection or virus isolation either with viral culture, electron microscopy, or one of the polymerase chain reaction (PCR) protocols. PCR is considered one of the most sensitive methods for viral diagnosis of VZV/herpes simplex virus (HSV).[11] A detailed discussion of the various PCR protocols available is beyond the scope of this chapter, but these include nested multiplex PCR, real-

time nested multiplex PCR, or reverse transcription PCR.[35,36,37] Serology *(Print pagebreak 451)* for detecting VZV-specific IgM, IgG, or IgA responses by ELISA is of little clinical value and is not routinely used in clinical practice.[8,11]

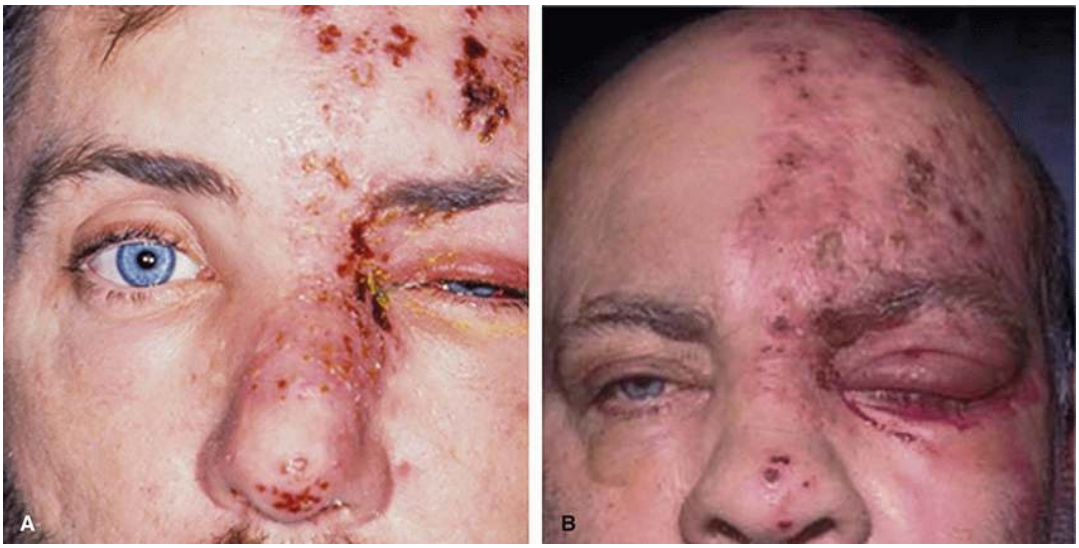

FIGURE 68.2 A and B, Late acute eruptive phase with bullous eruptions, eyelid erythema, edema, and ptosis.

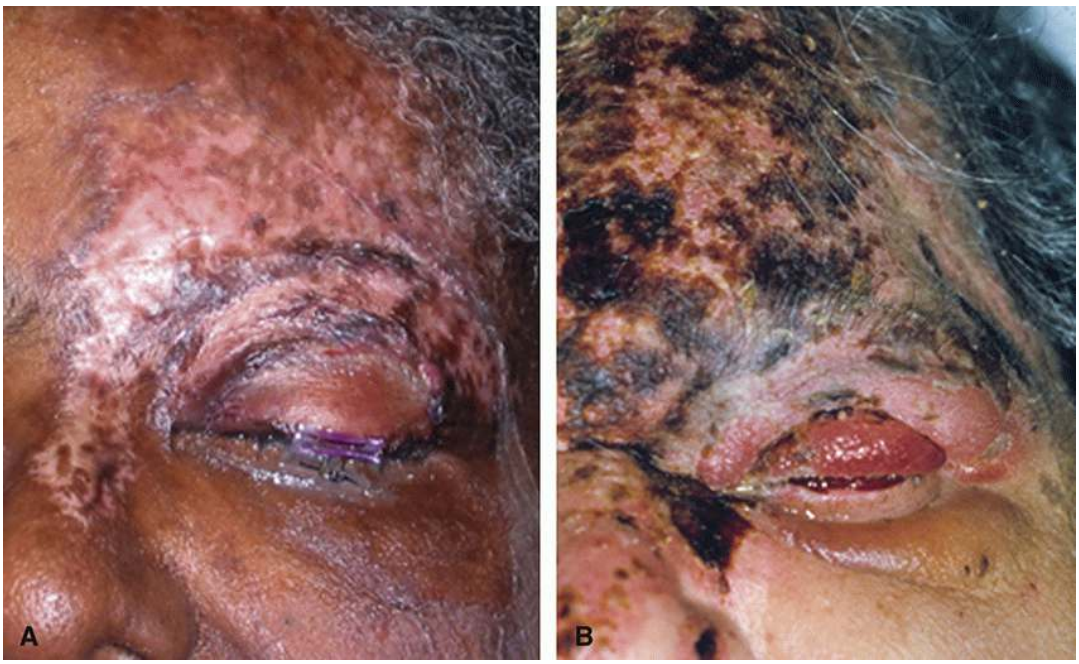

FIGURE 68.3 A and B, Chronic posteruptive phase with skin necrosis, ectropion, and depigmentation.

Differential Diagnosis

Rarely, HSV may mimic the evolution and morphology of herpes zoster and present with zoster-like eruptions, which acquire an appearance and pattern that simulates the lesion caused by VZV. This has been referred to as zosteriform herpes simplex, which may be difficult to differentiate clinically from HZO.[38,39] The lack of pain or other neurosensory problems before the advent of the eruptions may help confirm the diagnosis. But if the diagnosis is still in doubt, laboratory investigations like PCR or viral cultures may be required.[38,39] In patients with HZO and facial pain, other causes of periorbital pain should be excluded if the characteristics of the associated pain are not typical of HZO, as it may be referred *(Print pagebreak 452)* pain, may originate from migraine headache, or may even originate from an undiagnosed orbital tumor.[40] Because HZO patients may acutely suffer from significant eyelid edema, the differential diagnosis in early cases is broad and should include orbital or preseptal cellulitis and occasionally acute dacryocystitis.

Treatment

Chickenpox is a self-limiting disease and vesicular lesions on the eyelids heal spontaneously without treatment. Therefore, no therapy is necessary except in the rare event of punctal/canalicular involvement where local treatment with antivirals may prevent long-term lacrimal complications.[16,17]

Because HZO is a serious and sight-threatening illness, widespread vaccination for individuals older than 50 years is pivotal in reducing disease incidence and morbidity.[7] Two forms of antizoster vaccines exist. The first is a lyophilized live attenuated VZV strain (Zostavax, zoster vaccine live), which is the same strain used in the varicella vaccine, but 14 times more potent, used to stimulate cellular immunity.[7] The live attenuated vaccine is routinely recommended for all patients older than 60 years, although the verdict is still out about recommending the vaccine in the age group between 50 and 59 years.[7] The live attenuated vaccine is contraindicated in pregnant females, immunocompromised patients, and patients allergic to any component of the vaccine. More recently, a recombinant subunit varicella vaccine containing VZV glycoprotein E (Shingrix, recombinant zoster vaccine) was introduced. It is given as two intramuscular injections 2 to 6 months apart and is currently recommended by the Advisory Committee for Immunization Practices for all adults older than 50 years, regardless of whether they already received the live attenuated vaccine or not.[41] At the time of writing of this chapter, the verdict is still out about the safety of the subunit vaccine in immunocompromised patients although preliminary evidence suggests its safety.[42]

Treatment of HZO has three main objectives: treatment of the acute viral infection, amelioration of the acute pain associated with the infection, and prevention of PHN. Antiviral agents, corticosteroids, and analgesics are prescribed to address all three objectives.[43] Treatment should start immediately with oral acyclovir (800 mg five times daily), valacyclovir (1 g three times daily), or famciclovir (500 mg three times daily) for 7 to 10 days, preferably within the 72-hour window after onset of the rash.[29,40] Although valacyclovir and famciclovir have better bioavailability and consequently require less frequent dosing than acyclovir, acyclovir is still considered the mainstay of treatment.[29] Patients with severe disease may also be started on oral prednisolone concurrently with antiviral therapy to accelerate healing and reduce acute zoster pain. However, there is a lack of consensus about their efficacy in reducing the progression of ZAP to postherpetic neuralgia, as this role is not supported by conclusive clinical evidence.[40,43]
Systemic steroids are contraindicated in immunocompromised patients. Long-term (7-12 months), low-dose treatment with valacyclovir (1 g daily) or acyclovir (800 mg twice daily) may help reduce recurrences after acute HZO.[29] Treatment of postherpetic neuralgia includes the prompt administration of antivirals, along with tricyclic antidepressants, gabapentin, pregabalin, and opioids to decrease neuropathic pain.[29,40] In the postacyclovir era, surgery is rarely required to address long-term structural eyelid deformities because they are seldom encountered in modern clinical practice. However, if they do occur, they should be managed accordingly.

At the time of writing this chapter, there is insufficient evidence to recommend any specific topical treatment for acute HZO.[11] Accordingly, several authors refrain from using any form of local therapy and simply recommend keeping the lesions clean and dry using sterile saline solution or mild antiseptics such as polyhexanide 20% solution, which are applied to the affected areas for 20 to 30 minutes four to six times daily.[11] The use of zinc oxide lotions or ozone therapy is commonly used by some clinicians, but these methods lack clinical validation.[11] The topical application of local anesthetics or capsaicin cream to treat neuropathic pain is not advocated and is not supported by scientific evidence.[11]

Surprisingly, and despite its widespread use in clinical practice, the use of topical antivirals in HZO remains controversial.[11] It seems that despite the presumably better local penetration of topical acyclovir, it appears to have no therapeutic value in the management of skin lesions in acute HZO, and scientific evidence for its efficacy has not so far been demonstrated.[33,44,45] Based on consensus alone, topical acyclovir may be applied to the affected areas as adjuvant therapy five times daily, but should never be used as monotherapy without systemic acyclovir.[33,46]

Prognosis

Varicella (chickenpox) is a self-limited disease, and lesions heal without treatment,[12] except in neonates or in immunocompromised individuals where it can lead to serious complications such as pneumonitis or encephalitis.[8,12] However, HZO can be a fatal disease because of the attendant viremia that particularly occurs in immunocompromised individuals. This may lead to visceral involvement in 10% to 50% of patients in the form of hepatitis, pneumonitis, or even encephalitis.[8] The mortality rate in patients with visceral involvement ranges from 5% to 15%, and the majority of deaths occur due to pneumonitis.[8]

Between 10% and 12% of patients with HZO will develop vision impairment within 6 months, which usually results from corneal scarring. It is not entirely clear why some patients develop long-term structural complications with a devastating visual outcome

and/or significant deterioration in the quality of life, while others do not suffer any complications at all. Strain virulence and/or local host factors probably play a role.[8,28] The greater pain burden of PHN significantly affects the quality of life in HZO patients and is one of the leading causes of suicide in patients older than 70 years suffering from chronic pain.[8,28,47]

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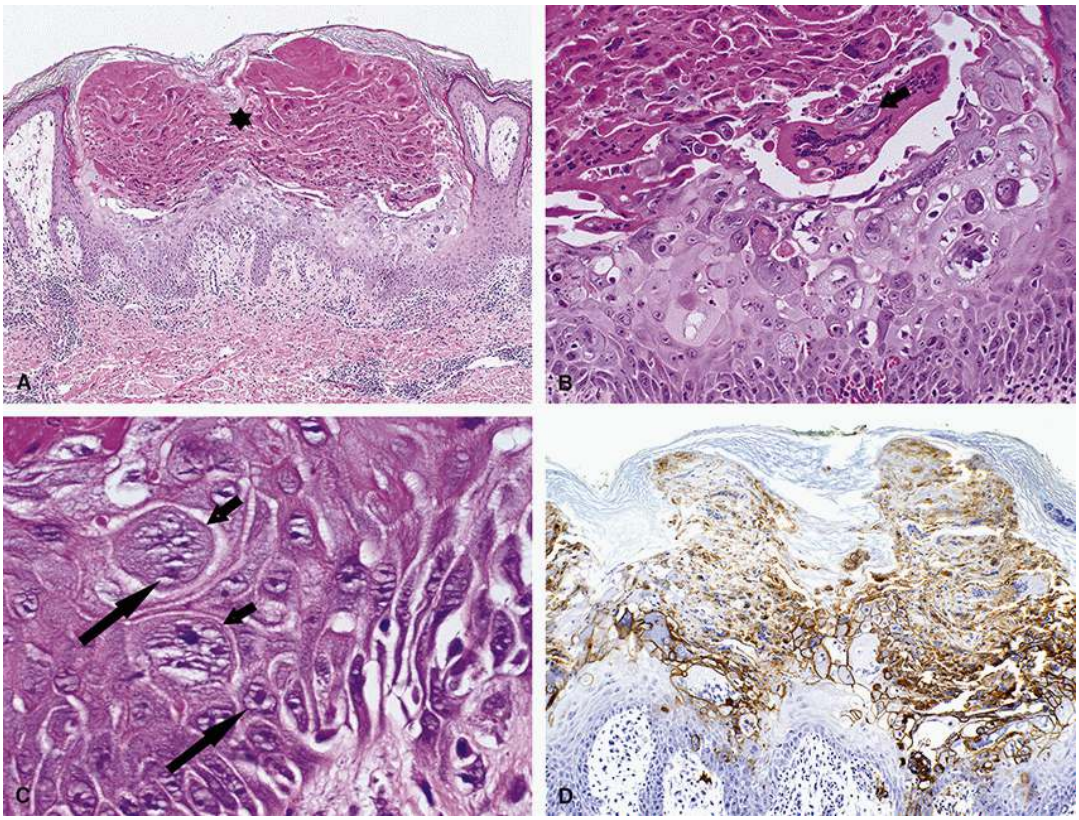

FIGURE 68.4 A, Varicella-zoster virus (VZV) infection has resulted in an intradermal vesicle (★). B, The vesicle contains infected cells, some of which are multinucleate (arrow). There are neutrophils among the infected keratinocytes. C, Close-up of multinucleated cells in the epidermis adjacent to the vesicle (short arrows). Eosinophilic intranuclear inclusions are in a multinucleated cell and a mononuclear keratinocyte (long arrows). D, Immunohistochemical staining using antibodies to VZV antigen confirms the diagnosis. Infected cells stain brown using diaminobenzidine as the chromogenic detection agent.

The classic dictum that Hutchinson sign is of special prognostic significance in acute HZO may not be entirely accurate. Involvement of the nasociliary nerve may indeed be a strong predictor for the development of sight-threatening ocular complications but only if both terminal branches of the nasociliary nerve (external nasal and infratrochlear nerves) are simultaneously involved.[8,10,23] It appears that the sparing of either of these branches is less predictive of serious ocular morbidity.[23] The severity and the extent of the skin rash may also be a predictor for the development of ocular complications because it underlies the immune status of the host.[23]

Histopathology

The histological features of skin infections by HSV and VZV are similar.[48,49,50,51] The characteristic lesion of herpes zoster infection is an intraepidermal vesicle (blister) with swollen multinucleate epidermal cells (Figure 68.4).[52] Swollen epidermal cells lose their attachment to adjacent cells and separate from them; a subepidermal vesicle may result if this process involves the basal epidermal cells. Eosinophilic nuclear inclusions are found in some of the multinucleated keratinocytes. Neutrophils are present within vesicles (Figure 68.4A and B) and within the subjacent dermis.[53] The lesions of herpes zoster resemble those of herpes simplex, but they can be distinguished using immunohistochemical stains (Figure 68.4D).[51]

Similar to cutaneous HSV infection, VZV may infect hair follicles, sebaceous glands, and, more rarely, eccrine glands.[49,50] The histological changes of herpetic infection of dermal structures may occur in the absence of classic changes in the epidermis.[49,50] Dermal inflammation usually accompanies herpetic skin infections and may mimic lymphoma.[49,50,51] Cutaneous reactions following VZV infection include granulomatous dermatitis, granuloma annulare, granulomatous vasculitis, and granulomatous

folliculitis.[54]

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CHAPTER 69

Hidradenoma

Key Points

- Most hidradenomas are probably of *apocrine* rather than *eccrine* origin
- Fifty percent of hidradenomas harbor the t(11;19) translocation: the fusion of *MECT1 gene* on chromosome 19p13, with the *MAML2* genes on chromosome 11q21
- Definitive treatment is via complete excision with clear margins
- Hidradenomas are generally benign lesions
- Recurrences are possible if the lesion is incompletely excised
- The malignant potential is rare or negligible
- The malignant variety is called hidradenocarcinoma and may occur de novo, or less commonly on top of a benign hidradenoma

The human skin contains several million sweat glands (also termed “sudoriferous glands”), which are small tubular structures in the skin that are concerned with the production of sweat, and of which there are two types, the water-producing eccrine sweat glands, which express their secretion by exocytosis (merocrine secretion), and the oil-producing apocrine sweat glands, which express their secretions by a process of apical decapitation of the secretory cells.[1,2,3,4,5,6,7,8,9,10] The glandular portion of both types is located in the dermis. The eyelid apocrine-pilosebaceous glands (also termed apocrine glands of Moll) are only observed at the eyelid margin, and they open into the infundibulum of the pilosebaceous unit (the hair follicles) leading to the surface of the skin.[1,4,5,9,10] However, eccrine sweat glands are not associated with hair follicles, and they open directly onto the epidermal surface via a long straight ductule, which has an apical intraepidermal portion (the acrosyringium).[10] Eccrine sweat glands are located in the pretarsal and preseptal regions but not in the eyelid margin. Although the human skin contains far more eccrine sweat glands than their apocrine counterpart, the eyelid is one of the few regions in the body where apocrine sweat glands (glands of Moll) are abundant. Both glands could be a source of origin of several sweat gland cystic swellings and neoplasms that are mostly benign but may rarely be malignant.[1,2,3,4,5,6,7,8,9]

Hidradenomas are relatively rare benign adnexal neoplasms arising from the tubular secretory epithelium of the sweat glands, but they are of uncertain eccrine or apocrine derivation.[1,2,3,4,5,6,7,8,9] The condition is alternatively known in the literature as eccrine hidradenoma, apocrine hidradenoma, clear cell hidradenoma, nodular hidradenoma, eccrine acrospiroma, solid-cystic hidradenoma, or nodulocystic hidradenoma.[3,4,8,11] This nomenclatorial complexity, besides its uncertain origin (eccrine vs apocrine vs both), has led to significant confusion in the literature when dealing with the condition and probably reflects the different approaches between pathologists in interpreting the histologic features of the disease.[3]

Etiology and Pathogenesis

The cellular origin of hidradenoma is controversial. The understanding of this rare neoplasm and its ultrastructural features has evolved over the years from the more traditional outlook in older textbooks, which considered these neoplasms to be of an exclusive eccrine origin. Currently, the consensus is to separate adnexal neoplasms of glandular or ductal origin into eccrine or apocrine hidradenomas, even though it is sometimes impossible to identify whether a lesion is displaying eccrine or apocrine differentiation.[8,11] Although it is currently accepted that hidradenomas can show either an eccrine or apocrine architecture, the apocrine characteristics are the predominant histological subtype that is demonstrable in the majority of lesions.[4,5,8,11,12] This is particularly true in the periocular region where it has been demonstrated recently that apocrine tumors are far more common than their eccrine counterparts, a histological subtype that may turn out to be extremely rare in the eyelids.[4,5]

The common denominators of apocrine glandular differentiation are the presence of decapitation secretions and intracytoplasmic zymogen granules. However, the identification of glandular components in follicular or sebaceous neoplasms, even in the absence of either defining feature (decapitation or zymogen granules), almost certainly represents apocrine differentiation. This premise is supported by embryologic evidence because the apocrine glands, hair follicles, and sebaceous glands have a shared origin from pluripotential germinative cells present in the follicles. All three structures are histologically integrated as the apocrine-pilosebaceous unit.[3,8,11,13] However, there is no single microscopic finding that is ultimately specific for eccrine glandular differentiation. When the hallmarks of apocrine disease are absent (decapitation secretion, intracytoplasmic zymogen granules, or accompanying follicular or sebaceous differentiation), an eccrine origin may be suspected but the lack of *(Print pagebreak 457)* these findings is not definitive. It may not be entirely implausible to suggest that the diagnosis of an eccrine hidradenoma may be one of exclusion.[3,11] What complicates matters further is that neither enzymatic studies nor electron microscopy or even immunohistochemical studies are of much help to elucidate the subtype of hidradenoma.[11] Therefore, the current consensus supports a presumed apocrine morphological predominance of hidradenomas.[3,4,5,8,11]

The histogenesis of hidradenomas is largely unknown, and only one genetic mutation has ever been described in patients with hidradenoma.[14,15] Some hidradenomas feature a t(11;19) translocation, which involves the fusion of both the mucoepidermoid carcinoma translocated 1 gene (*MECT1*, 19p13) and the mastermind-like 2 gene (*MAML2*, 11q21).[11,14,15] It is estimated that about 50% of patients with hidradenoma have the *CRTC1-MAML2* gene fusion, which is particularly common in the clear cell variant of hidradenomas.[15] There are no other known predisposing factors, although some authors note that trauma may accelerate the rate of growth of hidradenoma.[3]

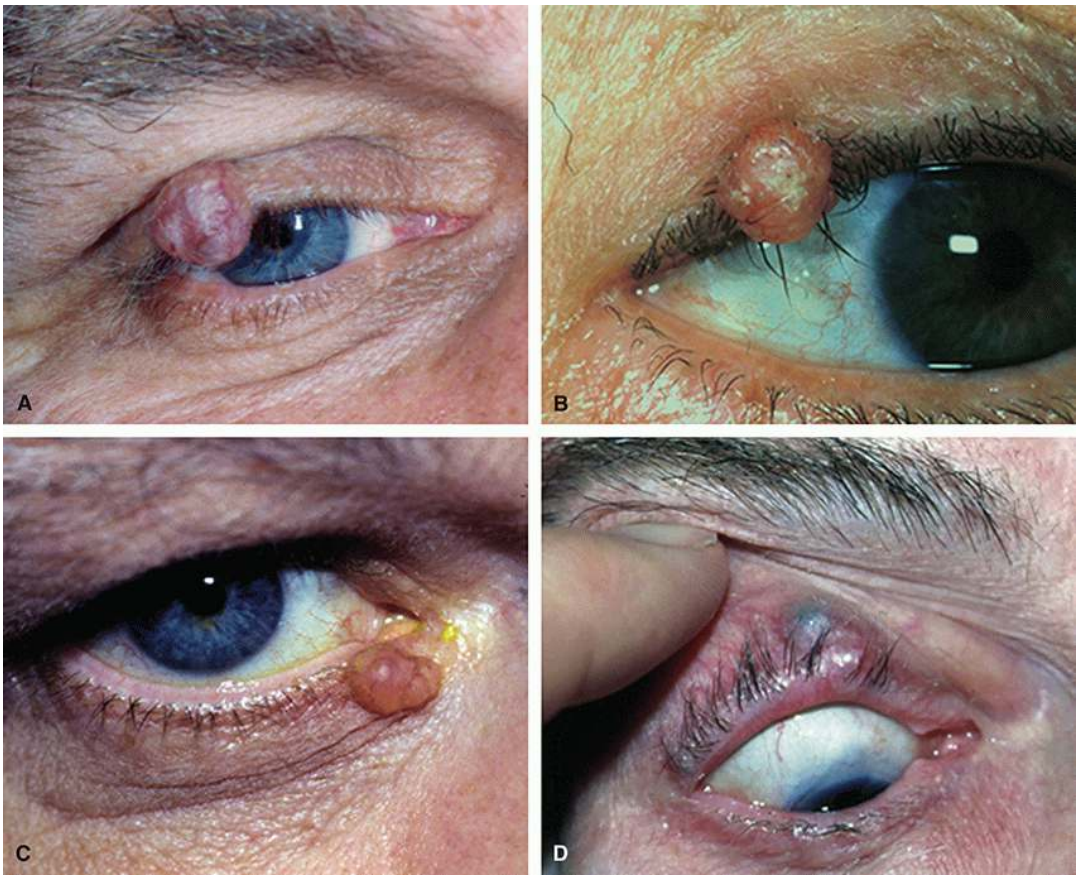

FIGURE 69.1 A-D, Hidradenoma. A (Courtesy of Dr. Bettina Meekins). B (Courtesy of Dr. David Jordan).

Clinical Presentation

Compared to hidrocystoma, eyelid hidradenoma is relatively rare. Most authorities agree that the disease has a 2:1 female preponderance,[7,8] although some authors suggest there is no sex predilection.[3] There is no specific age distribution although the maximum prevalence is generally observed between the fourth and the sixth decades.[3,8]

The clinical appearance of hidradenoma is nonspecific, and accurate diagnosis should rely on histopathology. Nevertheless, it generally presents as a solitary, well-circumscribed, slowly progressive pinkish or skin-colored solid nodule, which in the periocular region usually lies in close vicinity to the eyelid margin (Figure 69.1).[4] Occasionally, it may have a translucent appearance simulating a cystic lesion, with fine overlying telangiectatic vessels.[11]

The malignant variety is termed hidradenocarcinoma and is exceedingly rare, but if it does occur, it has a high potential for metastatic spread and is associated with low survival.[16] The malignant potential of benign hidradenomas *(Print pagebreak 458)* is unknown, and some authors consider it rare to negligible.[4,8] One large series identified the malignant counterpart of hidradenoma in 6.7% of excised lesions.[7] Whether hidradenocarcinomas represent a malignant transformation of a preexisting benign hidradenoma or a de novo lesion from the start is controversial. It should be noted that benign hidradenomas may exhibit a diverse morphological spectrum with variable differentiation; therefore, the original histology is not always an accurate predictor of the clinical behavior of their malignant potential.[8] Malignant transformation, if it occurs, is suggested by ulceration and infiltration around the borders of the lesion.[8,16,17]

Differential Diagnosis

Sweat gland lesions are ubiquitous in the periocular region, and as a result, any swelling involving the sweat glands, irrespective of its true nature, is usually dismissed as a trivial cystic swelling that may delay the proper diagnosis.[4,5] Therefore, it is important to make a clear distinction between hidradenomas, which are rare, and sweat gland cysts, including eccrine and apocrine cysts (hidrocystomas), which are ubiquitous.

Clinically, it may be difficult to differentiate hidradenomas from hidrocystomas, although other benign tumors arising from the eccrine ductal epithelium such as syringomas may be easier to discern based on clinical grounds alone. Eccrine hidrocystomas are retention cysts of the eccrine glands, whereas apocrine hidrocystomas probably represent cystic proliferations that arise from the apocrine secretory coil structure of the gland.[3] Syringomas are benign adnexal tumors derived from the intraepidermal eccrine ducts. They typically affect the lower eyelids and possibly the upper cheeks of middle-aged females more commonly than upper eyelid affection. By definition, they spare the eyelid margins, which points toward an eccrine origin.[4] They typically present with multiple soft to firm, skin-colored, yellowish, or translucent papules, 1 to 3 mm in diameter, which may coalesce together.[18] The differential diagnosis of hidradenoma should also include basal cell carcinoma and squamous cell carcinoma.[19]

Histologically, hidradenoma should be differentiated from tumors of the skin appendages, which exhibit follicular, sebaceous, or sweat gland differentiation including apocrine-mixed tumor, spiradenoma, cylindroma, chondroid syringoma, hidradenoma papilliferum, syringocystadenoma papilliferum, tubular apocrine adenoma, mucoepidermoid carcinoma, squamous cell carcinoma, as well as eyelid metastatic disease, particularly of renal origin.[3,8,12] Chondroid syringoma is a rare adnexal neoplasm that can arise in apocrine sweat glands and is an apocrine variant of pleomorphic adenoma.[20]

Hidradenoma papilliferum is an adenoma with apocrine differentiation, which almost exclusively involves the anogenital region in adult females, with few and rare reported ectopic exceptions in the periocular region or elsewhere.[21] It is not entirely clear in the literature whether ectopic hidradenoma papilliferum is indeed a true hidradenoma papilliferum or should simply be viewed as a hidradenoma with a definitive apocrine architecture, which is more likely because as we mentioned earlier, an apocrine architecture is probably the predominant histological form of most, if not all eyelid hidradenomas.[4,22,23]

Syringocystadenoma papilliferum is another benign eyelid lesion with a higher malignant potential than hidradenoma and should be differentiated from hidradenoma both clinically and histopathologically. This benign adnexal neoplasm is of apocrine origin; therefore, it arises almost exclusively near the eyelid margin. The condition is more common in females, the lesions are larger, with a rather more roughened or verrucous surface than typical hidradenomas, and the lesions may be more commonly encountered in clinical practice than hidradenoma.[19,24,25] Syringocystadenoma papilliferum may develop within a preexisting organoid nevus sebaceous, and basal cell carcinoma may occasionally develop on top.[24,25] The condition may coexist with hidrocystoma, tubular papillary adenoma, or hidradenomas,[24,25,26,27] and some authorities consider syringocystadenoma papilliferum, apocrine hidrocystoma, and tubular papillary adenoma with apocrine differentiation to represent a spectrum of the same disease rather than distinct entities.[6]

Eyelid tubular apocrine adenoma with apocrine differentiation is an extremely rare benign apocrine neoplasm, with only a few reported cases in the eyelids. Both lesions are clinically indistinguishable, and again, the distinction is usually morphological.[20,28] Although some authors make a clear distinction between apocrine papillary hidradenoma and the nonpapillary tubular variety with apocrine differentiation,[4] there are case descriptions in the literature of overlapping ultrastructural features.[29] It should be noted that apocrine *differentiation* does not automatically translate to apocrine *derivation*, and therefore both entities are perhaps indeed distinct.

Treatment

When removal is desired, complete surgical excision with clear margins is the treatment of choice to confirm the diagnosis

and prevent recurrences. Some authors have suggested Mohs micrographic surgery, although in most cases the lesion is well circumscribed and simple excision is all that is needed.[11]

Prognosis

Hidradenomas usually grow slowly, are generally considered benign lesions, and may exist for prolonged periods before the diagnosis is established because they may be initially dismissed as benign eyelid "cysts." Also, they may recur after inadequate surgical excision; therefore, regular follow-up is advised, particularly if the lesion is incompletely excised.

(Print pagebreak 459)

Because it may be difficult to establish the correct diagnosis of a sweat gland lesion based on clinical grounds alone, and because of the possibility of malignancy, it is generally preferred that any solitary sweat gland lesion that is excised from the periocular region should be routinely submitted to histopathology and should not be dismissed as a trivial cosmetic nuisance.[8,12,16,30]

Histopathology

These tumors, usually located in the dermis, are well circumscribed, solid or solid/cystic, and composed of lobules of cells forming acini and tubules or solid sheets.[3,8,31,32] The acini and tubules vary widely in luminal diameter and number, and cuboidal or columnar cells line them.[32] Solid areas of the tumor have a mixture of polyhedral cells with rounded nuclei and pale eosinophilic to slightly basophilic cytoplasm and round cells with clear cytoplasm due to glycogen dissolution during histological processing.[32,33,34] The proportion of the two cell types varies considerably between tumors.[32] Some authors consider clear cells the predominating cell type in hidradenomas,[31] but in a study of 41 hidradenomas by Winkelmann and Wolff, there were only 12 (29%) tumors of predominantly clear cells.[32] Polygonal squamoid cells with eosinophilic cytoplasm and occasional intercellular bridges are a common finding in hidradenomas, while less common cell types have mucinous or oncocytic features.[3,8,35,36,37] Apocrine cells with decapitation secretion are uncommon in hidradenomas.[8] In our experience, periocular hidradenomas most commonly have polyhedral cells with duct formation and small cystic spaces (Figure 69.2). We have seen only one eyelid hidradenoma with abundant clear cells (Figure 69.3).

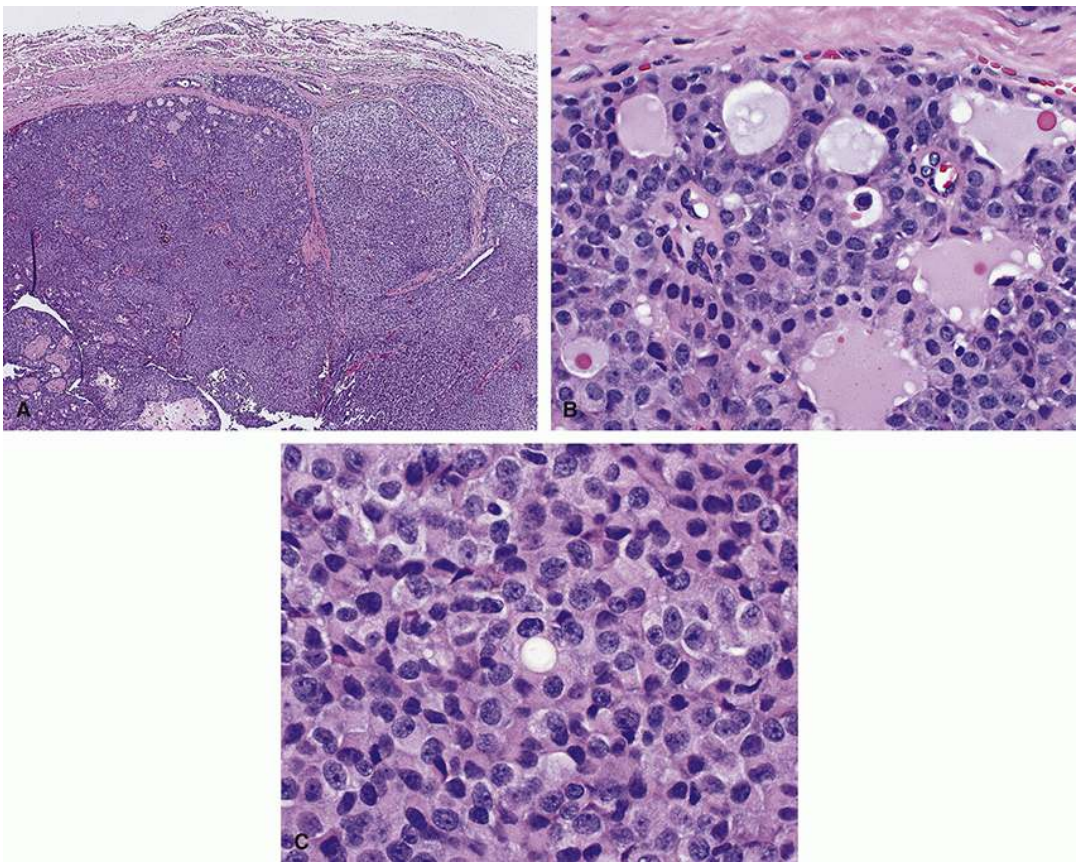

FIGURE 69.2 This hidradenoma of the right upper eyelid is typical of that we have encountered most often in the

periocular region. A, The tumor is based in the dermis, is well circumscribed, and has a lobular pattern. B, The tumor is predominantly solid with a few small cystic areas. C, Polygonal cells with pale eosinophilic cytoplasm form sheets or tubules.

A potential conundrum is a mucinous hidradenoma, which we have encountered several times in the eyelid (Figure 69.4). Mucinous hidradenomas are uncommon,[35,36] and they raise the specter of an endocrine mucin-producing sweat gland *(Print pagebreak 460) (Print pagebreak 461)* carcinoma (EMPSGC) when encountered in a periocular location.[38,39,40,41,42,43,44,45] EMPSGCs have a predilection for being periocular,[41] and 8 of 13 EMPSGCs in Shon and Salomão's study were classified originally as hidradenomas.[44] Expression of nuclear estrogen receptors cannot be depended on to distinguish EMPSGC from hidradenoma since some hidradenomas express estrogen receptors.[46,47] We recommend using a panel of immunostains including nuclear estrogen receptor, neuroendocrine markers (synaptophysin and chromogranin), and WT1 and classifying the tumor as an EMPSGC if the tumor expresses nuclear estrogen receptors, a neuroendocrine marker, and WT1.[38,39,41,43,44] We consider this prudent before diagnosing a tumor as hidradenoma because of the significant histological overlap with EMPSGC.

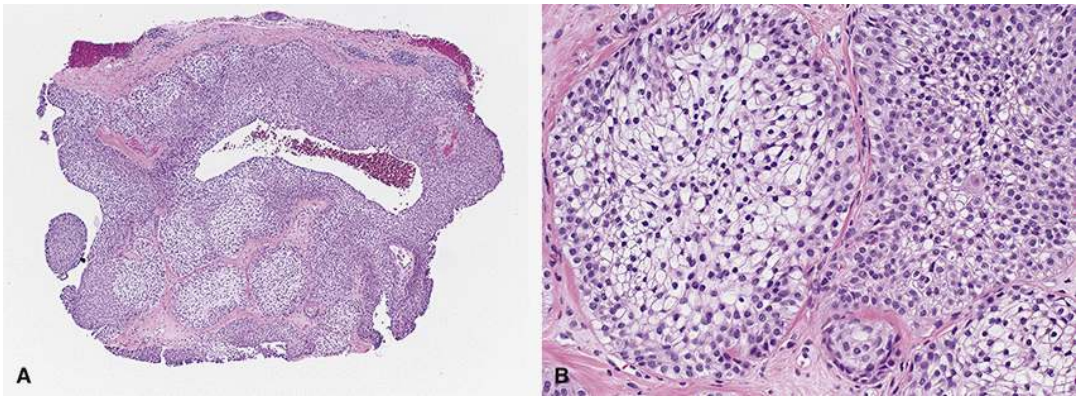

FIGURE 69.3 A and B, This hidradenoma of the left lower eyelid has a prominent population of clear cells containing glycogen. Much of the glycogen dissolves from the tissue during processing, leaving clear cytoplasm. Clear cells are often abundant in hidradenomas of other body sites, but they are uncommon in eyelid hidradenomas in our experience.

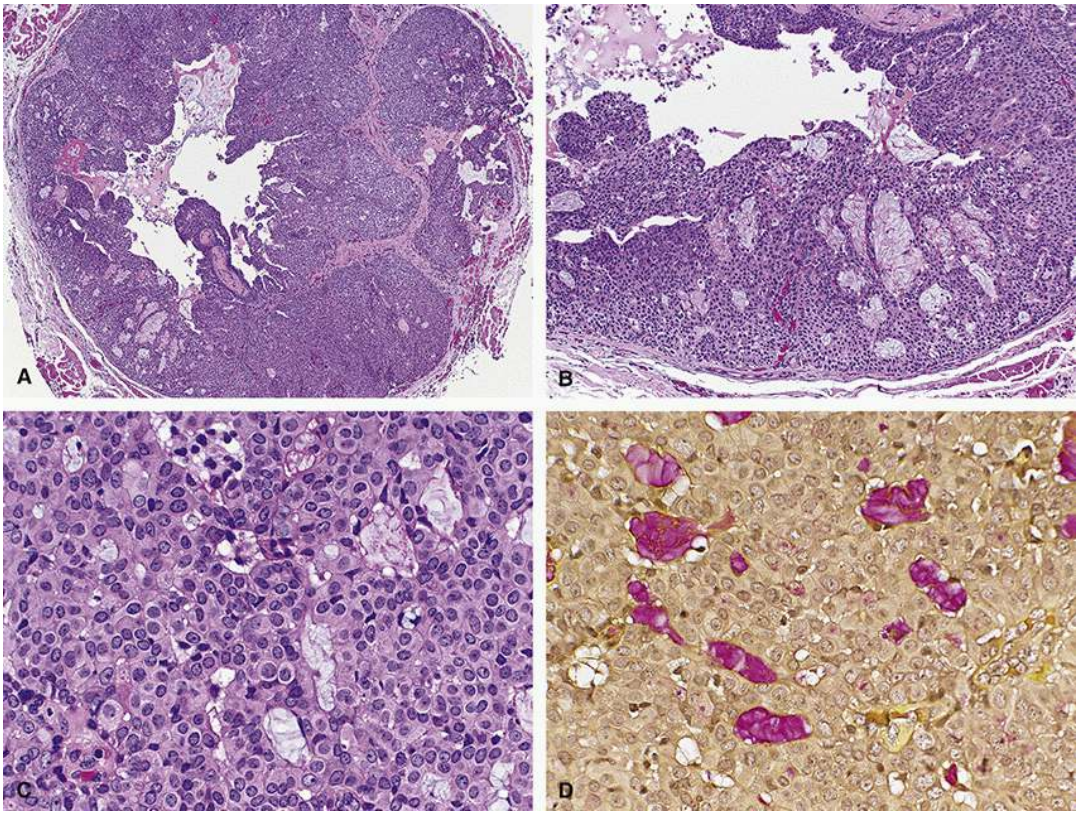

FIGURE 69.4 A, This hidradenoma of the right lower eyelid is well circumscribed with a solid and cystic pattern. B, There are scattered small pools of mucin among the sheets of polygonal cells. C, A majority of the cells are round or polygonal with lightly eosinophilic cytoplasm and round nuclei. Small pools of mucin are among the tumor cells. D, A mucicarmine stain highlights mucin pools and scattered small intracellular mucin globules.

A final consideration when evaluating hidradenomas is differentiating benign, atypical, and malignant tumors.[48,49] Hidradenocarcinomas have cytological atypia, infiltrative growth, deep extension, and ≥4 mitoses per 10 high-power fields.[48,49,50] Immunohistochemical stains using antibodies to Ki-67 and phosphorylated histone H3 may facilitate distinguishing benign and atypical hidradenomas from hidradenocarcinoma, with hidradenocarcinomas having much higher levels of Ki-67 and phosphohistone H3 expression.[49]

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CHAPTER 70

Hidrocystoma

Key Points

- Hidrocystomas are benign cystic lesions of sweat glands seen most commonly on the face, especially on the eyelids
- Hidrocystomas are categorized into apocrine and eccrine types
- Apocrine glands are found only at the eyelid margin, whereas eccrine glands are sparsely present in the dermis of the pretarsal and preseptal eyelid skin
- Eccrine and apocrine hidrocystomas are believed to result from ectasias of sweat gland secretory ducts and glands
- Apocrine hidrocystomas are intradermal, dome-shaped, translucent cystic nodules with a white layered precipitate
- Eccrine lesions are dome-shaped cysts with a clear amber or bluish tint and no precipitate
- Treatment is mostly with surgical excision or electrodesiccation

Hidrocystomas are benign cystic lesions of sweat glands seen most commonly on the face, especially on the eyelids, in the medial canthus, and less commonly the lateral canthal angle.[1,2,3,4,5,6,7] In a large series of more than 5000 benign and malignant noninflammatory lesions excised from the eyelids, 5.9% were hidrocystomas, and these were equally distributed in the upper and lower eyelids.[4] Other studies reported hidrocystomas to account for 8% to 10.5% of benign eyelid lesions.[8,9]

Based on their histologic characteristics and presumed histogenic derivation, hidrocystomas are categorized into apocrine and eccrine types. Apocrine glands are found only at the eyelid margin in association with cilia, and nowhere else in the eyelid skin. Eccrine glands, however, are not present on either the upper or lower eyelid margins or in the perimarginal skin but are sparsely present in the dermis of the pretarsal and preseptal eyelid skin.[10] So eccrine hidrocystomas develop within the eyelid skin away from the eyelid margins and pericilial skin, whereas hidrocystomas on or near the eyelid margins are always apocrine in origin.[11,12,13] De Viragh et al[12] reported that apocrine or eccrine hidrocystomas are often misdiagnosed because the usual histological criteria are masked, probably secondary to intraluminal pressure in the cysts, which flattens their walls and abolishes decapitation secretions.

Apocrine sweat glands are composed of a coiled secretory portion located in the dermis. A short straight excretory duct inserts into the upper infundibular portion of the hair follicle.[14,15,16] The apocrine gland secretes an oily fluid with proteins, lipids, and steroids. Secretions appear on the skin surface mixed with sebum since sebaceous glands open into the same hair follicle.[17] Apocrine glands secrete in periodic spurts and release their products by “decapitation,” where membrane-bound cytoplasm from the apical surface of the secretory cells bud off into the lumen of the duct.

Apocrine hidrocystomas were first described by Mehregan in 1964[18] and are thought to derive from the secretory portion of the apocrine gland. They are usually solitary lesions, but can also be multiple,[19] and vary in size from 3 mm to about 15 mm.[20] Multiple apocrine hidrocystomas have been described in two rare ectodermal dysplasias. Goltz-Gorlin syndrome (focal dermal hypoplasia syndrome) is a sporadic or X-linked dominant disease most common in females and characterized by atrophic hyperpigmented and hypopigmented macules, linear skin atrophy, microcephaly, microphthalmia, midface hypoplasia, malformation of the ears, apocrine hidrocystoma of the eyelids, syndactyly, and mental retardation.[21,22] Schopf-Schulz-Passarge syndrome is an autosomal recessive condition characterized by hypotrichosis, hypodontia, palmar and plantar hyperkeratosis, nail fragility, hypotrichosis, and multiple eyelid apocrine hidrocystomas.[23,24]

Eccrine glands are composed of an intraepidermal spiral duct, a dermal duct consisting of a straight and coiled portion, and a coiled secretory tubule deep in the dermis.[17] The eccrine gland opens directly onto the skin surface through a sweat pore. These glands produce a clear odorless secretion, consisting primarily of water.

Eccrine hidrocystomas were first reported by Robinson in 1893[25] in workers laboring in humid and warm environments. The cysts tend to enlarge with exercise and in warm environments, due to increased sweat retention.[26] Eccrine hidrocystomas are most prevalent in adults between 30 and 70 years and present as small, tense, thin-walled cysts 1 to 6 mm in diameter and can occur as single or multiple lesions.[2,20] They are very rare in children, and when present can be associated with ptosis and astigmatism.[27,28] Solitary eccrine hidrocystomas occur equally among males and females, but multiple cysts are mainly seen in females.[29]

Graves disease has been associated with multiple eccrine hidrocystomas.[30] It is suggested that these are due to hyperhidrosis, which can be seen in hyperthyroid patients, and the cysts tend to disappear after treatment of the hyperthyroidism.[30]

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Etiology and Pathophysiology

Eccrine and apocrine hidrocystomas are believed to result from ectasias of sweat gland secretory ducts and glands.[2,29,31,32,33,34,35] The apocrine sweat glands of Moll, which are present at the lid margin and empty into the infundibular portion of the lash follicles, give rise to cysts along the lash line.[10] These cysts derive from the secretory portion of apocrine glands in the dermis and are thought to develop as cystic proliferations of the coil structure of the gland, rather than as a simple retention cyst.[36,37,38] Eccrine hidrocystomas, however, are located in the dermis and empty directly onto the skin surface without any communication with the folliculosebaceous apparatus. Eccrine cysts are believed to result from blockage of the excretory duct, with sweat retention and cystic dilation of the eccrine gland.

Apocrine hidrocystomas differ from eccrine cysts by the presence of cyst content containing milky layered apical cytoplasmic decapitation debris. These represent shedding of adluminal snouts that become incorporated into the eosinophilic cyst secretions. Eccrine cysts contain a clear watery secretion with no snouts, and without cytoplasmic contributions.[10] Both of these types of cysts are distinguished from simple conjunctival cysts by the absence of goblet cells.

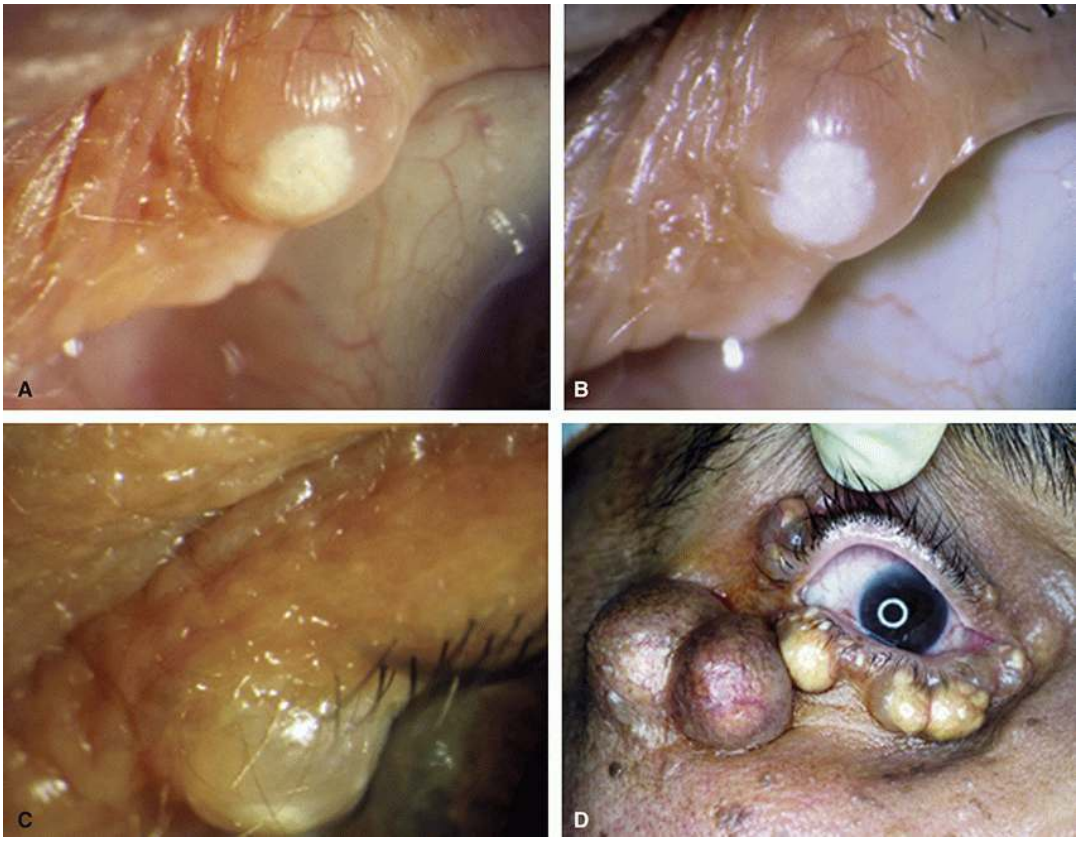

FIGURE 70.1 A-D, Apocrine hidrocystoma on the eyelid margins with a layered precipitate.

Clinical Presentation

Apocrine hidrocystomas are usually solitary lesions. They are found on the head and neck, commonly affecting the cheek and the medial canthus of the eyelid, but are also reported on the chest, shoulder, axilla, umbilicus, foreskin, penal shaft, vulva, and fingers. They typically are intradermal, moderately firm, dome-shaped, translucent, blue, bluish-black, grayish, or purple cystic nodules with

a white layered precipitant (Figure 70.1). Hidrocystomas on the eyelid margin are always of the apocrine type, may contain multiple loculated cystic spaces, and produce oily, foamy secretions. Peripheral linear vessels represent dilated vessels of the papillary dermis.[39,40,41] Cysts range in size from 3 to 15 mm in diameter, but occasionally can be larger. They may appear pigmented due to a Tyndall effect, but this may also occur due to the presence of lipofuscin pigments in the cystic fluid.[42,43]

Eccrine hidrocystomas can be solitary or multiple. They typically are dome shaped, have a clear amber or bluish tint, *(Print pagebreak 465)* and range from 1 to 6 mm in diameter. They are not located on the eyelid margins but can be seen on the pretarsal and preseptal eyelid skin. During hot or humid weather, these lesions tend to enlarge in size and can multiply in number due to increased sweat production and retention of secretions.[44] Eccrine cysts contain a single cyst cavity and produce a clear watery secretion (Figure 70.2).

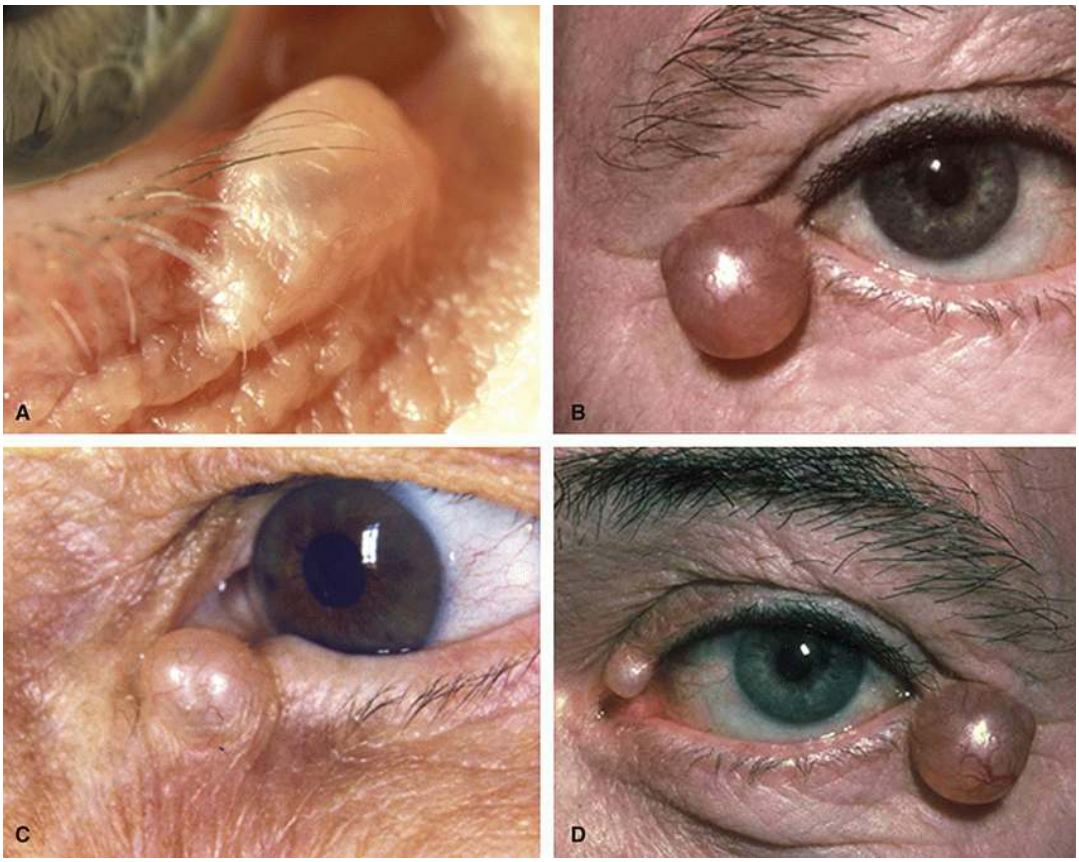

FIGURE 70.2 A-D, Eccrine hidrocystoma containing a clear watery secretion.

Both apocrine and eccrine hidrocystomas are seen equally among men and women and generally present in adults at a mean age of about 64 years.[10]

Differential Diagnosis

Eccrine and apocrine hidrocystomas have very similar clinical presentations. For both, the differential diagnosis includes epidermoid cyst, epidermal inclusion cyst, sebaceous duct cyst, mucoid cyst, lymphatic or venolymphatic malformations, and hidradenomas. They can also occasionally resemble malignant tumors such as basal cell carcinoma, yellowish sebaceous carcinoma, endocrine mucin-producing sweat gland carcinoma, and, when pigmented, melanocytic nevi and melanoma.[11,45,46,47,48] When multiple, the differential also includes syringomas, milia, and trichoepitheliomas. For cysts that involve the conjunctiva, the differential also includes conjunctival inclusion cyst and canaliculops.

Treatment

The most common treatment of apocrine hidrocystoma is surgical excision with narrow margins, although surgery for larger or multiple lesions can result in scarring.[49] Incision and drainage is a simple procedure but results in a high recurrence rate. Recurrence can be reduced with cauterization of the remaining cyst wall.[2] Trichloroacetic acid injection after cyst puncture is an alternative to surgery,[50] as is hypertonic glucose as a sclerosant.[51]

Other therapeutic methods include electrodesiccation, radiofrequency ablation, and laser treatment for smaller lesions.[19,49,52] Multiple lesions have been treated successfully with topical 1% atropine or scopolamine creams, but some patients have discontinued treatment because of anticholinergic side effects.[53] Botulinum toxin A also has been used effectively because acetylcholine is an effector sudomotor *(Print pagebreak 466)* neurotransmitter, and this toxin reduced sweat secretion.[43,54,55] Other anticholinergic agents such as glycopyrrolate, clonidine, and oxybutynin exert an inhibitory effect on sweat glands and have also been used to treat multiple hidrocystomas.[26,53,56,57,58]

Prognosis

Hidrocystomas are benign lesions, and unless very large, usually are only of cosmetic concern. With appropriate treatment, recurrences can be minimal and the prognosis is excellent.

Histopathology

Hidrocystomas are classified routinely as apocrine or eccrine based on their appearance in hematoxylin and eosin sections.[58,59,60] However, cysts resembling eccrine hidrocystoma may have an immunophenotype indicative of an apocrine origin, making histological classification as apocrine or eccrine of dubious value.[9,12] Some dermatopathologists even question whether eccrine hidrocystomas even exist.[61]

Apocrine hidrocystomas may be unilocular or multilocular and are lined by two layers of cells (Figure 70.3A and B).[58,60] The inner lining is composed of columnar cells with eosinophilic cytoplasm and decapitation secretion (buds of cytoplasm detaching from the luminal surface). Myoepithelial cells compose the outer layer; the cells are flat to low cuboidal. The epithelium may form papillary projections into the lumen. When papillae are more profuse and have a fibrous core or the epithelium has an adenomatous appearance, the lesions are now classified as apocrine cystadenomas (Figure 70.3C and D).[60,62] Cyst contents, when present, are lightly eosinophilic proteinaceous material.

Cysts classified as eccrine hidrocystomas are unilocular. At low magnification, the cysts often have a convoluted profile due to cyst collapse during surgical removal. They are lined by two layers of epithelium: an inner layer of cuboidal cells and an outer layer of low cuboidal to flat cells (Figure 70.4).[58,59,60] The cyst contents are often absent from histological sections; they are lightly eosinophilic proteinaceous material if present.

The epithelium of hidrocystomas and apocrine cystadenomas may be pigmented (Figure 70.5), especially in lesions classified as apocrine.[63,64,65] In some cases, the pigment has the histochemical properties of melanin,[63,64,65] while in others, it does not.

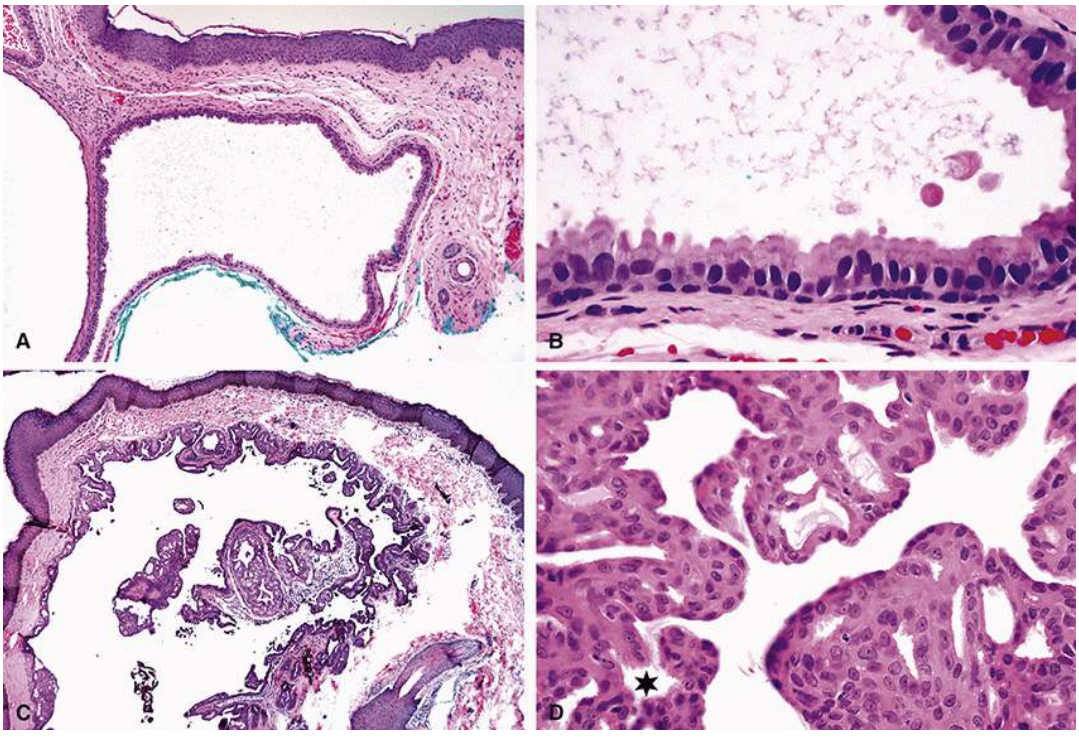

FIGURE 70.3 A, This left lower eyelid apocrine hidrocystoma is multiloculated. B, It is lined by two layers of cells. Columnar cells with eosinophilic cytoplasm and decapitation secretion form the inner layer. Flat to low cuboidal myoepithelial cells compose the outer layer. Lightly eosinophilic proteinaceous material is in the lumen. C and D, Apocrine cystadenomas have papillae with fibrous cores or an adenomatous appearance, as in this example from the right lower eyelid. Decapitation secretion is evident in some of the adenomatous glands (★).

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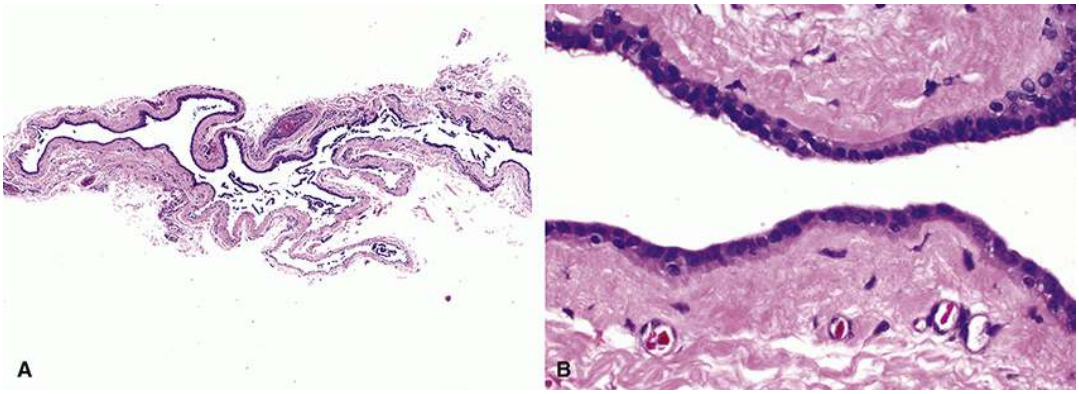

FIGURE 70.4 A, This cyst from the right lower eyelid was classified as an eccrine hidrocystoma since it was unilocular and lacked evidence of decapitation secretion by the inner lining of cells. At low magnification, the cyst has a convoluted profile due to collapse during surgical removal. B, The cyst is lined by two layers of epithelium: an inner layer of cuboidal cells and an outer layer of low cuboidal to flat cells.

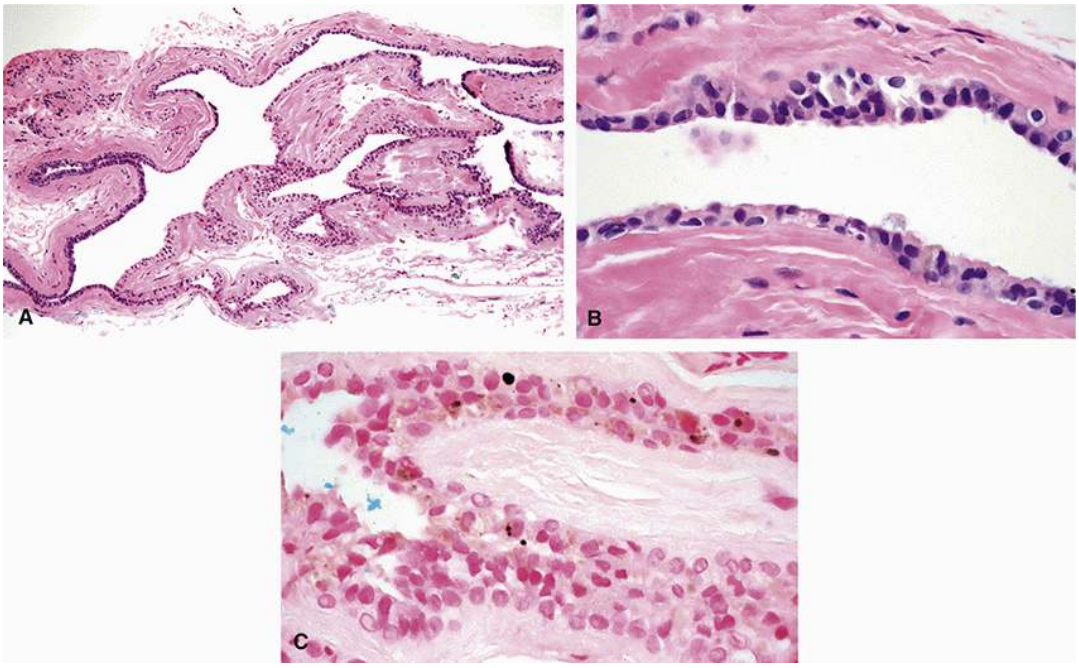

FIGURE 70.5 The epithelium of hidrocystomas and apocrine cystadenomas may be pigmented, as seen in this left medial canthus hidrocystoma. A, The cyst is unilocular with convolutions due to its collapse during removal. B, The cyst lining is two-layer thick, and the inner layer lacks features of decapitation secretion. The cells are less eosinophilic than a typical hidrocystoma and have a tan tinge. C, The intracytoplasmic pigment is more readily apparent in the section stained using the Fontana-Masson method for demonstrating melanin. The pigment has remained tan and brown, indicating that it is not melanin, which turns black utilizing this procedure.

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CHAPTER 71

Ichthyosis

Key Points

- Ichthyosis is a heterogeneous group of disorders characterized by abnormal cutaneous keratinization with scale formation
- These are divided into nonsyndromic and syndromic forms of inherited ichthyoses and less common acquired ichthyoses
- Ichthyosis vulgaris is the most common and mildest form of nonsyndromic ichthyosis, presenting with dry skin with rough patches and/or tiny bumps, and trichomegaly
- Lamellar ichthyosis is characterized by hyperkeratosis and thick scales, eyelid ectropion, and corneal complications
- Harlequin ichthyosis the most severe form with a high mortality rate
- Syndromic forms include a number of uncommon conditions such as Netherton syndrome, Refsum syndrome, and KID syndrome and are usually more severe
- Most inherited forms result from mutations in genes involved with skin barrier homeostasis
- There is no cure and management is mostly supportive
- Genetic testing is essential to identify the subtype, predict the clinical course, and allow for family counselling
- Ectropion is treated with ocular lubricants and skin grafting
- The prognosis depends on the subtype and varies from very good to lethal

The term “ichthyosis” is derived from the Greek word ichthys, meaning fish, and the clinical features of the ichthyoses were noted in early medical writings dating back to antiquity describing them as diseases resembling snakeskin or the scales of a fish.[1] The first historic reference to ichthyosis, “Ekakushtha, skin disease like scales of a fish,” appears in an Indian text in 250 BCE.[2]

Ichthyosis refers to a clinically and genetically heterogeneous group of inherited congenital disorders characterized by abnormal cutaneous keratinization with scale formation.[3,4,5] It is a general term for more than 50 types of related cutaneous diseases.[6] These diseases can be inherited and congenital or acquired later in life.

In 2009, the First Ichthyosis Consensus Conference divided the inherited ichthyoses clinically into two groups: nonsyndromic and syndromic forms.[5] Nonsyndromic ichthyoses are phenotypically expressed only in the skin and represent the most commonly seen phenotypes,[7,8] whereas syndromic ichthyoses have phenotypes that involve the skin, as well as other organs.[9] Takeichi and Akiyama[7] classified the inherited nonsyndromic ichthyoses based on clinical features and genetic mutations as follows:

Common Ichthyosis

Ichthyosis vulgaris

Recessive X-linked ichthyosis

Autosomal recessive congenital ichthyosis

Major types

Harlequin ichthyosis

- Lamellar ichthyosis
- Congenital ichthyosiform erythroderma (collodion baby)
- Minor types
  - Self-healing collodion baby
  - Acral self-healing collodion baby
  - Bathing suit ichthyosis

Keratinopathic ichthyosis

- Major types
  - Epidermolytic ichthyosis
  - Superficial epidermolytic ichthyosis
- Minor types
  - Annular epidermolytic ichthyosis
  - Ichthyosis Curth-Macklin
  - Autosomal recessive epidermolytic ichthyosis
  - Epidermolytic nevi
  - Congenital reticular ichthyosiform erythroderma

Nonsyndromic Ichthyoses

Ichthyosis vulgaris is the most common and mildest form of nonsyndromic ichthyosis, having an incidence of 1:250 to 1:1000.[5] It is characterized by xerosis, scaling, pruritus, and eczema, and it is strongly associated with atopic manifestations.[5] The most commonly affected sites are the extensor surfaces of the lower legs and the back. Other cutaneous features include palmoplantar hyperlinearity and keratosis pilaris (dry, rough patches, and tiny bumps), usually on the upper arms, thighs, cheeks, or buttocks. Trichomegaly with elongated eyelashes has been reported as a cutaneous marker for this disease seen in 13% of patients.[10] The causative genetic mutation is in the *FLG* gene that encodes profilaggrin,[11] a precursor protein of filaggrin, a protein that *(Print pagebreak 471)* facilitates terminal differentiation of the epidermis, and the formation of the protective skin barrier.[12] In terminal differentiation, filaggrin is cross-linked to the cornified cell envelope, which constitutes an insoluble barrier in the stratum corneum to protect the organism against environmental agents and to prevent epidermal water loss.[13]

Recessive X-linked ichthyosis is the second most common ichthyosis. It affects males and is more severe than ichthyosis vulgaris, with a prevalence of 1:2000 to 1:6000. It is clinically characterized by generalized dark brown, polygonal scales and dryness on the back of the scalp, ears, neck, back, and legs with sparing of the face that appears shortly after birth. Symptoms begin at birth, and by childhood or adolescence patients become severely affected. The skin is often exacerbated in cold weather but dramatically improves during the summer.[14] It is caused by a deficiency of the enzyme steroid sulfatase.[8] Approximately 90% of patients have large deletions involving the *STS* (steroid sulfatase) gene and adjacent DNA.[7]

Autosomal recessive congenital ichthyosis is uncommon with a prevalence of 1:100,000. It presents at birth with erythrodermic, scaly skin over almost the entire body.[5] Clinical presentation and severity of presentation can vary significantly and fall on a continuum. Takeichi and Akiyama[7] clinically divided this group into three major and three minor subtypes. Harlequin ichthyosis, also known as alligator baby or malignant keratosis,[15] is the most severe form of nonsyndromic inherited ichthyosis. Clinically, these babies are usually born prematurely with thick, platelike scales that severely restrict movement, severe eyelid ectropion, eclabium (out-turned lips) flattening of the ears, and scarring alopecia of the scalp and eyebrows.[16] Life-threatening complications in the immediate postnatal period include respiratory distress, feeding problems, and systemic infection.[17] The disease is associated with mutations in any one of more than 12 genes involved in the biosynthesis that regulate epidermal lipid synthesis and cornified lipid envelopes.[6] These include *ABCA12, ALOX12B, ALOXE3, CASP14, CERS3, CYP4F22, LIPN, NIPAL4, PNPLA1, SDR9C7, TGM1*, and *SLC27A4,* but 15% of affected families do not have pathogenic variants in any of the known genes.[17]

Lamellar ichthyosis is another phenotype of autosomal recessive ichthyosis that is less severe than harlequin ichthyosis. The severity of the hyperkeratosis and scales varies from patient to patient. The scales covering most of the body are large, thickened, and dark gray or brown. Other signs may include eyelid ectropion, hair loss, palmoplantar hyperkeratosis, abnormally formed fingernails and toenails, lips that are turned outward, hypohidrosis, increased sensitivity to heat, dehydration, and respiratory difficulties.[18] Less frequently, affected individuals may have joint abnormalities and rickets.[19] In a series of 13 patients with lamellar ichthyosis and ectropion, 2 cases (15.4%) resulted in corneal scarring.[20,21] In another series of 10 patients, corneal leukoma was seen in 30%.[22] Cruz et al[22] postulate that the corneal damage is not directly linked to lower ectropion but is multifactorial. Cicatricial ectropion can involve both upper and lower eyelids with lagophthalmos exacerbating evaporative dry eye disease and decreased tear breakup time.[23] The risk of corneal scarring increases especially in cases where Bell phenomenon is absent. A rare case of spontaneous subconjunctival abscess was described in a child with lamellar ichthyosis.[24] Eight causative genes have been identified associated with lamellar ichthyosis: *ABCA12* (adenosine triphosphate-binding cassette subfamily A member 12); *ALOXE3* (lipoxygenase 3); *ALOX12B* (12R-lipoxygenase); CERS3 (ceramide synthase 3); *CYP4F22* (cytochrome P450, family 4, subfamily F, polypeptide 22); *NIPAL4/ICHTHYIN* (NIPA-like domain containing 4); *PNPLA1* (patatin-like phospholipase domain-containing protein 1); and *TGM1* (transglutaminase 1).[7]

Congenital ichthyosiform erythroderma, also known as collodion baby, is a form of autosomal recessive congenital ichthyosis characterized by generalized, red, dry, pruritic, and rough skin with large coarse and fine white scales.[7] Erythroderma and scaling appear after several weeks when the collodion membrane is shed. The scales are typically fine and white or light gray. Systemic erythroderma is present, but this may improve in infancy.[18,25] Mutations have been identified in several causative genes including *ABCA12, ALOX12B, ALOXE3, CERS3, CYP4F22, LIPN, NIPAL4/ICHTHYIN, PNPLA1,* and *TGM1*.[26]

Self-healing collodion baby is a minor variant of autosomal recessive congenital ichthyosis accounting for approximately 10% of all cases. It is characterized by nearly complete resolution of scaling within the first 3 months of life.[5,27] It is associated with *TGM1*, *ALOX12B*, and *ALOXE3* mutations,[28] and two cases were described associated with homozygous mutations in the gene *CYP4F22*.

Acral self-healing collodion baby is a very rare variant of autosomal recessive congenital ichthyosis where the patients are born with the typical membrane but limited to the hands and feet only, and after it sheds, the skin appears completely normal.[29] This variant is associated with a novel mutation in the *TGM1* gene.[30]

Bathing suit ichthyosis is another minor variant of autosomal recessive congenital ichthyosis characterized by a unique distribution of lesions on the trunk, the proximal parts of the upper limbs, the scalp, and the neck. The central face and extremities are not involved.[5,31,32] Twenty missense mutations of *TGM1* have been reported, nine of which occurred only in patients with this phenotype.

Keratinopathic ichthyosis was proposed as a general term for another group of rare phenotypes that include epidermolytic ichthyosis, superficial epidermolytic ichthyosis, annular epidermolytic ichthyosis, ichthyosis Curth-Macklin, autosomal recessive epidermolytic ichthyosis, epidermolytic nevi, and congenital reticular ichthyosiform erythroderma. They are all associated with mutations in the keratin family genes, *KRT1*, *KRT2*, and *KRT10*. Epidermolytic ichthyosis is the most prevalent form of the keratinopathic ichthyoses characterized by generalized erythroderma and blistering at birth, *(Print pagebreak 472)* followed by hyperkeratosis later in life.[5,7,33] The blistering and erythema diminish with age. Superficial epidermolytic ichthyosis is characterized by mild epidermal hyperkeratosis over flexural areas and blister formation with a more superficial pattern than epidermolytic ichthyosis. It is caused by mutations in *KRT2*, rather than *KRT1* or *KRT10*.[5] Annular epidermolytic ichthyosis is another rare distinct phenotypic variant of epidermolytic ichthyosis characterized by the intermittent development of annular, polycyclic, erythematous, scaly plaques over the proximal extremities and the trunk.[34] It is associated with a unique mutation in *KRT10*. Ichthyosis Curth-Macklin is an autosomal dominant disorder characterized by spiky or verrucous hyperkeratosis affecting the large joints and the trunk.[35,36] Mutations of *KRT1* have been identified in patients with this disorder.[37] Autosomal recessive epidermolytic ichthyosis is a phenotype where babies are born with collodion skin and generalized erythroderma. The collodion membrane is shed early. In the first months after birth, infants develop skin erosions after mild mechanical trauma and progressive ichthyosis with generalized hyperkeratosis most pronounced on the big joints, elbows, and knee bends and show phenotypic variability from mild to lethal forms.[38] The condition is caused by autosomal recessive mutations in *KRT10* leading to a complete absence of the protein.[39,40] Epidermolytic nevus is characterized by single or multiple circumscribed verrucous lesions frequently presenting following Blaschko lines.[41,42] Mutations in *KRT1* and *KRT10* have been reported. Congenital reticular ichthyosiform erythroderma (also referred to as ichthyosis with confetti) is a very rare skin disease in which babies are born with erythroderma, prominent scales, and palmoplantar keratoderma.[43,44] Hundreds to thousands of pale confetti-like spots appear on body surfaces and increase in number and size with advancing age. Mutations in *KRT10* and *CRIE* have been described.[45]

Syndromic Ichthyoses

Among the syndromic forms of ichthyosis, several uncommon syndromes have been described.[8] Netherton syndrome is a rare

autosomal recessive disorder that mostly affects females with an incidence of 1 in 200,000 individuals.[46] The syndrome is caused by mutations of the *SPINK5* gene and includes congenital ichthyosis with double-edged scales, bamboo hair, and atopic predisposition. Hair is short, sparse, and dry.[8,47,48] The syndrome also includes a predisposition to allergies, asthma, and eczema, with hypereosinophilia, trichorrhexis invaginata, and elevated serum IgE levels.

Sjögren-Larsson syndrome is an autosomal recessive error of lipid metabolism due to biallelic mutations in the *ALDH3A2* gene that result in a deficiency of fatty aldehyde dehydrogenase. Premature birth is common, seen in 73% of cases.[49,50,51,52] Affected patients show a classical triad of congenital ichthyosis, mental retardation, and spastic paralysis of the limbs.[50] A collodion membrane is not seen. The skin has an erythematous and hyperkeratotic appearance that transforms over days to the dry scaly appearance of ichthyosis. They may also show alopecia, eclabion, and eyelid ectropion.[51] Patients display sparse to florid perifoveal crystalline inclusions (glistening white dots) located in the inner retina and may show retinal thinning, cystic macular degeneration, retinal pigment epithelium atrophy, and deficiency of macular pigment.

Refsum syndrome is an autosomal recessive disease that develops from age 7 months to older than 50 years, and patients are usually normal at birth. It is characterized by ichthyosis, retinitis pigmentosa, progressive panretinal degeneration, cataract, sensorineural deafness, peripheral neuropathy, cerebellar ataxia, anosmia, hemeralopia, muscular atrophy, cardiomyopathy, progressive myelin degeneration, functional disorders of the nervous system, cochlear hearing loss, and renal failure, and an increase in the cerebrospinal fluid level of protein.[53,54,55] It is caused by biallelic pathogenic variants in either *PHYH* (encoding phytanoyl-CoA hydroxylase), which accounts for more than 90% of Refsum disease, or *PEX7* (encoding the PTS2 receptor), which accounts for less than 10% of the disease.[56]

Multiple sulfatase deficiency is a rare autosomal recessive lysosomal storage disorder due to a deficiency in a formylglycine-generating enzyme, encoded by the sulfatase-modifying factor 1 (*SUMF1*) gene. Clinical findings include ichthyosis, metachromatic leukodystrophy, acidic mucopolysaccharidosis, developmental regression, intellectual disability, periventricular white matter disease, and reduced tooth germ size and enamel thickness.[57] At 2 or 3 years of age, patients become unable to sit and also show symptoms of blindness and speech impairment.[58,59]

Keratitis ichthyosis deafness (KID) syndrome is a congenital ectodermal disorder considered to be an autosomal dominant inherited disease. The disorder is characterized by the thickened granular skin with keratotic scaly plaques, recurrent facial abscesses and blepharitis, dry eye, corneal edema, bilateral retinopathy, keratitis with corneal neovascularization, sensory hearing loss, nail deformities, dental abnormalities, loss of eyebrows, and scarring alopecia of the scalp.[60,61,62] Genetically, KID syndrome may be caused by mutations in the connexin gene *GJB2* and/or *GJB6*, which encode connexin proteins (Cx) 26 and 30, respectively.[63] Most of the cases are sporadic, but they can be familial as well.[64]

CHILD syndrome (congenital hemidysplasia, ichthyosiform erythroderma, or nevus and limb defects) is an extremely rare X-linked recessive or dominant disorder that is lethal to males, who die in utero. Most surviving patients are females. It is related to mutations in the *NSDHL* gene that encodes for the enzyme 3β-hydroxysteroid dehydrogenase that is involved in cholesterol pathways.[65]

Unilateral ichthyosiform erythroderma is present at the time of birth or appears within a few weeks after birth. Ipsilateral limb reduction, nail thickening, and hair abnormalities or alopecia concomitantly occur.[66]

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IBIDS syndrome (ichthyosis, brittle hair, impaired intelligence, decreased fertility, and short stature) is an autosomal recessive complex neuroectodermal syndrome. It is associated with noncongenital ichthyosis that begins at several months of age, mild, brittle cystine-deficient hair, sparse eyelashes and eyebrows, impaired intelligence, neurologic disorders, and short stature. Cataract, retinal dystrophy, strabismus, and recurrent infections are additional features.[67,68] Patients have unusual facies that may include microphthalmia with apparent enophthalmos, receding chin, small and thin nose, small mouth, small ill-set teeth, and protruding ears. Some patients are born as collodion babies.[8] The specific genetic basis for this condition is unclear, but mutations in genes encoding subunits of the transcription/repair factor IIH (*TFIIH*) have been described.[69]

Conradi-Hünermann-Happle syndrome is a rare X-linked dominant ichthyosiform condition affecting approximately 1:400,000 births. It is caused by mutations in the *EBP* gene that result in a deficiency of 3β-hydroxysteroid-Δ8, Δ7-isomerase enzyme in the distal pathway of cholesterol biosynthesis.[70] This condition affects only females and manifests as ichthyosis following the lines of Blaschko, punctate cartilage aplasia, patchy scarring alopecia, and short stature.[71] Up to 67% of the patients have cataracts that are already present at birth or develop early in life. Occasionally, other eye findings such as microphthalmia, microcornea, glaucoma, or atrophy of the optic nerve have been reported.[70]

Etiology and Pathophysiology

Ichthyosis occurs when there is a disruption in the process of skin cornification, resulting in hyperkeratosis, scaling, and abnormalities of the stratum corneum barrier function.[72] A thickened stratum corneum results from an increased rate of cells entering this phase at an increased rate or of prolonged retention of corneocytes. All ichthyosiform dermatoses have abnormal cornification in common. Cornification and shedding of the stratum corneum is a complex and multistep process mediated by multiple enzymes operating in sequence. This process can be affected by a variety of genetic mutations that influence alterations in the water content or changes in the lipid composition of the intercellular material.[72]

The pathophysiology of most inherited forms of ichthyoses has been based on the identification of mutations in over 50 genes that encode structural proteins or enzymes involved in a variety of cellular functions from DNA repair to skin barrier homeostasis.[5] Abnormalities in these genes result in epidermal hyperplasia and increased stratum corneum accompanied by abnormal desquamation and visible accumulation of scales on the skin.[73]

Lamellar ichthyosis can be caused by mutations in any one of many genes. Mutations in the *TGM1* gene are responsible for approximately 90% of cases. The *TGM1* gene encodes for transglutaminase 1 that is involved in the formation of the cornified cell envelope and is essential for the development of the normal intercellular lipid layer formation in the stratum corneum.[4,74] This cell envelope is a structure that surrounds skin cells and helps form a protective barrier between the body and its external environment.[72] At least 14 different *TGM1* mutations have been identified,[75] which result in reduced or absent production of transglutaminase 1, which prevents the formation of the cornified cell envelope.[8] Epidermal turnover is accelerated resulting in proliferative hyperkeratosis.[4]

Acquired ichthyosis, usually appearing for the first time in adulthood, is a nonhereditary condition associated with a variety of internal diseases. These ichthyoses are rare and should elicit a search for an underlying systemic disease or cause. Acquired ichthyosis has been described in association with numerous malignancies, including Hodgkin disease, non-Hodgkin lymphoma, leiomyosarcoma, mycosis fungoides, multiple myeloma, Kaposi sarcoma, and carcinomas of the ovary, breast, gastrointestinal tract, lung, and cervix.[76,77,78,79,80]

When it is associated with malignancy, the severity of the cutaneous manifestations usually mirrors the course of the malignancy.[81] Acquired ichthyosis may represent a paraneoplastic syndrome from an underlying malignancy.[82,83,84]

Acquired ichthyosis also has been seen in the setting of infections such as active pulmonary tuberculosis[85] or associated with autoimmune disorders such as systemic lupus erythematosus[86] or autoimmune thyroiditis.[87] Cases have been attributed to the use of certain medications[88,89,90,91] and with nutritional deficiency.[92]

Clinical Presentation

Limbal stem cell deficiency can cause descemetocele and corneal perforation in ichthyosis.[61,62] Tarsorrhaphy with amniotic membrane transplantation can be used to treat persistent corneal epithelial defects.[93] Ichthyosis is associated with numerous eyelid and ocular manifestations.[94] Cicatricial ectropion is one of the most common findings, first reported by Arnold in 1834, resulting from shortening of the cutaneous anterior lamella (Figure 71.1).[4,95] The ectropion often results in ocular surface complications such as lagophthalmos, conjunctivitis, exposure keratopathy, corneal opacification, and rarely even corneal perforation (Figure 71.2). Photophobia, pain, epiphora, and foreign body sensation are prominent symptoms.[96] Symptoms usually begin at birth or in the first few months of life and persist throughout life.[6]

The severity of symptoms varies considerably depending upon the specific genotype of ichthyosis.[5,97,98] While the majority of patients have only mild to moderate skin symptoms, in some cases, they can be very severe with almost *(Print pagebreak 474)* complete ectropion and retraction of the lower eyelid (Figure 71.3).[98,99] Most patients have some degree of increased transepidermal water loss due to defects in the biosynthesis of proteins and lipids necessary for normal barrier formation.[100]

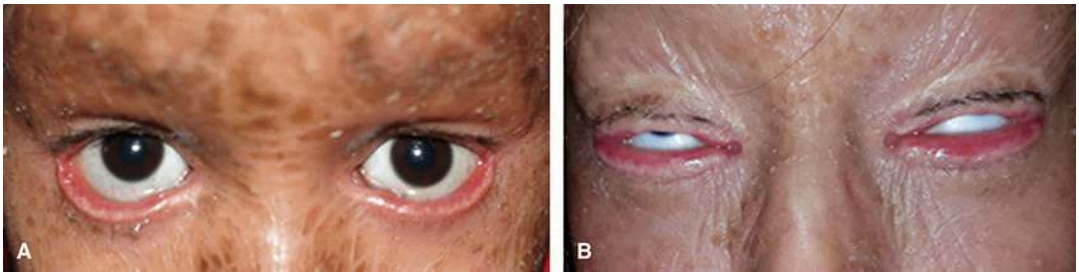

FIGURE 71.1 A, Bilateral cicatricial ectropion on the lower eyelids in ichthyosis. B, Bilateral severe cicatricial ectropion of the lower eyelid and mild ectropion of the upper eyelids.

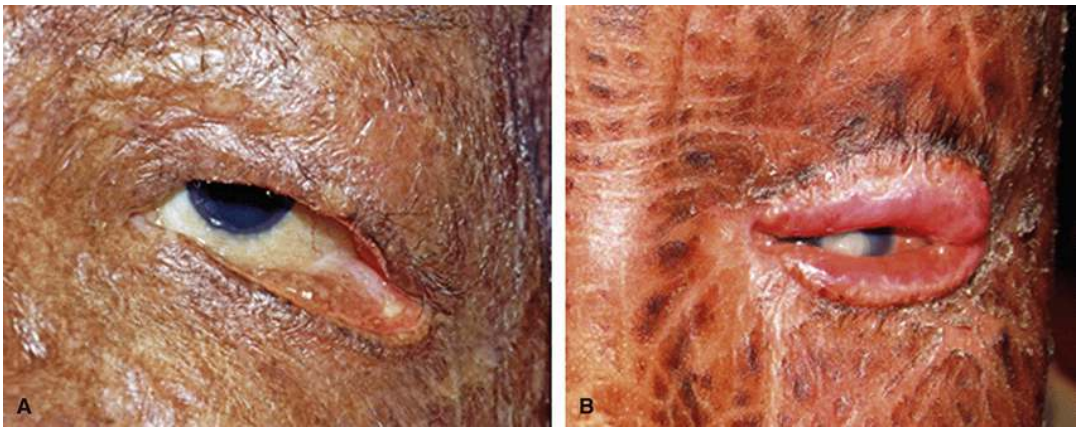

FIGURE 71.2 Corneal exposure secondary to cicatricial ectropion in ichthyosis. A, Inferior corneal haze with epithelial irregularities. B, Severe exposure with dense corneal opacification from upper and lower eyelid cicatricial ectropion.

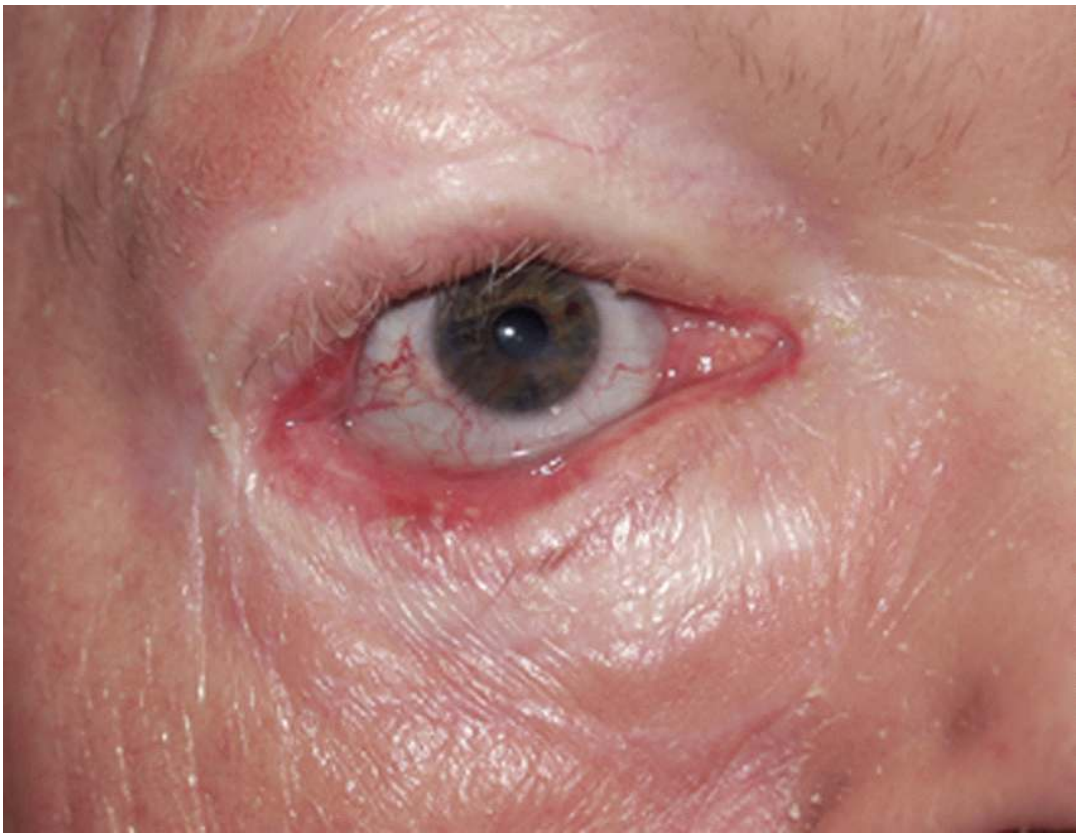

FIGURE 71.3 Severe lower eyelid retraction and ectropion from skin contraction in a case of ichthyosis.

Once the diagnosis of ichthyosis is established or suspected, an underlying cause should be sought.[72] The most important initial step in evaluation is a detailed family history, review of symptoms, and a physical examination. Genetic testing is important to distinguish among the various subtypes of ichthyosis.

In adults with acquired ichthyosis, questioning should inquire about a history of malignancy, constitutional symptoms, history of liver or kidney impairment, medication use, and dietary history. Laboratory studies should be considered, biopsy specimens should be obtained, and genetic testing is undertaken to differentiate the various types of ichthyosis.[101]

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Differential Diagnosis

The diagnosis of ichthyosis is usually obvious when it presents at birth or shortly thereafter. The major differential difficulty involves assigning the condition to one of the many subtypes. This is typically done with genetic testing of the child and family members, especially when the inheritance pattern is unclear.

Ichthyosis vulgaris is relatively mild and often mistaken for simple dry and scaly skin, so it can easily go undiagnosed. But this is an autosomal dominant congenital disease, so a positive family history is typical. The differential diagnosis for lamellar ichthyosis includes other ichthyoses, such as epidermolytic hyperkeratosis, self-healing collodion baby, Sjörgen-Larssen syndrome, X-linked ichthyosis, congenital ichthyosiform erythroderma, Comèl-Netherton syndrome, and trichothiodystrophy.[72] Later in life, lamellar ichthyosis is usually distinguished from other forms of ichthyoses based on history and clinical findings.[102]

Treatment

Genetic testing is an important tool in the successful management of congenital ichthyosis. Not only can it confirm the diagnosis but it also allows appropriate parental counseling.[103] Identifying the specific subtype of ichthyosis and its causative genetic mutations can help predict the clinical course of the disease.[100]

Currently, there is no cure for ichthyosis. Management is mostly supportive and must be based on individual signs and symptoms. In infants, a moist environment should be maintained to prevent infection.[8] Neonates should be monitored for fluid and electrolyte imbalances and temperature regulation. In older children and adults, humidification and lubrication may help to promote peeling and thinning of the stratum corneum.[8] The stratum corneum can absorb many times its weight in water so that emollients, such as petrolatum-based creams and ointments or water-in-oil preparations, should be applied after bathing while the skin is still wet.[8] Alpha hydroxy acids help reduce corneocyte adhesion and decrease the thickness of the epidermis, urea creams can help soften the scales, and topical retinoic acids can decrease thickened scales.[97,98] Tazarotene (Tazorac) 0.05% is a retinoid prodrug applied as a topical gel. Its active metabolite modulates the differentiation and proliferation of epithelial tissue, and it may also have anti-inflammatory and immunomodulatory properties.[8,104]

Ectropion can result in ocular sequellae including conjunctivitis, lagophthalmos, exposure keratopathy, and potentially vision-threatening side effects such as corneal perforation.[105] Therefore, cicatricial ectropion should be promptly managed either medically or surgically to aid in corneal protection. Early and extensive use of topical lubricants is the mainstay of initial ocular management. Definitive management of the ectropion is with surgery, usually with skin grafts to lengthen the anterior lamella. However, in many patients, healthy uninvolved skin may be difficult to find anywhere on the body.[96] The timing of surgery is also controversial. Whereas early surgery may be indicated to safeguard the cornea, the decision should be individualized according to the severity of the signs and symptoms because most forms of ichthyoses are progressive and the main postoperative issue after skin grafting is relapse.[103] Therefore, if early surgery is indicated, a close-followup, frequent wetting of the graft, as well as regular ocular lubrication are of paramount importance.[103] Oral mucus membrane grafts have been used as an alternative with good long-term results in preserving the functionality of the eyelid.[94,106] In a long-term follow-up of mucous membrane grafts for cicatricial ectropion, on histopathology the grafts showed evidence of acanthosis and mild metaplasia but no signs of dysplasia or marked fibrosis and contracture.[94] Human engineered skin was also reported to give good results.[105]

Prognosis

With appropriate care, mild cases of ichthyosis generally have an excellent prognosis, whereas patients with severe disease may be difficult to control. In cases of harlequin ichthyosis, the most severe form, there is a significant mortality rate and few children survive into young adulthood.

In the neonatal period, following the shedding of the collodion membrane, infants with ichthyosis are at risk for infection and dehydration. In childhood, hyperkeratosis interferes with normal sweat gland function, predisposing to heat intolerance.[4] The adhesion of platelike scales constricts and obstructs sweat ducts, causing heat intolerance, and contributes to caloric and water loss. In some children with ichthyosis vulgaris, the scales can become less noticeable during puberty or even disappear during childhood and return during the teen years or even adulthood. The patient may also suffer psychologically because of their physical appearance.

Eyelid ectropion, when not managed with lubricants and surgery when necessary, can result in lagophthalmos and exposure keratitis, and in some cases corneal scarring or perforation.

Histopathology

The histopathology of ichthyotic skin disorders depends on the disease variant.[7,107,108,109,110,111,112] The histopathological

features of ichthyosis vulgaris are seen best in biopsies from areas of maximum clinical hyperkeratosis.[110] The epidermis may be acanthotic, atrophic, or of normal thickness with mild to moderate orthohyperkeratosis forming a compact, laminated, eosinophilic stratum corneum (Figure 71.4A).[107,110] Parakeratosis is seen occasionally (Figure 71.4B),[111] especially when there is superimposed atopic dermatitis.[107] The granular cell layer is markedly thinned or absent, which is the key diagnostic feature of ichthyosis vulgaris.[107,109,110] Sebaceous glands are atrophic or absent, and there is a sparse lymphohistiocytic infiltrate around superficial dermal blood vessels.[110,111] Specimens from areas with only mild scales may be indistinguishable histologically from normal skin.[110]

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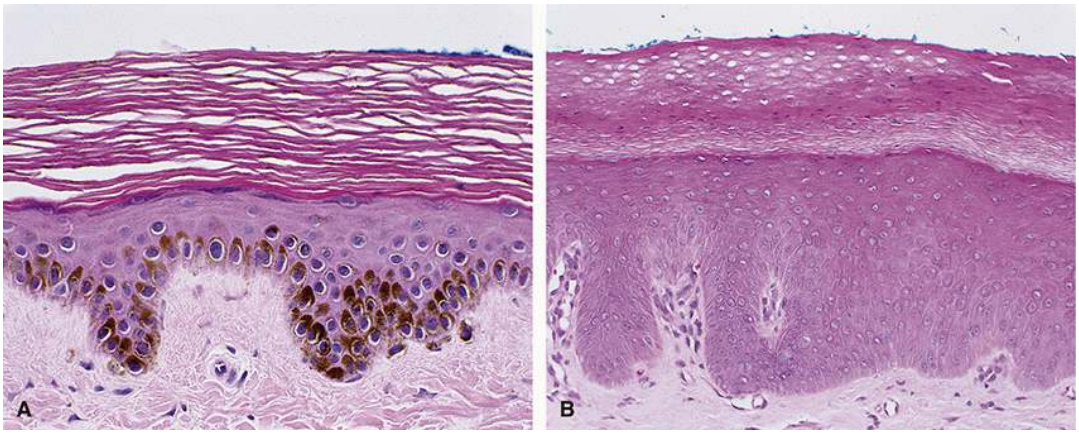

FIGURE 71.4 A, This example of ichthyosis vulgaris has an atrophic epidermis with a moderately thick layer of orthohyperkeratosis and a stratum granulosum reduced to one cell in thickness. B, This ichthyosis vulgaris biopsy has an acanthotic epidermis, an absent stratum granulosum, and a moderately to markedly thickened stratum corneum with a mixture of orthohyperkeratosis and parakeratosis.

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CHAPTER 72

Impetigo

Key Points

- Impetigo is a highly contagious bacterial skin infection
- It is most common in warm tropical climates, with crowded living conditions, poor hygiene, and lower socioeconomic conditions
- Impetigo is caused by *Staphylococcus aureus* or group A beta-hemolytic *Streptococcus pyogenes*, or both
- There are two common forms of impetigo, nonbullous (70%) and bullous (30%) with distinct causes and clinical appearances
- Nonbullous impetigo is caused by *S. aureus* or *S. pyogenes* and is characterized by superficial honey-colored crusted lesions on the face and extremities in areas of compromised skin
- Bullous impetigo is caused by *S. aureus* and presents as large bullae located in intertriginous areas of the body that rupture and ooze yellow fluid
- Impetigo is usually a self-limiting infection and usually resolves within 3 weeks
- Antibiotic treatment is usually initiated for faster resolution and to prevent the spread to other individuals
- The prognosis is excellent, but a small percentage of cases can progress to renal failure, septic arthritis, scarlet fever, and sepsis

Impetigo is a highly contagious bacterial skin infection of the superficial layers of the epidermis most commonly caused by gram-positive bacteria.[1,2] Major risk factors include warm tropical climates, crowded living conditions, poor hygiene, lower socioeconomic conditions, daycare centers, crowded schools, close-contact sports, and poor immunity status.[1,3,4,5,6,7] Impetigo is less frequently seen in northern climates during the summer months.[8] It is seen most often in children, where it accounts for approximately 10% of skin disorders in pediatric patients.[2]

Normal skin is inhabited by large numbers of bacteria that usually do not lead to medical problems, but in susceptible skin with various predisposing factors, some bacteria can lead to cutaneous infections.[1,9,10,11,12] Impetigo is a contagious infectious dermatosis caused by *S. aureus* or group A β-haemolytic Streptococcus (GAS) or both.[4,13] The most common type of GAS is *Streptococcus pyogenes*. Individuals of any age can be affected, but children between 2 and 5 years of age are most often involved.[1,14] In children, there is no gender predilection, but in adults, men are more commonly affected.[2] Globally, the number of children suffering from impetigo at any one time has been estimated to be more than 162 million.[1]

There are two common forms of impetigo, nonbullous and bullous with distinct causes and clinical appearances.[15] A third type that is frequently mentioned in the literature is ecthyma which is basically a deeper ulcerative form of impetigo, although some authors believe it is a unique form of skin infection.[6,15] Nonbullous impetigo comprises approximately 70% of all cases and is caused by *S. aureus* or *S. pyogenes*.[4] Lesions are most often located on the face and extremities. Bullous impetigo is caused by *S. aureus* and usually takes the appearance of large bullae, which tend to be located in intertriginous areas of the body.[4]

Etiology and Pathophysiology

Studies have shown that the streptococcal strains responsible for impetigo colonize the unbroken normal skin before the development of skin lesions by an average interval of about 10 days.[8] Nonbullous impetigo, also known as impetigo contagiosa, is caused by *S. aureus* or *S. pyogenes*.[4,13] It is characterized by superficial honey-colored crusted lesions on the face and extremities. The infection is highly contagious and can spread to adjacent areas by auto-inoculation.[3,4,14,16] Lesions develop from intradermal

inoculation of surface bacteria into broken areas of skin from abrasions, minor trauma, or insect bites. Occasionally, the infection may spread from the skin to the upper respiratory tract after 2 to 3 weeks.[2]

Bullous impetigo is caused by a toxin produced by *S. aureus.* It is seen in infants and tends to affect the trunk, extremities, and moist intertriginous areas such as the axillae, neck fold, and diaper area. Lesions are characterized by rapidly enlarging, flaccid bullae that rupture and ooze, revealing a collarette of scales.[17] When extensive, skin lesions may be accompanied by systemic symptoms including fever, diarrhea, and generalized weakness.[3,4,14,16]

Clinical Presentation

Clinically, impetigo presents as either nonbullous or bullous lesions. The nonbullous type is more common and is seen principally in children, although it can occur in adults less frequently.[18] Nonbullous impetigo can develop as either a primary or secondary infection and is generally seen on the face or extremities in skin that has been compromised.[19] The primary form results from direct inoculation of bacteria into the skin,[4] whereas the secondary form is associated with disruption of skin integrity following trauma or underlying dermatologic conditions.[4] Lesions usually begin *(Print pagebreak 480)* as maculopapular pustules that evolve to thin-walled vesicles (Figure 72.1A). These tend to rupture, exuding a purulent exudate that forms a characteristic honey-colored crust on an erythematous base (Figure 72.2).[4,13] Without treatment, these lesions generally persist for 2 to 3 weeks before resolving without a scar.[4,13] Mild regional lymphadenopathy is commonly associated. Systemic symptoms such as fever are typically absent.

Bullous impetigo is caused by *S. aureus* and is seen more commonly on intact skin in intertriginous regions of the trunk, groin, axillae, neck, buttocks, and extremities in infants.[4,9,11,18] The exfoliative toxin A produced by *S. aureus* causes loss of cell adhesion in the superficial epidermis resulting in large, fragile, flaccid bullae that can rupture and ooze yellow fluid.[4,11] These rupture leaving an erythematous base with a scaly rim and a thick brown crust.[2,11,18] Unlike nonbullous impetigo, regional lymphadenopathy is not seen, but systemic symptoms, such as fever, are common.

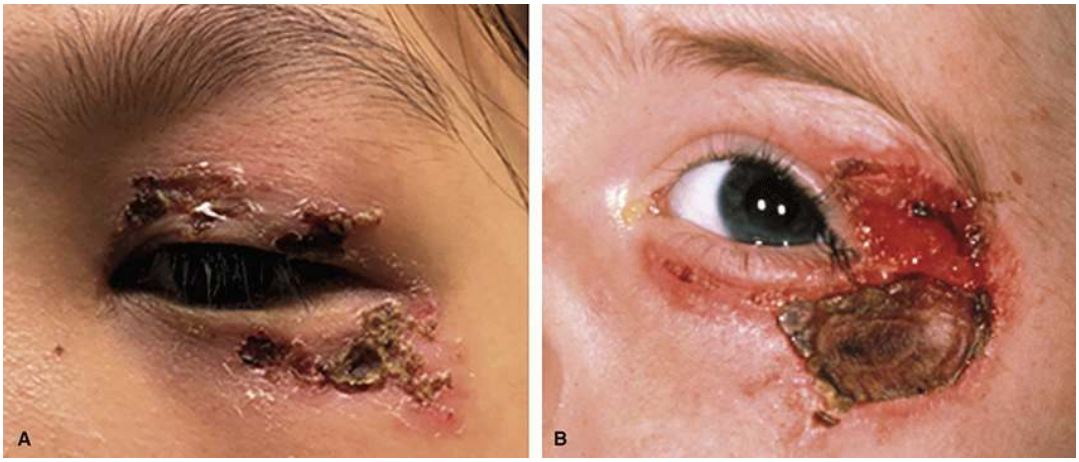

FIGURE 72.1 Eyelid impetigo. A, As maculopapular pustules. B, Ruptured bullae, exuding purulent exudate on an erythematous base. (A, Courtesy of Dr. Roman Shinder.)

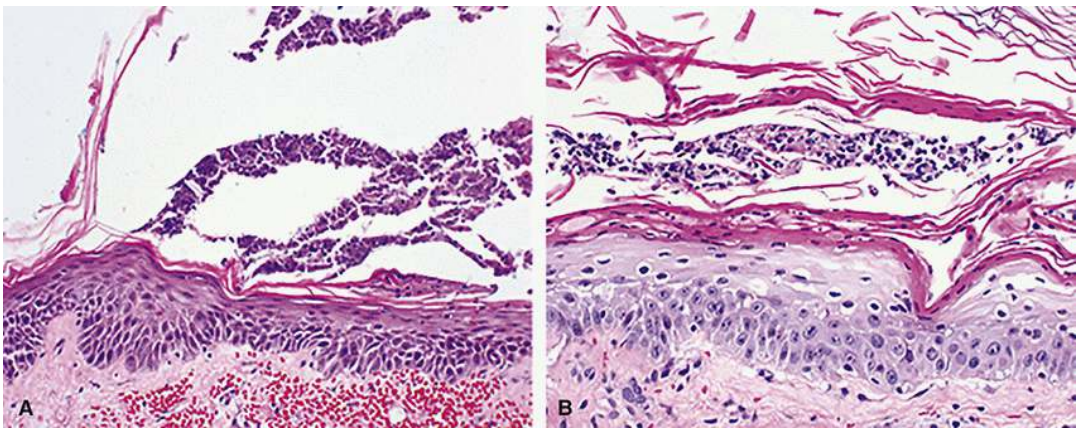

FIGURE 72.2 A, This example of bullous impetigo has a subcorneal blister containing neutrophils, debris, and bacteria. There is acute hemorrhage in the papillary dermis but no inflammation. B, Common impetigo has subcorneal accumulation of neutrophils and bacteria. In this example, there is parakeratosis, a feature of older lesions.

Differential Diagnosis

The differential diagnosis of impetigo includes a large variety of inflammatory and infectious cutaneous conditions and depends on whether the lesion is nonbullous or bullous.[14,20] For nonbullous impetigo, the differential includes lesions such as atopic dermatitis, contact dermatitis, scabies, *(Print pagebreak 481)* erysipelas, *Herpes simplex*, candidiasis, and tinea.[4,19] Atopic dermatitis is seen in children as thickening of the skin, with scaling and weeping papules. Contact dermatitis follows contact with a causative agent resulting in pruritic, edematous, erythematous papules and vesicles often with crusts and central erosions. Scabies is caused by the mite *Sarcoptes scabiei* that cause cutaneous burrows in which the mite deposits eggs. Lesions appear as intensely pruritic, pinhead-sized papules with punctate erosions, crusts, and scales, mostly in axillary folds, the umbilical region, and buttocks. The face is rarely involved. Erysipelas is a dermal streptococcal infection that spreads through superficial lymphatics forming a well-defined, painful, erythematous rash with raised edges and mostly affects older adults. *Herpes simplex* is a viral infection appearing as densely grouped pitted vesicles, blisters, and erosions associated with pain and pruritus. Candidiasis is a pathogenic yeast infection presenting as large confluent areas of scaly, erythematous lesions with satellite foci, and a collarette of scales, usually in intertriginous areas. Tinea is a mycotic infection appearing as sharply delineated scaling nummular patches and pustules.

For bullous impetigo, the differential diagnoses includes pemphigus vulgaris, insect bites, bullous pemphigoid, and second-degree thermal burns.[20] Bullous pemphigoid and pemphigus vulgaris are autoimmune conditions usually seen in older adults. Pemphigus vulgaris is characterized by generalized flaccid bullae and extensive erosions on an erythematous base. Bullous pemphigoid presents in elderly individuals as subepidermal blistering on normal or erythematous skin.

Treatment

Impetigo is usually a self-limiting infection and typically resolves within 3 weeks.[4] It is managed initially with general care beginning with proper hand hygiene, washing clothing, and not sharing towels to help limit the spread of the disease. Washing the lesions with soap and warm water can remove crusts and secretions.[11] However, impetigo may lead to secondary infection and occasionally can develop into more serious systemic conditions, so that some form of treatment is usually recommended. Antibiotic treatment is initiated for faster resolution, to prevent the spread to other individuals,[10,21] and to decrease the risk of complications involving the kidneys, joints, bones, and lungs.[21,22,23]

For localized nonbullous impetigo, mupirocin, retapamulin, and fusidic acid have been considered the agents of choice.[2,24,25,26] Mupirocin (pseudomonic acid A) is a metabolite of *Pseudomonas fluorescens* fermentation[11] and acts by inhibiting bacterial protein synthesis. Applied as a 2% cream or ointment, it is highly effective against *S. aureus*, *S. pyogenes*, and other species of streptococci.[11] Retapamulin 1% ointment is a novel pleuromutilin antibacterial drug derived from the fungus *Clitopilus passeckerianus*, with antibacterial activity against *S. aureus* (methicillin-susceptible isolates only) and *S. pyogenes*.[27] Ozenoxacin 1% cream is a novel nonfluorinated quinolone[17] approved for the topical treatment of nonbullous impetigo, with potent antimicrobial activity against staphylococci and streptococci, and a broad range of activity against methicillin-, mupirocin-, and ciprofloxacin-resistant strains of *S. aureus*.[28,29,30]

Systemic antibiotics are indicated for all cases of bullous impetigo and for cases of nonbullous impetigo with deep tissue involvement, signs of systemic infection, lymphadenopathy, oral lesions, or cases resistant to oral antibiotics.[2,16,31] Erythromycin and penicillin were standard treatments in the past, but they are no longer routinely used because of increasing drug resistance.[32] Beta-lactamase-resistant antibiotics such as cephalosporins, amoxicillin-clavulanate, and dicloxacillin are preferred for mixed infections. If MRSA infection is suspected, the recommended initial treatment is with trimethoprim/sulfamethoxazole, clindamycin, or a tetracycline (doxycycline or minocycline [Minocin]) pending culture results.[9]

Prognosis

Most cases of impetigo are expected to heal spontaneously in 2 to 3 weeks.[13] Scarring is uncommon but some patients may develop pigmentary changes. With antibiotic treatment, the resolution is faster, usually within 10 days.[2] In rare cases, neonates may develop meningitis and post-streptococcal glomerulonephritis seen more commonly with *Streptococcus* and appearing 7 to 14 days after onset of the skin infection. Other rare complications include septic arthritis, scarlet fever, sepsis, and staphylococcal scalded skin syndrome.[2]

Histopathology

The best descriptions of bullous impetigo histopathology (Figure 72.2A) are from Unna in 1896[33] and Kouskoukis and Ackerman in 1984.[34] Unna termed the entity "impetigo staphylogenes" and described pus, bacteria, and well-preserved individual and small groups of epithelial cells collecting between the epidermal horny and prickle layers with an outward expansion of the horny layer and flattening and posterior bowing of the posterior epidermis.[33] Kouskoukis and Ackerman examined biopsies from 42 patients.[34] They noted "blisters situated beneath the cornified layer, within the granular layer, or in the upper part of the spinous layer, acantholytic cells, and variable numbers of neutrophils within the blisters, epidermal hyperplasia, slight spongiosis, slight edema in the papillary dermis, and superficial perivascular and interstitial inflammatory cell infiltrates composed of lymphocytes, histiocytes, neutrophils, and eosinophils."[34] The feature that distinguished bullous impetigo from superficial pemphigoid was the presence of bacteria only within the blisters of bullous impetigo.[34] An adult case of bullous impetigo had intraepidermal cleavage beneath the granular layer with numerous acantholytic granular cells in the blister.[35]

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Early lesions of common nonbullous impetigo have subcorneal accumulation of neutrophils and gram-positive cocci (Figure 72.2B), and a few acantholytic cells may be present.[36] Neutrophils often extend through the underlying epidermis.[36] As the lesions age, there is a surface crust of serum, neutrophils undergoing degeneration, and parakeratosis.[36]

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CHAPTER 73

Infantile Hemangioma

Key Points

- Infantile hemangiomas are the most common benign soft-tissue tumors of infancy and childhood
- The pathogenesis of hemangiomas is not clearly understood
- Most cases are sporadic and are not inherited, but families with a Mendelian pattern of inheritance have been reported
- It is hypothesized that vascular stem cells that are normally present in the fetus occasionally persist and become dysregulated leading to hemangioma formation
- Infantile hemangiomas occur most frequently in the head and neck region
- They usually are not present at birth but may be preceded by a small area of pallor or a slightly purplish hue that gradually brightens and expands in size
- This is followed by a rapid proliferative phase for 6 to 12 months in which the tumor grows exponentially to a raised bright red lesion with a smooth or irregular outer surface
- The treatment of choice is systemic propranolol, which is believed to work by blocking the proangiogenic signaling of VEGF and bFGF, and also potentiates apoptosis
- Lesions tend to regress with time, but with treatment regression may be more rapid and dramatic

Infantile hemangiomas (IHs) are the most common benign soft-tissue tumors of infancy and childhood, with a prevalence that reportedly varies between 4% and 12%.[1,2,3,4,5,6,7,8,9,10,11] IH has unique growth characteristics with an explosive onset phase followed by regression. Although most hemangiomas tend to resolve spontaneously, some can cause life-threatening complications or may even lead to permanent disfigurement. Several synonyms for IH exist, some of which are no longer in use, and should be avoided including capillary hemangioma, strawberry hemangioma, strawberry nevus, juvenile hemangioma, angioma, or birthmarks.[2] Despite the repeated attempts by the International Society for the Study of Vascular Anomalies to simplify terminology,[12] hemangiomas remain a heterogeneous group and several of the aforementioned synonyms are still frequently used in the literature and in everyday medical practice. The term “hemangioma” or IH will be used predominantly throughout this chapter.

Etiology and Pathogenesis

Despite the considerable advances in our understanding of the pathogenesis of hemangiomas, many unanswered questions remain and the precise mechanisms dictating both proliferation and involution are not clearly understood.[3,13] Most cases are sporadic and are not inherited; however, families with a Mendelian pattern of inheritance have provided some insight into the genes that may one day prove to have a causal link or at least may be partially involved in the pathogenesis of IH through the proteins these genes encode.[9] These associations are mostly weak; however, candidate genes have been mapped to some specific locations including 2p13, 2q23, 4q12, 5q31, 7q33, and 15q26.[9,14,15]

However, it appears that somatic mutations may play a far more important role in the pathogenesis of congenital hemangioma (CH), which is the rarer variant of IH. Mutations in both GNAQ and GNA11 loci have been demonstrated recently in both variants of CH: the rapidly involuting type (RICH) and the noninvoluting type (NICH).[16]

The exact pathogenetic events leading to the development of hemangioma are unknown. It is hypothesized that vascular stem cells, the so-called hemangioma stem cells (HemSCs) that are normally present in the fetus, occasionally persist and become dysregulated leading to hemangioma formation, but it is not clear whether they originate from the placenta or the bone marrow.[17,18] A placental origin of IH has been proposed repeatedly over the years. Recent evidence is more in favor of a placental embolic origin during

early fetal life, in addition to a postnatal favorable environment that supports proliferation and differentiation of those embolized primitive cells.[19,20] Embolization usually occurs in the first trimester coinciding with the migration of neural crest cells, which leads to the integration of these cells along the neural crest migratory routes, thereby manifesting as segmental lesions. If embolization occurs later during fetal life, it usually results in discrete lesions which are the more frequently observed pattern in the periorbital region.[19,20] This placental origin of IH is supported by the expression of glucose transporter 1 (GLUT1) protein on the endothelium of hemangiomas and is also supported by the increased incidence of IH in infants born following amniocentesis and chorionic villus sampling.[19,20]

It is also not entirely clear whether the initial or proliferative phase of IH involves angiogenesis (formation of new blood vessels from existing ones through sprouting of endothelial cells) or vasculogenesis (de novo formation of vessels from *(Print pagebreak 484)* progenitor cells). The former theory is supported by the detection of angiogenic factors such as basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF-A) within the tumor. The vasculogenesis theory is supported by the presence of immature multipotent progenitor stem cells, which are capable of de novo blood vessel formation as well as adipogenesis.[1,21] It is not implausible that both mechanisms may play a role, with vasculogenesis as the initiating event, followed by angiogenesis, which amplifies the size of the lesion to become an irregular mass full of blood vessels.[21] The involution of IH is attributed to the gradual depletion of HemSCs.[17]

Recently, it has been shown that hemangioma patients have significantly increased serum levels of renin and angiotensinogen II. This discovery of a potential role for the renin-angiotensin system in the pathogenesis of IH provides a credible explanation for the programmed biologic behavior of IH and the accelerated involution that occurs with the use of β-blockers.[13,20] The insulin-like growth factor system and the TRAIL-osteoprotegerin antiapoptotic pathway are also possibly involved in the evolution of IH.[20]

Historically, vascular anomalies were classified according to the size of the lumen (capillary vs cavernous), or according to the nature of their fluid content (hemangiomas vs lymphangioma). This classification is no longer accepted and currently vascular anomalies are classified according to the proliferative potential of the vascular endothelium.[12] A distinction should thus be made between hemangiomas, which are true tumors that grow by endothelial cell hyperplasia or proliferation, are not present at birth, do not grow indefinitely, and have a regression phase, and vascular malformations, which occur as a result of a structural defect in vascular morphogenesis, are present at birth, grow in size with growth of the individual, do not possess a regression phase, and have a normal rate of endothelial turnover.[14,22] Because of their clinical diversity, the classification of hemangioma itself is difficult. While IH elsewhere in the body is usually classified morphologically into (1) localized, (2) segmental, (3) indeterminate, or (4) multifocal, the majority of periocular IHs are small and localized, and even if they are large or display a geographic pattern, they are not consistently associated with a particular segmental distribution.[10,12] Although periocular IH still can be classified zonally into the aforementioned groups, which may indeed be of useful prognostic value, larger periocular lesions may not follow a specific dermatomal distribution,[11] which may hinder a strict classification. From a clinical standpoint, it may be better to classify periocular lesions according to their depth into superficial, deep, or mixed lesions where the lesions acquire characteristics of both subtypes.[4,5,12]

Clinical Presentation

IHs represent the most common vascular tumors in infancy. It most frequently involves the head and neck region, followed by the trunk, and the extremities. IH is found in greater frequency in girls (3:1-5: 1 ratio), whites, premature infants, and twins, and more commonly develops when the mother is of higher maternal age.[1,2,14] Obtaining an accurate natural history as regard the age of onset, ethnicity, and rate of progression/regression is extremely important in patients with hemangiomas to differentiate IH from closely related lesions but less common ones like CHs where the lesion is fully developed at birth, does not show a proliferative phase, and may either rapidly involute by 12 to 18 months (RICH) or may never regress at all, but instead grows with the growth of the child (NICH).[2,9] An intermediate form exists where partial regression may be observed (partially involuting congenital hemangioma, PICH).[12]

The classic dictum that IHs are not present at birth may not entirely be accurate.[1] Not infrequently, there is a precursor lesion, usually a small area of pallor or a slightly purplish hue that gradually brightens and expands in size. In actual clinical practice, those lesions become more apparent in the first few weeks of life as a flat macular area of telangiectatic vessels that usually blanches on compression.[1,4,5] This is followed by a rapid proliferative phase for 6 to 12 months, in which the tumor grows exponentially. Subsequently, this is followed by a phase of gradual involution or spontaneous regression.[2,4]

In superficial lesions that involve the skin, the infant usually presents with a flat to slightly elevated bright red tumor with a smooth or irregular outer surface (Figure 73.1). The surface may resemble a strawberry, and hence the old name strawberry nevus. During the proliferative phase, lesions enlarge rapidly, often resulting in aesthetic and functional disability (Figure 73.2). Deep lesions may be located subcutaneously where the eyelid assumes a deep bluish hue or may be located deep within the orbit where it causes a mass effect in the eyelid without any discoloration (Figure 73.3).[4,5,12] Deeper orbital lesions may displace the globe, causing axial

or nonaxial proptosis, optic neuropathy, or bony deformities.[4,13] Mixed lesions may involve both the skin and the deeper tissues. Rapidly growing superficial lesions may cause deprivation amblyopia in as little as 1 week during the proliferative phase because of occlusion of the visual axis.[4] IH is considered a relative oculoplastic emergency in the first year of life as the prevalence of amblyopia may be as high as 63%.[4,23] Deeper lesions are also potentially amblyogenic due to anisometropia or strabismus.[4,23]

The clinical behavior of CH is rather different. Because RICH develops in utero, it can be detected prenatally as early as 12 weeks of gestation. In the newborn, it presents as a raised, grayish solitary tumor with fine telangiectasias and a pale halo. RICH rapidly regresses, leaving a patch of subcutaneous atrophy, and dilated veins. However, NICH presents as a plaque-like, well-circumscribed telangiectatic tumor with a purple-pink rather than a grayish hue, and usually remains unchanged throughout childhood. However, there are exceptions where partial involution occurs (PICH).[12,16]

The proliferative phase usually lasts about 1 year. Afterward, hemangiomas tend to involute. Previously it was taught that IHs involute roughly at a rate of 10% per year, and that 30% of tumors completely regress at the age of 3 years and 75% to 90% *(Print pagebreak 485)* by the age of 7 years, although some lesions may take more than 10 years to resolve.[13,23] More recent evidence suggests that involution of IH is usually complete by the age of 3.5 to 4 years.[24,25]

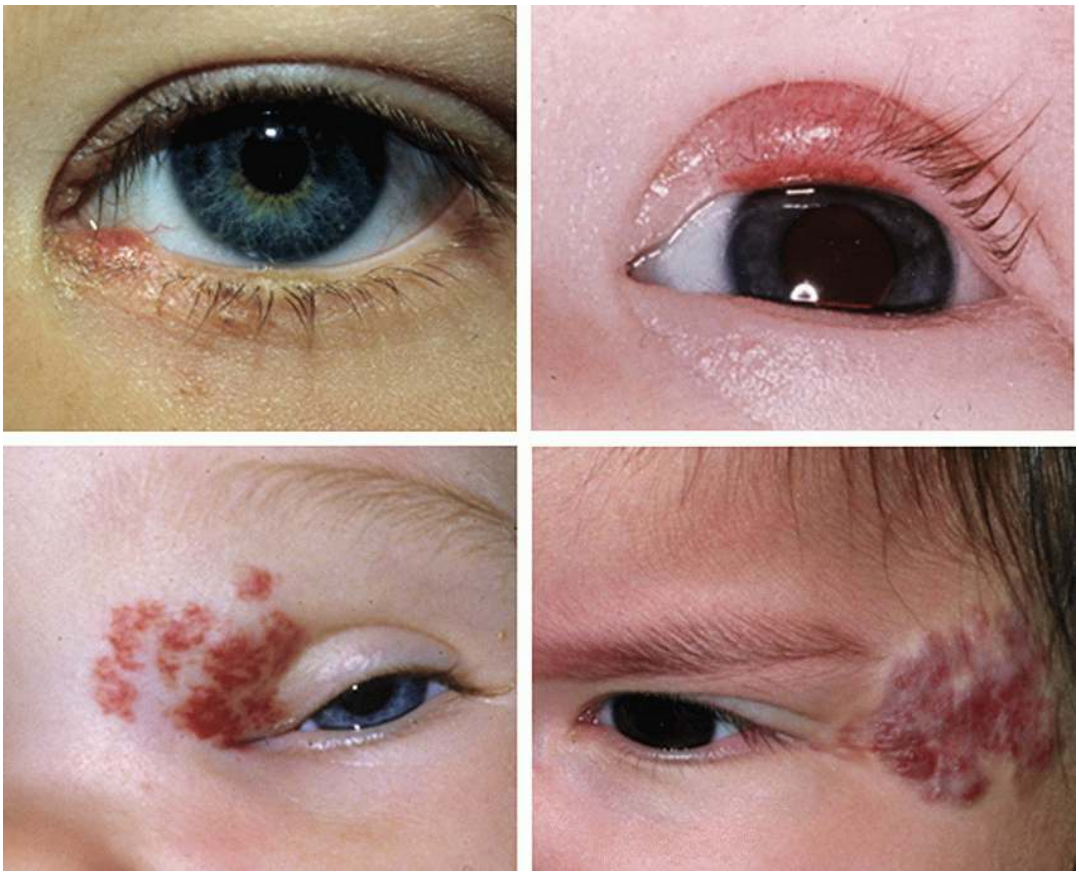

FIGURE 73.1 Early minimally elevated infantile hemangiomas on the eyelids and periorbital region.

Although solitary lesions are the most common form of presentation in the periocular region,[1,14] segmental or diffuse involvement of the face, which generally follows the embryonic fusion lines, may occasionally be observed.[11] Larger IH lesions of the face (>5 cm in diameter) are prone to pain, bleeding, or ulceration, the frequency of which triples with diffuse hemangiomas. They are more commonly associated with other congenital anomalies including the PHACE syndrome, which is characterized by posterior fossa abnormalities, hemangioma, arterial abnormalities, cardiac defects, and eye anomalies, or the closely related LUMBAR syndrome (lower body hemangioma, urogenital anomalies, myelopathy, bony deformities, anorectal malformations, and renal anomalies).[1,4,5,26] IH may also be associated with extensive visceral hemangiomatosis, which can trap platelets within their vascular channels, leading to thrombocytopenia and secondary coagulopathy, and which can prove fatal (Kasabach-Merritt syndrome).[5] The current consensus, however, is that Kasabach-Merritt syndrome is not typically associated with the classic IH and only occurs in the setting of more aggressive hemangiomas like kaposiform hemangioendothelioma and tufted angiomas.[13] Multifocal hemangiomas may be associated with other systemic complications according to the location of the lesion including high output heart failure, airway obstruction, postural inability to turn the head in neck lesions, or auditory canal occlusion.[11] RICH could also be associated with congestive cardiac failure and transient low-grade thrombocytopenia and may occasionally result in overwhelming complications from heart failure or hemorrhagic ulceration.[16]

Although the clinical diagnosis of IH is straightforward, the diagnostic workup should include radiology in doubtful cases. Doppler ultrasound will reveal a high-flow lesion with a typical wave characteristic of IH,[1] while computed *(Print pagebreak 486)* tomography usually shows a lobulated multispatial heterogeneous mass with intense enhancement after contrast administration. MRI is the preferred modality of choice for the initial evaluation of these tumors because of the lack of ionizing radiation when compared to CT, and because it yields better tissue characterization. IH is isointense on T1-W images and hyperintense on T2-W images, demonstrating avid contrast enhancement.[4]

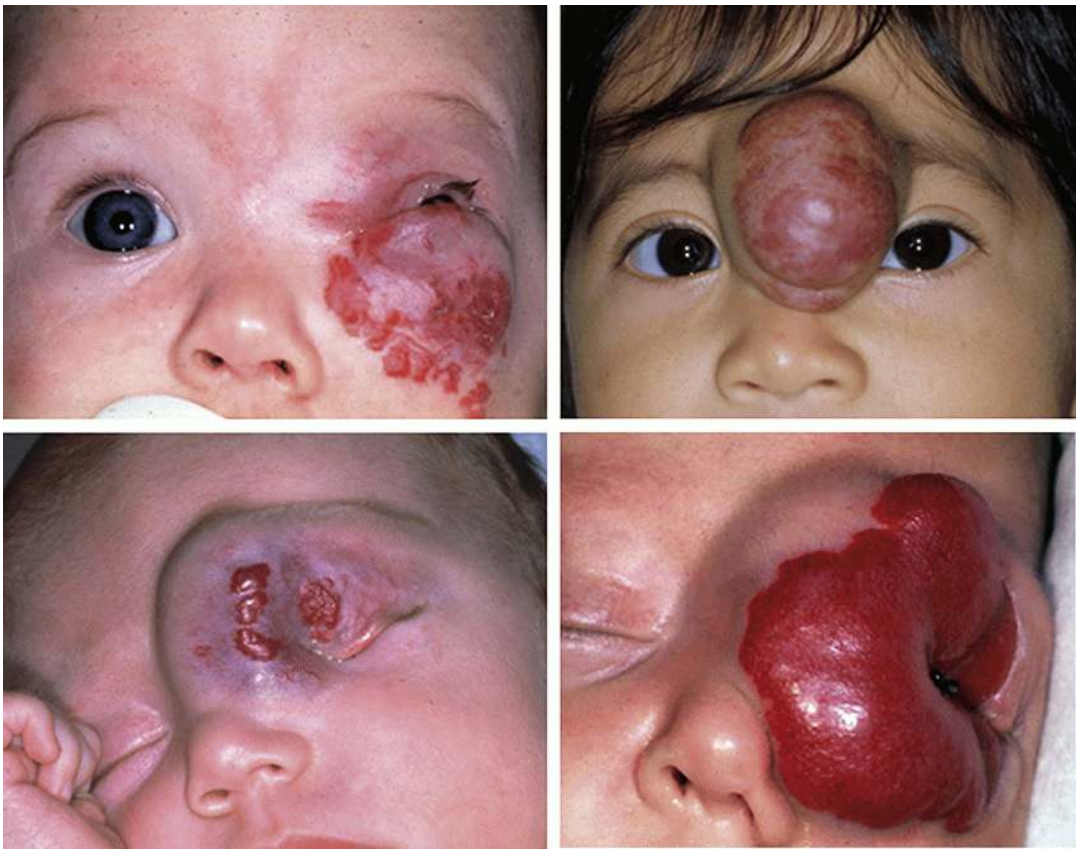

FIGURE 73.2 Late proliferative phase hemangiomas causing significant functional limitation of the eyelids or severe aesthetic disability.

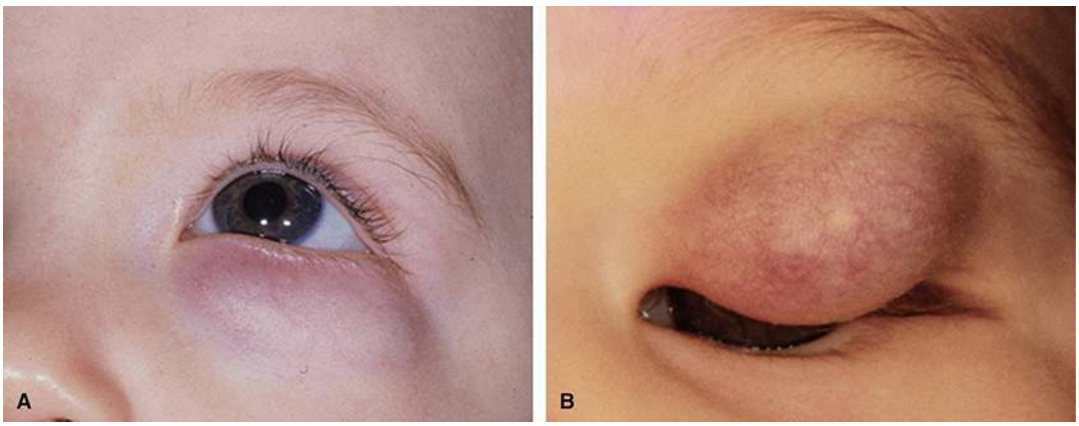

FIGURE 73.3 A and B, Deep subcutaneous infantile hemangiomas in the eyelid may extend into the anterior orbit.

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Differential Diagnosis

When the hemangioma is superficial or involves the cutaneous surface, the diagnosis is usually effortless, and even in the setting of cutaneous capillary malformation (also called port-wine stain, PWS), establishing the diagnosis is not difficult. PWS, which develops as a result of a somatic mutation in the GNAQ gene, is present since birth as flat red macules that follow a typical trigeminal nerve distribution (V1, V2, or combined).[27] They grow proportionately with the growth of the child, progressively

acquiring a darker coloration. They may also become slightly thickened or raised (cobblestone appearance) as the individual reaches middle age.[27] PWS may occur in isolation or may be associated with Sturge-Weber syndrome (SWS) particularly if V1 is involved. SWS is a neurocutaneous disorder characterized by the presence of ipsilateral vascular malformations in the cerebral cortex.[27] Ipsilateral glaucoma should always be ruled out in patients with PWS regardless of the presence or absence of SWS. On the molecular level, IH is GLUT1 positive, while PWS is not.[4,27] Differentiating IH from RICH/NICH can be difficult if the history is not clear. However, in the rare event where a biopsy is needed, IH cells positively stain with GLUT1, while RICH and NICH are GLUT1 negative.[4,16]

Diagnostic problems arise when the superficial component of IH is missing, and differentiation from other space-occupying lesions, particularly vascular malformations or soft-tissue malignancies that involve the orbit or eyelids, is required.[4] When in doubt, the clinical characteristics, radiologic imaging including a CT angiography, MRI, computed tomography. or Doppler ultrasound, and possibly even tissue biopsy are used to confirm the diagnosis.[4]

Treatment

Several grading scales of IH have been developed to assess disease severity and guide the treatment protocol as well as follow-up.[13] The two most popular systems are the Hemangioma Severity Scale, which categorizes patients and gives a score based on the risk of complications, and the Hemangioma Activity Score (HAS), which grades IH according to the color profile.[13,28,29,30] The HAS score is a more valuable tool in assessing the response to medical therapy.[13,28,29,30]

Rarely, very small localized superficial IH may not require medical treatment. Management should include reassurance and close observation with photographic documentation, and the HAS scoring system to monitor the rate of growth particularly during the explosive early phase of the disease.[13]

The treatment of hemangiomas was revolutionized in 2008 with the accidental discovery of the beneficial effects of propranolol, a lipophilic nonselective β-blocker in the management of IH.[31] Because of its potency and its low-risk profile, propranolol rapidly became the first line of therapy in patients with IH, and FDA approval was obtained in 2014.[13,32] Propranolol works through several possible physiologic mechanisms, the most accepted being that it arrests the growth of IH by blocking the proangiogenic signaling of VEGF and bFGF, and also potentiates apoptosis.[13] Treatment is usually continued for 6 to 12 months although deeper lesions may require a longer duration.[13]

Propranolol is more effective in the proliferative phase where patients may achieve complete or near-complete resolution of the lesion after 3 to 6 months of treatment; however, it may still accelerate resolution in untreated older cases that are slow to involute.[13] The initial oral dose is in the range of 0.5-1 mg/kg/d, which is gradually increased over the first 2 weeks of treatment to ultimately reach 2 mg/kg/d.[13] Hospitalization usually is not required except in infants <5 weeks of age, or for patients with hypoglycemia, cardiovascular or respiratory diseases, or critically ill patients where parenteral therapy may be required.[33,34]

Propranolol is contraindicated in patients with PHACE syndrome who commonly suffer from aortic coarctation. All patients with PHACE syndrome should be prescreened with echocardiography or cardiac MRI.[13] Propranolol is also contraindicated in preterm infants and in patients with chronic hypotension, chronic sinus bradycardia, second- or third-degree heart block, heart failure, or history of airway disease.[13]

The most commonly encountered side effects are mild; however, severe intolerable side effects are encountered in 2.1% of patients.[35] Side effects include mild respiratory symptoms such as wheezing or respiratory hyperactivity (bronchospasm), hypoglycemia, mood and sleep disturbances, bradycardia, hypotension acrocyanosis, and diarrhea.[13] If mild side effects are encountered, reducing the dose of propranolol may suffice; however, if side effects are intolerable particularly sleep disturbances or respiratory problems, a shift to an alternative β-blocker with a more selective β1 effect and lesser β2 action like nadolol or atenolol may be required. Alternatively, another treatment modality may be chosen.[35,36,37,38]

While systemic therapy is required for vision-threatening cases,[13] small superficial lesions can be treated effectively with topical agents including topical timolol or propranolol. Topical agents may also be required as adjuvant therapy while patients are being tapered off systemic β-blockers to reduce the rate of regrowth or as a form of dual therapy in patients with severe disease.[13,39] Interestingly, topical agents may have some potential role in the management of deeper lesions within the orbit.[40,41]

Alternatives to β-blockers include oral, topical, or intralesional corticosteroids, topical imiquimod, interferon-α, intralesional injection of bleomycin, or angiotensin-converting enzyme inhibitors.[13,42] Currently, the role of systemic or intralesional corticosteroids is limited to patients with a contraindication to β-blockers or in patients who have failed systemic propranolol

therapy.[13,35] In the past, corticosteroids were highly effective in the management of IH, achieving more than 90% success, but the complication profile in the pediatric age group was not trivial.[4] Hypothetically, corticosteroids disrupt vasculogenesis by inhibition of VEGF expression.[13] Intralesional bleomycin may be contraindicated because of the need for multiple injections and because of the higher frequency of development of cutaneous problems including surface ulceration.[13,31]

Historically laser therapy had a more predominant role in the management of IH. Again, this role has been eclipsed by propranolol. Its use is currently limited to patients with residual *(Print pagebreak 488)* postinvolutional cosmetically disfiguring lesions.[13,43] Laser therapy is the only line of therapy for PWS because propranolol has no role in its management.[13,44] If laser therapy is indicated, a pulsed dye laser, argon laser, or CO_2 laser may be used.[13]

Surgical excision of IH is challenging, and its role is limited to patients with a failed response to propranolol or recurrence of the lesion after cessation of therapy. Eager parents who push for surgery should be notified that surgical interference may be fraught with complications including partial recurrence, bleeding, or rarely lid necrosis if excessive cautery is required. Surgery may also be indicated in some cases of CHs (RICH, NICH, PICH) because they do not respond to propranolol and may require surgical excision or embolization if they do not spontaneously involute.[45]

Prognosis

Although regression of IH may be dramatic, and some lesions may disappear without a trace even without treatment,[5] some patients may suffer residual sequelae. The skin in the involved areas could become variably pigmented or redundant from stretch, with residual telangiectasia or fibrofatty tissue.[1,13,24] Those residual lesions are more common with deep and mixed IH, in lesions which take a longer time to involute, and in untreated cases where significant or severe sequelae may persist in 50% to 69% of patients.[23,24,46]

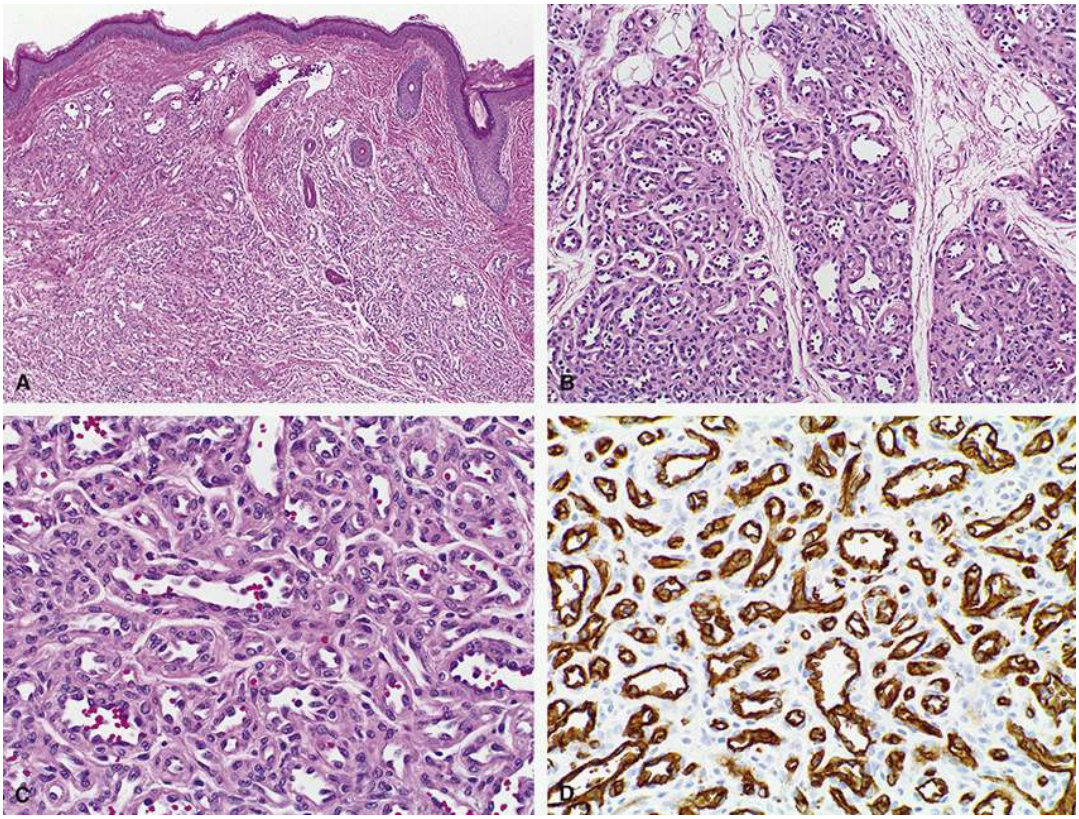

FIGURE 73.4 A, This infantile hemangioma of the glabella is a well-defined unencapsulated dermal mass of closely apposed capillaries. B, The capillaries form lobules separated by thin fibrous septa. C, The capillaries have small lumina and are lined by plump endothelial cells rimmed by plump pericytes. D, The endothelial cells highly express glucose transporter 1, while the pericytes are negative for this protein.

Rebound growth of IH is not uncommon after cessation of propranolol therapy. Large segmental hemangiomas, as well as deep lesions, may be more frequently associated with rebound growth.[47] Roughly 1% of IH are propranolol resistant. The lack of a demonstrated therapeutic response after 3 weeks of treatment should suggest alternative management options or that the initial diagnosis is wrong.[48]

Histopathology

The histological appearance of an IH depends on the phase during which it is examined.[25,49,50] During the early proliferative phase, IHs are well-defined unencapsulated dermal and/or subcutaneous masses of closely apposed capillaries with small lumina and lined by plump endothelial cells rimmed by plump pericytes (Figure 73.4).[25,49] The capillaries *(Print pagebreak 489)* form lobules separated by thin fibrous septa or normal intervening tissue.[25] Smooth muscle cells are absent.[25] Normally configured mitotic figures are usually abundant during the proliferative phase. During involution, the capillaries variably dilate and gradually disappear.[25,49] Mitotic figures decrease while mast cells and apoptotic increase during early involution.[25] The basement membrane of capillaries thickens and hyalinizes and contains apoptotic debris as involution progresses.[25,49] End-stage lesions have residual "ghost" vessels with thickened rinds of basement membrane and absent endothelial cells and pericytes embedded in loose fibrous or fibrofatty stroma.[25,49] The endothelial cells of IHs highly express GLUT1 during both the proliferative and involuting phases (Figure 73.4D).[25,50] Expression of GLUT1 distinguishes IHs from NICHs, pyogenic granulomas, tufted angiomas, kaposiform hemangioendotheliomas, and vascular malformations, all of which lack GLUT1 expression.[51,52,53]

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CHAPTER 74

Intravascular Papillary Endothelial Hyperplasia

Key Points

- Intravascular papillary endothelial hyperplasia is a vascular lesion that usually arises in veins or arteries
- It is a reactive lesion representing an unusual form of organizing thrombus rather than a neoplastic process
- IPEH may occur as a primary lesion developing within the lumen of a distended vessel or associated with other vascular lesions or in a hematoma
- The pathogenesis is not understood, but may involve an autocrine loop of endothelial basic fibroblast growth factor secretion stimulating endothelial cell proliferation
- On the eyelid, lesions generally present as a bluish to reddish, painless, firm, mobile swelling, or nodule
- Treatment is surgical by opening the vessel and removing the mass, or by excision of the involved portion of the vessel
- The prognosis is usually excellent following surgical resection

Intravascular papillary endothelial hyperplasia (IPEH), also known as Masson tumor, is a vascular lesion of the skin and subcutaneous tissue that usually arises in veins or arteries situated either in the dermis or subcutis.[1,2] It consists of a reactive proliferation of endothelial cells occurring within an organizing thrombus.[3] The condition was first described in 1923 by Pierre Masson in a 68-year-old man with a painful, nonhealing subcutaneous lesion with endothelium-covered papillae and trabeculae that obstructed a vein. He proposed that this lesion was a peculiar angiosarcoma-like lesion arising as a primary process resulting from benign proliferation of endothelial cells with secondary thrombosis and fibrin deposition. He termed it hemangioendotheliome vegetant intravasculaire, believing it to be a true neoplasm.[4] Later, Clearkin and Enzinger recognized it as a reactive lesion representing an unusual form of organizing thrombus rather than a neoplastic process. They introduced the name IPEH.

IPEH occurs most commonly on the extremities and in the head and neck, and only rarely in the ocular adnexa and orbit.[5,6,7,8,9,10,11,12] When the eyelid is involved, 60% of lesions occur in the upper eyelid, 20% in the lower eyelid, and 20% in the medial or lateral canthal angles.

IPEH may occur as a primary lesion developing within the lumen of a distended vessel or associated with other lesions,[13] and they have been classified into several types. Type I represents the primary (pure) form, characterized by the presence of the lesion within a distended vessel. Type II, or secondary (mixed) form, shows an IPEH in a preexisting vascular lesion such as a hemangioma or pyogenic granuloma.[14,15,16] Type III is rare and indicates an extravascular location of the lesion in a hematoma often following recent trauma. These have been described in the adrenal and parotid glands, heart, intestine, kidney, liver, retroperitoneum, spine, maxillary sinus, and orbit.[16,17,18,19,20,21,22]

MRI is the preferred imaging technique for identifying IPEH. Lesions appear hypo- to isointense on T1-weighted imaging and hyperintense on T2-weighted imaging with homogenous enhancement following contrast administration.[23,24]

Etiology and Pathogenesis

The precise etiology and physiopathology of IPEH are incompletely understood. It is considered to be a reactive process, and not a true neoplasm, characterized by exuberant endothelial proliferation, mostly within the lumen of blood vessels.[25] It was proposed that this reactive process could be related to endothelial trauma or inflammation and subsequent thrombus formation.[3,14,15] However, in a review of 314 cases of IPEH from the literature, Pins et al[26] found that only 4% were related to known trauma.

Levere et al[27] studied five pooled cases of IPEH by Northern blot and immunoblot and showed a 5- to 10-fold increase in basic fibroblast growth factor transcripts and a 10- to 20-fold increase in immunoreactive basic fibroblast growth factor protein compared

to non-IPEH organizing thrombi and cavernous hemangiomas. The results suggested that the pathogenesis of IPEH might involve an autocrine loop of endothelial basic fibroblast growth factor secretion stimulating endothelial cell proliferation.

Clinical Presentation

IPEH is usually seen in middle-aged adults and presents as a bluish or reddish mass within the dermis or subcutaneous tissues. In most cases, it is confined to the intraluminal space of either an artery or vein and the walls of the vessel form the "capsule" of the mass. Patients generally report that the lesion has grown slowly over months to several years.[2] In the eyelid, as the lesion enlarges, it can compress adjacent soft tissues, resulting in ptosis.[28] It may occur deep in the orbit where it can involve the ophthalmic artery and other orbital vessels, and larger lesions can be associated with motility disturbance or visual loss.[8,29]

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The overall gender distribution shows no specific predilection with a M:F ratio of about 1:1.3.[2,13,30] However, for periorbital lesions, males predominate in a ratio of 2:1. IPEH can occur at any age from early childhood to the 9th decade, with most cases in the 3rd to 5th decades. The extremities are involved in 52% of cases, the head and neck in 27%, the trunk in 13%, and the periorbital region in 7%.

Eyelid and eyebrow lesions generally present as a bluish to reddish, painless, firm, mobile swelling, or nodule (Figure 74.1). Zakka et al[31] described an eyelid IPEH with three stages of evolution. The oldest event was represented by a dystrophically calcified focus (phlebolith), formed on an ancient thrombus with a fibrous wall or pseudocapsule. There was adjacent fresh hemorrhage that displayed an internal network of CD34-positive proliferating endothelial cells that had permeated the thrombus but had not yet assumed a clear-cut papillary architecture. At another level, recanalization of an antecedent thrombus was signified by a labyrinth of vascular channels with collagenized septa that were covered by endothelial cells.[31]

While the symptoms and course of IPEH are usually benign, Weber and Babel[32] reported a case of orbital IPEH that infiltrated the temporal fossa by eroding the lateral orbital wall. Aggarwal et al[33] reported a case that presented with supraorbital nerve anesthesia from an IPEH abutting the supraorbital nerve at the supraorbital notch, and Fasina et al[8] described a case with severe visual loss from a large orbital IPEH.

Differential Diagnosis

The differential diagnosis of IPEH includes some more common benign and malignant vascular tumors. In most cases, the diagnosis must be based on histologic examination. IPEH can be distinguished from intravascular pyogenic granuloma, which displays a characteristic lobular growth pattern.[1] Kaposi sarcoma is a diffusely infiltrating spindle cell tumor that appears violaceous to red clinically and is histologically unrelated to any well-formed preexistent vascular structure.[34] A phlebolith usually has a fibrous capsule, which is a remnant of a preexistent vascular wall, and subepidermal calcified nodule features acanthotic epidermis covering spherical calcified deposits in the dermis.[35] Osteoma cutis exhibits lamellar bone, lacunae, Haversian canals, and osteoblasts. Other lesions in the differential include pleomorphic adenoma, mucocele,[13] hemangioma, thrombosed vein, traumatic fibroma, and nevus.[14]

The most important lesion in the differential diagnosis of IPEH is angiosarcoma from which it must be distinguished. The differentiation between these two lesions has caused some confusion in the literature.[3,18] In 1975, Salyer and Salyer examined the histology of 275 arterial thromboemboli and 140 venous thrombi and compared them to *(Print pagebreak 493)* 12 angiosarcomas. They postulated that in IPEH endothelial cells enter the mass of the thrombus material, which may become fragmented from intravascular pressure, and that additional thrombus material may be deposited focally due to endothelial trauma. The combination of these phenomena plus an ingrowing network of anastomosing vascular channels results in the apparent papillary structures within the vascular lumen.[3] This process is different from angiosarcoma characterized by mitoses and invasion into the perivascular space.

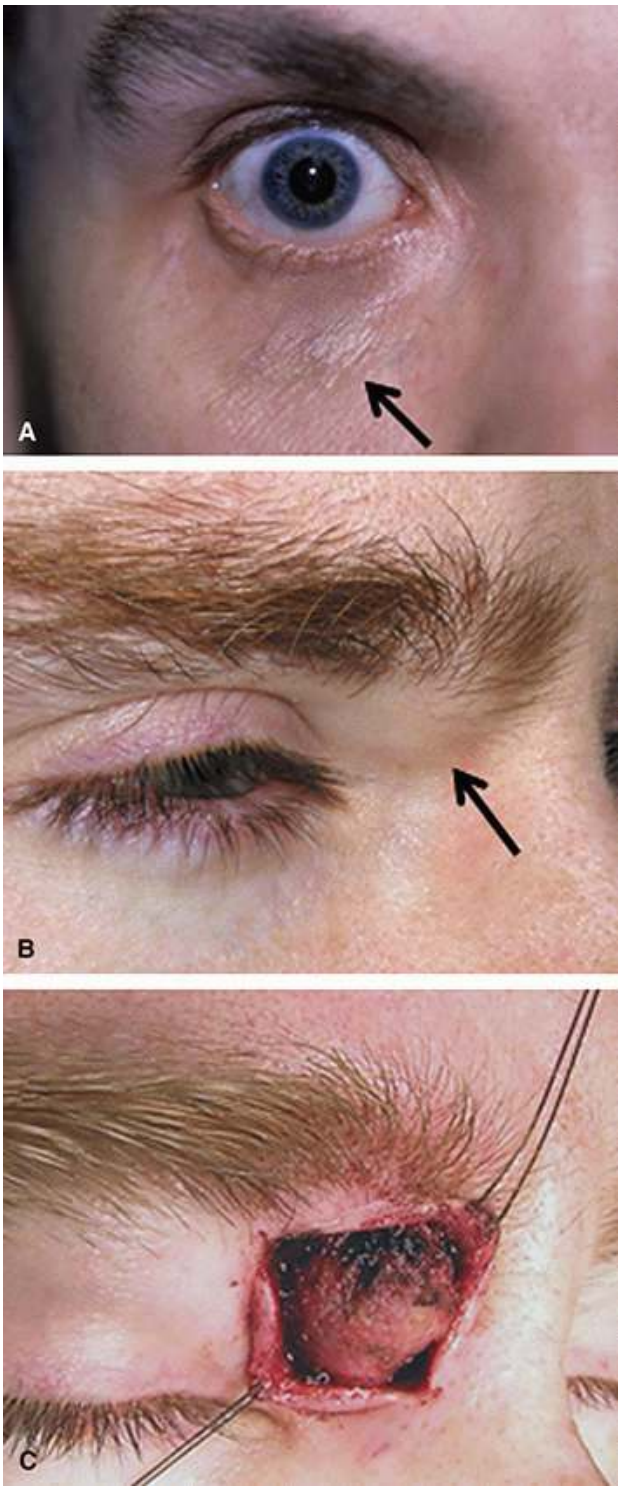

FIGURE 74.1 Intravascular papillary endothelial hyperplasia (IPEH). A, Vascular lesion in the medial lower eyelid (arrow). B, Medial brow and upper eyelid IPEH (arrow). C, Surgical excision of the lesion in Figure B. (B and C, Courtesy of Dr. Tamara Fountain.)

Treatment

Biopsy of IPEH is often required for diagnosis. For relatively superficial subcutaneous lesions, management is surgical by opening the vessel and removing the mass, or by excision of the involved portion of the vessel. For lesions in areas that are not readily accessible surgically or where surgery could result in functional compromise, like the deep orbit or intracranial compartment, radiosurgery has been reported to be effective.[29,36] Radiotherapy may also be successful for rare cases of

recurrence following excision.[37,38]

Prognosis

The prognosis of IPEH typically runs a benign course and is usually excellent following surgical resection,[38] except in cases where the lesion results in vascular compromise.[39]

Histopathology

IPEH arises within a dilated blood vessel of the dermis or soft tissue, and the histological appearance of orbital and periocular lesions[5,6,11,31,40] is similar to that elsewhere in the body.[2,13] It is composed of numerous, small, eosinophilic papillae formed of collagenous tissue and fibrin covered by a layer of endothelial cells that may be multilayered, plump, or flattened (Figure 74.2). The endothelial cells lack cytological atypia and mitotic activity. Thrombus is often adjacent to the lesion and is often in varying stages of organization.

The principal histological differential diagnosis is angiosarcoma. The lack of tissue necrosis, confinement within the vascular lumen without infiltration of the vessel wall, and the association with thrombus are histological features distinguishing IPEH from angiosarcoma.[13,31]

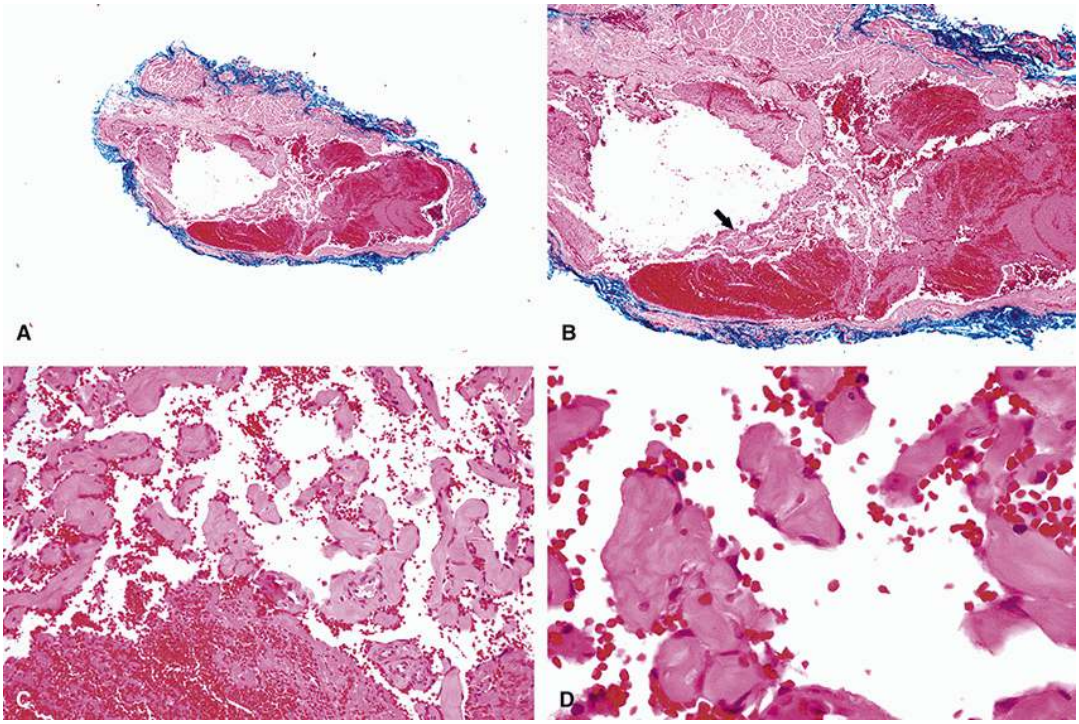

FIGURE 74.2 A, This example of intravascular papillary endothelial hyperplasia arose within a partially thrombosed varix of the right lower eyelid. B, The IPEH is present overlying thrombus (arrow). C, Small, eosinophilic papillae covered by a layer of endothelial cells overlie thrombus. D, The endothelial cells in this lesion are flat, but they may be plump or multilayered in other cases.

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CHAPTER 75

Inverted Follicular Keratosis

Key Points

- Inverted follicular keratosis (IFK) is a rare benign epithelial tumor
- It originates from the infundibular portion of the hair follicle
- Ninety percent of IFK cases occur on the head and neck with a strong male predominance
- They usually present as a solitary lesion, seen most often in adults at a mean age of 50 years
- They usually present as asymptomatic, firm, pink-to-white scaly papules, and occasionally can be associated with a cutaneous horn
- IFKs are easily confused with other keratinizing cutaneous lesions such as viral warts, seborrheic keratoses, keratoacanthoma, adnexal tumors, and malignant cutaneous tumors
- Surgical excision has been the treatment of choice for IFK, with a low recurrence rate
- The prognosis for IFK is excellent following surgery

Inverted follicular keratosis (IFK) is a rare benign tumor that usually presents as a nonpigmented verrucous papule seen most often in middle-aged or elderly individuals.[1,2] In 1954, Helwig[3] described this tumor as an inverted cup-shaped crypt at the summit of an epithelial mass, which he named IFK. He felt that the apical crypt might be analogous to the opening of a pilosebaceous apparatus, which accounts for his use of the term “follicular” in the name. Several years later, Lund[4] used the term basosquamous cell epidermal tumor (basosquamous cell acanthoma) as a synonym for this tumor,[5] but that term is rarely used.

IFK is an epithelial neoplasm originating from the infundibular portion of the hair follicle.[2,6,7] It manifests as an exo-endophytic tumor with large lobules or fingerlike projections of tumor cells that extend into the dermis.[2,8] Several distinct histopathological variants exist, including a papillomatous wartlike pattern (exophytic), a keratoacanthoma-like pattern (exo-endophytic), and a solid nodular form (endophytic).

About 90% of IFK cases occur on the head and neck. Most previous larger series showed a male predominance ranging from 58% to 100%,[2,5,8,9,10,11,12] but in a small series of 11 periocular IFKs,[13] 64% were female.

Clinically, IFK is often misdiagnosed as a more common keratotic lesion. Some studies have estimated that fewer than 2% of IFK lesions are correctly diagnosed before surgical removal and histopathologic examination.[14,15] The clinical diagnosis is most often as a viral wart, actinic keratosis, keratoacanthoma, or a variety of malignancies such as basal cell carcinoma, squamous cell carcinoma, and adnexal tumors.[8,11]

IFK usually presents as a small solitary lesion, seen most often in adults at a mean age of 50 years,[8] and is rarely seen in children or adults in the second and third decades.[5,11,12,13,14,15,16,17] They are most often found on the face, particularly on the cheek, upper lip, chin, forehead, eyebrow, and nose. Occurrence on the trunk is uncommon, and involvement of the extremities is rare.[11] Lesions may have a history of slow growth over 2 to 6 months, but occasionally they may have been present for many years.[18] Most of the lesions are small, ranging from 3 to 8 mm in diameter. They rarely involve the eyelids, with a predilection for the eyelid margins.[19,20,21] In general, IFK appears as an asymptomatic, firm, pink-to-white scaly papule and occasionally can be associated with a cutaneous horn.[5,11,21]

Dermoscopy has been useful in the clinical diagnosis of IFK.[9,22] Llambrich et al[9] described the dermatoscopic features of 12 IFK and reported a distinct white structureless area in or near the center of the lesion present in all cases, and white scales were found in 75%. Vascular structures were also present in all cases, showing a monomorphic pattern in 58% and a polymorphic pattern in 42%. The most common vascular structure was hairpin vessels surrounded by a whitish halo, which was found in 83%. Keratin was

observed in 67% of lesions, mostly in the central area.

Vascular patterns, in general, have been considered important in the differential diagnosis of many nonpigmented skin tumors.[23] Hairpin vessels surrounded by a whitish halo are a common dermoscopic vascular pattern,[9,24] indicating epithelial differentiation,[25] that can be seen in benign and malignant keratinizing lesions including squamous cell carcinoma, verruca vulgaris, poroma, and thick melanoma.[23,26] In contrast to the arrangement of hairpin vessels in the keratoacanthoma type of squamous cell carcinoma,[26] those of IFK often show a central white or yellowish amorphous area.[24]

Etiology and Pathophysiology

The pathogenesis of IFK is not exactly known. Helwig[3] believed it arose from the pilosebaceous apparatus, and Boniuk and Zimmerman[5] suggested a possible viral etiology. Other authors believed IFK to be a variant of a viral wart[27] or irritated seborrheic keratosis.[28] Whether or not IFK is related to verruca vulgaris or seborrheic keratosis has been questioned.[8,27,29] Several studies failed to detect human *(Print pagebreak 496)* papillomavirus in the majority of IFK lesions, differentiating it from verruca vulgaris.[1,2]

It is now believed that IFK is derived from the infundibulum of the hair follicle above the sebaceous duct opening.[1,2,6,13,30] Mehregan and Butler[31] first coined the term “tumor of the follicular infundibulum” because the tumor cells contained glycogen like the outer root sheath. Schirren and Maciejewski[32] reported the rare occurrence of ductal structures resembling sebaceous ducts, hair germ papillae, and follicular papillae in several tumors of the follicular infundibulum.

Clinical Presentation

In 1953, Boniuk and Zimmerman[5] summarized data for 65 lesions from 64 patients with eyelid IFK from the Armed Forces and Veterans Administration. Of these, 57 (89%) were men and 7 were women, likely reflecting the bias of patients largely from the military. The age of the patients ranged from 17 to 74 years, with a mean of 45 years, and 95% were solitary lesions. The clinical presentation varied but most appeared as a painless, asymptomatic, skin-colored, brownish, gray, or pink lump or swelling (Figure 75.1), while others were elevated, nodular, papillary, or papillomatous (Figure 75.2). They may have a verrucous scaly appearance and some can be heavily pigmented, clinically mimicking a melanoma (Figure 75.3).[22] In five cases, the lesion presented as a cutaneous horn. The upper and lower eyelids were equally involved and accounted for more than three-fourths of the tumors. Lesions were generally small, with most 5 mm or less in diameter. But in several cases, they exceeded 10 mm. Of the 65 lesions, 40% occurred on the upper eyelid, 38% on the lower eyelid, 7.7% at the medial canthus, 1.6% at the lateral canthus, and 6.3% on the eyebrow.

FIGURE 75.1 A and B, Inverted follicular keratosis as a mild swelling on the mucocutaneous eyelid margin.

In five other smaller series of head and neck IFK with a total of 47 patients, the median age was 57.7 years with a range of 26 to 91 years, and males accounted for 68%.[9,10,11,24] In the 11 cases summarized by Díez-Montero et al,[13] IFK occurred on the upper eyelid in 36.4%, and the lower eyelid lid in 27.3%. In contrast to the report by Boniuk and Zimmerman, the medial canthus was involved in 36.4% of cases, equal to the upper eyelid.

One case of IFK has been reported on the conjunctiva.[33] This was in a 21-year-old man. The lesion was slow growing over 2 months. On examination, it was hard, yellowish in color, 5 mm in diameter, free from the underlying sclera, and adjacent to the corneal limbus.

Differential Diagnosis

The clinical appearance of IFK is easily confused with keratinizing and other cutaneous lesions. Initial clinical diagnoses include actinic keratosis, seborrheic keratosis, verruca vulgaris, papilloma, cutaneous horn, fibroma, molluscum contagiosum, and intradermal nevus. It is also frequently confused with keratoacanthoma and malignant cutaneous tumors.[9,22,24] The diagnosis is usually not made clinically, but only after histopathologic examination.[22] Seborrheic keratosis usually contains horny invaginations, many of which are unrelated to hair follicles, and melanin pigmentation is often more prominent. Keratoacanthoma can be distinguished easily on histopathology by its ballooned pale-staining squamous epithelium and the infiltrative pattern of the deep edge.[11]

Malignant tumors such as squamous cell and basal cell carcinoma are perhaps the most important lesions to be considered in the differential diagnosis since a misdiagnosis can lead to unnecessary radical surgery. Both are frequently in *(Print pagebreak 497)* the initial clinical diagnosis of IFK. Squamous carcinoma often lacks the lobular blunt-edged architecture of IFK and frequently shows a transition to abnormal epidermis.[11] Also, abnormal mitoses are not found in IFK.

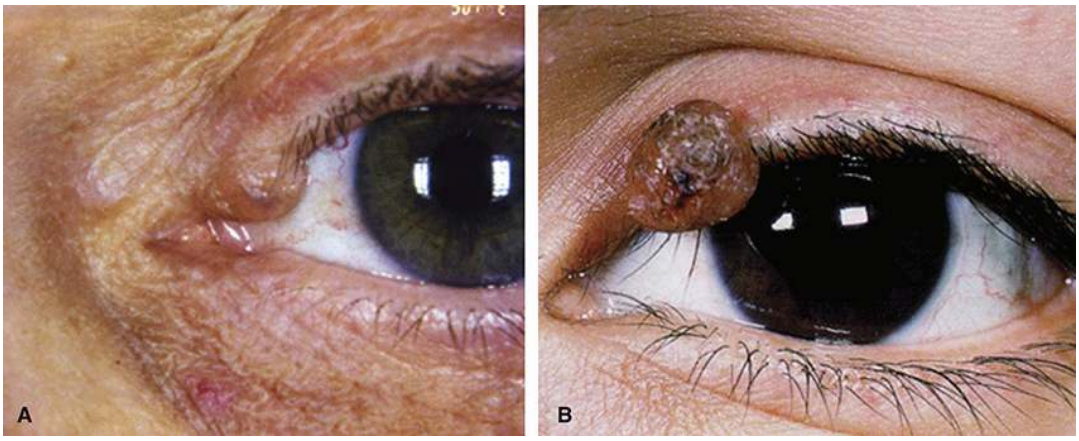

FIGURE 75.2 A and B, Nodular inverted follicular keratosis.

Treatment

Surgical excision has been the treatment of choice for IFK, with low recurrence rates of 0% to 9%.[5,10,13,34] Imiquimod is an immunomodulatory drug that modulates and upregulates the immune system and thus has both antitumoral and antiviral activity. It is most frequently used in the treatment of actinic keratosis, genital warts, and superficial basal cell carcinoma through its induction of cytokines from antigen presenting cells including toll-like receptor 7/8.[35] It also inhibits vascular tumor development by causing a decrease in tumor cell proliferation, an increase in apoptosis, and a decrease in matrix metalloproteinase 1 and 9 activity.[36] Karadag et al[37] reported a case of IFK successfully treated with topical 5% imiquimod cream resulting in near-complete tumor regression after 2 months of treatment.

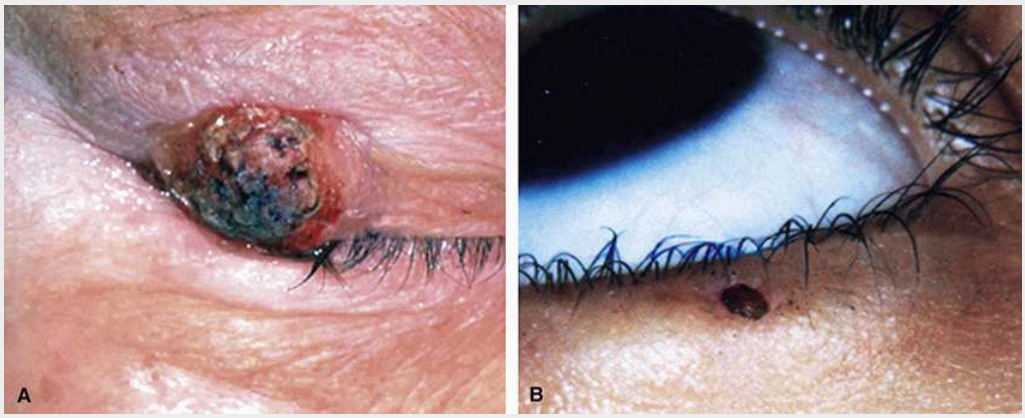

FIGURE 75.3 A, Large inverted follicular keratosis (IFK) with a rugose scaly surface. B, Small pigmented IFK. (Courtesy of Dr. Gregg Gayre.)

Prognosis

The prognosis for IFK is excellent. No tumor-related deaths have been reported and recurrences after surgery are uncommon. Schweitzer and Yanoff[20] reported two cases of eyelid IFK that recurred within weeks of primary excision. They recommended careful excision of the primary lesion, attempting to remove all of the lesion initially. Excisional *(Print pagebreak 498)* biopsy of any secondary lesion was recommended before contemplating more drastic surgery, with a careful review of the original specimen to determine if the initial diagnosis was IFK rather than a malignant tumor.

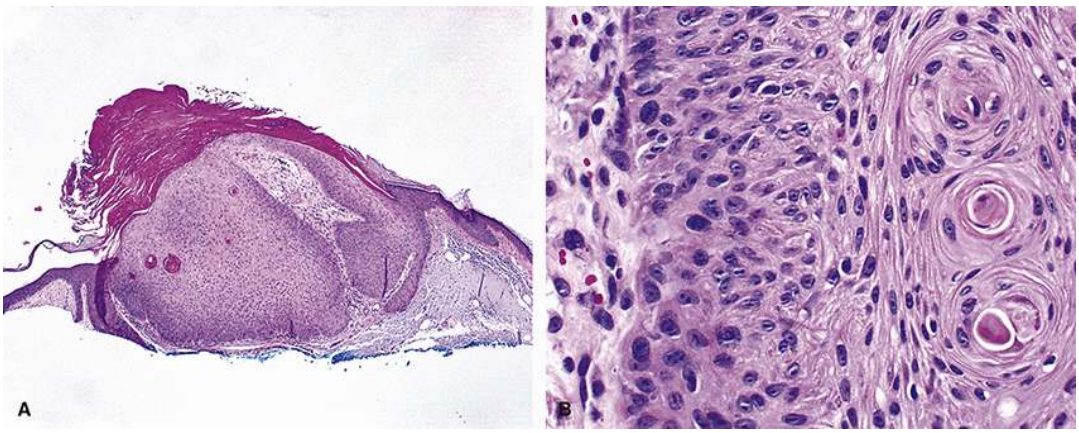

FIGURE 75.4 A, This nodular inverted follicular keratosis has a thick layer of hyperkeratosis and parakeratosis overlying a tumor composed of a large and small lobule and a fingerlike projection into the actinically damaged dermis. The tumor cells around the periphery of the lobules are basaloid, resulting in the darker blue staining. B, Squamous eddies with concentric layers of flattened squamous cells in a whorled pattern are usually most frequent at the junction of the basaloid cells and squamous cells.

Histopathology

Inverted follicular keratoses are predominantly endophytic lesions composed of lobules or broad, blunt-tipped, fingerlike projections of neoplastic epithelial cells into the dermis (Figures 75.4 and 75.5).[5,8,12,38,39,40,41] The outer portion of the lobules and fingerlike projections are composed of basaloid cells that may exhibit palisading, while the central areas are composed of larger squamous cells. Inverted follicular keratoses characteristically have squamous eddies with concentric layers of flattened squamous cells in a whorled pattern (Figure 75.4B).[5,38] The squamous eddies may have central keratinization and form small keratinous cysts,[38] and they tend to be most frequent at the junction of the basaloid and squamous cells.[5] Clefts may be present between squamous eddies.[12] Larger tumor masses may have funnel-shaped parakeratotic plugs in the center of invaginating tumor masses.[38] There is a variable degree of hyperkeratosis and parakeratosis overlying most tumors.[5] The tumor and dermis are sharply *(Print pagebreak 499)* demarcated,[12] and the dermis may exhibit increased vascularity, mild fibrosis, and mild nonspecific inflammation.[38]

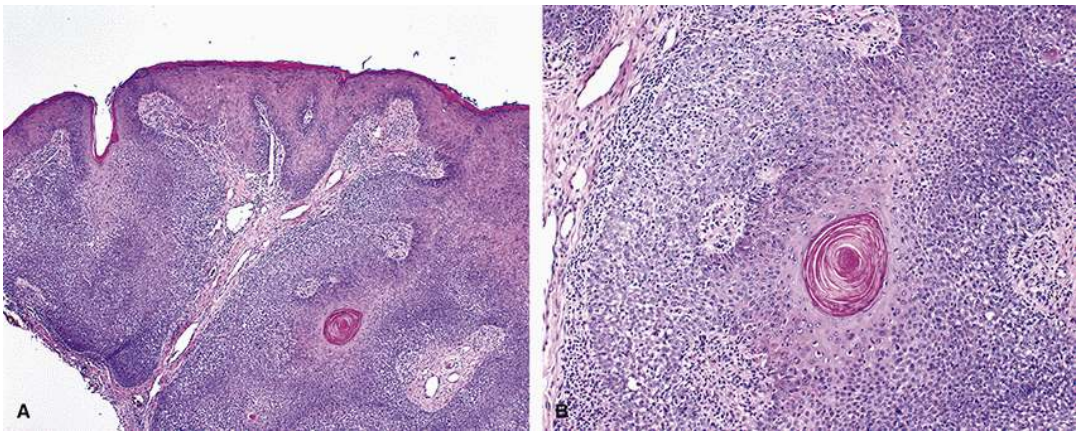

FIGURE 75.5 A, This nodular inverted follicular keratosis has lobules and broad interdigitating cords of tumor cells within the dermis. The basaloid layer around the periphery of the lobules and cords is prominent. B, The basaloid layer has a cuff of mononuclear inflammatory cells, and scattered lymphocytes infiltrate the basaloid layer. A small

keratinous cyst is in the squamous portion of the tumor.

While inverted follicular keratoses most often have a nodular pattern, they may also have a papillomatous or wartlike appearance, resemble a keratoacanthoma with surrounding epidermis forming a marginal buttress, or be cystic.[5,8] Lack of cellular anaplasia differentiates an IFK from squamous cell carcinoma or keratoacanthoma, while the presence of squamous eddies in an IFK distinguishes it from a verruca vulgaris.[38]

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(Print pagebreak 500)

CHAPTER 76

Keratoacanthoma

Key Points

- Keratoacanthoma is a common tumor
- It is seen most frequently in fair-skinned individuals with a predilection for sun-damaged skin
- Keratoacanthoma can be solitary or multiple
- Solitary KA presents as a rapidly growing nodule with a central keratotic crater
- After a stable phase lasting several months, they often undergo spontaneous regression
- Multiple KAs are rare and can be sporadic or familial
- The pathophysiology of KA and its relation to squamous cell carcinoma is unknown, but they have been thought either to be separate entities, or related, lying on two ends of the same disease spectrum
- Surgical excision with histologic control of margins is considered the gold standard for the management of KA

Keratoacanthoma (KA) is a common tumor, originally described by Hutchinson in 1889.[1] It is seen most frequently in fair-skinned individuals and has a predilection for sun-damaged skin.[2] KA has been reported to show a seasonal presentation with a peak incidence noted in the summer and early autumn months.[3] The annual incidence of cutaneous KA varies depending on the geographic location. In Hawaii, the annual incidence was estimated to be 104 cases per 100,000 population,[4] and in northern Australia, the incidence was 150 cases per 100,000 population.[5]

KA is seen most frequently in middle-aged individuals.[6] The peak age at presentation is between 45 and 69 years old.[7] In a series of 108 patients with KA, lesions were seen in patients from teens to old age, with 80% older than 40 years and a mean age of 56 years. Males are affected more commonly than females, in a ratio of 2:1.[8] These tumors can occur on any part of the body but show a predilection for the face.[9] Periocular involvement is uncommon, and in one review of 592 cases of KA, more than 70% were located on the face, and 5.6% involved periorbital skin.[10]

The two major types of KA are solitary and multiple KA. Solitary KA is the most common type, and this group is further subdivided into several subtypes.[11] Typical solitary KAs present as a rapidly growing nodule with a shiny epidermis and a central keratotic crater. They generally are small, ranging in size from a few mm to 2 cm, with a multilocular keratin-filled central crater where dermal papillae undergo necrosis.[12] After a stable phase lasting several months, these lesions generally undergo complete regression. Giant KA rapidly grows to sizes larger than 3 cm. They are seen mostly in males (74%), with a predilection for the head, predominantly on the eyelids and nose. They show a downward vertical growth pattern, invading the dermis with the destruction of underlying tissue, and persist for long periods before undergoing variable degrees of regression.[13,14] Subungual KA is a rare solitary variant appearing under nails. It usually occurs in Caucasian men with a predilection for the first three fingers of the hand.[15] It grows rapidly over several weeks and shows an aggressive behavior with destruction of the underlying bone of the terminal phalanx and rarely undergoes spontaneous regression. Mucosal KA is another rare variant seen mostly in the oral cavity and occasionally on the conjunctiva or vulva. Lesions grow rapidly over 2 to 8 weeks, and like some other variants, they show little tendency to regress. KA centrifugum marginatum is another variant reported to occur after trauma and is characterized by progressive peripheral extension with raised rolled-out margins showing multiple comedonal orifices. They are seen more frequently on the dorsum of hands and legs, can attain a size of up to 20 cm, and do not show a tendency for spontaneous regression.[16,17]

Multiple KAs are rare and can be sporadic or familial.[2] They have been described in the literature as several types. Multiple familial KAs of Ferguson-Smith type, also known as multiple self-healing squamous epithelioma, are a rare autosomal dominant genodermatosis characterized by the development of recurrent KAs and well-differentiated squamous cell carcinomas (SCCs).[18] Slow-growing lesions appear in continuous waves on the face and limbs at any age from childhood to old age. Like common KAs,

they do tend to undergo spontaneous regression over several months. Generalized eruptive KA of Grzybowski is an extremely rare variant of KA affecting the skin and mucous membranes on both sun-exposed and sun-protected sites. It occurs in older individuals in the fifth to seventh decades of life. Hundreds to thousands of tiny 1 to 2 mm dome-shaped KA lesions without a central crater appear with an eruptive onset.[2,19] Multiple KAs of Witten and Zak type are assumed to have a familial predisposition. Lesions have a predilection for sun-exposed areas and arise as 1 to 30 papules that can remain small or increase to a very large size. These lesions undergo regression over several months.[20]

Three clinical stages are recognized in the natural history of solitary KA.[21] An initial proliferative stage is characterized *(Print pagebreak 501)* by rapid growth over 1 to 2 months. This is followed by a mature stage appearing as a nodule, often with a central keratotic crater. After several months to years depending on the size, a spontaneous involutional phase is seen resulting in a hypopigmented scar.[2,22] The spontaneous regression can be partial or complete.

In a retrospective histopathologic study of 50 patients with KA, Lawrence and Reed[21] found carcinoma-like foci (invasive cords of atypical epithelium) in the majority of specimens, most of which occurred in stable-stage lesions. They speculated that stage I lesions break into the reticular dermis and incite an immune response. Typical, possibly neoplastic clones of keratinocytes are held in check by the body's immune response in stage II. Stage III lesions are equivalent to a senescent phase of a cell-mediated immune response with an associated desmoplastic reaction.[21] In some instances, alteration in the immune response may allow the emergence of neoplastic clones with the possible development of SCC.

There is no consensus as to whether KA is a benign or malignant neoplasm.[23] KA progressing to SCC with metastatic spread is rare,[24,25,26,27] and KA-like SCCs have been described in numerous publications.[6,12] Perineural invasion of facial KA is uncommon, seen in only 1% to 4% of excised specimens.[28] This can lead to tumor extension into facial mimetic muscles, tumor recurrence, and metastasis to regional lymph nodes.[29]

Etiology and Pathogenesis

Debate concerning the pathogenesis of KA has persisted for more than 60 years, and it is not clear whether these tumors always regress or whether, under certain circumstances, they can progress to invasive SCC.[30] One thought is that KA and SCC are separate entities, KA being a benign lesion undergoing rapid initial growth followed by spontaneous regression and SCC being a malignant invasive tumor with metastatic potential.[31] Another thought is that KA and SCC are distinct but related entities on two ends of the same disease spectrum.[32,33,34]

While the pathogenesis of KA is unknown, several features of this tumor are suggestive of possible etiologies. These include its apparent derivation from hair follicles, its association with ultraviolet (UV) radiation exposure, the proposed linkage with occupational chemicals such as tars and mechanical oils, association with human papillomaviruses (HPVs), genetic abnormalities in the Ferguson-Smith type of multiple KA, the association of KA with syndromes such as the Muir-Torre syndrome and familial incontinentia pigmenti, and the expression of tumor suppressor genes, oncogene expressions, and mutations, and telomeric alterations in some KAs.[30,35,36,37,38] The epithelium of the hair follicle has been proposed as the origin of some KAs,[39] although this does not explain the occurrence of KA on mucosal surfaces. It has been proposed that KAs arising in mucous membranes represent a variant of pseudoepitheliomatous hyperplasia.[21]

Cabibi et al[40] studied 43 lesions of KA and SCC and reported differences in GLUT1 antibody expression that distinguished typical KA from SCC and also highlighted an intermediate group of atypical KA, supporting the hypothesis of a progression along the spectrum from KA to SCC. The atypical KA showed focal areas with some features of KA that overlapped with those of SCC, consisting of a higher degree of cytologic atypia, a higher nuclear/cytoplasmic ratio, several mitoses, and focal aspects of irregular infiltration at the deep boundary.[40] When these features were limited to less than 30% of the tumor, it was defined as an atypical KA. The authors suggested that KA may regress as the result of functioning immunity, but when local immunity was deficient, some KAs might develop into SCCs.

The predilection of KA for sun-exposed areas suggests UV radiation might be an important etiological factor, similar to SCC.[3,4,5,6,41] This is supported by the association of KA with other UV-induced tumors such as xeroderma pigmentosum.[6] Papillomavirus-related DNA has been found in some KAs,[42] but the relationship is inconsistent, and no conclusive etiology has yet been established.[43] Occupational exposure to pitch, tar, coal, or machine oil was reported to occur in 20.3% of 108 patients with KA compared with only 2.7% in 147 controls without KA, suggesting a possible chemical-induced KA etiology.[8] KA has also been reported as a complication of damaged skin previously treated with CO_2 laser, radiotherapy, and PUVA photochemotherapy.[44,45,46]

Some gene alterations have been found in KA.[47,48] Expression of Bcl-2 protooncogene was found in some KA, but to a much less degree than in SCC. Sleater et al[49] suggested that KA could be an SCC that is deficient in Bcl-2 expression. Transforming growth factor beta receptor 1 also has been described in KA lesions associated with multiple familial KAs of Ferguson-Smith type,[50] and

mismatch repair genes were found in KA seen with the Muir-Torre syndrome.[51]

KA is known to have a relationship with some systemic syndromes. Muir-Torre syndrome is an autosomal dominant genodermatosis combining malignancies, most notably colon cancer, with sebaceous neoplasms.[52] The syndrome is caused by germline mutations of hMSH2 and hMLH1 genes, involved in the mismatch repair system, and KA are seen in Muir-Torre syndrome as solitary or multiple lesions. KA occurring with this syndrome is explained by the common pilosebaceous gland origin of sebaceous neoplasms and KA.[6] KAs have also been observed in patients with xeroderma pigmentosum, a rare autosomal recessive genodermatosis that results from mutations in nucleotide excision repair. Patients demonstrate severe photosensitivity, skin pigmentary changes, malignant tumor development, and sometimes progressive neurologic degeneration,[53,54] resulting in the development of cutaneous melanoma, basal cell carcinoma, SCC, and KA in early childhood. Other rare associations include florid cutaneous papillomatosis[55] and nevus sebaceous of Jadassohn.[56,57]

Clinical Characteristics

KAs are frequently seen in older individuals with light skin and a history of chronic sun exposure.[58] Common areas of involvement include the lips, cheeks, nose, eyelids, and the *(Print pagebreak 502)* back of the hands. Males are affected slightly more frequently than females.[7,59] During the initial proliferative phase, the tumor grows rapidly as a firm papule. The border is skin colored or erythematous, occasionally with fine telangiectatic vessels (Figure 76.1).[6] In the mature phase, it becomes dome shaped with a central keratinous crater (Figure 76.2). During the involutional phase, the lesion becomes flattened with less of a crater, more hyperkeratotic, with granulation tissue at the base (Figure 76.3), ultimately resulting in an atrophic scar.[41,60]

Of 66 cases of periorbital KA from the literature with some data, 55% were males.[61] The mean age at presentation was 53.3 years with a range of 19 to 96 years. The mean duration from tumor appearance to clinical diagnosis in most cases was about 8 weeks, with a range of 1 to 20 weeks. Rare cases had a duration of 2 to 20 years.[61,62] The tumor was located in the lower lid in 63% of cases, the upper lid in 20%, and the medial or lateral canthus in 13% and 6%, respectively. The lesion ranged in size from 2 mm to 8 cm, with a mean of 1.7 cm. In one case, a very large lower eyelid KA extended into the anterior orbit.[24]

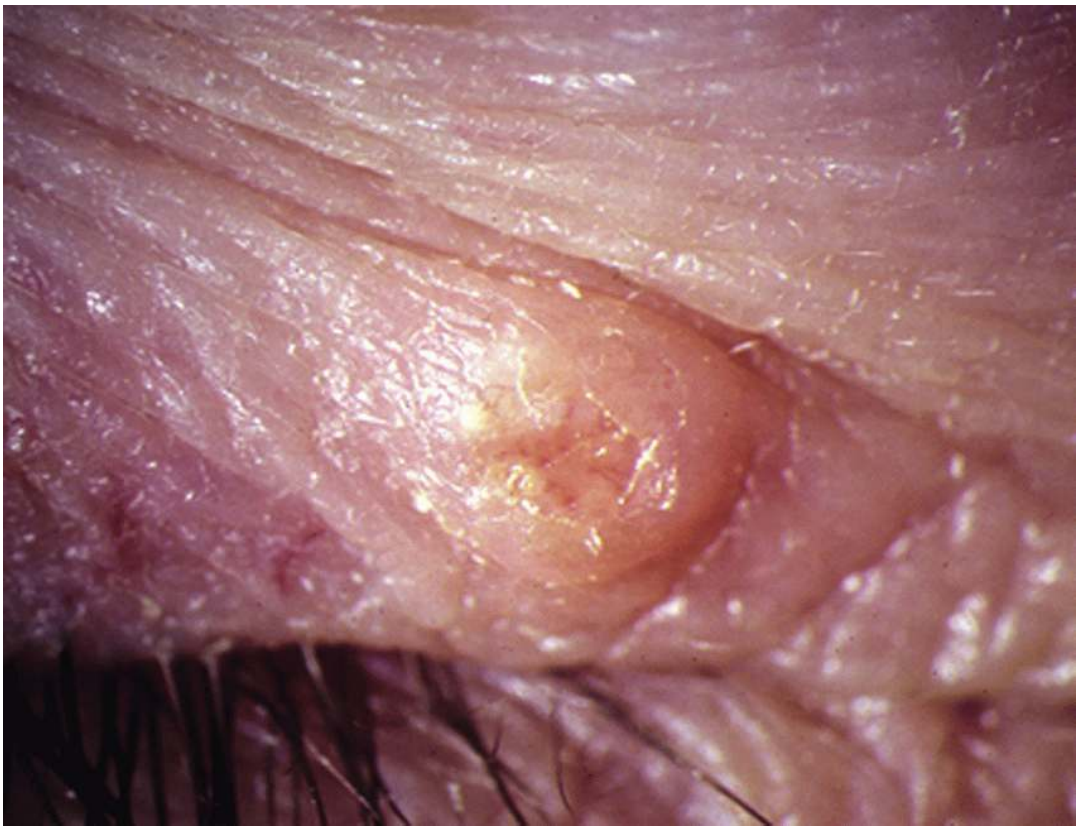

FIGURE 76.1 Early-stage keratoacanthoma on the eyelid margin with an incipient central crater.

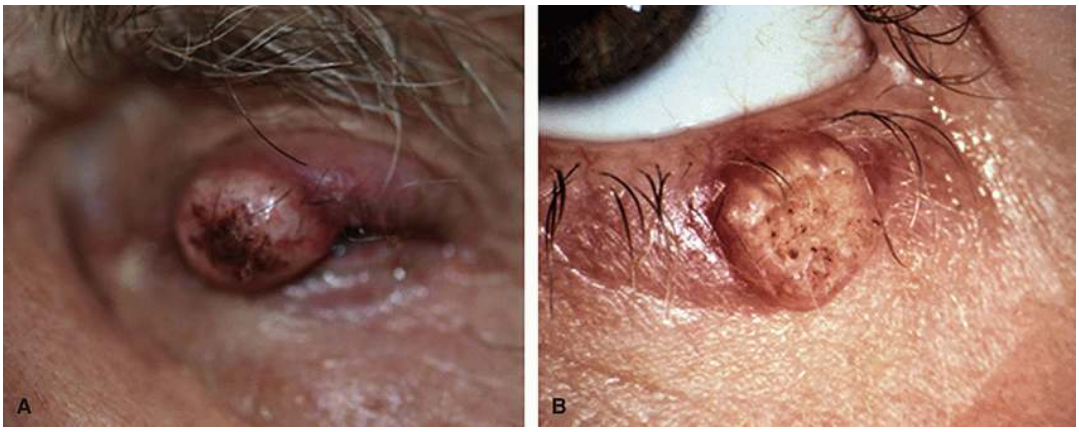

FIGURE 76.2 A and B, Mature phase domed keratoacanthoma with a central keratinous crater. A, (Courtesy of Dr. Suzanne Freitag). B, (Courtesy of Dr. Alan McNab).

Conjunctival KAs are rare. The first case was reported by Freeman et al in 1961, and since then, fewer than 20 additional cases have been described.[27,63,64,65,66] Conjunctival KAs are seen in younger patients than seen with cutaneous KA, with a mean of 42.1 years and range of 17 to 83 years. They appear as elevated, dome-shaped, white hyperkeratotic nodules almost always at the corneal limbus. They are usually associated with conjunctival injection and can bleed spontaneously.[63] Because ocular surface lesions are rare and are usually excised early, the natural course of conjunctival KAs is not clear.

Differential Diagnosis

The differential diagnosis of KA includes any rapidly growing mass on the skin or conjunctiva. For cutaneous KA, the most important tumor in the differential is SCC. In one study of 1949 biopsies with histologic characteristics of KA (crateriform architecture, epithelial lip, sharp demarcation), 1547 specimens (79.3%) were classified as "classic" SCC with KA-like features, based on histopathologic features and in situ hybridization studies.[9] Another 389 cases (19.9%) were diagnosed as HPV papilloma with KA-like features, and 15 cases (0.8%) were reported as "verrucous seborrheic keratosis (VSK) with KA-like features." Tas et al[67] reported a case of parotid carcinoma misdiagnosed as KA.

Several other neoplasms with crateriform architecture should be distinguished from KA. These include crateriform Bowen disease that shows an exoendophytic silhouette with a central keratotic horn, crateriform seborrheic keratosis which is an exoendophytic lesion, often with finger-like *(Print pagebreak 503)* exophytic projections, and crateriform verruca characterized by an epithelial liplike structure at the periphery, with a central keratinous plug resembling KA.[68]

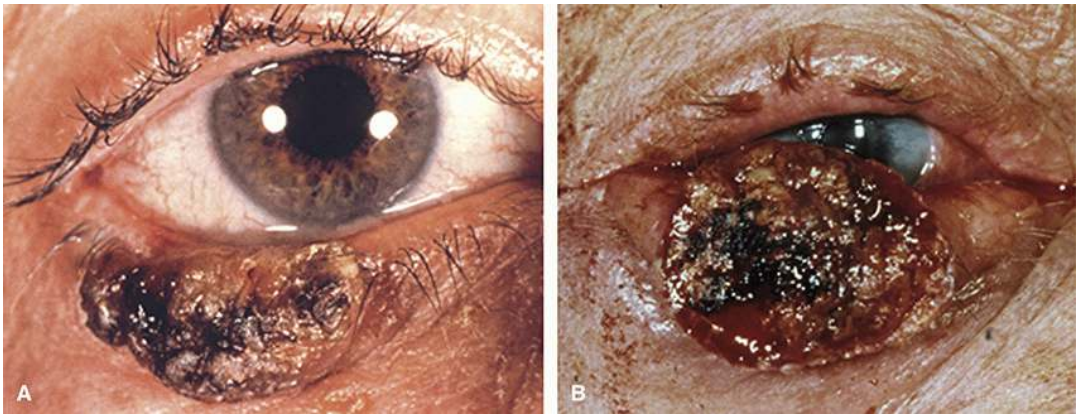

FIGURE 76.3 A and B, Late-stage hyperkeratotic keratoacanthomas with surface necrosis.

Conjunctival KA typically presents as a white, hyperkeratotic lesion, often seen in the interpalpebral bulbar conjunctiva adjacent to the limbus. They grow rapidly over a short period.[66] Simulating conjunctival lesions include pyogenic granuloma and malignant tumors such as ocular surface squamous neoplasia and amelanotic melanoma.[69] Pyogenic granulomas present as red, elevated masses, often associated with or following ocular surface surgery. Conjunctival melanomas clinically appear as elevated, amelanotic, or pigmented lesions with prominent feeder vessels.[70]

Treatment

Surgical excision with histologic control of margins is considered the gold standard for the management of KA, except when they are present in anatomic locations that could compromise function. Tumor eradication is generally excellent with few complications.[13,62,71] Surgery is preferred by many clinicians because of the uncertain behavior of some lesions. The importance of complete excision and histologic examination of KA was demonstrated by the study of Leibovitch et al,[41] who found 2/12 (16.7%) of lesions clinically diagnosed as KA eventually proved to be invasive SCC on histopathology. Because of this risk, it has been suggested that the role of more conservative therapies should be limited to patients unable to undergo surgery.[41] Even so, the recurrence rate following surgical excision of cutaneous KA has been reported at 0% to 8% during follow-up periods of up to 11 years.[6,61,62] Curettage has also been used for small solitary KA, sometimes together with electrodesiccation. Recurrence following this approach has been reported at 3.6%.[5,6,72,73] Mohs micrographic surgery is another potential option, especially in locations like the eyelids where maximum preservation of tissue is critical for function. It has been reported in several isolated case reports.[6,74]

5-Fluorouracil was advocated either as an intralesional injection of a 5% solution directly into the base of the KA every other day or as a topical cream or ointment up to five times daily.[75] This approach resulted in a 60% to 80% decrease in the size of the lesions after an average of 3 weeks.[76] Intralesional corticosteroids,[77] bleomycin,[78] methotrexate,[71,79] and interferon alpha[80] have all been used in isolated reports with up to 100% clearance of lesions. Topical imiquimod as a 5% cream every other day for 4 to 12 weeks resulted in regression of solitary facial keratoacanthomas.[81]

Radiotherapy has been used as primary therapy for KA or after tumor recurrence, resulting in tumor regression over several months with good to excellent cosmetic results,[82,83,84] but recurrences have been reported.[85] Radiotherapy has also been used for more aggressive lesions with perineural invasion with good results. Argon laser ablation can be employed for small early KAs in locations that are difficult to treat with other modalities. Sixty-five percent of patients achieved excellent results with re-epithelialization at 2 to 3 weeks and no recurrences after 2 years. However, 35% healed with mild scarring.[86] Cryosurgery with liquid nitrogen was reported to be of value as primary treatment for small KAs, and as adjunctive therapy following curettage or surgical excision.[87]

For multiple KAs such as generalized eruptive KA of Grzybowski where other treatment modalities fail, systemic chemotherapy with cyclophosphamide at 100 mg/d for 1 to 3 months can result in clearance of thousands of cutaneous and oral KAs without scarring.[88,89,90]

Conjunctival KAs are most often managed with surgical excision and double freeze cryotherapy to the corneal and conjunctival margins and the scleral bed. This can be supplemented with adjuvant topical chemotherapeutic agents, such as interferon alfa-2b 1 million IU/mL or cycles of 5-fluorouracil 1% for 2 months postoperatively.[91,92]

Prognosis

Savage et al[23] reviewed 445 cases of KA from 113 reports published between 1954 and 2013, with follow-up data from 1 week to 288 months. Of these 445 cases, spontaneous regression was reported in 52 (11.6%) patients who had no *(Print pagebreak 504)* treatment, and in 393 (88.3%) patients following medical or surgical treatment. In 46 (10.3%) cases, perineural or perivascular invasion was identified. Local recurrence was seen in 18 (4%) cases, all with previous treatment. There were no cases of metastatic disease. Regardless of the treatment option, the prognosis is generally good, and recurrences are generally less than 10%.

Histopathology

The histopathological features of cutaneous KAs vary by clinical stage.[6,61,68,93,94,95] The early or proliferative stage has a few keratin-filled invaginations of the epidermis or infundibulocystic structures that have not merged to form a large keratotic horn characteristic of the well-developed stage of KA development.[94] The invaginations have epithelial cells with prominent keratohyaline granules and laminated keratinization.[6,94] In the deeper aspect of the invaginations, the epithelial cells have pale pink cytoplasm with a glassy appearance.[94] There is poor differentiation of the deep border from the stroma,[94] and nuclear atypia is scant.[68] At this stage, KAs have an immunophenotype characteristic mainly of follicular infundibular differentiation.[94,95]

The well-developed or fully developed stage of cutaneous KA formation is usually seen in skin biopsies,[94] including the eyelid.[61] Well-developed KAs are exoendophytic lesions with a proliferation of well-differentiated, keratinizing squamous epithelium forming lobules at the sides and bottom of the lesion, with a central keratin-filled crater that enlarges as the lesion matures (Figures

76.4 and 76.5). A key diagnostic feature is a lip of epidermis (collarette) overlapping the central crater (Figure 76.4).[6,68] Squamous cell keratinization results in eosinophilic glassy cytoplasm (Figure 76.5).[6,68] The lesion's lower border usually remains superficial to the eccrine sweat glands.[6] The adjacent dermis contains a mixture of lymphocytes, macrophages, plasma cells, neutrophils, and varying numbers of eosinophils.[6,61,93] Well-developed KAs have a follicular isthmus immunophenotype.[94,95]

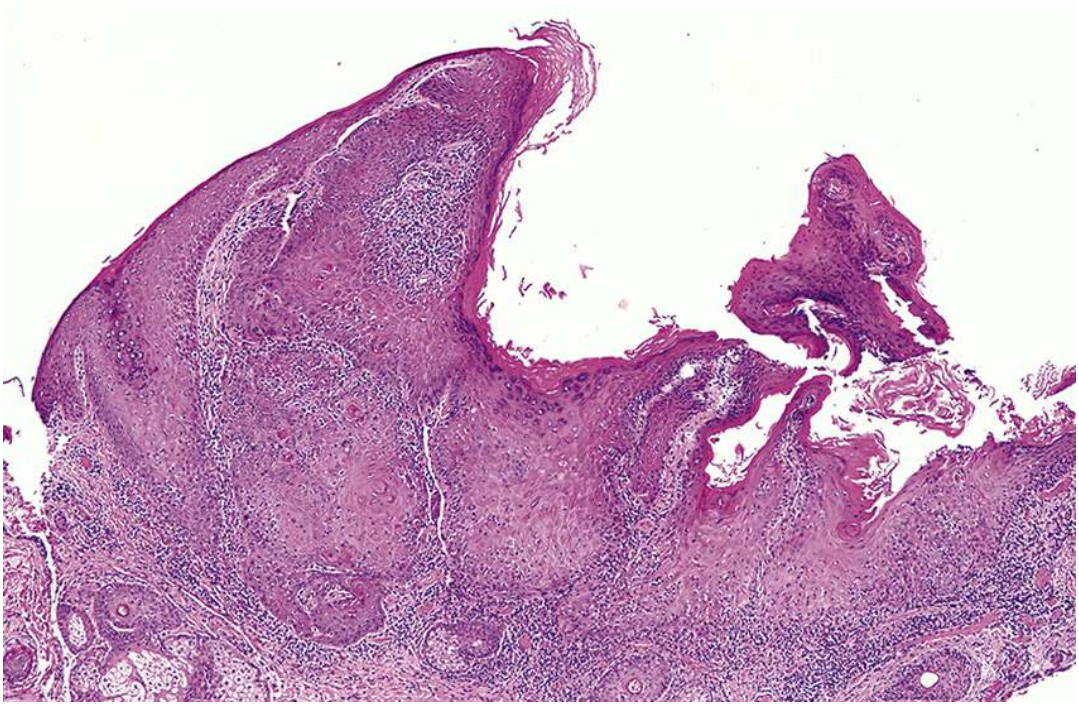

FIGURE 76.4 This right upper eyelid keratoacanthoma arose over several months and appeared clinically to be a cutaneous horn. The lesion has features characteristic of a fully developed exoendophytic lesion with a proliferation of well-differentiated, keratinizing squamous epithelium forming lobules at the sides and bottom of the lesion, a central keratin-filled crater, and a lip of epidermis (collarette) overlapping the central crater. The dermis has a moderately intense infiltrate of lymphocytes, plasma cells, and macrophages.

Regressing- or involutional-stage KAs become flattened and less crateriform, most cells are keratinized, and shrunken *(Print pagebreak 505)* apoptotic cells with brightly eosinophilic cytoplasm may be adjacent to the large tumor cells and within the stroma.[6,68,96] The dermis may have multinucleated foreign body giant cells as a response to keratin.[6] Granulation tissue and fibrosis are at the base of regressing KAs.[6,96] Lesional cells lose immunohistochemical features of follicular differentiation and assume epidermal characteristics at this KA stage.[94]

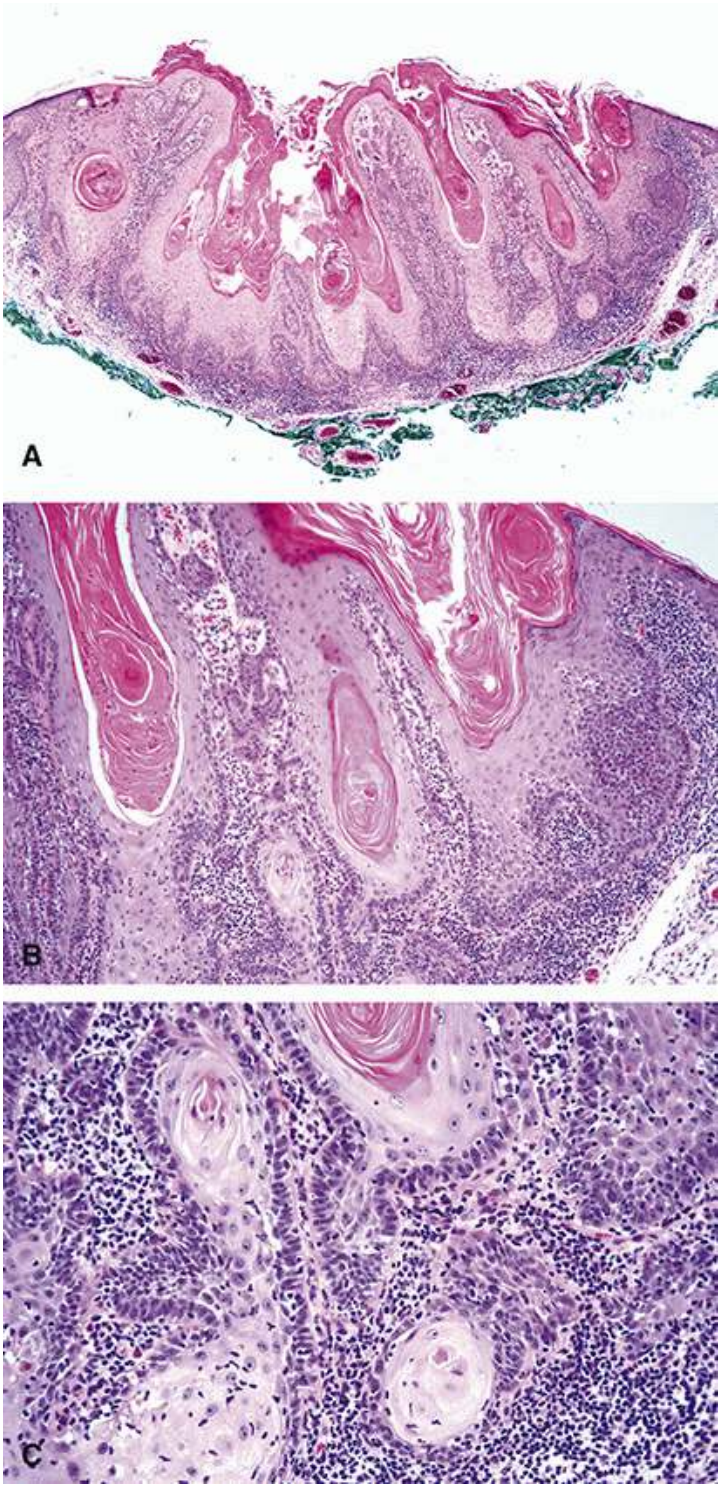

FIGURE 76.5
A, This medial right upper eyelid lesion appeared over 1 month. There is a lobular proliferation of well-differentiated squamous epithelium with keratin filling the central crater. B, The lobules are predominantly composed of epithelial cells with lightly eosinophilic (pale pink) glassy cytoplasm surrounding laminated keratinization. C, The periphery of lobules had basophilic cells, and the borders were minimally infiltrative. The dermis has a dense infiltrate of mononuclear leukocytes without fibrosis.

KAs must be differentiated from infundibular SCCs, crateriform Bowen disease, crateriform seborrheic keratoses, and crateriform verruca.[68,97] The principal differential diagnosis is SCC, with which it may be histologically indistinguishable.[2,93] The overlap in histological appearance is why many dermatopathologists classify these lesions as "SCC, KA type" or "probable KA; SCC cannot be ruled out."[2] Conjunctival and caruncular KAs have an appearance similar to their cutaneous counterpart.[98]

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CHAPTER 78

Keratinous Cyst, Intratarsal

Key Points

- Intratarsal keratinous cysts arise from the meibomian glands of the tarsal plates
- They do not arise from the dermis, and therefore are distinct from epidermoid cysts of the eyelid
- 80% are located in the upper eyelids without a history of trauma, inflammation, previous eyelid surgery, or preexisting lesions
- The etiology of these cysts is unclear, but blockage of meibomian ducts appears to be responsible for their formation
- They present as a yellow-white to skin-colored, smooth, well-circumscribed, noninflammatory lesion that can appear as a prominent bulge beneath the eyelid skin over the tarsus, or may only be detectable when the eyelid is everted
- Treatment includes complete excision of the entire cyst, exposure of the capsule, amputation from the tarsus, and generous cautery at the base wall to prevent a recurrence
- With inadequate excision or drainage, the recurrence rate is high, but with complete excision the prognosis is excellent

Intratarsal keratinous cysts (IKC) are a recently described entity that arises from the meibomian glands of the tarsal plates.[1,2] After chalazion and sebaceous carcinoma, IKC is the third most common cause of primary tarsal swelling.[1] This lesion has also been referred to in the literature as a tarsal keratinous cyst, intratarsal inclusion cyst, intratarsal epidermal inclusion cyst, meibomian gland ductal cyst, epidermal cyst, and epidermoid cyst.[1,3,4,5,6,7,8] However, these lesions arise within the meibomian glands of the tarsal plates, not from the dermis, and therefore are distinct from epidermoid cysts of the eyelid.

The term “intratarsal keratinous cyst” was introduced by Jakobiec et al[1] based on six cases and a review of cases previously described in the literature as intratarsal inclusion cyst.[3] All of these cases were characterized by progressive growth of a mostly palpable cystic lesion on the eyelid fixed to the tarsus. Larger series were subsequently described by Kim et al[9] who added 11 cases, and Zhang et al[10] who reported 15 new cases lacking external signs on the eyelid skin. Among all of these cases, the incidence was equal between men and women, and only 7% of patients were younger than 20 years of age. To date, only 59 cases have been described, although, among 35 cases of all eyelid cysts, Suimon et al[11] diagnosed IKC in 14%, so that the incidence may be higher than appears in the literature.

About 80% of IKCs are located in the upper eyelids, and typically there is no history of trauma, inflammation, previous eyelid surgery, or preexisting lesions. The mean age at presentation has been reported to be 45 to 68 years,[1,9,10,11] and there is no gender predilection.

Patients usually present with an eyelid lump that may have been present for several months to up to 5 years. Initial diagnosis is frequently missed, usually made as a more common lesion such as chalazion. Patients most commonly present with complaints of a foreign body sensation, but pain and epiphora are rare symptoms reported in only about 20% of cases.[10]

Etiology and Pathogenesis

The etiology of IKC and other eyelid cysts is not clear, but previously they were considered to result as a complication of previous eyelid surgery.[12,13] However, attachment of the cysts to the tarsus as well as the histopathology and immunohistochemistry suggests that these lesions originate from the meibomian glands or their ducts. Meibomian gland ducts are lined with keratinizing stratified squamous epithelium without a granular layer and with an innermost cuticle layer,[14,15] similar to the lining of IKC. Also, both IKC and meibomian ducts stain positive for epithelial membrane antigen (EMA) on immunohistochemistry. Blockage of these ducts appears to be responsible for the formation of IKCs.[10] IKC is distinct from a chalazion, which is a chronic granulomatous inflammatory lesion of the meibomian gland or gland of Zeiz resulting from lipid breakdown products leaking into surrounding

tissues.

Clinical Presentation

The main symptoms of IKC include foreign body sensation, irritation, tenderness, or photophobia, mostly from the nodular elevation beneath the conjunctiva. Some lesions are very prominent as a bulge beneath the eyelid skin and are easily visible and palpable externally (Figure 78.1). Others point posteriorly and are only detectable when the eyelid is everted (Figure 78.2).[10] With the eyelid everted, lesions appear as a yellow-white, smooth, well-circumscribed, noninflammatory nodule ranging from 1 to 10 mm in diameter on the palpebral conjunctival surface.[10] Lesions with an anterior extension may have a slight blue color beneath the skin, probably from the Tyndall effect.[9] Clinically, lesions appear as a firm subcutaneous nodule mostly on the upper eyelid. The lesion is fixed to the tarsus and the skin is freely mobile over it, normal in color, and without inflammatory signs. Lesions are usually isolated, although multiple IKCs have *(Print pagebreak 517) (Print pagebreak 518)* been known to occur.[2] Transconjunctival leakage of the keratinous cyst contents may occasionally occur and cause irritation.[2]

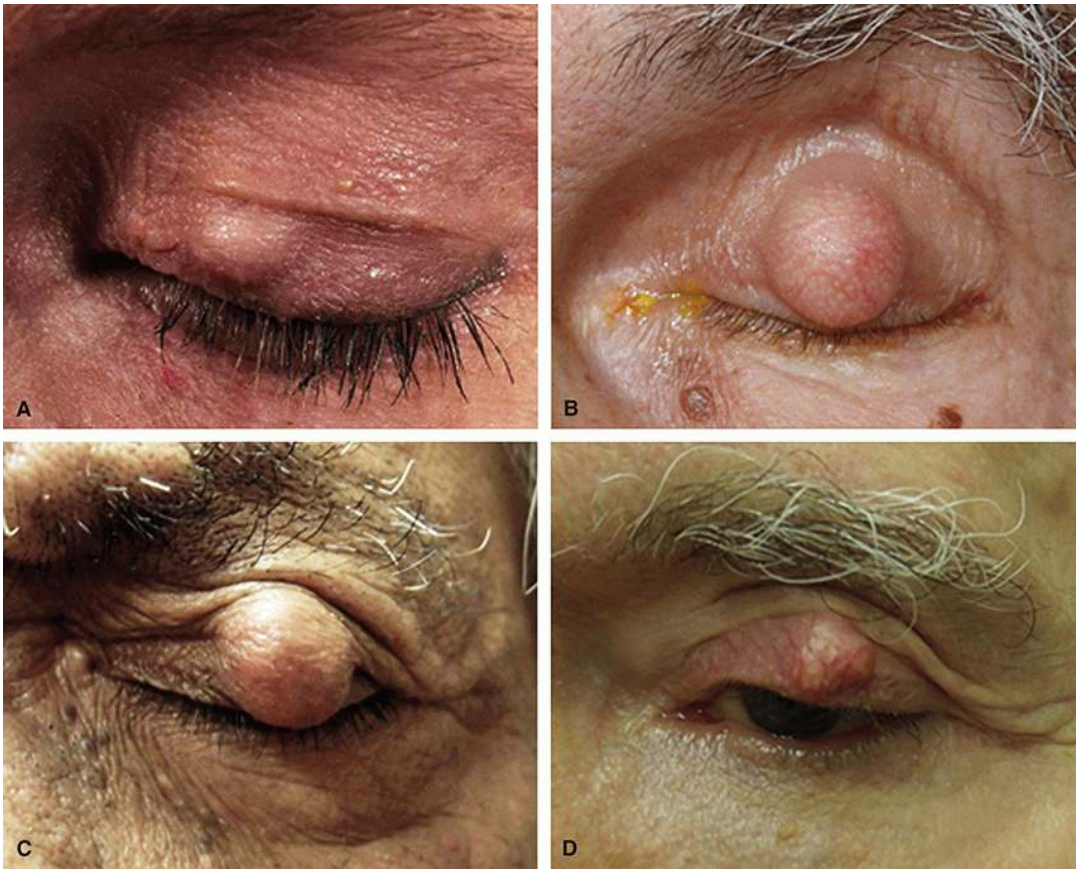

FIGURE 78.1 A-D, Anterior nodules of intratarsal keratinous cysts of the eyelids. A and B (Courtesy of Dr. Reza Vagefi). C (Courtesy of Dr. Suzanne Freitag). D (Courtesy of Dr. Robert Kersten).

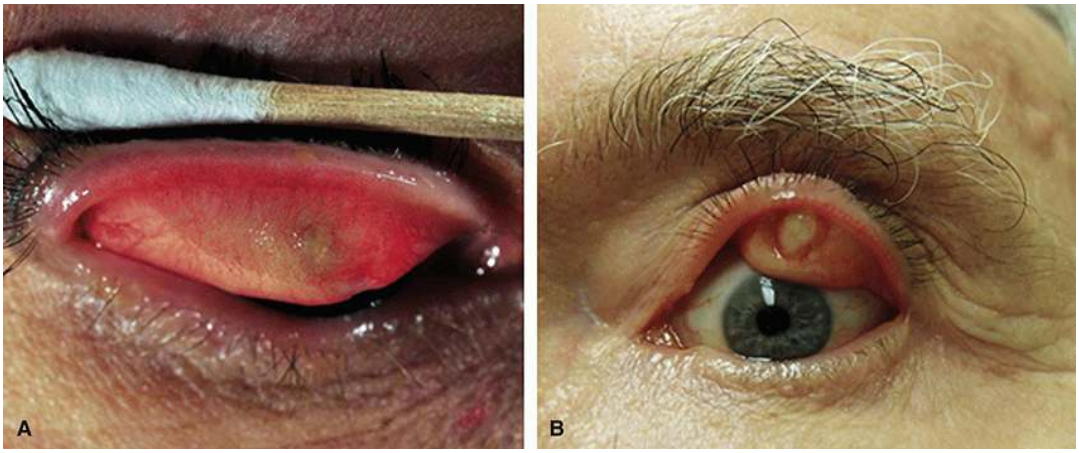

FIGURE 78.2 A and B, Posterior intratarsal keratinous cysts pointing on the conjunctival surface. A (Courtesy of Dr.

Reza Vagefi). B (Courtesy of Dr. Robert Kersten).

Differential Diagnosis

The main differential diagnoses of IKC include epidermoid and epidermal inclusion cysts, steatocystoma, chalazia, and meibomian gland carcinomas. Epidermoid cysts are situated in the dermis and are freely moveable over the tarsus, unlike the fixed position of IKC. Steatocystoma occurs in younger individuals, usually less than 30 years old, the cyst is lined with nonkeratinizing squamous epithelium, and the cyst contents consist of yellow sebum with scattered hair shafts.[16,17] Chalazia are typically fluctuant inflammatory lesions.

Treatment

Treatment of IKCs must include complete excision of the entire cyst, exposure of the capsule, amputation from the tarsus, and generous cautery at the base wall to prevent a recurrence.[18] This requires a more aggressive approach than that used for epidermoid cysts or chalazia. The recurrence rate is significant following more limited procedures such as incision and drainage (I&D), or curettage as is commonly performed for chalazia. A full-thickness pentagonal eyelid wedge resection or transconjunctival tarsectomy including all of the cyst walls is usually recommended.[1,5,6] At surgery, the cyst wall is thick and well-developed and fused to the tarsus, making more limited dissections difficult. If the cyst is opened, a milky to viscid fluid is released.[1]

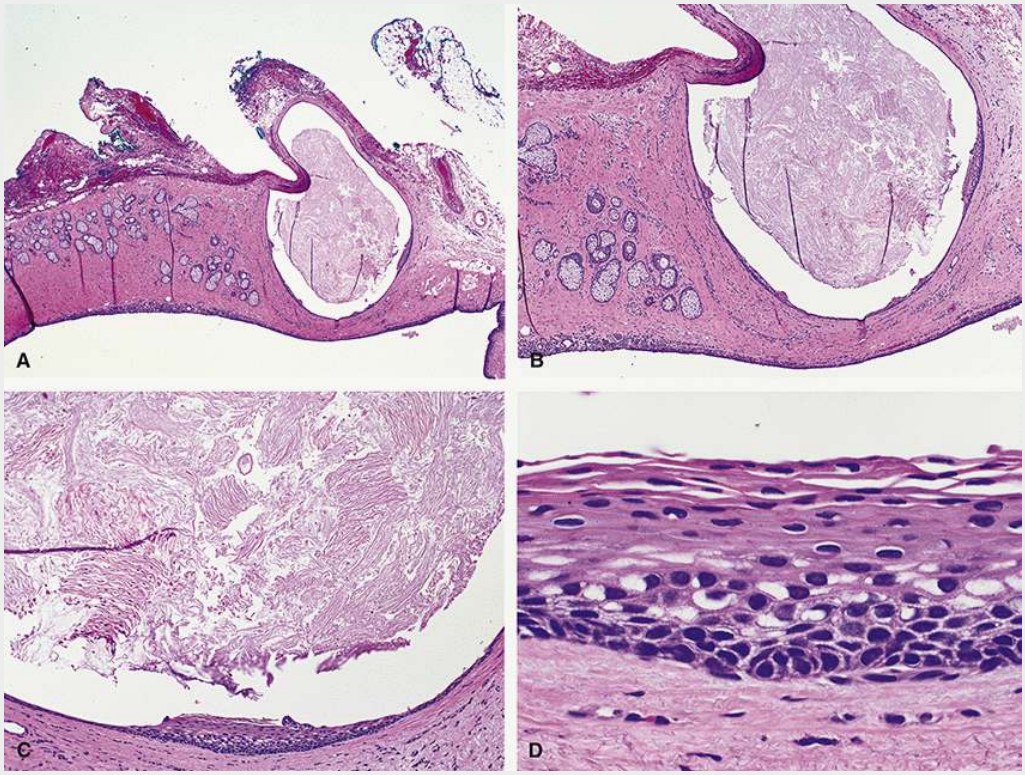

FIGURE 78.3 A and B, Intratarsal keratinous cyst located within the dense collagenous tissue of the tarsus. C and D, The cyst is lined by stratified squamous epithelium with an inner layer that may be undulating or corrugated and lacks keratohyalin granules, goblet cells, or sebaceous cells. The lumen contains loose, eosinophilic keratin (C).

Prognosis

With inadequate excision or drainage, the recurrence rate is high. Following complete excision, by wedge resection or anterior or posterior tarsectomy, the prognosis is excellent, with no recurrences reported.

Histopathology

IKCs are located within or attached to the tarsus (Figure 78.3).[1] They are lined by stratified squamous epithelium with an inner layer that may be undulating or corrugated.[1,6,8,19,20] The *(Print pagebreak 519)* lining lacks keratohyalin granules, goblet cells, or sebaceous cells.[1] The lumen contains loose, eosinophilic keratin (Figure 78.3C), though we recently had a case with the typical epithelial lining but only minimal luminal contents (Figure 78.4). The epithelial lining and keratin contents express cytokeratin 17 and carcinoembryonic antigen, while those of epidermoid cysts do not.[1,20] Immunohistochemical stains are not needed for diagnosis if the cyst is located within the tarsus and has an appropriate histological appearance.

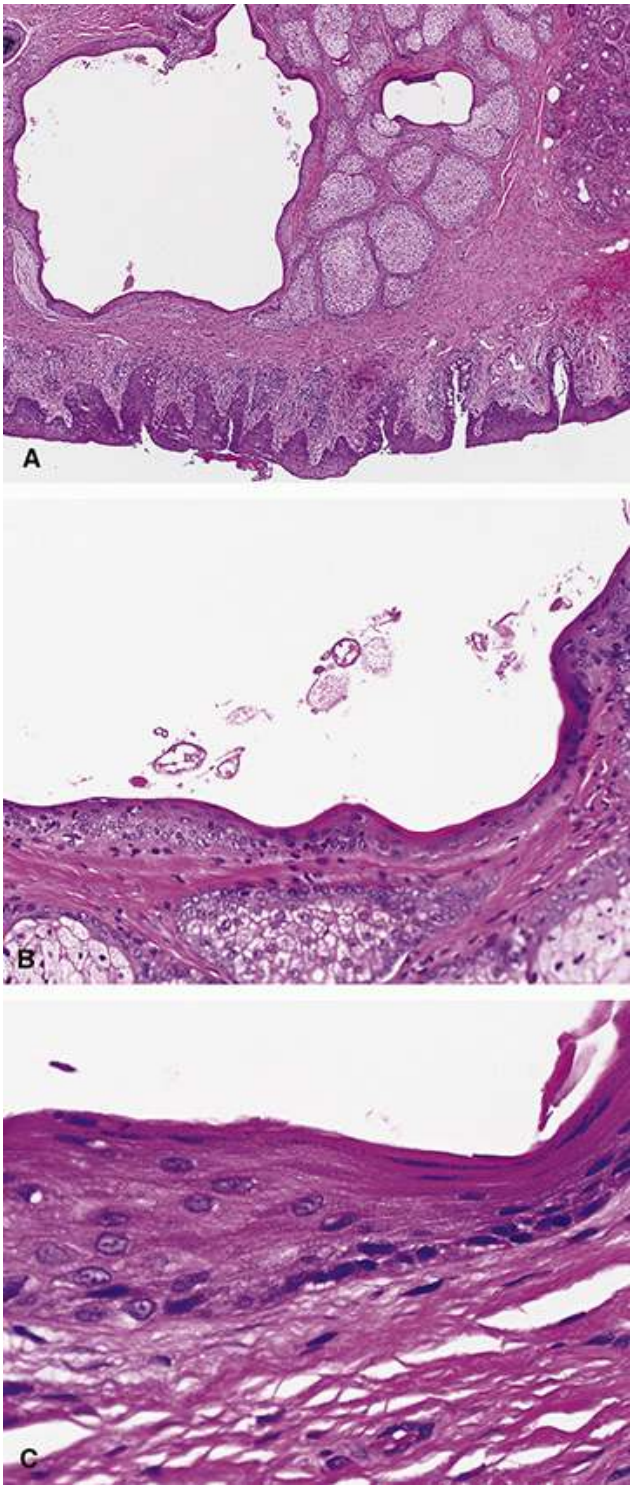

FIGURE 78.4 This intratarsal (A) cyst has the typical epithelial lining (B and C) of an intratarsal keratinous cyst but only minimal luminal contents (B). It is not possible to determine if the minimal luminal content is due to this being an early cyst lacking time for the keratin to accumulate or if the contents drained before or during surgery.

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CHAPTER 79

Leiomyoma

Key Points

- Leiomyoma is a benign soft-tissue neoplasm arising from smooth muscle
- Cutaneous leiomyomas are divided into three subtypes: piloleiomyomas originate from the attachment points of the arrector pili muscle; angioleiomyomas originate from vascular smooth muscles of the tunica media of small-to medium-sized arteries and veins; and dartoic leiomyomas arise from the smooth muscles of genital skin and areola
- The pathogenesis of leiomyomas is unknown
- Genetic mutations have not been associated with sporadic solitary piloleiomyomas, but multiple cutaneous leiomyomas possess a heterozygous germline mutation in fumarate hydratase
- In angioleiomyomas, 35% exhibit DNA copy number changes involving one or two chromosomes
- Piloleiomyomas on the eyelid appear as painful, red, bluish-black or yellow, slow-growing, smooth, firm, rubbery papules or nodules
- Angioleiomyomas are slow-growing, asymptomatic, solitary skin-colored, well-defined, firm, vascularized, deep dermal or subcutaneous nodules
- The gold standard for treatment is surgical excision for small, localized tumors
- Morbidity associated with untreated lesions is primarily from pain, but following surgical excision the prognosis is excellent

Leiomyoma is a benign soft-tissue neoplasm arising from smooth muscle that was first described by Virchow in 1854 as "tuberculum dolorosum."[1] These lesions are found most commonly in the uterine myometrium in 95% of cases, followed by the skin in 3%, and the gastrointestinal tract in 1.5%. Less than 1% are seen in the head and neck region.[2] These tumors are typically asymptomatic, slow-growing lesions, most often seen in the 4th and 5th decades of life with a slight predilection for females.

Cutaneous leiomyoma has been divided into three subtypes according to the site of origin.[2,3] Pilar leiomyomas or piloleiomyomas originate from the attachment points of the arrector pili muscle, proximal to the hair follicle and distal to multiple attachment points within the papillary and reticular dermis and basement membrane zone.[4] Angioleiomyomas originate from vascular smooth muscles of the tunica media of small- to medium-sized arteries and veins. Dartoic or genital leiomyomas arise from the smooth muscles of genital skin and areola.[1] The angioleiomyoma and dartoic subtypes usually present as solitary lesions, whereas pilar leiomyomas can manifest as solitary or multiple cutaneous tumors.

Superficial leiomyoma can occur at any age from infancy to old age, with most patients in middle age[5,6,7] and a peak incidence between 40 and 60 years.[8] Various studies have shown male or female predilection, but overall the sexes are equally affected. There is no racial predilection for leiomyoma, except in oral angioleiomyomas, for which the white-to-black ratio has been reported to be 3:1.[9]

Leiomyoma can appear in any body location where smooth muscle is present. In the head and neck region, about 23% of tumors involve the lips, tongue oral cavity, buccal mucosa, soft palate, larynx, esophagus, trachea, nasal cavity, salivary glands, paranasal sinuses, thyroid gland, intraosseous sites in the maxilla, and mandible, and orbit. Other rare sites include the ear, cheek, neck, forehead, and scalp.[10,11]

Piloleiomyomas usually present as a papule or nodule on the face, trunk, or extremities, either solitary or as multiple nodules that may be in a clustered, linear, dermatomal, or scattered distribution. Nodules range in size from 2 to 20 mm and vary in color from skin color, to pink, red, or brownish. Solitary piloleiomyomas are more common on the lower extremity, whereas multiple

piloleiomyomas more often occur on the trunk or the extensor surface of the extremities.[2] Pain is a common presenting symptom, which may occur spontaneously or initiated by pressure or low temperature.[12]

In 1973, Reed et al reported the association of multiple cutaneous leiomyomas with leiomyomas of the uterus, a condition known as Reed syndrome.[13] The condition is also referred to as multiple cutaneous and uterine leiomyomatosis (MCUL) and also can occur with renal cell carcinoma.[14,15,16] When MCUL is associated with renal cancer, it is referred to as hereditary leiomyomatosis and renal cell cancer. The inheritance pattern is thought to be autosomal dominant with incomplete penetrance,[17] so that not all women in a family are similarly affected; some may only have cutaneous tumors, others only uterine tumors, and some may have both cutaneous and uterine leiomyomas.[18,19] When this condition occurs as a genetic syndrome, the piloleiomyomas tend to occur earlier in life, with an average age of onset at 25 years and a range of 10 to 50 years.[2]

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Angioleiomyoma, also known as vascular leiomyoma, most commonly involves the lower extremities and head and neck region.[10] Orbital and eyelid involvement is extremely rare.[20,21,22,23] They usually present in females in the 5th to 7th decades as a firm, painful, solitary subcutaneous nodule and are more common in women than in men, with a ratio of about 2:1.[24,25,26,27] Angioleiomyomas have been further subclassified based on histopathology as capillary (or solid), which is the most common type; venous; and cavernous types.[28]

Genital leiomyomas typically develop on the genitals, including the scrotum, penis, and vulva, and also on the nipple-areolar region. The lesions usually present as an asymptomatic, solitary nodule.

Etiology and Pathogenesis

The pathogenesis of leiomyomas remains unknown. Genetic mutations have not been associated with sporadic solitary piloleiomyomas. Contrary to sporadic solitary leiomyoma, approximately 89% of patients with multiple cutaneous leiomyomas possess a heterozygous germline mutation in fumarate hydratase (FH),[29] an enzyme in the Krebs cycle that functions in the conversion of fumarate to malate.[2] In 85% to 90% of female patients with FH mutations, both cutaneous and uterine leiomyomas may be present. The FH mutation is also associated with renal cell carcinoma, seen in approximately 15% of these patients.[2] The pathophysiology of heterozygous FH deficiency and the production of leiomyomas is not known, but it has been suggested that FH may function as a tumor suppressor.[30,31,32] In dominantly inherited, multiple cutaneous piloleiomyomas associated with uterine leiomyomas, evidence has been reported for linkage to chromosome 1q42.3-q43.[33]

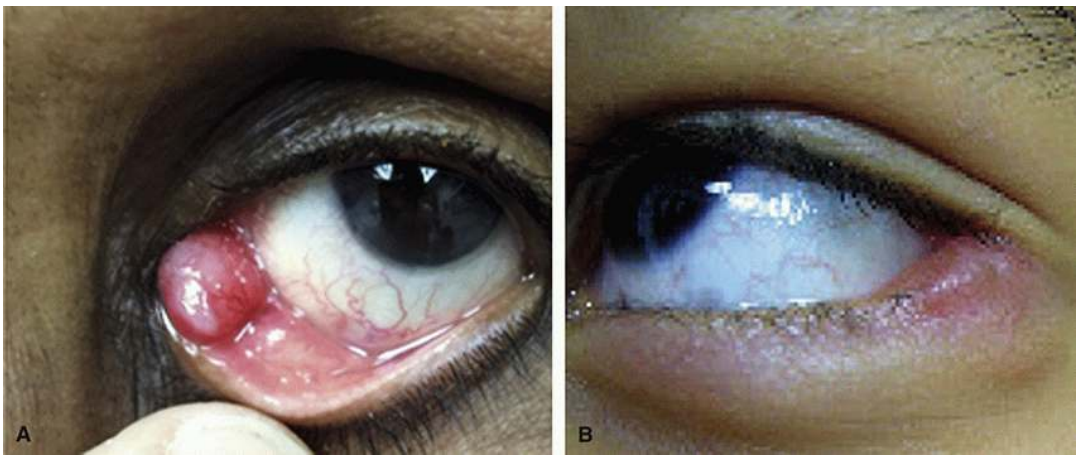

FIGURE 79.1 A, Leiomyoma on the conjunctival surface at the medial lower eyelid. B, Piloleiomyoma nodular mass of the right upper eyelid in a 13-day old infant. (A, Courtesy of Dr. Roman Shinder. B, Reprinted with permission from Alam S, Banerjee P, Subramanian K. A rare case of congenital piloleiomyoma of the eyelid. *Orbit*. 2020 Aug 26, Online ahead of print.)

In a series of 23 cases of angioleiomyoma, 35% exhibited DNA copy number changes involving one or two chromosomes, with the most common recurrent loss found at chromosome 22q11.2.[34] Genital leiomyoma has been associated with several chromosomal anomalies including clonal translocation between chromosomes 7 and 8 (7;8)(p13;q11.2)[35] and pericentric inversion involving chromosome 12 (12) (p12q13-14).[36]

The pathogenesis of pain associated with leiomyomas is not known. Various theories have proposed that pain could result from local pressure on cutaneous nerves, or that specific infiltrating cells play a role, or that muscle contraction be contributory.[26]

Clinical Characteristics

Individual piloleiomyomas on the eyelid appear as slow-growing, smooth, firm, rubbery papules or nodules.[37] They can be skin-colored, red, reddish-brown, bluish-black, or yellow and can even be hypopigmented in color and are usually less than 2 cm in diameter (Figure 79.1). The skin may be irregularly thickened and when located on the eyelid margin can be associated with madarosis, tearing, and mattering.[38] Since these lesions develop in the superficial dermis, they are fixed in the skin, but not adherent to deeper structures.[26] Ninety percent of piloleiomyomas are painful, described as burning, pinching, or stabbing, exacerbated by tactile pressure, or even emotion.[26,39,40,41] Multiple cutaneous leiomyomas occur on the face, trunk, or extremities and may be bilateral. The distribution pattern can be grouped, dermatomal, and linear.[42]

Angioleiomyomas are usually slow-growing, asymptomatic, solitary skin-colored, well-defined, firm, vascularized, deep dermal or subcutaneous nodules on the lower *(Print pagebreak 522)* extremities, but occur less commonly on the trunk and head.[26,27,43,44,45,46,47] In the head and neck region, they can occur on the oral or nasal mucosa, or the skin of the face, lip, or eyelid.[48] Other rare locations include the larynx, salivary glands, and retropharyngeal space.[49,50,51,52]

Differential Diagnosis

The appearance of solitary cutaneous leiomyoma is nonspecific so that the differential diagnosis is extensive and includes a large variety of dermal lesions and connective tissue tumors that clinically can be similar.[3] These include chalazion, dermal nevus, lipoma, neurofibroma, dermatofibroma, glomus tumor, eccrine tumors, fibrosed epidermoid inclusion cyst, and trichoepithelioma, among others. Most of these can be distinguished from leiomyoma on histopathology.[2]

The most important lesion in the differential diagnosis of leiomyoma is leiomyosarcoma. Like leiomyoma, these malignant tumors arise from similar smooth muscle tissues. Leiomyosarcomas have been associated with a history of various types of insults such as trauma, burns, inoculation sites, tick bites, radiation, and lupus vulgaris.[26] The majority occur on the hair-bearing surfaces of the extremities, particularly the lower extremities, but occasionally they can be seen on the head and neck.[53,54,55] Contrary to benign leiomyomas, they may be poorly demarcated and occasionally bleed.

Treatment

If left untreated, cutaneous leiomyomas continue to grow slowly and new lesions may appear over many years.[39] Specific treatment depends on the number of lesions, the anatomical location, and the symptoms. The gold standard for treatment is surgical excision for small, localized tumors.[26]

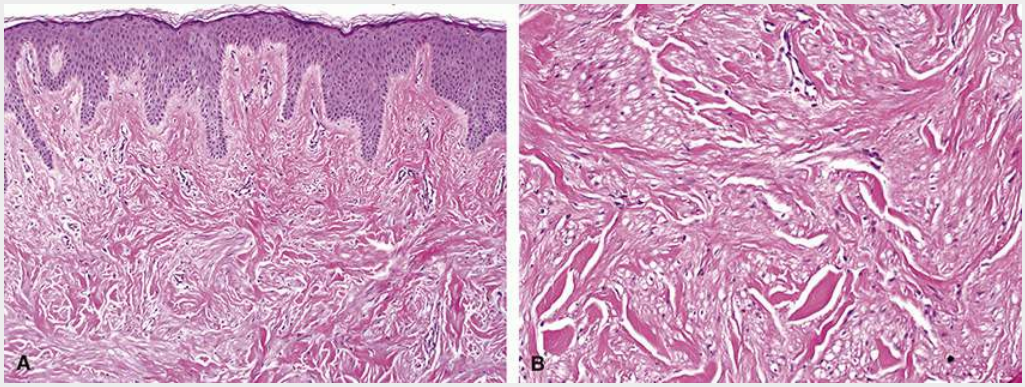

FIGURE 79.2 A, This piloleiomyoma has acanthotic epidermis separated from intersecting bundles of palely eosinophilic smooth muscle cells with entrapped brightly eosinophilic collagen bundles. A thin layer of normal dermis (grenz zone) separates the epidermis from the dermal tumor. B, The well-differentiated neoplastic smooth muscle cells have palely eosinophilic cytoplasm, perinuclear vacuoles, and fibrillary cytoplasm. The intersecting smooth muscle bundles have entrapped brightly eosinophilic collagen bundles.

Nonsurgical ablative treatments have occasionally been used with variable results. Cryotherapy has been applied to the resection bed in several cases of tracheobronchial leiomyoma.[56,57] In a case of multiple piloleiomyomas in Reed syndrome, liquid nitrogen cryotherapy resulted in a marked improvement in the pain and size of the skin lesions.[58] Laser ablation has been advocated for some deep mucosal lesions, and for larger cutaneous lesions where surgical excision might be

cosmetically unacceptable.[59,60,61]

Contraction of the smooth muscle in leiomyoma combined with the presence of the increased number of nerve elements has been proposed as mechanisms for the pain associated with these lesions.[12,26,62] Smooth muscle is primarily under the control of the autonomic nervous system, and increased cytoplasmic calcium concentration is the primary stimulus for the contraction of smooth muscle.[63,64] Therefore, smooth muscle relaxing agents, such as receptor inhibitors or calcium channel blockers, have been used to reduce the pain of leiomyomas.[62,65,66] Injection of botulinum toxin into the lesion has shown mixed results for symptomatic relief.[63]

Prognosis

The morbidity associated with untreated cutaneous leiomyoma is primarily from pain, either spontaneous or evoked by cold and or touch. Multiple piloleiomyomas also can be cosmetically disfiguring. Following surgical excision of solitary lesions, the prognosis is excellent and recurrences are rare.[10]

Histopathology

Piloleiomyomas are poorly demarcated, nonencapsulated, dermal nodules of intersecting fascicles of smooth muscle with entrapped collagen bundles (Figure 79.2).[67,68] *(Print pagebreak 523) (Print pagebreak 524)* The tumor cells are well-differentiated spindle cells with elongated, blunt-ended nuclei, perinuclear vacuoles, and eosinophilic fibrillary cytoplasm.[67,68] Neoplastic cells with enlarged, hyperchromatic nuclei are encountered occasionally.[67,68] There may be rare mitoses.[67] Tumor cells have fuchsinophilic cytoplasm using Masson trichrome stain,[68] and their smooth muscle nature may be confirmed using immunohistochemical staining using antibodies to desmin, smooth muscle actin, and caldesmon.[67] The epidermis over the tumor may be hyperplastic, and a thin band of normal dermis (grenz zone) usually separates the epidermis from the neoplasm.[68]

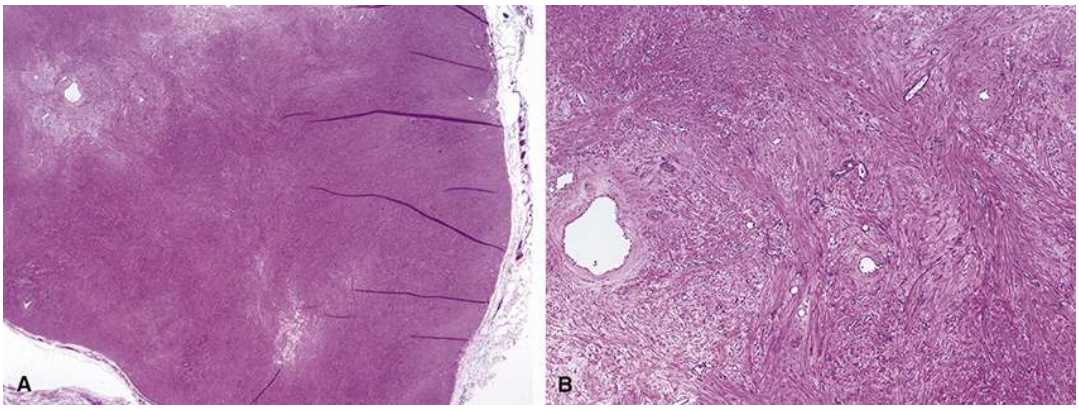

FIGURE 79.3 A, This angioleiomyoma has the typical sharp circumscription of these neoplasms. B, Cytologically bland smooth muscle cells form fascicles arrayed around blood vessels.

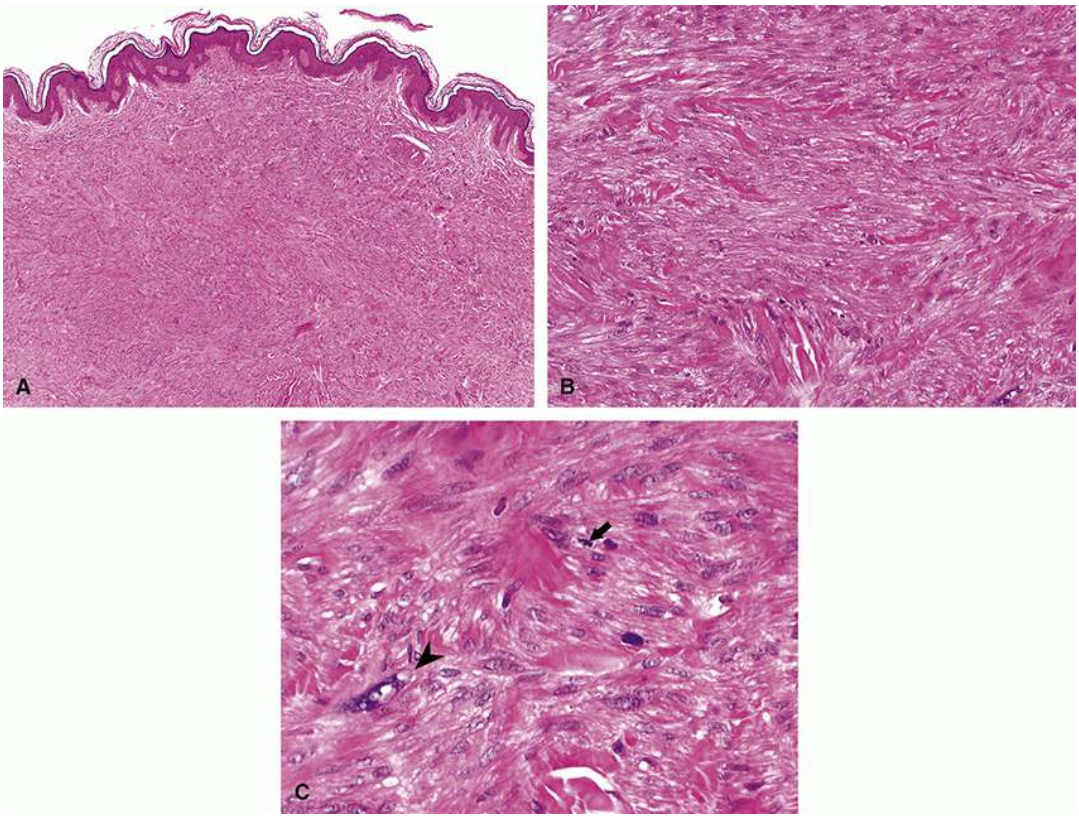

FIGURE 79.4 A, This dermal atypical smooth muscle tumor is separated from the epidermis by a thin layer of normal dermis. B, Brightly eosinophilic collagen bundles are entrapped by fascicles of well-differentiated smooth muscle cells with more lightly eosinophilic cytoplasm. C, Tumor cells have elongated nuclei with blunt ends. Atypical smooth muscle neoplasms differ from piloleiomyomas by nuclear atypia (arrowhead) and more frequent mitotic figures (arrow).

Angioleiomyomas are sharply circumscribed dermal or subcutaneous nodules of cytologically bland smooth muscle cells arranged in fascicles arrayed around blood vessels (Figure 79.3).[68,69] Mitotic figures are infrequent.[69] The neoplastic cells express smooth muscle actin, muscle-specific actin, desmin, calponin, and sometimes caldesmon.[68,69]

Atypical smooth muscle tumors, often termed “cutaneous leiomyosarcomas,” are dermal tumors usually composed of well-differentiated smooth muscle cells forming fascicles (Figure 79.4).[70,71] The tumors typically infiltrate the surrounding dermis and may extend into the subcutaneous fat.[71] Atypical smooth muscle tumors are differentiated from piloleiomyomas by greater cellularity, nuclear enlargement and hyperchromatism, and increased mitotic activity.[71] Smooth muscle actin, desmin, and caldesmon are typically expressed by tumor cells.[67,70] There may be scattered cells immunoreactive to cocktails of antibodies reactive to low- and high-molecular-weight cytokeratins.

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CHAPTER 80

Lipoblastoma and Lipoblastomatosis

Key Points

- Lipoblastoma and lipoblastomatosis are rare, benign, soft-tissue tumors of embryonal fat occurring primarily in children
- Lipoblastoma refers to a circumscribed encapsulated form, and lipoblastomatosis refers to a more diffuse, infiltrative form of the tumor
- This tumor is believed to arise from altered embryogenesis of human white fat resulting in the uncontrolled proliferation of lipoblasts well into the postnatal period
- Various types of cytogenetic aberrations including translocations, insertions, and derivatives are found in lipoblastoma
- It presents clinically as a painless, soft, lobulated, yellowish, white, or tan palpable mass that may be associated with swelling and erythema simulating cellulitis
- Complete surgical excision is the recommended treatment
- Recurrences have been reported in up to 46% of cases, mostly related to incomplete excision, especially in lipoblastomatosis

Lipoblastoma and lipoblastomatosis are rare, benign, soft-tissue tumors of embryonal fat occurring primarily in children younger than 3 years. They arise from the continued proliferation of lipoblasts in white fat after birth.[1,43]

Jaffe first used the term “lipoblastoma” in 1926 for lipomatous tumors containing immature fat cells, which did not metastasize.[2] In 1958, Vellios et al[3] applied the term “lipoblastomatosis” to these tumors. They noted the presence of adipocytes in various stages of differentiation and compared these with the temporal stages of embryonic white fat development based on morphologic criteria. They suggested that these tumors represent an arrest in the development of fat maturation primarily in areas of the body where postnatal fat maturation occurs, such as the axilla, mediastinum, and retroperitoneum. In 1977, Gibbs et al[4] applied the term “lipoblastomatosis” to all benign lipoblastic adipose tumors and used the term “lipoblastoma” for tumors of brown fat, otherwise known as hibernomas. More precise morphologic criteria for diagnosis were established in 1973 when Chung and Enzinger[5] distinguished two distinct forms of this same entity. They designated the term “lipoblastomatosis” for a more diffuse, infiltrative form of the tumor and reserved the term “lipoblastoma” for the more circumscribed encapsulated form. Aside from this difference, these two forms of the tumor have identical cell morphology histologically. In 2000, O'Donnell et al[6] argued that because lipoblastoma does not metastasize, the term *blastoma* was confusing. They proposed replacing it with the term “infantile lipoma.” However, the terminology proposed by Chung and Enzinger is still the most commonly used nomenclature.

Of the 410 cases of lipoblastoma and lipoblastomatosis reported in the literature to date, approximately 68% were encapsulated and represented lipoblastoma, and 32% showed a more diffuse growth pattern, more consistent with lipoblastomatosis.[7] Tumors occurred most frequently on the trunk and extremities (80%) and much less commonly on the head and neck (17%). Of the latter group, most were seen in the neck, with only 5% occurring on the face and head.

Lipoblastoma is a well-circumscribed encapsulated lesion.[7,8] It has been reported in patients from birth to 60 years of age, but the mean age at presentation is 3.2 years.[7] Nearly 80% of patients are younger than 3 years, and 94% are younger than 10 years. Only 2% are older than 20 years at presentation. Although some earlier reports suggested a strong male predominance of as high as 4:1,10 larger reviews have shown only a slight male predominance of 1.5:1.[7] The most common sites of involvement are on the extremities and trunk,[7,10,11,12] and less frequently in the abdomen, retroperitoneum, mediastinum, axilla, groin, inguinoscrotal, labia, vulva, and gluteal region. Occurrence on the head and neck is relatively uncommon.[7,10,11,13,14,15,16]

To date, only three cases of lipoblastoma have been described in the eyelid. Enghardt and Warren[17] reported a congenital lipoblastoma in a 13-month-old female patient with a mass in the eyelid anterior to the orbital septum. Adams et al[18] presented a

case of a 16-month-old male patient with a lipoblastoma in the eyelid and anterior lateral orbit associated with eyelid edema and strabismus. Singh et al[19] presented a rare case of a large congenital lipoblastoma of the scalp that extended into the brow and eyelid. Three additional cases involved the orbit. Seider et al[20] described a newborn infant with a congenital lipoblastoma involving the nasal cavity and orbit. Hwang et al[21] reported a 3-month-old infant with an orbital lipoblastoma since birth, 2 cm in size, and causing 4 diopters of astigmatism. A previous case of orbital lipoblastoma was described by Bernolet and Jaeger in 1949.[22] One case of lipoblastomatosis has been described extending from the eyelid into the anterior orbit.[7]

Diagnostic imaging of lipoblastoma and lipoblastomatosis can be helpful in clinical diagnosis. Ultrasound may demonstrate a diffuse to well-defined mass with weak heterogeneous *(Print pagebreak 527)* echogenicity.[23] High internal echoes represent cellular and septate areas, and low echoes represent myxoid and fatty areas. On radiologic imaging, the appearance depends on the amount of myxoid stroma and fibrous septa among the fat. On CT, lipoblastoma appear as a well-defined or diffuse, heterogeneous, hypodense mass. Areas of low attenuation represent fat,[24,25,26] and enhancement can be seen in areas of rich capillary network and in the interlobular septa.[27] MRI is the modality of choice to define the extent of the mass and the possibility of local invasion. T1-weighted images demonstrate a heterogeneous mass that is isointense to slightly hypointense to subcutaneous fat. T2-weighted images reveal a heterogeneous lesion with areas of high signal intensity.[28,29,30] Lesions become markedly hypointense with fat suppression.

Malignant transformation has not been documented in lipoblastoma or lipoblastomatosis. Recurrent tumors may transform into more mature lipomatous tumors, such as a lipoma.[9,31,32]

Etiology and Pathogenesis

Lipoblastoma is believed to arise from altered embryogenesis of human white fat.[32] This results in the uncontrolled proliferation of lipoblasts well into the postnatal period. Various types of cytogenetic aberrations including translocations and insertions have been found in lipoblastoma. Sandberg et al[33] were the first to demonstrate a translocation with a break point at chromosome locus 8q12 in a lipoblastoma and this has been confirmed in several subsequent reports.[34,35,36,37,38,39] Batanian et al[35] described a recurrent common chromosomal break point in a number of rearrangements at 8q11.2-8q12, and the critical region of chromosome 8q11.2 seen in lipoblastomas may contain an important gene that plays a role in the pathophysiologic pathway of the tumor.[35]

It has been proposed that the developmental gene pleomorphic adenoma gene 1 (*PLAG1*) at 8q12 may be the putative target oncogene responsible for lipoblastoma development.[40,41] Approximately 70% of lipoblastomas have a rearrangement of the *PLAG1* gene located in 8q12.1, possibly resulting in transcriptional upregulation of this oncogene through a promoter swapping event, while 18% of lipoblastomas present polysomy for chromosome 8 with or without a *PLAG1* rearrangement.[42,43,44]

Coffin et al[45] reported the presence of central nervous system disorders such as seizures, autism, and developmental delay, congenital anomalies, Sturge-Weber syndrome, or a family history of lipomas in 17% of 59 patients with lipoblastoma. They suggested that these observations raise the question of whether predisposing genetic or other constitutional factors contribute to the development of lipoblastoma or whether this tumor is indicative of a syndrome.

Clinical Characteristics

The most common clinical manifestation of lipoblastoma/lipoblastomatosis is a painless, soft, lobulated, yellowish, white, or tan palpable mass.[7,8], It may be associated with swelling and erythema simulating cellulitis.[7] Most lesions are 5 cm or less in size, but larger tumors have been reported. When symptoms do occur, they tend to be associated with a mass effect in the area of tumor growth.[38] In the eyelid, this can manifest as upper eyelid ptosis (Figure 80.1).[7] Growth may be slow or rapid but generally is slowly progressive. Most tumors occur superficially, but occasionally they can appear as deep lesions that cause organ dysfunction, such as respiratory insufficiency when the lesion is located in the neck,[24,46,47,48,49,50,51] or even hemiparesis.[52] In rare instances, these tumors may rupture, resulting in a significant inflammatory reaction.[47]

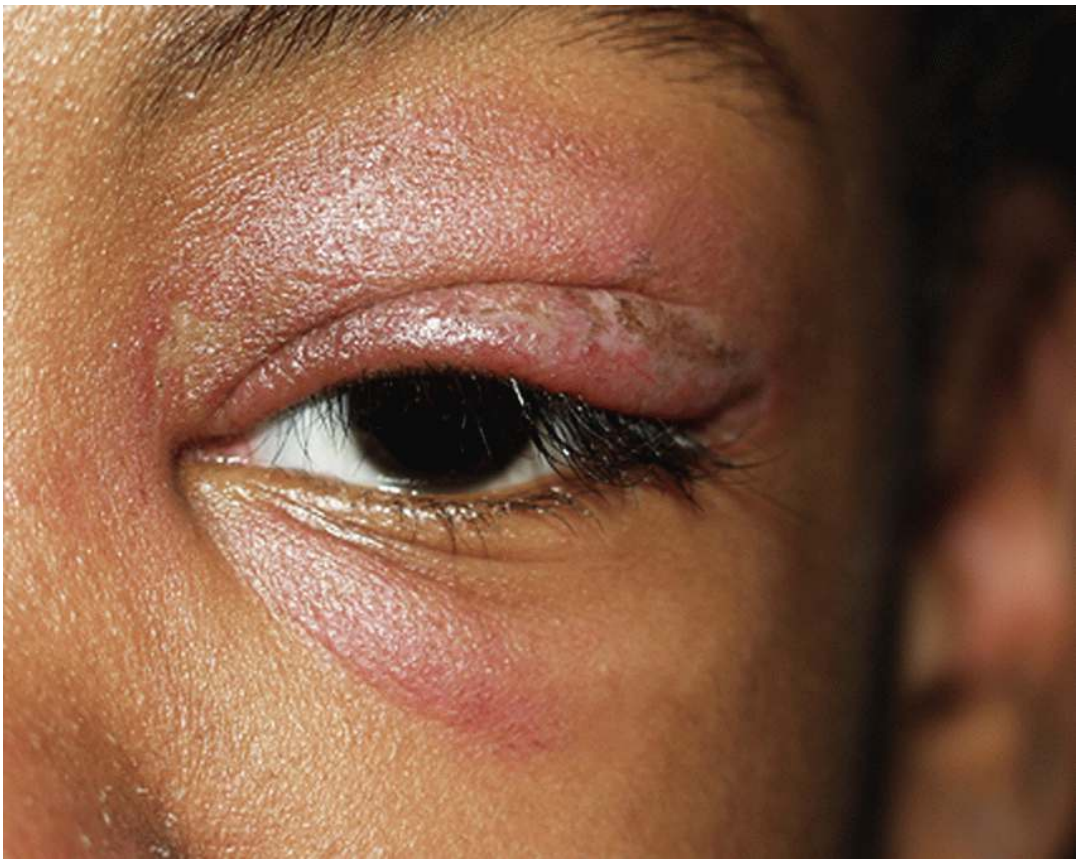

FIGURE 80.1 Lipoblastomatosis of the left upper and lower eyelids with erythema, crusting, and mechanical ptosis.

Differential Diagnosis

The differential diagnosis for lipoblastoma includes other adipose-derived mesenchymal tumors. These include lipoma, fibrolipoma, hibernoma, liposarcoma, and fibroliposarcoma, as well as a dermoid cyst, teratoma, and fibrosarcoma. Most teratomas and dermoid cysts contain calcifications or cystic areas in addition to soft-tissue and fatty elements. Hibernomas are mostly seen in the 3rd to 4th decade of life, frequently with prominent branching and serpentine vascular structures. Malignant myxoid liposarcomas are most similar histologically, but they are extremely rare in patients younger than 10 years[14,53,54] and occur most often during the third to sixth decades of life.[55] Myxoid liposarcomas also show a more hypocellular spindle cell proliferation having a predominantly myxoid appearance with atypical bizarre lipoblasts, nuclear cellular atypia, necrosis, and mitoses.[56,57]

Treatment

While both lipoblastoma and lipoblastomatosis are considered benign, complete surgical excision is the recommended treatment. In most reports, recurrence rates have been seen in up 28% of cases,[5,58,59,60] but Coffin et *(Print pagebreak 528)* al[45] reported recurrence in 46% of 30 patients with lipoblastoma. Most recurrences are related to incompletely excised tumors or in those where complete excision is not possible for functional reasons. Lipoblastomatosis has a higher recurrence rate because of its infiltrative nature and the greater difficulty in achieving complete excision. Given the relatively high recurrence rate in incompletely resected tumors, close follow-up is recommended for at least 2 to 5 years.[1,59,61]

Prognosis

After complete surgical resection, most cases of lipoblastoma and lipoblastomatosis do well. Several cases of lipoblastoma have been reported to undergo spontaneous regression,[62,63] but this is a very rare event. A case of maturation of a lipoblastoma to mature fat has also been reported.[64] Following incomplete excision, recurrence has been reported in from 0% to 46% of cases and may occur after several years, so close follow-up is necessary.[59,65]

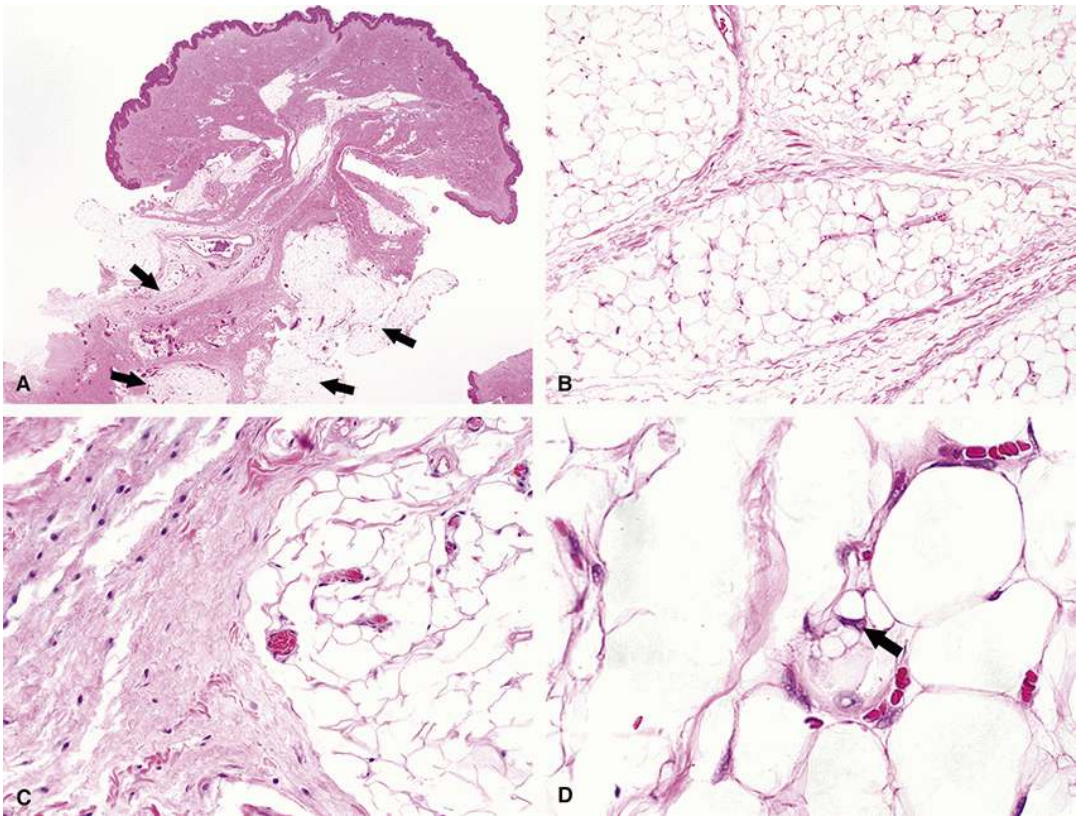

FIGURE 80.2 A, A well-differentiated lipoblastoma in the subcutis (arrows). B, Fibrovascular septa separate the adipocytes into lobules. C, The tumor cells have a variable appearance ranging from primitive stellate or spindled mesenchymal cells (preadipocytes) to mature adipocytes. D, The number of lipoblasts (arrow) is variable, and they may be rare in mature lipoblastomas.

Histopathology

Cutaneous lipoblastomas are usually circumscribed tumors composed of lobules of adipocytes separated by fibrovascular septa (Figure 80.2A and B).[8,66,67,68] The fat cells feature a spectrum of differentiation ranging from primitive stellate or spindled mesenchymal cells (preadipocytes) to mature adipocytes (Figure 80.2C).[66,67] The proportion of cells in different maturation stages varies from one case to another and between lobules. Primitive areas typically appear myxoid. The adipocyte lobules have a fine vascular network (Figure 80.2B and C). Tumors composed of mature fat cells resemble fibrolipoma but are distinguished by rare lipoblasts (Figure 80.2D).[66] Lipoblasts have indented or scalloped nuclei and mono- or multivacuolated cytoplasm and must be distinguished from mimics such as adipocytes with intranuclear vacuoles (lockern cells) and lipoblast-like cells resulting from starvation, malnutrition, or trauma.[69] The lipoblasts in lipoblastoma do not exhibit cytological atypia or mitotic figures, distinguishing them from those in liposarcoma.[68] *(Print pagebreak 529)* Primitive mesenchymal cells may express desmin,[8,67] CD34 is expressed by adipocytes and vascular endothelial cells,[8] and adipocytes are immunoreactive using antibodies to S100 protein[66] and CD56.[66] Cutaneous lipoblastomatosis differs from lipoblastoma by infiltrating the dermis and underlying muscle.[67]

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CHAPTER 81

Lipoid Proteinosis

Key Points

- Lipoid proteinosis is a rare autosomal recessive dermatosis that presents with dermatological, ophthalmological, otolaryngological, and neurological manifestations
- It is a multisystem disease due to multiple mutations in the *ECM1* gene
- A hoarse cry is usually the first clinical sign, usually present at birth
- Enlargement of the tongue with a thickened frenulum manifests as restricted tongue movements
- Moniliform blepharosis is considered a pathognomonic feature presenting as small yellow-white beaded papules on the eyelid margins
- There is no cure for lipoid proteinosis
- Medical treatment for skin lesions includes acitretin, dimethyl sulfoxide, steroids, D-penicillamine, and intralesional heparin
- Prognosis for life is good, but there is usually significant effect on quality of life

Lipoid proteinosis (LP), also known as Urbach-Wiethe disease and hyalinosis cutis et mucosae, is a rare autosomal recessive dermatosis that usually presents with dermatological, ophthalmological, otolaryngological, and neurological manifestations. It was first described by Siebenmann in 1908[1] and later established as a distinct clinical and histologic entity by Urbach and Wiethe in 1929.[2,3] It is characterized by generalized infiltration of amorphous hyaline material in the skin, vocal cords, mucosa, and multiple internal organs.[3,4,5]

The clinical diagnosis is based on the triad of early-onset hoarse voice, typical skin lesions, and beaded papules on the eyelids. Various laboratory tests can help confirm the diagnosis. The skin tissue strongly stains with PAS because of the presence of hyaline. Immunohistochemical staining for antibodies against the EMC1 protein is reduced in LP.[4] Staining with anti-type III, anti-type IV, or anti-type VII collagen antibodies reveal bright, thick bands at the dermal-epidermal junction. More than half of the patients also show bilateral symmetrical damage in the amygdaloid region of the brain on a CT scan.[6,7]

Etiology and Pathophysiology

LP is a multisystem disease due to multiple mutations in the *ECM1* gene on chromosome 1 at 1q21.2 encoding extracellular matrix protein 1 (ECM1), present in the epidermis. This is a secretory glycoprotein expressed in the dermis and other tissues.[4,8,9,10] More than 50 mutations in the *ECM1* gene have been documented including missense, nonsense, frameshift, or splice site mutations with the majority occurring in exons 6 and 7.[4,10,11,12,13] Hamada et al[14] reported that patients with mutations in exon 7 of the *ECM1* gene tend to have a milder phenotype as compared with patients having mutations in other parts of the gene.

The ECM1 protein functions in epidermal differentiation, binding of dermal collagen and proteoglycans, and regulation of angiogenesis.[15] Reduced expression of this protein results in aberrant deposition of eosinophilic hyaline-like material in the skin and viscera, leading to the clinical features of this disease.[16,17]

Clinical Presentation

The clinical manifestations of LP involve respiratory, cutaneous, and neurologic tissues, but any organ can be involved. A hoarse cry is usually the first clinical sign, typically present at birth or shortly thereafter due to infiltration of the laryngeal mucosa.[18,19,20,

[21] Enlargement of the tongue with a thickened frenulum manifests as restricted tongue movements and is another reliable clinical sign of LP. In addition, there are yellow-white submucous infiltrates on other mucosal surfaces such as the pharynx, soft palate, and esophagus. Dental anomalies and dental caries also may be seen.[16,20] Skin lesions are a later finding appearing as blisters and erosions in early childhood and progressing to more distinct yellow waxy and warty papules and nodules, hyperkeratosis, facial and extremity spontaneous or trauma-induced acneiform or pocklike scars, and alopecia.[22,23]

Ocular manifestations can involve any part of the eye and ocular adnexa.[24] Moniliform blepharosis is considered a pathognomonic feature of LP and presents as small yellow-white beaded papules on the eyelid margins and skin (Figure 81.1).[25] Other less common ophthalmic findings include hyaline deposits on the iris, cornea, and the trabecular meshwork. Chorioretinitis, conjunctival nodules, uveitis, cataract, and lens subluxation are other possible findings.[26,27,28,29] Focal degeneration of the macula and drusen formation in Bruch membrane is seen in about 30% to 50% of patients.[29] The lacrimal gland can be infiltrated with hyaline material resulting in dry eyes.[24] Open-angle glaucoma and retinitis pigmentosa have also been reported.[29] Infiltration of meibomian glands and glands of Zeiss and Moll is seen, often associated with madarosis, trichiasis, and sometimes *(Print pagebreak 532)* distichiasis.[16,24] Cystic punctal lesions and nasolacrimal duct obstructions are other rare complications of LP.[28,30,31,32,33] Neurological manifestations usually present as migraines, seizures, mental retardation, anxiety, depression, and panic attacks,[7] associated with intracranial calcifications within the amygdala or the temporal lobes.[34]

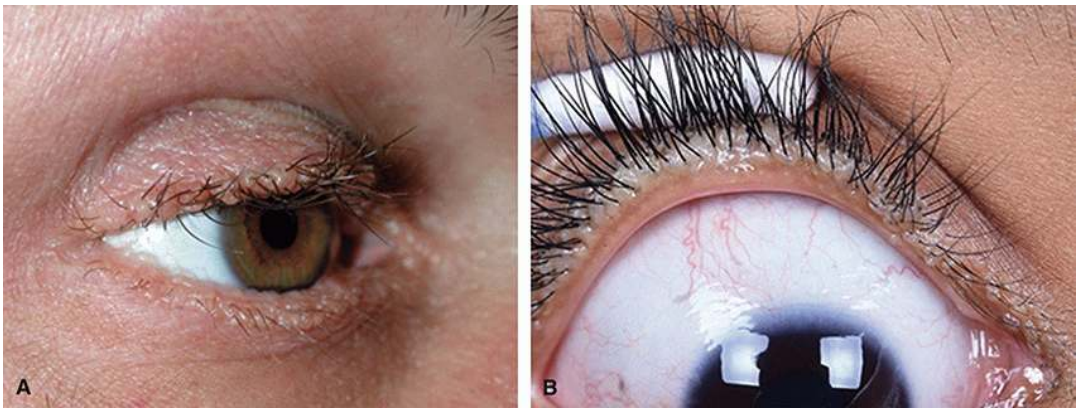

FIGURE 81.1 Moniliform blepharosis of the eyelid margins in lipoid proteinosis. A, Tiny beaded papules along the upper and lower eyelid margins. (Courtesy of Dr. Alan McNab.) B, Small papules on the medial upper eyelid margin. (Courtesy of Dr. Mohammad Javed Ali.)

Differential Diagnosis

The diagnosis of LP is generally straightforward with the presence of the typical findings of hoarseness and moniliform blepharosis. The diagnosis is confirmed by histopathology, which shows deposition of periodic acid-Schiff-positive hyaline material at the dermal-epidermal junction, along blood vessels, and along the adnexal epithelium.[16] The differential diagnoses include erythropoietic protoporphyria, lichenmyxedematosus, amyloidosis, hyalinosis, and blepharitis.

Treatment

There is no cure for LP. Many treatments have been used, but none have resulted in sustained benefit.[16] Medical treatment for the skin lesions has been reported with oral acitretin at an initial dose of 0.5 mg/kg/d.[18,35] After 6 months of treatment with oral acitretin, symptoms were partly improved and there was an improvement in voice hoarseness, but no effect on the skin lesions was reported. Complications included dry mouth and lips and scaly skin. Recurrence occurred after the discontinuation of treatment. Oral dimethyl sulfoxide, steroids, D-penicillamine, and intralesional heparin have also been used with inconsistent results.[36]

CO_2 laser ablation of the eyelid and vocal cord lesions were reported to help in some patients,[37,38] but the results were not corroborated in a large case series.[39] Cutaneous lesions have also been treated with dermabrasion and chemical peeling.[36,38]

Prognosis

Patients with LP have a normal life span but some manifestations, such as laryngeal involvement, can lead to airway compromise necessitating a tracheostomy.[28] The disfiguring cutaneous lesions and the permanent hoarseness often lead to significant impairment in quality of life.

Histopathology

LP manifests histologically as hyaline eosinophilic material accumulating in the dermal connective tissue, in the basement membrane around sebaceous glands, and surrounding dermal blood vessels, eccrine sweat glands, apocrine glands, and nerves (Figure 81.2).[40,41,42,43,44,45,46] The hyaline deposits stain positively using periodic acid-Schiff reagent and resist diastase digestion.[45] Deposits are green-yellow with van Gieson stain,[40] dark red (fuchsinophilic) with Mallory trichrome stain,[40] and red using Fat Red [40] and Oil Red O stains.[45] Congo red stain for amyloid is negative, while Alcian blue and Hale colloidal iron stains for glycosaminoglycans are variably positive.[45,47] Collagen type IV and laminin are detected immunohistochemically in early but not well-developed lesions.[47]

The earliest histological manifestation of LP in the skin is wall thickening of upper dermal capillaries due to deposition of hyaline material beneath the basement membrane.[45] Concentric, laminated rings of the hyaline material develop around the vessels (Figure 81.2A and C) culminating in adjacent vessels' fusion.[45] Early lesions also have lamellae of hyaline material along hair follicles, nerves (Figure 81.2B), and sweat glands (Figure 81.2B).[47]

Well-developed cutaneous LP lesions have masses of amorphous eosinophilic material in the upper and mid *(Print pagebreak 533)* dermis.[47] The deposits initially push aside the normal dermal connective tissue, but the connective tissue is incorporated within the deposits in the late stages.[45] Sebaceous glands are unaffected by their basement membrane thickening, while eccrine sweat glands become atrophic and eventually completely hyalinized.[45] Apocrine glands have surrounding hyaline lamellae, but they do not become atrophic.[45] The epidermis usually has hyperkeratosis and pigmentary incontinence in the basal layer.[46]

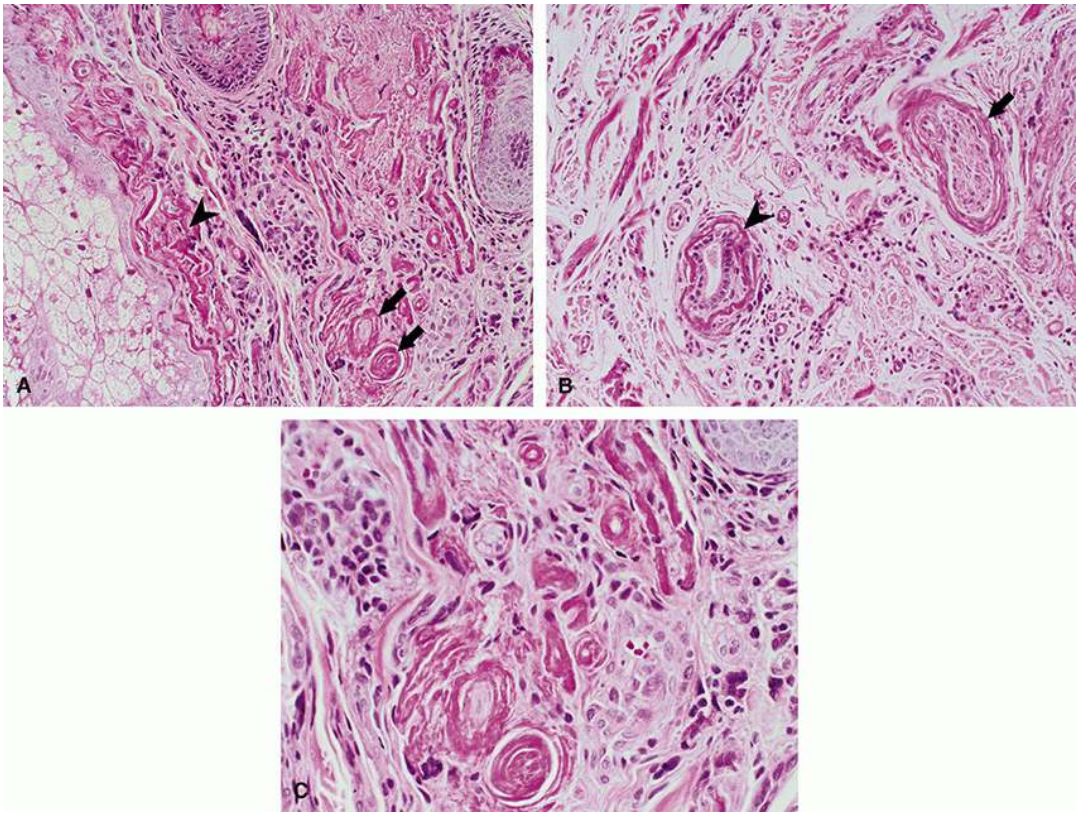

FIGURE 81.2 A, This lipoid proteinosis example shows lamellae of hyaline eosinophilic material adjacent to a hair follicle seabceous gland (arrowhead) and concentrically surrounding dermal capillaries (arrows). B, Hyaline eosinophilic deposits surround an eccrine sweat gland (arrowhead) and nerve (arrow). C, Hyaline eosinophilic material encompasses all of the dermal capillaries, several of which have occluded lumens.

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CHAPTER 82

Lipoma

Key Points

- Lipomas are the most common benign soft-tissue mesenchymal tumors
- They are classified into subtypes depending on the types of tissues, including simple, spindle cell lipoma, hibernoma, pleomorphic lipoma, angiolipoma, chondroid lipoma, myolipoma, myxolipoma, myelolipoma, fibrolipoma, intramuscular lipoma, and osteolipoma
- Simple lipoma is the most common form, composed of mature adipocytes
- Spindle cell lipomas are rare, characterized by an admixture of adipocytes and small uniform spindle cells
- The etiology is not well established, but theories include chronic intermittent compression, an origin from lipoblastic embryonic cell nests, fatty degeneration, hormonal causes, infection and infarction, metaplasia of muscle cells, and chronic irritation
- Genetic aberrations have been associated with many types of adipocytic tumors including chromosomal aberrations involving 12q13˜q15
- Lipomas present as a slow-growing, painless, soft, fluctuant, lobulated, well-circumscribed, mobile subcutaneous mass with freely mobile overlying skin
- The usual treatment of lipoma is complete surgical excision
- The prognosis for benign lipomas is excellent and recurrence following surgical excision is uncommon

Lipomas are the most common benign soft-tissue mesenchymal tumors.[1] They are slow-growing, benign adipose lesions that form soft, lobulated masses enclosed by a thin, fibrous capsule. They have a prevalence rate of about 2.1 per 1000 population[2] and occur mostly in the fifth and sixth decades of life.[3] Lipomas are uncommon in children. Males are affected more frequently than females in a ratio of about 2.5 to 3:1.[4] Although lipomas may develop in any organ throughout the body, only 13% occur in the head and neck area.[5] Within the head and neck region, the most common location is the cheek, followed by the tongue, buccal mucosa, lip, and neck. Occurrence on the eyelid is relatively rare.

Lipomas are classified histopathologically into several distinct subtypes depending on the admixture of other types of tissues. These include simple lipoma, spindle cell lipoma, hibernoma, pleomorphic lipoma, angiolipoma, chondroid lipoma, myolipoma, myxolipoma, myelolipoma, fibrolipoma, intramuscular lipoma, and osteolipoma.[1] Among eyelid lipomas, the most common types are simple lipoma and spindle cell lipoma, but other described forms include fibrolipoma, intramuscular lipoma, and osteolipoma.

Simple lipoma is the most common form, accounting for 80% of head and neck lipomas.[4] They are composed of mature adipocytes and usually occur just under the skin, but occasionally may be deeper. Most are less than 5 cm in size. The most common locations include the upper back, shoulders, and abdomen, and in a review of 338 simple lipomas, 17% occurred in the head and neck.[4] The male to female ratio is about 2.5:1. Occurrence in the eyelid is very rare and only two cases of simple lipoma have been reported in this location.[6,7]

Spindle cell lipomas are rare tumors that were first described by Enzinger and Harvey in 1991,[8] characterized by an admixture of adipocytes and small uniform spindle cells. They are benign, painless, slowly growing subcutaneous tumors that occur most often on the upper back, shoulders, and posterior neck with a predilection for middle-aged men.[9] Rare cases have been reported in the orbit,[10,11,12,13] and one case was reported in the eyelid.[14]

Myolipoma of soft tissue was first described in 1991 by Meis and Enzinger[15] as a rare benign neoplasm characterized by the admixture of mature adipocytes and well-differentiated smooth muscle cells. They are seen predominantly in middle-aged to older

females in a male to female ratio of 16:1.[16] The most frequently affected sites are the retroperitoneum (47%), pelvis (15%), abdominal wall (12%), and intra-abdominal sites (9%). One case was reported in the eyelid.[17]

Fibrolipoma is an extremely rare subtype of lipoma found most commonly in males. They are characterized by the presence of adipose tissue and abundant amounts of fibrous tissues[18,19,20,21,22] and present clinically as a well-circumscribed, firm to soft, asymptomatic, slowly growing subcutaneous mass.[18,23] Transformation to liposarcoma has been reported in several cases of fibrolipoma.[23] One case was described in the eyelid.[24]

Angiolipoma consists of an admixture of mature fat and numerous small blood vessels and usually affects adolescent males.[25] This variant accounts for 6% to 17% of all lipomas, but is rare in the head and neck. Only two cases have been described involving the eyelids and two in the orbit.[26]

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Osteolipoma is a very rare variant of lipoma.[27] It is a type of lipoma that undergoes osseous metaplasia to become an ossifying lipoma or osteolipoma. Only a few cases affecting the head and neck are reported in the literature.[28] One case was described involving the upper eyelid as a nodular swelling that gradually increased in size over 5 years.[29] It presented as a 2 cm, firm, freely mobile, painless mass with a smooth surface that was initially diagnosed clinically as a dermoid cyst.

An intramuscular lipoma is a subgroup of lipoma usually seen in large muscles of the extremities and which diffusely invades skeletal muscles. They have also been referred to as infiltrating lipoma.[30] It is a rare variant that accounts for about 1.8% of all lipomas[31] and is very rarely reported in the small muscles of the head and neck.[32] Charles and Palu[33] reported a case of an unencapsulated intramuscular lipoma within the lower eyelid orbicularis oculi muscle consisting of mature adipocytes traversed with sheets of striated muscle fibers. A second case was described involving the upper eyelid orbicularis muscle by Buller et al.[34] Shiraki et al[35] reported a case of intramuscular lipoma in the medial rectus muscle of the orbit. The recurrence rate of intramuscular lipoma after treatment is higher than for most other types reported to be 3% to 62.5%,[36,37] most likely due to incomplete resection of the involved muscle.

A pleomorphic lipoma is characterized by the presence of spindle cells and bizarre hyperchromatic giant cells. It occurs most often in the neck and upper body of middle-aged to elderly males, but also has been reported in the orbit,[38,39,40,41] and the bulbar conjunctiva.[38,39,41] Although it is distinguishable from other variants of lipoma by floret-like cells as a specific histological feature, there is some debate as to the relationships of this tumor.[39] Ebrahimi et al[42] evaluated 146 cases of normal orbital and prolapsed orbital fat and found these cells in 16% and 43% of specimens, respectively. They concluded that floret-like cells may be present in orbital and prolapsed orbital fat as a degenerative process and that what has been called “orbital pleomorphic lipoma” may only be age-related orbital fat.

Nasopalpebral lipoma-coloboma syndrome is an extremely uncommon autosomal dominant craniofacial disorder characterized by upper eyelid and nasopalpebral lipomas, colobomas of upper and lower eyelids, telecanthus, a broad nasal bridge, broad forehead, widow's peak, flaring of medial eyebrows, telecanthus, and maxillary hypoplasia. Other features can include aplasia of the lacrimal puncta with epiphora, aberrant eyelashes, conjunctival hyperemia, opacities of the cornea and lens, and divergent strabismus. This syndrome was originally described as a familial disorder, but several sporadic cases have been described.[43,44,45,46] The condition is usually bilateral, but rarely it can be unilateral.

Excepting the nasopalpebral lipoma-coloboma syndrome, only 12 cases of lipoma have been reported in the eyelid.[3,6,7,14,17,24,29,33,34,47,48,49] Of these 12 cases, four were simple lipomas, two were intramuscular, two were a spindle lipoma, two were a fibrolipoma, one was a myofibroma, and one was an osteolipoma. The case by Thyparampil et al[48] was found on surgery to be a soft, yellow lesion surrounding the orbital septum with significant adhesions to the underlying conjunctiva and the levator aponeurosis laterally, so technically it can be considered to be a combined eyelid and anterior orbital lipoma.

Etiology and Pathogenesis

The etiology of lipomas and their variants is not well established. Some theories include chronic intermittent compression, an origin from lipoblastic embryonic cell nests, fatty degeneration, hormonal causes, infection and infarction, metaplasia of muscle cells, and chronic irritation.[21,25] Some studies reported that trauma may be a risk factor by causing injuring to the fibrous septa and connections between the skin and deep fascia, allowing the adipose tissue to proliferate rapidly.[50]

An association with genetic aberrations has been described for many types of adipocytic tumors. Chromosomal aberrations have been observed in the majority of lipomas, 50% to 65% of which involve chromosomal region 12q13˜q15.[51,52,53,54,55,56] The target gene for rearrangements involving 12q13-15 is *HMGA2*, which encodes a protein belonging to a family which is important for the regulation of chromatin structure and gene expression.[54,57,58] Genes derived from the fusion of the *HMGA2* with other

partners play a probable role in the development of benign mesenchymal tumors.[54] *HMGA2/LPP* (Lipoma Preferred Partner) is the most frequent gene aberration seen in lipomas.[57,58,59] However, it is not specific for lipoma suggesting that gene fusion as such may not be decisive for tumor cell differentiation, but may activate the regulatory pathway leading to the development of benign tumors.[54,60]

In simple lipomas, deletions of 13q are also reported in around 15% of cases. Spindle cell/pleomorphic lipomas show heterozygous deletions in 13q14,[61] a locus that contains the *RB1* gene and can lead to loss of RB1 protein expression.[62] Also, spindle cell/pleomorphic lipomas also show deletions in chromosome 16.[61]

Clinical Characteristics

Lipomas usually present as a slow-growing, painless, soft, fluctuant, lobulated, well-circumscribed, mobile subcutaneous mass with freely mobile overlying skin (Figure 82.1). They are mostly solitary lesions but rarely may be multiple. About 80% of lipomas are less than 5 cm in size,[4] but occasionally can present as a giant lipoma, between 10 and 40 cm diameter (Figure 82.2A).[63,64] On the eyelid, reported lipomas range from 1 to 2.5 cm in size. Females are affected slightly more frequently than males (55%), and the lesion usually has been present for 1 to 5 years, but in one case was present for 50 years.[17] Of the reported eyelid lipomas, the upper eyelid was involved in 78% of *(Print pagebreak 537)* cases, and the left side in 67%. Most patients were in the sixth to seventh decades of life with a mean age of 63.1 and a range of 47 to 82 years. Rarely, an eyelid lipoma can cause functional impairment such as ptosis.[7]

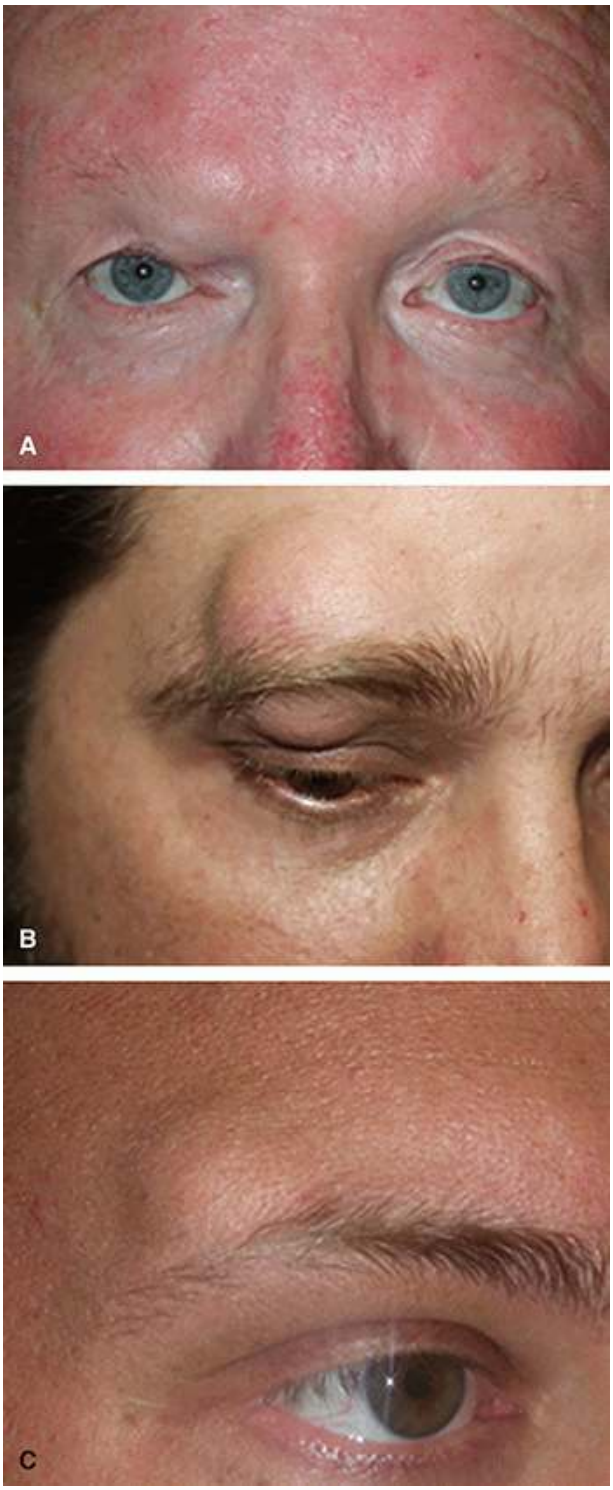

FIGURE 82.1 Lipomas of the brow and eyelid. A (Courtesy of Dr. Alan McNAb). C (Courtesy of Dr. Philip Custer).

Differential Diagnosis

For subcutaneous lipomas, the differential diagnosis most often includes a sebaceous cyst or abscess. Both lipoma and sebaceous cyst are rounded and fluctuant, but the sebaceous cyst originates in the dermis and is situated in the skin at the dermal-epidermal junction. They can be differentiated from lipomas by the presence of a central punctum and surrounding induration and the fact that lipoma is subcutaneous with freely mobile overlying skin. An abscess is usually associated with overlying cutaneous induration and erythema, which are not seen with lipomas.

Lipoma should also be distinguished from prolapsed orbital fat, nodular fascitis, erythema nodosum, nodular subcutaneous fat necrosis, sarcoidosis, rheumatic nodules, hematomas and infections, schwannoma, and other subcutaneous tumors and metastatic tumors. In addition, giant intramuscular lipomas should be differentiated from liposarcomas, metastatic carcinomas, and malignant

histiocytomas.[3,65,66]

The differential diagnosis of nasopalpebral lipoma coloboma syndrome includes other syndromes associated with eyelid colobomas such as Goldenhar syndrome, Treacher Collins syndrome, frontonasal dysplasia, and Delleman syndrome. These syndromes differ from nasopalpebral lipoma coloboma syndrome by various features such as preauricular tags, vertebral anomalies, epibulbar dermoid, and eyelid coloboma in Goldenhar syndrome; antimongoloid slant, lateral lower eyelids colobomas, microphthalmos, cataract, and nasolacrimal duct atresia in Treacher Collins syndrome; orbital hypertelorism, bifid nose, and median facial cleft in frontonasal dysplasia; and orbital cysts, agenesis of the corpus callosum, and lip defects in Delleman syndrome.[43]

MRI is very useful for the diagnosis of lipomas and in distinguishing them from other lesions. High signal intensity is seen on T1-weighted images and a relatively low signal on T2-weighted images similar to orbital fat. A fat-suppressed MRI is particularly beneficial for diagnosis. On CT images, lipomas appear as a nonenhancing hypodense mass.[23]

Treatment

The usual treatment of lipoma is complete surgical excision (Figure 82.2B). Removal is most often indicated for esthetic concerns or functional compromise of adjacent structures from focal compression. The tumor can usually be excised completely within its capsule. Since lipomas may be lobulated, it is essential to dissect and remove all lobules. When fatty tumors cause symptoms or grow large, a biopsy may be required for histopathologic examination to rule out more dangerous lesions such as liposarcoma. Following excision, the local recurrence rate is less than 5%.[3,67,68]

Nonsurgical techniques have included intralesional injection of triamcinolone acetonide that results in local *(Print pagebreak 538)* fat atrophy, and this is best utilized on smaller lesions.[69] Liposuction has been used in selected patients with lipomas,[70,71] but should be avoided in lesions with an atypical evolution or suspicious clinical presentation that might suggest a more ominous diagnosis such as liposarcoma.[72]

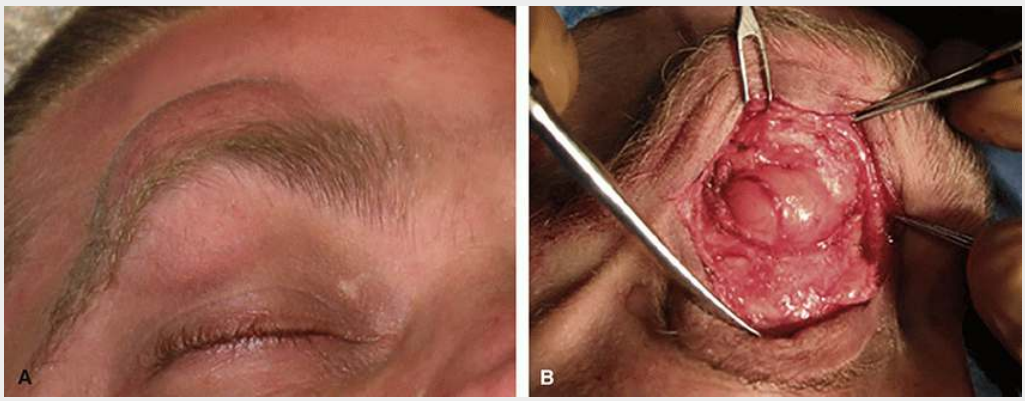

FIGURE 82.2 A, Massive lipoma involving the right upper eyelid and brow. B, Surgical excision of the lipoma in A through an upper eyelid crease incision.

Prognosis

The prognosis for benign lipomas is excellent. Recurrence following surgical excision is uncommon but may develop if the excision is incomplete.

Histopathology

Conventional cutaneous lipomas are sharply circumscribed, thinly encapsulated masses formed by sheets of mature adipocytes with thin, incomplete fibrous septa containing blood vessels (Figure 82.3).[73,74] The adipocytes have uniform nuclei without atypia and may be slightly larger than the adipocytes in adjacent subcutaneous tissue.[73] Dermal lipomas have scattered groups of mature adipocytes between collagen bundles and are less circumscribed than conventional lipomas (Figure 82.4).[75] The histological features of other lipoma variants are described in detail elsewhere.[73,74,75]

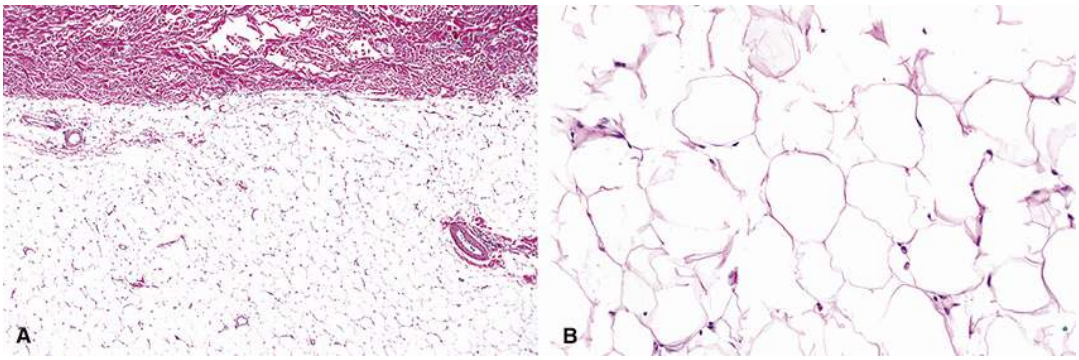

FIGURE 82.3 A, This conventional lipoma is sharply circumscribed and composed of mature adipocytes with thin, incomplete fibrous septa containing blood vessels. B, The adipocyte nuclei are uniform and without atypia.

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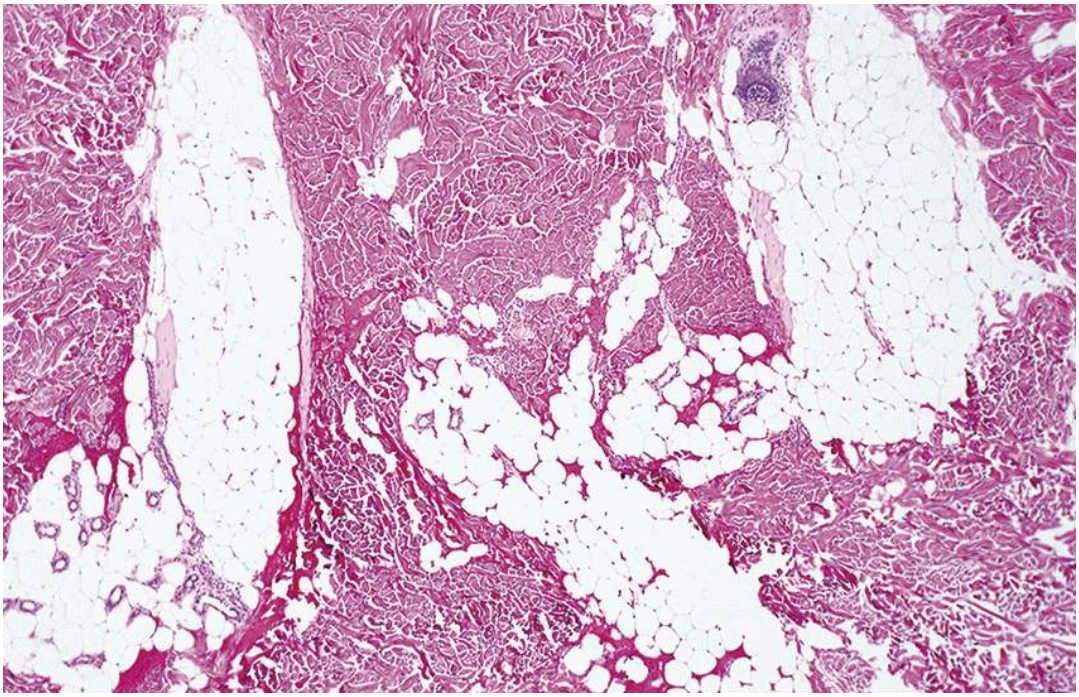

FIGURE 82.4 Dermal lipomas feature scattered groups of mature adipocytes between collagen bundles and are less circumscribed than conventional lipomas.

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CHAPTER 83

Lupus Erythematosus

Key Points

- Lupus erythematosus (LE) is a multisystem, chronic autoimmune disease with a wide spectrum of presenting symptoms
- Cutaneous manifestations appear in 72% to 85% of patients with SLE, and in 23% to 28% it can be the presenting sign of the disease
- Acute cutaneous LE is characterized by a butterfly rash over both cheeks, seen in 87% of patients
- Discoid LE is a chronic condition that presents as well-demarcated, scaly, erythematous macules or papules that gradually develop into indurated discoid plaques
- LE is caused by dysfunction in the immune system, involving loss of self-tolerance through the production of autoantibodies
- Sunlight can precipitate cutaneous disease de novo or it can aggravate existing lesions
- Eyelid lesions often begin as erythematous scaly maculae or papules that gradually grow peripherally into larger discoid plaques and may be associated with blepharitis and madarosis
- Management involves avoidance of UV exposure and topical steroids, tacrolimus, antimalarial drugs, or immunosuppressant agents
- The prognosis for cutaneous LE depends on the specific clinical variant and on the presence and severity of any associated systemic manifestations
- 5% to 10% of patients with CLE will evolve to SLE over 5 years

Lupus erythematosus (LE) is a multisystem, chronic autoimmune disease with a wide spectrum of presenting symptoms ranging from mild manifestations in localized cutaneous LE (CLE) to severe, life-threatening systemic LE (SLE) with involvement of internal organs.[1] In Europe, the prevalence of SLE is estimated to be 39.2 cases per 100,000 individuals, and the annual incidence rate is 1 to 3.8 per 100,000 individuals.[2,3] Cutaneous manifestations appear in 72% to 85% of patients with SLE, and in 23% to 28% it can be the presenting sign of the disease.[4] Moreover, isolated CLE, while rare, is still several times more common than SLE and can occur in the absence of systemic disease.[5]

CLE may present in various forms and it must be determined if it is isolated or a manifestation of SLE. The association with SLE varies depending upon the specific phenotype of CLE. The association has been reported at 100% in acute cutaneous lupus erythematosus (ACLE),[6] to 50% in subacute cutaneous lupus erythematosus (SCLE),[7] to only 5% for localized discoid lupus erythematosus (DLE).

In 1982, the American College of Rheumatology (ACR) developed a widely used classification of criteria for the diagnosis of SLE.[8] The ACR classification included 11 clinical and laboratory criteria, including four cutaneous features (malar rash, discoid lesions, mucosal ulcers, and photosensitivity). However, skin features seen in CLE occur with a broader spectrum of clinical presentations beyond those listed in the ACR criteria for SLE.[9] In 2012, the Systemic Lupus Collaborating Clinics (SLICC) revised the ACR criteria to comprise 17 clinical and immunological criteria, including some minor revisions of the cutaneous criteria, omitting photosensitivity, and adding nonscarring alopecia.[10]

Criteria for the diagnosis of the subtypes of CLE are still largely based on the classification system proposed by Gilliam in 1981.[11] CLE was divided into LE-specific lesions and LE-nonspecific lesions.[12] LE-nonspecific lesions included findings that are not usually characteristic of SLE and may be present in other diseases. These include Raynaud's phenomenon, periungual telangiectasias, livedo reticularis, and leukocytoclastic vasculitis.[12,13] The phenotypes included under the umbrella of LE-specific

lesions encompass several subtypes defined by clinical features, the average duration of the cutaneous lesions, histologic findings, as well as laboratory abnormalities. These subtypes include acute, subacute, and chronic CLE.[11] Chronic CLE included several subgroups: DLE, LE profundus (LEP), and chilblain LE (CHLE). In more recent years, new subtypes of CLE have been added, including LE tumidus (LET),[14,15] although there is still no agreement whether this form should be considered as a subtype of CCLE or should be differentiated as a separate category of CLE.[16,17]

Acute Cutaneous Lupus Erythematosus

ACLE is characterized by a transient malar, or "butterfly" rash, over both cheeks, induced by sun exposure, seen in 87% of patients, and sometimes associated with fine surface scales and/or edema.[1] A discoid rash can be seen in 20%, and oral ulcers in 33%. The condition may be associated with diffuse hair thinning.[6] ACLE typically presents in the third decade of life[12] and is frequently associated with active SLE.[18,19] It can be associated with arthritis, renal disorders, or neurologic involvement in 20% to 60% of cases.

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Subacute Cutaneous Lupus Erythematosus

SCLE occurs primarily in young to middle-aged women.[17] It presents clinically with a photosensitive malar rash in 30% to 40% of cases, which can either be annular or papulosquamous or occasionally with features of both.[12,20] The annular type is characterized by scaly annular erythematous plaques, which tend to coalesce.[17] Lesions occur in sun-exposed areas of the throat, upper back, and the extensor surfaces of arms, generally with sparing of the face and scalp. About 50% of cases meet the criteria for SLE,[21] but most of these patients usually have only mild systemic symptoms, and renal or neurologic involvement is seen in 4% to 20% of these patients.[1]

Chronic Cutaneous Lupus Erythematosus

Chronic cutaneous LE (CCLE) includes four subtypes that include DLE, LEP, CHLE, and LET. They differ by relatively minor clinical and histopathologic features. Unlike ACLE and SCLE, CCLE only rarely shows systemic involvement.[22]

Discoid lupus erythematosus (DLE) - Discoid lesions are the most common photosensitive rashes seen in CCLE, occurring in 90% of patients.[1] They occur more frequently in females in their fourth and fifth decades of life.[17] Localized DLE typically involves the head and neck, whereas generalized DLE occurs both above and below the neck. DLE lesions present as well-demarcated, scaly, erythematous macules or papules that gradually develop into an indurated discoid plaque.[12,23] Hair follicles become involved resulting in scarring alopecia. Rarely, squamous cell carcinoma can occur within a DLE lesion.[24]

Lupus erythematosus profundus (LEP) - LEP, also known as lupus erythematosus panniculitis, presents as a painful firm, tender, subcutaneous nodules in areas of increased fat deposition, such as the upper arms and legs, face, and breasts. They run a chronic course with episodes of remission and exacerbation, finally healing as depressed, atrophic plaques.[19,24] Occasionally, systemic or other forms of cutaneous LE may occur concurrently with LEP. Several cases have been associated with dermatomyositis.[25]

Chilblain lupus (CHLE) - Chilblain lupus is a rare form of CCLE that presents as painful, pruritic, infiltrative, violaceous erosions or ulcerations on skin areas exposed to cold, including the fingers, toes, nose, and ears. Involvement of the face is uncommon. Lesions tend to improve during warmer months. Two-thirds of patients may also have hypergammaglobulinaemia. Most cases are sporadic, but there have been familial cases inherited in an autosomal dominant manner.[26] About 20% of these patients will eventually develop features of SLE.[27]

Lupus erythematosus tumidus (LET) - Lupus tumidus is another subtype of chronic CCLE. It occurs mostly in men and is characterized by photosensitive, elevated, erythematous, and edematous lesions on the face and neck.[28] It is considered to be the most benign form of CLE, rarely associated with SLE. Skin lesions have an annular or semiannular appearance without scales, ulceration, or crust formation. Lesions heal without scarring or postinflammatory pigmentary changes.[29] Drugs are considered to be minor risk factors for LET, reported to be associated with infliximab, adalimumab, etanercept, thiazide diuretics, and bortezomib.[29]

Etiology and Pathophysiology

Lupus erythematosus is caused by dysfunction in the adaptive and innate immune system, involving a loss of self-tolerance through the production of autoantibodies.[30] Skin lesions in CLE can be induced by both UVB (290-320 nm) and UVA (320-400 nm) radiation.[31,32,33] Sunlight can precipitate cutaneous disease de novo or it can aggravate existing lesions. Also, phototherapy (UVB)

and tanning beds (UVA) have been reported to either induce or exacerbate SLE.

UV light has multiple effects on living tissue and molecular targets include DNA, RNA, proteins, and lipids. It can induce the binding of antibodies to selected nuclear antigens associated with LE and photosensitivity.[31] UV radiation can also induce apoptosis in keratinocytes by a variety of mechanisms including ligand-independent activation of membrane death receptors, sensitization of keratinocytes to TNF-induced apoptosis, DNA damage, or through the mitochondrial pathway.[31] Apoptotic cells accumulate in the epidermis of patients with cutaneous LE after UV irradiation,[34,35] It has been proposed that the biochemical processes of apoptosis can generate novel antigens that can be targeted by autoantibodies.[36,37] Proteins phosphorylated during apoptosis become targets for autoantibody production in patients with SLE, and these might be important in the initiation of autoimmune responses.[31]

This model of the pathogenesis of CLE originally proposed by Norris[38] presupposes an abnormal susceptibility to UV light resulting in altered cytokine expression and induction of increased keratinocyte apoptosis, the presence of antibodies with appropriate specificities targeting keratinocyte components, and the presence of activated lymphocytes specific for autoantigens.[31] Since this model was proposed, new data have been presented supporting this concept and uncovering genetic abnormalities in apoptosis induction or apoptotic cell clearance, as well as various cytokines linked to CLE. Details are beyond the scope of this chapter and are well discussed elsewhere.[39,40,41,42,43]

Erythema is a normal response to UV light and is mediated by a wide range of vasoactive mediators, neuropeptides, and cytokines released from keratinocytes, mast cells, endothelial cells, and fibroblasts.[31] UV light can induce significant and persistent erythema in patients with CLE. UV light can also induce cutaneous inflammation through the release of inflammatory mediators, cytokines, and chemokines that attract inflammatory cells to the skin.[44]

Cigarette smoking may have phototoxic effects[45] and is an important environmental trigger for CLE, linked with increased disease activity and a poor response to antimalarial therapy.[46,47] In a series of 405 patients with CLE and SLE, 45.9% were smokers, and in LET the rate was 83%, *(Print pagebreak 543)* both significantly greater than the 33.2% of smokers in the matched general population.[48]

Twin studies in SLE have shown a much higher disease concordance in monozygotic twins (24%-57%) than in dizygotic twins, indicating there is a genetic predisposition to the disease.[49,50,51,52,53] In a study of 183 CLE patients, Kunz et al[54] identified polymorphisms in genes responsible for antigen presentation, regulation of apoptosis, RNA processing, and interferon response (*HLA-DQA1, MICA, MICB, MSH5, TRIM39,* and *RPP21*). There are likely genetic predispositions and environmental triggers that underlie the development of SLE and CLE. While no single gene or single environmental factor is associated in most individuals, genetic studies have shown a relationship between smoking and several genes, including *TNFRSF1B, NAT2,* and *CYP1A1/GSTM1,* with an increased risk of SLE in the presence of both factors.[55,56]

Clinical Presentation

Eyelid lesions often begin as erythematous scaly maculae or papules (Figure 83.1).[57] They gradually grow peripherally into larger discoid plaques that heal, leaving an atrophic scar and pigmentary changes.[58] With SLE and some variants of CLE, ocular presentation can begin with localized eyelid erythema and edema.[59,60,61,62,63,64,65,66] In a meta-analysis of 41 articles with 111 patients having CLE affecting the eyes, Arrico et al[57] evaluated the ocular complications associated with cutaneous lupus. The most common phenotype was DLE. Facial lesions were seen in 93% of these patients with the most frequent lesions on the eyelid, forehead, philtrum, malar region, nose, and cheek, and 65% had ophthalmic complications. Of the latter, 53.5% were unilateral and 46.5% bilateral. Among those patients with ophthalmic complications, the main site of involvement was the eyelid, seen in 88.7% presenting as plaques, erythematous papules or maculae, or eyelid edema. Blepharitis was seen in 53.5%, almost cases in the lower eyelid. Madarosis was relatively common, occurring in 28.2%, and areas of skin depigmentation or hyperpigmentation, and skin ulceration were rarely reported (Figure 83.2). Corneal involvement was uncommonly seen in 5.6% of cases as punctate keratopathy or stromal keratitis.

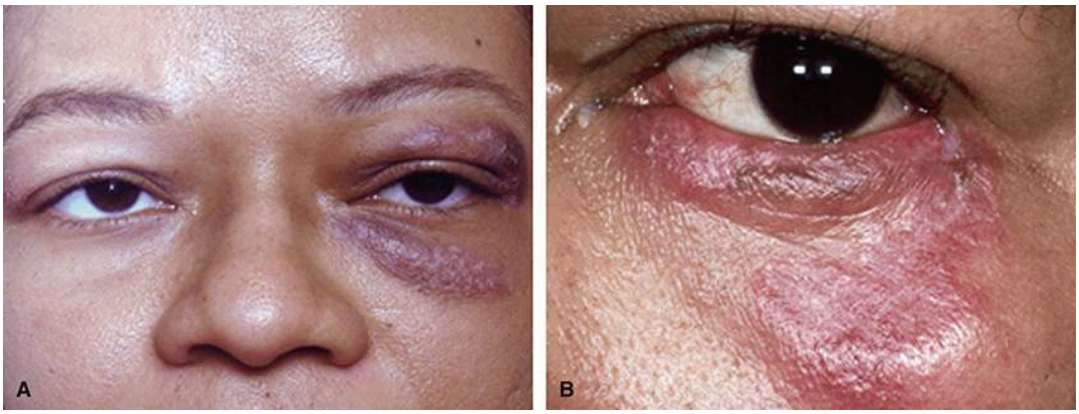

FIGURE 83.1 A and B, Eyelid lupus erythematosus manifesting as erythema and edema. A, (Courtesy of Dr. Robert Goldberg). B, (Courtesy of Dr. Charles Soparkar).

In a series of 25 cases of SLE presenting with periorbital erythema and edema, 68% were female.[67] The average age was 46.7 years with a range of 19 to 77. The upper eyelid was involved in 72% of patients and the lower eyelid in 24.0%. One patient (4%) presented with skin lesions involving both the upper and lower eyelids. The duration of symptoms before presentation ranged from 2 weeks to 4 years with a mean of 58.8 weeks. Three-fourths of the patients were initially misdiagnosed as contact dermatitis, eczema, dermatomyositis, lymphoproliferative disorder, cellulitis, chalazion, or angioedema.

Differential Diagnosis

Unilateral periorbital erythema and edema seen with CLE can be confused clinically with contact dermatitis, eczema, lymphoproliferative disorders, or a chalazion. However, CLE is typically exacerbated by sun exposure and runs a more protracted course. Most of these masquerading lesions can be differentiated on histopathology. Dermatomyositis or angioedema should be included in the differential diagnosis when the CLE is bilateral. Dermatomyositis is an inflammatory muscle disease associated with a violaceous facial rash and progressive muscle weakness. Angioedema is usually a very acute reaction with onset over minutes to hours and is often associated with hives. It usually affects the face, oral mucosa, tongue, and hands, and patients may show other hypersensitivity reactions such as dyspnea. In a large series of 716 patients with SLE, the initial clinical diagnoses were SLE (41%), rheumatoid arthritis (17%), myositis (8%), chronic cutaneous lupus (7%), undifferentiated connective tissue *(Print pagebreak 544)* disease (6%), vasculitis (5%), primary antiphospholipid antibody syndrome (5%), scleroderma (4%), and fibromyalgia, Sjögren syndrome, rosacea, psoriasis, sarcoidosis, and juvenile idiopathic arthritis, all 4% or less.[10]

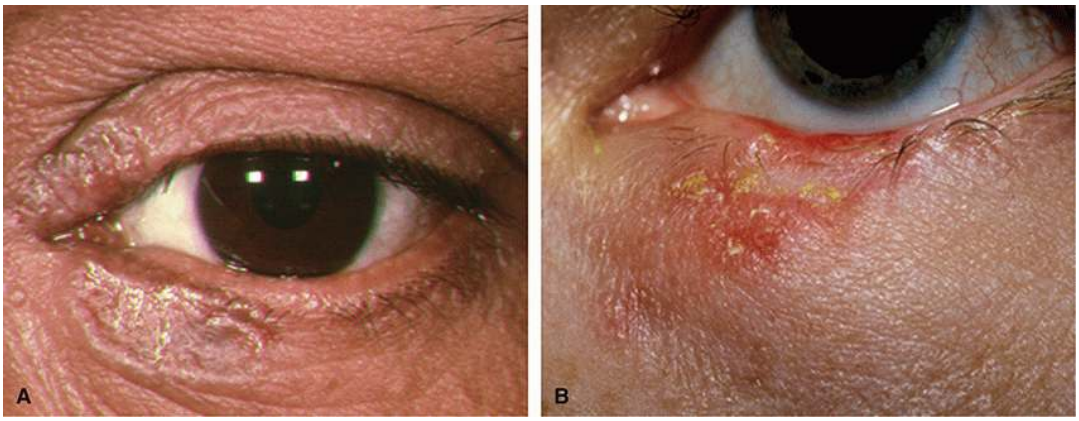

FIGURE 83.2 Advanced systemic lupus erythematosus (SLE) of the eyelids. A, Scaly plaque on the lower eyelid. B, Central lower eyelid SLE with depigmentation, madarosis, and ulceration. A, (Courtesy of Dr. Charles Soparakar). B, (Courtesy of Dr. Gordon Klintworth).

The malar rash can be confused with acne rosacea and seborrheic dermatitis; however, the former is associated with the formation of papules and pustules, and the latter typically occurs within the nasolabial folds.[68] Generalized ACLE may resemble dermatomyositis since both diseases can involve the dorsum of the hands. However, dermatomyositis affects the distal interphalangeal, proximal interphalangeal, and metacarpophalangeal joints, whereas these sites are not involved in ACLE.[68] Other conditions that should be included in the differential diagnosis include atopic dermatitis, contact dermatitis, granuloma annulare, tinea corporis, pemphigus erythematosus, drug-induced photosensitivity, photocontact dermatitis, and drug eruptions.

Treatment

The treatment of CLE is initially aimed at prevention of the disease or slowing the progression of skin lesions. Topical sunscreens are recommended, as well as UV-blocking films on windows.[69] Patients should avoid sunbathing, extended outdoor work, and recreational activities. Klein et al[70] analyzed UV radiation from indoor fluorescent light bulbs and its risk of exacerbating photosensitive diseases, especially with repeated daily exposure. They concluded that bulbs with the lowest UV irradiance should be used to minimize the cumulative dose. Even so, shielding of bulbs or indirect lighting is preferred. In CLE patients who avoid sun exposure, vitamin D deficiency can be a problem, so that levels should be monitored and oral supplementation given as indicated.[71]

Once the cutaneous disease has appeared, the treatment of CLE lesions should begin with topical therapy. Higher dose topical steroids, such as fluocinonide 0.05%, were shown to be more efficacious in improving or eliminating lesions compared to low-dose hydrocortisone 1% cream.[72] However, topical steroids can be complicated by significant side effects such as atrophy, telangiectasia, and dermatitis. On the face and eyelids, low potency steroids, such as hydrocortisone 1% or fluocinolone acetonide 0.01%, are preferred.[12] Scalp lesions are more appropriately treated with steroid foams or solutions, and refractory lesions anywhere may require intralesional injections of triamcinolone.[73]

Calcineurin inhibitors, such as tacrolimus, have been introduced as a topical treatment for various subtypes of CLE.[74] A randomized clinical trial of 30 patients with various types of CLE showed that topical application of tacrolimus 0.1% ointment twice daily may provide at least temporary benefit for acute edematous, nonhyperkeratotic lesions, but the benefit did not persist for more than 2 to 3 months.[75] However, other studies have shown conflicting results.[76]

Pulsed-dye laser therapy has been reported to show some efficacy in the treatment of CLE, with significant improvement in lesions and high levels of patient satisfaction.[77,78,79] However, side effects can include local pain, purpura, and pigmentary changes.

Systemic therapy is indicated for patients with widespread disease or in cases refractory to topical treatments. The oral antimalarial drugs, hydroxychloroquine, chloroquine, and quinacrine, have been considered first-line therapy for all subtypes of CLE, with response rates of 50% to 82%.[80] Hydroxychloroquine sulfate at a dose of up to 6.5 mg/kg/d is considered the drug of choice because of its lower complication profile.[12] Reported side effects include xerosis, exanthematous urticaria, hyperpigmentation, ocular toxicity, gastrointestinal upset, myopathy, cardiomyopathy, dizziness, headache, insomnia, and psychosis.

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For patients refractory to antimalarials, immunosuppressant agents are another option.[81] Methotrexate at doses of 7.5 to 25 mg orally or subcutaneously once a week has been reported to yield improvement in 98% of cases, but 16% developed severe side effects including gastrointestinal toxicity, bone marrow suppression, nephrotoxicity, and hepatotoxicity.[71] Mycophenolate mofetil and mycophenolate sodium also are effective in treating SCLE.[82]

Oral retinoids, such as acitretin and isotretinoin, offer another alternative therapy. They have been used for mixed CLE subtypes and acitretin was shown to be effective in 50% of patients with CLE.[73] Complications of retinoids include hyperlipidemia and hepatotoxicity.

Rituximab is a chimeric monoclonal antibody that targets CD20 and has been reported to be efficacious for refractory cases of SCLE.[83] Two doses of IV 1000 mg given 2 weeks apart are accompanied by intravenous cyclophosphamide or methylprednisolone, but response rates are variable, reported between 35% and 76%.[84,85,86]

Overall, all treatment responses tend to be mostly unsatisfactory with the resolution of lesions seen in only about one-third of cases.[67] About 25% of patients with CLE may go on to develop SLE.

Prognosis

The prognosis of SLE depends on the severity of the disease and the extent of visceral involvement. Most fatalities result from active renal or central nervous system involvement, or various infections.[87] Nevertheless, with oral corticosteroids and immunosuppressive drugs, the 10-year survival rate is 80% or better.[88,89,90] For CLE the prognosis depends on the specific clinical variant and on the presence and severity of any associated extracutaneous manifestations.[87] Risk factors such as genetic

predisposition, race, sex, age at disease onset, and triggering factors such as ultraviolet light exposure likely influence the clinical course and ultimate prognosis of CLE.[87] The overall prognosis is generally more favorable than that of SLE.[87] However, over time 5% to 10% of patients with DLE will experience a transition to SLE, although in most cases the transition will take 5 years or longer.[91,92,93,94,95] Other studies have shown that when mild signs of systemic manifestations are present in patients with CLE, such as proteinuria and arthralgia, 14% to 27% of patients with DLE and 67% to 70% of patients with SCLE will have extracutaneous involvement.[21,96,97,98,99,100] In rare cases, severe life-threatening complications from renal or neurologic involvement will be seen.[92]

Histopathology

The cutaneous histopathology of lupus erythematosus has been studied extensively over the past 65 years,[101,102,103,104,105,106] and Crowson and Magro have provided a thorough summary of lupus erythematosus cutaneous histopathology.[107] A summary of the histopathological features of the most common subtypes of lupus is as follows:

1. *Systemic lupus erythematosus* [107]: Macular eruptions of SLE have subtle histological changes, including cell-poor vacuolar interface dermatitis, absent or slight epidermal atrophy, absent or patchy parakeratosis, normal basement membrane zone thickness, and prominent papillary dermal edema and mucin accumulation. Mucin accumulation is a particularly useful finding that helps to differentiate lupus erythematosus from other forms of cell-poor interface dermatitis such as morbilliform drug reactions, acute graft vs host disease, acute erythema multiforme, vitiligo, and viral exanthemata. Other common cutaneous histological findings in SLE are erythrocyte extravasation, telangiectasia, and focal basement membrane zone duplication around blood vessels and at the dermal-epidermal junction.

2. *Subacute cutaneous lupus erythematosus* [102,107]: SCLE biopsies exhibit interface dermatitis with prominent suprabasilar exocytosis of lymphocytes (migration of lymphocytes into the suprabasal epidermis), dyskeratosis extending into the upper spinous (prickle cell) layer, prominent epidermal atrophy, and a mild to moderate infiltrate of mononuclear leukocytes confined to the superficial dermis. Follicular plugging and basement membrane zone thickening are minimal or absent. The interface dermatitis has a mixture of cell-poor foci of vacuolopathy with small vacuoles within, above, and below the basal lamina alternating with band-like (lichenoid) dermatitis zones. SCLE is thus a form of lichenoid connective tissue disease syndrome that includes SCLE, anti-Ro-associated SLE, and mixed connective tissue disease; these require differentiation using serological tests.

3. *Discoid lupus erythematosus* [103,107,108]: Active lesions of DLE are manifest histologically by a lymphocyte-rich interface dermatitis involving the epidermis and hair follicles with lymphocyte extension into the basal layer of adnexal and interfollicular epidermal keratinocytes, basal layer epithelial destruction with homogenous eosinophilic, round bodies termed hyalin, colloid, or Civatte bodies in the basal cell layer and upper papillary dermis, pigment incontinence, dyskeratotic cells in the epidermis, marked hyperkeratosis with keratotic follicular plugging, variable epidermal acanthosis and atrophy, basement membrane zone thickening that often appears as a broad eosinophilic homogeneous band of basement membrane material in sections stained with hematoxylin and eosin, a moderate to marked superficial and deep perivascular and peri-appendageal lymphocytic infiltrate, and dermal mucin accumulation. Healing lesions of DLE have hyperkeratosis, generally atrophic epidermis with loss of rete ridges, prominent basal vacuolar degeneration, markedly thickened epidermal basement membrane, decreased to absent dermal lymphocytic infiltrate, dermal fibrosis, abundant dermal mucin, and marked follicular plugging. All lupus erythematosus eyelid biopsies that we have examined exhibited histological features of DLE (Figure 83.3).[109]

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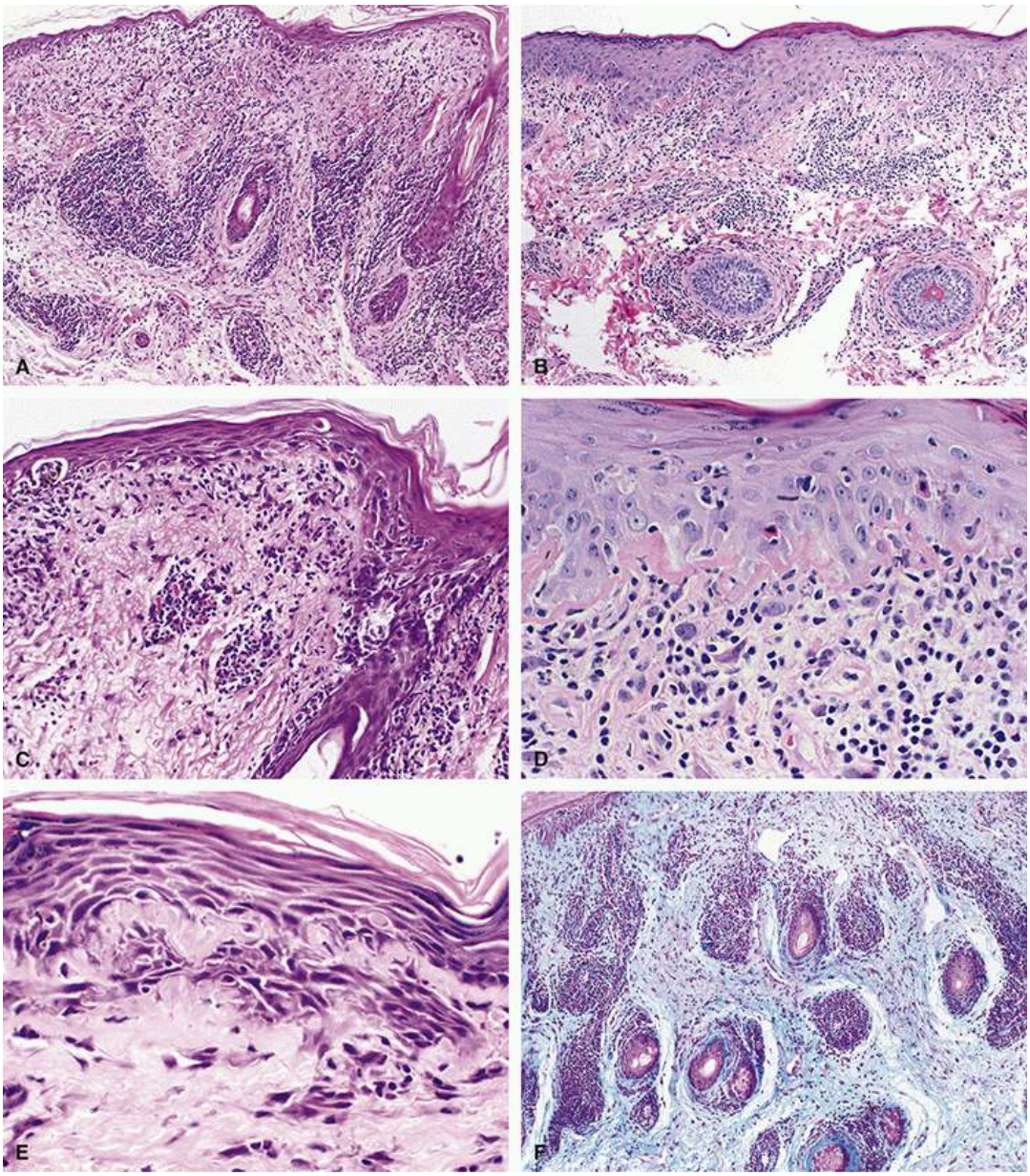

FIGURE 83.3 These eyelid biopsies were all diagnosed as discoid lupus erythematosus (DLE) based on correlating the histopathological and clinical findings. A, Interface dermatitis with superficial and deep perivascular and periadnexal chronic inflammation. The epidermis is atrophic, and the hair follicle on the right has keratotic plugging. B, The epidermis has parakeratosis and acanthosis, and there is superficial perivascular and periadnexal chronic inflammation. C, Interface dermatitis extends down the hair follicle with keratinocyte cell death. D, The epidermis is infiltrated with lymphocytes, and there are two cells undergoing apoptosis with brightly eosinophilic cytoplasm in the basal epidermis. The epidermal basement membrane is eosinophilic, markedly thickened, and undulating. Lymphocytes and macrophages infiltrate the papillary dermis. E, Pseudoepitheliomatous (pseudocarcinomatous) epidermal hyperplasia. The angulated nuclei, thickened basement membrane, and Civatte bodies are clues to DLE diagnosis and are not features expected in squamous cell carcinoma, which this lesion mimicked clinically. F, Alcian blue stain highlights prominent derma mucin accumulation. Alcian blue stains normal skin only faintly, if at all.

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CHAPTER 84

Lymphatic Malformation

Key Points

- Lymphatic malformations (LM) are benign developmental vascular channels lined by endothelial cells and composed of anomalous, usually dilated, lymphatic channels and spaces
- The pathogenesis of LM is incompletely understood but developmental malformations take place due to a genetic hit to the vascular endothelial cells very early during embryogenesis
- LM are usually present at birth, grow in size with the growth of the individual until adulthood, and do not possess a regression or involutional phase
- They usually present with eyelid swelling or blepharoptosis, and occasionally pain, proptosis, diplopia, or strabismus when the orbit is also involved
- They often appear as a crop of small superficial cutaneous vesicle-like lesions or cyst-like excrescences which may become hyperkeratotic or verrucous and can be hemorrhagic especially following manipulation
- Patients may experience an abrupt onset of enlargement and pain due to sudden intralesional hemorrhage
- For small, minimally symptomatic lesions, conservative measures are appropriate
- For more extensive and symptomatic or amblyogenic lesions, percutaneous sclerotherapy is now the treatment of choice
- The prognosis varies from completely innocuous lesions to those with very high morbidity

Lymphatic malformations (LM) are benign tumor-like developmental vascular channels that are lined by endothelial cells and are composed of anomalous, usually dilated, lymphatic channels and spaces. LM commonly involve the orbit together with the eyelids and conjunctiva, but isolated eyelid involvement is rare.[1,2,3,4,5,6,7,8,9]

LM are not true tumors, and the previous name for LM (lymphangioma) is incorrect because the suffix *angioma* implies a proliferative and an involutional phase which does not occur with LM.[1,2,3,4,5,6,7,8,9] Unfortunately as late as 2018, the term "lymphangioma" is still occasionally used in the ophthalmic literature.[10] Other synonyms for LM which were frequently used in the past include cystic hygroma and lymphangioma circumscriptum.[11,12]

Etiology and Pathogenesis

The pathogenesis of LM is incompletely understood due to the lack of proper understanding of lymphatic development.[7] Very early during embryogenesis, there is no visibly discernible difference between the arterial or venous endothelium and arteries and veins, either in the orbit or elsewhere in the body, and they remain virtually indistinguishable until the dynamics of venous flow starts by the end of the fourth week.[13] Around this time, endothelial specification into either an arterial or venous fate (arteriovenous specification) is observed, as evidenced by the expression of distinct arterial and venous markers in separate endothelial populations.[1,14] After the arteriovenous specification is already established, a third endothelial cell type appears later, which is the lymphatic endothelial cell (LEC). There are two competing theories about the embryonic origins of lymphatic vessels and lymphatic development, and these two theories have been debated for over a century.[14,15] The centrifugal or venous theory maintains that primary lymph sacs bud off from primitive veins from a subset of venous endothelial cells that downregulate genes concerned with venous development and upregulate lymphatic ones.[14,16] This theory maintains that the lymphatic vessels grow out centrifugally from these sacs by endothelial budding and lymphangiogenesis.[16] In contrast, the centripetal (nonvenous) model maintains that lymphatic vessels and sacs arise from the mesenchyme parallel to the venous circulation which transforms into LEC. These LECs later develop a primitive lymphatic network and subsequently make secondary connections with the venous system.[15,16]

Recently, attempts have been made to reconcile both theories, and a dual venous and nonvenous origin of lymphatic vessels has been suggested.[15] The discovery that the *Prox1* gene, one of the most important genes that is involved in lymphatic development, is specifically expressed in a subpopulation of venous endothelial cells supports the centrifugal theory.[15] In contrast, some recent experimental animal studies have demonstrated that while the deep lymphatic vessels are indeed of venous origin, the superficial lymphatic vessels are derived from nonvenous dermatomes.[15]

Developmental vascular malformations take place due to a genetic hit to the vascular endothelial cells very early during embryogenesis. This genetic hit usually occurs before endothelial specification into an arterial or venous fate.[1,9,14] Because all vascular components including the lymphatic ones are born from the very same primitive capillary plexus, *(Print pagebreak 551)* conceptually every single tumor or malformation listed in the International Society for the Study of Vascular Anomalies (ISSVA) classification may occur in the orbit as pure (venous, lymphatic, etc.) malformation or in combination (venolymphatic, etc.).[1,14] It must be stressed that because of the plasticity of the progenitor vascular elements destined to form arterial, venous, or lymphatic vessels, it should come as no surprise that lymphatic vascular malformations may occur in the orbit, a location where the very existence of normal lymphatics is questionable in the first place. This plasticity also helps to explain why the most typical form of LM is a mixed lymphovenous type.[1,9]

Despite this apparent embryological complexity, one of the two major molecular pathways is deregulated in vascular anomalies, the RAS/MAPK pathway and the PI3K/AKT/mTOR.[17] LM appear to occur due to abnormalities in the PIK3CA catalytic subunit, which is a part of a family of intracellular transducer enzymes called the PI3K (phosphoinositide 3-kinase), which are generally involved in the activation of the mTOR pathway.[7,17,18] The mTOR pathway is a master regulator of cellular growth and development, and its dysregulation results in a variety of diseases besides LM, including cancers, diabetes, obesity, neurological diseases, and genetic disorders.[18] Most cases of LM are sporadic in onset due to somatic or *de novo* germline mutations, although dominant, recessive, and paradominant (two-hit model) inheritance have been reported.[17]

Because LM is a vascular malformation that occurs as a result of a structural defect in vascular morphogenesis, they are usually present at birth, grow in size commensurately with the growth of the individual until the patient reaches adulthood, do not possess a regression or an involutional phase, and have a normal rate of endothelial turnover.[19,20,21,22] LM may enlarge with upper respiratory tract infections due to the proliferation of lymphoid aggregates within the tumor.[2,23,24] Other predisposing factors that may cause upregulation in the lymphatic system and cause LM to enlarge include infection, hormonal changes, trauma, or even surgical intervention such as needle aspiration for biopsy or therapeutic purposes which can “ignite” an explosive LM growth.[9,21] Regardless of the predisposing factor, the sudden expansion of the anomalous lymphatic channels can lead to disruptions in the normal capillary network that feeds the malformation, with subsequent bleeding into the dead-end lymphatic channels, which may, in turn, become hemorrhagic cysts.[21]

Clinical Presentation

LM have no sex predilection and the exact prevalence is unknown, although some studies estimate an overall incidence throughout the body to be one in every 2000 to 5000 live births.[12,25,26,27] Seventy-five percent of LM occur in the head and neck.[12] Within the orbit, it constitutes 4% of all orbital tumors and around 25% of all vascular masses.[8] Although LM are generally present at birth, it may not become clinically apparent until late in the first or second decades of life, typically following an upper respiratory tract infection or trauma, when bleeding into a previously undetected subclinical LM prompts an ophthalmic evaluation.[2,28]

Patients with periorbital LM usually present with eyelid swelling or blepharoptosis. Ptosis which may be observed in up to half of the patients with periorbital LM is usually mechanical.[27,28] Other less common presentations include pain, proptosis, diplopia, or strabismus which may be more related to orbital LM.[28] LM are generally classified into macrocystic (>2 cm^2), microcystic (<2 cm^2), or mixed lesions, although some authors prefer to bring the cutoff figure for orbital lesions to 1 cm rather than 2.[1] Regardless of the correct cutoff value, from a clinical standpoint, a microcyst should be defined as a cyst which cannot be safely accessed with a needle.[27] Of note is that macrocystic LM (previously called cystic hygroma) are more common in the posterior orbit and are often observed with orbital imaging displaying fluid levels, while microcystic LM (previously called lymphangioma circumscriptum) are more common in the anterior orbit, eyelids, and the conjunctiva.[21,22]

Periorbital LM are rarely pure LM and are more commonly mixed-type malformations that contain venous channels and less commonly arterial or capillary channels.[21] Based on the predominance of one vascular element, they are sometimes classified as venous-dominant or lymphatic-dominant.[22] It should also be pointed out that isolated eyelid LM are exceptionally uncommon, as eyelid lesions are either anterior extensions of orbital LM or eyelid extensions of facial LM.[2]

Eyelid involvement (either with or without orbital/conjunctival involvement) may present with one of the two different forms. They may present as small superficial cutaneous vesicle-like lesions or cyst-like excrescences which may become hyperkeratotic or verrucous and can be hemorrhagic especially following manipulation.[2] Fluid levels may be seen within some of the cysts which are typically observed near the eyelid margin. Alternatively, eyelid LM may occur deep to the epidermis as a dark blue solid lesion,

which may be soft to firm, fluctuant, and may infiltrate eyelid tissue causing a diffuse or localized thickening of the eyelid (Figure 84.1), and in extreme cases may lead to elephantiasis of the eyelid.[2,21,22] Both forms of presentation may be observed together.[22] LM by definition do not enlarge with the Valsalva maneuver.[21,22] With a mass in the upper eyelid, significant ptosis can result in obstructing vision (Figure 84.2).

Patients with orbital LM may present with an abrupt onset of proptosis due to sudden hemorrhage within the dead-end lymphatic channels (Figure 84.3), but a detailed description of concomitant orbital involvement is beyond the scope of this text. Conjunctival involvement which is not infrequently associated with eyelid LM may present with solitary, diffuse, or multiloculated cyst-like lesions on the bulbar and palpebral conjunctiva which may contain clear fluid (lymph) (Figure 84.4). Similar to eyelid LM, conjunctival LM usually present as a superficial component of a deeper or diffuse orbital LM. These conjunctival lesions may be present at *(Print pagebreak 552)* birth and may remain asymptomatic (nonhemorrhagic) or may spontaneously bleed.

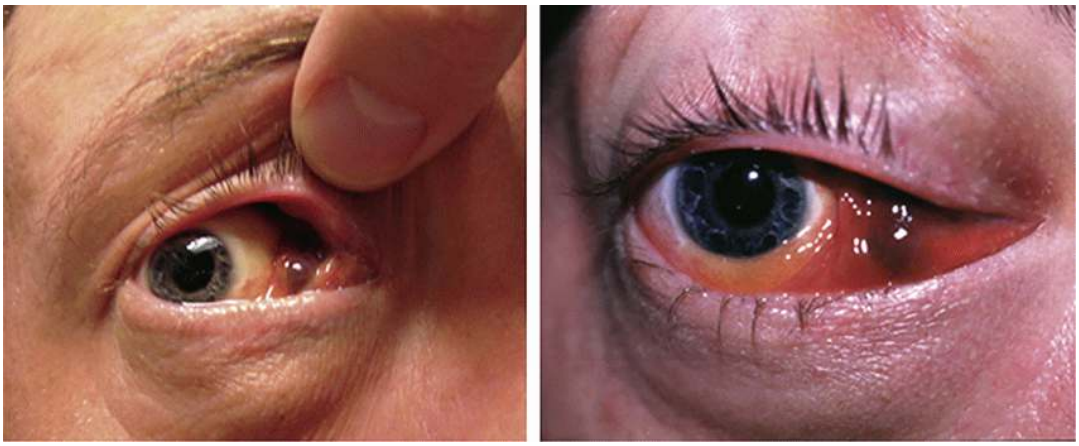

FIGURE 84.1 Deep lymphatic malformations lesion in eyelids and orbit.

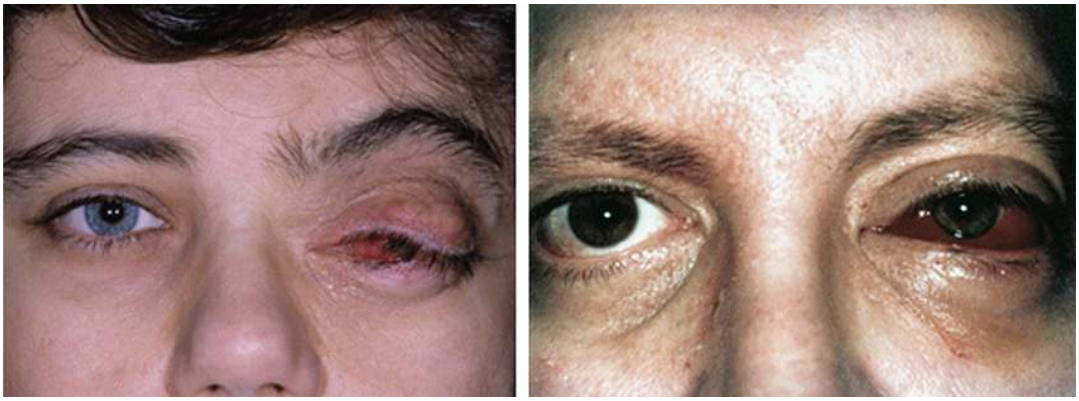

FIGURE 84.2 Eyelid lymphatic malformations with upper eyelid ptosis.

Rarely, patients with LM malformations can present with intense eyelid and orbital inflammatory changes which may be indistinguishable from orbital cellulitis.[5] This rare form of presentation is usually due to a secondary bacterial infection, but an acute aseptic inflammatory episode is also occasionally observed.[5,29]

The diagnostic workup for patients with suspected LM should include ultrasonography, color Doppler sonography, contrast-enhanced magnetic resonance imaging (MRI), dynamic MRI imaging with DWI-ADC (diffusion-weighted imaging-apparent diffusion coefficient) series, and TRICKS (time-resolved imaging of contrast kinetics) sequences.[1,9] Biopsy is rarely required to diagnose an eyelid LM, as they most commonly show typical clinical and radiologic findings, but if any uncertainty exists, a biopsy may be required.[6,8]

Differential Diagnosis

The list of simulating lesions includes infantile hemangioma, venous malformation, rhabdomyosarcoma, fibrosarcoma, or eyelid lymphoma.[2,28,30] Rhabdomyosarcoma, in particular, may occasionally present a diagnostic challenge. Both entities occur in the same age group, both typically present with a rapid or explosive onset of proptosis, and both may have conjunctival involvement. Although radiology will usually clinch the diagnosis, rhabdomyosarcoma may occasionally show cavitation on MRI which may be difficult to differentiate from the fluid levels of macrocystic LM, and a biopsy may be required to establish the correct diagnosis.[31,

LM may be clinically similar to a venous malformation, but the majority of LM lesions in the orbit are mixed venous/lymphatic lesions, and differentiation may be exceptionally difficult.[9] Intense inflammatory signs are not common in *(Print pagebreak 553)* LM, but if an LM presents with a hot orbit, the condition may be confused with orbital cellulitis or idiopathic orbital inflammation.[5]

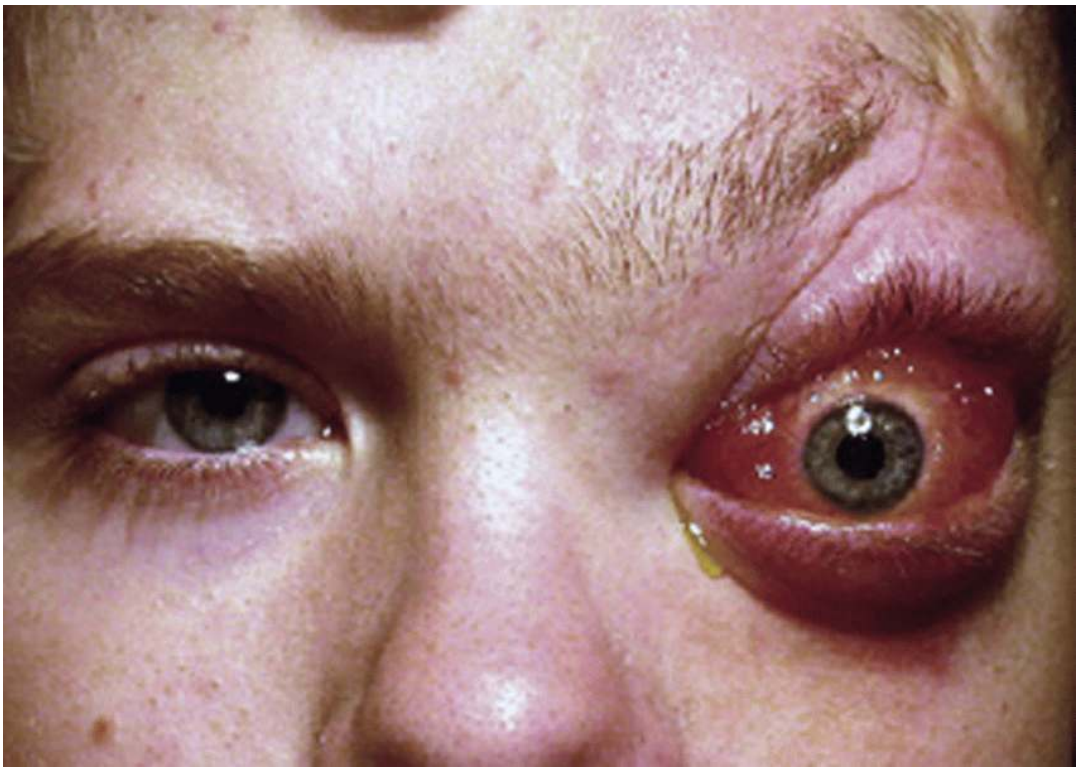

FIGURE 84.3 Infiltrative lymphatic malformations involving the eyelids, conjunctiva, and orbit with massive proptosis. (Courtesy of Dr. Michael Hawes.)

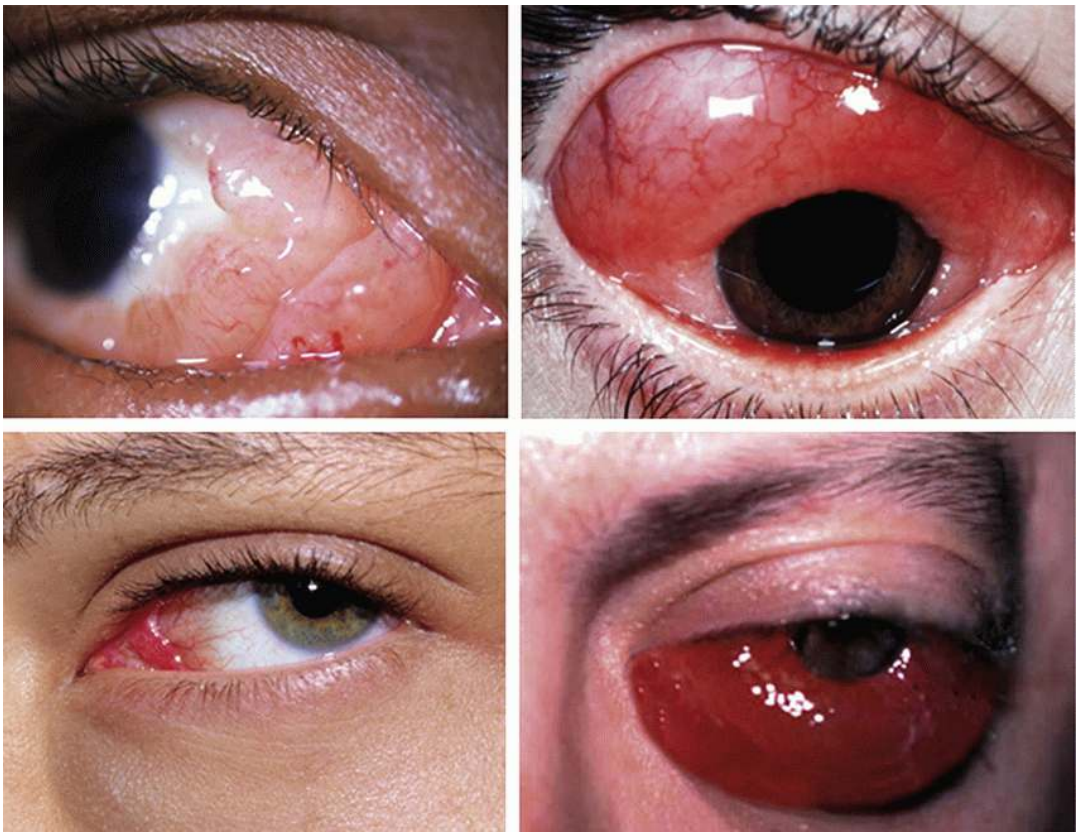

FIGURE 84.4 Lymphatic malformations of the conjunctiva.

Treatment

Currently, there is no gold standard for treatment, and therapy should be standardized according to the presentation which varies from one patient to the other. Watchful observation of focal, cosmetically nondisfiguring, minimally symptomatic, or functionally insignificant (nonamblyogenic) lesions is an acceptable first line of management.[21,24,33] Conservative measures include limitation of strenuous physical activity and bedrest, cold compresses, monitoring of visual functions (visual acuity and pupillary light reaction), and the use of systemic steroids. Corticosteroids are recommended for symptomatic relief and to prevent loss of vision, but they do not always work.[23,34,35] Patching of the *(Print pagebreak 554)* contralateral normal eye may be tried to fend off amblyopia, and a temporary tarsorrhaphy may be indicated if the cornea is threatened. If periorbital lesions are complicated by a secondary bacterial infection, intravenous antibiotics may be required.[28]

Patients with isolated superficial cystic lesions are usually minimally symptomatic; although occasional bouts of hemorrhage may be observed, they typically resolve spontaneously. However, if hemorrhage persists, or if they are cosmetically disfiguring, simple excision of these small, superficial cystic lesions has been somewhat successful and is usually bloodless,[22] but it may occasionally be a frustrating experience because the margins are hard to define, and large confluent cysts which are not infrequently observed as crops covering a large area of the anterior surface of the eyelid may have to be excised en bloc, therefore complete excision may require a skin graft.[22]

For more extensive subepidermal lesions, most authors agree that surgery is the definitive form of therapy to effect a complete cure in potentially amblyogenic lesions.[26,28] However, because of the vascular and infiltrative nature of LM, these lesions may bleed significantly during surgery, and the surgeon may face tremendous difficulty in obtaining a clear cleavage between the mass and the normal tissue planes which is almost impossible particularly in microcystic LM.[1,3,9,21,22] Therefore, although complete surgical excision of anterior orbital/eyelid lesions may be tried, it may be hazardous because of the possibility of iatrogenic damage to adjacent eyelid structures,[1,3,9] and in the event of incomplete excision or subtotal debulking, it may be associated with frequent recurrences.[6] Therefore, some authors believe that surgery should be reserved for patients with vision-threatening lesions alone, a rare situation in isolated eyelid LM. If debulking is undertaken, ptosis usually improves following surgery, but if levator resection surgery is required to address the ptosis it should be deferred to a second stage 6 months later, and any residual LM from the previous first stage surgery may be further excised,[27] but it should be stressed again that because of the aforementioned risks, surgery based on cosmetic indications alone is discouraged.[1]

Within the orbit several options are available for management of LM, embolization followed by surgical excision, or sclerotherapy alone. Simple evacuation of the hemorrhagic macrocysts compressing the optic nerve may be tried but this will probably result in slow transudative reformation of the cyst and recurrences.[22,36] Surgical resection of macrocystic LM in the posterior orbit may be performed alone or as an adjunct to sclerotherapy where the cysts are partially evacuated followed by embolization of the cysts with one of the traditional sclerosants like *n*-butyl cyanoacrylate. The solidified lesion is subsequently debulked or excised in the same session.[22,27,28] An alternative approach in facial LM is to debulk the lesion as a first-line measure and reserve the intratumorous injections of sclerosant agents for future recurrences.[27]

Because of the obvious challenges of surgical ablation outlined earlier, percutaneous sclerotherapy alone is suggested as an alternative to surgery in the treatment of macrocystic superficial periocular LM.[3,6] The modality is, in fact, a well-established option in superficial vascular lesions elsewhere in the body; however, sclerotherapy for microcystic LM which is more common in the eyelid has a less favorable outcome possibly because there are no obvious cysts to target with the sclerosant, and the sclerosant agent may extravasate and cause serious consequences as it may damage normal adjacent eyelid tissue.[9] However, in selected cases, sclerosants may be tried, and the recommended sclerosing agents include sodium tetradecyl sulfate (STS), bleomycin, doxycycline, ethanol (not recommended in the periorbital region), pingyangmycin, and OK-432 (Picibanil), which is a killed strain of group A *Streptococcus pyogenes*.[3,6,9,37,38,39] Intravenous injection of STS, a synthetic surfactant, causes an intimal inflammation and subsequent thrombus formation which usually occludes the injected vein, followed by fibrous tissue deposition.[3] Bleomycin is an antineoplastic antibiotic that was isolated from the fungus *Streptomyces verticillus*, and besides its use in the management of vascular malformations, it is used as a chemotherapeutic agent in squamous cell carcinoma, lymphoma, and testicular carcinoma.[6] The proposed mechanisms of action of bleomycin involve apoptosis of rapidly dividing endothelial cells, inhibition of DNA synthesis, followed by involution of the lesion by fibrosis.[6]

Lesions involving the eyelids or anterior orbit are clinically visible on the surface and are usually prominent; therefore, the injections if indicated can be carried out under direct visualization without ultrasonographic or digital subtraction angiography guidance. Injections are carried out with general anesthesia for children or local anesthesia for adults. A 21, 23, or 25 gauge needle or a scalp vein set is used, and partial or complete aspiration of the lesion is performed first.[3,6] With the needle in the same position, intralesional injection of the sclerosing agent like bleomycin (0.5 IU/kg body weight, arbitrarily around 20% of

the aspirate) or STS (0.1 mL STS 1%) follows.[3,6] Because these injections may not always result in complete lesion obliteration, and because the effects may not be permanent, injections may be repeated every 4 to 6 weeks until the desired effect is achieved.[3,6,39]

Commonly encountered complications are mild and include pain at the site of injection, red itchy skin (hives), temporary skin hyperpigmentation, lid edema, ecchymosis, erythema, transient increase in proptosis, and rarely eyelid necrosis due to drug extravasation. Anaphylactic shock and catastrophic vascular embolic events are extremely rare but should be promptly diagnosed and treated if encountered.[3,6] It is important to understand that partial lesion aspiration is not solely intended to clear up space for the injection of the sclerosing agent, but it is also a safeguard precautionary measure to make sure the needle is not misplaced intraarterially.[3,6] Although some authors claim a good long-term outcome with transcutaneous and/or transconjunctival non-image guided sclerotherapy in patients with orbital/adnexal lymphatic malformations,[39] a recent cross-sectional cohort study which focused on orbital venolymphatic malformations demonstrated that sclerotherapy alone may only provide initial temporary improvement, however, in the *(Print pagebreak 555)* medium to long term, recurrence were universal.[40] In contrast, embolization with excision appears to provide more definitive management with far fewer recurrences.[40]

Of note is that the vascular channels of LM are not amenable to endovascular approaches; however, other possible forms of therapy for superficial lesions include oral medications, radiofrequency, or carbon dioxide laser (CO_2) resurfacing/ablation.[26,40,41,42] Because of its inhibitory effects on the mTOR pathway, rapamycin (sirolimus), a macrolide drug that was initially discovered as an antifungal metabolite produced by *Streptomyces hygroscopicus*, was later found to possess immunosuppressive and antiproliferative properties, as well as life span extension properties.[7,18] Sirolimus was shown to be effective in venous as well as LM both within the orbit and in extraorbital locations throughout the body.[7,17,18] Because of the low risk-benefit profile of the drug and the infrequent side effects, rapamycin may be a safer alternative for the treatment of microcystic orbital LM than surgical excision or sclerotherapy where they may not be particularly useful.[7] Of note is that the recommended dose range, as well as the duration (6-53 months) of drug therapy, is not yet standardized.[7] Phosphodiesterase type 5 inhibitors like sildenafil (Viagra, Pfizer) or tadalafil (Cialis, Lilly) have also shown some promise in the management of systemic LM.[21]

Prognosis

The clinical course of LM varies from completely innocuous lesions to lesions with very high morbidity which may cause progressive anatomic distortions and serious functional problems.[28,33] Amblyopia is common and is attributed both to ptosis (occlusive amblyopia) and strabismus (strabismic amblyopia).[28] Relapses are common, and recurrent hemorrhages may cause a disfiguring cosmesis which may be very difficult to treat.[24] Visual loss may be profound and is also multifactorial (amblyopia, corneal complications, and/or optic nerve compression). True regression, which may be seen with infantile hemangioma, does not occur with LM.[2] Relentless bleeding with severe associated pain which may require exenteration for palliation is unusual and is a sequel of orbital rather than eyelid disease.[24]

It should be noted that because of the rarity of LM, the condition does not lend itself to large, randomized controlled trials, and evidence-based information is lacking.[26,43] Furthermore, the literature is plagued with inconsistent reporting and all the information that can be retrieved is obtained either from small case series or even single case reports, some of which do not take into account the size/extent/depth of the lesion or the histopathologic subtype as a variable affecting the prognosis or clinical therapeutic outcome.[26] More robust clinical studies are needed to compare the results of different treatment modalities side by side.[26]

The consensus that the treatment of macrocystic LM is more successful than the treatment of microcystic LM may not hold true in the orbit where both forms of presentation whether in the posterior or anterior orbit are intermixed with vital structures.[38] Patients should be notified that except in very rare situations, complete surgical resection is not possible,[24,28] and sclerotherapy usually requires more than one session until the lesion resolves. Patients should also be informed that regardless of the treatment option chosen, success is variable, recurrence is the rule, and a complete cure is an exception.[26]

Histopathology

Superficial LM may arise in the superficial dermis (previously termed “lymphangioma circumscriptum”) or deep dermis, often with extension into the superficial subcutis (previously termed “lymphangioma cavernosum”).[44,45] The lymphatic channels in both are thin-walled and empty or contain lightly eosinophilic, homogenous fluid (lymph) with few or no erythrocytes unless there has been spontaneous hemorrhage into the lesion. In contrast to hemangiomas, the endothelial cells lining the lymphangioma vascular channels are widely spaced, the channels in fixed specimens often have irregular shapes with acute bends, and they usually lack a

muscular layer.[45] Immunohistochemical stains using antibodies to podoplanin (D2-40), lymphatic vessel endothelial hyaluronan receptor 1 (LYVE1), or prospero homeobox protein 1 (PROX1) highlight LECs and may be employed to confirm the diagnosis of an LM.[44]

Superficial LMs, formerly termed "lymphangioma circumscriptum," feature enlarged lymph vessels immediately beneath the epidermis, causing it to become elevated with a vesicle-like appearance.[45,46,47] Lymphatics protruding into the acanthotic epidermis may simulate intraepidermal vesicles.[45] A few lymphocytes may be found in the stroma around the lymphatics.[45] In some cases, a superficial LM (lymphangioma circumscriptum) arises over a macrocystic LM (previously called cystic hygroma).[48] In these cases, the superficial lymphatics are horizontally oriented, while deeper lymphatics are vertically oriented, have thicker walls, and communicate with a subcutaneous lymphatic cistern.[48]

Lymphangioma cavernosum has a variable histological appearance.[45] Simple cases have lymphatics that appear to push apart the stroma (Figure 84.5), while complex lesions have connective tissue around the lymphatics that varies from loose stroma to compact stroma to fibrosis.[45] The stroma frequently contains a few lymphocytes, and larger lesions may have aggregates of lymphocytes.[45]

Eyelid cutaneous LMs are poorly demarcated lesions with wide variation in the amount of stroma accompanying the lymphatics.[49] Some eyelid LMs have back-to-back lymphatics with minimal stroma, and others have lymphatics widely spaced in the stroma.[49] The channels in a given lesion vary from small caliber to cavernous spaces[49,50]; Jones noted that the smaller caliber lymphatics tended to be more superficially located.[49] Stromal lymphocytes vary from scattered to lymphoid follicles.[49] An adventitial coat of the lymphatic spaces is inconspicuous in most eyelid LMs, but there may be focal investment by smooth muscle cells.[50] Hemorrhage into eyelid LMs is common.[50]

Conjunctival LM may be an extension of a deeper process,[51] or they may rarely be isolated lesions.[49,52] Conjunctival LMs usually have closely packed, dilated lymphatics with scant stroma (Figure 84.6).[49] Stromal lymphocytes may be sparse[49] or form lymphoid follicles.[52]

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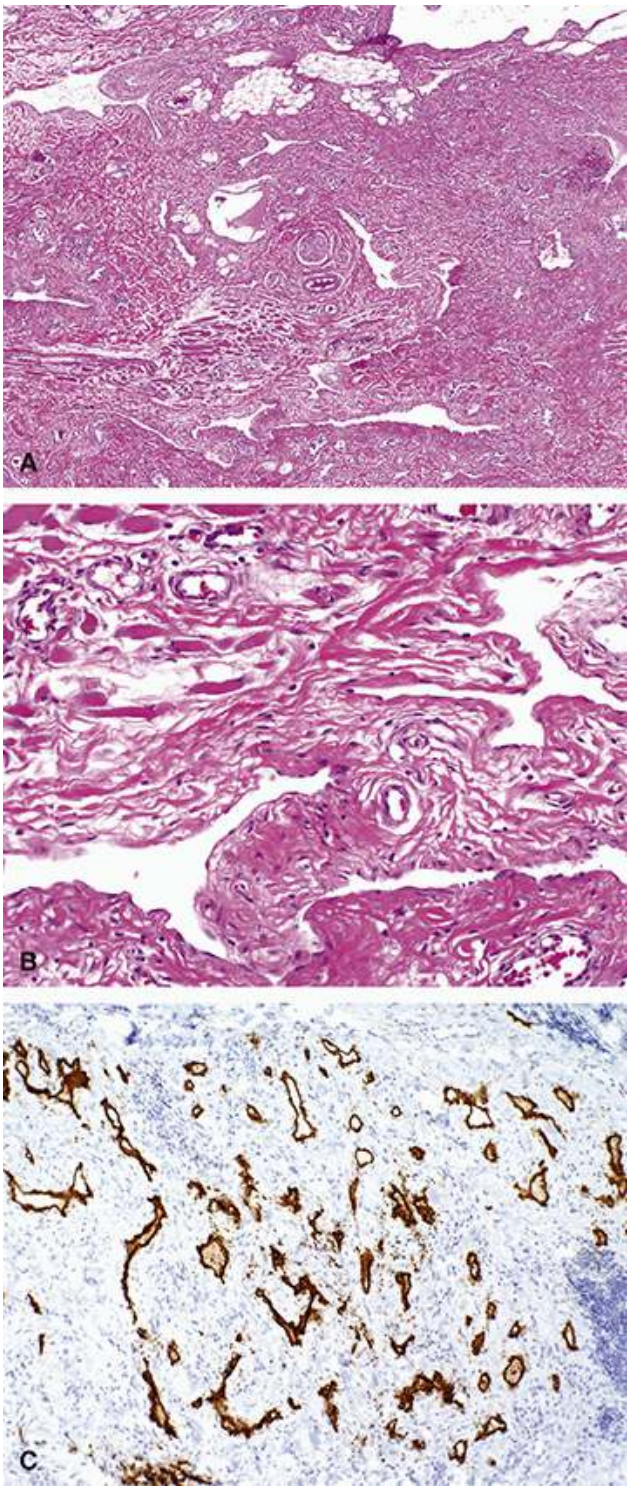

FIGURE 84.5 A, This biopsy is from the left upper eyelid of a child with a congenital lymphatic malformation (LM) involving the eyelid and preseptal orbit. At low magnification, dilated, irregularly shaped lymphatics dissect between the eyelid stroma. B, Lymphatics lacking an adventitial coat extend through the orbicularis muscle. C, An immunohistochemical stain using antibodies to podoplanin highlights variability in the size and shape of lymphatic channels in this LM involving the right eyelid and anterior orbit.

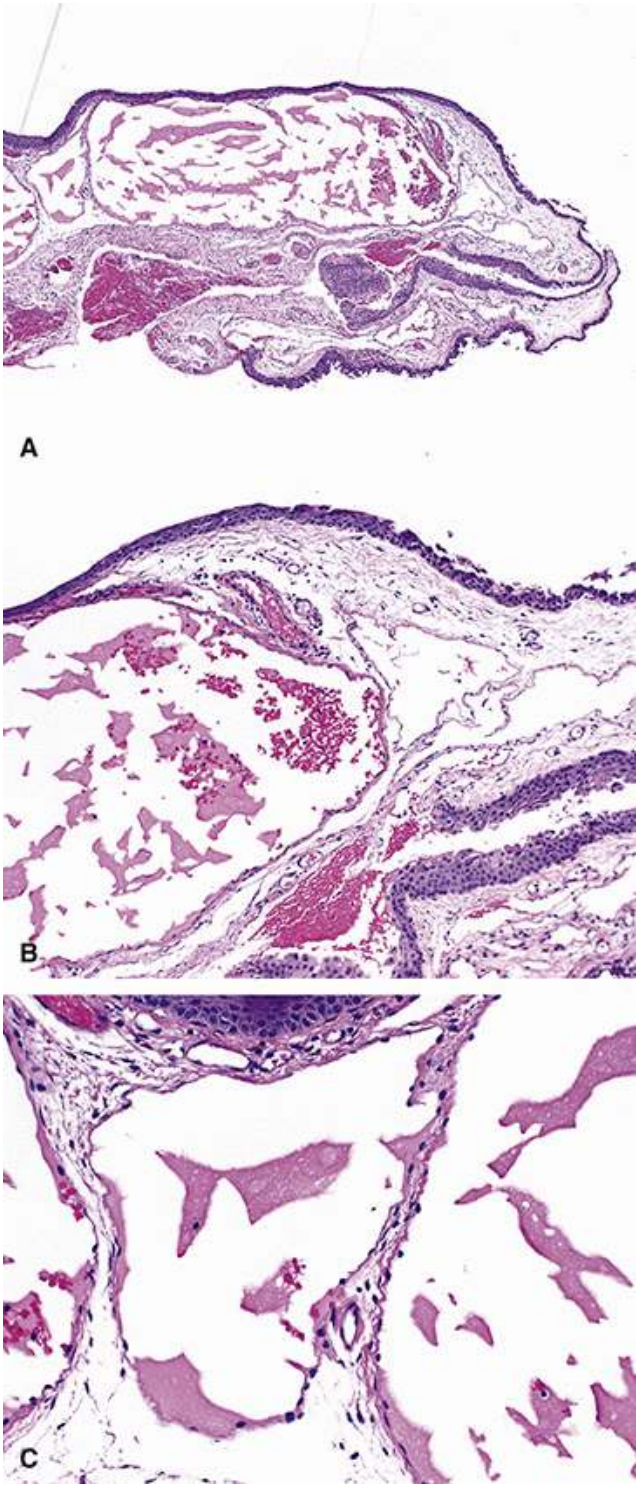

FIGURE 84.6 A, This conjunctival lymphangioma was a discrete lesion in the inferolateral quadrant of the left eye just inside the palpebral fissure of a middle-aged woman. Minimal stroma separates widely dilated lymphatics containing eosinophilic lymph. B, The lymphatics have thin walls, and focal hemorrhage is manifest as erythrocytes mixed with the lymph. C, The lymphatics have widely spaced endothelial cells, no adventitial coat, and sparse, loose stroma between them.

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CHAPTER 85

Lymphedema

Key Points

- Lymphedema is a chronic disease characterized by localized eyelid swelling caused by an impairment of lymphatic drainage, resulting in the excessive retention of protein-rich lymphatic fluid in the interstitial compartment
- Primary lymphedema is due to aplasia or hypoplasia of the lymphatic vessels but has not been reported in the eyelid
- Secondary periocular lymphedema is associated with chronic inflammatory conditions, surgical or nonsurgical trauma, infections, neoplastic processes, and miscellaneous causes such as hypothyroidism, amyloidosis, nephrotic syndrome, alcoholism, continuous positive airway pressure nasal masks, or malar festoons
- Clinically, the edema is initially pitting and pendulous, but later becomes doughy, firm, and nonpitting
- Treatment options are palliative at best depending on the associated systemic disorders and include tetracycline antibiotics, isotretinoin, or oral steroids
- Surgical debulking is another option
- Chronic eyelid lymphedema, regardless of the etiology, is a progressive disease with serious physical and psychosocial implications that may be challenging to diagnose and is notoriously difficult to eradicate

Lymphedema is a chronic progressive disease characterized by a localized form of eyelid swelling that is caused by an impairment of lymphatic drainage, which results in the excessive retention of protein-rich lymphatic fluid in the interstitial compartment.[1,2,3,4,5] The term “elephantiasis” is synonymous with the term “lymphedema.”[3]

Etiology and Pathogenesis

Although lymphedema is not uncommon, our understanding of its basic underlying pathogenetic mechanisms is still limited. A brief overview of the lymphatic eyelid anatomy may shed some light on its etiology.[4] Eyelid lymphatics lie superficial and deep to the orbicularis muscle forming superficial and deep systems that drain to the parotid and submaxillary nodes.[2,6] The deep vessels traverse through the suborbicularis oculi fat and drain the conjunctiva and tarsus directly into the parotid (preauricular) lymph nodes. On the other hand, the superficial system which runs anterior to the orbicularis muscle drains the skin of the eyelids and orbicularis muscle.[6] Medially, this superficial system collects lymphatic drainage from the medial aspects of both eyelids and drains into the submandibular lymph nodes, while the lateral aspect of both eyelids is drained by a separate system that flows into the parotid (preauricular) lymph nodes.[6,7]

If these channels are blocked, lymph stasis ensues which causes an accumulation of tissue protein and fluid, resulting in edema.[2] Accumulation of lymph increases oncotic pressure which draws even more fluid into the interstitium, which in turn may cause inflammation, further compromising support for lymphatic vessels. As the eyelid edema progresses, fibrotic changes ensue, and the already dysfunctional lymphatic channels are even more impaired by fibrosis of the surrounding tissues.[8,9] This vicious cycle causes the initially soft eyelid subcutaneous tissue to become thickened, fibrotic, and solid.[8]

Lymphedema is subdivided into primary and secondary types. Primary or hereditary lymphedema due to aplasia or hypoplasia of the lymphatic vessels has not been reported in the eyelid; therefore eyelid lymphedema is usually a localized form of secondary lymphedema. The list of periocular conditions associated with lymphedema includes (1) chronic inflammatory conditions like rosacea, Melkersson-Rosenthal syndrome (MRS), or oculofacial granulomatosis; (2) trauma either surgical or nonsurgical; (3) infections like erysipelas; (4) conditions including giant cell angiofibroma or neurofibroma; and (5) miscellaneous causes, including hypothyroidism, amyloidosis, nephrotic syndrome, alcoholism, continuous positive airway pressure nasal masks, malar festoons, or it may be idiopathic.[8,10,11,12,13,14,15,16,17,18,19,20,21,22,23]

Concomitant injury to both the deep and superficial lymphatic drainage systems explains the increase in the rate of persistent chemosis/eyelid edema that has become more prevalent as cosmetic procedures that combine traditional transcutaneous blepharoplasty with trans-eyelid midface suspension have become more common.[6] Historically, placement of surgical incisions over the inferior orbital margin to access the anterior orbit not only resulted in an unsightly scar but these incisions caused significant lymphedema as well.[17] Another procedure that can be associated with considerable lymphedema is myectomy for essential blepharospasm.[18] Eyelid lymphedema does not occur only from trauma or surgery involving the periocular region, and several cases have been reported following modified radical neck dissection for head and neck cancer metastases.[2,8]

Rosacea is a chronic inflammatory skin condition affecting approximately 10% of adults and is characterized by *(Print pagebreak 560)* facial erythema, papules, pustules, telangiectasia, sebaceous gland hyperplasia, and meibomian gland dysfunction.[13,14,15] In the absence of a history of a surgical or a nonsurgical traumatic insult, rosacea is by far the most common underlying etiologic condition associated with lymphedema and is observed in roughly 50% of patients. While ophthalmologists are familiar with the classic ocular manifestations of rosacea, such as conjunctivitis or blepharitis, rosacea is often overlooked as a common cause of eyelid lymphedema.[24]

MRS is a rare locally infiltrative granulomatous disease of obscure etiology, which is characterized by a triad of idiopathic eyelid or lip edema, facial palsy, and fissured tongue. However, the classic triad is encountered in one-third of patients only,[11,12,25] and patients can present solely with eyelid lymphedema (Figure 85.1). The disease has a worldwide distribution, with no racial predilection, but is diagnosed more often in females.[25]

Orofacial granulomatosis (OFG) is an uncommon non-necrotizing granulomatous disorder of the orofacial tissues. The term is a catch-all term that was coined in 1985[25] to encompass several entities that share two common features: orofacial swelling and the histologic evidence of noncaseating granulomas.[26] This condition has a multifactorial etiology and uncertain pathogenesis, but an underlying genetic or immunologic (delayed hypersensitivity) mechanism that favors a granulomatous inflammatory response is possible.[25,26,27,28,29] Although the term is nonspecific, establishing the diagnosis of OFG is still important because it should prompt the clinician to thoroughly search for the underlying disease, including granulomatous cheilitis, Miescher cheilitis, Crohn disease, or MRS.[26] Unfortunately, the diagnosis remains elusive in a significant proportion of patients,[26] and in these individuals, the term “OFG” can be used alone, a situation which is not quite dissimilar to the use of the term “idiopathic orbital inflammation” in orbital disease.

An often overlooked clinical condition that is at least partially attributable to lymph stasis is malar mounds, the other contributory or comorbid mechanism being anatomical laxity of dermal attachments. Both factors (laxity and lymph stasis) contribute to the characteristic clinical appearance of festoons.[16]

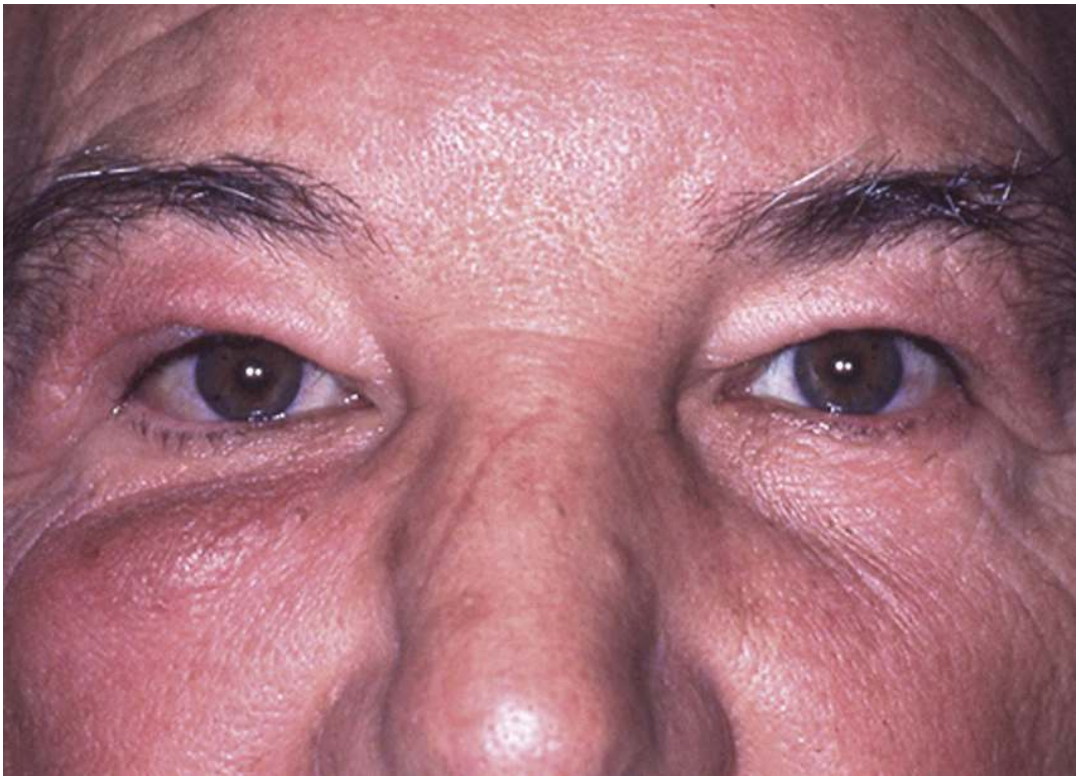

FIGURE 85.1 Lymphedema associated with Melkerson-Rosenthal syndrome.

Comorbid factors that may increase the risk of developing lymphedema include genetic factors, obesity, radiation, and infections.[1,2,3,4] Interestingly, genetic factors do not only play a role in primary lymphedema but may be implicated in cases of secondary lymphedema.[4] An increased rate of mutations in the HGF/MET pathways which regulate lymphangiogenesis, as well as mutations in the CJC2 protein which regulates lymphatic flow, have been observed in patients with secondary lymphedema.[30,31] Obesity has repeatedly been shown to impair lymphatic function and patients with a higher body mass index have a higher incidence of lymphedema, but this may be reversible after weight loss.[4] Radiation per se is associated with an increased risk of lymphedema but is an important comorbid risk factor if performed following surgery.[4] Infections can also cause significant destruction of the lymphatic system.

Clinical Presentation

The prevalence of lymphedema is unknown because lymphedema is not a reportable disease.[20] Pain is usually absent, but patients are concerned about the nature of the edema and the associated cosmetic disfigurement which is bothersome because chronic lymphedema may cause a significant change in orbital and facial contour.[5] On physical examination, the eyelid tissue initially shows a variable degree of mild edema, which later progresses to severe or profound lymphedema (Figure 85.2). If the upper eyelid is involved, the visual axis may partially or completely be occluded, but the levator function is difficult to assess amidst the edema.[2]

The edema is initially pitting and pendulous, but as fibrosis and chronic inflammation progress, lymphedema becomes doughy, then later becomes firm and nonpitting or woody, and the overlying skin becomes thickened and hyperpigmented.[8,10] Rosacea patients often present with solid persistent facial edema coupled with erythema which is referred to in the literature as rosacea lymphedema or Morbihan disease.[3,5] These patients typically suffer from edema involving the upper two-thirds of the face not circumscribed to the eyelids but may involve the forehead, glabella, nose, and cheeks (Figure 85.2).[5] Patients with OFG, including patients with MRS, may also present with severe nontender upper and lower eyelid edema and induration which may be associated with mechanical ptosis and obscuration of the visual axis.[29]

Eyelid lymphedema can be associated with conjunctival chemosis if the deep lymphatic plexus is also involved, a situation that is commonly observed in patients with trauma or surgery. Other than conjunctival chemosis, the rest of the ocular examination is typically normal in lymphedema patients. Systemically, the association of lymphedema with a fissured tongue (lingua plicata) or facial nerve paralysis may point to the diagnosis of MRS, but monosymptomatic or *(Print pagebreak 561)* oligosymptomatic variants of the disease are the rule rather than the exception.[11,12,25,26,27,28] Of note is that lingua plicata may be a normal variant in the population and is not diagnostic of MRS. Other subcategories of OFG are commonly associated with upper or lower lip edema rather than eyelid edema,[25,26,27,28] but a recent study has demonstrated that eyelid lymphedema may also be a common associated finding.[29]

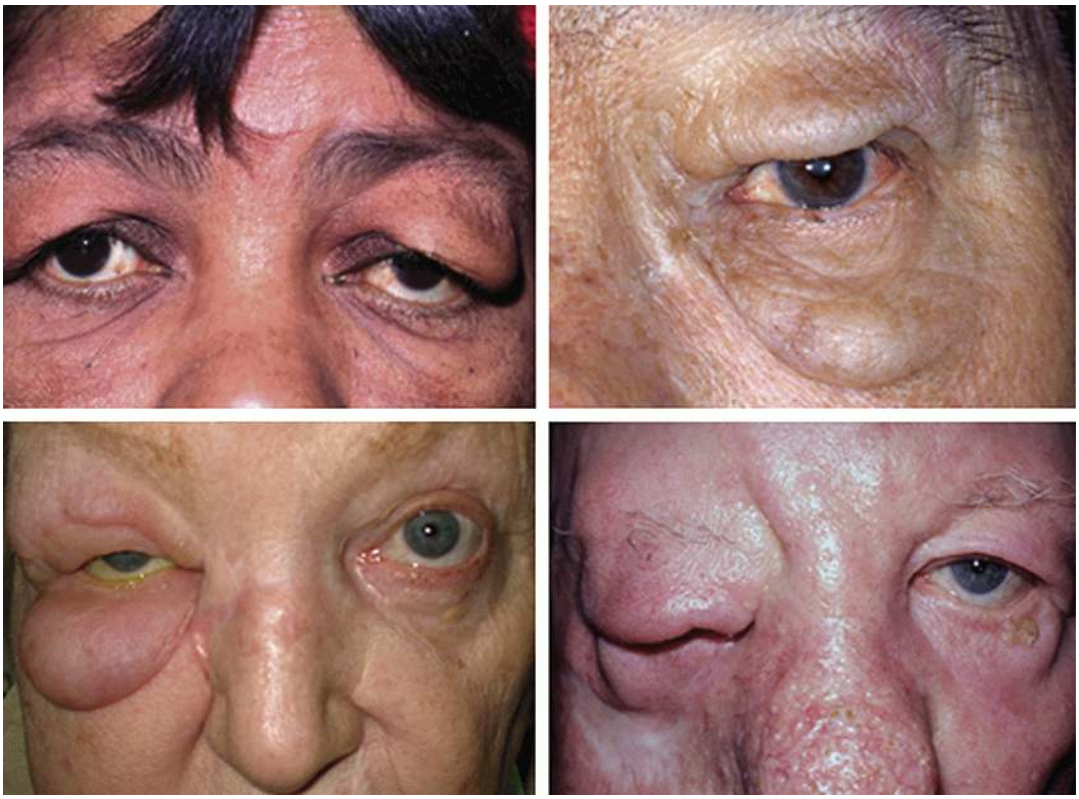

FIGURE 85.2 The spectrum of manifestations of lymphedema involving the eyelids.

Differential Diagnosis

The generic use of the term "lymphedema" has been applied to any patient with eyelid edema, but lymphedema is a specific condition, and it is important to avoid the liberal use of the term in every patient with a swollen eyelid since this might lead to serious clinical errors.[1,32] An analogy can be made with the erroneous use of the term "hemangioma" in every patient with an orbital vascular lesion.[32] The list of disease conditions mimicking lymphedema is extensive and is summarized elsewhere in the literature.[11,12] Detailed history taking is pivotal in establishing the diagnosis of lymphedema as most patients are not aware of a causal association except in cases related to trauma or surgery. However, even after an exhaustive diagnostic workup, the diagnosis may still be elusive.[3] The diagnostic workup should include all the diseases causing chronic eyelid edema, categorized into inflammatory, infectious, neoplastic, or miscellaneous causes. The more important causes to consider include thyroid orbitopathy, idiopathic orbital inflammation, blepharochalasis, sarcoidosis, floppy eyelid syndrome, and angioedema.[3,11,12,33,34] There is a significant clinical, histopathological, and even immunohistochemical overlap between lymphedema and giant cell angiofibroma which is a curious neoplasm suspected of being a variant of solitary fibrous tumor.[20,23,35] This overlap is so substantial that some authors suggest that giant cell angiofibroma and lymphedema represent variations of the same process.[23]

It should not be difficult clinically to differentiate lymphedema from angioedema, which is an abrupt inflammatory allergic reaction of the subcutaneous tissue and the reticular dermis.[36] Unlike lymphedema, the onset of angioedema typically is more rapid, usually over a few hours, and is associated with a history of intake of a known allergen through ingestion, inhalation, or via parenteral administration, at least in patients with nonhypersensitivity angioedema (Chapter 48).[37] In addition to acute onset, the edema in angioedema is usually nonpitting, asymmetric, and has a tendency not to involve gravitationally dependent areas.[34]

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Treatment

Because the underlying pathophysiologic and cellular mechanisms that cause lymphatic dysfunction remain poorly understood, the available treatment options for lymphedema are palliative at best.[4] In patients with Morbihan disease, oral preparations include the use of tetracycline-based antibiotics for prolonged periods (200 mg daily for 4-6 months); however, the response is usually partial.[5] The underlying mechanisms behind the efficacy of tetracyclines in rosacea include downregulation of proinflammatory cytokines, inhibition of neutrophil chemotaxis, and inhibition of matrix metalloproteinases.[1,2,3] Alternatively, oral isotretinoin may be prescribed in rosacea lymphedema (40 mg daily for 6 months), but the results are underwhelming.[5] Oral steroids also have been tried in patients with eyelid lymphedema, but the response is partial and the disease tends to recur after cessation of steroids.[5] A steroid/antibiotic combination oral therapy may provide a better treatment response than either treatment alone, although it may be associated with more sinister side effects.[5]

OFG and its subentities including MRS are difficult to treat, and there is no gold standard of treatment at this time.[27,29] The list of therapeutic options is long and is mostly based on case reports. These include corticosteroids (local, intralesional, and systemic), antibiotics (metronidazole, minocycline, or doxycycline), antileprosy therapy (dapsone, clofazimine), and immunosuppressive therapy (azathioprine, infliximab, adalimumab, or etoposide).[27,28,29]

As a general rule, the aforementioned systemic medications either in oral or even parenteral form do not usually work because they fail to be delivered locally in ample concentration, as the chronic perivascular inflammation and the abundance of interstitial fluid that accompanies lymphedema limit their reach.[3] Therefore, local injections theoretically may have a potential role in management.[3] Some patients may show a partial response to intralesional injection of steroids, either alone or in combination with surgical debulking.[3] Injection techniques vary, but a general rule is to inject a 50:50 mixture of triamcinolone and dexamethasone locally into the eyelid tissue. A total volume of 1.5 to 2 mL is distributed evenly in three divided doses and injected in three different regions of the eyelid.[3] Injections may be repeated after 6 months if recurrence occurs.[3]

Patients with festoons and malar edema may benefit from the intralesional injection of tetracyclines including doxycycline.[38] Theoretically, the therapeutic benefit is twofold. In addition to the profound immunomodulatory potential of tetracyclines, their sclerosing potential, whereby they induce collagen and fibrin deposition and create dense adhesions and fibrosis, also is significant.[16,38] It is not entirely implausible that the periocular injection of tetracycline/doxycycline may be beneficial in patients with Morbihan disease as well, and at least with regards to rosacea, although this has not been reported previously and remains hypothetical at best.

More recently, promising results were observed with the topical application of anti-T cell immunosuppressive drugs such as tacrolimus in lymphedema patients both in experimental and clinical studies. This was shown to be highly effective in treating established lymphedema, with a dramatic improvement in lymphatic function in treated animals.[39,40,41] Topical tacrolimus has not been used for eyelid lymphedema, and the dramatic response mentioned earlier was observed in lymphedema elsewhere in the body, as well as in lip edema in patients with OFG.[39,40,41] There are, however, a few case reports where tacrolimus was used with variable success in other types of eyelid edema like psoriatic eyelid edema, and eyelid edema associated with dermatomyositis.[42,43] It is quite possible, though unproven, that topical tacrolimus may have a therapeutic role in eyelid lymphedema as well.

Surgical excision of the lymphedematous tissue may be the most beneficial option particularly in patients with a significant functional and cosmetic impairment.[1,2] Through a standard blepharoplasty incision, debulking of the lymphedematous subcutaneous tissue along with the thickened pretarsal and preseptal orbicularis muscle is undertaken. This should be coupled with fixation of the lateral canthal tendon if the lymphedema involves the lower eyelid or levator tightening if the upper eyelid is involved. Frost sutures may also be used to fix the eyelid in position.[8] A slightly more involved approach consists of a pinch excision of the skin and subcutaneous tissue akin to the pinch technique used in upper eyelid blepharoplasty. The pinched skin is marked, and the base is gently clamped with artery forceps and excised. This is followed by the debulking of subcutaneous tissue.[33] Combining surgical debulking with the control of the inflammatory component using anti-inflammatory medications (steroids or tetracyclines) may be the most logical approach.[3] This dual therapy may be particularly relevant in rosacea lymphedema, but then again residual disease almost always persists.[3]

Prognosis

Chronic eyelid lymphedema, regardless of the etiology, is a progressive disease with serious physical and psychosocial implications that may be challenging to diagnose and notoriously difficult to eradicate.[2,3,4,44] The inflammatory signs in patients with Morbihan disease, the archetypal example of chronic lymphedema, may respond to medical therapy but with the persistence of lymphedema,[3] and even if surgical debulking is undertaken, patients could still have a residual degree of edema.[1,2,3] In short, lymphedema has no definitive cure.[45]

Histopathology

Localized lymphedema features dilated lymphatics and dermal edema manifest as pallor of the connective tissue with increased spacing between collagen bundles (Figure 85.3).[3,20] Dermal inflammation is a constant feature and was minimal *(Print pagebreak 563)* in 50%, moderate in 12%, and marked in 38% of biopsies in the study of 23 cases of localized lymphedema by Lu et al.[20] The inflammatory infiltrate was superficial perivascular in 38% of cases, deep perivascular in 20%, superficial and deep perivascular in 42%, or follicular/perifollicular in 29%.[20] The inflammatory infiltrate may be lymphocytic with focal histiocytes[3] or predominantly plasma cells.[20] Lu et al observed lymphoid follicles in 25% of biopsies, granulomas in 12%, and neutrophils in 12% of the cases.[20] Fibroplasia with an increase in fine, widely spaced, dermal collagen bundles was present in all 24 lymphedema cases examined by Lu et al, and there were dense dermal scars in two-thirds of the biopsies.[20] All biopsies had fragmentation, clumping, and/or loss of mature elastic fibers in the reticular dermis.[20] Sebaceous hyperplasia with a peri-infundibular infiltrate of lymphocytes, histiocytes, plasma cells, and mast cells is a histological finding in extreme eyelid lymphedema associated with rosacea.[3]

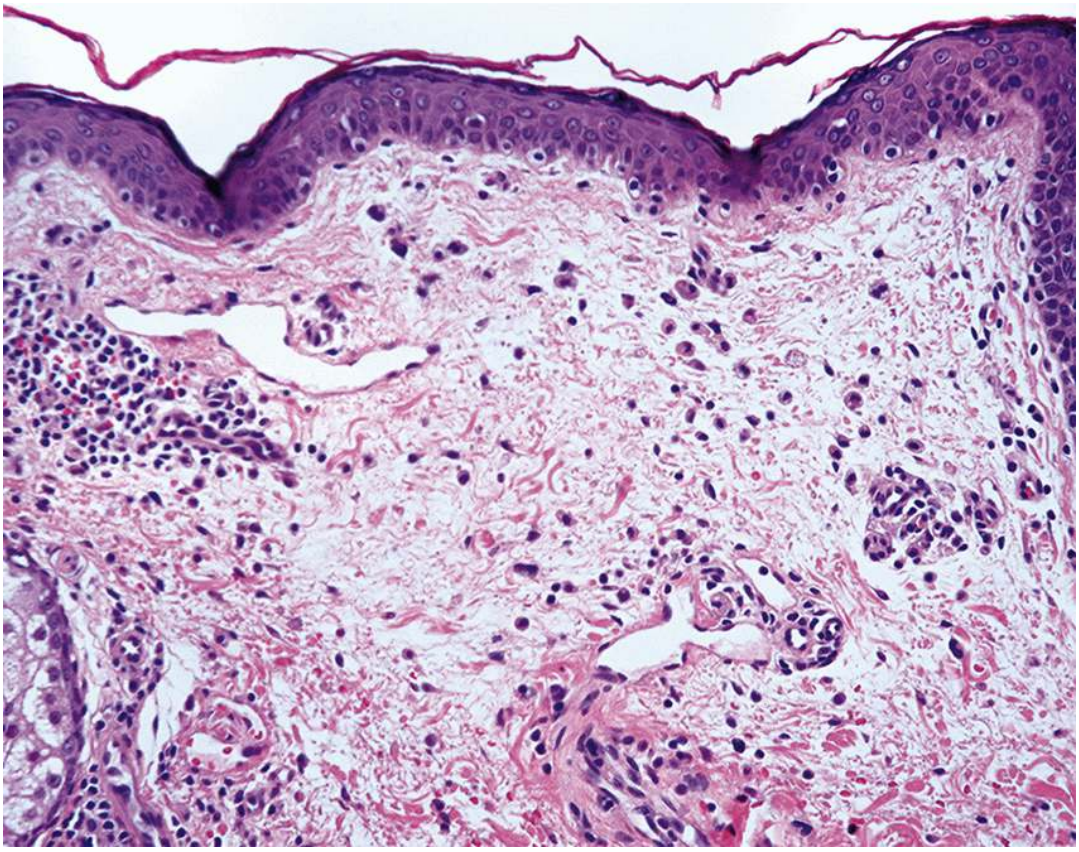

FIGURE 85.3 This right upper eyelid biopsy is from a man in his late 40s with edema for 4 months. There is lymphangiectasia, dermal edema with increased spacing between collagen bundles, and perivascular inflammatory infiltrates of lymphocytes, macrophages, and mast cells.

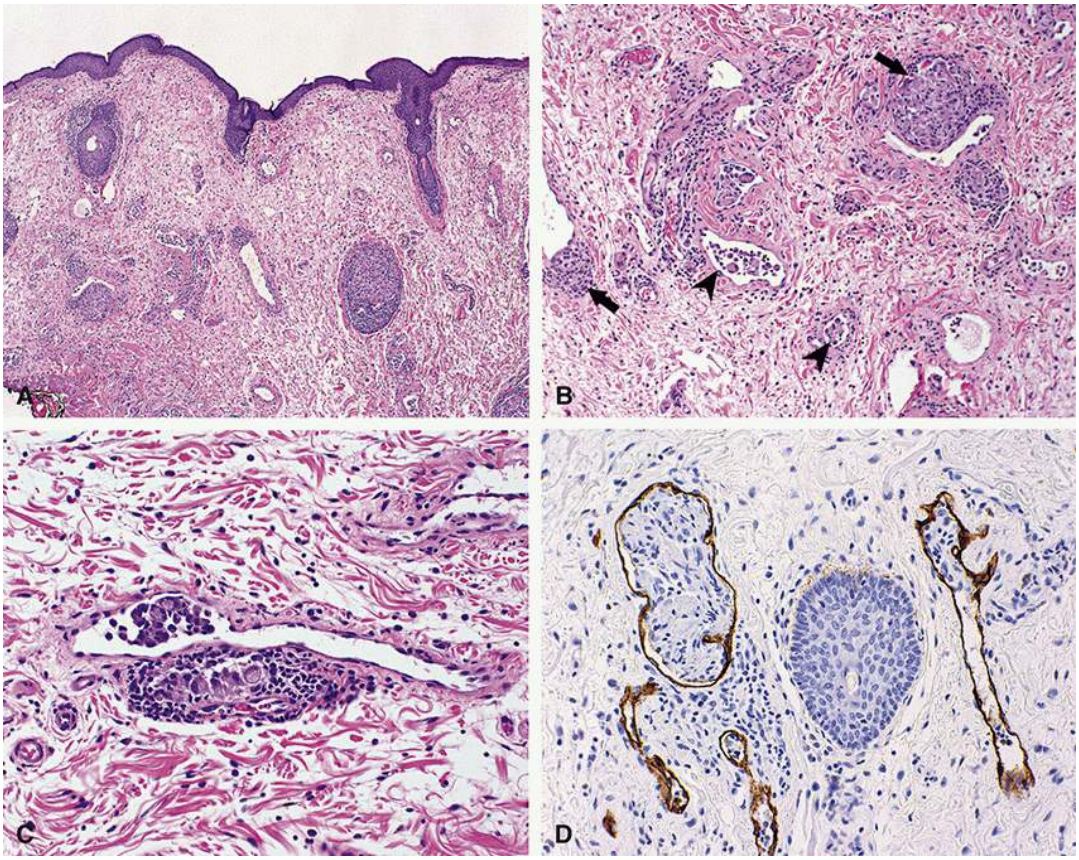

FIGURE 85.4 This woman in her middle 60s with orofacial granulomatosis had unilateral swelling of the right upper eyelid for 1.5 years. A, Lymphangiectasia and dermal edema, manifest as pallor, are prominent at low magnification. B, Perilymphatic noncaseating granulomas (arrows) and intralymphatic histiocytes (arrowheads) were frequent in this

case, but they are sparse in some cases. C, High magnification photomicrograph showing a perilymphatic noncaseating granuloma and a cluster of histiocytes and multinucleated giant cells within the lymphatic lumen. D, An immunohistochemical stain using D2-40 antibodies to podoplanin highlights the lymphatic endothelial cells. Histiocytes are in all of the lymphatics, with the large lymphatic on the left distended by histiocytes.

OFG (Figure 85.4)[29,46,47] and MRS[48,49] are characterized by dermal edema, lymphangiectasia, perivascular lymphohistiocytic inflammation, perilymphatic noncaseating *(Print pagebreak 564)* granulomas, and sometimes intralymphatic histiocytes or granulomas. Eyelid biopsies typically have perilymphatic and/or intralymphatic granulomas.[29,48,49] In our experience with 12 eyelid biopsies diagnosed with OFG, there were perilymphatic noncaseating granulomas with or without intralymphatic histiocytes or granulomas in all cases. In a few cases, granulomas were sparse, and multiple sections were needed to identify them. Immunohistochemical staining using antibodies (D2-40) to podoplanin helped confirm the intralymphatic histiocytes or granulomas (Figure 85.4D). In contrast to our results in the eyelid, Marcoval and Penin, in a study of 22 patients with OFG causing lip swelling, identified perilymphatic granulomas in 12 lip biopsies, intralymphatic granulomas in 2 biopsies, and intralymphatic histiocytes in 2 biopsies.[46] OFG may resemble cutaneous sarcoidosis or cutaneous lesions of Crohn disease, and OFG may be the initial presentation of Crohn disease in some patients.[50] The perilymphatic and/or intralymphatic distribution of granulomas, together with prominent clinical and histological edema, help to distinguish OFG from sarcoidosis, in our experience.

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CHAPTER 86

Melanocytic Nevus

Key Points

- Melanocytic nevus refers to common moles on the skin and is composed of nests of altered melanocytes
- Cutaneous melanocytic lesions are designated by the histopathologic location of melanocyte cells relative to the dermis-epidermis junction
- Junctional nevi have nests of nevus cells only at the junction
- Intradermal nevi are the most common type in adults and are confined to the dermis
- Compound nevi contain nevus cells at the junction and in the dermis
- Congenital melanocytic nevi have been associated with mutations in proteins of the MAPK signal transduction pathway, particularly NRAS and BRAF
- Congenital melanocytic nevi appear at birth or within the first 6 months of life and as small, flat, smooth to irregular, lightly pigmented lesions
- Divided nevi span across the palpebral fissure and lie on adjacent portions of the upper and lower eyelids
- Acquired nevi develop later in life and sunlight exposure is a risk factor for their development
- Management includes surveillance for changes in size, texture, shape, or color suggestive of malignant transformation
- Surgical removal is indicated for cosmetic concerns, or for changes in size, color, or progressive elevation
- The prognosis is generally good and the risk of malignant transformation is about 14% during a lifetime

The term “nevus” is used to describe a variety of benign neoplasms or hamartomas composed of melanocytes.[1] Melanocytic nevus refers to common moles on the skin. Melanocytes are derived from the neural crest, and during embryogenesis, they migrate to selected ectodermal sites in the skin, meninges, eyes, inner ear, vaginal epithelium, bones, and heart. In the skin, melanocytes normally are located evenly distributed in the basal layer of the epidermis. In melanocytic nevi, nests of altered melanocytes are distributed in the epidermis and/or the dermis. Cutaneous melanocytic lesions are broadly designated by the histopathologic location of melanocyte cells relative to the dermis-epidermis junction. Junctional nevi have nests of nevus cells only at the junction. Dermal nevi have nests of nevus cells only in the dermis, and compound nevi contain nevus cells at the junction and in the dermis.[2]

Junctional nevi clinically present as flat, well-circumscribed brown to black macules anywhere on the body. They appear during childhood or early adolescence.[3] Intradermal nevi are the most common type of melanocytic nevi and are mostly found in adults.[3] They show essentially no junctional activity and are confined to the dermis where they are arranged in nests and cords.[4] They may show a depigmented halo around the pigmented lesion.[3,4] The depigmented halo shows an absence of melanin pigment and melanocytes with inflammatory cells.[3] Compound nevi occur more commonly in children and adolescents.[3] Clinically, they appear as a pigmented papule or plaque.[4]

Melanocytic nevi can be congenital, present at birth or shortly thereafter, or they may be acquired. The acquired type usually begins in childhood in the basal epithelium where it presents as a junctional nevus and gradually migrates into the dermis in young adults where it becomes a compound nevus. Later in life, they tend to reside entirely in the dermis as a dermal nevus.[5] The average young adult has about 15 cutaneous nevi and the eyelid is occasionally affected.[3] The most common types of melanocytic nevi that can affect the eyelids are congenital, acquired, blue nevus, and Spitz nevus.

A congenital melanocytic nevus (CMN) may be defined as a lesion present at birth or within the first 6 months of life. It can be seen

on the skin anywhere on the body and is seen in about 1% to 2% of newborn infants.[4,6,7] Most are less than 10 mm in diameter, but occasionally they may be large.[4] Giant CMN is very rare, occurring in 1/20,000 to 1/500,000 newborns.[8] They are an important entity to recognize because potentially they can be associated with complications, such as developmental anomalies, neurocutaneous melanocytosis, melanoma, and psychosocial impairment.[9] The most recent consensus classification of CMN is based on several factors including the predicted adult size, the number of satellite lesions, the anatomic location, color heterogeneity, surface rugosity, presence of hypertrichosis, and presence of dermal or subcutaneous nodules.[10]

On the eyelid, lesions can vary in size, and the intensity of pigmentation can diminish during the first year.[11] Congenital melanocytic nevi occurring on the eyelid are uncommon.[12] They may be small and isolated only to the eyelid, or they can be large, extending to the adjacent periorbital or facial skin.[13,14,15] Large or heavy nevi on the upper eyelid can be associated with mechanical ptosis. On the lower lid, exophytic growth of the nevus may produce a warty excrescence that can cause secondary entropion.[12] Growth of eyelashes associated with CMN can be disorderly resulting in corneal abrasion.

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For small-sized CMN, the risk of malignant transformation to melanoma is very rare,[16] estimated to be less than 1%, and it tends to begin at puberty.[8,17] But large and giant melanocytic nevi carry a greater risk during the first 5 years,[18] estimated to be 4.6% over 30 years.[9,19,20,21] But regardless of size, rapid growth, color change, nodular elevation, pain, or bleeding are worrisome and should prompt immediate evaluation.

Divided congenital nevus of the eyelids, also known as a kissing nevus, split ocular nevus, or panda nevus, was first described in 1919 by Fuchs.[22] This is a congenital compound nevus that affects portions of both the upper and lower eyelids. These nevi extend to the eyelid margins so that when the eyelid closes the two nevi touch, or “kiss.”[13] Kissing nevi arise during melanocyte migration from the neuroectoderm to the epidermis during the 12th to 14th-week stages of gestation. The nevus forms on the eyelids during the period of eyelid fusion.[23,24,25,26] During this period, the nevus is a single lesion overlying the zone of future eyelid separation that begins in the 20th to 24th week of gestation,[27,28] dividing the nevus into segments that lie on adjacent portions of the upper and lower eyelids.

Acquired melanocytic nevi (AMN) develop later in childhood, adolescence, or in adults most commonly in the 30 to 40 year age range. The major environmental risk factor for their development is exposure to sunlight.[29,30,31,32,33] Other risk factors include fair skin color, red hair, blue eyes, a tendency to freckle, and a propensity to sunburn.[33,34]

The risk of malignant transformation of AMN has been estimated to be 1 per 2000,[35,36,37] but the molecular events responsible for the progression from AMN to melanoma remain unclear. An increased risk for melanoma occurs in patients with more than 50 melanocytic nevi and those with clinically atypical nevi. Additional risk factors include a family history of melanoma, a history of excessive UV light exposure, and lightly pigmented skin with a tendency to burn.[38,39] In children with acquired nevi, the lifetime risk of transformation from benign nevus to melanoma is only approximately 1 in 10,000, with more than 50% of melanomas occurring de novo, on previously normal skin.[40,41] Children with a history of chemotherapy or other immunosuppressive medications, such as for organ transplantation, are also at increased risk of both irregular moles and melanoma.[42,43]

Melanocytic lesions of the conjunctiva include nevus, melanosis, intermediate melanocytic proliferations, and malignant melanoma,[44,45,46] of which the circumscribed nevus is the most common. They generally become clinically apparent in the first or second decades of life where 58% of cases are seen in pediatric and adolescent patients. Three-fourths of conjunctival nevi are of the compound type, with 24% subepithelial, 3% junctional, and 1% blue nevus.[45] Conjunctival nevi present as dwell-defined, variably pigmented, slightly elevated lesions that may become more pigmented over time.[45,46] They most commonly are located on the bulbar conjunctiva (60%-83%), followed by the caruncle (12%-29%), and the palpebral conjunctiva (1%-2%), and less than 1% may involve the cornea.[44,45,46] Less than 1% may transform into malignant melanoma.[45]

The common blue nevus is composed of melanocytes in the mid- and upper dermis. It is most common in children and young adults but can occur at any age.[3,47] They present most often as small, solitary, pigmented papules, plaques, or nodules with a dark-bluish or blue-black coloration.[48,49,50] The bluish color is caused by the Tyndall effect resulting from the scattering of the short-wavelength component of visible light by melanin particles. Blue nevi occur on any part of the body, including on the eyelid and conjunctiva.[51,52,53,54,55,56,57,58]

The cellular blue nevus is a variant of blue nevus composed of melanocytes with islands of neural crest-derived epithelioid and spindle cells that fail to complete their normal migration to the epithelium.[59,60] The most typical sites of occurrence are the dorsal aspects of extremities, scalp, and buttocks. Other locations include male and female genital tract, breast, subungual mucosa, eyelids, orbit, and conjunctiva.[61,62,63,64] It is seen in all age groups, but are most common in adults younger than 40 years.[65]

Spitz nevus, also known as spindle cell nevus, epithelioid cell nevus, and benign juvenile melanoma, is rare and diagnosed in only 0.5% to 1.0% of excised nevi in children.[3] Spitz nevi occur on the trunk, extremities, the lower face, and have rarely been described

in the eyelid,[66,67,68] or the conjunctiva.[69,70] It usually appears as a dome-shaped, hairless, small pink to lightly pigmented papule or nodule less than 1 cm in size.[4,66] These lesions may appear suddenly and undergo rapid growth, hemorrhage, and change of color or may cause pruritus.[71] They are more common in children, but can also be seen in adults. Spitz nevi are rare in black patients and more common in females, especially in patients older than 15 years.[72] Nonpigmented lesions predominate in the head and neck and pigmented ones in the lower extremities.[66]

The pigmented spindle cell nevus of Reed may be a morphologic variant of Spitz lesion with histologic features concerning for melanoma.[73,74,75] It is usually a small, rapidly growing, well-circumscribed, darkly pigmented lesion and has only rarely been reported on the eyelid[76] and conjunctiva.[77]

Etiology and Pathogenesis

Melanocytic nevi are benign clonal proliferations of cells that express a melanocytic phenotype.[78] They are a heterogeneous group of neoplasms with varying clinical and molecular features,[79] and they share associated mutations with melanomas. Congenital melanocytic nevi (OMIM #137500, 1p13) have been associated with mutations in proteins of the mitogen-activated protein kinase (MAPK) signal transduction pathway, particularly NRAS and BRAF, and a relationship between nevus size and the corresponding genetic mutation has been described.[79,80,81,82] Smaller congenital nevi more frequently have a BRAF mutation, but NRAS mutations are more frequently seen in medium and large nevi.[79,83,84,85,86] AMN and blue nevi also harbor oncogenic mutations in BRAF and NRAS, but Spitz nevi (OMIM #137550, 11p15) have been *(Print pagebreak 568)* linked to HRAS and BAP1 alterations and kinase fusions.[79] Most of the gene alterations associated with melanocytic nevi have also been described in the development of melanoma, but contrary to melanomas, nevi undergo senescence where the initial growth phase is followed by loss of proliferative activity and stabilization of size.[79] Therefore, at least some melanocytic nevi are likely benign clonal tumors that temporarily undergo proliferation through BRAF signaling followed by growth arrest.[87]

Not only do acquired nevi and melanomas share a common genetic basis, but they also share common environmental risk factors such as fair skin and a tendency to sunburn.[37,88] Also, 20% to 30% of melanomas arise from preexisting melanocytic nevi, emphasizing the genetic basis underlying both.[89]

Clinical Characteristics

Congenital melanocytic nevi appear at birth or within the first 6 months of life. They are generally small, initially flat with smooth to irregular borders, and can be pink, lightly pigmented or more darkly pigmented in shades of tan, brown, or black (Figures 86.1 and 86.2). They usually are not associated with telangiectasia, madarosis, or ulceration, which helps to distinguish them from some common simulating lesions. Most CMN are solitary, but they may be multiple or even confluent.[10] They may show heterogeneous pigmentation and sometimes develop coarse dark hair and become more elevated and rugose over time (Figure 86.3).[90,91] Rarely they can be flat and diffuse (Figure 86.3D). Occasionally, proliferative nodules may develop within the nevus.[92] Small satellite lesions can be present at birth or develop later in infancy or childhood. Occasionally, CMN may regress spontaneously,[93] sometimes preceded by the development of a local depigmented halo surrounding the lesion.[94]

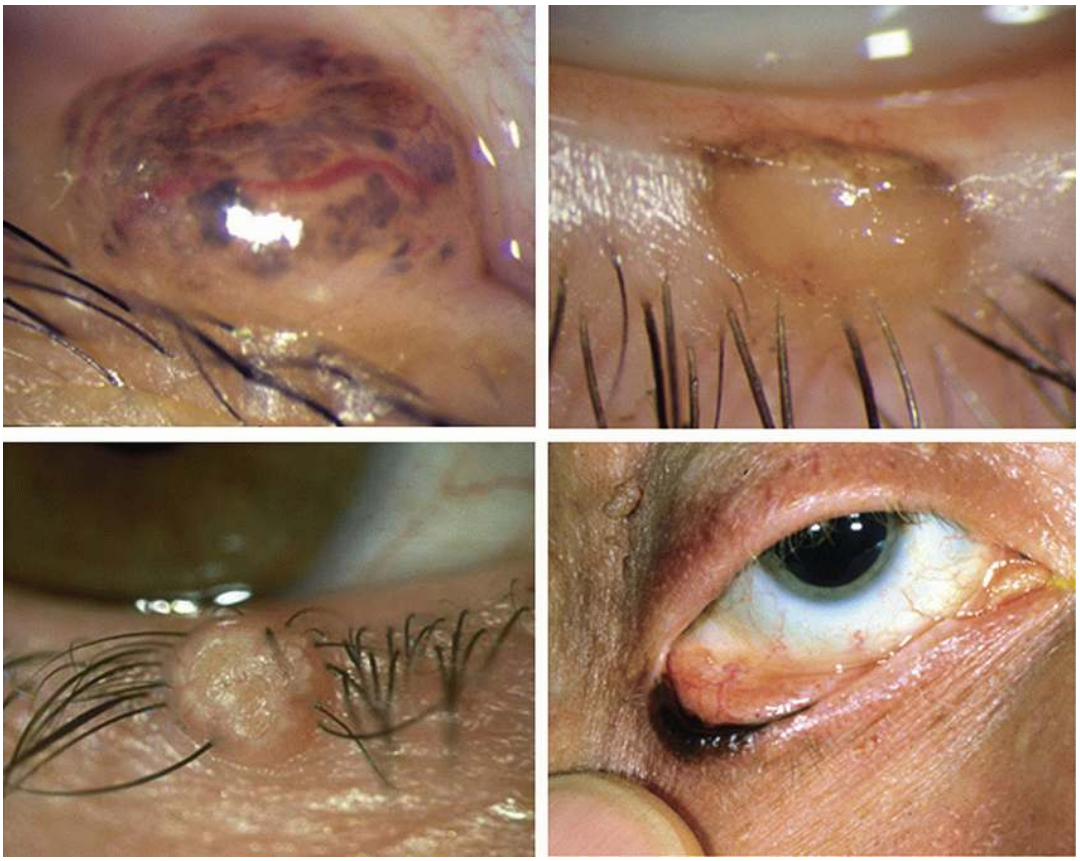

FIGURE 86.1 Marginal nevi along the cutaneous/conjunctival border.

Divided nevi span across the palpebral fissure and lie on adjacent portions of the upper and lower eyelids (Figure 86.4). They vary in size and may be small, located on the middle thirds of the eyelid margins, or they can be large, extending across the canthal angles onto the forehead, nose, or cheek.[95,96] Occasionally the bulbar conjunctiva may also be involved.[97]

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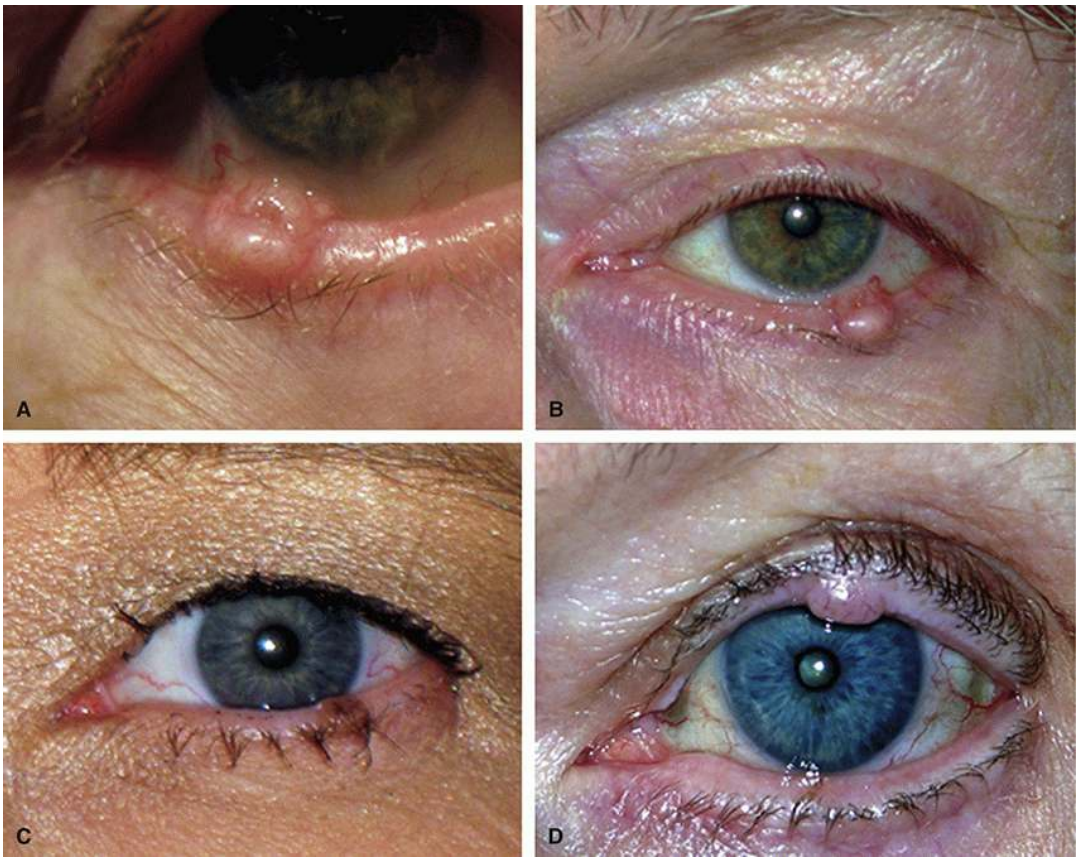

FIGURE 86.2 A and B, Compound melanocytic nevi. C and D, Intradermal melanocytic nevi.

AMN usually appear during childhood, adolescence, or early adulthood, initially appearing as flat, smooth, light to dark brown macules, and less commonly black or flesh-colored lesions. They may be elevated in about 25% of cases and may be papillomatous or have a course rugose surface in 20% of lesions.[98] Most lesions begin as junctional nevi but later develop into compound nevi with a more nodular appearance. Lesions are often multiple, with about 39% located on the head and neck, and 39% on the trunk.[98] Most patients with acquired nevi have a Fitzpatrick skin type of III or IV.

Sun exposure represents an important environmental factor influencing the number and location of nevi that develop during childhood.[99] White children living in tropical climates tend to develop a greater number of nevi at an earlier age than those living in temperate locations.[40]

Cutaneous blue nevi present as a flat to slightly elevated, smooth macule or papule, with a gray, blue, or bluish-black color (Figure 86.5).[55,100] The blue appearance is due to the Tyndall effect, but the specific color is affected by the thickness and the depth of the lesion.[101] They frequently appear during the first and second decades of life, most commonly on the extremities, buttocks, scalp, and the eyelid margin.[52] Cellular blue nevi on the conjunctiva appear as black lesions with diffuse margins and may be unifocal or multifocal.[57,61,102,103]

Differential Diagnosis

The most important lesion in the differential diagnosis of melanocytic nevus is malignant melanoma. However, these are usually more often asymmetric, irregular in outline, with heterogeneous pigmentation, and may be associated with focal erythema, atrophy, or ulceration. Pigmented basal cell carcinomas tend to arise in older individuals, more often on the lower rather than the upper eyelid. They often have central ulceration with upraised telangiectatic margins. Pigmented apocrine hidrocystomas are usually restricted to the eyelid skin at or near the margins or the caruncle, have a smooth surface, and are compressible. Pigmented seborrheic keratosis (melanoacanthoma), actinic keratosis, and squamous papilloma can also be confused with melanocytic nevi. *(Print pagebreak 570)* Mucinous neuroendocrine carcinoma is another bluish-appearing lesion on the eyelid margin that can be confused with a blue nevus. Postinflammatory hyperpigmentation occurs after an inflammatory event, acne, or cosmetic surgery and is seen more commonly in patients with darker skin types. Other conditions in the differential diagnosis include iatrogenic pigmentation caused by drugs such as minocycline and tattoos.

FIGURE 86.3 A-C, Elevated, rugose melanocytic nevi with hair. D, Flat diffuse nevus of the lower eyelid and face. A, (Courtesy of Dr, Richard Anderson).

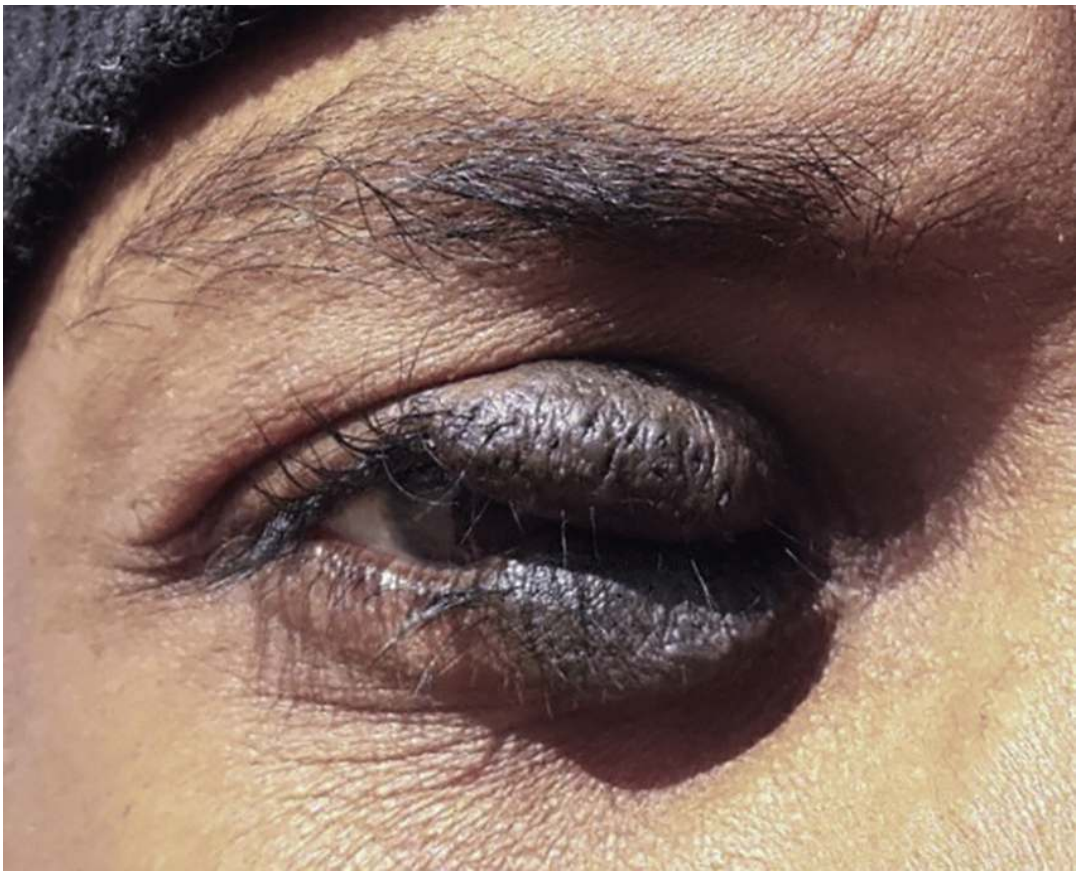

FIGURE 86.4 Divided (Kissing) nevus involving the medial upper and lower eyelids.

Treatment

The management of small- and medium-sized CMN depends upon factors such as location, size, and aesthetic concerns.[104] Surveillance for changes in size, texture, shape, or color suggestive of malignant transformation is most important after puberty since the risk of melanoma in small nevi is extremely low before adolescence.[40] Sun protection should also be stressed in all patients with melanocytic nevi.

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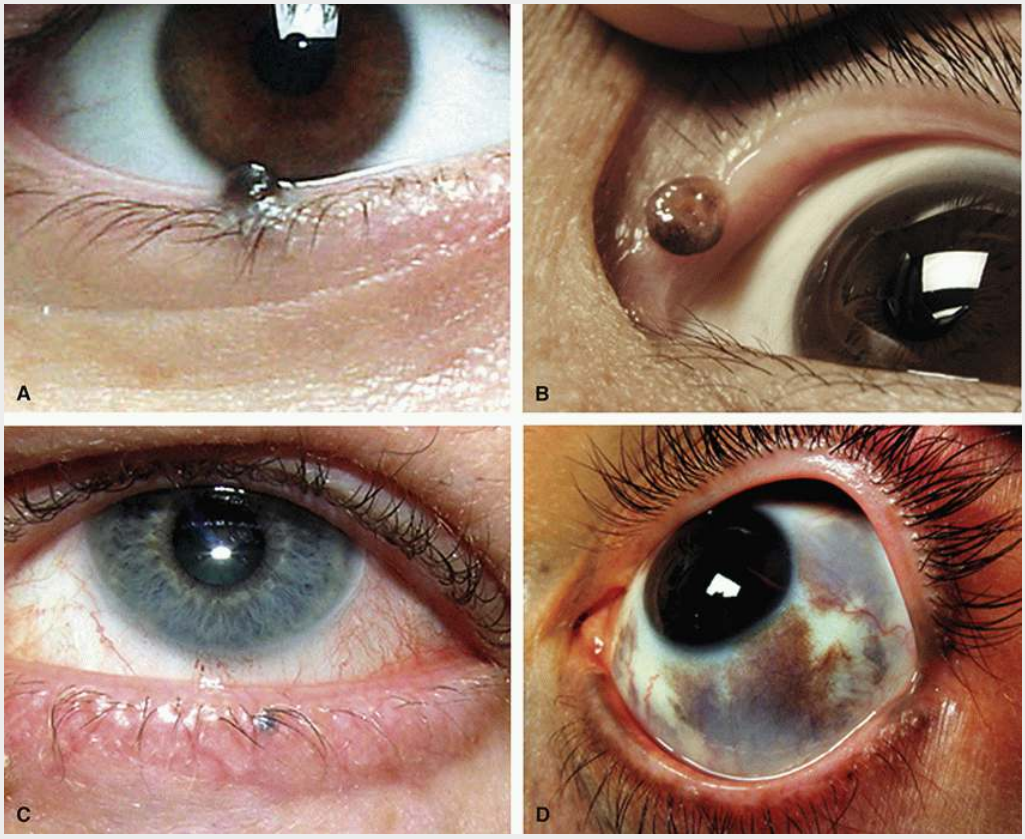

FIGURE 86.5 A-D, Congenital blue nevus of the eyelids. C and D, (Courtesy of Dr. Robert Goldberg).

Removal of melanocytic nevi at any age is indicated primarily for cosmetic concerns, and less frequently for worrisome changes in size, color, or progressive elevation. Depending upon size and location, the most common techniques have been surgery, laser therapy, and dermabrasion. Even though the goal of surgery is mostly for aesthetic improvement, some nevus tissue may have to be left behind to minimize any functional compromise to the eyelid margin. Small lesions can be excised with anterior lamellar skin resection with primary closure. Nevi involving up to one-fourth of the upper or lower eyelid margin can be excised with full-thickness wedge resection and primary layered repair. Larger eyelid resections, particularly in younger patients where there is no significant tissue laxity, may require more complex reconstruction techniques, including lid-sharing procedures. Nevi extending onto the forehead, temple, and cheek may require local flaps and skin grafts. It is important to understand, however, that more than half of cutaneous melanomas seen in these patients arise from previously normal skin and not from the transformation of benign nevi so that prophylactic excision of a nevus does not necessarily prevent a melanoma.

The Q-switched Nd:YAG laser is the laser of choice for the treatment of dermal and junctional pigmented lesions, especially in dark skin.[105] This laser targets melanosomes in melanocytes with an ultrashort pulse width and adjustable spot size.[106] The Q-switched Nd:YAG laser at a wavelength of 1064 nm is ideal for dermal lesions because of its deeper penetration and poor absorption by epidermal melanin.[105,107] Laser treatment of large nevi in the periorbital area has been suggested for the shallower, peripheral portions of the lesion to reduce it to a smaller size for surgical excision.[108]

Dermabrasion has been described as a treatment for a divided nevus that is limited to the superficial dermis.[109,110] Limited reports have shown that dermabrasion can result in an appreciable and stable reduction of hyperpigmentation, although many patients may still require reconstructive surgery to improve the aesthetic result.[111] However, when the deeper dermis or

subcutaneous tissue is involved, recurrence can be seen as quickly as 4 weeks after treatment.[13,112]

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Prognosis

The prognosis for patients with melanocytic nevi of the eyelids is generally good and acceptable aesthetic results are often attainable. Lesions on the upper eyelid may cause mechanical ptosis with obstruction of the visual axis resulting in amblyopia in young children.[113,114] There is a risk of malignant transformation to malignant melanoma, particularly for large nevi with an average risk of 14% during a lifetime.

Histopathology

The histopathological features of melanocytic nevi of the eyelid skin and periocular region are similar to those occurring elsewhere on the body,[115] except for nevi at special sites that have site-related atypia (occurring on acral sites, genitalia, ears, scalp, breast, flexural skin, legs, back, and shoulder).[116,117] Melanocytic nevi are composed of nevus cells (nevomelanocytes), which are melanocytes[78] that have lost their long dendritic processes and are characteristically arranged in nests.[115,118,119] Epidermal nevus cells (type A melanocytes) are large and polygonal with eosinophilic cytoplasm, a variable amount of melanin, and sometimes form nests or clusters.[120] Upper dermis nevus cells (type A melanocytes) are large polygonal or oval cells with eosinophilic cytoplasm, a variable amount of melanin, and usually form nests or clusters surrounded by a reticulin network.[120] Cytoplasmic invagination into the nucleus often creates nuclear pseudoinclusions in dermal melanocytes,[121] but true inclusions are rare.[118] Nevus cells in the mid dermis (type B cells) are smaller than those in the upper dermis, melanin is rare, and the nevus cells may resemble lymphocytes.[120] Deep dermal nevus cells in the deep dermis tend to be smaller than those of the upper dermis, round or spindle-shaped, and only rarely contain melanin.[120] The fusiform nevus cells in the deep dermis (type C cells) may resemble fibroblasts or Schwann cells.[120] Goovaerts and Buyssens showed that the diameter and area of the nevus cell nucleus progressively decreased with the depth of localization of the cells, but there was no difference in size between cells in the epidermis and upper dermis or between cells in the middle and deep dermis.[120]

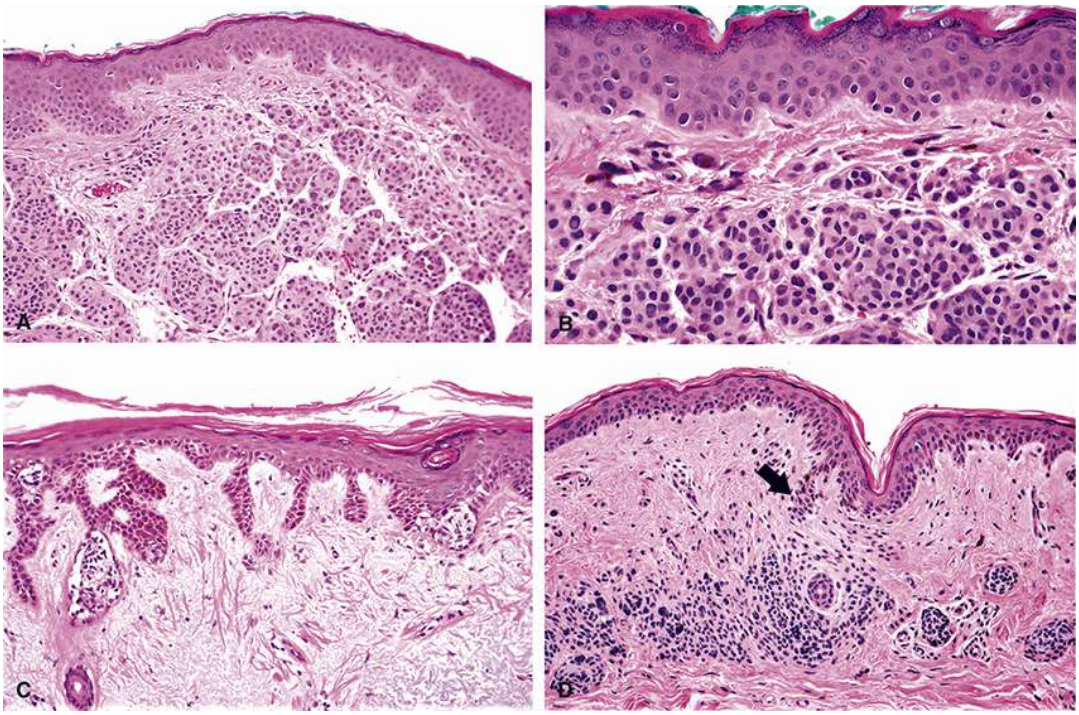

FIGURE 86.6 Common melanocytic (nevocellular) nevi are classified according to the location of nevus cells. A and B, Intradermal nevi are the most frequent nevus in the eyelid and feature nests and cords of nevus cells in the dermis separated from the overlying epidermis by an intact zone of dermal collagen. C, Junctional nevi have discrete nests of nevus cells at the junction of the epidermis and dermis, usually on the rete ridges, which often exhibit some elongation. Junctional nevi are very uncommon in the eyelid skin. D, Compound nevi have junctional (arrow) and intradermal nests of nevus cells.

The vast majority of cutaneous nevi of the eyelid are common melanocytic (nevocellular) nevi.[115,119,122] Intradermal nevi are the

most frequent nevus in the eyelid[115,119] and feature nests and cords of nevus cells in the dermis separated from the overlying epidermis by an intact zone of dermal collagen (Figure 86.6A and B).[115,118,119] Junctional nevi have discrete *(Print pagebreak 573)* nests of nevus cells at the dermoepidermal junction, usually on the rete ridges, which often exhibit some elongation (Figure 86.6C).[118] Compound nevi have both junctional and intradermal nests of nevus cells (Figure 86.6D). Junctional nevi of the eyelid skin are uncommon; only 4 of 839 eyelid melanocytic nevi (0.2%) in the study by Deprez and Uffer were junctional.[122] If a junctional nevus is present in initial sections, deeper sections often reveal compound nevi.[115,119] On the eyelid, compound and intradermal nevi may be keratotic[123] with a seborrheic keratosis-like appearance to their epidermis. Dysplastic nevi[124] of the eyelid are exceptionally uncommon in our experience, possibly due to nevi being removed early for cosmetic reasons. Dysplastic nevi accounted for only 4 of the 839 nevi (0.5%) in the study of Deprez and Uffer.[122]

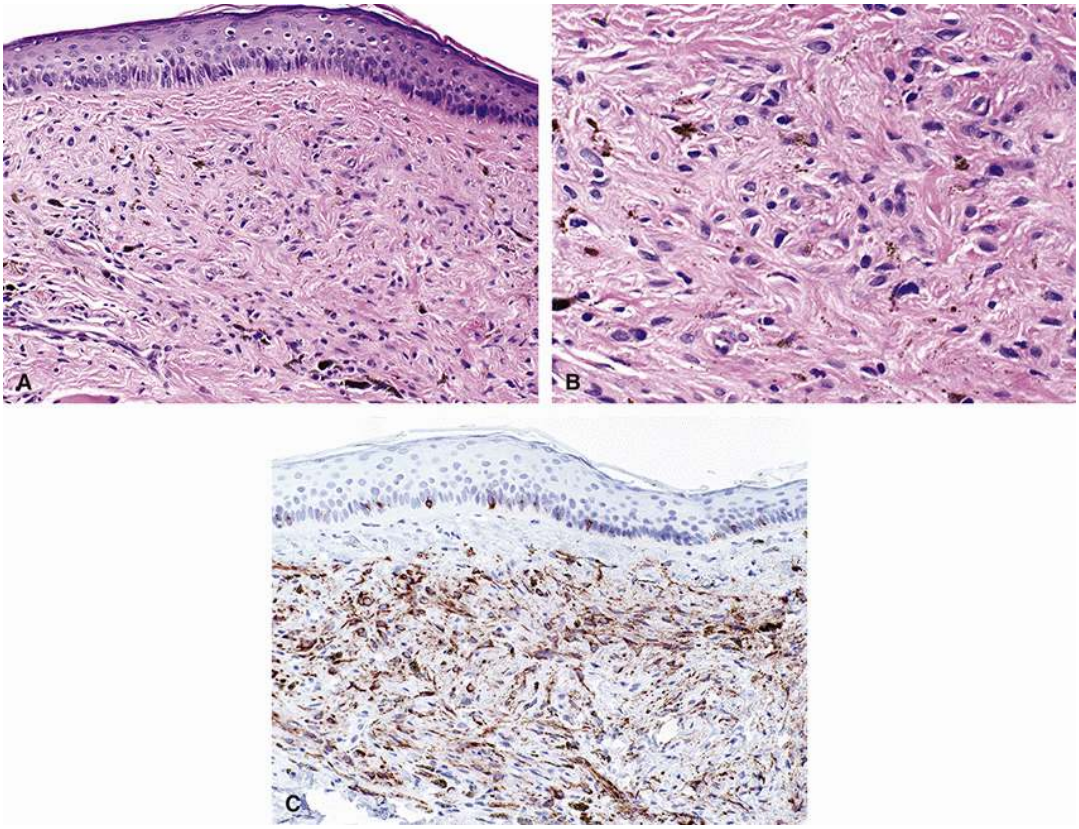

FIGURE 86.7 This common blue nevus was in the right lower eyelid of a man in his early 30s. A, The blue nevus has only scattered heavily melanin-laden spindle cells. There is a zone of normal dermis separating the blue nevus from the overlying epidermis. B, The melanin-laden spindle cells are intermixed with nonpigmented or minimally pigmented oval to spindle melanocytes. There is no cytological atypia or mitotic figures. C, An immunohistochemical stain using antibodies to MART-1 (Melan-A) highlights the spindle melanocytes comprising the common blue nevus. The presence of melanin-containing dermal melanocytes interspersed with the nonpigmented cells aids in differentiating lightly pigmented blue nevi from other spindle cell tumors such as dermatofibroma. Immunohistochemical stains using antibodies to melanocytic markers, such as MART-1, may be helpful to confirm the identity of lightly pigmented blue nevi.

Blue nevi are second in frequency to common melanocytic nevi in the eyelid skin, but they are uncommon, accounting for only 1.2%[115] to 1.5%[122] of eyelid skin nevi. The diagnostic cells in blue nevi are variably pigmented spindle-shaped dendritic melanocytes.[50,63,125] The cells are spindle-shaped, bipolar, dendritic cells thickest at their center and gradually tapering at both ends to a fine point; some have branching or dendritic processes.[126] The dendritic processes are seen best by staining with silver nitrate (Fontana-Masson stain).[126] Common blue nevi are usually in the lower two-thirds of the dermis, with a zone of normal dermis separating the blue nevus from the overlying epidermis.[126] The dendritic melanocytes are typically intermixed with elongated, oval to spindle melanocytes that resemble intermediate (type B) or deep (type C) dermal melanocytes of common (nevocellular) nevi.[50] Dendritic melanocytes are often only a minor component of a blue nevus (Figure 86.7).[50] Blue nevi lack significant cytological atypia or mitotic *(Print pagebreak 574)* figures.[50] Melanophages are present in varying numbers and are distinguished from the blue nevus cells by the absence of fine wavy bipolar dendritic processes.[126] Cellular blue nevus is a biphasic variant of blue nevus with varying proportions of classic (common) blue nevus and sharply demarcated cellular areas of spindled to oval melanocytes with clear, pale, or lightly pigmented cytoplasm.[50,63,125] The cellular areas are most often at the lesion base and extend into the deep reticular dermis and subcutaneous tissue, though sometimes the cellular areas are surrounded by classic blue nevus or form the bulk of the nevus.[50,125] Mitotic figures are usually absent or infrequent (<1 mitosis/mm^2).[127] The melanocytes in

all variants of blue nevus are usually positive for expression of HMB-45, SOX10, and Melan-A (MART-1; Figure 86.7C) but may be negative for S100 protein.[127,128] Eyelid cellular blue nevi are rare and may be confused histologically with melanoma.[56] Features that help to differentiate cellular blue nevus from melanoma are a low mitotic rate, absence of necrosis, a low Ki-67 proliferation index, and mostly uniform HMB-45 immunoreactivity.[56]

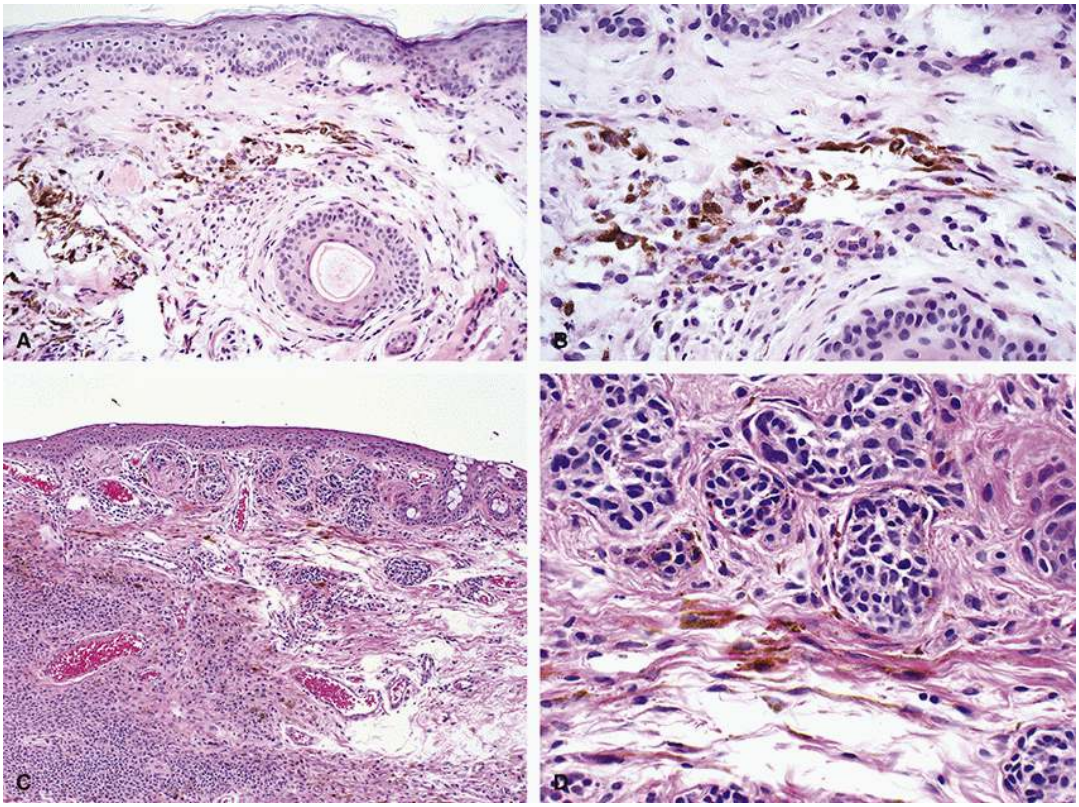

FIGURE 86.8 A and B, This combined nevus was in the central left lower eyelid of a man in his early 70s. The melanin-laden spindle blue nevus cells and nests of round to oval nevocellular nevus cells are easiest to discern at high magnification (B). C and D, This combined nevus arose in the right caruncle and plica semilunaris of a woman in her late 20s. The melanin-laden spindle melanocytes tended to be around the periphery of the round to oval nevocellular nevus cell nests.

Combined nevi feature two (or occasionally three) cytologically distinct populations of melanocytes in the same lesion[129,130,131] and may occur in the eyelid skin[122] or conjunctiva[45,55,132] (Figure 86.8). The two populations of nevus cells may be side by side or intermingled.[131] The most frequent combination is common nevus cells and spindle or dendritic blue nevus cells.[129,131] Pulitzer and coworkers found spindle cells to be more frequent than dendritic cells,[129] but Massi and LeBoit state "the dendritic cells of a 'common' blue nevus are far more often seen in combined nevi than are spindled blue nevus cells."[131] Other combined nevi are combinations of common nevus and Spitz nevus, common nevus and deep penetrating nevus, Spitz nevus and blue nevus, and common nevus and melanocytoma,[131] but we have not encountered any of these combined nevus types in our clinical practices.

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Congenital nevi are mostly compound or intradermal but have varying histological appearances.[133,134,135,136,137,138,139] Mark and colleagues were the first to report differences between congenital (n = 60) and acquired (n = 60) melanocytic nevi in 1973.[133] They concluded that congenital nevi have three diagnostic features distinguishing them from acquired nevi: (1) Nevus cells were in the lower two-thirds of the reticular dermis in 59/60 cases and the fibrous septa and adipose tissue of the subcutis in 35/60 of the congenital nevi. Acquired nevi involved the lower two-thirds of the reticular dermis and subcutis in only 2 of 60 cases. (2) The most distinctive feature of congenital nevi was the permeation of nevus cells between collagen bundles of the lower reticular dermis as single cells or in a single file (Figure 86.9), while this was "virtually absent" in acquired nevi. In congenital nevi involving the fibrous septa and subcutaneous fat, the nevus cells occurred singly as single cells or in a single file. (3) In the lower two-thirds of the reticular dermis in congenital nevi, nevus cells involved arrector pili in 42/60 cases (Figure 86.9C), nerves in 28/60, sebaceous glands in 21/60, eccrine ducts in 14/60 (Figure 86.9C), hair follicles in 10/60, blood vessels in 8/60, and lymphatics in 4/60 cases. None of the acquired nevi had nevus cell involvement of appendages, nerves, or blood vessels in the lower two-thirds of the reticular dermis.[133] Subsequent studies confirmed the observations of Mark and coworkers but noted that some congenital nevi, especially those that are small,[134,136] are indistinguishable from acquired nevi.[135,140] For example, Everett reported *(Print pagebreak 576)* that all 9 congenital nevi <1.5 cm in diameter had nevus cells only in the papillary and upper reticular dermis, 9 of

21 nevi between 1.5 and 10 cm had nevus cells confined to the papillary and upper reticular dermis, but only one of 9 congenital nevi >10 cm in diameter exhibited that pattern.[136] Barnhill and Fleischli reported slight cytological atypia in 14.9%, slight to moderate atypia in 8%, moderate atypia in 4.6%, and severe atypia in 2.3% of 87 congenital nevi removed from infants 12 months of age or younger.[137] Simons and colleagues observed cytological atypia in 70% of 197 congenital nevi, with most having mild atypia.[139] Architectural disorder and pagetoid spread of nevus cells were present in 67% and 62% of congenital nevi, respectively.[139] Only 2/197 nevi had mitotic figures.[139] Atypia did not correlate significantly with nevus size in either study.[137,139] All 130 subjects with outcome data in the study by Simons and coworkers were alive and without a diagnosis of melanoma after a mean follow-up of 8.4 years (range 7 months to 21.3 years).[139] Congenital melanocytic nevi may also display proliferative nodules that are usually <5 mm in diameter.[141] The proliferative nodules are cohesive cellular aggregates in the dermis with higher cellularity and larger cells than the associated nevus.[141] The cells in the proliferative nodule blend with the adjacent nevus cells without an abrupt interface.[141] Proliferative nodules have little or no inflammation and lack necrosis unless ulcerated.[141] Proliferative nodules were present in 5% of the 197 congenital nevi studied by Simons et al, and none of the subjects developed a melanoma.[139] Other studies have noted proliferative nodules in 2.9% to 19% of giant congenital melanomas.[142] Proliferative nodules may exhibit atypia,[92] potentially causing difficulty differentiating them from melanoma.[142,143] Histological features that distinguish atypical from routine proliferative nodules are sharp demarcation, expansile growth that does not invade adjacent adnexal structures, effacement of the epidermis with loss of rete ridges, variable pleomorphism, and the presence of mitoses.[92] Both the Ki-67 proliferation index and phosphohistone H3 labeling index are significantly higher in atypical vs routine proliferative nodules, but these indexes are not significantly different between atypical proliferative nodules and dermal melanoma.[92] In lesions with numerous mitosis, histological features that help to distinguish an atypical proliferative nodule from a dermal melanoma are a destructive growth pattern with obliteration of local structures, ulceration, necrosis, uniform high-grade nuclear atypia, and the presence of atypical mitoses.[144,145] Reduced immunohistochemical expression of H3K27me3, a regulator of chromatin remodeling-controlled transcription, favors the diagnosis of nodular melanoma in congenital melanocytic nevi.[146,147] Despite the atypical features, there are no reported examples of metastatic disease arising from an atypical proliferative nodule.[92]

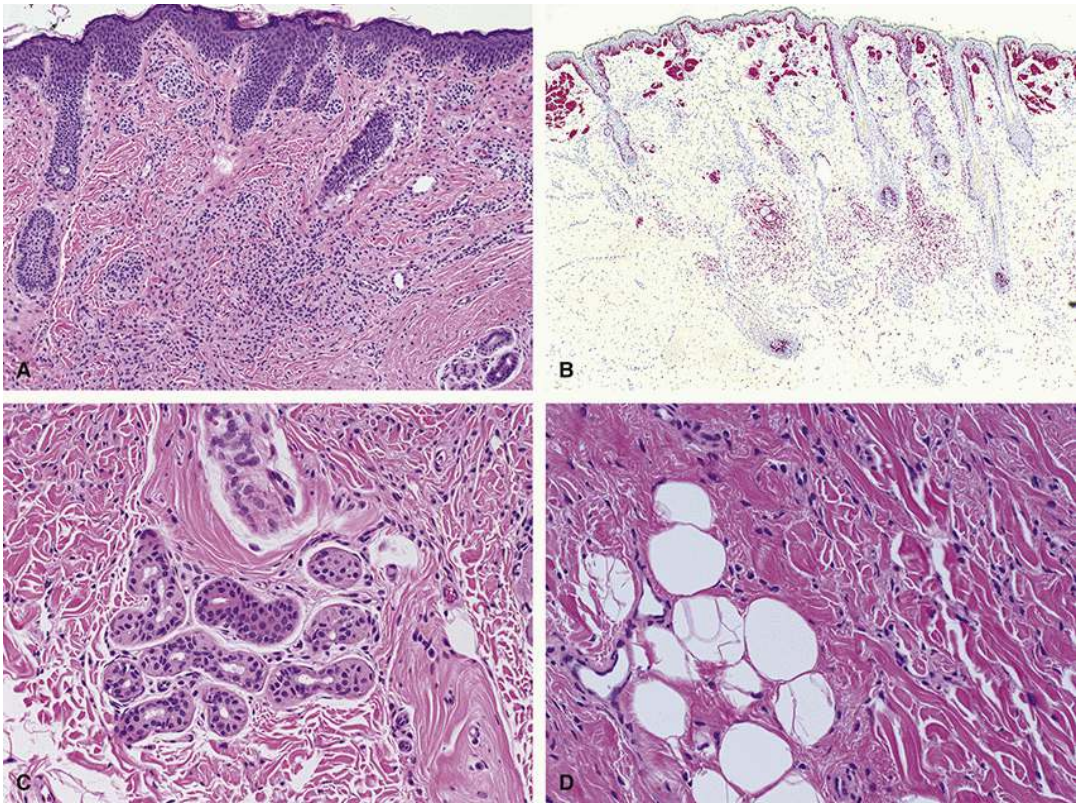

FIGURE 86.9 This congenital compound nevus from the right lower eyelid of a 3-year-old girl also involved the upper cheek. It was visible at birth and grew slowly larger and darker over the next 3 years. A, The compound nevus has small nests of nevus cells at the epidermal-dermal junction, in the papillary and superficial reticular dermis, and in the deep reticular dermis. In the deeper aspect of the lesion, the nevus cells percolate between collagen bundles as individual cells or in a single file. B, A section stained using antibodies to MART-1 shows the nevus cells extending into the deep reticular dermis. The superficially located nevus cells are nested, while those in the deep dermis form single files or occur individually. C, Nevus cells form single files between collagen bundles, insinuate into an eccrine lobule, and infiltrate an arrector pili muscle. D, Nevus cells form single files between collagen bundles in the deep reticular dermis.

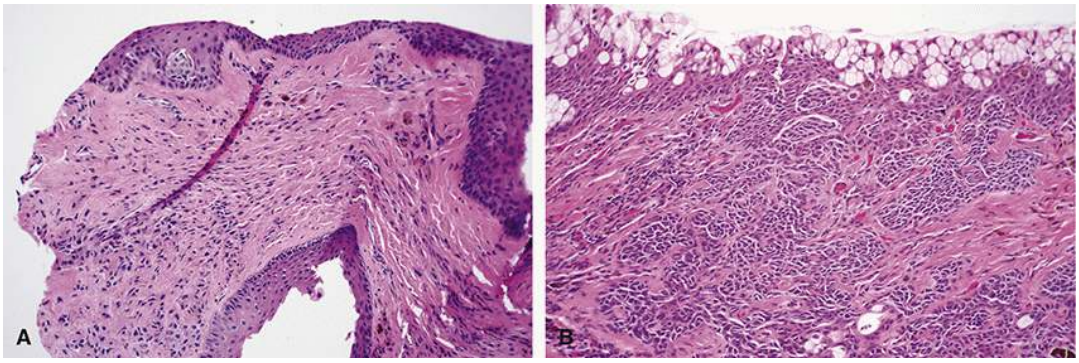

FIGURE 86.10 A, This compound combined conjunctival nevus is composed of a mixture of nevocellular nevus cells and spindle blue nevus cells. The nevus was present around the punctum of the right upper eyelid for 35 years before being biopsied due to a change in color over 8 months. The tissue was sectioned parallel to the epithelial surface resulting in epithelium on both sides of the substantia propria. B, This compound nevus involved the medial right lower eyelid conjunctiva in a child who had other nevi in the right caruncle and the right lower eyelid skin. The numerous goblet cells in the conjunctival epithelium result from the biopsy being from the medial lower eyelid.[150]

Conjunctival nevi rarely involve the eyelid.[45,148,149] Shields and coworkers noted only three nevi of the tarsal conjunctiva in 410 consecutive patients with conjunctival nevi (0.7%),[45] while Kim and colleagues identified four tarsal nevi in a pathology database of 116 cases of conjunctival nevi (3.4%).[149] In our practices, we identified four nevi involving the tarsal conjunctiva in a database of 297 conjunctival nevi examined pathologically (1.3%): two nevi (one compound nevus and one combined nevocellular and blue nevus (Figure 86.10A) arose adjacent to the lacrimal punctum on the eyelid margin; a subepithelial nevus arose on the margin of the right lower eyelid and involved both the skin and conjunctiva; and one compound nevus involved the medial right lower eyelid conjunctiva (Figure 86.10B).

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CHAPTER 87

Milia

Key Points

- Milia are small, benign, superficial keratinous cysts that resemble miniature infundibular cysts on histopathology
- Congenital milia are common in newborns and present with a few or numerous lesions on the face, scalp, upper aspect of the trunk, and upper extremities, and tend to resolve spontaneously within weeks to several months
- Benign primary milia develop spontaneously and tend to be more persistent than congenital lesions, without spontaneous resolution
- Multiple eruptive milia occur spontaneously in very large numbers over weeks to months
- The etiology of milia remains controversial; some authors argue that they are retention cysts, and others argue that they represent a simple keratinizing type of benign tumor
- On the eyelids, milia appear as multiple unilateral or bilateral 0.5 to 2 mm, or sometimes larger white to yellowish, firm, asymptomatic papules or cysts on the upper or lower eyelids
- Conservative treatments include topical or systemic retinoids and oral minocycline
- For deeper dermal milia, electrodesiccation, dermabrasion, CO_2 laser ablation, and cryosurgery may be effective
- The prognosis is very good with most treatment options resulting in a reduction in lesion number with improvement in esthetic appearance

Milia are small, benign, superficial keratinous cysts that resemble miniature infundibular cysts on histopathology.[1] Hubler et al[2] followed the Epstein and Kligman[3] classification in dividing milia into primary spontaneous milia and secondary milia associated with various skin conditions or trauma, but they also proposed the additional term “milia en plaque” (MEP) for unusual cutaneous lesions consisting of multiple milia on an erythematous edematous base. Primary milia have been further classified into several different forms based on demographic and clinical characters. These are congenital, benign primary of children and adults, en plaque, and multiple eruptive milia.

Congenital milia are common in newborns. In various studies of cutaneous lesions in newborn infants with patient databases of 420 to 5387 infants, the incidence of milia was found to be between 7.5% and 36%.[4,5,6,7,8,9,10,11] Congenital milia present with a few or numerous lesions and most occur on the face, scalp, upper aspect of the trunk, and upper extremities. There are no significant racial or gender differences. Lesions tend to resolve spontaneously within weeks to several months.

Benign primary milia of children and adults develop spontaneously. Unlike congenital primary milia, they occur most often on the cheeks, eyelids, forehead, and genitalia, and lesions tend to be more persistent than congenital lesions, without spontaneous resolution.[1]

MEP is a relatively rare variant characterized by erythematous plaques containing numerous milia.[2,12,13,14,15,16] Lesions are generally unilateral, may be indurated, and are usually located on the head and neck, the periorbital region, the nasal bridge, or the trunk. MEP is more common in middle-aged adults with a female predominance.[1] It can be associated with pseudoxanthoma elasticum,[17] discoid lupus erythematosus,[18] lichen planus,[19] trauma, and renal transplantation,[20] but also arises in healthy individuals. Dogra et al[20] suggested that cyclosporine immunosuppression may predispose patients to MEP.

Multiple eruptive milia occur spontaneously in very large numbers.[21,22,23,24,25] Cases have been reported in patients from teens to old age, occurring most often on the head, upper trunk, and upper extremities. Lesions continuously erupt over weeks to months. Ratnavel et al[26] described a variant of eruptive milia restricted to the eyelids in a family over three generations.

Milia can be associated with several genodermatoses, rare inherited disorders with skin manifestations.[1] Bazex-Dupre-Christol syndrome (BDCS) is an X-linked dominant disorder consisting of congenital hypotrichosis, follicular atrophoderma, and basal cell carcinoma, and milia are seen in 75% of cases.[27] Rombo syndrome resembles BDCS with atrophoderma vermiculatum of the face, multiple milia, telangiectases, acral erythema, and a propensity to develop basal cell carcinomas.[28] Atrichia with papular lesions is an autosomal recessive disorder,[29] characterized by alopecia and widespread milia, especially on the cheek, scalp, elbows, and knees.[30] They tend to appear during the first decade of life and lesions may increase in number with age or partially regress.[31] Hereditary vitamin D-dependent rickets type IIA is an inherited disorder in which 50% of patients have milia on the face, scalp, and upper trunk, appearing in childhood. Basal cell nevus syndrome (Gorlin syndrome) is an autosomal dominant disorder characterized by numerous basal cell carcinomas, odontogenic keratocysts, rib abnormalities, abnormal facies, spina bifida occulta, calcified falx cerebri, comedones, palmoplantar pitting, chalazion, and cleft palate or lip. Milia occur in about 30% of patients,[32,33] mostly located in the periorbital region or on the forehead.

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Secondary milia represent a localized form of milia that may be associated with systemic disease, medication, or trauma. Diseases reported with secondary milia include bullous pemphigoid, herpes zoster,[34] contact dermatitis,[35] bullous lupus erythematosus,[36] lichen sclerosus,[37] Stevens-Johnson syndrome,[38] bullous erysipelas,[39] bullous amyloidosis,[40] lichen planus,[41] leprosy,[42] pseudoxanthoma elasticum,[17] lupus erythematosus,[43] phototoxic reactions,[44] and allergic contact dermatitis.[45]

Several medications have been associated with secondary milia. These include sorafenib for the treatment of unresectable hepatocellular carcinoma,[46] benoxaprofen,[47] topical steroids,[48] 5-fluorouracil,[49] cyclosporine,[20] and penicillamine.[50]

Superficial trauma is a common cause of secondary milia in children. Other traumatic injuries causing secondary milia include dermabrasion,[51] radiotherapy,[52] chemical peels,[53] skin grafts,[54] and ablative laser therapy.[55]

Milia have been reported to occur within tattoo pigments.[56] They can occur weeks to months following placement of the tattoo but have also even been reported within long-standing tattoos. There is usually no accompanying history of other trauma. Lesions typically manifest as asymptomatic small, yellowish to white papules but can also be pruritic. The pathogenesis of tattoo-related milia remains unknown.[57]

Etiology and Pathogenesis

The etiology of milia is not clear. Primary milia are situated within the undifferentiated sebaceous collar that surrounds vellus hair follicles.[3] They are thought to be derived from the lowest portion of the infundibulum of vellus hairs at about the level of the sebaceous duct.[58] Secondary milia may develop from any epithelial structure, such as a hair follicle, sweat duct, sebaceous duct, or epidermis.[37,59,60,61,62,63,64] Sweat duct milia represent the majority of all secondary milia and have been widely believed to be retention cysts of eccrine origin following an injury to the skin.[65,66,67] However, the etiology of milia remains controversial, and some authors have argued that milia are not retention cysts, but rather represent a simple keratinizing type of benign tumor.[3] Honda et al[58] examined milia specimens and found them to consist of an epithelial cyst filled with a lamellated keratinous mass. In some specimens, the cyst opened to the skin surface (incomplete milia), but in others, the cyst was not connected with the overlying epidermis (complete milia). In both incomplete and complete milia, the cyst wall was composed of three or four layers of epithelial cells. An eccrine duct penetrated into the cyst wall at the center of its base, forming a circular path within the wall, and opening into the inner cavity. This circular path of the eccrine duct within the cyst wall suggests an acrosyringeal (that part of the eccrine duct that spirals through surface epidermis) origin of milia. The authors proposed that an incomplete milium is the result of a fusion between cells derived from an eccrine duct and those derived from the surrounding epidermis, while the formation of a complete milium does not involve this fusion.[58]

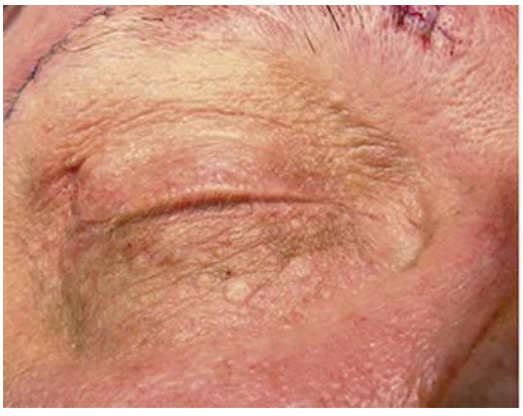


FIGURE 87.1 Milia involving the upper and lower eyelids.

Clinical Characteristics

On the eyelids, milia appear as multiple tiny, 0.5 to 2 mm, white to yellowish, firm, asymptomatic papules or cysts (Figure 87.1).[12,13,14,15,26,68,69,70,71,72,73] They may be unilateral or bilateral and can involve the upper, lower, or both eyelids. The appearance of lesions is gradual over months to years. There is usually no history of trauma, or skin manipulation such as surgery or dermabrasion, or of drug use. Affected patients generally are in their teens to middle age, and there is a slight predominance of females.

Differential Diagnosis

The differential diagnosis for milia includes multiple trichoepitheliomas, fibrofolliculomas, eccrine hidrocystomas, and syringomas. Trichoepithelioma is inherited in an autosomal dominant manner and presents as multiple translucent *(Print pagebreak 582)* yellow or pink nodules on the cheeks, eyelids, and nasolabial folds.[74] Multiple fibrofolliculomas may also be autosomal dominantly inherited and usually appear as yellow or flesh-colored papules on the face, forehead, or neck.[75] Both are distinguished from milia by histopathology.

Eccrine hidrocystomas can be solitary or multiple. They typically are dome-shaped, have a clear amber or bluish color, and range from 1 to 6 mm in diameter.[76,77] They are not located on the eyelid margins but can be seen on the pretarsal and preseptal eyelid skin and may increase in size during warm summer months.[78] Syringomas typically appear as soft to firm, skin-colored, yellowish, or translucent, dome-shaped papules 1 to 3 mm in diameter.[79,80] Lesions can occur at any age, but the age distribution shows a bimodal peak in the third and fifth decades.[81] Lesions most commonly occur on the face, eyelids, armpits, abdomen, chest, extremities, and genitalia.

Treatment

Conservative treatment options for milia include topical or systemic retinoids,[82] or oral minocycline but all options show variable success with a high incidence of local recurrence after discontinuation of therapy. Superficial milia tend to respond better to these conservative measures and to manual expression. Periocular superficial milia have also been reported to respond to manual expression either alone or in combination with oral minocycline 100 mg/d for 2 to 3 months.[12,16,73] However, manual expression is rarely effective for milia located in the mid-to-deep dermis.

For milia located in deeper dermal layers, invasive methods such as electrodesiccation, dermabrasion, CO_2 laser ablation, and cryosurgery have been described to be effective in the literature.[71,83,84] However, all of these options are associated with an unpredictable risk of mechanical or thermal injury, pigmentary changes, and scarring to the eyelid margins and other structures such as the lacrimal puncta.[85,86] The erbium:YAG laser offers an alternative tissue ablative option with less thermal damage to surrounding tissue and can reduce the risk of scarring compared to CO_2 laser.[68,87] Photodynamic therapy with 20% topical aminolevulinic acid has resulted in partial remission of MEP.[13] Radiosurgical destruction of small superficial cysts has been successful and causes less collateral tissue damage than electrodesiccation.[88,89] While this can reduce the number of milia and improve the esthetic appearance, it does not result in complete remission.

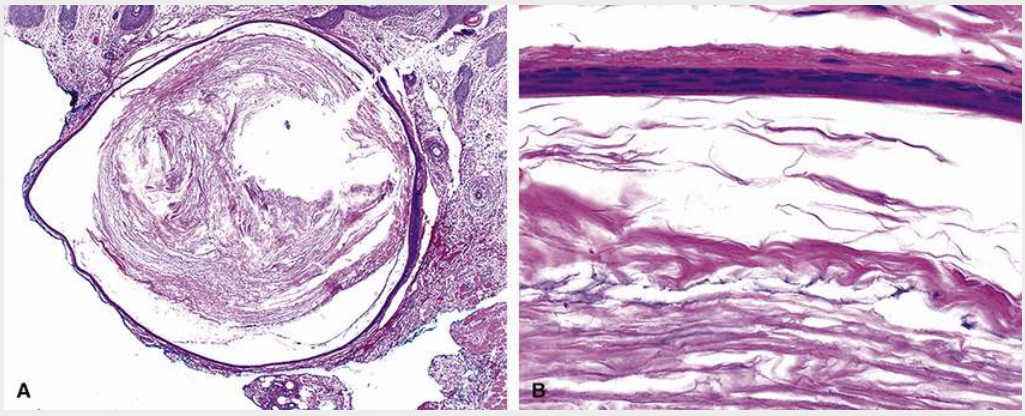

FIGURE 87.2 A, This eyelid milium was an incidental finding in an excision of a right lower eyelid seborrheic keratosis. The milium resembles a miniature epidermoid cyst in the superficial dermis. B, The epithelial lining is

thin and resembles that of an epidermoid cyst with keratinized, stratified squamous epithelium and prominent keratohyaline granules in the cells nearer the cyst lumen. Laminated keratin fills the cyst lumen.

Inconsistent response has been reported with topical tretinoin.[2,90] Oral etretinate 50 mg/d for 3 months followed by 10 mg every other day for 11 months was reported to decrease the number of milia but did not result in complete remission.[82]

Prognosis

In general, the prognosis for milia is very good with most treatment options resulting in a reduction in lesion number with improvement in esthetic appearance and a relatively low recurrence rate. Complete resolution is often not possible with more conservative modalities, but more aggressive therapies carry a risk of scarring or pigmentary changes.

Histopathology

Milia are miniature epidermoid cysts present in the superficial dermis, usually measuring 1 to 3 mm in diameter.[91] As with epidermoid cysts, the lining is keratinized, stratified squamous epithelium, and keratohyaline granules are often prominent in the cells nearer the cyst lumen.[92] Laminated keratin fills the cyst lumen (Figure 87.2).

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CHAPTER 88

Molluscum Contagiosum

Key Points

- Molluscum contagiosum (MC) is a benign viral infection found more commonly in warm, moist climates
- It is transmitted from one host to another by direct contact with infected skin or through fomites on clothing or towels
- MC is caused by a large double-stranded DNA virus, a member of Poxvirus
- Eyelid lesions typically present as asymptomatic, single or multiple, firm, dome-shaped, pink, or flesh-colored papules with a central area of umbilication that range in size from 2 to 6 mm, although lesions as large as 1.5 cm have been described
- MC lesions are usually self-limited and will resolve over 6 to 9 months if left untreated in immunocompetent hosts
- Treatment with topical preparations have been advocated, including retinoids, salicylic acid-lactic acid, and imiquimod
- No single intervention is completely effective, but most patients can achieve resolution of a high proportion of lesions

Molluscum contagiosum (MC) is a benign viral infection characterized by flesh-colored, dome-shaped papules on the skin or mucous membranes. It was first described in 1811 by Thomas Bateman.[1] In 1841, Henderson[2] and Paterson[3] in separate papers described intracytoplasmic inclusion bodies, referred to as molluscum bodies or now often referred to as Henderson-Paterson bodies, that distinguish these lesions histologically.

MC infection is very common, often cited to occur in between 2% and 8% of the population.[4] However, more recent studies based on serology testing suggest a much higher infection rate in Australian and European healthy populations ranging from 14.8% to 30.3%.[5]

The virus is found more commonly in warm, moist climates worldwide[6] and is transmitted between individuals by close physical contact.[7] It most often affects children, immunosuppressed individuals, and sexually active adults.[6,8] In immunosuppressed individuals, the disease is typically more extensive.[6] Rarely, vertical transmission can result in congenital MC.[9,10]

MC is transmitted from one host to another by direct contact with infected skin or through fomites on clothing or towels,[11] and it can even be transmitted from contact sports.[12] The average incubation time is between 2 and 7 weeks but can be as long as 6 months.[13] Individual lesions are mostly 2 to 5 mm in diameter with a central umbilication, and papules usually occur in clusters. Swimming has been associated with a higher risk of developing MC.[14] Among children, the risk of MC among swimmers is nearly twice that of nonswimmers,[15] and the risk for children who swim frequently is about twice as high as the risk for those who use swimming pools infrequently.[16]

Several studies in Europe and the United States have reported an association between atopic dermatitis and MC ranging from 18.2% to 43%.[17,18,19] However, a prospective observational pediatric study in Brazil found no relationship between MC and the development of atopic dermatitis.[20]

The eyelid is the most commonly involved ophthalmic site,[21] but conjunctival lesions also have been described,[22,23,24] and a case of intraocular MC was reported following a corneoscleral laceration.[25] Eyelid lesions are often associated with chronic conjunctivitis or keratitis.[26,27]

Etiology and Pathogenesis

MC is a contagious viral skin infection caused by the MC virus. This is a large double-stranded DNA virus, a member of the Poxvirus family.[28] There are four subtypes of the molluscum contagiosum virus (MCV-1, MCV-2, MCV-3, and MCV-4), based on

genetic polymorphisms, but their clinical manifestations are all similar.[29] MCV-1 is the most common genotype seen in 75% to 96% of cases.[11,30,31] The MCV is distinct from other poxviruses and is specialized to infect human skin, both because of its growth habit and its ability to evade local immune defenses.[31] The virus propagates in differentiating cells of the human epidermis but does not cross the basement membrane, thus avoiding immune surveillance that would otherwise cause a systemic immune response. Free virus cores have been found in all layers of the epidermis, and the molluscum bodies contain large numbers of maturing virions. These are intracellular collagen-lipid-rich saclike structures that are thought to deter immunological recognition by the host.[32]

Clinical Characteristics

In children, the most commonly affected sites are the trunk, extremities, genitals, and face.[33,34] Involvement of the oral mucosa is also seen but is rare.[35] In adults, lesions are more often located on the lower abdomen, thighs, genitals, and perianal area,[36] reflecting the common mode of acquisition *(Print pagebreak 586)* through sexual contact.[37] Less common sites include the areola, eyelids, and fingers. MC rarely involves the mucosa of the lips,[38] buccal mucosa,[39] and conjunctiva.[40] In immunosuppressed patients, lesions may be more extensive, larger, and more refractory to treatment.[41,42,43]

Eyelid MC typically presents as asymptomatic, firm, dome-shaped, pink, or flesh-colored papules (Figure 88.1). They may be single or multiple (Figure 88.2), occur on the upper or lower eyelid or both, and range in size from 2 to 6 mm, although lesions as large as 1.5 cm in diameter have been described (Figure 88.3).[44] When multiple, the number of individual lesions on any individual is generally fewer than 20 in immunocompetent hosts, but occasionally can be more than 100.[45] MC papules contain a white, waxy curd-like core and a central area of umbilication is a distinguishing feature. But, in some lesions, the umbilication may not be visible. Occasionally, lesions can be pruritic, tender to touch, or even painful. A case of MC papule has been associated with a cutaneous horn.[46] Several cases of eyelid MC with secondary infection, abscess, and cellulitis have been reported.[47,48,49] Rarely, MCV lesions occur on the conjunctiva.[23,50,51] MC infects patients at all ages from early childhood to old age, but 65% of cases are aged 40 years or younger, with a mean age of about 30 years.[52] Females represent slightly more than half of the reported cases. In immunocompromised hosts, lesions may be very numerous, very large, and confluent.

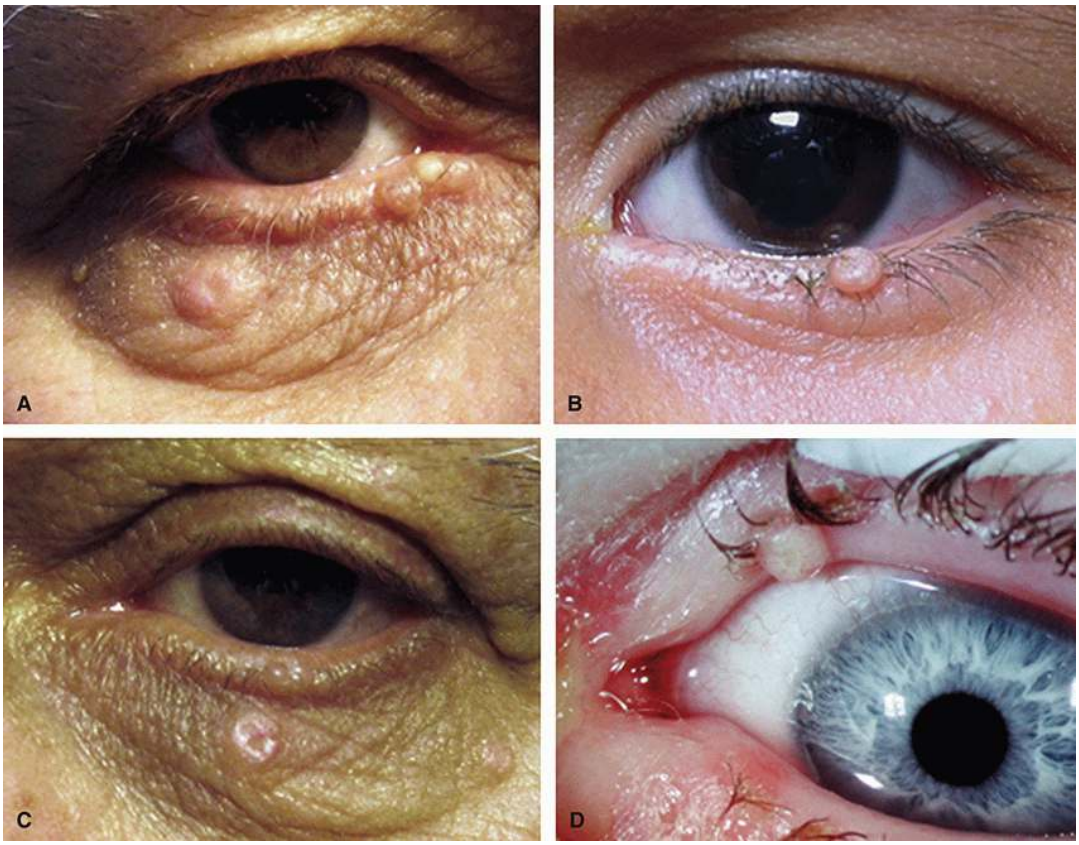

FIGURE 88.1 A-D, Solitary, dome-shaped, umbilicated molluscum lesions of the eyelid. (B, Courtesy of Dr. Mohammad Javed Ali; D, Courtesy of Dr. Alan McNab.)

Recently, Rosner and Zloto[53] proposed a classification of periocular MC based on six different presentations. These are (1) umbilicated nodular; (2) big/giant; (3) conglomerated; (4) erythematous; (5) inflamed; and (6) pedunculated. The umbilicated nodular type is the most common,[21] seen in nearly 66% of cases.[53] This type may be singular or multiple, present at any age, and

appear as white, pink, or flesh-colored, dome-shaped nodules with a central umbilication. The upper eyelid is more commonly involved, and lesions are usually unilateral, but occasionally can be bilateral. The inflamed type of MC lesion is reddish, tender, erythematous, and umbilicated with an inflammatory reaction.[47] Big MC are lesions between 5 and 10 mm in diameter, and giant MC are larger than 10 mm.[44] They are more common in children 1 to *(Print pagebreak 587)* 5 years of age and in immunocompromised adults. Lesions are white, pink, or flesh-colored, dome-shaped nodules with no central umbilication.[53,54] The erythematous presentation of MC appears with extensive erythema and surrounding scaling.[53,55] The conglomerated type is not umbilicated so that the diagnosis is more difficult. Lesions are well-demarcated, white, sessile, and papillomatous aggregates of multiple microscopic MC nodules. The pedunculated type of MC is rare and protrudes like squamous papilloma.[25,52]

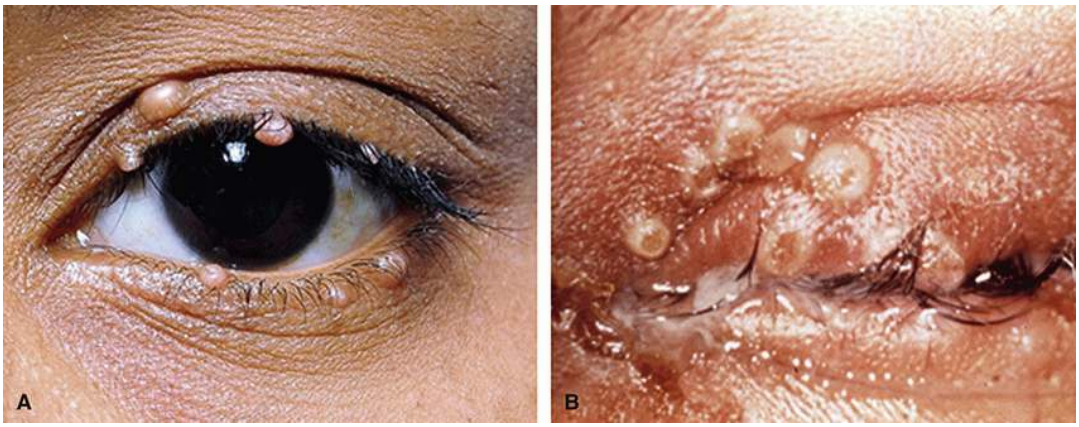

FIGURE 88.2 A and B, Multiple molluscum lesions. (A, Courtesy of Dr. Mohammad Javed Ali.)

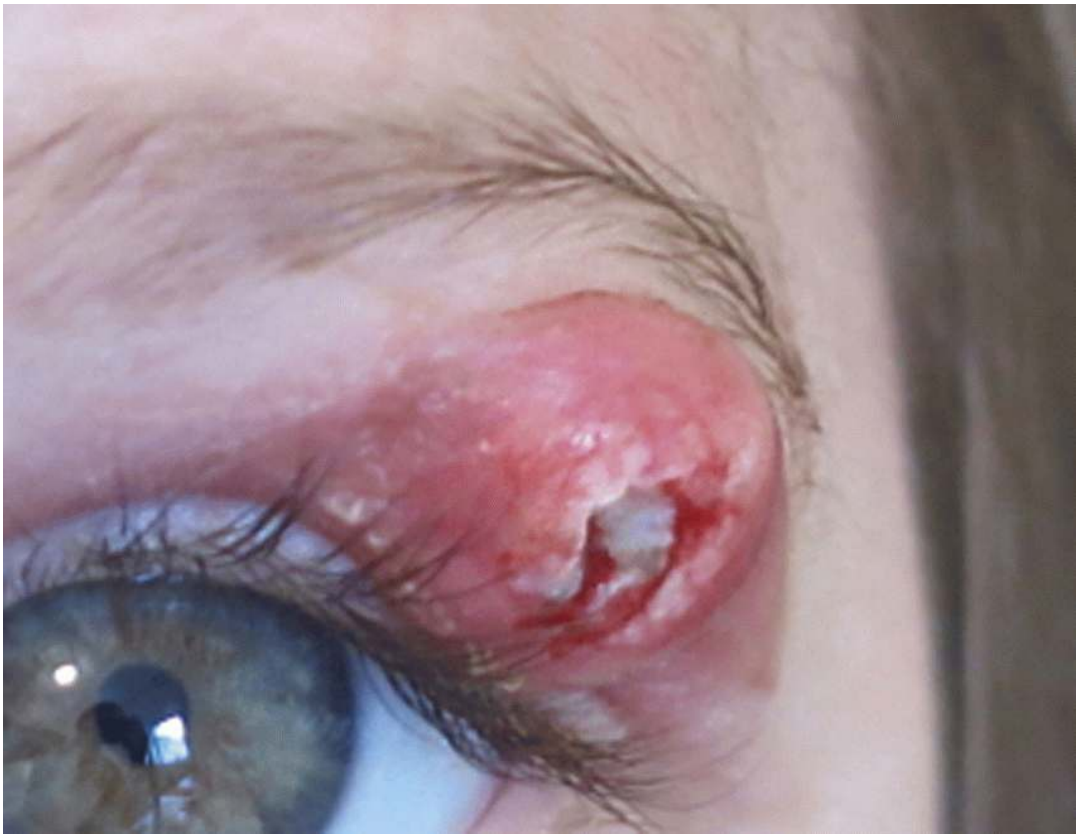

FIGURE 88.3 Giant molluscum on the upper eyelid. (Courtesy of Dr. Gary Lelli.)

Differential Diagnosis

MC usually can be identified as a small nodule with a unique central umbilication. However, some lesions may not have a well-defined umbilication, and others, especially larger ones, can have varied presentations that make initial diagnosis more difficult, so that pathologic examination may be necessary for a diagnosis.[13,56] The major lesions in the differential diagnosis of MC lesions must include benign adnexal tumors such as verruca vulgaris, syringoma, condyloma accuminata, papilloma, epithelioma, juvenile xanthogranuloma, epidermal inclusion cyst, papular granuloma annulare, keratoacanthoma, and lichen planus; infectious lesions

such as varicella, herpes simplex, cutaneous cryptococcosis, and coccidiomycosis; and some malignant tumors such as basal cell carcinoma.

Treatment

MC lesions are usually self-limited and will resolve over 6 to 9 months if left untreated in immunocompetent hosts so that observation is appropriate in most cases.[57] In immunocompromised hosts, however, lesions may persist for several years. When patients desire removal, there are several options available that can speed resolution. Many publications have suggested the efficacy of various treatment modalities for MC, but most reports have been small with methodological shortcomings so that there is little clear evidence for or against the most commonly used treatment options for MC.[57]

A number of topical preparations have been advocated for the treatment of MC that can be used by patients at home. A preparation of povidone-iodine (PVP-I)/dimethyl sulfoxide gel comprising 2% PVP-I in a dimethyl sulfoxide vehicle preparation was reported to achieve complete resolution in 8 (67%) of 12 patients and partial resolution in the rest.[58] Hydrogen peroxide has antimicrobial properties possibly associated with its oxidizing ability. Topical preparations of 5% to 10% have been effective in the treatment of MC lesions.[59,60] In a study of 21 immunocompetent children who were treated with hydrogen peroxide 1.8% cream applied twice daily for 21 days, 3/21 children showed complete remission of lesions, and in 18/21 children, there was a 37.8% reduction in the number of lesions.[61]

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Retinoids act by their ability to control abnormal growth and differentiation of keratinocytes.[62] Several randomized controlled trials comparing topical tretinoin cream 0.05% with hydrogen peroxide[63,64] suggested that both agents reduced the number of MC lesions after 4 weeks of treatment, although the rate of resolution was slower with tretinoin.[65]

Topical salicylic acid-lactic acid 16.7% combination solution was reported to be equally effective as 10% hydrogen peroxide with 83% complete remission of MC lesions over 6 weeks, although 35% also acquired new lesions during this period.[66] A solution of 5% podophyllotoxin cream has also been used for MC, showing a 92% rate or lesion resolution in as little as 3 days with no recurrence after 9 months.[67] But its use is contraindicated during pregnancy.

Oral cimetidine is a histamine 2 receptor antagonist that stimulates delayed-type hypersensitivity. Significant clearance of lesions has been reported in patients treated with a 2-month course,[68,69] and successful treatment has been seen in cases of severe MC infections.[70]

Imiquimod is a toll-like receptor 7 agonist capable of immune modification. It acts by stimulating an immune response via cytokines such as interferon-alpha, interferon-gamma, interleukin-12, interleukin-8, and tumor necrosis factor.[71] Topical imiquimod 5% cream has been reported to be effective for MC.[72,73] In a study of imiquimod 5% cream three to five times per week for 12 weeks for MC on the head and neck, extremities, trunk, and genitals in immunocompetent children aged 2 to 12 years old, 91.8% showed complete clearance in 6 to 12 weeks. Results were slower than with cryotherapy, but eventually equally effective with less pain and better cosmetic acceptance.[74,75] More invasive treatments include some degree of mechanical ablation of MC lesions.

Curettage involves removal of the epithelial surface of the papule with a needle and scraping away the viral core.[76,77] Side effects include pain, bleeding, and occasionally infection. But the recurrence rate can be as high as 66% over 4 to 8 weeks.[78] Cryotherapy is equally effective as imiquimod or hydrogen peroxide in clearing MC les ions,[74,79,80] but it is usually associated with pain, bleeding, dyspigmentation, and blistering at the freeze site. Pulsed dye laser has been used to effectively and safely treat MC.[81,82,83] Complications include pain, erythema, pigmentary changes, and occasionally atrophic scarring and ulceration.

Immunocompromised patients often have lesions that are resistant to standard therapies,[84] although in HIV-positive patients lesions may resolve after highly active antiretroviral therapy.[85,86] For resistant lesions, combined treatment involving several different modalities may be beneficial.[87,88] In immunocompromised patients with severe infections recalcitrant to standard treatment, it may be necessary to discontinue immunosuppressive therapy.[89,90] Cidofovir, an antiviral nucleoside analog of deoxycytidine monophosphate, has been reported to be effective for giant MC lesions in immunocompromised patients.[91,92,93]

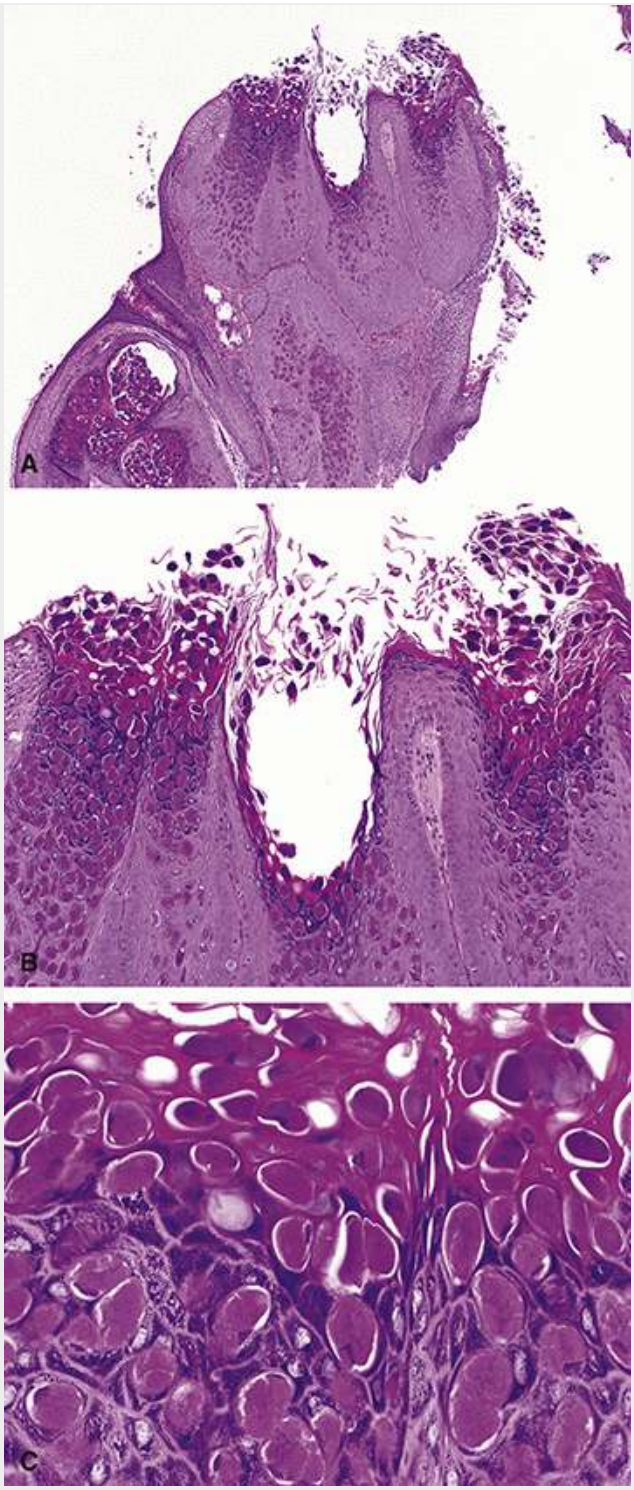

FIGURE 88.4 A, This eyelid molluscum contagiosum shows the characteristic lobules of hyperplastic squamous cells expanding into the underlying dermis with fine septa of dermis between lobules. Keratinized debris and viral inclusion bodies are being discharged onto the skin surface through a dilated ostium. B, Close-up of the ostium showing the keratin debris and molluscum bodies being discharged. Molluscum bodies are eosinophilic but may become basophilic near the skin surface, as seen in this case. C, Molluscum bodies may occupy almost the entire cell with compression of the nucleus toward the periphery of the cell.

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Prognosis

MC is a benign lesion that generally is self-limiting. The average duration of a single lesion is about 2 months,[94] but because the virus spreads by autoinoculation following scratching or trauma, the infection may persist for 8 to 12 months or even longer.[95]

Topical therapies can be effective in eradicating lesions, but their action is usually slow. Mechanical ablative treatments give more rapid results but can cause pain, hyperpigmentation or hypopigmentation, and scarring. While no single intervention is completely effective or acceptable to all patients, most can achieve complete clearance of the lesions, although recurrences may occasionally be observed after complete lesion eradication.

Histopathology

Cutaneous lesions of MC have lobules of hyperplastic squamous cells that expand into the underlying dermis (Figure 88.4A).[2,3,96,97,98,99,100] Fine septa of dermis separate the lobules. Keratinized debris and viral inclusion bodies are discharged from the lobules into dilated ostia leading to the skin surface (Figure 88.4A and B).[2,3,96,97,98,99,100] Infected cells are recognizable by cytoplasmic molluscum bodies that begin to form in keratinocytes just above the cells at the margin of the lobule (termed "the basal layer").[99] Molluscum bodies progressively enlarge toward the center of the lobule or ostium, where they may occupy almost the entire cell (Figure 88.4C).[3] Inclusion bodies are eosinophilic but may become basophilic near the skin surface (Figure 88.4B).[98] Whether the primary site of cutaneous infection is the epidermis or hair follicles has been debated for over a century,[96,97] and infection may likely begin at either site either directly[96] or by follicular neogenesis.[101] The stroma surrounding the infected lobules is edematous or myxoid in about one-half of the cases[102] and may rarely be inflamed.[103]

Shedding of viral particles into the conjunctiva from a molluscum lesion on the eyelid margin may result in follicular conjunctivitis,[104] manifest histologically as lymphoid follicles in the substantia propria of the conjunctiva. In conjunctival lesions, the epithelium is thickened, and molluscum bodies lie within the epithelial cells.[104,105]

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CHAPTER 89

Mucormycosis

Key Points

- Mucormycosis is a rapidly progressive angioinvasive infection in immunocompromised patients
- It is caused by saprophytic fungi of many genera related to Phycomycetes (Zygomycetes) of the order Mucorales
- Mucormycosis may affect the pulmonary, rhinocerebral, gastrointestinal, cutaneous, or the central nervous systems
- Primary cutaneous mucormycosis is the least common form, often secondary to direct skin trauma most frequently on the face and extremities
- The gold standard for treatment is aggressive surgical debridement of infected necrotic tissues with adjunctive intravenous antifungal therapy and management of predisposing factors
- The prognosis for patients with rhino-orbito-cerebral mucormycosis, in general, is poor

Mucormycosis is an angioinvasive infection that causes a rapidly progressive invasive disease in immunocompromised patients, particularly those with poorly controlled diabetes, hematologic malignancy, posttransplant status, and iron overload states.[1] It is caused by saprophytic fungi of many genera related to Phycomycetes (Zygomycetes) of the order Mucorales,[2] which are ubiquitous in the environment. The first cases of pulmonary mycosis caused by mucor were presented by Cohnheim in 1865[3] and mucormycosis was later described by Paltauf in 1885[4] based on the findings of focal mucor lesions in the brain, lungs, pharynx, and ileum of a 52-year-old patient.

Although most cases of mucormycosis are seen in patients with unregulated diabetes mellitus, the number of these cases has been decreasing. Over the past several decades, there has been an increase in mucormycosis among immunocompromised patients, particularly among transplant patients.[5,6,7,8] Studies have indicated that 1% to 3% of bone marrow transplant patients present with mucormycosis.[6,8,9] The incidence of mucormycosis in adult leukemia patients was reported at around 2%.[10] Leukemia patients who have developed neutropenia are particularly susceptible to mucormycosis.

The annual incidence of mucormycosis in the general population is estimated to be 1.7 cases for every 1 million individuals in the United States or approximately 500 affected individuals per year.[11] Nosari et al[12] felt that this is likely to be an underestimate because a large number of cases remain undiagnosed due to the low rate of antemortem diagnosis (23%-50%) and the decline in autopsies over the years to less than 5% today.[13,14,15,16]

Mucormycosis has been classified according to the anatomic sites of involvement. These include rhino, maxillary, orbital, central nervous system, cutaneous, pulmonary, disseminated, and miscellaneous,[17] and the site depends on whether the fungal spores are inhaled, ingested, or inoculated.[18] The most common sites for involvement are the paranasal sinuses (39%), lungs (24%), skin (19%), brain (9%), and gastrointestinal tract (7%).[19]

Mucormycosis in children is associated with prematurity, low birth weight, immunodeficient states, febrile neutropenia, corticosteroid or broad-spectrum antibiotic treatment, malnutrition, and local skin trauma.[20,21] Pediatric cases of cutaneous mucormycosis have been associated with wooden tongue depressors, cotton stockinettes, and adhesive bandages.[18] The patterns of distribution in pediatric patients are cutaneous (27%), gastrointestinal (21%), rhinocerebral (18%), and pulmonary (16%).[22]

Primary cutaneous mucormycosis is the least common form. Inoculation is often secondary to direct skin trauma[23,24] or from adhesive skin bandages or intravenous catheter insertion.[18,23,24,25,26] It can present as superficial or gangrenous infections.[27] The superficial form is characterized by a slow onset of erythematous cellulitis with vesicles or pustules. The gangrenous form is usually more aggressive. Angioinvasion by the fungal hyphae produces thrombi that occlude the arteries leading to progressive ulceration, eschar formation, ischemia, and tissue necrosis.[18,23] The infection can extend to involve deeper structures such as tendons, muscles, or bone, and 19% can spread to other organs by hematogenous dissemination.[27]

Etiology and Pathogenesis

The causative organisms of mucormycosis are of the class Phycomycetes, subclass Zygomycetes. The most commonly seen genera are from the Mucoraceae family,[18,23,25,28] but an increasing number of infections from the Cunninghamellaceae family are also being reported.[29,30,31] The most commonly identified organisms are *Rhizopus* species in 44% of cases and *Mucor* species in 15%.[22] These fungi are ubiquitous saprophytes commonly found in soil, decomposing vegetation, and in healthy human respiratory and digestive tracts.

Mucormycosis typically presents as rhino-orbital or rhinocerebral disease but also occurs as a disease involving *(Print pagebreak 593)* the lungs, skin, and gastrointestinal tract.[32] Environmental fungal spores are inhaled and enter the sinuses where the fibrous mycelium and thin-walled aseptate or hyposeptate hyphae grow rapidly within the host tissues. Increased availability of soluble iron in the host is believed to play a role in promoting Mucorales growth, especially in patients receiving deferoxamine iron chelation therapy.[33,34,35] The infection progresses to soft tissues causing facial swelling, numbness, and pain. It may extend to the orbits and brain, causing vision loss and cerebral abscesses. Hematologic dissemination with seeding of visceral organs can follow.[36] As the hyphae grow, they invade the blood vessels leading to thrombosis and tissue necrosis.[37]

For optimal growth in humans, Mucorales fungi require the host to have decreased levels of neutrophils.[38] In healthy individuals, neutrophils are a key defense against the fungi in the host tissue and phagocytize these pathogens, but in neutropenic individuals, the pathogens proliferate leading to infection.

Once the infection is initiated, mucormycosis has an affinity for arterial blood vessels,[39] where they adhere to the arterial wall and grow along the internal elastic lamina causing thrombosis, ischemia, and necrosis of the surrounding tissues.

During the COVID-19 pandemic, coronavirus disease-associated mucormycosis (CAM) has become a growing threat globally, especially in tropical regions. The emergence of CAM cases has been attributed to environmental, host, and iatrogenic factors.[40] In COVID-19 patients, virus-induced endothelial dysfunction, hyperglycemia, and immune dysfunction following corticosteroid use is believed to increase the risk of acquiring mucormycosis by the interaction of Mucorales spores with damaged epithelial cells, followed by endothelial invasion.[40] Corticosteroid treatment, frequently required by COVID-19 patients, further reduces or abolishes the innate immune functions of phagocytic cells contributing to the pathogenesis of CAM.[40]

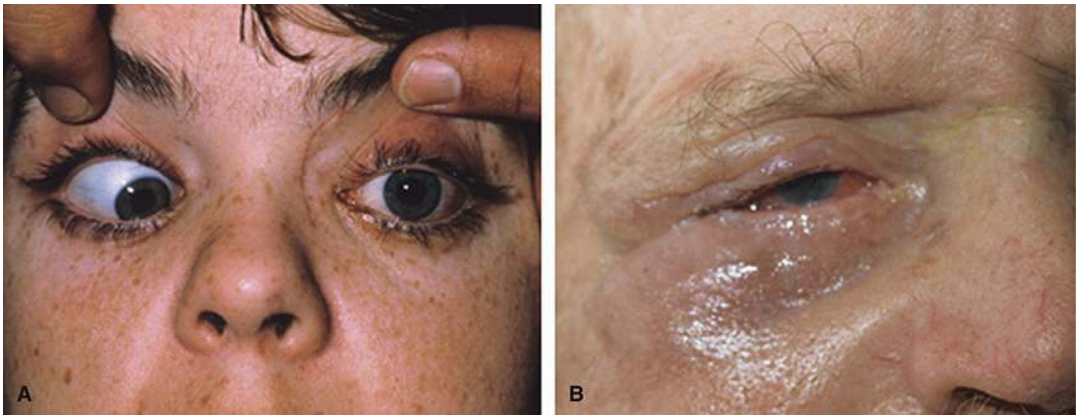

FIGURE 89.1 A, Sinus and orbital mucormycosis with proptosis and ophthalmoplegia. B, Orbital-cutaneous mucormycosis with progressive facial and eyelid induration, edema, and cellulitis.

Clinical Characteristics

Mucormycosis commonly presents in five forms: it may affect the pulmonary, rhinocerebral, gastrointestinal, cutaneous, or central nervous systems.[37] Systemic dissemination, where infection affects two or more noncontiguous organ systems, may also occur due to the highly invasive nature of this fungus.[37] Of the five forms, pulmonary and rhinocerebral are the most common. Cases of rhinocerebral mucormycosis present with facial pain, periorbital cellulitis, proptosis, ophthalmoplegia (Figure 89.1A), visual deficiencies, black necrotic lesions, discharge from the nasal and palatal mucosa, and fever.[41,42,43] CNS mucormycosis is not common by itself but is usually a result of dissemination of the fungal infection from pulmonary or rhinocerebral sources.[44]

Cutaneous involvement by mucormycosis is most often seen on the face and extremities. Patients present with fever and rapidly progressive facial and eyelid induration, edema, and cellulitis (Figure 89.1B), with ulceration, purulent discharge, occasionally bleeding, and necrosis (Figure 89.1B and 89.2).[20,27,45,46,47,48,49,50] There may be a history of trauma, burn, insect bite,

uncontrolled diabetes, or hematologic malignancy. Chronic infections may sometimes persist for months or years.[51]

In a series of 115 cases of cutaneous mucormycosis in Mexico, 18/115 cases (16%) were considered primary cutaneous infections, and 97/115 cases (84%) as secondary cases. Primary cutaneous cases are caused by implantation of the Mucorales due to disruption of the cutaneous barrier, and most cases are associated with adhesive bands or trauma. Secondary cases result as a part of the disease process, and most are associated with rhinocerebral mucormycosis and diabetes.[52]

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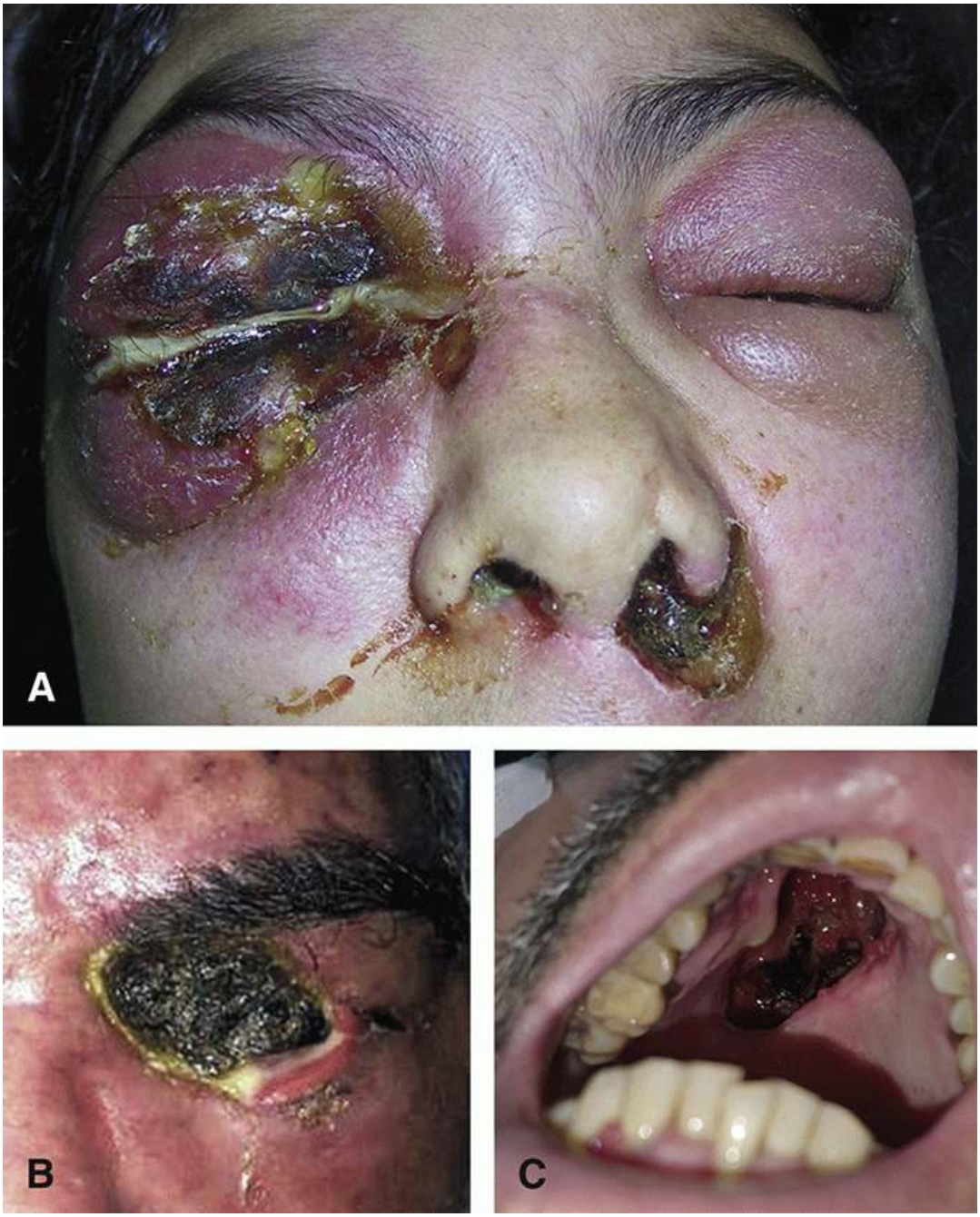

FIGURE 89.2 Cutaneous mucomycosis with necrosis of the lateral nose and eyelid in a patient with lymphocytic leukemia. (Reprinted with permission from Bonifaz A, Tirado-Sánchez A, Hernández-Medel ML, et al. Mucormycosis with cutaneous involvement. A retrospective study of 115 cases at a tertiary care hospital in Mexico. *Autralas J Dermatol*. 2021;62:162-167, Figure 2C.)

Differential Diagnosis

The differential diagnoses of mucormycosis are varied due to the different clinical presentations and organ systems that can be involved. The most commonly employed technique for differentiating between mucormycosis and other diseases is a

histopathological study.[53] However, Mucorales may be difficult to distinguish from other filamentous fungi.[54] There are many similarities in the clinical presentations of aspergillosis and mucormycosis.[38] The drugs usually used for the treatment of aspergillosis are generally ineffective for the treatment of mucormycosis so that it is important to confirm the diagnosis as early as possible in the course of the disease. Rhino-orbital and rhinocerebral mucormycosis can be confused with more routine cases of sinusitis. Cutaneous mucormycosis has also been misidentified as cutaneous malignancy or an infected sebaceous cyst.

Treatment

Mucormycosis can be a fatal infection and early diagnosis and treatment are critical for the successful eradication of the infection and patient survival. The gold standard of treatment is aggressive surgical debridement of infected necrotic tissues with adjunctive intravenous antifungal therapy and management of predisposing factors.[32] Medical antifungal therapy alone is generally ineffective because extensive tissue invasion and necrosis limit drug penetration into infected areas.[23,24] Liposomal amphotericin B (L-AmB) has better tissue penetration than amphotericin B, has less hepatotoxicity, and is considered a first-line treatment.[19] Intravenous liposomal amphotericin B is preferred also because of its ability to penetrate the central nervous system.[32,55] The latest guidelines of the European Confederation of Medical Mycology/European Society of Clinical Microbiology and Infectious Diseases and the European Conference on Infections in Leukemia recommend the use of L-AmB with a daily dosage of at least 5 mg/kg/d for mucormycosis,[56,57] and dosages of 10 mg/kg/d are strongly supported for cerebral infections.[57] The duration of antifungal treatment is still a matter of debate but should be determined on an individual basis and adjusted based on the underlying condition. Some authors propose a treatment for at least 3 weeks.[58] The total duration of antifungal drug treatment in mucormycosis varies, but at least 12 weeks is recommended.[59]

Salvage therapies with drugs like posaconazole and isavuconazole have shown promising results when combined with L-AmB even without surgical debridement,[5,60,61,62,63,64,65] but are not considered first-line medical therapy.[66,67,68]

Hyperbaric oxygen therapy has a fungistatic effect and helps the revascularization of ischemic tissue. In selected cases, it can be combined with antifungal agents.[69] Several studies reported improved survival rates using hyperbaric oxygen as an adjuvant therapy to amphotericin B and surgical debridement.[70,71]

Retrobulbar injection of amphotericin B has been reported as a minimally invasive, globe-sparing intervention for orbital aspergillosis[72,73,74,75] and has been reported as a successful treatment in combination with systemic antifungals and endoscopic sinus debridement.[76]

Prognosis

The prognosis for patients with rhino-orbito-cerebral mucormycosis, in general, is poor. In a retrospective study of 63 patients (79 eyes) with biopsy-proven disease, the presence of a frozen globe, nasal mucosal involvement, and shorter duration of antifungal therapy were significantly associated with lower patient survival.[77] Exenteration did not significantly change survival. Globe survival was seen in 43% and vision survival was observed in 25.3%, in whom younger age was significantly associated with a worse vision survival.

Improved survival of patients with mucormycosis is related to earlier diagnosis and institution of early and aggressive multidisciplinary treatment.[78,79,80] Even with treatment, mucormycosis has a high rate of morbidity and mortality.[81,82] The survival rate has improved with combination therapy, but the overall mortality rate remains high, especially in immunocompromised patients and in young *(Print pagebreak 595)* children.[22] Delayed diagnosis of more than 5 days is associated with an increased risk of mortality.[83]

The all-cause mortality rates for mucormycosis range from 40% to 80% depending on underlying conditions and sites of infection.[78,84,85,86,87] The highest survival rates are reported in patients with a healthy immune status and without comorbidities. The poorest prognosis is reported in patients with hematologic malignancies, bone marrow transplant recipients, and patients with severe burns.[84,87] Patients with disseminated disease and CNS involvement can be associated with mortality rates greater than 80%.[84]

Localized sinus or cutaneous infections usually carry a more favorable prognosis since earlier diagnosis is likely and intervention can be instituted more quickly.

In a review of 113 articles published between 1943 and 2004, it was shown that mucormycosis patients older than 46 years, with frontal sinus involvement, and with fever were less likely to survive compared with those without these conditions,[88] and patients treated with amphotericin B were more likely to survive. While patients with fever undergoing orbital exenteration were more likely

to survive compared with nonexenterated patients, no standard of care was found among surveyed orbital surgeons with regard to exenteration for cases of orbital mucormycosis.[88]

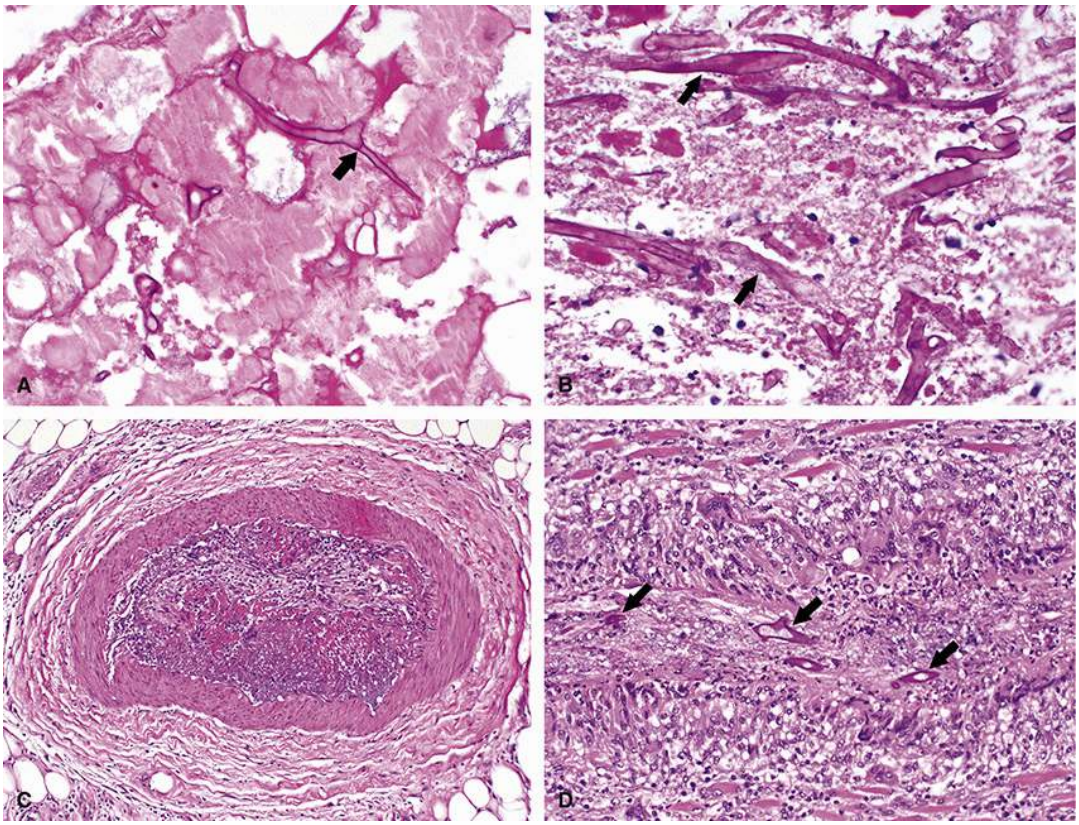

FIGURE 89.3 A, The hyphae of mucormycosis are basophilic in sections stained with hematoxylin and eosin. The hyphae are broad (5-20 µm), thin walled, irregularly contoured, pleomorphic, and typically branch from 45° to 90°. The hyphae are pauciseptate (arrow) and are in infarcted adipose tissue in this patient with cerebro-rhino-orbital mucormycosis. B, The hyphae are often twisted (arrows), folded, and collapsed due to their thin walls. Many hyphae have absent cytoplasm and appear clear. C, Vascular invasion and thrombosis are ubiquitous with mucormycosis. D, Mucormycosis may stimulate a granulomatous reaction, as seen in this case with basophilic fungal hyphae (arrows) enveloped in a granuloma.

Histopathology

The hyphae of mucormycosis are usually apparent in sections stained with hematoxylin and eosin in which they are basophilic (Figure 89.3). The hyphae are broad (5-20 µm), thin walled, irregularly contoured, pleomorphic, and typically branch from 45° to 90°.[54,89] The hyphae are pauciseptate *(Print pagebreak 596)* (not nonseptate, as often described), but septa are only rarely seen in tissue sections and may be simulated by folds in the hyphae (Figure 89.3A).[54,89] The hyphae are often twisted, folded, and collapsed due to their thin walls (Figure 89.3B).[89] Many hyphae have absent cytoplasm and appear clear.[89] Vascular invasion and thrombosis are ubiquitous with mucormycosis (Figure 89.3C),[54,90] but their presence may require a careful search of multiple sections. Arterial thrombosis results in ischemic (coagulative) necrosis, and infarcted adipose tissue may have birefringent crystals of fatty acid calcium salts.[91,92] Perineural invasion is also a common histological feature in mucormycosis, occurring in 90% of cases in the study by Frater and Procop.[54] Tissue infection may result in a neutrophilic response, a mixed neutrophilic and granulomatous response (Figure 89.3D), or less commonly a pure granulomatous response or no inflammation.[54,90]

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CHAPTER 90

Myasthenia Gravis

Key Points

- Myasthenia gravis (MG) is an acquired neurological autoimmune disease characterized by skeletal muscle fatigability and weakness
- 75% to 80% of patients have IgG1 and IgG3 antibodies directed against the acetylcholine receptor and 1% to 10% of patients have antibodies directed against muscle-specific tyrosine kinase
- 40% to 50% of myasthenia patients initially present with purely ocular symptoms, but 50% to 80% of those develop generalized myasthenia within 2 years
- Ocular MG (OMG) usually presents with variable pupil-sparing ptosis and extraocular muscle weakness that worsens with sustained muscle use and improves with rest or sleep
- Patients may complain of difficulty chewing solid food, dysphagia, or dysarthria
- Treatment requires long-term acetylcholinesterase inhibitors, immunosuppressants, or a drug combination of both which should be individualized according to the response to therapy
- If ptosis surgery is indicated, silicone slings are the preferred suspensory material, and the open sky approach is preferred over the closed Fox method
- MG may be visually disabling and cosmetically disturbing, but the quality of life and life expectancy have improved with modern therapy

Myasthenia gravis (MG) is an acquired neurological autoimmune disease hallmarked by skeletal muscle fatigability and weakness which is caused by impaired synaptic transmission across the neuromuscular junction. It is one of the five main causes of neurogenic blepharoptosis.[1,2,3,4,5,6,7,8,9,10,11,12]
The other causes include oculomotor nerve palsy, Horner syndrome, Marcus-Gunn Jaw wink, and ptosis induced by botulinum toxin injections which are discussed separately in Chapters 12, 36, and 38.

Etiology and Pathogenesis

Under normal conditions, the process of neuromuscular transmission is initiated by an action potential that depolarizes the terminal membrane of the motor nerve axon. This opens the voltage-dependent calcium channels, increasing calcium permeability which elicits the release of acetylcholine (ACh) and agrin molecules from the nerve terminal into the synaptic cleft.[5,12] ACh diffuses across the synapse, binds to receptors on the striated muscle, and depolarizes the postsynaptic membrane, thus producing muscle contraction.[12] The postsynaptic skeletal muscle fiber membrane (the sarcolemma) is a convoluted structure with a high density of acetylcholine receptors (AChR) at the crests of the folds and acetylcholine molecules within the clefts. To ensure successful neuromuscular transmission, normally there is a vast excess (safety margin) of released acetylcholine molecules and available postsynaptic receptors. Ultimately, the acetylcholine molecules that are released are rapidly eliminated from the synaptic cleft by the acetylcholinesterase enzyme.[12] As we shall see later, the released agrin is involved in the normal process of AChR clustering, an integral step of neuromuscular junction transmission.[5,12] Any disruption of the aforementioned delicate processes predisposes to failure of neuromuscular transmission, ultimately causing muscle weakness.[12]

MG is an autoimmune disorder caused by antibodies targeting the neuromuscular junction. These antibodies bind to the postsynaptic muscle end plate, attack, and destroy the postsynaptic molecules, consequently impairing signal transduction which ultimately results in muscle weakness and fatigability.[5] Although MG is considered the archetypal example of an autoimmune disease involving the neuromuscular junction,[4,5,6,7,8,9] it is an etiologically as well as an immunologically heterogeneous disease.

Different autoantibody patterns, as well as the diverse clinical manifestations, may help identify the disease subgroups which include (1) early-onset MG, (2) late-onset MG, (3) muscle-specific kinase MG (MuSK$^+$ MG), (4) low-density lipoprotein receptor-related protein 4 MG (LRP4 MG), (5) seronegative MG, (6) thymoma MG, and (7) OMG.[5] In MG patients, three major antibody types predominate including (1) antibodies directed against the acetylcholine receptors (AChR), (2) antibodies directed against MuSK, and rarely (3) LRP4 antibodies, but other antibodies may be observed as well.[5]

The two major antibodies (AChR and MuSK) probably represent two distinct immunopathologic mechanisms as they are mutually exclusive and rarely manifest simultaneously in the same individual. Also, the clinical picture, the ocular findings, and thymic pathology are different.[5,9,10] On the other hand, the clinical picture in patients with AChR and LRP4 antibody positivity may overlap, particularly regarding their ocular symptoms.[5]

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In the great majority of MG patients, antibodies directed against acetylcholine receptors are the ones responsible for the characteristic muscle fatigability, and they can be detected with routine assays or more-sensitive cell-based assays in up to 75% to 80% of patients.[5] Anti-AChR antibodies are usually IgG1 and IgG3 antibodies which are directed against the α-subunits (more pathogenic) or the β-subunits of the acetylcholine receptor and cause disease morbidity through three distinct mechanisms.[5] The predominant antigenic mechanism is that they activate the complement cascade (C1), which in turn binds to the extracellular domains of the ACh receptors at the neuromuscular junction. This results in the formation of membrane attack complexes on the sarcolemmal cell membranes, which destroys the typical folds in the sarcolemma, thereby indirectly impairing signal transduction.[5] Another less frequent mechanism for blocking the signaling pathway also exists, as AChR antibodies are bivalent and are capable of direct antigenic modulation which may result in AChR conformational changes and additional damage to the AChR function.[5] The third and least common mechanism is that anti-AChR antibodies may directly target the acetylcholine ligand-binding site of the receptor itself without complement activation, also potentially blocking the signaling pathway.[5] Although total AChR antibody concentration does not appear to correlate with symptom severity, fluctuations in AChR antibody levels in an individual patient have been reported to correlate with the severity of muscle weakness.[5]

A small minority of MG patients (1%-10%) have monovalent antibodies to muscle-specific tyrosine kinase (MuSK) and not to the acetylcholine receptors (MUSK$^+$ MG).[5] MuSK is a protein that is concentrated in the neuromuscular junctions of skeletal muscles where it colocalizes with the densely packed acetylcholine receptors. It is responsible for AChR clustering, a key event in neuromuscular transmission,[11] so that MuSK plays a critical role in establishing and maintaining neuromuscular synapses.[4,5] However, this interaction also requires the presence of the low-density lipoprotein receptor-related protein 4 (LRP4) and the motoneuron-secreted heparan sulfate proteoglycan agrin to co-stimulate MuSK.[4,5,11] MuSK is, therefore, one of the components of the agrin-mediated AChR clustering signaling cascade (*agrin-LRP4- MuSK* signaling).[4,11]

Autoantibodies that are directed against MuSK are predominantly of the IgG4 subclass; therefore, MuSK$^+$ MG belongs to the relatively new class of autoimmune diseases which are hallmarked by the predominance of IgG4 autoantibodies. In contrast to AChR antibodies that bind to complement and crosslink their antigenic target, MuSK antibodies are directly pathogenic.[5] They act by reducing the postsynaptic density of AChRs and impairing their alignment.[5] Of note is that the association with MuSK positivity and ocular symptoms (MuSK-OMG) is extremely rare.[5,9,10] To the best of our knowledge, only nine cases of MuSK-OMG have been described in the literature so far.[10] In addition, thymus pathology is also different, as the thymus is frequently involved in AChR MG, whereas in MUSK$^+$ MG, it is not.[8,12]

A small proportion of MG patients who do not have either AChR or MuSK antibodies may possess antibodies directed against another component of the agrin-LRP4-MuSK signaling cascade, LRP4, which is a receptor for agrin that relays the signal to MuSK to initiate AChR clustering.[5] It should be noted the prevalence of ocular symptoms and signs is similar among MG patients with either anti-AChR or anti-LRP4 antibodies, although LRP4$^+$ patients usually present with milder disease and thymomas are rare.[5]

Patients who have no detectable antibodies against any of these three antigens are referred to as seronegative MG, although some of these patients may have antibodies against other cytoplasmic muscle proteins (agrin, titin, Kv1.4, ryanodine receptor antibodies, collagen Q, or contractin antibodies). However, the exact role played by these antibodies in MG pathogenesis or any relevance to diagnosis, treatment, or prognosis remains to be proven.[5]

The primary autoimmune form mentioned earlier is not the only underlying cause of MG. Thymic pathology, acute infections, and several medications may trigger or exacerbate myasthenia probably through presynaptic or even postsynaptic inhibition of acetylcholine release.[13] Pathological thymic changes, including thymic hyperplasia (follicular or diffuse thymitis) earlier in the course of the disease, and thymomas, as well as an atrophic thymus gland (late in the disease), are seen in 80% of seropositive myasthenia patients.[14] Systemic infections (viruses, bacteria, and even fungi) may also trigger a myasthenic crisis.[15,16] The list of drugs inducing MG is extensive,[12] but drugs that are relevant to the current discussion are antibiotics including fluoroquinolones (ciprofloxacin and levofloxacin), macrolide antibiotics (telithromycin and azithromycin), and aminoglycosides (amikacin and gentamycin).[13,17,18,19,20] Therefore, if a patient develops an acute exacerbation of MG due to a systemic infection, the very

antibiotics used to treat the infection may exacerbate the symptoms even more.[13]

Clinical Presentation

The incidence of generalized MG is 5.3 per million person-years, and the estimated prevalence is 77.7 cases per million of the population.[9] MG affects all age groups, genders, and ethnicities; however, it has a bimodal age distribution, being more prevalent both in young females (less than 30 years of age) and older males (more than 50).[7,21] The exact incidence and prevalence of OMG is largely unknown, and a recent metanalysis of population-based epidemiological MG studies did not list a single study singularly concerned with OMG.[9] But in general, OMG is considered rarer than generalized disease,[22] shows a predilection for men, and appears to be more prevalent in Asian populations.[6,23]

MG patients are substratified not just according to their seropositivity toward antibody markers, but also according to thymic pathology, as well as the clinical presentation. Although each patient should be stratified into one group, some patients with ocular myasthenia may progress to *(Print pagebreak 600)* systemic MG during their disease, thus necessitating a diagnostic revision.[5] AChR MG patients are classified into either early-onset MG (onset <50 years) or late-onset MG (onset >50). This stratification does not have any prognostic significance except regarding thymic pathology as thymectomy in early-onset MG may have a clear clinical benefit, while in late-onset MG the benefit is doubtful.[5] The vast majority of $MuSK^+$ MG patients are females with profound muscle weakness that may even progress to muscle atrophy. Although respiratory muscle weakness is severe, ocular muscles are usually spared, and therefore this type is rarely seen in everyday ophthalmology practice.[5] In contrast, LRP4 MG is a milder form of AChR MG and thymomas are not reported.[5] Seronegative MG constitutes about 10% of patients with generalized MG and is a heterogeneous disease. It includes patients with very low concentrations of antibodies, patients with antibodies against antigens that have not been defined yet, and possibly patients with nonautoimmune myasthenic mechanisms, although repeated testing can sometimes lead to a diagnostic revision.[5] Around 30% of patients with thymoma develop MG, and another 15% have asymptomatic anti-AChR antibodies. Overall, thymoma-associated MG represents about 10% of all MG patients, but this type is not typically associated with any other antibodies except AChR.[5]

About 40% to 50% of MG patients initially present with purely ocular symptoms, with a history of chronic remitting, but generally progressive painless weakness or fatigability of the extraocular muscles manifesting with double vision and ptosis. Over the course of the disease, the symptoms may alternate between both the eyes, and an acute onset may rarely be encountered.[7,23,24] Overall, ocular muscles are involved in 90% of patients with generalized myasthenia.[12] On the other hand, 50% to 80% of ocular myasthenics ultimately develop generalized disease, which usually occurs within the first 2 years from onset; however, the use of immunosuppressants may reverse this trend.[8,12,25]

On examination, OMG is hallmarked by the presence of pupil-sparing ptosis (Figure 90.1) and extraocular muscle weakness (Figure 90.2), which is typically characterized by being variable, increasing with sustained muscle use even for brief periods, and improving with rest or sleep.[23] Ptosis may be unilateral or bilateral and is usually asymmetrical.[26] When ptosis is unilateral or markedly asymmetrical, two phenomena may be observed, and both are attributable to the Hering law of equal innervation.[12,27] The first is apparent or "pseudoretraction" of the contralateral normal upper eyelid,[23,27] and the second phenomenon is "enhanced ptosis." After manually elevating the more ptotic eyelid, ptosis may appear to be increased or "enhanced" in the contralateral less ptotic eyelid.[12,28] A more characteristic, albeit rarer and more difficult to elicit phenomenon is the Cogan lid twitch sign, which is characterized by a brief episode of lid retraction after a vertical upwards saccade from a downgaze position.[23] Clinicians should also be aware that MG may cause orbicularis muscle weakness.[23,29] When OMG patients are instructed to close their eyelids and keep them closed, a few seconds later the palpebral fissure widens and the cornea is exposed because of orbicularis fatigue.[29] This sign has been dubbed the "eyelid peek" or "peek-a-boo sign" because the patient appears to peep or peek at the examiner.[12,29] Orbicularis muscle weakness may also manifest with "afternoon ectropion" and "nocturnal lagophthalmos."[29,30]

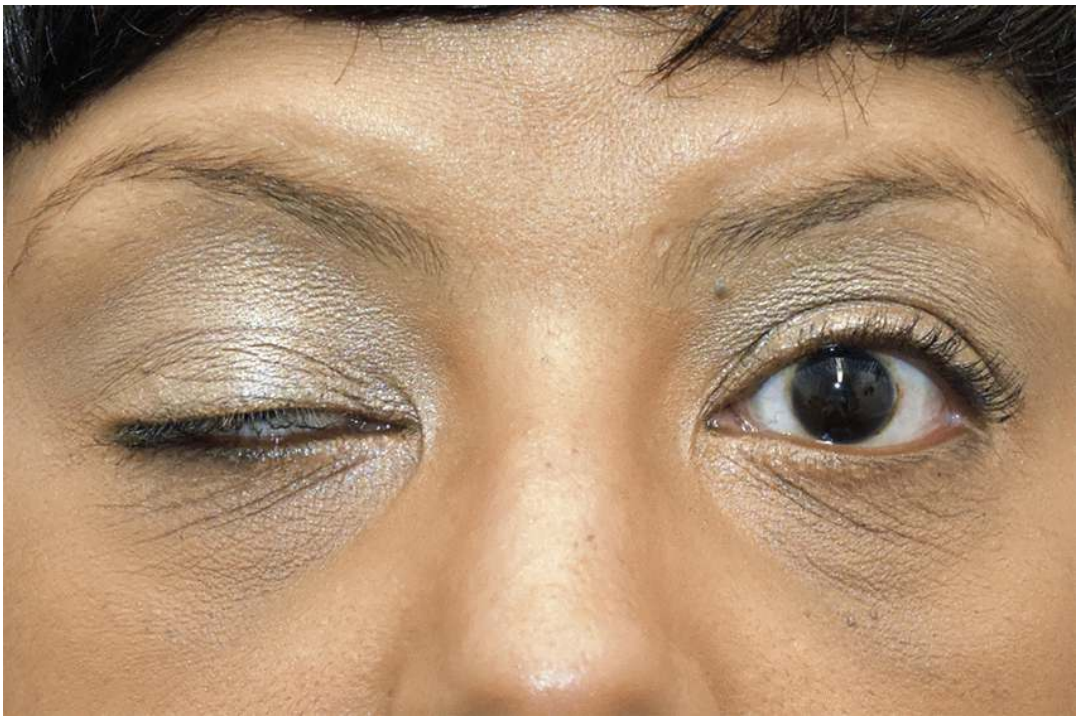

FIGURE 90.1 Myasthenia gravis presenting with asymmetric blepharoptosis of the right eyelid. (Courtesy of Dr. Kyle Godfrey.)

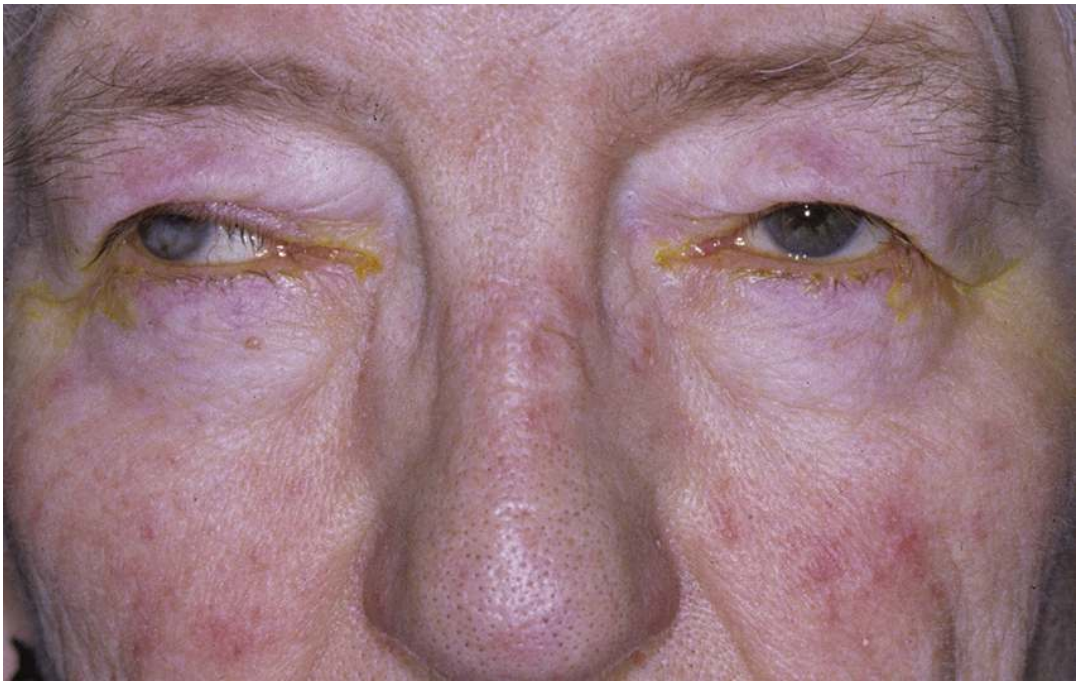

FIGURE 90.2 A patient with myasthenia gravis showing asymmetric blepharoptosis and pupil-sparing adduction weakness on the right side.

Several office-based tests can be performed in the clinic to help establish the diagnosis of OMG including the ice test, the sleep test, the eyelid fatigability test, and the rest test.[12] Local cooling of the eyelids is a rapid, safe, and inexpensive test for OMG with a high degree of specificity and sensitivity. Cooling is believed to reduce the activity of the acetylcholinesterase enzyme, indirectly increasing the amount of available ACh at the neuromuscular junction. The ice test is performed by having the patient apply ice compresses over a closed eyelid for 2 to 5 minutes, and the patient is photographed before and after the application of ice to provide accurate documentation of the test outcome (Figure 90.3). An upper eyelid elevation of ≥2 mm is considered suggestive of MG, but the effect usually lasts less than 1 minute.[12] In the eyelid fatigability test, the patient is asked to look upward for *(Print pagebreak 601)* 2 to 5 minutes. The sustained muscle fatigue results in exacerbation of the eyelid ptosis in patients with OMG (Figure 90.4). The sleep test is performed by letting the patient sleep alone in a dark quiet room for 30 minutes. Again, measurements are taken, and the patient is photographed before and after sleeping, but the results are also very transient lasting no more than a minute or 2.

The rest test is essentially a mini-sleep test where the patient is asked to gently close the eyelids for 2 to 5 minutes which is reportedly sufficient in a sizable proportion of patients to document a diagnostic improvement. It should be noted that in a busy clinical setting, the sleep test is less practical than the other tests, and it appears that the ice test is more sensitive than the rest test.[12]

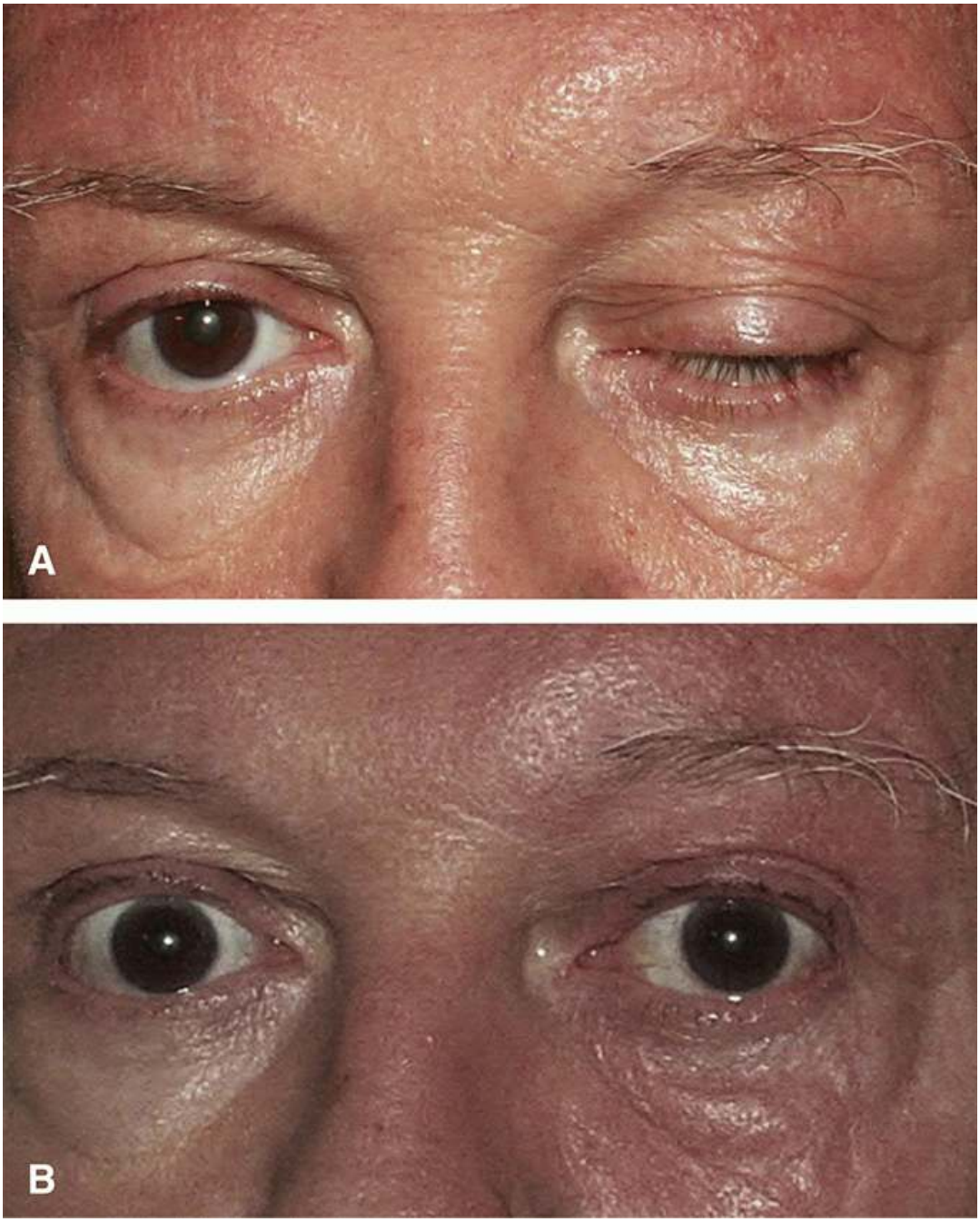

FIGURE 90.3 The ice test. A, Left eyelid ptosis before the ice is applied. B, Immediately after the ice pack is applied to the left eyelid for 5 minutes, the patient is asked to open the eyelids. The rest test should provide similar results.

Extraocular muscle involvement is also a common symptom in OMG and is found in as many as 90% of patients, usually associated with ptosis.[12] It can mimic any pupil-sparing ocular motility disorder, ranging from a single extraocular muscle paresis to complete external ophthalmoplegia, but OMG patients may also present with full ocular motility.[12]

Systemically, patients may complain of difficulty in chewing solid food, dysphagia, or dysarthria, as well as difficulty whistling, using straws, or inflating balloons. MG patients may exhibit a nasal tone of voice which becomes increasingly apparent if history taking is prolonged. Patients with generalized MG may also demonstrate a depressed or expressionless facial appearance, and the characteristic myasthenic snarl may also be observed on an attempted smile.[26] Air readily escapes through the lips, and liquid may escape through the nose during attempted swallowing with nasal regurgitation. Patients with limb weakness may complain of *(Print pagebreak 602)* difficulty climbing the stairs or performing overhead tasks with their arms.[26]

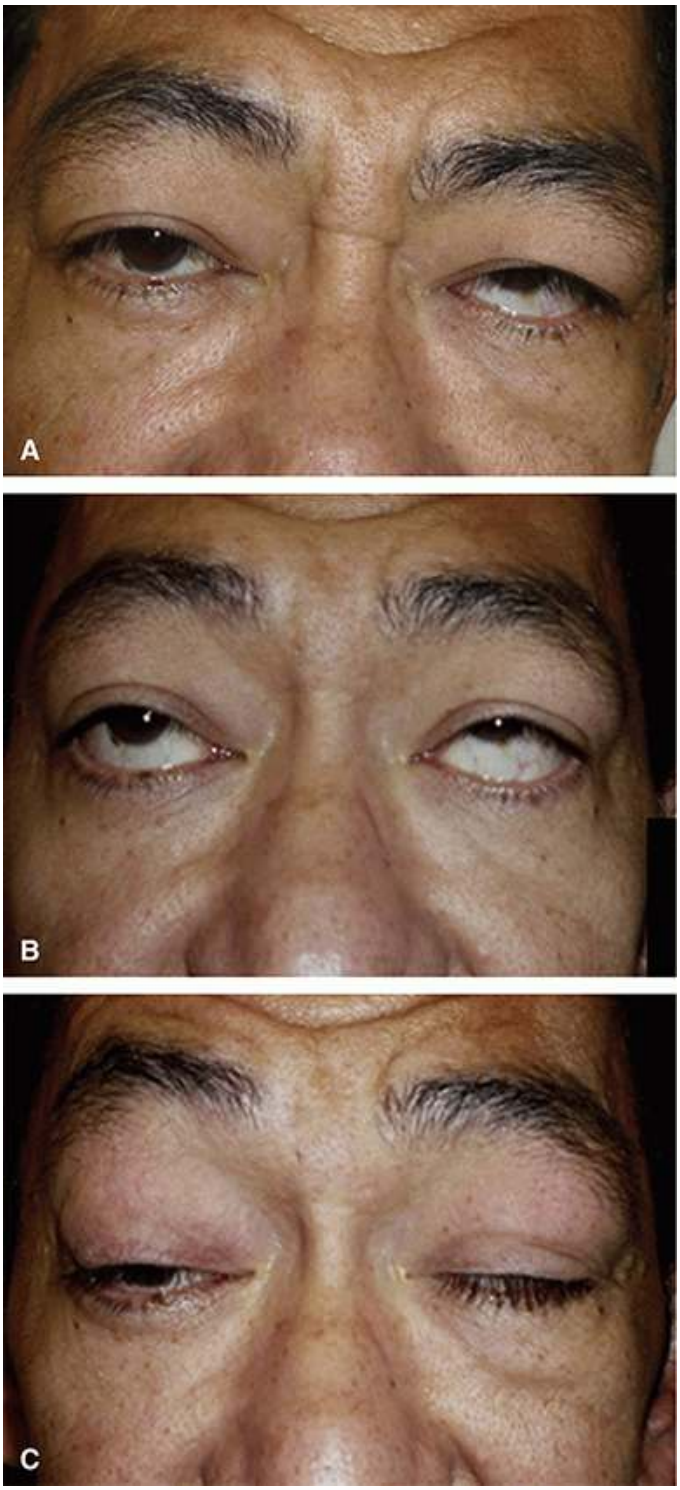

FIGURE 90.4 The eyelid fatigability test. A, Before the start of levator muscle contraction. B, Sustained upgaze for 2 to 5 minutes. C, Immediately following the test, the ptosis is increased. (Courtesy of Dr. Robert Kersten.)

The diagnosis of MG and in particular OMG is primarily a clinical one, and OMG should be suspected in any patient presenting with painless, pupil-sparing ptosis with ophthalmoparesis even if the results of antibody testing and nerve stimulation are negative. Nevertheless, this statement should not undermine the fact that diagnostic tests are still of utmost importance to support the diagnosis of generalized myasthenia and to a lesser extent OMG. These tests can be categorized into clinical, laboratory, electrophysiologic, pharmacologic, and radiologic tests.[31] The typical workup of suspected MG/OMG usually includes anti-AChR antibody testing, anti-LRP4 antibody testing, anti-MuSK antibody testing, single-fiber electromyography, and CT or MRI of the mediastinum, but MuSK antibodies are virtually nonexistent in OMG and therefore the test should not be ordered if ocular signs are the sole presenting findings of the disease.[5,21] One important clinical point that should not be overlooked is that 10% of MG patients will have a thymoma on chest radiology and 70% will have thymic hyperplasia. Those relatively high figures are not observed in healthy patients, which argues for a central role of the thymus gland in the pathogenesis of the disease.[32] Therefore, a negative antibody workup does not rule out MG/OMG if the clinical signs are highly suggestive.[12]

Differential Diagnosis

Ptosis due to OMG should be differentiated from other types of acquired ptosis like aponeurotic, myopathic, or neurogenic ptosis; however, because of the concomitant involvement of the extraocular muscles, the list of other simulating conditions is not short.[3] The diagnosis of OMG is rarely in doubt when the patient presents with the proper history and characteristic clinical findings. However, excluding MG may occasionally be challenging because some myasthenia patients may not present with the typical muscle use-dependent fatiguability and may test negative for AChR antibodies. Signs that should raise suspicion against a diagnosis of MG/OMG include the lack of variability or fatigability, the presence of pupillary abnormalities, diminution of vision, and the presence of pain or strictly persistent unilateral signs and symptoms.[12]

The most common type of ptosis that may be confused with OMG in clinical practice is aponeurotic ptosis. Although aponeurotic dehiscence immediately springs to mind when an adult presents with acquired ptosis, clinicians should always be on high alert for OMG particularly if the variability of symptoms is marked or if there is a history of diplopia. A normal levator excursion would suggest an aponeurotic etiology, while a diminished levator function (<10 mm) in an adult should direct the clinician to a myopathic or a neurogenic etiology.

The types of myopathic ptosis that may be confused with OMG include oculopharyngeal muscular dystrophy (OPMD), myotonic dystrophy (MD), and mitochondrial myopathies like the chronic progressive external ophthalmoplegia. The orbicularis muscle is exceptionally weak in MD, much more than in patients with mitochondrial myopathy, whereas in OPMD it may be normal.[33] The presence of meibomian gland dysfunction could suggest MD,[33] while a relative sparing of the extraocular muscles and a good Bell phenomenon may point to OPMD. Cogan lid twitch and the eyelid peek sign may help clinch the diagnosis,[29] but they are not 100% pathognomonic of MG and have been documented in other conditions.[12,34] The coexistence of poor eyelid closure and ptosis with ophthalmoparesis is strongly suggestive of OMG because the facial nerve and the third cranial nerve have separate courses,[12] but this combination has been observed in several types of myopathic ptosis as well (see Chapter 11).[33] Systemic features may not be of much help either, because some symptoms such as dysphagia and dysarthria may also be shared with OMG and myopathic ptosis.[12,23]

Other causes of neurogenic ptosis should be excluded as well. Patients with oculomotor nerve palsy usually present with a specific pattern of ophthalmoplegia in the form of sudden onset of diplopia with one eye turned down and out, with partial or more commonly complete ptosis. The presence or absence of pain, as well as pupillary abnormalities, may help clinch the diagnosis, but these findings vary according to the etiology of the nerve palsy. Angiographic imaging studies, as well as standard radiology (CT/MRI), are often required for diagnosis.[35] Patients with Horner syndrome typically present with minimal ptosis (1-2 mm) and therefore are not usually confused with OMG. Ptosis following botulinum toxin injections may also pose a diagnostic dilemma particularly if the patient denies or the physician fails to inquire specifically about a recent episode of injection. Acute onset of ptosis with diminution of levator function in an otherwise healthy middle-aged female should always raise suspicion.

OMG may simulate virtually any pupil-sparing eye movement disorder like internuclear ophthalmoplegia and the one-and-a-half syndrome because of its predilection to affect the medial rectus muscle particularly early in the course of the disease.[23] But because of the variable patterns of ocular motility disturbances encountered in OMG, it may also mimic trochlear, abducens, or even oculomotor nerve dysfunction.[12] On the other hand, many intracranial sinister etiologies may masquerade as MG (pseudomyasthenia).[27,34]

Although OMG patients may present with lid retraction due to Hering law, thyroid eye disease should be ruled out in any known MG patient who presents with unilateral or bilateral retraction, because both conditions may coexist in 4% to 10% of patients.[12] Similarly, the presence of proptosis should not exclude a diagnosis of MG.

It is also important to differentiate MG from paraneoplastic disease (Lambert-Eaton myasthenic syndrome [LEMS]) which is a distinct autoimmune disease of neuromuscular junction transmission caused by paraneoplastic antibodies directed against the presynaptic voltage-gated calcium *(Print pagebreak 603)* channels (VGCCs).[36] An aggressive search for an underlying malignancy is central to the management of LEMS as it is associated with a small lung cell cancer in approximately 40% to 50% of patients but other malignancies may be observed as well.[36,37] The initial presentation may be similar to MG/OMG with variable ptosis and diplopia which are not as rare as was previously thought.[12,36] Systemically, LEMS may suffer more proximal muscle weakness/fatigability, hyporeflexia, and an important differentiating point is that LEMS may rarely manifest with autonomic dysfunction symptoms like pupillary abnormalities.[12,36] Antibodies to VGCCs may also clinch the diagnosis as they are positive in 75% to 100% of patients with LEMS and only 5% with MG, while the reverse is true if anti-AChR ABs are tested.[37] Other neurologic disorders that should also be differentiated from MG include neuromyotonia, the Miller Fisher variant of Guillain-Barré syndrome, and genetic and toxic myasthenic syndromes.[5]

Treatment

Acetylcholinesterase inhibitors remain the mainstay treatment modality in MG. However, any long-term treatment plan should include immunosuppression, which is required in generalized MG.[38] Glucocorticoids, azathioprine, cyclosporine A, mycophenolate mofetil, cyclophosphamide, methotrexate, and tacrolimus have all been tried as single agents or in combination.[38] In OMG, treatment with acetylcholinesterase inhibitors may be sufficient in milder cases, but the indications for use of immunomodulating agents are less clear-cut.[38,39] A recent randomized, double-blind, placebo-controlled trial (the EPITOME study) showed a beneficial effect of an initial low dose of prednisone with gradual escalation when OMG is resistant to acetylcholinesterase inhibitors.[22] Immunosuppressants do not only ameliorate the symptoms of the disease but may also reduce the rate of progression of OMG to generalized MG.[12] In severe or drug-resistant cases, co-treatment with intravenous immunoglobulins or plasmapheresis may be considered.[38] More recently, rituximab[40] and a newer monoclonal antibody eculizumab (Soliris) have shown some promise in cases refractory to conventional treatment.[41]

Any thymic enlargement detected on CT scan or MRI should be removed. Some authorities recommend routine transsternal/endoscopic thymectomy even in nonthymoma patients, particularly children and adults up to the 5th decade, provided it is performed during the first year into the disease in the hope of achieving a medication-free remission.[26,32,42] A recent randomized clinical trial (the MGTX trial) conducted over 3 years has demonstrated clinically significant improvement in nonthymomatous MG patients and a more favorable outcome than prednisolone.[32] A 5-year follow-up study confirmed a possible beneficial effect of thymic resection in nonthymoma patients;[43] however, patients with $MUSK^+$ MG and patients with late-onset MG may not benefit from the procedure.[5,8]

Nonsurgical management of ptosis in OMG may involve taping the ptotic eyelid up or the use of ptosis crutches, but these measures may exacerbate corneal dryness, as well as corneal exposure,[12] and the crutches may cause chronic ocular pain. Ptosis surgery in OMG is considered high risk due to a combination of perioperative considerations, poor ocular motility, poor Bell phenomenon, and the reduced orbicularis muscle strength which may further impair eyelid closure mechanisms following surgery.[44] Perioperative considerations in the surgical management of OMG include the choice of anesthetics and the choice of postoperative antibiotics.[7] Although general anesthesia no longer poses an untenable risk to myasthenic patients, local anesthesia may be preferred, as resistance to neuromuscular blocking agents may result in a higher likelihood of prolonged postoperative recovery.[7] Postoperatively, the choice of antibiotics used is another critical issue. As we mentioned earlier, fluoroquinolones, aminoglycosides, and macrolide antibiotics should be used with caution.

MG patients with esthetic concerns pushing for full correction should be counseled that the main goal of surgery is to clear the pupillary axis while minimizing the risk of corneal exposure. When a frontalis suspension procedure is considered, silicone slings are the preferred sling material because of their elastic nature and their potential for easy reversibility if corneal exposure is observed postoperatively. The open technique is generally favored over the closed Fox method for brow suspension.[44,45,46,47] Surgical management of ptosis in OMG and other causes of neurogenic ptosis is discussed in further detail in Chapter 12.

Prognosis

Before the widespread use of immunosuppressants in the management of MG, the disease-specific mortality rate was as high as 30%; however, with the use of immunomodulators along with advances in mechanical ventilation and intensive care, the overall mortality rate has dropped to less than 5%,[26] but despite the improved management, MG patients may remain dependent on long-term immunosuppressants and acetylcholinesterase inhibitors, which may be required for life, and some patients with severe disease may still develop a permanent disabling weakness.[15,26,42] Luckily, patients with mild to moderate disease who constitute the majority of MG patients can still lead essentially normal lives as the daily life functions may only be modestly impaired or may not even be affected at all, and some may enter a phase of complete stable remission without a reduction in life expectancy.[15,42,48] Thymoma patients pose a different problem as the prognosis is related to the histological staging of the tumor.[42,49]

Histopathology

Europa, Nel, and Heckmann recently reviewed skeletal muscle histopathology in MG patients.[50] Nonocular skeletal muscles exhibit neurogenic atrophy, with groups of skeletal muscle fibers being atrophic and angulated.[50] Prolonged disease *(Print pagebreak 604)* duration may cause atrophy with fatty replacement of skeletal muscle.[50] Extraocular muscles in MG patients have severe fatty change and mitochondrial stress alterations, though similar findings occur in extraocular muscles from strabismus patients.[50] Europa and coworkers postulate that “extraocular muscles may be more susceptible than limb muscles to poor contractility as a

consequence of myasthenia, resulting in a cascade of atrophy signaling pathways and altered mitochondrial homeostasis which contribute to the tipping point in developing treatment-resistant myasthenic ophthalmoplegia."[50] Our experience is limited to examining one inferior oblique muscle from a patient with MG for 1 year. No histological abnormality was identified in this muscle removed as part of enucleation for fungal endophthalmitis.

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CHAPTER 91

Necrotizing Fasciitis

Key Points

- Necrotizing fasciitis is an uncommon soft-tissue infection characterized by extensive suppurative fasciitis, vascular thrombosis, and cutaneous gangrene
- The infection progresses rapidly over hours to several days, spreading along superficial and deep fascial tissue planes to involve subcutaneous tissue and fascia, with secondary necrosis of the overlying skin
- Patients often suffer from diabetes mellitus, alcoholism, collagen vascular disease, or conditions requiring immunosuppression
- Type I necrotizing fasciitis usually occurs after trauma or surgery caused by polymicrobial anaerobic and facultative bacteria
- Type II necrotizing fasciitis is a monomicrobial infection usually with virulent subtypes of *Streptococcus pyogenes*
- Patients are usually febrile and present with extensive, rapidly progressive eyelid swelling, and erythema, pain, crepitus, a foul-smelling watery wound discharge, and areas of necrosis
- Treatment includes broad-spectrum antibiotics, surgical debridement, fluid resuscitation, and cardiorespiratory supportive care when necessary to maintain vital organ function
- Systemic complications are frequent and the prognosis generally is poor with a mortality rate up to 50%

The first description of necrotizing fasciitis (NF) is generally attributed to Fournier in 1883,[1] although a very similar gangrene-like infectious process was previously described by Ambrose Paré in 1575.[2] However,

the term, NF, was only introduced by Wilson in 1952.[3] NF is an uncommon soft-tissue infection characterized by extensive suppurative fasciitis, vascular thrombosis, and cutaneous gangrene.[4,5] The infection progresses rapidly over hours to several days, spreading along superficial and deep fascial tissue planes to involve subcutaneous tissue and fascia, with secondary necrosis of the overlying skin.[5,6] The most common causative organism is group A β-hemolytic *Streptococcus*, but other gram-positive, gram-negative, and anaerobic bacteria, and even fungi, can also be involved.[7,8] NF commonly occurs on the extremities, abdomen, and perineum, and less commonly in the head and neck.

NF only occasionally involves the eyelids, with about 150 cases reported.[7,9,10,11,12] Patients often suffer from diabetes mellitus, alcoholism, collagen vascular disease, or conditions requiring immunosuppression,[13,14,15] although in many cases, there are no obvious predisposing risk factors for infection. Periorbital NF has been reported after trauma,[16,17] after surgery including dacryocystorhinostomy,[18] and blepharoplasty,[19] and following an insect bite.[9]

Eyelid NF can be caused by aerobic, anaerobic, or polymicrobial infections, although the vast majority of bacterial isolates are group A β-hemolytic streptococci or *Staphylococcus aureus*.[10,20,21] In a report of 67 cases of NF at a Philippine University Medical Center, *Escherichia coli* was the most common isolate seen in 44% of patients.[22] A case of NF caused by *Apophysomyces* belonging to the order *Mucorales* was reported in a burn patient.[23]

Etiology and Pathogenesis

Necrotizing soft-tissue infections are potentially lethal infections that require early recognition and aggressive management.[24,25,26] These infections most frequently involve the abdomen, perineum, and lower extremities, but can occur in any part of the body. Surgery and trauma are the most common predisposing factors, but it rarely has been reported following diverse etiologies such as spinal anesthesia,[27] measles vaccine,[28] as a complication of infectious mononucleosis,[29] following dental procedures,[30] and

associated with insect bites.[31] Immunocompromised individuals, especially those with diabetes, are more likely to develop necrotizing infections. However, in many cases, there is no identifiable preceding event.

All necrotizing infections are best viewed as a spectrum of clinical conditions with similar pathophysiological features and common treatment approaches.[26,32,33] NF has been classified according to the types of microbial organisms involved. Type I NF usually occurs after trauma or surgery.[3,34] Initially, the subcutaneous fat and fascia are primarily involved, and later may extend into the muscle. But most commonly, widespread necrosis is present in the subcutaneous fat and fascia, with relative sparing of muscle. Polymicrobial anaerobic and facultative bacteria are involved in tissue destruction, and gas may or may not be present. The clinical pace of the disease is usually slower than that seen with type II NF.[8] Patients usually have a predisposing risk factor, such as diabetes mellitus.

Type II NF is a monomicrobial infection usually with virulent subtypes of *Streptococcus pyogenes*.[5,35,36] It presents clinically in a similar fashion to type I NF, but the presence of gas in tissues is unusual.[8] Varicella infection and the use *(Print pagebreak 607)* of nonsteroidal anti-inflammatory drugs may be additional predisposing risk factors besides trauma or surgery.[5,37,38,39] This form of NF is also more frequently associated with streptococcal toxic shock syndrome.[40]

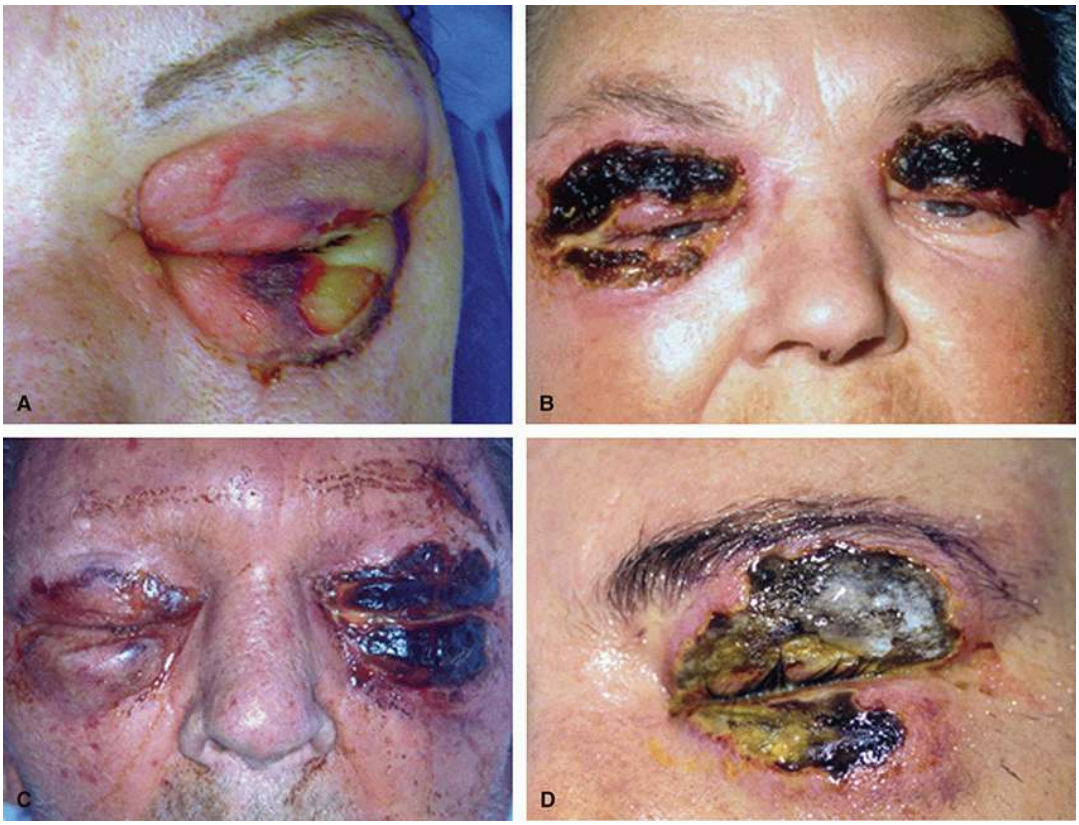

FIGURE 91.1 Necrotizing fasciitis involving the eyelids. A, Upper and lower eyelid edema, erythema, and early devitalization of eyelid skin. B, Bilateral skin necrosis and crusting. C, Bilateral involvement with necrosis of the left eyelids. D, Severe necrosis of upper and lower eyelids with extensive loss of tissue. (A, Courtesy of Dr. Charles Soparkar; B, Courtesy of Dr. Grant Gilliland; C, Courtesy of Dr. James Gigantelli; D, Courtesy of Dr. John Holds.)

Clinical Characteristics

In the eyelids, NF is often identified earlier than elsewhere in the body because of the thin skin and the orbicularis oculi muscle that lies superficial to the fascial layers allowing the infection to become more easily recognized.[9] Of the reported eyelid cases, nearly half are bilateral, and deep orbital involvement by spread of the infection along the orbital fibrous septae and blood vessels can result in arterial thrombosis with diffuse ophthalmoplegia, central artery occlusion, papilledema, and blindness.[9,41]

Patients with periorbital NF are usually febrile and present with extensive eyelid swelling and erythema rapidly progressive over several days.[11] Other clinical features include pain, crepitus, a foul-smelling watery wound discharge, violaceous discoloration, serosanguinous skin blisters, and areas of necrosis (Figure 91.1).[8] In early cases, the skin wound may appear only mildly infected, unlike deeper fascial layers, and this may contribute to devastating diagnostic delay. Soft-tissue gas is a classic sign but is not always present.[42] The past medical history may include immunosuppression, diabetes, hyperglycemia, acidosis, and severe dehydration. Even with early recognition and timely appropriate treatment, some cases may progress rapidly to septic shock and

death.[24,25,34,42]

Differential Diagnosis

The differential diagnosis of periorbital NF includes any infectious or inflammatory processes in the periorbital region such as preseptal and orbital cellulitis.[6] Dacryocystitis, erysipelas, and *herpes zoster* are also included.

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NF should also be differentiated from other causes of necrotizing soft-tissue infections such as clostridial myonecrosis (gas gangrene), which is a life-threatening infection that affects the skeletal muscle and is most commonly caused by *Clostridium perfringens* or to a lesser extent *Clostridium septicum*.[42,43] Although both entities fall under the rubric of necrotizing soft-tissue infections and may indeed look identical clinically, the presence of an extremely pungent foul-smelling discharge, as well as the presence of air or gas in tissues in radiological studies, is more suggestive of clostridial myonecrosis, which may have up to a 100% mortality without prompt and repeated debridement.[43] Clostridial myonecrosis is occasionally referred to in the literature as type III NF, but it is rarely encountered in the periocular region (Figure 91.2).

Treatment

Prompt diagnosis and aggressive treatment of periorbital and orbital NF are critical for the preservation of vision and life.[9,10,44] Appropriate treatment includes broad-spectrum antibiotics, surgical debridement, fluid resuscitation, and cardiorespiratory supportive care when necessary to maintain vital organ function.[15,45,46,47,48,49] Empiric antibiotic treatment should be broad to cover both polymicrobial (mixed aerobic and anaerobic microbes) and monomicrobial (group A streptococci and community-acquired methicillin-resistant *S. aureus*) organisms. These can include vancomycin or linezolid plus piperacillin-tazobactam, or carbapenem, and ceftriaxone and metronidazole.[50] For documented group A streptococcal NF, penicillin plus clindamycin is recommended.[51,52]

Complete subcutaneous debridement of affected tissue and removal of all necrotic skin are critical. The extent of debridement is determined by the surgical findings, retaining maximal amounts of viable skin and orbicularis oculi muscle to prevent disfiguring facial deformities. Tissue debridement should be repeated until the local infectious process is under control.[53] Hyperbaric oxygen therapy has been advocated, but it has an uncertain role. Whereas some studies have suggested a survival benefit,[42,46,54,55] others have not shown any benefit.[56,57]

Although most cases will require a combination of intensive parenteral antimicrobial therapy and prompt surgical debridement, mild cases may respond to medical therapy alone.[58] Intravenous pooled immunoglobulin and heparinization may also have beneficial roles by neutralizing superantigen activity and aiding antibiotic perfusion.[4]

Prognosis

Because NF progresses rapidly and systemic complications are frequent, the prognosis generally is poor. Despite aggressive therapy, the mortality rate has been reported to be up to 50%.[24,26,35,45,52,53,56,59,60] When the eyelids are involved, NF has a more favorable prognosis, reported in from 10%[10] to 18%,[13] probably owing to the eyelid's more extensive vascular supply and the typically earlier recognition and treatment of infection. Mortality in these cases is often secondary to inadequate treatment or delayed debridement resulting in *(Print pagebreak 609)* systemic sepsis and shock with multiorgan failure. Visual loss in patients with periorbital or orbital involvement can be seen in 13% to 30% of cases.[10]

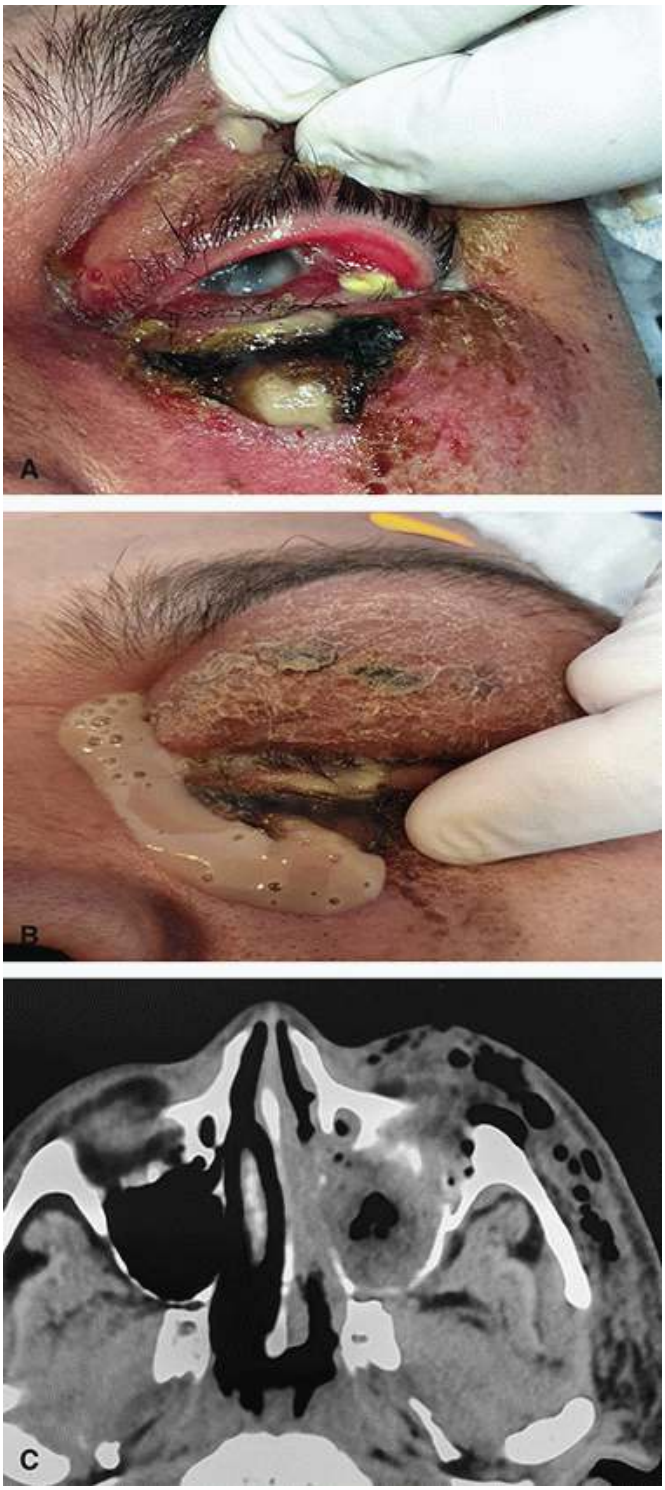

FIGURE 91.2 Clostridial myonecrosis (gas gangrene). A, Clinically, clostridial myonecrosis looks remarkably similar to necrotizing fasciitis. B, On closer examination, gas bubbles can be seen coming out of necrotic eyelid tissue. C, Noncontrast CT scan of the orbit shows the presence of an extensive amount of air along fascial planes and muscles of the periorbital region.

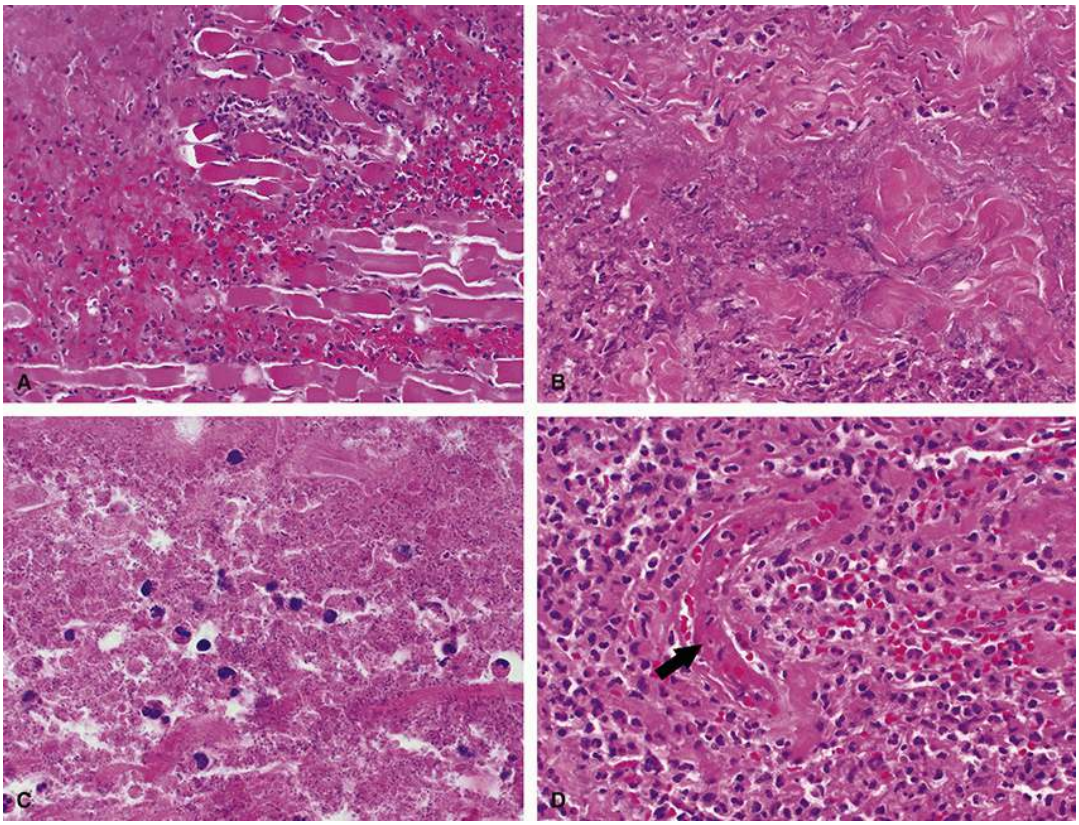

FIGURE 91.3 A 12-month-old boy developed necrotizing fasciitis of the left lower eyelid after blunt trauma.[36] Skeletal muscle (A) and fascial connective tissue (B) were infiltrated by neutrophils and macrophages, accompanied by extensive necrosis. C, Areas with numerous bacterial cocci caused a stippled appearance in the hematoxylin- and eosin-stained sections D, Rare vessels (arrow) contained fibrin thrombi.

Histopathology

The histopathology of NF varies depending on the disease's duration.[61,62,63,64] Stamenkovic and Lew[63] used these criteria for diagnosing NF: "(1) necrosis of superficial fascia, (2) polymorphonuclear infiltration of the deep dermis and fascia, (3) fibrinous thrombi of arteries and veins passing through the fascia, (4) angiitis with fibrinoid necrosis of arterial and venous walls, (5) the presence of microorganisms within the destroyed fascia and dermis in a tissue specimen with Gram stain, and (6) an absence of muscle involvement." Early in the course of NF, thrombi are more frequent[61] and inflammatory cells may be sparse.[62] Features of clinically established streptococcal NF include subepidermal blisters, eccrine gland necrosis, and myonecrosis with neutrophilic inflammation (Figure 91.3).[62]

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CHAPTER 92

Neurofibroma, Solitary

Key Points

- Neurofibromas are tumors that arise from nonmyelinated Schwann cells and perineural fibroblasts
- Isolated neurofibromas are benign, slowly growing, unencapsulated neoplasms that usually arise from cutaneous nerves, with the occasional involvement of deep organs or bone nerves
- As many as 90% of solitary lesions occur sporadically, but 10% are associated with neurofibromatosis type 1 or 2
- The pathophysiology of both sporadic and syndromic cases of neurofibroma is similar and results from a deletion in the NF1 gene
- Solitary lesions on the eyelid present as circumscribed, oval, smooth, firm, immobile, subcutaneous nodules ranging in size from 4 to 15 mm
- Small, asymptomatic eyelid tumors can be followed conservatively, but for lesions that show significant growth, are painful, or cause ptosis or visual symptoms, surgical resection is indicated
- The prognosis for eyelid lesions is excellent following adequate surgical resection

Benign peripheral nerve sheath tumors are divided into three broad categories: neuroma, neurofibroma, and schwannoma.[1,2] Neurofibromas are tumors that arise from nonmyelinated axons, Schwann cells, fibroblasts, and perineural cells. Most neurofibromas are sporadic lesions, but multiple neurofibromas, plexiform neurofibromas, and large neurofibromas are almost always associated with neurofibromatosis type 1 (NF-1).[3]

Three distinct forms of neurofibroma are described: plexiform, diffuse, and solitary subtypes. Plexiform neurofibroma is mostly associated with NF-1 and is the most common benign peripheral nerve tumor occurring in the eyelid, where it typically tracks along peripheral branches of the trigeminal nerve. It can attain massive sizes and cause significant functional and cosmetic compromise (Chapter 93). Diffuse neurofibromas are uncommon, poorly defined, infiltrative cutaneous, subcutaneous, or soft-tissue tumors, seen most often in the head and neck of children and young adults. They extend between tissue planes, along connective tissue septa, and surround adjacent normal structures, encasing vascular and neural structures.[4,5] Unlike the plexiform subtype, only about 10% of diffuse lesions are associated with neurofibromatosis.

Isolated neurofibromas are benign, slowly growing, unencapsulated neoplasms that usually arise from cutaneous nerves, with the occasional involvement of deep organs, bones, or nerves. They can be seen in patients with NF-1 where they tend to be multiple and are seen more commonly in deep locations. However, in most cases, isolated neurofibromas occur in patients who do not have NF-1, and in such cases, they are termed solitary neurofibroma.

The solitary neurofibroma is usually a well-circumscribed tumor that forms an ovoid or fusiform cutaneous or subcutaneous mass.[6,7] As many as 90% of solitary lesions occur sporadically, while 10% are associated with NF-1 or NF-2.[3,6] In the head and neck region, solitary neurofibromas most often involve the trigeminal (fifth) and facial (seventh) cranial nerves. The most frequently affected sites include the tongue, buccal mucosa, and lips,[8,9,10,11] and deep lesions typically present as a facial mass.

Solitary neurofibroma of the eyelid is rare. Woog et al[12] mentioned 65 cases of orbital and periorbital neurofibroma but without specific details. Of these cases, 40% were associated with NF-1, and 55% involved the eyelid. It was not clear how many of the eyelid cases were nonsyndromic or how many were plexiform vs solitary lesions.

To date, only 15 cases of solitary neurofibromatosis involving the eyelids have been described with sufficient clinical detail.[13,14,15,16,17,18,19,20,21,22] Of these cases, 79% were female. The ages ranged from 38 to 81 years with a mean of 63.3 years. Lesions presented on the upper eyelid in 57% of the cases and the lower eyelid in 43%.

Neurofibroma involving the conjunctiva has also been described, of which 75% are solitary and 25% are syndromic.[23,24,25,26,27,28,29,30,31,32,33,34,35,36] Conjunctival tumors occur equally among males and females, and the age at presentation is somewhat younger than for eyelid lesions, ranging from 22 to 78 years with a mean of 51 years.

Malignant transformation of a neurofibroma to malignant peripheral nerve sheath tumor is seen occasionally with plexiform neurofibromas but is exceptionally rare in solitary neurofibroma not associated with neurofibromatosis, although it can be seen with recurrent lesions.[37]

Etiology and Pathogenesis

The pathophysiology of both sporadic and syndromic cases of neurofibroma is similar and results from a deletion in the NF1 gene. In syndromic cases, the neurofibroma results from a germline mutation in the NF1 gene *(Print pagebreak 613)* on chromosome 17q11.2, which encodes the tumor suppressor protein neurofibromin.[38,39] This genetic defect results in overexpression of the p21 *RAS* proto-oncogene, a cellular protein that plays a role in mitogenic signaling pathways. Heterozygous loss results in Schwann cell and fibroblast proliferation that forms neurofibromas. In sporadic cases, only the lesional cells and their somatic progeny carry the mutation.

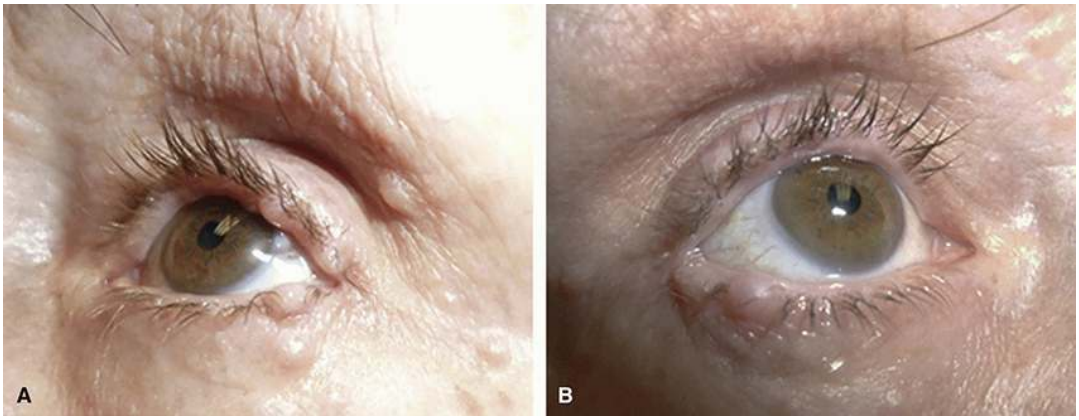

FIGURE 92.1 A and B, Solitary neurofibroma of the eyelids.

Several studies have shown a loss of heterozygosity at the NF1 locus in dermal and plexiform neurofibromas,[40,41,42,43] or inactivation of both copies of the *NF1* gene in the *NF1* gene in some isolated neurofibromas.[43,44,45,46] Although some authors have suggested that sporadic neurofibromas may arise through a different genetic mechanism,[47,48] Storlazzi et al[49] showed that biallelic somatic inactivation of the *NF1* gene through chromosomal translocation can lead to the cellular proliferation of Schwann cells associated with neurofibroma. Other chromosome studies of neurofibromas have reported clonally abnormal karyotypes, such as monosomy 22, hyperdiploid tumors, and complex translocations that may play a role in tumor growth.[50,51,52,53,54,55] Marocchio et al[56] considered that solitary neurofibroma may be a hyperplastic hamartomata rather than a neoplastic tumor.

Solitary neurofibroma can also rarely arise in patients with germline changes in the *NF1* gene but with no clinical evidence of neurofibromatosis.[57] One case has been reported of a solitary neurofibroma that was thought to be related to local trauma 3 months earlier.[57]

Clinical Characteristics

Most neurofibromas involving the eyelid are solitary lesions and present as a circumscribed, oval, smooth, firm, immobile, subcutaneous nodule. Lesions are usually small, ranging in size from 4 to 15 mm in diameter with normal overlying skin (Figure 92.1). While generally painless, they may sometimes be tender or even painful. Lesions are slow growing over months to as long as 5 years.[21] In patients with NF-1, cutaneous neurofibromas tend to be multiple[58,59,60,61,62] and appear as discrete, subcutaneous nodules that can involve the eyelids and adjacent periorbital skin (Figure 92.2).

On the conjunctiva, a solitary neurofibroma appears as a smooth, white, reddish, or yellow-gray; sessile, pedunculated, or dome-shaped mass located in the conjunctival stroma (Figure 92.3).[63] It may be firm to gelatinous and associated with corneal pain, photophobia, or dellen formation.[20,24,32]

Differential Diagnosis

The differential diagnosis of eyelid neurofibroma includes a wide variety of clinically similar lesions. Most frequently, it has been mistaken for a chalazion.[15,16,17,20] In the case by Shibata et al[20] the tumor occupied the full thickness of the *(Print pagebreak 614)* tarsal plate, was surrounded by normal acini of the meibomian glands, and apparently developed from a small nerve coursing through the tarsal plate.

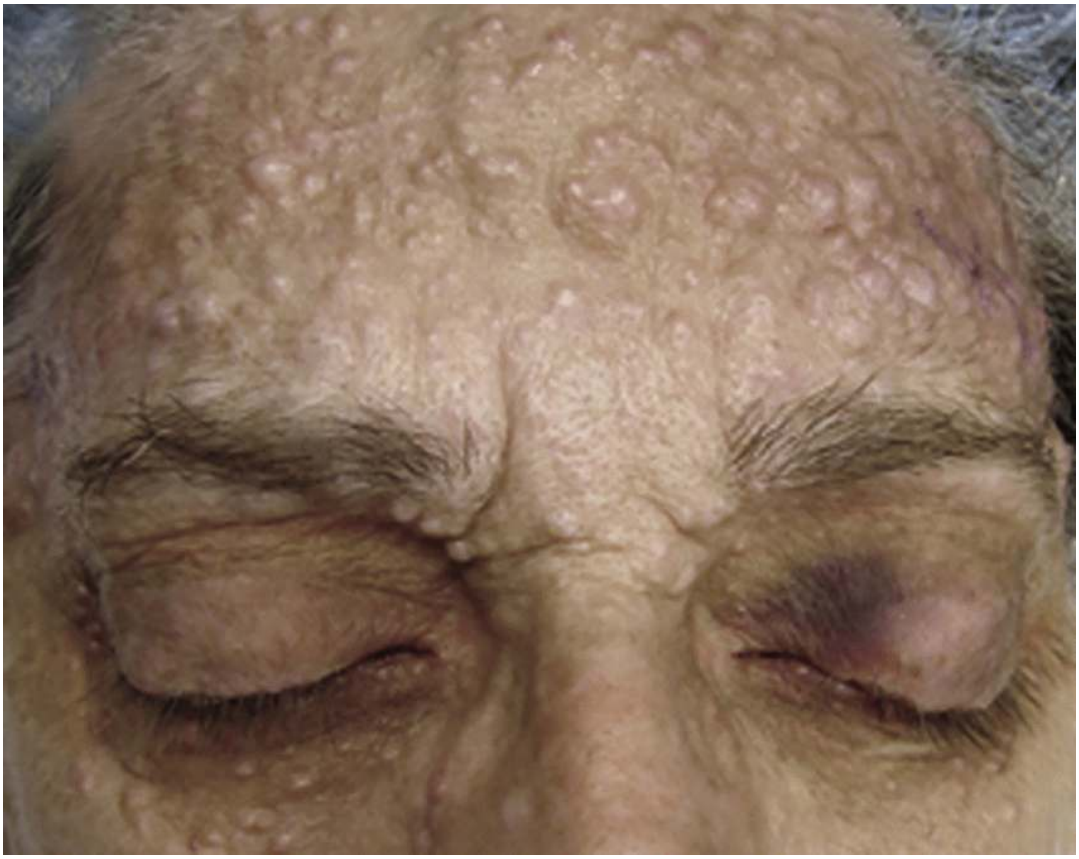

FIGURE 92.2 Neurofibromas in the setting of neurofibromatosis type 1. Hundreds of small lesions on the face, forehead, and eyelids.

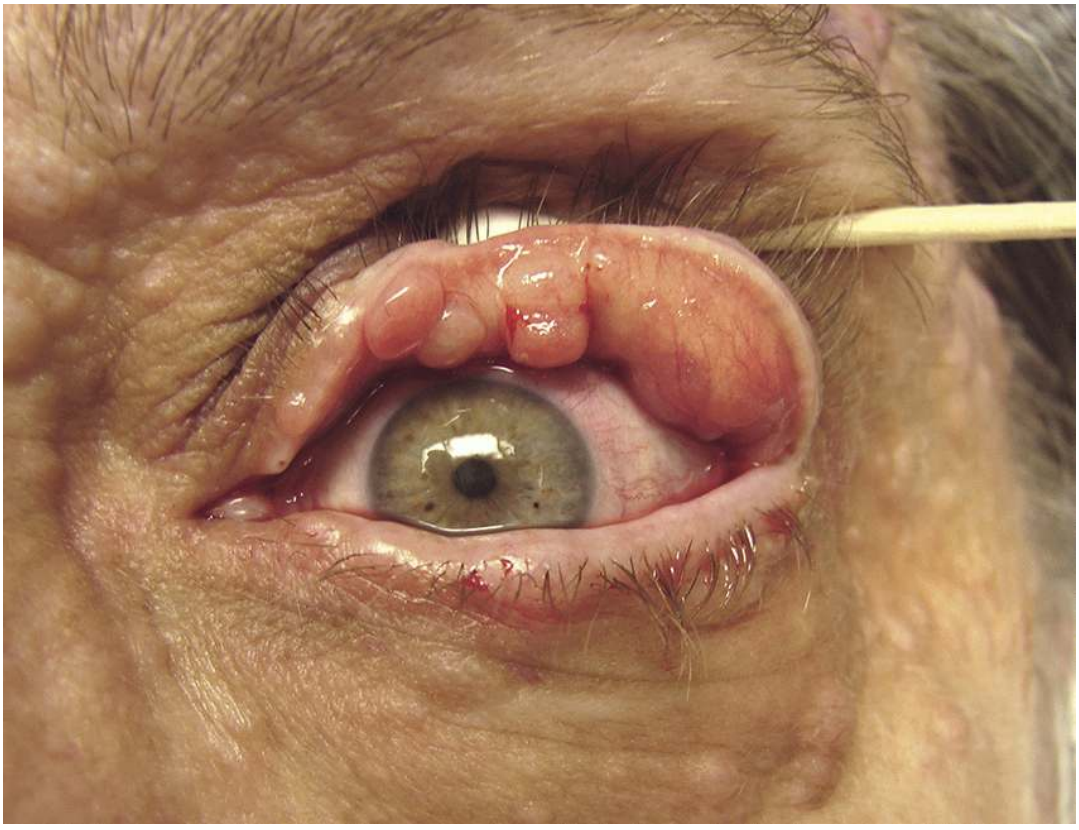

FIGURE 92.3 Nodular neurofibromas on the eyelid skin and conjunctival surfaces.

Other conditions simulating neurofibroma on the eyelid include amelanotic or poorly pigmented nevomelanocytic nevus, apocrine hidrocystoma, early basal cell carcinoma, benign apocrine gland tumor, dermal leiomyoma, and molluscum contagiosum. Hidrocystomas are often white to yellow in color, and early basal cell carcinomas frequently have central ulceration with elevated pearly borders. Molluscum contagiosum is usually characterized by a prominent central umbilication. Nevi and molluscum contagiosum generally occur in children.

Rare lesions that might be considered in the differential diagnosis also include malignant peripheral nerve sheath tumor, schwannoma, perineurioma, dermatofibroma, dermatofibrosarcoma protuberans, superficial leiomyoma, ganglioneuroma, and desmoplastic melanoma. Most can be differentiated from solitary neurofibroma by their association or lack thereof with NF-1, by immunohistochemistry, and by their genetic profile.

Treatment

Because the malignant potential of solitary cutaneous neurofibromas is minimal, small, asymptomatic eyelid tumors often can be followed conservatively. For lesions that show significant growth, are painful, or are large enough to cause ptosis or visual symptoms, surgical resection is indicated. Unlike diffuse or plexiform neurofibromas on the eyelids, solitary lesions can often be resected via a skin crease incision with the preservation of overlying skin. The tumor cannot easily be separated from the involved nerve so that complete excision usually requires sacrificing the nerve. Tumor recurrence following surgical excision is rare[17,20,29] and is usually related to incomplete resection.

There are currently no widely accepted alternative therapies for a solitary neurofibroma.[64] Diode and CO_2 laser therapy have been used successfully for oral, laryngeal, and multiple cutaneous tumors, including the eyelids. However, laser therapy is only useful in removing superficial neurofibromas and has been reported to cause hypertrophic, depigmented scars.[65,66] Electrodessication and scoop diathermy were reported to achieve good results in treating several hundred lesions in a single setting with minimal complications in patients with recurrent cutaneous neurofibromas,[67,68] but these techniques have not been repeated.

Prognosis

The prognosis for patients with a solitary neurofibroma of the eyelid is excellent following adequate surgical resection. Recurrence can be seen with incomplete resection. Several cases of recurrence were previously misdiagnosed as a chalazion and treated with incision and curettage.[15,17]

Malignant transformation of neurofibroma associated with NF-1 is unusual and less common in solitary tumors than in plexiform neurofibroma. Transformation of solitary neurofibroma, without association to NF-1, is extremely rare.[37] Malignant peripheral nerve sheath tumors are insensitive to radiotherapy and chemotherapy and carry a poor prognosis, with a 5-year disease-specific survival rate of 32% to 50%, worse for head and neck tumors.[69,70,71,72,73,74]

Histopathology

We have examined only a few solitary eyelid neurofibromas over the past 30 years (Figure 92.4). They may resemble isolated neurofibromas in patients with NF-1 (Figure 92.5) and are indistinguishable from solitary cutaneous neurofibromas at other body sites. Classic solitary (sporadic) cutaneous neurofibromas are nonencapsulated, poorly to well-circumscribed dermal tumors that often extend into the subcutis.[75] The tumors are palely eosinophilic (Figures 92.4 and 92.5),[76] with a band of normal dermis separating the tumor from the overlying epidermis (Figures 92.4 and 92.5B).[77,78] Solitary neurofibromas are composed of spindle-shaped cells with scant palely eosinophilic cytoplasm, indistinct cytoplasmic borders, and oval or S-shaped nuclei (Figures 92.4C, D and 92.5C, D) set in fibrillar, collagenous, and sometimes myxoid stroma[75,78,79] containing mast cells (Figure 92.5D).[75,80] The tumor cells may form delicate, loosely arranged fascicles that are only one-or two cell thick.[75] Tumor cells surround but do not destroy hair follicles and dermal glands (Figure 92.5B).[75,76,77] A variable number of axons,[75] demonstrable using Bodian silver stain or immunohistochemistry, are present and may assist in distinguishing cutaneous neurofibromas from schwannomas that consist almost solely of Schwann cells.[77] Multinucleated floret-type giant cells are present in about one-fourth of neurofibromas.[78] Immunohistochemical stains are not usually needed for diagnosis; if performed, tumor cells express S100 protein while the admixed fibroblasts express CD34.[76,78] *(Print pagebreak 615)* Immunostaining for CD34 has a “fingerprint” pattern that is useful for

differentiating cutaneous neurofibroma from desmoplastic melanoma.[81]

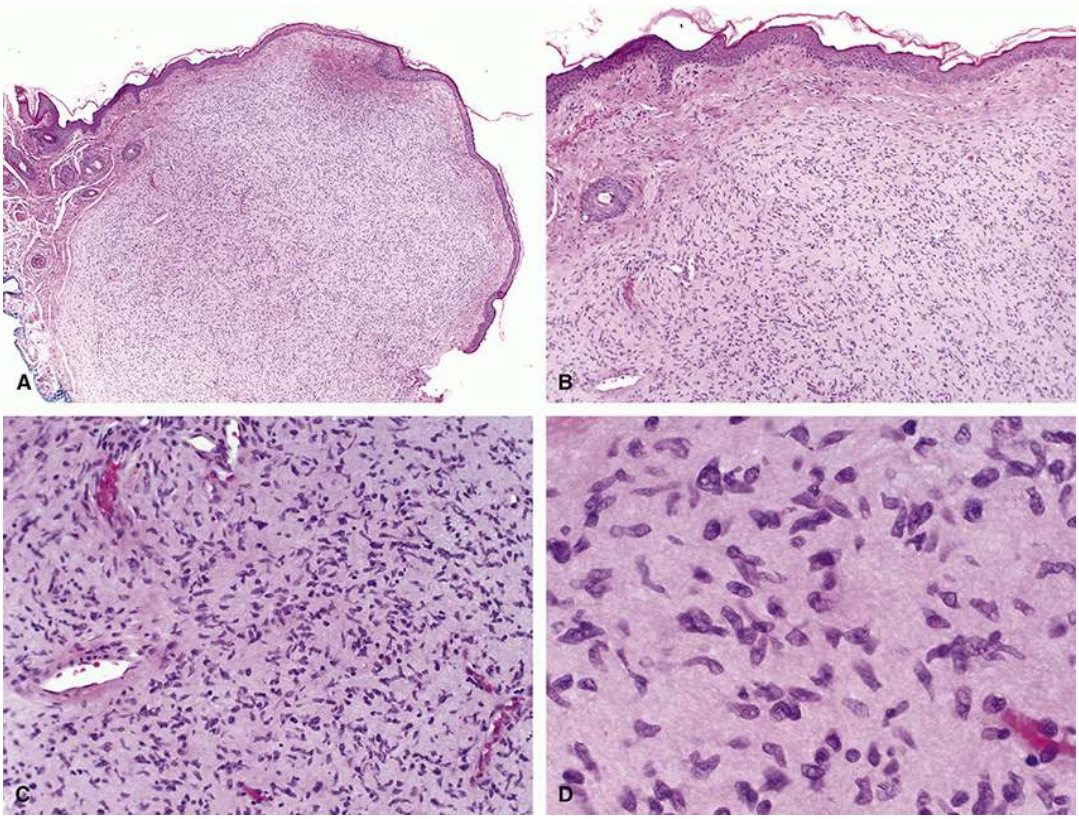

FIGURE 92.4 A, This solitary (sporadic) neurofibroma arose in the medial right upper eyelid of a woman in her early 60s without a history or clinical manifestations of neurofibromatosis type 1. The dermal tumor is nonencapsulated, well circumscribed, and more palely eosinophilic than the surrounding dermis. B, A band of the normal dermis (grenz zone) separates the tumor from the overlying epidermis. C, This solitary neurofibroma is composed of spindle-shaped cells with scant palely eosinophilic cytoplasm and indistinct cytoplasmic borders. D, The tumor cells have oval and curved nuclei.

A lesion that may be confused with eyelid neurofibroma is a solitary circumscribed neuroma, formerly termed palisaded encapsulated neuroma.[78,82] These tumors have a predilection for the face[78,82,83] and may involve the eyelid.[18,83,84,85] Solitary circumscribed neuromas are well-circumscribed dermal nodules with a delicate, often incomplete, epithelial membrane antigen-positive fibrous capsule surrounding broad fascicles of S100 protein-positive Schwann cells and numerous neurofilament protein-positive axons.[77,82,85] Artifactual clefts often separate the tumor cell fascicles.[82,85] Tumor cells may focally align in a “vaguely”[85] parallel arrangement, but classic palisading or Verocay body formation is uncommon.[82,85]

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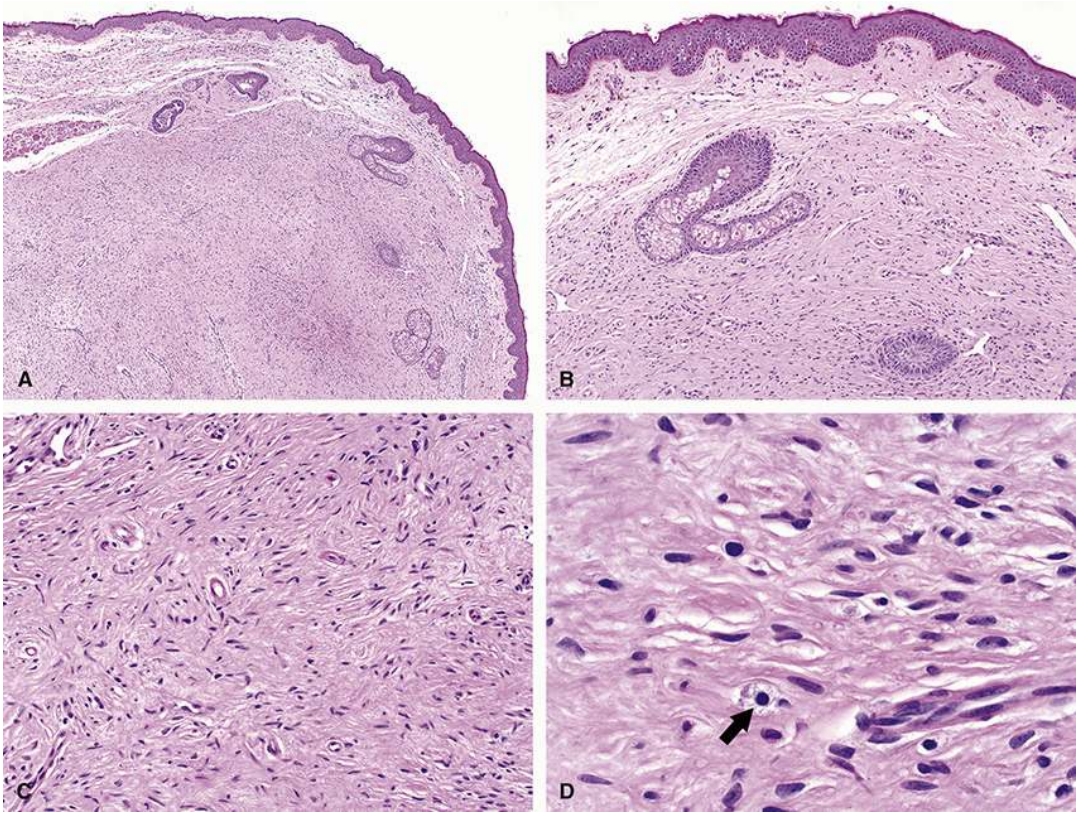

FIGURE 92.5 A, This isolated neurofibroma developed in the right upper eyelid of a woman in her early 50s with a history of neurofibromatosis type 1. The tumor is indistinguishable from a sporadic solitary neurofibroma. The lightly eosinophilic neurofibroma was centered between the orbicularis oculi muscle and the tarsal plate. B, A band of normal dermis separates the tumor from the overlying epidermis. Tumor surrounds hair follicles and sebaceous glands without altering their structure. C, The tumor is composed of spindle cells in a vascularized fibrillary stroma. D, The tumor cells have oval and occasionally wavy nuclei. A mast cell is present among the tumor cells (arrow).

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CHAPTER 93

Neurofibroma, Plexiform

Key Points

- Neurofibromatosis type 1 is an inherited multisystem neurocutaneous disorder
- The disease results from mutations in the *NF1* gene that results in the loss of neurofibromin function and overall increase in active Ras leading to unchecked cellular proliferation and possibly cancers
- Plexiform neurofibroma (PN) is the most common benign peripheral nerve tumor
- Eyelid tumors typically occur along the peripheral branches of the trigeminal nerve and can assume a massive size with significant visual compromise
- PN may have extensive infiltration of the levator muscle and its aponeurosis with impairment of levator function
- Surgery may be indicated for cosmesis and for prevention of amblyopia in children from visual obstruction
- Because of the infiltrative nature of the tumor and the lack of a circumscribed capsule, complete surgical debulking is impossible
- Repeated sessions of surgical debulking are usually required as the tumor gradually continues to grow. Eyelid functional disturbances are almost inevitable

Neurofibromatosis type 1 (NF1) is an inherited multisystem neurocutaneous disorder with considerable clinical variability that has been extensively studied in the literature by almost all medical disciplines, yet proper management still eludes practitioners. Plexiform neurofibroma (PN) is one of the many striking features of NF1 involving the periorbital region, and it has assumed a variety of names in the literature, including orbital, orbitopalpebral, orbitofacial, or orbitotemporal neurofibromatosis, and more recently, the more complex yet all-encompassing name, orbital-periorbital plexiform neurofibroma.[1,2]

Etiology and Pathogenesis

NF1 is inherited in an autosomal dominant fashion with full penetrance and variable expression.[3,4] The gene responsible for NF1 is an unusually long tumor suppressor gene spanning a length of over 280 Kb of genomic DNA on the long arm of chromosome 17 (17q11.2).[1,2,3,4] Because of this unusual length, almost 1500 mutations have been identified in the gene so far,[4] with approximately half of these mutations being de novo.[3,4] The *NF1* gene codes for a protein called neurofibromin, which during embryonic and fetal life is involved in the differentiation of neural crest-derived cells. Neurofibromin has significant homology to GTPase-activating proteins, which in turn are negative regulators of the RAS-MAPK signal transduction pathway. Ras proteins are signaling molecules involved in physiologic control of cellular proliferation, as well as several pathological processes such as cancer. When the *NF1* gene mutates, this results in the loss of neurofibromin function, which in turn reduces GTPase activity within the cell, and therefore results in an overall increase in active Ras proteins leading to unchecked cellular proliferation and possibly cancers. Therefore, NF1 is a cancer predisposition syndrome, and NF1 individuals are at a greater risk than the general population for developing malignancies.[5,6] Because NF1 was the first syndrome to be associated with a germline mutation in the RAS pathway, NF1 is considered by some researchers as belonging to a large genetic family called the RASopathies, which are a well-studied group of medical genetic syndromes caused by germline mutations in genes that encode the components or regulators of the RAS-MAPK pathway.[4,5,6]

Clinical Presentation

NF1 is one of the most frequently seen neurocutaneous syndromes with a reported incidence between 1/2300-1/3500 live births.[7,8] The clinical presentation which usually involves the skin and the nervous system is remarkably variable with some patients having

very few manifestations, whereas others are seriously affected.[1,2,9,10]

PN is the most common benign peripheral nerve tumor occurring in the eyelid and typically tracks along the peripheral branches of the trigeminal nerve.[1,2] They can assume massive sizes, which may cause significant visual compromise, as well as placing a substantial psychological burden on the patient. PN, which usually occurs as part of the typical constellation of signs and symptoms of NF1, may affect up to 20% of NF1 patients.[11,12] Contrary to some textbooks that emphasize that PN is practically diagnostic of NF1, PN is no longer considered pathognomonic of the disease.[13] This is because a variant of NF1 may affect the periorbital region in an isolated segmental manner without the other National Institutes of Health (NIH) stigmata of the disease.[13,14] exclusively affects the orbital region.[13] This so-called orbitotemporal variant or segmental NF is reportedly more common in females, and an *NF1* gene mutation may be absent.[13,15,16,17] *(Print pagebreak 620)* To settle the argument whether this is a segmental form of NF1 or an entirely separate entity[13,17] requires that tumor tissue from the periorbital region in this subset of patients be directly investigated for this mutation.[13]

For reasons that are not yet clear, PN is usually a unilateral disease,[18] but bilateral cases have been reported.[9,12] PN in the periorbital region typically assumes a more aggressive course than neurofibromas elsewhere in the body, for reasons that are yet known, this aggressive behavior does seem to level off as the patient matures.[12,18] Upper eyelid involvement is usually full thickness extending to the conjunctiva in more than one-half of the patients.[9] The tarsus and the levator aponeurosis are also significantly involved (Figure 93.1).[19] Ptosis initially occurs due to the mechanical "weight" of the plexiform eyelid lesion even in the presence of good levator muscle function. However, as the neurofibroma enlarges, extensive infiltration of the levator and its aponeurosis may result in distortion of the muscle and disinsertion of its aponeurosis, with impairment of levator function.[19] Initially, the temporal part of the upper eyelid is more infiltrated, resulting in a typical early S-shaped deformity (Figure 93.2).[1,9,18] As the disease progresses, the entire eyelid becomes infiltrated, and the temporal region beyond the eyelid becomes extensively involved with occasional involvement of the entire lateral face. Exclusive involvement of the lower eyelid is extremely rare (Figure 93.3), although combined involvement of the upper and lower eyelids is not uncommon (Figure 93.4).[9] Lateral and medial canthal malpositions are commonly associated with PN with a reported incidence between 50%-60%,[9,18] although predictably lateral canthal involvement always precedes medial canthal malposition.[20] Although NF1 often causes vision loss secondary to optic pathway gliomas, it should be noted that decreased visual acuity in NF1 is multifactorial, and PN of the eyelid and orbit can independently cause significant visual morbidity secondary to deprivational amblyopia.[2] A recent study showed that more than three-fourths of patients with unilateral PN have a visual acuity less than 20/60.[12]

Differential Diagnosis

Except for very early cases in which the upper eyelid may assume an S-shaped contour or lateral ptosis, where PN may be confused with lacrimal gland enlargement or simple congenital ptosis, the condition on the eyelid is relatively easy to diagnose. However, in other parts of the body, PN has been confused with rare lesions such as plexiform spindle cell lipoma, plexiform schwannoma, hemangioma, sarcoma, and plexiform fibrohistiocytic tumor.[20,21,22,23,24,25]

Treatment

Although the literature is replete with various innovative techniques for the surgical management of PN, there are no universal agreements or formal recommendations for clinical care of children or adults with eyelid and orbital PN. Management decisions are particularly problematic when there is significant bony involvement with disfiguring alteration in the globe position. In an attempt to standardize management, Marchac and Britto proposed a classification system based on the severity of ptosis, canthal position, and eye-globe relation,[26] but in our opinion as well as others, the treatment approach should be tailored to each patient, with an open visual axis as the main goal of surgery, followed by improving the cosmetic appearance.[9]

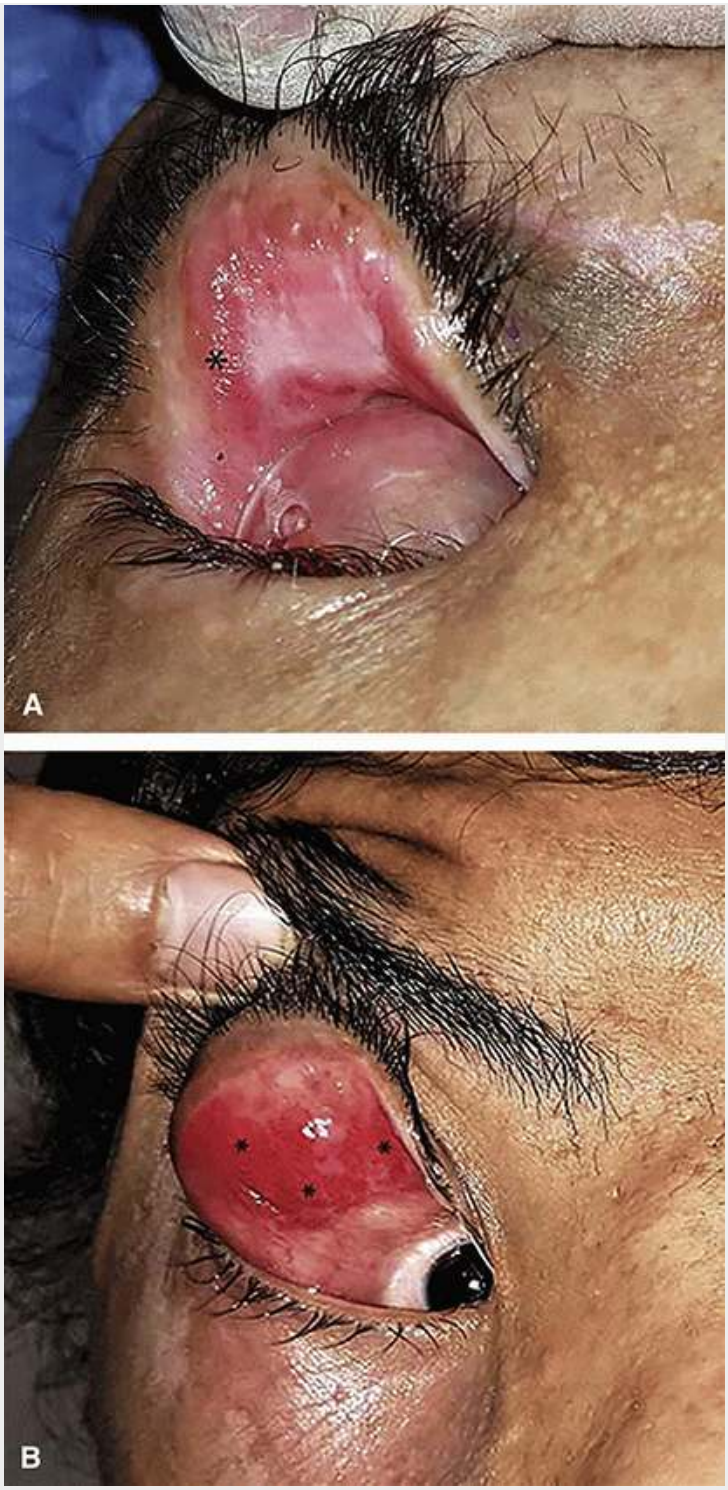

FIGURE 93.1 Plexiform neurofibroma. A, Involvement of the tarsus (asterisk). B, Involvement of the conjunctiva (asterisks). The lateral canthal tendon has become disinserted allowing the ease of eyelid eversion.

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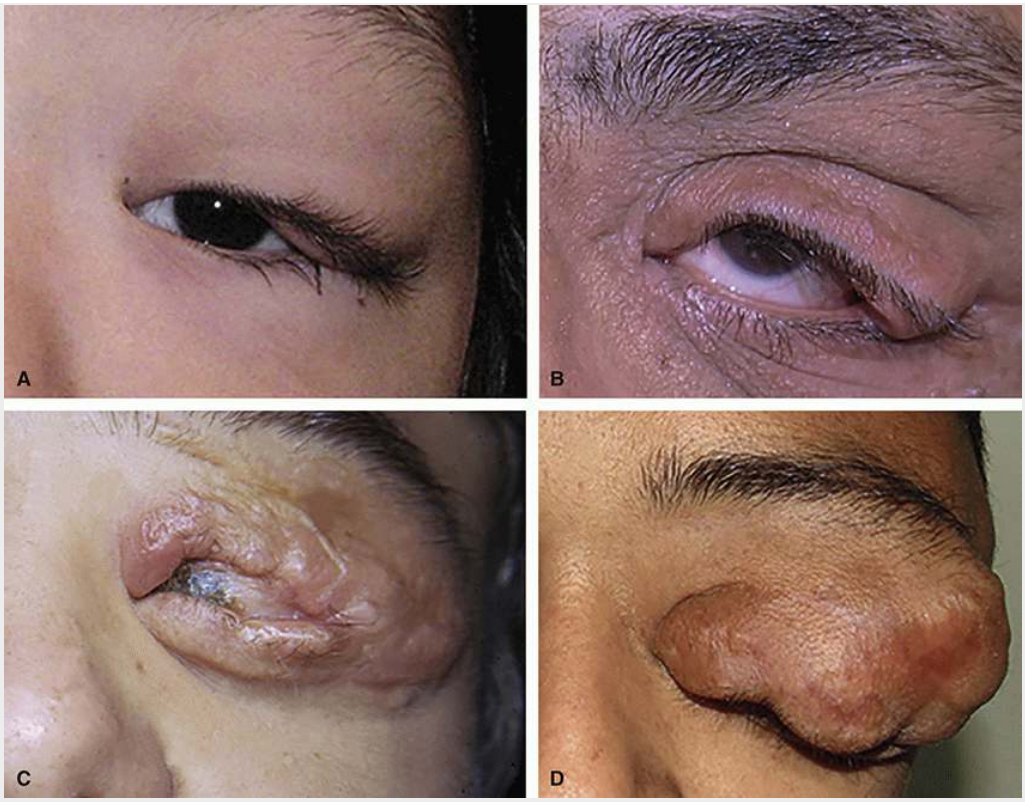

FIGURE 93.2 Variations in upper eyelid plexiform neurofibroma. A, Mild ptosis. B, Moderate eyelid infiltration with an S-shaped contour. C, More extensive disease with irregular eyelid infiltration extending beyond the lateral canthus. D, Heavily infiltrated bulky eyelid with complete ptosis and poor apposition of both eyelids.

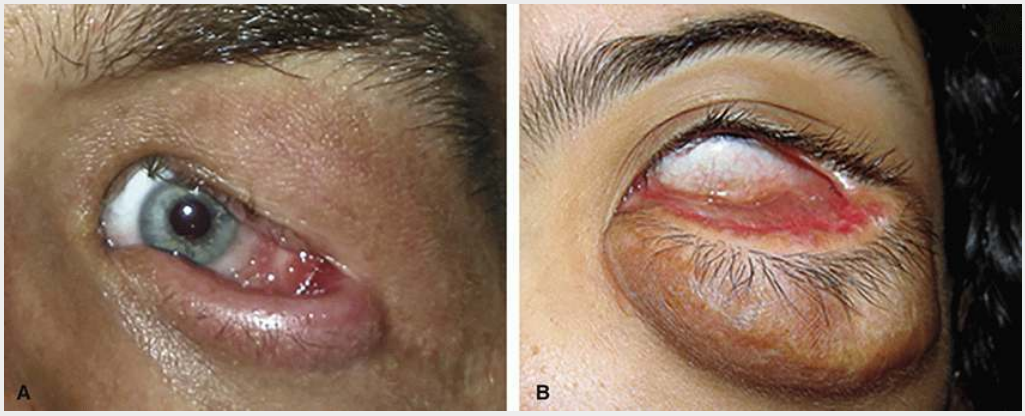

FIGURE 93.3 A and B, Rare plexiform neurofibroma involvement of the lower eyelids.

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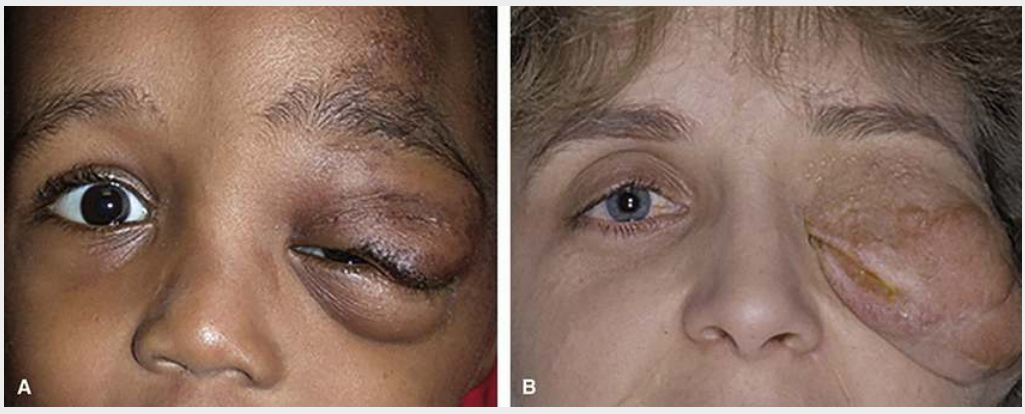

FIGURE 93.4 A and B, Combined involvement of both upper and lower eyelids with plexiform neurofibroma.

(B, Courtesy of Dr. Charles Soparkar.)

Although some authors recommend delaying surgery[27] because of the high recurrence rate if the child is operated upon very early, it should be borne in mind that surgery should be performed promptly and without delay in younger children regardless of age if occlusion of the visual axis is progressing rapidly.[28] However, rushing to surgery to debulk the eyelid in all patients presenting with rapidly advancing PN and defective vision may not be the most prudent approach before excluding other causes of visual compromise. These include optic nerve glioma or globe enlargement, which is not uncommonly observed in NF1 patients with or without glaucoma[28,29] and may cause concurrent refractive amblyopia.[12]

Because of the infiltrative nature of the tumor and the lack of a circumscribed capsule, complete surgical debulking is impossible.[9] Additionally, surgery may be complicated with extensive hemorrhage,[9] and in our experience, it may also be associated with prolonged postoperative edema. Hemorrhage is particularly bothersome when debulking the temporal region beyond the eyelid. Eyelid remodeling in the form of partial-thickness debulking of the upper eyelid through an extended blepharoplasty incision, combined with en bloc vertical resection of the lateral palpebral area, or full-thickness pentagonal wedge in the lateral part of the eyelid is performed. The contralateral normal eyelid serves as a model or template for determining the extent of debulking, but the extent of eyelid tissue resection also depends on the quality of the Bell phenomenon.[26] Debulking is usually followed in the same session with lateral canthal tendon tightening or reconstruction, and aponeurotic advancement.[9,26] Some authors warn against extensive full-thickness eyelid resection in the upper temporal quadrant to avoid damaging the lacrimal gland and its ductules,[27] although, in our experience, the lacrimal gland is usually extensively infiltrated and difficult to define.

Meticulous control of bleeding is required throughout the procedure. However, as the medial part of the eyelid is approached, cautery should be used with caution. It should be borne in mind that after debulking, what remains of upper eyelid tissue is technically a composite axial flap hinged medially, and based on the medial palpebral artery only. Another precaution to safeguard against vascular compromise is that although generous debulking of eyelid tissue may be required especially in older individuals where definitive surgery is important, the emphasis is placed on minimizing tissue excision near the eyelid margin. Despite being heavily infiltrated by neurofibromatous tissue, the levator aponeurosis is usually not difficult to identify and it is relatively easy to reattach it to the tarsus. The lateral canthal tendon should be tightened before reattaching the levator aponeurosis. When there is a cosmetically disfiguring downward and/or forward displacement of the entire orbit due to bony factors or herniation of the temporal lobe of the brain into the orbit, maxillofacial and/or neurosurgical repair is required to achieve bony symmetry of the midface before embarking on soft-tissue reconstruction.[9,26]

Prognosis

These tumors typically are diffuse and infiltrative into eyelid tissues so that complete surgical removal is usually impossible. Repeated sessions of surgical debulking are usually required as the tumor gradually continues to grow. Eyelid functional disturbances are almost inevitable. The most severe outcome is malignant transformation to malignant peripheral nerve *(Print pagebreak 623)* tumor that rarely can arise within the eyelid, and in other areas, and may show a high mortality rate of over 70%.

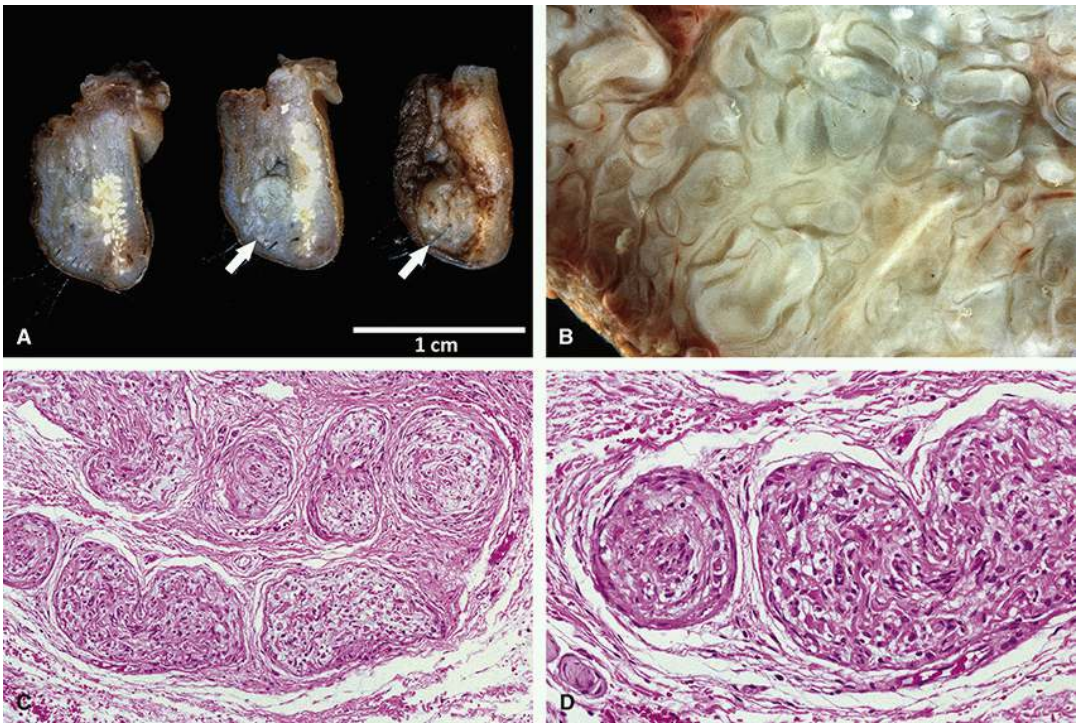

FIGURE 93.5 A, This child with neurofibromatosis type 1 had a plexiform neurofibroma in the right upper eyelid dermis forming a nodule near the eyelid margin (arrows). B, A close-up view shows large segments of enlarged convoluted peripheral nerve fascicles that correspond to a "bag of worms" texture on palpation. C, The dermis has expanded nerve fascicles, each surrounded by a thickened perineurium. The expanded fascicles have a patchy pale appearance due to glycosaminoglycan accumulation in the endoneurium. Dense fibrous tissue is between the nerve fascicles and appears as an extension of the thickened perineurium. D, Expanded fascicles contain wavy nerve fibers, spindle-shaped Schwann cells, fibroblasts, mast cells, small blood vessels, and glycosaminoglycan-rich endoneurium.

Histopathology

PNs are the most common subtype of ocular adnexal peripheral nerve sheath tumors.[30] PNs feature large segments of enlarged convoluted peripheral nerve fascicles that may be grossly discernible (Figure 93.5A and B) and correspond to a "bag of worms" texture on palpation.[31,32] Other cases appear as large multinodular masses.[32,33] Microscopically, the dermis and/or subcutis[34,35] have a tortuous mass of expanded nerve branches, each surrounded by a thickened perineurium (Figure 93.5C and D).[35,36] The expanded fascicles contain nerve fibers (axons) that are often centrally situated, spindle-shaped Schwann cells, fibroblasts, mast cells, blood vessels, and mucin (glycosaminoglycan)-rich endoneurium.[31,32,34,36,37,38] The Schwann cells immunohistochemically express S100 protein, the nerves stain using antibodies to neurofilament protein, and epithelial membrane antigen antibodies highlight perineurial cells.[31,35] The endoneurium often has a pale myxoid appearance (Figure 93.6A and B) due to Alcian blue-positive glycosaminoglycan accumulation, sometimes with the formation of mucin pools.[36,37,38] Collagen may accumulate in the endoneurium, often in longstanding PNs, making them firm.[32] Dense fibrous tissue is between the nerve fascicles and may appear as an extension of the thickened perineurium.[36] Approximately 5% of periocular neurofibromas are a mixture of diffuse and plexiform subtypes (Figure 93.6).[30] PNs usually have a distinctive histological appearance, but other lesions such as plexiform schwannoma, plexiform granular cell tumor, and plexiform nevi should be considered in the differential diagnosis.[35]

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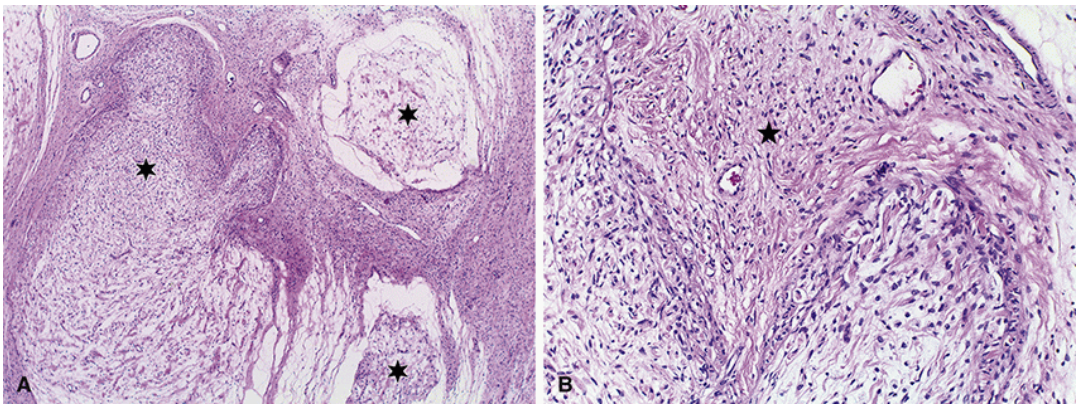

FIGURE 93.6 This teenager with neurofibromatosis type 1 had a plexiform and diffuse neurofibroma involving the right orbit and entire upper eyelid. A, The tumor's plexiform component (★) is very pale due to marked endoneurial accumulation of glycosaminoglycans. B, The diffuse component of the tumor (★), composed of spindle-shaped cells with eosinophilic cytoplasm and indistinct cell borders, surrounds the plexiform fascicle.

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CHAPTER 94

Neurothekeoma

Key Points

- Neurothekeoma includes several lesions previously reported as nerve sheath myxoma or cellular neurothekeoma
- While some studies have questioned the relationship between these two entities, other authors have supported the idea that these lesions are variants of the same entity
- Immunohistochemical and ultrastructural data indicate that nerve sheath myxomas exhibit true nerve sheath differentiation, whereas such evidence is lacking for cellular neurothekeomas
- Several studies have demonstrated distinct genetic mutations in these two entities
- On the eyelids, 60% of neurothekeomas present on the upper eyelids as small, slow-growing, painless, pink to flesh-colored nodules that may be mobile and cystlike or firm and immobile
- The treatment of choice for neurothekeoma is surgical excision
- The prognosis following surgical excision is generally good with a recurrence rate of about 15% associated with incomplete excision

Several types of lesions have been included under the broad term of "neurothekeoma" (NTK), most commonly nerve sheath myxoma (NSM) and cellular neurothekeoma (CNTK). Over the years, the classification of these tumors has been in a constant state of flux.[1] NSM and CNTK have been classified as benign primary neurogenic tumors arising from peripheral nerves.[2] NSM was first described as a distinct pathologic entity by Harkin and Reed in 1969 and designated as a benign myxomatous cutaneous tumor believed to be of peripheral nerve sheath origin.[3] Gallager and Helwig[4] later reported a series of cutaneous tumors that bore the same histologic features as the previously described NSM, but which they named NTK. Over subsequent years, the terms "NSM" and "NTK" frequently have been used interchangeably in the literature. In 1986, Rosati et al[5] described a cellular variant of NSM, termed "CNTK." However, other studies have questioned the relationship between CNTK and NSM. Some authors supported the idea that these lesions are variants of the same entity.[6,7] Others, however, felt that they are unrelated.[8,9,10] In 2008, Weiss and Goldblum[11] proposed the term "classic NTK" for NSM to distinguish it from CNTK based on immunoreactivity to S-100. While it is generally accepted that a classic NTK is a true benign nerve sheath tumor, the etiology of CNTK remains unknown.[8,10]

It has been thought by some authors that cellular and myxoid NTK represent two ends of a spectrum of the same neoplasm.[6,12,13,14,15] According to this view, cellular NTK is considered a neoplasm with immature or poorly developed nerve sheath differentiation, whereas the myxoid type shows well-developed nerve sheath differentiation.[3,4,6,8,13,14,15,16] Others have questioned this concept, suggesting that cellular NTK should be classified as a fibrohistiocytic tumor and myxoid NTK as a tumor with nerve sheath differentiation.[10,16,17,18]

NTKs occur most commonly in the head and neck, especially the nose and scalp. Less frequently, they are seen on the cheeks, chin, eyelids, lower extremities, and trunk.[10,19] They are seen most commonly in young individuals, ranging in age from 1 to 85 years, with a mean of 21 to 25 years.[9,10,20] The male-to-female ratio is approximately 1:2.[9,10]

NTKs involving the eyelid are often referred to as NTK palpebrae and are very uncommon with less than a dozen cases reported. Slightly more than half of the eyelid cases have been classified as NSMs or classic NTKs,[1,21,22,23,24,25,26,27] and the rest as CNTKs.[28,29,30] Where location was specified, about two-thirds of these lesions occurred in the upper eyelid. The duration of symptoms before presentation ranged from 6 weeks to 8 years.

Etiology and Pathogenesis

Based on light microscopic similarities, CNTKs and NSMs previously were considered to be related to cutaneous neoplasms of

peripheral nerve sheath origin. However, immunohistochemical and ultrastructural data indicate that NSMs exhibit true nerve sheath differentiation, whereas such evidence is lacking for CNTK. Although CNTK lack a specific immunohistochemical profile, evidence related to antigen expression and histopathologic patterns suggest that they may be categorized as fibrohistiocytic tumors.[8,10,12,16,17,18]

In a study of 10 spinal NSMs, 80% showed loss of chromosome 22q, typically encountered in peripheral nerve tumors, and 2 demonstrated mutations of the *NF2* gene.[31] This may indicate the involvement of other tumor suppressor genes on 22q in NSMs. In another study on 25 CNTK, 8 mixed NTK, and 1 NSM, SOX-10 and S-100 were found to be absent in CNTK but present in NSM.[32]

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The cell of origin of CNTK is not known, but ultrastructural and immunohistochemical studies suggest a possible origin from Schwann cells of the perineurium or from fibroblasts.[17] CNTK has a less prominent myxoid component, lacks immunoreactivity to most neuronal markers, and is characterized by large size, extension into subcutaneous fat and muscle, infiltrating borders, vascular invasion, high mitotic rate, and cytologic pleomorphism.

Clinical Presentation

In general, NTKs present as slow-growing, painless, nodular lesions measuring 0.5 to 4 cm in size, with a duration of symptoms from 3 months to 12 years.[20] Among 57 cases of NSM, 86% percent occurred in the extremities, with the most common locations being the hand/fingers (n = 22), knee/pretibial region (n = 10), and ankle/foot (n = 7). Only seven cases (12.3%) involved the trunk or head and neck region.[10]

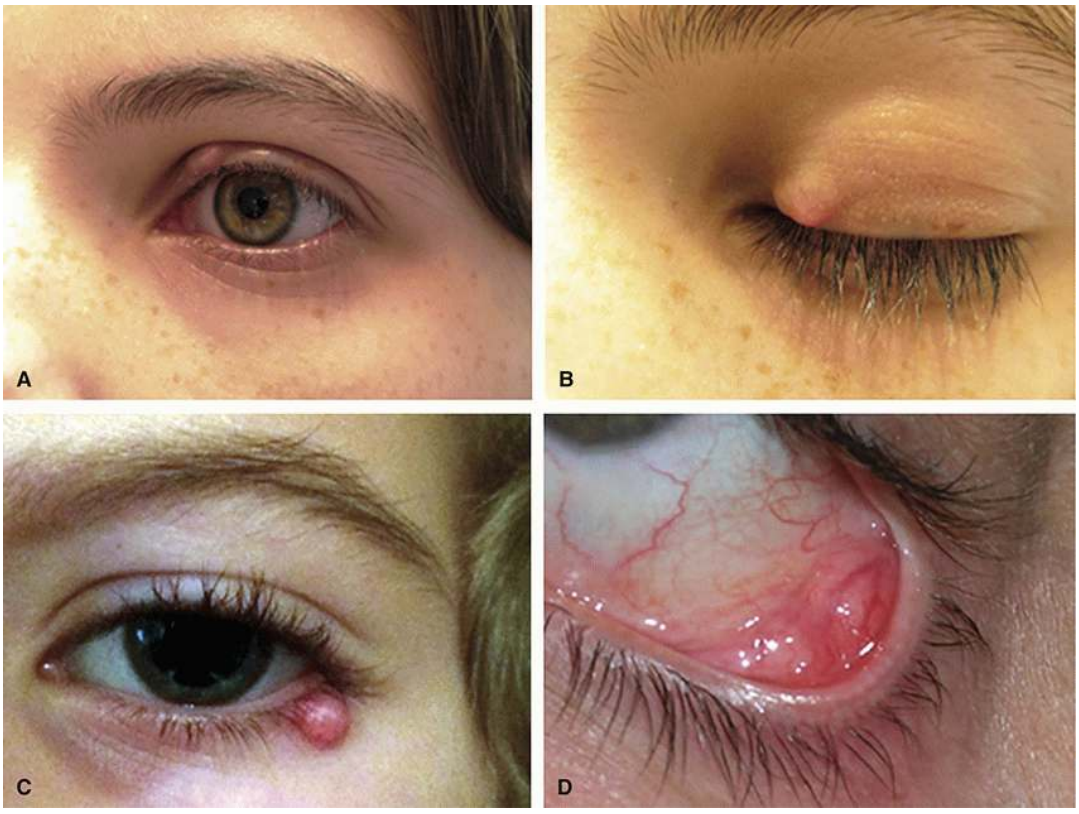

FIGURE 94.1 A-D, Neurothekeoma of the eyelids and conjunctiva. (C, Reprinted with permission from Gray ME, Palileo CM, Sheridan RM. Cellular neurothekeoma of the eyelid in a 6-year-old boy. *JAAPOS*. 2016;20:374-376; D, Courtesy of Drs. Daniel Lefebvre and Michael Migliori.)

Of the lesions described on the eyelids, the mean age at presentation was 35.9 years with a range of 4 to 76 years. The male-to-female ratio was 1:5. The size at presentation was 4 to 10 mm, with a mean of 7.5 mm, and 60% were located on the upper eyelid. Lesions were generally slow growing and the duration of symptoms ranged from 6 weeks to 10 years, with 60% being 12 months or less. Clinically, lesions appear as small, pink to flesh-colored, painless nodules that may be mobile and cystlike or firm and immobile (Figure 94.1).[1,21,22,23,24,25,26,27,28,29,30]

Differential Diagnosis

The differential diagnosis of NTK includes epidermal inclusion cyst, intradermal nevi, lipoma, pilomatrixoma, fibroma, and dermatofibroma. For eyelid lesions, the initial clinical diagnosis most frequently is chalazion or epidermal inclusion cyst. Epidermal inclusion cysts are usually isolated asymptomatic, freely moveable cystic intradermal or subcutaneous *(Print pagebreak 628)* nodules. Chalazia are red, often tender, inflammatory lesions typically involving the meibomian glands along the eyelid margins. Dermatofibroma are asymtomatic, nontender cutaneous, dome-shaped nodules that may have central dimpling. Lipomas are painless, soft, fluctuant mobile subcutaneous masses with freely moveable overlying skin.

Treatment

The treatment of choice for NTK is surgical excision. Recurrence has been reported in about 15% of cases so that wide margins[9,10] and frozen-section control of margins are recommended.[19] Patients with tumor recurrence have been reported to be younger, be female, have facial lesions, and harbor tumors with a myxoid pathology pattern.[10]

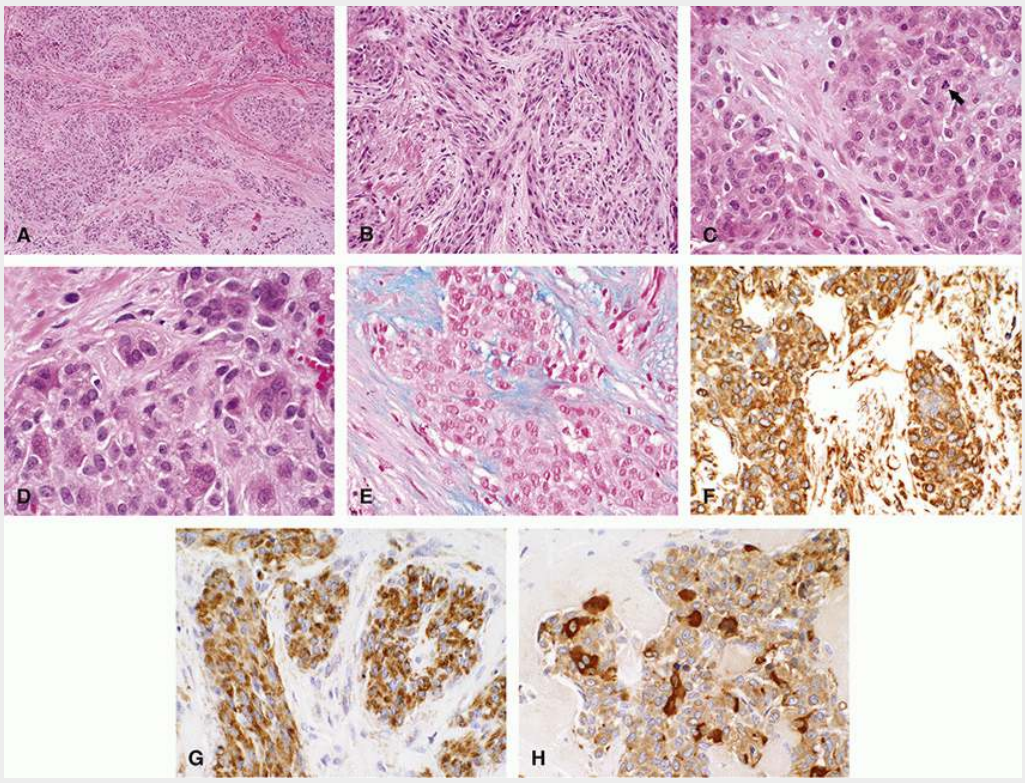

FIGURE 94.2
This cellular neurothekeoma (CNTK) presented as a 5.5 mm tumor of the left upper eyelid in a 4-year-old girl. A, Tumor cells form variably sized and shaped nodules within the dermis with sclerotic areas of brightly eosinophilic collagen. B, Tumor cells are spindle shaped or epithelioid with lightly eosinophilic cytoplasm and mostly indistinct cell borders. C, The matrix between cells and between nodules stains palely indicative of myxoid change (glycosaminoglycan accumulation). An atypical tripolar mitotic figure is present (arrow) but is not indicative of malignancy in CNTKs.[10] D, Some areas of the tumor feature large multinucleated cells. E, Myxoid matrix in and between tumor nodules is highlighted blue using Alcian blue stain. F, Tumor cells and stromal fibroblasts between nodules are uniformly immunoreactive using antibodies to vimentin. G, All of the tumor cells stain intensely using antibodies to NKI/C3 (CD63). H, The tumor cells express CD68, with the most intense staining being in the large multinucleated cells.

Prognosis

The prognosis following surgical excision is generally good. Recurrence is associated with incomplete excision.[9] In a series of 34 cases of NSM managed by simple surgical excision, where almost all instances showed tumor extending to the resection margin,

47% experienced local recurrence over a follow-up period of 8 months to 28 years (median, 14 years 3 months).

Histopathology

The histological features of periocular CNTKs are similar to those occurring elsewhere on the body.[1,33] CNTKs are multinodular, nonencapsulated, poorly marginated tumors of the dermis that often extend into the subcutaneous tissue (Figures 94.2 and 94.3).[4,10] Tumor nodules vary in size and *(Print pagebreak 629)* shape, but they are most often round or ovoid.[4] The nodules are separated from the epidermis by a layer of normal dermis,[9] and they are separated from each other by variable amounts of dermal collagen that may be sclerotic (hyalinized).[4,10,34] The amount of myxoid matrix in the tumor nodules ranges from <10% of the area to >50%, leading Fetsch and coworkers to classify the tumors as cellular (<10% myxoid matrix; 35% of NTKs), mixed (>10 and ≤50% myxoid matrix; 38% of NTKs), or myxoid (>50% myxoid matrix; 27% of NTKs).[10] NTKs usually have both spindled and epithelioid tumor cells, though Hornick and Fletcher found 21% of 133 cellular NTKs with only spindle cells and 16% with only epithelioid cells.[9] Tumor cells have abundant lightly eosinophilic cytoplasm, indistinct cytoplasmic cell borders, ovoid nuclei, and fine chromatin.[9] Tumor cells may be organized randomly or form whorls.[10] Cytological atypia was minimal (35%), mild (61%), focally moderate (12%), generalized moderate (11%), or focally marked (1%) in the 178 NTKs examined by Fetsch and colleagues.[10] The average mitotic rate was 3 per 10 high-power fields (range 0-22) in Hornick and Fletcher's study[9] and 2.0/mm^2 in Stratton and Billing's report of 37 NTKs.[34] Fetsch and coworkers also noted wide variability in the mitotic rate ranging from no apparent mitoses in 15% of cellular NTKs to >20 mitoses in 25 wide-field high-power fields in 3% of tumors.[10] Fetsch et al identified multinucleated osteoclast-like giant cells in 39% of NTKs.[10] Atypical histological features, including cellular pleomorphism, high mitotic rate, entrapped skeletal muscle, and infiltration of the subcutis, do not seem to have any clinical significance if the tumor is resected completely (Figure 94.3).[9] NTKs may also exhibit perineural[9,34] and vascular[9] invasion in a small minority of cases, but these features do not signify malignancy.

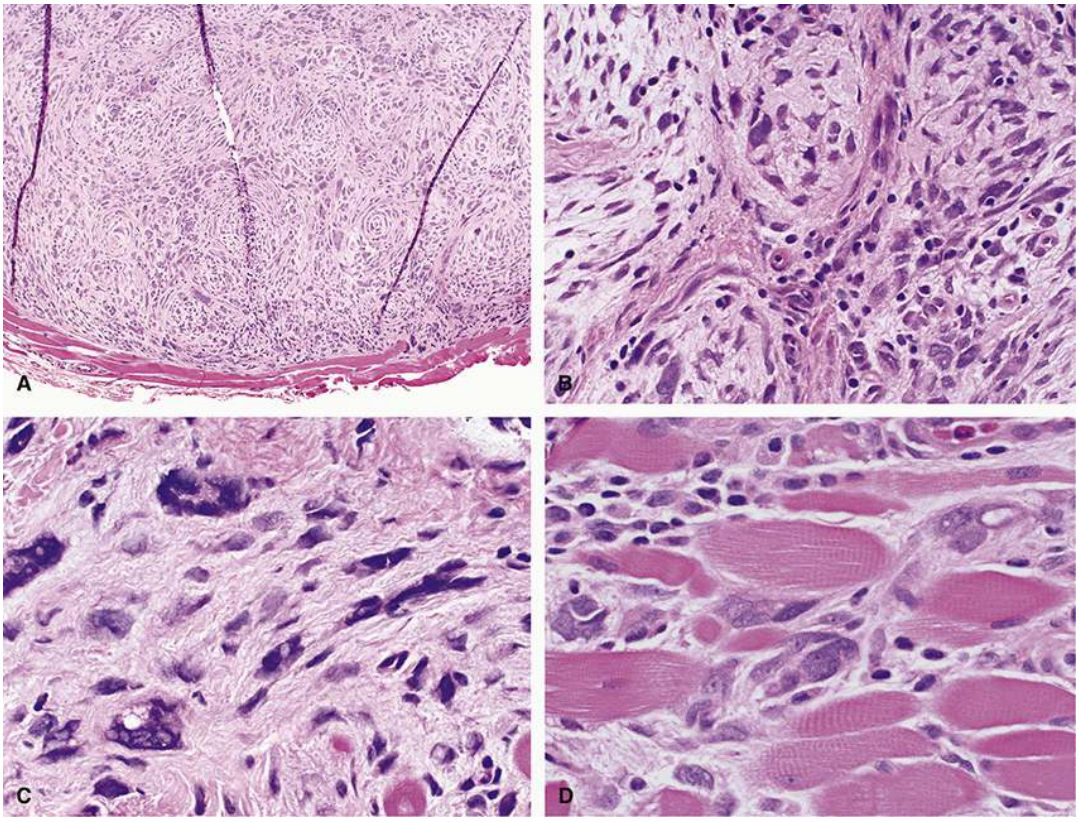

FIGURE 94.3 This cellular neurothekeoma (CNTK) was a 6 mm nodule in the medial left upper eyelid of a 13-year-old girl. A, The tumor features coalescent nodules, many with a whorled configuration. Numerous large multinucleated tumor cells are seen even at this low magnification. Orbicularis oculi muscle is at the bottom of the picture. The bright vertical streaks are sectioning artifacts. B, The islands of spindle-shaped and epithelioid cells have pale myxoid stroma, and thin dermal collagen bands separate them. C, Marked nuclear pleomorphism, such as seen in this photomicrograph, does not indicate malignancy in CNTKs. D, Tumor cells infiltrate between orbicularis oculi muscle fibers, but this does not signify malignancy in CNTKs.

Immunohistochemistry helps confirm the diagnosis of NTK, especially in tumors with pleomorphism or a high *(Print pagebreak 630)* mitotic rate. The most extensive immunohistochemical studies were by Fetsch and colleagues: 100% of 39 tumors expressed vimentin (Figure 94.2F), 100% of 47 tumors expressed NKI/C3 (CD63), 100% of 41 tumors were CD10 positive, 83% of 52 cases

expressed microphthalmia transcription factor, 80% of 10 cases were CD99 positive, 80% of 10 cases expressed collagen IV, 66% of 35 cases expressed neuron-specific enolase (NSE), 60% of 50 tumors were positive for PGP9.5, 59% of cases were CD68 positive (Figure 94.2H), and 38% of 56 cases expressed smooth muscle actin.[10] None of the tumors examined in the Fetsch study expressed S100 protein (n = 119), glial fibrillary acidic protein (GFAP; n = 12), melanoma antigen recognized by T cells 1 (MART-1, Melan A; n = 11), tyrosinase (n = 4), neurofilament protein (n = 27), CD34 (n = 29), desmin (n = 31), CD163 (n = 25), CD117 (n = 11), MAC387 (n = 10), lysozyme (n = 5), polyclonal carcinoembryonic antigen (n = 6), or factor VIII-related antigen (n = 5).[10] Hornick and Fletcher reported that 100% of tumors were positive for NKI/C3 (CD63; n = 130), 89% expressed NSE (n = 123), 57% had at least focal staining for smooth muscle actin (n = 127), one tumor (0.9%) expressed GFAP, and no tumor expressed S100 protein.[9] The absence of expression of S100 protein in NTKs distinguishes them from NSMs, which are consistently positive for that protein.[8]

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CHAPTER 95

Nevus Flammeus

Key Points

- Nevus flammeus or port-wine stain (PWS) is a congenital, low-flow vascular malformation of the skin that represents a progressive ectasia of the superficial cutaneous vascular plexus
- It does not involute, but gradually enlarges in size and can darken due to progressive vascular ectasia
- It can occur as an isolated cutaneous birthmark or it can be associated with structural abnormalities such as Sturge-Weber syndrome
- The pathogenesis of nevus flammeus is unknown, but hypotheses include vascular denervation and genetic mutations
- Whole-genome sequencing of DNA from patients with nevus flammeus suggests a somatic activating mutation in *GNAQ* as a possible underlying cause
- The lesion presents as a painless, well-demarcated flat pink macule that thickens and darkens over time
- They are unilateral and appear to involve the distributions of one or more divisions of the trigeminal nerve
- The current treatment of choice for PWS is pulsed dye laser
- Improvement and lightening of lesions and decrease in size are likely after laser therapy, but complete clearance is achieved in fewer than 10% of cases

Nevus flammeus, also known as port-wine stain (PWS), is a congenital, low-flow vascular malformation of the skin that represents a progressive ectasia of the superficial cutaneous vascular plexus.[1,2] According to the most recent iteration of the International Society for the Study of Vascular Anomalies (ISSVA) classification for vascular anomalies (May 2018), the term “PWS” is retained, while the term “nevus flammeus” is discarded, and the disease is listed as one of the subtypes of capillary malformations. The prevalence of PWS is estimated to be 3 to 5 per 1000 live births.[3,4,5,6] The inheritance pattern is generally sporadic, and males and females are equally affected.[7]

Approximately 90% of PWSs are located on the face, and much less frequently on the neck, trunk, and extremities.[8,9] Most facial PWSs are unilateral and are approximately located in the distribution of the trigeminal nerve dermatomes.[10] Pyogenic granulomas and eczematous dermatitis can develop within PWS.[11,12] Larger and more advanced lesions can cause functional limitations of speech or vision.[13,14] In addition to facial skin, PWS can involve the mucosa of the oral cavity, tongue, larynx, and nose, as well as soft tissues of the neck and even the parotid gland. These can cause gingival bleeding, epistaxis, and upper airway obstruction.[13,15]

Unlike infantile hemangiomas, PWS does not involute, but lesions gradually enlarge in size as the body grows, and can darken due to progressive vascular ectasia. With age, approximately two-thirds of patients develop soft-tissue or bony hypertrophy and vascular nodules.[1,16,17,18]

PWSs can occur as isolated cutaneous birthmarks or they can be associated with structural abnormalities involving the choroidal vessels in the eye and leptomeningeal vessels in the brain (Sturge-Weber syndrome [SWS]).[19,20] In one study of 274 patients with PWS localized to the face, 8% also had eye and/or central nervous system (CNS) involvement.

SWS is a neurocutaneous disorder that was described by Sturge in 1879[20] as a triad of facial, scalp, and trunk capillary malformation (PWS), focal seizures, and intraocular vascular malformation with glaucoma. The incidence is unknown but is estimated to be 1 in 20,000 to 50,000 live births.[21] SWS usually manifests with facial PWS, and rarely with PWS on the trunk or extremities. The risk of developing glaucoma is up to 50%, almost always ipsilateral to the facial PWS.[21] SWS occurs sporadically with equal frequency in males and females. Although some early studies on the relationship between facial PWS and the risk of SWS implicated PWS in the ophthalmic division of the trigeminal nerve, bilateral distribution, and involvement of the upper

eyelids,[22,23] more recent studies suggest that extensive PWS within a V1 distribution (and to a lessee extent V2 and V3) of the trigeminal nerve is a strong predictor for an underlying neurological and/or ocular disorders (SWS).[24]

Acquired PWSs are rare skin lesions that are morphologically and histopathologically identical to congenital PWSs[25] and can be associated with telangiectasia and local heat from increased blood flow within the affected skin.[26] They can be associated with trauma, chronic actinic exposure, oral contraception, cluster headache, acoustic neuroma, and medications such as isotretinoin, simvastatin, and metformin.[25,27,28,29] One case was reported to develop after repeated episodes of sunburn.[30] In a review of 59 patients with acquired PWS, trauma was found to be a causative factor in 17 (29%) cases.[31] It has been proposed that injury may result in loss of a previously effective sympathetic regulation of the cutaneous blood flow, leading to development of the lesions,[31] or that traumatic injury of the skin induces perivascular atrophy leading to vessel dilation or that impaired reparative processes in vessels result in dilated vessel walls.[32]

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Etiology and Pathogenesis

The pathogenesis of PWS and SWS is unknown, but there are at least two major competing hypotheses: the neural (nerve degeneration) theory, and the vascular (genetic mutation theory).[33] However, recent confirmatory evidence favors the genetic mutation theory. A deficiency of nerve innervation in PWS led to speculation that this could be a cause of these abnormal hypervascular skin lesions.[23,34,35] Smoller and Rosen[36] reported that S-100-positive nerve fibers were found in only 17% of PWS blood vessels, while 89% of normal dermal vasculature had S-100-positive nerve fibers. Rydh et al[34] showed that defective nerve innervations were found only in pathologically dilated PWS vessels, but not in other normal skin structures. Selim et al[35] found that there is a significant decrease in nerve density in all PWS sites compared to normal skin. The absence of nerve innervation to blood vessels may cause a decrease in the basal tone of the vessels and/or a loss of neuronal trophic factors, which contribute to the development of PWS.[33]

However, whole-genome sequencing of DNA from patients with PWS and SWS has suggested a somatic activating mutation in GNAQ as a possible underlying cause. A nonsynonymous single-nucleotide GNAQ variant (c.548G→A, p.Arg183Gln) was identified in 88% of 26 patients with SWS (OMIM #185300, 9q21) and from 92% of 13 patients with apparently nonsyndromic PWSs (OMIM #16300, 9q21).[37,38,39] This is a somatic activating mutation in the GNAQ gene, which increases cell proliferation and inhibits apoptosis due to increased downstream signaling through the RAS effector pathways. The cell of origin affected by the mutation is not known, but it may be that the mutation occurs earlier during embryonic development in SWS than in isolated PWS, thus affecting a more primitive progenitor with wider potential effects.[40] These mutations may lead to dysregulation of vascular MAPK and/or PI3K signaling pathways during embryonic development causing the pathogenesis and progression of PWS/SWS.[33] Interestingly, the GNAQ mutation is found significantly more frequently in lesions located on the forehead, eyebrow, and upper eyelid than in those located in other facial regions, and PWS in these regions are more likely to be associated with SWS.

Waelchli et al[40] examined 192 children with PWS and divided the face into several areas on each side that were involved with PWS, including the forehead, upper eyelid, lower eyelid, maxillary area, mandibular area, ear, and chin, and correlated these with clinical complications such as seizures and glaucoma and abnormal head magnetic resonance imaging findings. They considered the adult arterial supply and venous drainage, and the embryological origin of the face and its vasculature. Based on their results, they proposed that the distribution of facial PWS appears to follow the embryological vasculature of the developing face rather than the trigeminal nerve distribution.

Dutkiewicz et al[41] evaluated the distribution patterns of facial lesions in children with PWS and those with SWS. They identified six phenotypes: linear, frontotemporal, cheek and canthus, combined linear and cheek, hemifacial, and median. These phenotypes support the idea that PWS lesions may not strictly correspond to dermatomes of trigeminal innervation.

Clinical Characteristics

PWSs are capillary malformations that occur in up to 0.5% of newborns. They initially present as painless, well-demarcated flat pink macules and patches that may be mistaken for a superficial bruise (Figure 95.1).[42] Over time, these lesions thicken and darken, with some developing significant nodularity (Figure 95.2).

The majority of PWS lesions are unilateral and superficially appear to involve the distributions of one or more of the divisions of the trigeminal nerve (ophthalmic [V1], maxillary [V2], mandibular [V3]). In a study of 310 patients with PWS, 32% involved the dermatome innervated by V2 (Figure 95.1), 41% in the distribution of both V1 and V2, 5% in the distribution of V2 and V3, and 10% in all three.[23] In another study of 192 PWS patients, 14.6% involved V1 alone, 32% V2 alone, and 5.3% V3 alone, while 41% involved V1 and V2, 5% V2 and V3, and 10% all three dermatomes.[40] When all three dermatomes were involved with PWS, there

was a significantly higher likelihood of ophthalmic or CNS complications.[23]

There are a number of other ophthalmic complications that can be associated with PWS. Glaucoma is seen in about 18% of cases, more common with bilateral lesions and in those cases involving both the upper and lower eyelids.[43] In PWS patients with glaucoma, 91.3% have involvement of V1, and they are more likely to have multiple trigeminal dermatome involvement (88.3%).[10] Other ophthalmic complications include the so-called episcleral hemangioma (35%), and the so-called choroidal hemangioma (23%), and iris *(Print pagebreak 633)* heterochromia (6%). Face and eyelid involvement can cause significant negative effects on quality of life, lead to psychological disabilities, and result in adaptation problems toward the social environment, especially in children.[44]

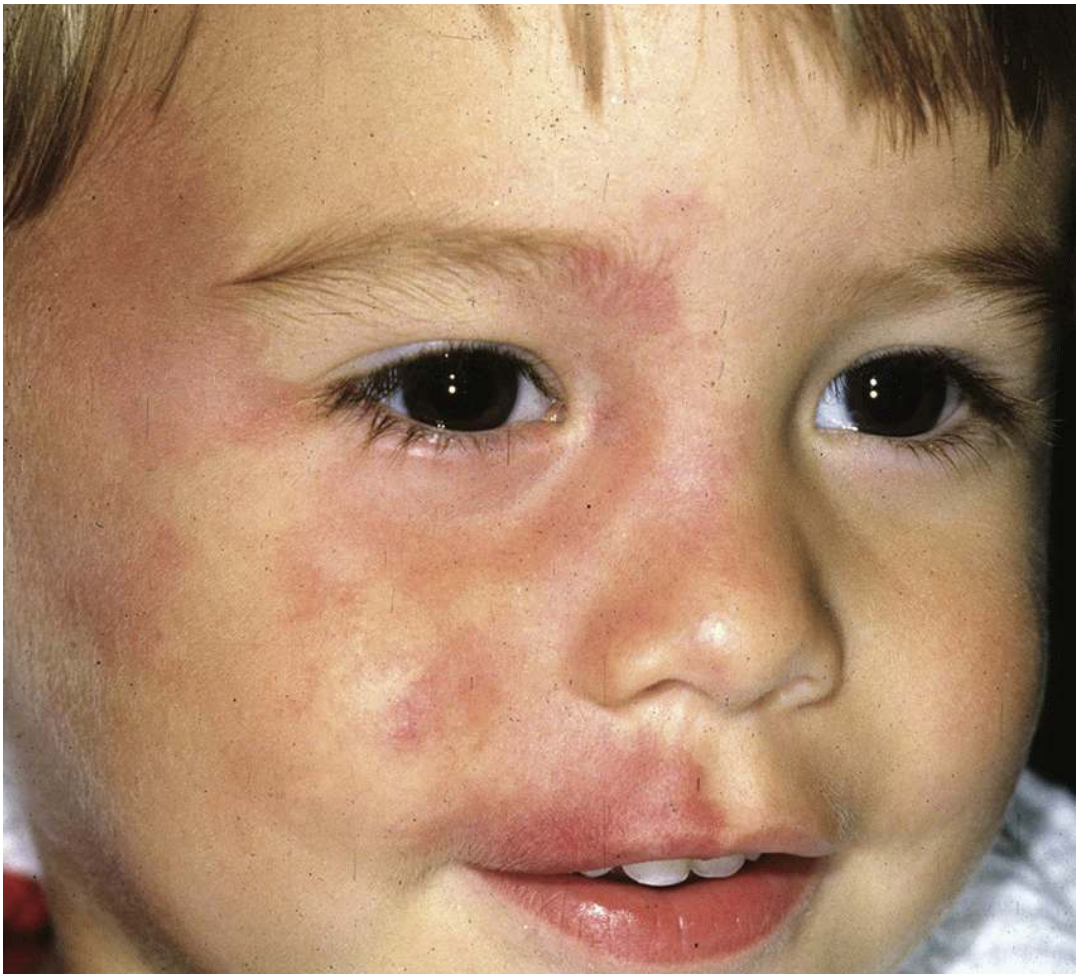

FIGURE 95.1 A child with numerous unilateral patchy port-wine stains primarily in the distribution of the maxillary division of the trigeminal nerve.

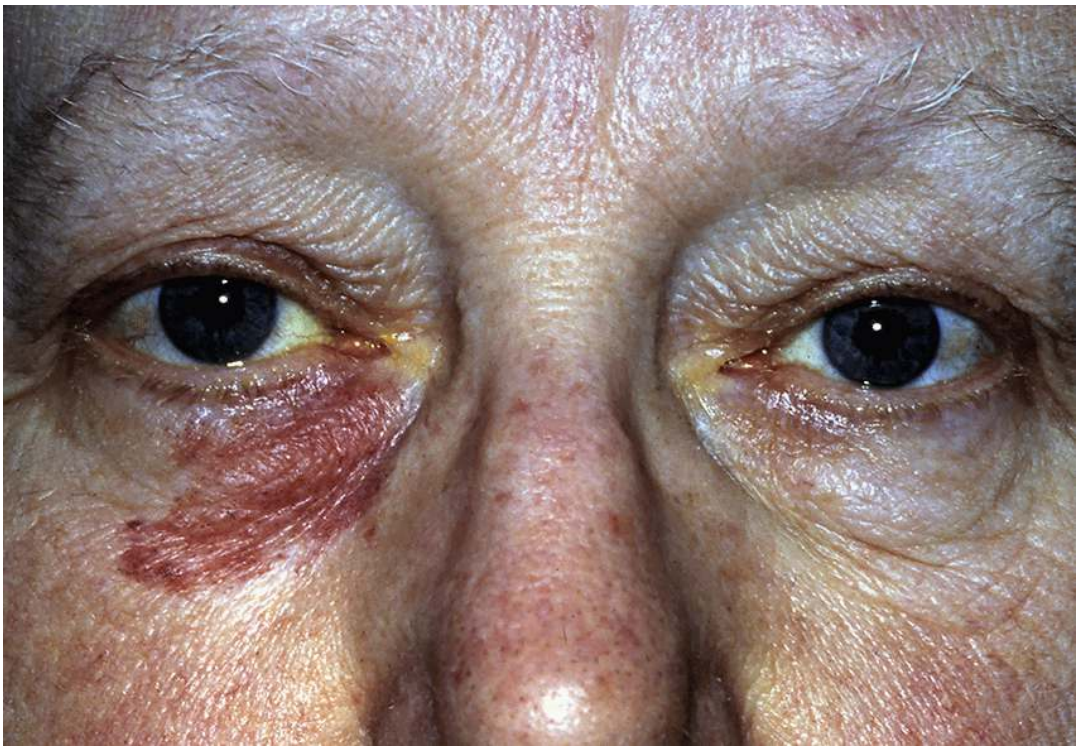

FIGURE 95.2 An older individual with a well-defined nevus flammeus of the medial lower eyelid. (Courtesy of Dr. Alan McNab.)

PWSs do not involute over time, but often continue to evolve into adulthood. With increased age, there is progressive vascular ectasia, and the color changes from pink to purple.[1] While PWS lesions first appear as macular lesions, by the fifth decade of life, 65% may become hypertrophied or nodular.[45] In these cases, there is an increased risk of pyogenic granulomas and spontaneous bleeding or hemorrhaging following minor trauma. Intralesional basal cell carcinoma,[45,46,47] squamous cell carcinoma,[48] and melanoma[49] have been described rarely in these hypertrophic and nodular lesions, some of which had been previously treated, but others untreated. While some cases of malignant association may have been related to previous treatment, its occurrence in untreated lesions suggests a chance occurrence for others.[1]

Certain facial PWS distribution phenotypes are associated with a greater potential for having SWS with neurological and ocular associations.[40] These high-risk phenotypes include the hemifacial, forehead, and median PWS types and involve skin-derived embryologically from the frontonasal placode, which shares common progenitor cells with the brain.[40,41,50]

Seizures occur in 75% to 100% of children with PWS and SWS,[51,52,53] so that early recognition and treatment of seizures is crucial to prevent neurodevelopmental complications.

Differential Diagnosis

The differential diagnosis of PWS includes infantile hemangiomas, but these usually involute later in childhood,[54] in contrast to PWS which behaves in a similar manner to other vascular malformations and grows with the growth of the individual. Early inflammatory morphea can present with erythematous or violaceous patches or plaques similar to PWS, but this lesion usually develops later in childhood.[55,56,57] Localized scleroderma has also been confused with PWS, presenting as an erythematous or purplish patch. But they are often also hypo- or hyperpigmented and can be associated with alopecia and bone atrophy.[56,58]

Treatment

The current treatment of choice for PWS is pulsed dye laser (PDL),[59] where selective photothermolysis is used to destroy subsurface but relatively superficial targets without injuring adjacent normal tissue. The PDL wavelength of 595 nm is preferentially absorbed by hemoglobin in blood vessels where it is converted into heat, leading to necrosis of the blood vessel walls. Skin cooling technology can be used to prevent light absorption and injury to nearby melanin,[60] and thus to help reduce dyspigmentation.[61] To target blood vessels situated deeper in the skin, other laser wavelengths have been used, including alexandrite 755 nm, diode 800 to 940 nm, and Nd:YAG 1064 nm.[7,62]

In a study of 73 children with PWS treated with PDL, 87% showed 50% or greater skin lightening after one to three treatments, but only three had complete clearance.[63] In another study of 102 PWS patients treated with PDL, 15.3% showed >90% lesional lightening, 65.3% showed 50% to 90% lightening, 17.8% showed 11% to 49% lightening, and 1.7% showed <10% lightening. However, 50% of these patients experienced recurrence 1 to 4 years after treatment.[64]

Clinical trials have investigated the use of topical agents as an adjunct to PDL. These have included timolol, imiquimod, and rapamycin.[65] Topical timolol combined with PDL did not show any improvement in efficacy compared with PDL alone,[66] but imiquimod did show enhanced lightening of PWS compared with controls.[67,68] Several trials of topical rapamycin combined with PDL have shown variable and inconclusive results.[69,70,71,72]

Surgical treatment has been advocated for patients with large PWS lesions that fail to respond adequately to laser therapy. Various techniques have included full-thickness skin graft, local skin flap, free flap transfer, and prefabricated expanded flap transfer.[73,74,75]

Prognosis

Although treatment options for PWS are varied and include lasers, cosmetic tattooing, electrotherapy, cryosurgery, dermabrasion, and skin grafting, none of these alternatives is completely satisfactory and none can provide consistent, satisfactory responses or cures.[76] Improvement with lightening of the lesion and decrease in size after PDL treatment are well documented, but complete clearance is achieved in fewer than 10% of cases, and roughly 20% of lesions show no response.[77] Recurrent darkening of treated lesions occurs secondary to revascularization of the capillary bed. Between 16% and 50% of patients report redarkening of their PWS as early as 5 years after PDL treatment.[64,78] Also, response to treatment differs not only between affected individuals but *(Print pagebreak 634)* also within the same lesion due to the heterogeneous nature of PWS.

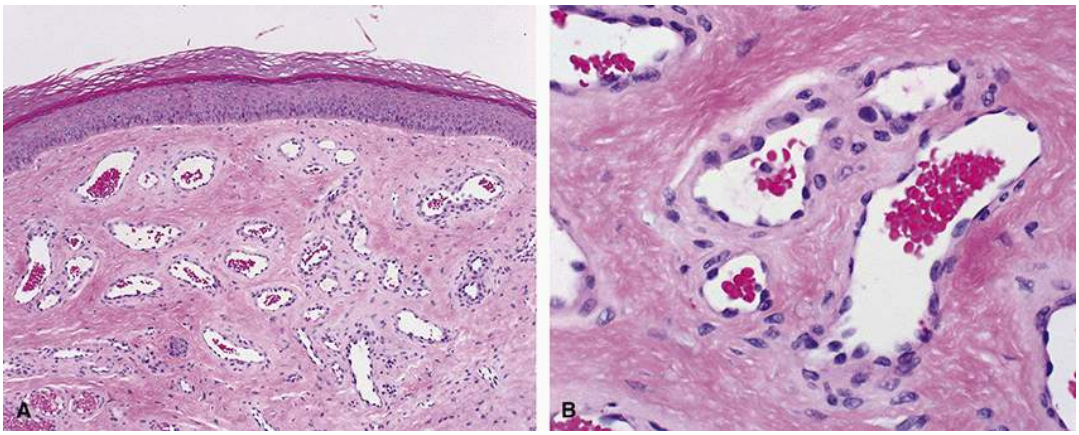

FIGURE 95.3 A, Port-wine stain with numerous capillaries of varying caliber within the dermis. B, Higher magnification of the varying caliber capillaries lined by endothelial cells and lacking a muscle layer.

One study involving 83 patients aged between 2 weeks and 17 years compared treatment outcomes based on patient age alone. They found that when treatment was initiated before the age of 1 year, 32% of cases achieved lesion clearance compared with only 18% in older patients.[79] Nguyen et al[80] also reported that patients less than 1 year of age at the time of PDL treatment showed an average of 63% decrease in size compared with a 48% decrease in children aged 1 to 6 years. A better response rate was also shown for smaller lesions less than 20 cm in size compared with those greater than 40 cm in size.[80]

A decrease in the size of lesions treated with PDL was also shown to be correlated with anatomical location. Central forehead PWS showed 100% clearance after five treatments, whereas those on the peripheral face achieved 58% clearance and those in the central face showed a clearance rate of 48%.[80] Renfro and Geronemus[9] reported that central facial lesions were more resistant to PDL treatment as evaluated by percent lightening than forehead and lateral facial lesions.

Histopathology

PWS is characterized histologically by ectatic capillaries and venules of varying caliber within the dermis (Figure 95.3).[44,81,82,83] The most common site is the superficial reticular dermis, but vessels may occasionally extend into the superficial subcutaneous tissue.[83] Narrow and intermediate caliber vessels predominate before 20 years of age, while vessels of intermediate and wide caliber

prevail after age 20 years.[81] The area of dermis occupied by vessels also increases with age,[82] due to progressive vascular ectasia.[44]

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CHAPTER 96

Nevus Sebaceous of Jadassohn

Key Points

- Nevus sebaceous of Jadassohn (NSJ) is a congenital hamartoma of the pilosebaceous follicular unit
- The pathogenesis of NSJ is unknown, but a developmental arrest during the seventh or eighth month of gestation leading to a disturbance of cell migration and differentiation due to toxic or infectious agents has been suggested
- Another possible etiology proposed that a defect of fusion and separation of tissue during early embryogenesis may result in the ocular malformations associated with nevus of Jadassohn
- NSJ is initially characterized in early childhood by papillomatous hyperplasia and immature hair follicles, followed by hormonally driven rapid growth at puberty, and the development of benign and malignant epithelial neoplasms seen in 10% to 20% of cases in adulthood
- Surgical excision is the treatment of choice
- The prognosis of nevus sebaceous depends on whether it is benign or malignant, and with only benign neoplasms, the prognosis is excellent
- For lesions associated with malignant tumors, most are basal cell carcinomas, which carry a good prognosis

In 1968, Solomon et al[1] coined the term “epithelial nevus syndrome” as a single entity containing a group of disorders characterized by the coexistence of epidermal nevi and extracutaneous anomalies. More recently, it has become obvious that the original concept of that term was erroneous and contained several different entities that could be distinguished by the type of associated epidermal nevus and by the criterion of heritability in some of them.[2,3] Genetic mosaicism in this group of diseases results in different syndromes, all of which include epidermal nevi.[3] Each syndrome presents a different phenotype with a spectrum of abnormalities. These can vary from isolated epidermal nevus with no other manifestations to epidermal nevi with multiple organ involvement.[2] The best known epidermal nevus syndromes include Proteus syndrome, CHILD syndrome, nevus comedonicus syndrome, pigmented hairy cell nevus syndrome, and nevus sebaceous syndrome.[4]

Nevus sebaceous of Jadassohn (NSJ) is one of the nine well-defined groups of epidermal nevus syndrome[5] and was comprehensively described in 1957 by Schimmelpenning.[6] This phenotype is the best known of the epidermal nevus syndromes and is still referred to as epidermal nevus syndrome by some authors.[7,8] The terminology of this birth defect is further confused with other names applied to it in the medical literature, such as Schimmelpenning syndrome, Feuerstein-Mims syndrome, Schimmelpenning-Feuerstein-Mims syndrome, Solomon syndrome, Jadassohn nevus phacomatosis, Jadassohn-Schimmelpenning-Feuerstein-Mims syndrome, organoid nevus phacomatosis, organoid nevus syndrome, sebaceous nevus syndrome, linear sebaceous nevus syndrome, and Jadassohn sebaceous nevus syndrome.[5]

NSJ represents a congenital hamartoma of the pilosebaceous follicular unit. The clinical features were mentioned in 1895 by the dermatologist Josef Jadassohn,[9] who referred to this condition as “organoid nevus” to describe the combination of sebaceous gland changes with nevi. Later, the term “NSJ” was established for lesions of the facial skin characterized by sebaceous gland enlargement. The condition affects approximately 0.3% of newborns. The incidence is equal between males and females and it affects all races and ethnicities. Overall, nevus sebaceous appears as a solitary lesion right after birth, or it may appear sometime before puberty. However, the classic features may not fully develop until after puberty.[10] Clinical features include an epidermal nevus of the sebaceous type on the head and neck area, with ocular and neurological abnormalities.[11,12] Ocular findings can include epibulbar choristomas, corneal pannus, colobomas of the eyelid, iris, retina, choroid, or optic nerve, macrooptic discs, and optic nerve hypoplasia.[13,14,15,16,17,18,19] The major neurological features are mental retardation, seizures, hemiparesis, quadriparesis, hypotonia, reflex abnormalities, gait disorders, diencephalic syndrome, and microcephaly.[20,21,22] Structural abnormalities seen on neuroimaging include hemimegalencephaly, gyral malformations, enlarged ventricles, intracerebral calcification, intracranial vascular abnormalities, porencephalic cysts, and, rarely, intracranial tumors including astrocytoma, pineal germinoma, choroid

plexus papilloma, and lipoma of the corpus callosum.[20,23] Previous estimates of neurologic abnormalities were approximately 15%,[12] but in a larger study of 196 patients with sebaceous nevi, the incidence was less than 7%.[24]

A variety of tumors can arise within NSJ. In an evaluation of 21 reviews involving 4823 cases of nevus sebaceous, benign tumors developed in 16% of cases (range 0%-51%) and malignant tumors developed in 8% of cases (range 0%-22%).[25] Benign tumors included pilar, sebaceous, apocrine, and eccrine neoplasms, such as trichoblastoma and *(Print pagebreak 638)* tricholemmoma, sebaceous adenoma, tubular apocrine adenoma, syringocystadenoma papilliferum, syringoma, and nevocellular nevus.[26] Cutaneous horn arising from an NSJ has also been described.[27]

Malignant tumors often begin with the sudden appearance of discrete, large, often ulcerating nodules.[28,29] They may include basal cell, squamous cell, and sebaceous carcinoma; apocrine carcinoma; adnexal carcinoma; and eccrine porocarcinoma.[26,30] The vast majority of the malignant lesions reported have been basal cell carcinoma (BCC). Earlier published studies reported a higher incidence of both benign and malignant tumors compared with later studies published after 1990. Cribier et al[31] published a retrospective study of 596 nevus sebaceous cases and reported a 0.8% incidence of BCC, with more than 90% of the other tumors being trichoblastomas.[31] They described a common histologic change consistent with benign epidermal hyperplasia and suggested that many previously reported cases of BCC arising in this condition were really benign trichoblastomas. Of the true malignant neoplasms associated with NSJ, BCC is by far the most common, followed by squamous cell carcinoma. Occasionally, more than one malignant lesion can occur in the same NSJ lesion. Although most of these tumors develop during adulthood, malignancies have been reported in children younger than 18 years.[32,33,34,35,36,37,38]

While NSJ is not usually considered to be an inherited disorder, West et al[39] reported three cases localized to the scalp in a mother and two daughters, supporting an underlying genetic association with an autosomal dominant transmission.

Etiology and Pathogenesis

The pathogenesis of NSJ is unknown, but a developmental arrest during the seventh or eighth month of gestation leading to a disturbance of cell migration and differentiation due to toxic or infectious agents has been suggested.[15] Kruse et al[14] reported a case with corneal pannus that could be explained by such a disturbance of differentiation of corneal epithelial stem cells at the limbus. Another possible etiology proposed that a defect of fusion and separation of tissue during the early weeks of pregnancy may result in NSJ associated with ocular malformations[13] and may also be consistent with colobomas of the optic disc with deep cupping and abnormal blood vessels described by Shields et al,[16] as well as the macrooptic discs described by Kruse et al.[14] Other studies have pointed to a possible link with the human papillomavirus[40] or mutations in the patched gene (PTCH).[41]

Although nevus sebaceous is not an inherited skin lesion, it carries postzygotic somatic mutations of the RAS protein family. One study reported 95% of NSJ with *HRAS* mutations and 5% with KRAS mutations. These RAS mutations have also been described in the secondary tumors associated with NSJ, such as trichoblastomas.[10,42,43]

Clinical Presentation

The natural history of NSJ is traditionally divided into three stages.[44] The first is an early infantile stage, characterized by papillomatous hyperplasia and immature hair follicles. The second stage involves expansion at puberty, characterized by rapid growth of the nevus. This is hormonally driven, related to the development of sebaceous glands and maturation of apocrine glands, transforming the lesion from a smooth to a verrucous plaque. The third stage is seen in adults with the development of benign and malignant epithelial neoplasms seen in 10% to 20% of cases.

The symptoms and severity of nevus sebaceous syndrome vary greatly. In childhood, they may be inconspicuous and unrecognized. However, in most cases, NSJ presents as an asymptomatic cutaneous sebaceous nevus lesion. The scalp, neck, and face are most often affected, with the arms, legs, and trunk involved less frequently. Sebaceous nevi are usually hairless, salmon, or yellowish-colored smooth patches in childhood (Figure 96.1), becoming more pronounced and thickened during puberty, and may even appear warty (Figure 96.2).[44] When located on the scalp, they are usually associated with alopecia. Neurological abnormalities can include seizures, developmental delay, intellectual impairment, hemimegalencephaly, malformation of certain brain vessels, agenesis of the corpus callosum, agyria, microgyria, and pachygyria.[20,21,22,23,24]

Ophthalmic manifestations are common and include complex limbal choristomas,[17,18,19] peripapillary yellowish dermal lesions,[17] limitations of extraocular movement,[18,45,46,47] eyelid coloboma,[17,44] and absence of the superior rectus muscle.[48]

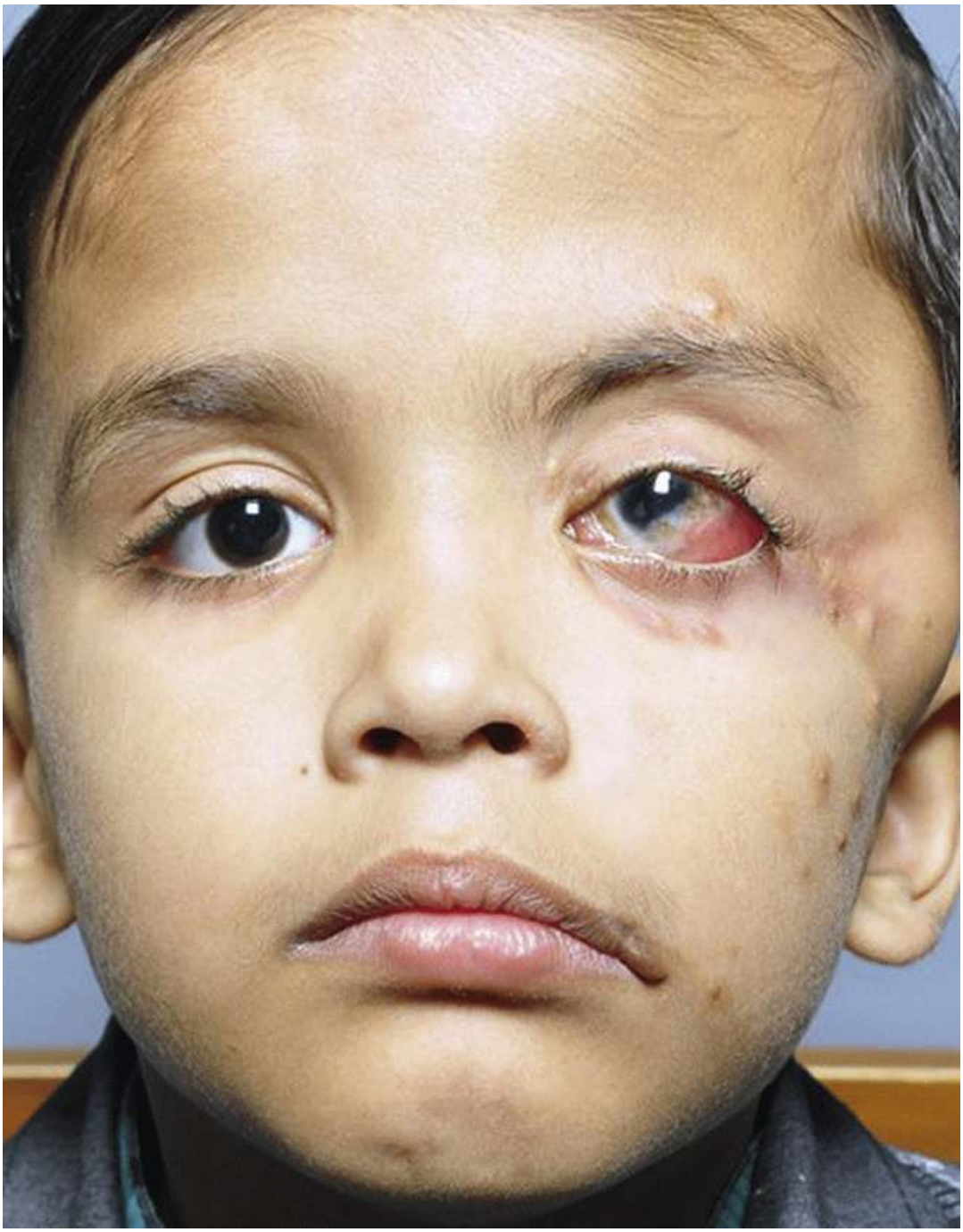

FIGURE 96.1 Lateral canthal and facial lesions in nevus sebaceous of Jadassohn. (Courtesy of Dr. Mohammad Javed Ali.)

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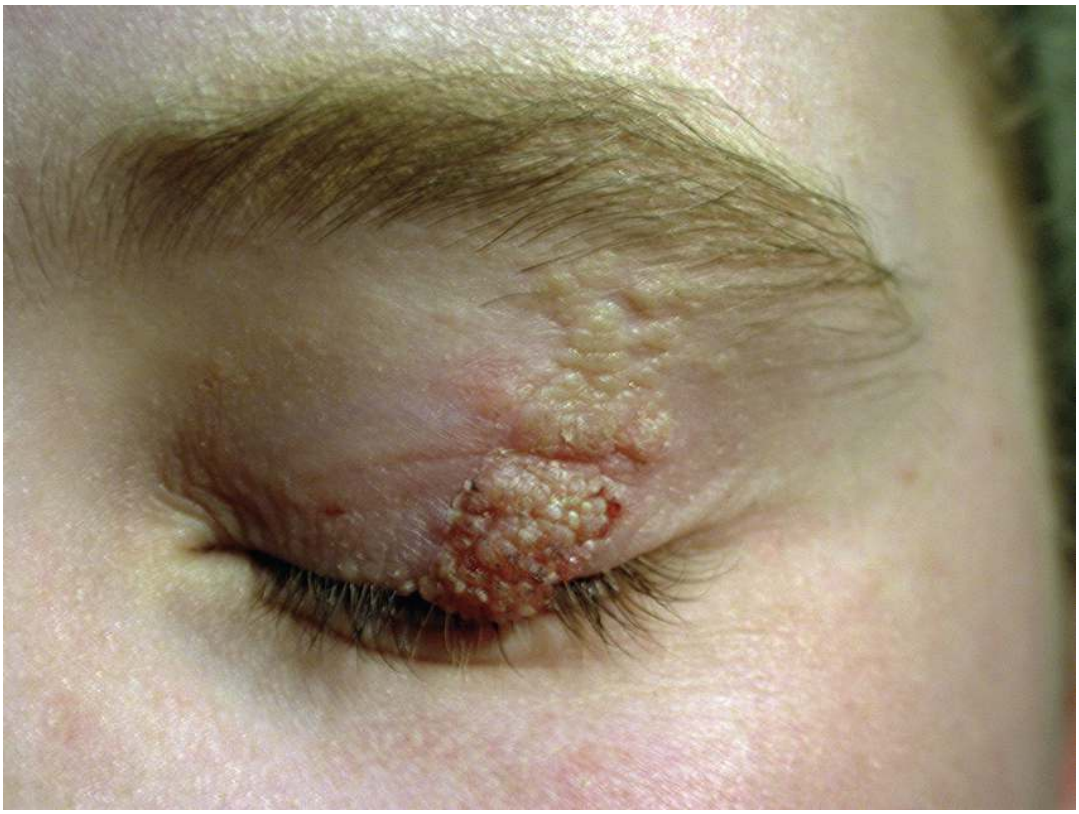

FIGURE 96.2 Warty nevus sebaceous of Jadassohn of the upper eyelid. (Courtesy of Dr. Alan McNab.)

Affected individuals may also have skeletal malformations including abnormal curvature of the spine, dislocation of the hip, limb bone hypoplasia, osteopenia, and multiple insufficiency fractures.[49] Craniofacial skeletal findings can include frontal bossing, asymmetry of cranial facial and orbital bones, sphenoid bone malformation, and premature closure of the sphenofrontal suture.[50] Additional skeletal malformations may include bone cysts, underdevelopment of the pelvis, and incomplete formation of certain bony structures including the ankle, foot, and vertebrae.

Differential Diagnosis

The differential diagnosis of nevus sebaceous depends on the stage of development. In early infancy, the differential diagnosis may include aplasia cutis congenita or mastocytoma. In later stages of development, the differential includes congenital and epidermal nevi, seborrheic keratosis, verruca, early juvenile xanthogranulomas, and other epidermal nevi such as phacomatosis pigmentokeratotica, nevus comedonicus syndrome, and Proteus syndrome. Nevus psiloliparus is a distinct scalp lesion also associated with alopecia and fatty tissue and should be distinguished from NSJ.

Treatment

The specific treatment of NSJ depends upon symptoms, the extent of the disorder, patient age, health, and personal preferences of the patient and clinician. Treatment may require the coordinated efforts of a team of specialists. Pediatricians, pediatric neurologists, dermatologists, orthopedists, orthopedic surgeons, ophthalmologists, and other healthcare professionals may need to collaborate on the treatment options.

The two main reasons to treat NSJ include the development of malignancy and cosmetic improvement. Once a malignant lesion arises within NSJ, the entire nevus should be removed. However, in children with no evidence of malignancy, recommendations regarding prophylactic excision to decrease the risk of future malignant growths have been controversial. Although earlier studies showed high rates of BCC that led to recommendations for early prophylactic excision, during the past several decades, larger studies showed very low rates of BCC arising in these lesions, in the range of 1% or less. As a result, the current opinion is that uncomplicated NSJ lesions can be observed with close follow-up. Despite the low risk of malignant development, surgical removal is appropriate for cosmetic improvement given that these lesions are common on the face and scalp and can cause alopecia.[25]

Once the decision for treatment is made, surgical excision is the treatment of choice. Shave removal is usually unsuccessful because it leaves deep dermal tissue and residual nevus behind.[51,52,53] A full-thickness dermal and epidermal surgical excision should be the goal. For associated ocular lesions such as epibulbar choristomas, surgical excision combined with amniotic membrane transplantation when necessary is an acceptable treatment yielding a good cosmetic outcome.[54]

Ablative laser therapy has shown good aesthetic benefit and treatment response for cutaneous nevi,[55,56] but the long-term efficacy for nevus sebaceous has been questioned.[57] Photodynamic therapy has also been reported to yield moderate to marked improvement in lesions with no significant side effects.[58]

Whether the brain should be imaged in all children with large sebaceous nevi is a controversial issue.[59] Some authors argue that neuroimaging is appropriate only if clinical signs of central nervous system involvement are found or in patients with large nevi involving the centrofacial area.[24]

Prognosis

The prognosis of nevus sebaceous depends on whether it is benign or malignant at the time of diagnosis. In cases with only nevi or benign neoplasms, the prognosis is excellent. For lesions associated with malignant tumors, most are BCCs, which carry a good prognosis following complete surgical excision. The rarer squamous cell carcinomas and melanomas can be associated with local recurrence, regional lymph node involvement, distant metastasis, and mortality.[60,61]

Histopathology

NSJ's histological appearance depends on the patient's age at the time of biopsy, as documented in a study of 150 patients by Mehregan and Pinkus.[44] Mehregan and Pinkus categorized the histological appearance according to patient's age: 0 to 6 years (n = 19 cases), 7 to 12 years (n = 28 cases), 13 to 18 years (n = 35 cases), and 18 years and older (n = 68 cases). One hundred nine patients had their nevus since birth, 33 had their nevus for "many years," and the duration of the nevus was unknown in 8 cases.[44] One hundred seven of the nevi were from the scalp, 35 from the face (2 from *(Print pagebreak 640)* the eyelids), and the remainder from the arm (n = 3), chest (n = 2), back (n = 1), or site unknown (n = 2).[44] Mehregan and Pinkus's histological findings are summarized here according to skin structure and age groups[44]:

1. Epidermis: The epidermis was hyperplastic in 84% of patients from 0 to 6 years, 93% from 7 to 12 years, 97% between 13 and 18 years, and 94% in ages 18 years and older. The hyperplastic epidermis was papillomatous, but it was milder in early lesions and more prominent in older nevi (Figures 96.3 and 96.4). The hyperplasia was due to an increased number of prickle cells with a thickened stratum spinosum and was accompanied by hypergranulosis and hyperkeratosis. Approximately 6% of nevi had an appearance of seborrheic keratosis with basaloid cell hyperplasia. Pedunculated nodules of hyperplastic epidermis projected from the surface in 7% of cases.

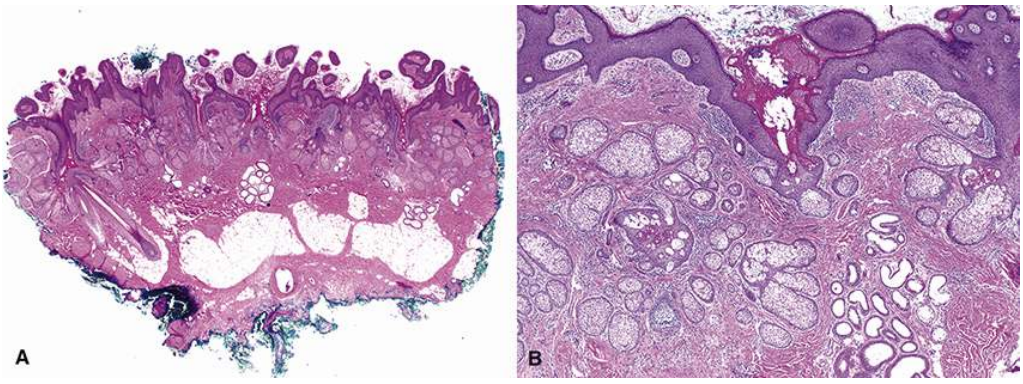

FIGURE 96.3 This nevus sebaceous of Jadassohn (NSJ) of the left occipital scalp was excised at age 12 years after a new papule developed. A, Papillary epidermal hyperplasia with hyperkeratosis, sebaceous gland hyperplasia, and apocrine gland hyperplasia is prominent at scanning magnification. B, Epidermal acanthosis and hyperkeratosis, hyperplasia of sebaceous and apocrine glands, and dermal fibrosis are common features of NSJ after 11 years. The hair follicle is maldeveloped with an absent hair shaft.

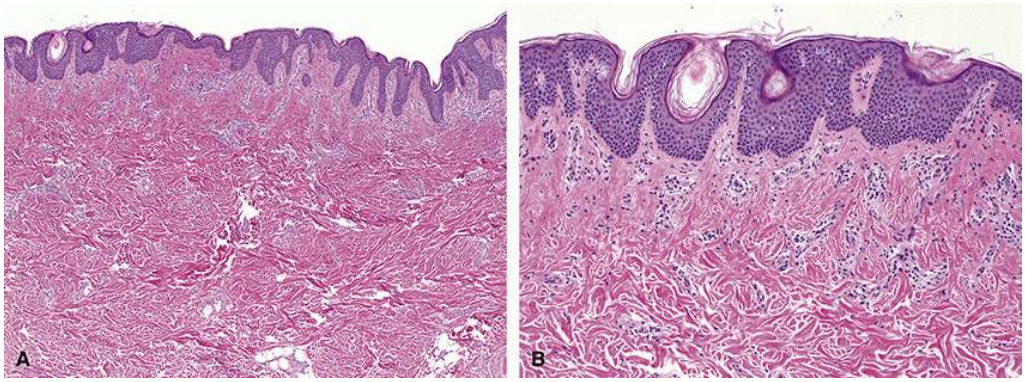

FIGURE 96.4 This scalp nevus sebaceous of Jadassohn was noted at birth and excised at 10 years of age due to increasing size and itchiness. A, The epidermis is acanthotic, and pilosebaceous units and apocrine glands are absent. B, The acanthosis is due to thickened stratum spinosum, and the papillary dermis is fibrotic.

2. Hair follicles: Hair follicles were abnormal in all nevi from patients between 0 and 6 years (Figure 96.5), 93% between 7 and 12 years (Figure 96.3), 91% between 13 and 18 years, and 88% in patients 18 years or older. Early lesions manifest clinically as an area of alopecia had abnormally developed hair follicles with cords of undifferentiated cells resembling embryonic follicles (Figure 96.5B). There were papillae and matrix-like epithelial arrangements surrounded by connective tissue in some areas and occasional keratinization or formation of small hair shafts. The older lesions had many normal-appearing hair follicles with hair shafts along with scattered buds of undifferentiated basaloid cells surrounded by fibrous connective tissue connected to the lower border of the epidermis or pilosebaceous structures. Hair follicles were absent in 8%, 9%, 12% in *(Print pagebreak 641)* age groups 7 to 12 years, 13 to 18 years, and 18 years and older (Figure 96.4).

3. Sebaceous glands: Between 0 and 6 years, 95% of cases had numerous small undeveloped lobules of sebaceous glands connecting to incompletely formed hair follicles (Figure 96.5C). Between 7 and 12 years, there were small sebaceous glands in 39%, small and large glands in 25%, large sebaceous glands in 25% (Figure 96.3), and absent glands in 11% of cases (Figure 96.4). The number of small immature sebaceous glands decreased, and large, well-developed glands increased in the older age groups. Between 13 and 18 years, there were small sebaceous glands in 9%, small and large glands in 20%, large in 57%, and absent glands in 14% of cases. For cases 18 years or older, there were small sebaceous glands in 3%, small and large in 6%, large in 79%, and absent glands in 12%. In older lesions, the sebaceous glands sometimes had excessive size and formed "massed arrangements."[45]

4. Apocrine glands: Apocrine glands were absent in 89% of cases between 0 and 6 years, 50% between 7 and 12 years, 31% between 13 and 18 years, and 40% from age 18 years or older. The apocrine glands, when present, had active secretion.

5. Dermis: The dermis was abnormal in 87% of cases, with the most common abnormalities being increased thickness, increased vascularity, and proliferation of fibrous connective tissue. The changes were most marked in the papillary and anterior reticular dermis and at the periphery of pilosebaceous units. Twenty-eight percent of cases had a moderate to heavy infiltrate of lymphocytes, plasma cells, and "some eosinophils." Melanophages were present "occasionally," 5% of cases had a foreign body granulomatous reaction to degenerating pilosebaceous structures, and 2% had small areas of dermal calcification.

6. Secondary tumors: Tumors increased in frequency in older lesions. Tumors developed in 5% of cases between 0 and 6 years, 4% between 7 and 12 years, 9% between 13 and 18 years, and 41% of patients 18 years or older. Mehregan and Pinkus identified 52 tumors in 33 cases, with BCC being the most common (40% of the tumors), followed by syringocystadenoma papilliferum (15%) and solid hidradenoma (12%).

Mehregan and Pinkus summarized the life history of NSJ as underdevelopment of hairs and sebaceous glands in the early stage; massive development of sebaceous glands, papillomatous epidermal hyperplasia, and maturation of apocrine glands during a second phase usually beginning at puberty; and development of secondary benign and malignant tumors in the lesions in the third stage.

Morioka confirmed age-related changes in the histological appearance of NSJ in a study of 86 cases.[62] Sebaceous glands were absent in 6% of lesions, normal in 26%, slightly proliferated in 38%, and markedly proliferated in 30%.[62] Morioka identified sebaceous gland proliferation in lesions *(Print pagebreak 642)* of any age, but most of the cases of marked proliferation were in subjects aged 11 years or older.[62] Apocrine glands were absent in 72% of lesions, normal in 8%, slightly proliferated in 10% (Figure 96.4B), and markedly proliferated in 10%. Apocrine gland proliferation was most common in the subjects aged 11 years or older, similar to the finding for sebaceous glands.[62]

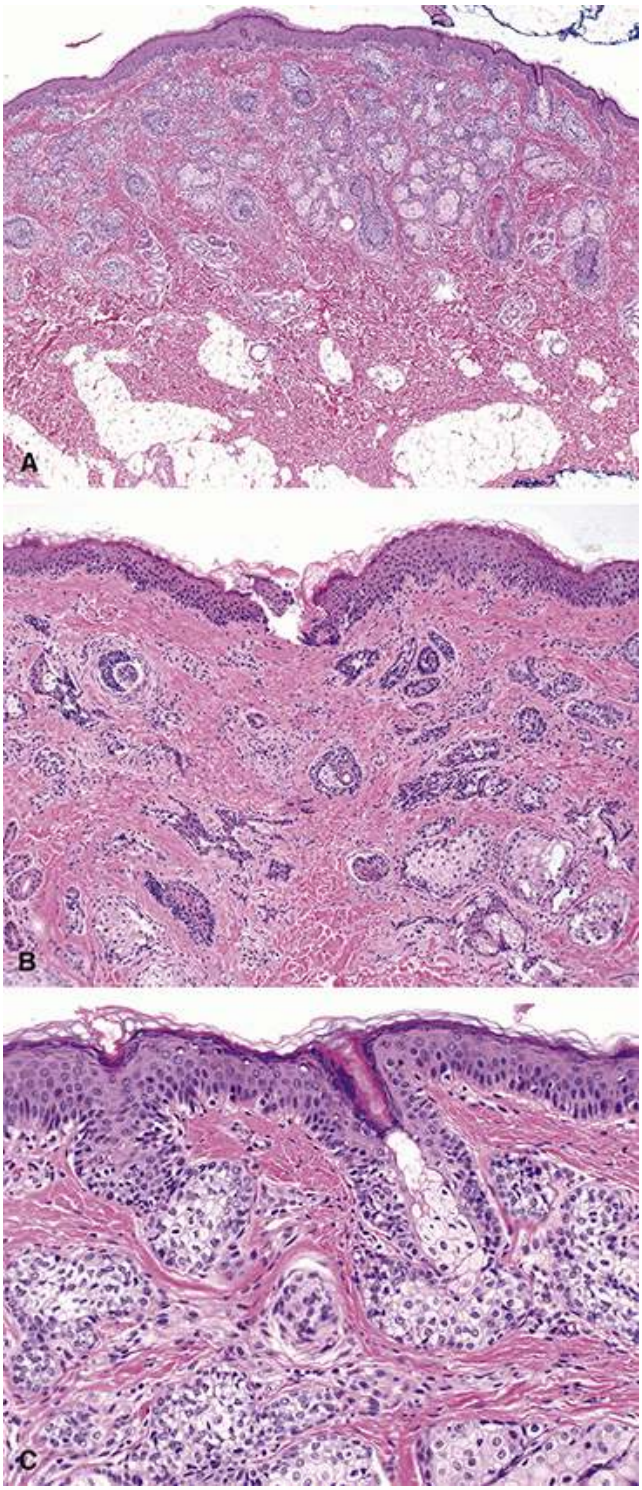

FIGURE 96.5 This nevus sebaceous of Jadassohn of the right medial canthus was noted at birth and excised at the age of 1 year. A, There are an increased number of sebaceous glands and no normal hair follicles at scanning magnification. B, The superficial dermis has many abnormally developed hair follicles with cords of undifferentiated cells and rudimentary follicles. C, Small lobules of sebaceous glands connect to incompletely formed hair follicles.

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CHAPTER 97

Nodular Fasciitis

Key Points

- Nodular fasciitis is a rare benign reactive lesion characterized by a proliferation of fibroblasts and myofibroblasts that involve subcutaneous tissue, skeletal muscles, and fascia
- It is classified according to the plane of tissue that is primarily involved, including subcutaneous, dermal, intramuscular, and fascial types
- The etiology of NF remains unknown but a traumatic etiology has been proposed
- Gene rearrangements suggest that nodular fasciitis may be an unusual phenomenon of transient or self-resolving neoplasia
- The clinical presentation is usually a skin-colored to light brown firm, smooth, mobile subcutaneous nodule that grows rapidly and measures 1 to 2 cm in diameter
- Surgical excision is recommended as the treatment of choice to exclude malignancy, and lesions can be cured with a conservative surgical resection
- The prognosis is usually good, and recurrence is exceptionally rare

Nodular fasciitis (NF) is a rare benign reactive lesion of unknown etiology characterized by a proliferation of fibroblasts and myofibroblasts[1,2] that involves subcutaneous tissue, skeletal muscles, and fascia.[3,4] It was first described by Konwaler and Weiss[5] in 1955 as "subcutaneous pseudosarconiatous fibromatosis (fasciitis)." In that report, the authors reported eight cases of a rapidly growing nodule that histologically resembled fibrosarcoma.

NF can appear in any part of the body, but the most common sites of involvement are the upper extremity, followed by the chest and back. Approximately 7% to 20% of cases occur in the head and neck region,[6,7,8,9,10,11,12,13] and these cases are more often seen in younger children.[6,14,15,16] In the facial region most lesions are located in the skin, parotid gland, and subcutaneous tissues of the mandible and zygoma.[7] The eyelid is rarely involved,[17,18,19,20,21,22,23,24,25,26,27] but several cases of orbital involvement have been described.[22,28,29]

There is no clear gender predilection, with reports varying from male and female equivalence, male predominance, to female predominance.[7,11,30,31] NF is often initially misdiagnosed as a sarcoma because of its rapid growth and its histologic appearance and has been referred to as pseudosarcomatous fasciitis.[8,14,32]

Nodular fasciitis can be classified according to the plane of tissue that is primarily involved. These include subcutaneous, intramuscular, and fascial types.[7] A fourth variant, the dermal NF, is more commonly found in the head and neck region.[2] Among 16 cases of facial NF, all lesions involved subcutaneous tissues, but 7 (43.8%) also involved the muscle layers and 10 (62.5%) had dermal involvement.[33]

Lesions are usually attached to the fascia from which they arise and extend into the subcutaneous fat. Occasionally they arise from the fibrous septa of the subcutaneous fat and only secondarily extend to the fascia.[7] In 1966, based on 17 personal and 314 cases from the literature, Mehregan[34] defined the clinical appearance, epidemiology, and histologic findings of NF as a freely mobile, subcutaneous nodule, sparing the dermis, with an aggressive appearing, fibroblast-like histologic picture. Lesions typically grow rapidly, with a duration of <1 month in 57% of cases and >3 months in only 15%. Tenderness or pain was reported in 55% of cases.

Etiology and Pathogenesis

The etiology of NF remains unknown but a traumatic etiology has been proposed.[34] In a study of 50 patients with NF, 5 (10%)

recalled antecedent trauma.[16] In another study of 16 patients with facial NF, 9/16 (77%) had a history of trauma or stimulation before development of the lesion.[33] However, most other studies show only a small number of patients who report even a vague history of trauma.[5,11,12,31,32,34,35,36,37] Because some cases of nodular fasciitis appear to arise after minor trauma and then spontaneously resolve, it has not been clear whether these lesions arise as a reactive process or as a true neoplasm.[38] Erickson-Johnson et al[39] reported that 92% of NF tumors contain a gene rearrangement involving *USP6* on 17p13, with the most common fusion partner being *MYH9* on 22q12. This leads to overexpression of *USP6* under *MYH9* promoter and appears to drive *(Print pagebreak 645)* tumorigenesis.[40] These results suggest that nodular fasciitis may be an unusual phenomenon of transient or self-resolving neoplasia.[39]

Clinical Characteristics

The clinical presentation of nodular fasciitis is usually a firm, smooth, mobile subcutaneous nodule that grows rapidly over weeks to several months (Figure 97.1). Lesions are skin colored to light brown and measure 1 to 2 cm in diameter, but they can be up to 4 cm.[41] When involving the upper eyelid, larger lesions can cause mechanical ptosis.[1,17] In rare cases, NF can be immobile due to infiltration into the dermis and underlying muscle.[19]

Lesions may be painless and asymptomatic, but 55% are tender or even painful.[34,36] One case was reported to have a cystic appearance that could be transilluminated.[19] While most periorbital lesions involve the eyelid skin, rare cases have been described located beneath the episcleral conjunctiva (Figure 97.2).[24,27] Periorbital NF lesions tend to be smaller than those in other parts of the body, possibly due to the less abundant subcutaneous fat and fascia.[42]

Differential Diagnosis

The clinical features of NF are not pathognomonic and can lead to diagnostic confusion. The differential diagnosis includes solitary fibrous tumor, dermatofibroma, fibrous histiocytoma, fibroma, fibrolipoma, lipoma, neurofibroma, neuroma, neurilemmoma, dermoid and epidermoid cyst, leiomyoblastoma, fibrosarcoma, and sarcoma.[1,25,26,34]

FIGURE 97.1 Large subcutaneous lesion of nodular fasciitis at the lateral brow. (Courtesy of Dr. Gordon Klintworth.)

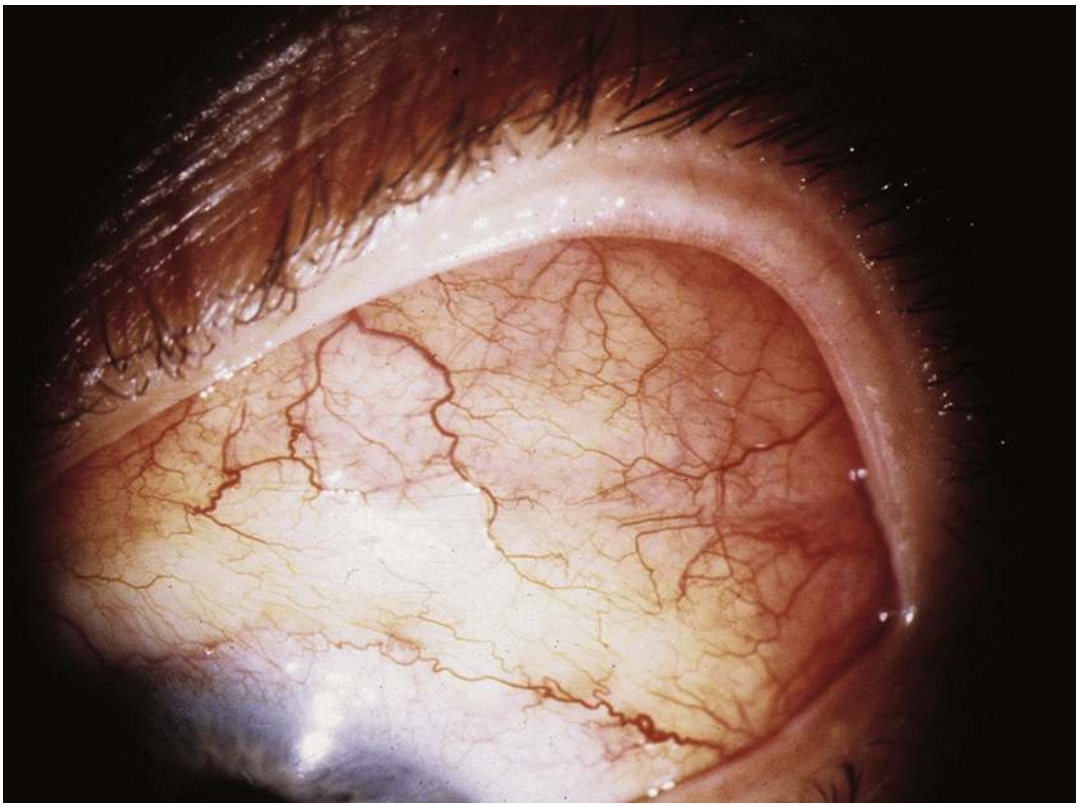

FIGURE 97.2 Nodular fasciitis beneath the superior episcleral conjunctiva.

Treatment

Because NF is frequently mistaken for sarcoma both clinically and histopathologically, surgical excision is usually recommended as the treatment of choice to exclude malignancy.[43] Nodular fasciitis usually can be cured completely with a conservative surgical resection.[8] Local recurrence is uncommon, generally reported at 8% or less.[16,44] Of 18 cases of recurrence noted by Bernstein and Lattes,[35] on re-excision all were reclassified histologically as inflammatory fibrous histiocytoma. It has even been proposed that any recurrence of supposed NF should lead to a reconsideration of the diagnosis.[45] However, in a series of nine cases of histologically confirmed facial NF treated surgically, seven (77%) recurred,[33] likely due to incomplete resection with more conservative surgery to minimize scarring. Therefore, for lesions occurring on the face, nonsurgical treatment and regular follow-up has been proposed as an alternative approach.[33]

For nonsurgical treatment, intralesional injection with triamcinolone has been proposed, assuming that NF is a benign reactive or inflammatory condition of mesenchymal fibroblasts.[46] Intralesional steroid injection has been reported to result in significant improvement[33] or even complete resolution of NF lesions in 1 to 3 days,[19,46] but data are limited.

NF on the face is frequently of the intradermal type. Facial muscles are located superficially beneath the skin so that NF lesions can extend beyond the fascia and subcutaneous tissue to invade the skin.[47] Such superficial, intradermal types of NF are more easily managed by laser treatment. CO_2 laser therapy can decrease the size of the lesion through tissue contraction using a pinhole method.[33,48] This technique may especially be effective for lesions on the face that may be of greater aesthetic concern.

Spontaneous regression has been reported after incomplete excision,[15,33] so that in such cases it may be appropriate to follow the patient closely and wait for regression before considering further surgery.

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Prognosis

The prognosis of NF is usually good. Following surgical excision, most cases can be cured and recurrence is exceptionally rare.[2,26,28]

Histopathology

NF is far more common in the subcutis than the dermis.[49,50,51] Subcutaneous lesions may be well circumscribed but unencapsulated,[51] or they may have "a central body of more solid cellular growth sending outward in all directions numerous processes within the connective tissue septa of the surrounding fat lobules" creating the appearance of an infiltrating tumor.[34] The lesions are composed of variably sized spindle cells without a consistent or distinguishing pattern.[35] The spindle cells may have a vague storiform pattern, form interconnecting fascicles (Figure 97.3A and B), be randomly oriented, appear similar to granulation tissue with proliferating fibroblasts associated with fine capillaries, or lie within a myxoid matrix that may have small cystic spaces.[34,35,52] Lesional cells may be plump, oval, stellate, or fusiform[34] with pale eosinophilic cytoplasm.[42] Nuclei may be plump,[34] oval,[34] vesicular,[34] or stellate[52] with one or more prominent[34] or small, round, and basophilic[52] nucleoli. Scattered multinucleated giant cells are in 10%[51] to 50%[35] of cases (Figure 97.3C). Mitoses are usually easily noted, although the number varies widely from one area of the lesion to another.[35] Bernstein and Lattes counted mitotic figures in 20 high-power fields (HPF) and noted an average of one mitotic figure/HPF in 8% of cases, one mitotic figure in 2 to 5 HPF in 49%, and one mitotic figure in >5 HPF in 41% of cases.[35] Atypical mitotic figures are absent[42,52] or rare[35] in NF. The stroma usually has areas of extravasated erythrocytes (Figure 97.3B)[5,34,35,42,52] and scattered acute and chronic inflammatory cells.[52] Rare lesions may have plasma cells or lymphoid tissue with germinal centers.[35] Mehregan observed occasional areas of granulomatous inflammation near the junction of NF and the adjacent fat tissue.[34] Stromal capillaries may exhibit endothelial cell proliferation or be dilated and engorged with erythrocytes.[34] Collagen within NF may be almost absent[34] or heavily hyalinized with a keloidal appearance.[42,51] Foci of osteoid were identified in 3/116 (2.6%) and foci of osteoid and cartilage in 4/116 (3.4%) of the cases studied by Bernstein and Lattes.[35]

Immunohistochemical studies of subcutaneous NF have yielded somewhat variable results. Montgomery and Meis, in a study of 53 lesions, reported immunoreactivity for muscle-specific actin (MSA) in 100% of cases, smooth-muscle actin (SMA) in 98% (Figure 97.3E), CD68 (KP1) in 98%, vimentin in 94%, and no reactivity to keratins, S-100 protein, or desmin in any case.[52] SMA immunoreactivity was diffuse and, in many cases, was weak compared with vascular smooth muscle.[52] CD68 (KP1) stained a minority of the spindle cells and all of the giant cells (Figure 97.3F).[52] "KP1 reactive cells were clearly lesional rather than part of the inflammatory background; they were indistinguishable from nonreactive spindle cells in the H&E-stained sections".[52] Weinreb and coworkers identified SMA immunoreactivity in 100% (24/24) cases; the staining was diffuse and strong staining in 19/24 (79%) and focal in 5/24 (21%) of cases.[42] "The lesional fibroblastic/myofibroblastic cells were negative for S-100 (0/22), desmin (0/19), CD34 (0/19), CD68 (0/15), and factor XIIIa (0/15)."[42] Lu and colleagues reported diffuse expression of SMA; positive staining for calponin, MSA, and CD10; expression of CD68 by "intralesional histiocytes and small multinucleated giant cells"; and no staining using antibodies to desmin, h-caldesmon, β-catenin, AE1/AE3, CD34, and S-100 protein.[51] Fluorescent in situ hybridization analysis using a break-apart probe to detect *USP6* gene rearrangement has a sensitivity of 74%[53] to 86%[54] and a specificity of 100%[53,54] for diagnosing NF.

Cutaneous NF involves the dermis with extension into the superficial subcutis in about 40% of cases (Figure 97.3).[40,47,55] In a review of 24 cases of dermal NF by de Feraudy and Fletcher, 23 cases were well circumscribed but unencapsulated, one had ill-defined margins, and the epidermis was ulcerated in 11/24 (46%).[47] Lesional cells were uniform plump spindle cells, cytologically bland without significant atypia or pleomorphism, and arranged in short intersecting fascicles (Figure 97.3A and B) within a focally microcystic myxoid stroma with extravasated erythrocytes (Figure 97.3B) and scattered lymphocytes.[47] There were one to six mitoses per 10 HPF.[47] All cases were diffusely positive for SMA, but tested cases were negative for expression of desmin, caldesmon, CD68, CD34, AE1/AE3, CAM52, pan-cytokeratin, S100 protein, MART-1 (melanin A), microphthalmia-associated transcription factor, and HMB-45.[47]

Intravascular fasciitis (IF) is a rare variant of nodular fasciitis[56,57,58,59] that may involve the periocular skin (Figure 97.4).[60] It may involve small veins or arteries, usually with a predominant extravascular component.[56,59] IF may appear to be NF with a multinodular growth pattern, with vascular involvement becoming apparent only using elastic and muscle stains.[59] Most cases affect the intima, media, and adventitia.[56] The histological appearance is similar to NF, although prominent myxoid stroma is uncommon.[56,58] The spindle cells are immunoreactive using antibodies to vimentin, smooth muscle actin, and muscle-specific actin, and they lack expression of desmin, cytokeratins, S100 protein, CD31, and CD34.[57,58,61]

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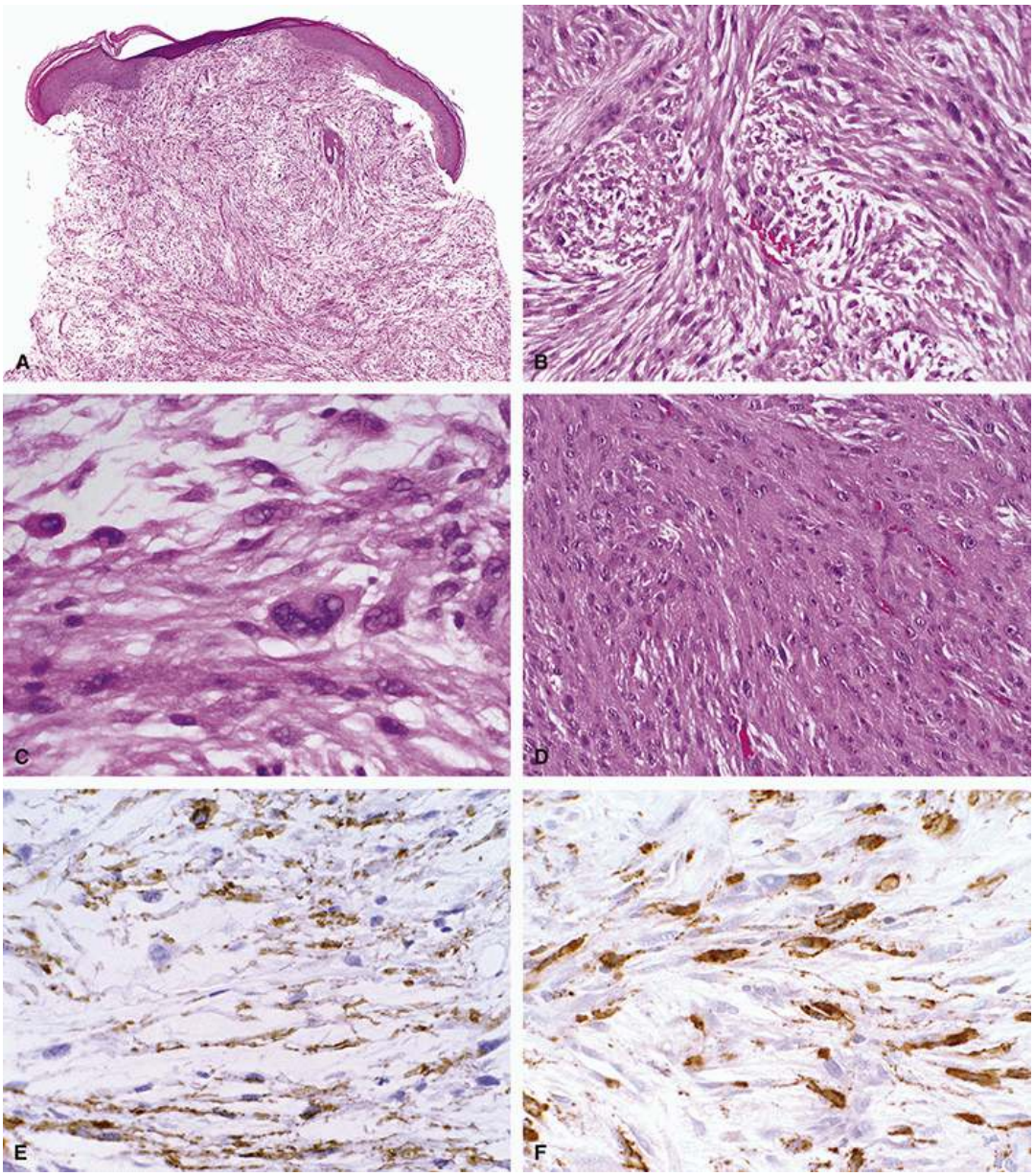

FIGURE 97.3 This NF arose at the right lateral canthus in a woman in her late 20s. The NF was painless, nontender, and erythematous and grew continuously over 7 months to 1.5 cm in diameter. A, The NF extends from the papillary dermis through the reticular dermis. In this area, the NF has a fascicular pattern, with many of the fascicles having a loose appearance. The epidermis has an artifactual fold. B, The fascicular appearance is prominent in this area, and there is a focus of extravasated erythrocytes in the stroma. C, There were scattered multinucleated giant cells throughout the tumor. D, Some areas of the NF had a more compact appearance with sheets of spindle cells and intervening capillaries. E, Immunohistochemical staining with antibodies to smooth muscle actin is positive in >95% of cases of NF. F, Immunohistochemical expression of CD68, a marker of macrophages (histiocytes), was present in this case of NF, but the proportion of cases expressing CD68 has varied widely in published series of NF.

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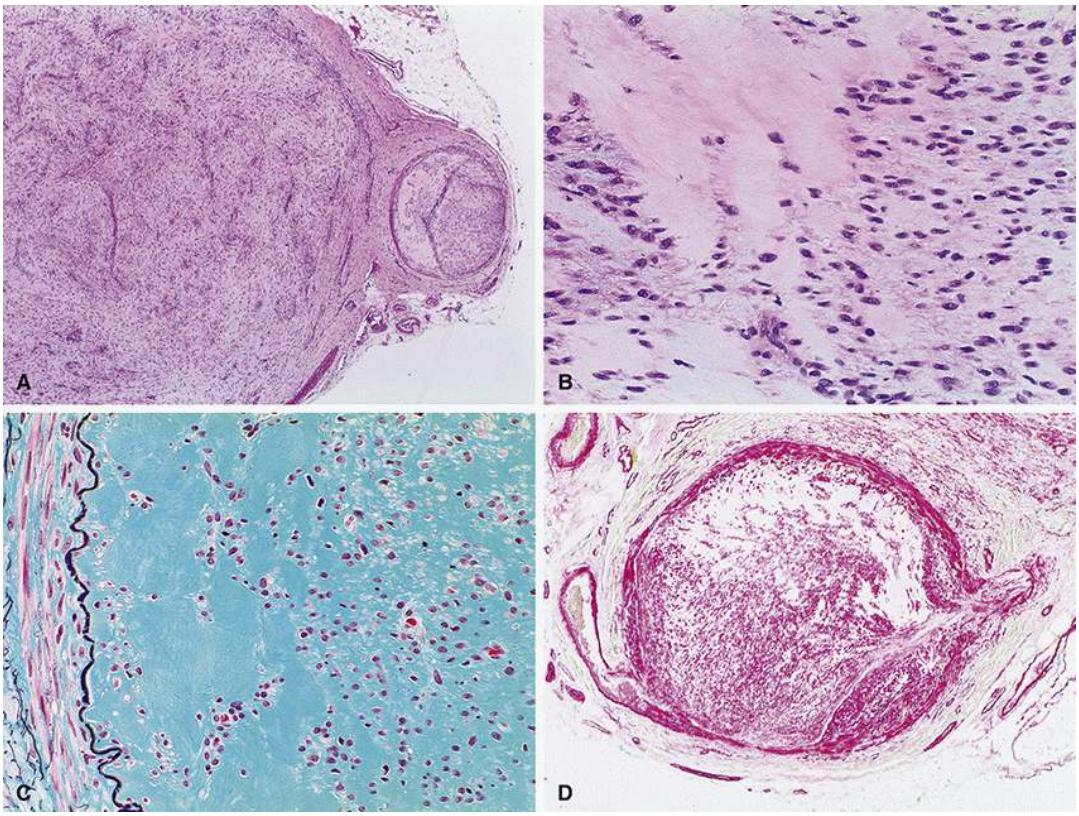

FIGURE 97.4 A septuagenarian woman developed a round, firm, mobile mass of her right upper eyelid that increased to a diameter of 5 to 6 mm over 6 months. A, Excisional biopsy disclosed a bilobed mass with intravascular fasciitis (IF) of a small artery on the right, and a larger adjacent extravascular nodule of fasciitis. B, The IF had cells with oval nuclei and indistinct cell borders embedded in a predominantly myxoid stroma. C, Movat pentachrome stain highlights the arterial smooth muscle light red, the internal elastic lamina black, and the myxoid IF stroma blue. D, Immunohistochemical staining with antibodies to smooth muscle actin showed intense staining of the arterial wall smooth muscle and slightly less intense staining of the IF cells.

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CHAPTER 98

Ocular Cicatricial Pemphigoid

Key Points

- Mucous membrane pemphigoid describes a heterogeneous group of autoimmune disorders characterized by chronic inflammatory, mucous membrane blistering involving the ocular, oral, genital, nasopharyngeal, esophageal, or laryngeal regions and the skin
- It is characterized by the presence of linear deposits of C3, IgG, IgA, or IgM along epithelial basement membranes, and more than 10 target antigens have been identified
- Ocular and palpebral findings are attributable to subepithelial fibrosis
- It manifests initially with unilateral or bilateral chronic conjunctivitis, tearing, and redness, followed by progressive obliteration of the conjunctival fornix and ultimately complete bilateral occlusion of the fornices or ankyloblepharon with lagophthalmos
- Aggressive immunosuppression is required to suppress inflammation, promote healing, and prevent further cicatrization
- The treatment for trichiasis is destruction of the cilia follicles responsible for the aberrant eyelash growth with electrolysis, cryotherapy, or laser
- The success rates for the surgical correction of the cicatricial entropion and trichiasis generally are very good, but management of systemic disease shows only partial success, and recurrence rates are high

Mucous membrane pemphigoid describes a heterogeneous group of autoimmune disorders bearing several names in the literature, which are characterized by chronic inflammatory, mucous membrane-dominated, subepithelial blistering at the body orifices involving the ocular, oral, genital, nasopharyngeal, esophageal, or laryngeal regions and the skin (Figure 98.1). Blindness or life-threatening complications may occur.[1,2,3,4,5,6,7,8,9] Occasionally, the clinical manifestations may primarily involve the eyes, and in such patients, the term “ocular cicatricial pemphigoid” (OCP) is often used.[4,5]

Etiology and Pathogenesis

Mucous membrane pemphigoid is characterized by the presence of linear deposits of C3, IgG, IgA, or IgM along the epithelial basement membranes. More than 10 target antigens have been identified in mucous membrane pemphigoid, and these are all components of the epithelial basement membrane.[3] Autoantibodies against these basement membrane components include Bullous pemphigoid antigen 1 and 2, Laminin 5 and 6, and type VII collagen. These probably play a role in the pathogenesis of this group of diseases,[3] and in the case of OCP, in particular, one antigen, the β4 subunit of α6β4 integrin, has been identified as the target conjunctival basement membrane autoantigen.[4] When the circulating autoantibodies bind to antigens within the basement membrane, they activate the complement cascade with complement deposition at the level of the lamina lucida with release of inflammatory cytokines and hydrolytic enzymes.[4]

Conventional histopathologic examination is not usually conclusive in OCP, but there are some suggestive findings including the predominance of T cells, neutrophils, and histiocytes; a decrease in goblet cell density; and a mild capillary proliferation.[4,5] The predominance of T cells has led some authors to hypothesize a model for the pathogenesis of OCP. This model postulates a shift away from T suppressor cells to T helper cells that allow the B cells, which are normally prevented by T suppressor cells from releasing autoantibodies against basement membrane components, to escape this surveillance mechanism and promote the activation or release of rogue clones of B lymphocytes, which synthesize these autoantibodies.[4] It must be underscored that the gold standard for diagnosis of OCP is with the use of immunofluorescence and not conventional histology.[4] Although the demonstration of linear deposits of IgA, IgG, IgM, or C3 along epithelial basement membranes is one of the essential criteria for the diagnosis of mucous membrane pemphigoid,[3] the situation with OCP is more complicated,[3,4,7] and the range of positive biopsies vary from 20% to

67% only. Therefore, although a positive biopsy establishes the diagnosis, a negative one does not exclude OCP.[3,4,7,9] It should be noted that demonstration of linear IgG alone is nonspecific as it can be demonstrated in any inflammatory eye condition.[4] Certain precautions, however, may improve the diagnostic yield: (1) the biopsy specimen should be obtained from conjunctival tissue immediately adjacent to the inflamed tissue and not from the inflamed tissue itself, let alone scarred tissue; (2) if there is multiorgan involvement, a nonocular site should be chosen; (3) fresh tissue should be immediately submitted for immunofluorescence; and (4) the routine use of immunoperoxidase staining in addition to immunofluorescence significantly increases the diagnostic yield.[3,4,7]

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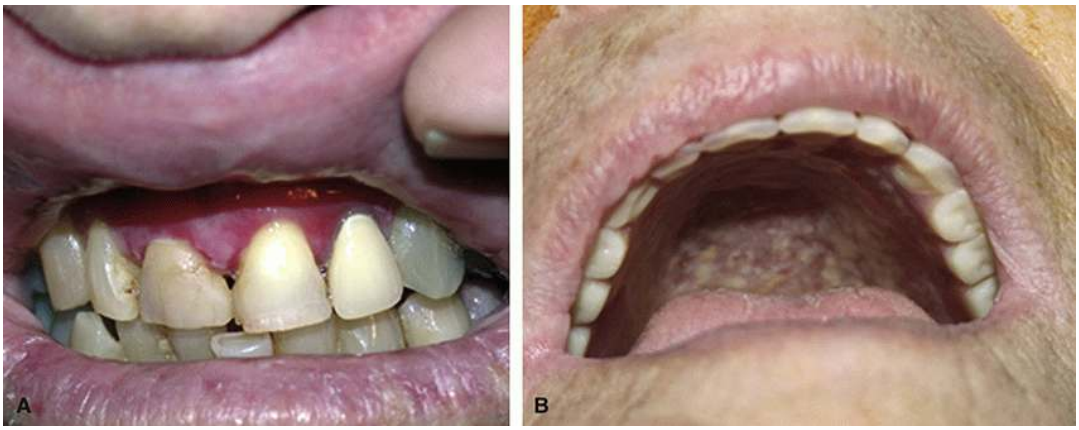

FIGURE 98.1 A and B, Oral mucous membrane involvement with cicatricial pemphigoid. A, (Courtesy of Dr. Charles Soparkar.)

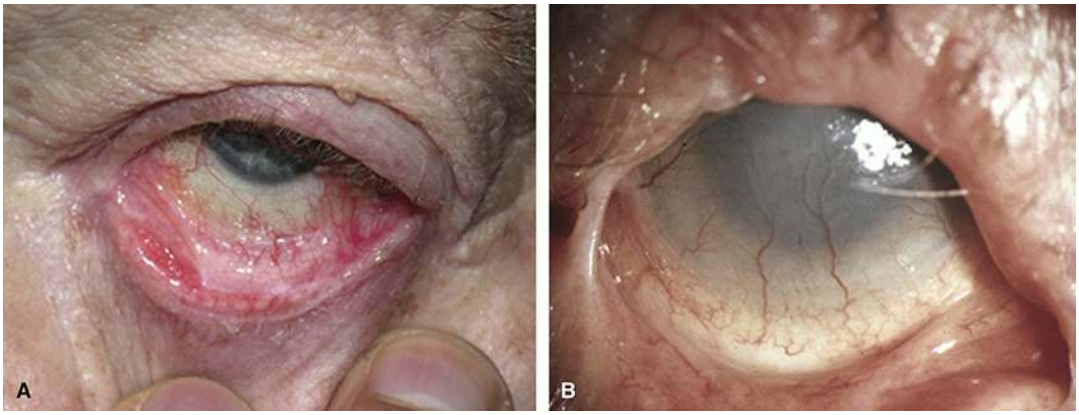

FIGURE 98.2 A and B, Early OCP with conjunctivitis, fornix shortening, and symblepharon formation.

Clinical Presentation

The age of onset of OCP peaks during the 7th and 8th decades, but this may be partially attributable to a delay in presentation rather than just a delay in onset.[5,9] The ocular, as well as the palpebral findings of OCP, are all attributable to subepithelial fibrosis,[4,7] which usually manifests initially with unilateral or less commonly bilateral chronic conjunctivitis, and nonspecific symptoms of tearing, redness, and foreign body sensation. This is followed by progressive shortening of the conjunctival fornix and symblepharon formation, which usually starts in the lower followed by the upper eyelid (Figure 98.2). Progressive fibrosis results in deformed eyelids with loss of normal architecture, ankyloblepharon with lagophthalmos, keratinization of the mucocutaneous junction, trichiasis, distichiasis, or frank cicatricial entropion (Figure 98.3). The process is progressive and ultimately results in complete bilateral occlusion of the fornices (Figure 98.4). An important clinical finding that is rarely discussed in the literature is that the palpebral, as well as the conjunctival, findings usually start medially. Trichiasis and distichiasis are not uncommon medially and may extend to the lacrimal portion of the eyelids, which is normally devoid of lashes. Ankyloblepharon also starts medially with effacement of the plica semilunaris before advancing laterally as the disease progresses. Additional ocular findings include punctal and canalicular fibrosis, which typically precede occlusion of the ducts of the main and accessory lacrimal glands. Thus, patients with OCP initially present with tearing followed years later by symptoms of severe dry eyes that may also be exacerbated by progressive destruction of the goblet cells.[7] It is always important to rule out OCP in all patients presenting with tearing and punctal/canalicular fibrosis before rushing to lacrimal surgery that could exacerbate *(Print pagebreak 652)* dry eyes in the future. This vicious cycle of entropion, trichiasis, dry eyes, and lagophthalmos eventually leads to corneal scarring and even corneal

perforation.[7] The clinical manifestations of OCP might not always conform to a strict classification scheme, so it is necessary to keep a broad categorization in mind to serve as a framework for therapeutic decision making. Several classification schemes have been proposed over the years, but the most accepted staging system is the Foster staging system, which classifies ocular/periocular changes in OCP into four stages: Stage I findings include conjunctivitis with discharge and conjunctival subepithelial fibrosis, stage II is characterized by inferior fornix foreshortening, stage III is defined by the appearance of a symblepharon, and stage 4 is an end-stage disease with marked ocular surface keratinization and ankyloblepharon (Figure 98.2B).[5,8] Foster stages II and III are further classified into four subcategories (a-d) according to the degree of fornix shortening.[10]

FIGURE 98.3 OCP with (A) entropion and trichiasis and (B) ankyloblepharon.

FIGURE 98.4 Late-stage OCP with (A) corneal opacification and symblepharon and (B) complete obliteration of upper and lower fornices.

It is important to underscore the fact that OCP is still a systemic disease with frequent involvement of extraocular sites, like the oral mucosa (desquamatous gingivitis in 65% of patients), the skin (small vesiculobullous lesions in the extremities and/or the inguinal region, or flat erythematous plaques on the face or scalp in 4% to 15%), esophagus *(Print pagebreak 653)* (strictures and aspiration on swallowing, 26%), and larynx (intermittent hoarseness and dysphonia).[4,5] Less frequently involved sites include the vagina, urethra, and anus.[5] Conversely, 70% of patients with mucous membrane pemphigoid have ocular involvement (ocular MMP).[7]

Differential Diagnosis

Differentiating OCP from trachomatous entropion trichiasis (TT) may be challenging in areas endemic with trachoma, and even in nonendemic areas because of emigration. Although symblepharon and effacement of the plica may be encountered in OCP as well as TT,[11] symblephara or fornix shortening are earlier findings in OCP (Foster stages II or III),[5,8,10] while it is a very delayed manifestation of severe TT.[11] Although ankyloblepharon is a delayed feature of both OCP (Foster stage 4)[5,8] and TT, when encountered in patients with trachoma it is of a much milder variety. Another differentiating clinical point is that, although TT preferentially involves the upper eyelids, OCP does not show a peculiar affinity to involve either the upper or the lower eyelids. A positive conjunctival biopsy may also settle the diagnosis in favor of OCP, although a negative biopsy does not rule out the ongoing autoimmune process.

Several other peculiar conditions may be confused with OCP. Stevens Johnson syndrome (SJS), ocular rosacea, atopic keratoconjunctivitis, paraneoplastic pemphigus, and scleroderma however these conditions lack the characteristic progression of cicatrizationn that is so characteristic of OCP.[10,12] Several topical medications like pilocarpine, epinephrine, timolol, latanaoprost, and rarely systemic medications (eg, practolol [now withdrawn], Dupilumab, & penicillamine) can induce a pseudopemphighoid-like picture, which may be virtually indistinguishable from OCP both clinically or even with immunofluorescence.[4,10,12] A notable exception occurs in cases of unilateral application of the offending topical medication, where the disease is confined to the eye receiving the medication while the untreated eye remains normal.[10] In cases of bilateral use of topical medications, a subtle differentiating point is that the fibrotic changes are concentrated in the inferior fornix and medial canthi, areas that are more prone to damage because they come in maximal contact with the medication as it is cleared from the eye.[12] This process usually quiesces after discontinuation of the medication. The term pseudopemphigoid is loosely applied in the literature as an umbrella term for several conditions like SJS that simulate OCP, and recently, some authors have started to use the more specific term drug-induced cicatrizing conjunctivitis (DICC).[12]

Treatment

OCP is a systemic autoimmune disorder with evidence of immune activation. Topical medications will not suppress OCP activity effectively, and aggressive immunosuppression is required to suppress inflammation, promote healing, and prevent cicatrization regardless of whether surgery is contemplated in the near future or not.[10] Because most patients with OCP are diagnosed when they are already Foster stage III or even IV,[5] and because OCP is usually a disease of the elderly, and most importantly because of the cumulative toxicity of long-term immunosuppressants,[4,10] systemic immunotherapy is only offered to patients with active progressive disease, and not to patients with burnout end-stage disease where the prognosis is notoriously poor.[10] All patients with OCP should accurately be staged before initiating therapy, and this should include a formal assessment by an internist to rule out systemic disease.[10] Patients also need to be informed of the potential risks involved with each drug and to be reminded that immunosuppressive therapy can only arrest the disease process but will not reverse it.[10] A detailed review of systemic immunomodulating options are beyond the scope of this chapter, but the list of drugs includes high-dose oral corticosteroids, diaminodiphenylsulfone (Dapsone), mycophenolate mofetil (CellCept), methotrexate, cyclophosphamide (Cytoxan), Rituximab, or intravenous immunoglobulins.[4,10]

The optimal treatment for trichiasis manifesting in patients with OCP without frank entropion is the destruction of the cilia follicles responsible for the aberrant eyelash growth, with electrolysis, cryotherapy, or Argon laser.[10] This is essential in patients with OCP to prevent damage to the ocular surface epithelium. It could also help eliminate confusion about the exact cause of ocular redness, whether it is of a mechanical nature from the eyelashes or due to immunologic activation in OCP.[10]

The consensus is that rotational eyelid surgery to correct cicatricial entropion trichiasis is a key component in management to prevent potentially blinding corneal scarring.[3,6] Patients with active OCP requiring entropion surgery represent a special challenge, and surgery should be deferred if possible until disease activity is controlled.[5,8,13] However, if surgery is inevitable, it should be performed under an umbrella of profound immunosuppression.[10] A detailed discussion of the recommended procedures for cicatricial entropion in OCP is discussed in detail in Chapter 19, but tarsal sparing procedures, like anterior lamellar recession or reposition with or without a gray line split, may be the preferred approach in the majority of patients with OCP, since neither tissue resection nor a conjunctival incision is required.[13] In addition, techniques that involve a tarsotomy usually require a conjunctival incision. Conjunctival surgery should be avoided in OCP if possible, since this may trigger conjunctival inflammation or aggravate tarsal cicatrization, eventually resulting in surgical failure and disease activation. The management of symblepharon is usually challenging and should be undertaken only after proper systemic control of disease activity. Amniotic membrane transplantation, preferably coupled with intraoperative application of mitomycin C, may help achieve successful fornix reconstruction in patients with cicatrizing conjunctival diseases like OCP.[14,15]

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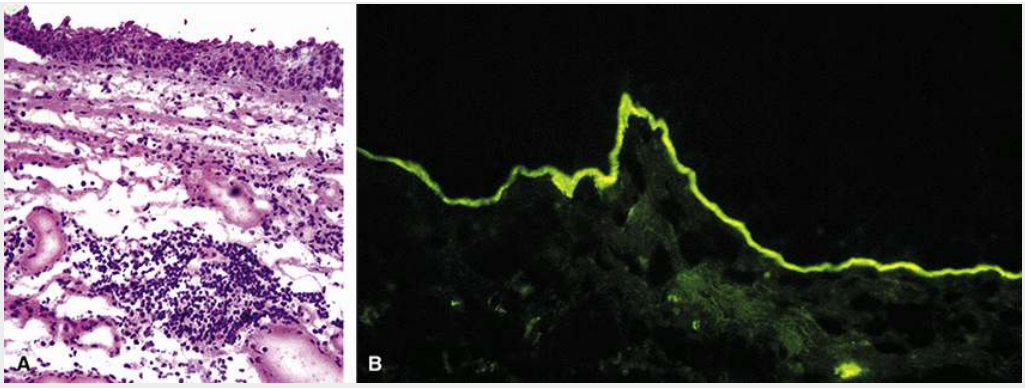

FIGURE 98.5 A, This conjunctival biopsy frozen section has normal epithelium, a mild diffuse infiltrate of lymphocytes and macrophages in the substantia propria, and focal perivascular accentuation of the mononuclear inflammation. B, The same biopsy had a continuous linear band of IgA deposited along the basement membrane zone.

Prognosis

Untreated OCP may eventually lead to chronic inflammation and conjunctival scarring, and possible blinding keratopathy. Ophthalmologists not comfortable with prescribing and monitoring the available immunomodulatory and biologic therapies should seek collaboration with appropriate specialists.

The success rates for the surgical correction of the cicatricial entropion and trichiasis seen in this disease generally are very good and parallel those for Steven-Johnson syndrome (see Chapter 117). For the systemic disease, data show only partial success and recurrence rates are high. Dapsone and methotrexate have been the first line of treatment in mild-to-moderate OCP, but adverse effects such as skin rash, malaise, vomiting and diarrhea, anemia, hepatotoxicity, and leukocytopenia have led to high rates of discontinuation of 30% to 100% in several trials.[16,17,18,19]

Mycophenolate mofetil has a lower rate of discontinuation, and the rate of inflammation control is reported at 58% to 70%.[20,21] Topical medications have not been found to reliably and consistently halt progression or induce remission of OCP, but they may assist in the treatment of conjunctival scarring.

Histopathology

Routine light microscopy of conjunctival biopsies usually reveals squamous metaplasia of the epithelium with loss of goblet cells,[5,22,23,24] although the number of residual goblet cells varies widely.[5] There is hyperproliferation of conjunctival epithelial cells,[24] with keratinization and parakeratosis in 25% and 75% of biopsies, respectively.[22] Subepithelial bullae are seldom observed in conjunctival biopsies.[4,25] The substantia propria is infiltrated by plasma cells, lymphocytes, and macrophages, along with fewer mast cells and occasional eosinophils and neutrophils.[5,22] The chronic inflammatory infiltrate may be diffuse or have a perivascular predominance (Figure 98.5A).[5] Patients with acute manifestations of OCP present clinically as diffuse conjunctival hyperemia with chemosis or a localized conjunctival mound with ulceration and intense hyperemia.[26] Biopsy of acute OCP shows a heavy infiltrate of neutrophils in the epithelium and substantia propria, along with the typical chronic inflammatory infiltrate.[26] Substantia propria scarring may be absent or present,[22,27] and there may be mild ectasia or proliferation of substantia propria capillaries.[4]

Light microscopic features are nonspecific; histological diagnosis rests on demonstrating by direct immunofluorescence the continuous linear deposition of immunoglobulin and often of complement component C3 along the basement membrane zone (BMZ).[4,5] IgA (Figure 98.5B) and IgG are the most frequent immunoglobulins deposited along the BMZ, although IgM, IgD, and IgE may also be detected, and there is often more than one immunoglobulin deposited.[5] The rate of positive biopsies varies widely in the literature from about 20% to 70%,[4] and a negative biopsy does not exclude the diagnosis of OCP.[7]

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CHAPTER 99

Oculodermal Melanocytosis

Key Points

- Oculodermal melanocytosis is a benign congenital anomalous pigmentation of deep facial skin and ocular tissues
- It is a dermal melanocytic hamartoma that presents with unilateral or bilateral, brown or blue discoloration on facial skin areas that are innervated by the ophthalmic and maxillary divisions of the trigeminal nerve
- It is 10 to 25 times more common among Asians than in Caucasian and black individuals
- The pathogenesis is not known but is considered to be a dermal hamartoma that represents a failure of migration of melanocytes from the neural crest to the dermal-epidermal junction and subsequent arrest within the dermis
- Lesions usually present as poorly defined separate or contiguous areas of pigmentation on the facial skin and nasal and oral mucosa, but in some patients only ocular involvement may be present
- In addition to eyelid skin, the sclera, conjunctiva, cornea, and lens can be involved as well as orbital tissues and bone
- Malignant degeneration is rare, but most cases occur in Caucasian patients
- Treatment includes surgical excision with skin grafting, cryosurgery, and dermabrasion, but Q-switched laser therapy has become the treatment of choice
- Laser therapy has significantly improved the prognosis with 80% to 90% of patients attaining a satisfactory cosmetic outcome
- Malignant change is seen in 4% to 5% of patients

Oculodermal melanocytosis (ODM), or nevus of Ota, is a benign congenital anomalous pigmentation of deep facial skin and ocular tissues. It was first described by Hulke in 1861[1] in a patient with unilateral pigmentation of the face and sclera. That case was complicated by the presence of an ipsilateral choroidal malignant melanoma. In 1939, Ota[2,3] described additional patients in Japan, defining the syndrome as a clinical entity. Since that time over 1000 cases have been described.

ODM is a dermal melanocytic hamartoma that presents with unilateral or bilateral, brown or blue discoloration on facial skin areas that are innervated by the ophthalmic and maxillary divisions of the trigeminal nerve.[4] Approximately 50% to 55% of cases involve both the ophthalmic and maxillary divisions, 25% the maxillary division alone, and 20% the ophthalmic division alone.[5] The occurrence of pigmentation in the distribution of the mandibular division of the trigeminal nerve is very rarely observed, with only one case described involving the buccal mucosa[6] and another case involving the oral mucosa and the jaw.[7] Several other cases of blue nevus have been described involving the buccal mucosa or oral floor,[8,9,10] and some authors have grouped ODM and blue nevus together as variants of dermal dendritic melanocytic proliferations.[11,12]

The incidence of oculodermal melanocytosis is difficult to assess since many mild cases go unrecognized or unreported. Yoshida[5] reported 110 cases among 27,082 consecutive clinic patients in Japan, an incidence of 4 per 1000 population (0.4%). Tanino[13] found 26 cases among 2300 dermatologic patients in Japan, for an incidence of 11 per 1000 (1.1%). Among a series of 8680 subjects in Shanghai, Wang et al[14] found acquired bilateral nevus-of-Ota-like macules in 2.5%. The only comparable figures for the United States are four affected patients among approximately 25,000 (0.016%) seen in the ophthalmology clinic at Philadelphia General Hospital.[15] Gonder et al[16] examined 13,150 white and black patients in an ophthalmology clinic and found an ODM incidence of 0.038% (2/5251) among white patients and 0.014% (1/6915) among black patients. Thus, oculodermal melanocytosis is at least 10 to 25 times more common among Asians than in Caucasian and black individuals.[4,17]

In 1939, Tanino[18] observed several patients with oculodermal melanocytosis and divided them into four types according to the extent of skin involvement, and these were further divided into seven subtypes based on their location.[17,19,20] These types were Ia,

eyelids, periorbital and temporal areas; Ib, zygomatic area, nasolabial fold, and the lower eyelid; Ic, forehead area; Id, nostril area; II, upper and lower eyelids, zygomatic area, cheek, temple area; III, scalp, forehead, eyebrow, and nose; and IV, bilateral.

However, other authors found that Tanino's classification failed to accurately include all affected patients. Huang et al[21] reported that 19.7% of their 1079 patients with oculodermal melanocytosis were not accommodated by the Tanino classification, and Nam et al[22] found an even higher rate at 35.8%. The Peking Union Medical College Hospital (PUMCH) classification is a newer system developed by a Chinese group in 2013 based on five large categories and 15 subdivisions according to the extent of involvement in the distribution of the trigeminal nerve branches.[21] These are I, pigmentation involving one branch of the trigeminal nerve; *(Print pagebreak 657)* II, pigmentation involving two branches of the trigeminal nerve; III, pigmentation involving all three branches of the trigeminal nerve; IV, bilateral type; and V, melanocytosis accompanied by other cutaneous complications. In 2017, Nam et al[22] introduced a three-point severity scale based on the proportion of the melanocytosis on the half-face as follows: mild, ≤one-third of the half-face; moderate, >one-third to ≤two-thirds; and severe, >two-thirds.

Several families have been reported in which some close relatives were affected with ODM. Hidano et al[23] found a father and son in one family and two sisters in another with the syndrome. Yoshida[5] reported a mother, her son, and his cousin, all similarly affected. Two families were noted by Watanabe,[24] one involving a mother and daughter, and in the other, two sisters. In the Hidano et al series of 240 patients,[23] 15 of 208 for which family histories were obtained, were related to each other, usually as first cousins. However, they could not recognize any definite pattern of hereditary, nor was there any consistent history of consanguinity. Goyal et al[25] reported a case of a brother and sister with bilateral familial nevus of Ota. Previous reports of familial cases suggest that inheritance may be autosomal recessive or autosomal dominant, with variable expressivity; however, definite hereditary patterns have not been established.[26,27,28,29]

Etiology and Pathogenesis

The pathogenesis of ODM is not known. It is usually considered to be a dermal hamartoma that represents a failure of migration of melanocytes from the neural crest to the dermal-epidermal junction and subsequent arrest within the dermis.[4] Melanocytic cells are not normally found in deep dermal layers of adult humans, and their presence in ODM suggests an embryonic anomaly. The etiology of melanoblasts is from neuroectoderm, either directly from neural crest precursors or from dermal Schwann cells.[30] In other anthropoid apes, such dermal melanocytes are normally seen in the adult,[30] and they can also be found beginning in the 11- to 12-week embryonic stage in humans.[31] Whether or not these dermal melanocytes gradually disappear or migrate up into the epidermis is not clear, but dermal melanocytes in adult humans are usually not present. They represent a developmental defect in which these cells persist abnormally and therefore represent an abnormal migration.[30,32] In this regard, it has been suggested that the pathogenesis of blue nevus, the Mongolian spot, and oculodermal melanocytosis are all related, if not identical.[30]

Because the incidence of ODM is so much greater in females, a hormonal relationship has been proposed for the development of pigment in previously nonpigmented cells.[33] Wang et al[14] reported that, among 196 females with ODM-like pigmentation, the prevalence of the disease increased after the age of 15 years and sharply declined after the age of 50 years, with nearly half of the cases observed within ages 45 to 55 years. Age, contraceptive use, and sun exposure were independently associated with the disorder. These findings suggested that sex hormone alteration and UV exposure may independently play important roles in the pathogenesis of ODM.

Histologically, ODM shows significant overlap with a blue nevus. Blue nevi show mutations in *GNAQ*, a GTPase acting downstream of G protein-coupled receptors.[34,35] This mutation has also been found in ODM, although at a lower frequency.[35] There is a clear relationship between ODM and uveal melanoma, and about 50% of uveal melanomas also harbor the *GNAQ* mutation, suggesting a link between these two conditions.[35] Although ODM is far more common in Asians, the risk of melanoma is mostly seen in white populations.[4] In Caucasian patients with ODM, the risk of developing uveal melanoma is approximately 20 times higher than seen in the general population. The development of cutaneous malignant melanoma in ODM is less frequent.

Clinical Presentation

ODM is characterized by dermal involvement of the face and ocular tissues, but in about one-third of patients, the eye is not involved.[36] In a series of 28 Chinese cases with ODM,[37] the most frequent areas involved were the eyelids (82%), forehead (79%), cheek (71%), and temporal regions (64%). In 96.4% of cases, more than three regions were involved, and ocular and nasal mucosal involvement was observed in 57%. Among Japanese with ODM, pigmentation of the eustachian tube and tympanic membrane may be seen in up to 55% of patients, the nasal mucosa in 24%, and the palate and pharynx in 18%.[23,38] Pigmentation may also occur in the underlying periosteum, bone, dura mater, cerebral cortex,[39] the maxillary sinus,[40] and the orbicularis and temporalis muscles. The condition is usually unilateral, and bilateral involvement is rare, seen in only approximately 5% to 13% of cases.[2,5,37,38]

Lesions of ODM usually present as areas of pigmentation on the facial skin and nasal and oral mucosa,[41] and in some patients only

ocular involvement may be present. The cutaneous lesions typically consist of macular, poorly defined, separate, or contiguous areas of hyperpigmentation that are not associated with increased vascularization or hair (Figure 99.1). There may be elevated nodules of denser pigmentation within it. Color varies from light brown to blue-black, to purple,[5] and may be so subtle as to be missed clinically.

ODM has been reported to occur in two peak age groups. In 48% to 61% of cases, it presents at birth or soon afterward in the perinatal period.[4,5,17,23] In a report on the occurrence of ODM in Korea, Lee et al[42] noted that 32% of the patients had lesions from birth, 18% from childhood, 25% from puberty, and 25% experienced onset in adulthood. It is not uncommon for such lesions to enlarge or darken under hormonal influences such as menstruation, pregnancy, or puberty.[5,23] ODM also occurs predominantly in females, which represent about 77% to 90% of all reported cases.[14,17,23,43]

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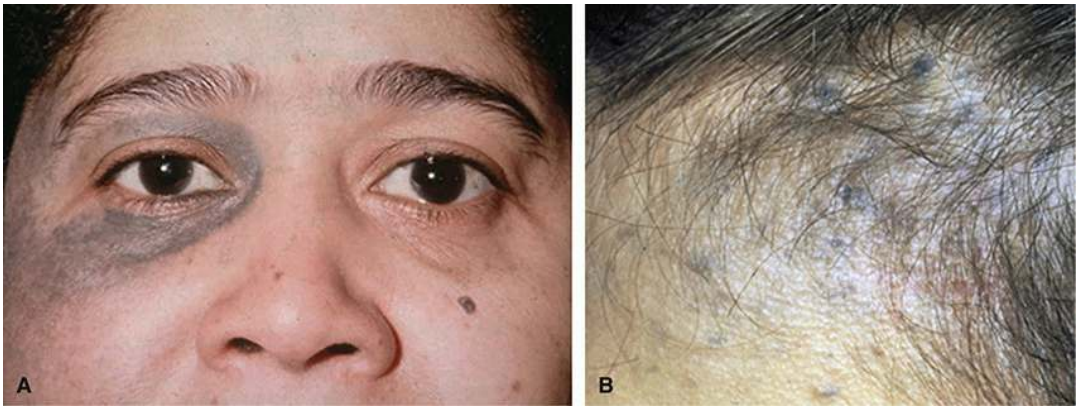

FIGURE 99.1 Cutaneous pigmentation in oculodermal melanocytosis. A, Pigmentation involving the periocular upper and lower eyelids. B, Scattered pigmentation on the forehead. This patient also had pigmentation of the choroid, orbital fat, orbital bones, and intracranial dura.

In the periocular region, ocular pigmentation is seen clinically in 49% to 65% of patients with this syndrome.[5,13,38] In addition to eyelid skin, the sclera is almost always involved with pigmentation,[15] typically appearing as discrete spots or diffuse blue-black pigmentation most commonly in the superior or temporal quadrants. The conjunctiva is involved in 40% of cases. Other ocular tissues that can be involved include the sclera, corneal epithelium, stroma or endothelium, and the anterior part of the lens (Figure 99.2).[36,44] The iris stroma shows pigmentation in about 50% of cases,[15] and in up to 18% the choroid is thickened and diffusely infiltrated with pigment cells.[15,45,46,47] These cells have been seen histologically to extend out of the globe along emissary veins.[47] The retina and optic nerve head are rarely involved, in 1% to 4% of cases.[48,49,50,51,52]

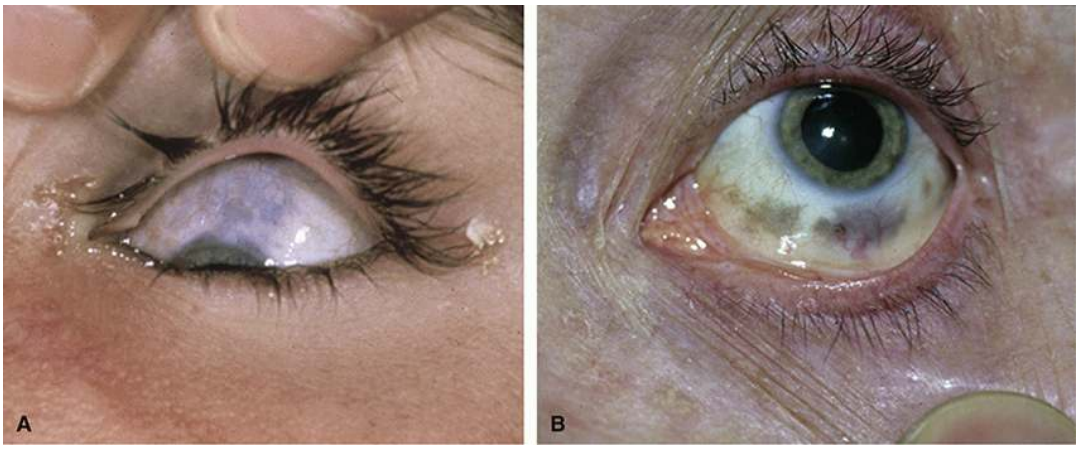

FIGURE 99.2 Ocular pigmentation with ODM. A, Conjunctiva. B, Sclera.

Melanocytes may also be seen in orbital fat, extraocular muscles, and in the orbital periosteum.[4,53,54,55,56] The actual incidence of orbital pigmentation is not known since these structures are not typically seen clinically. It becomes apparent only during orbital surgery if the ODM undergoes malignant transformation. Of the approximately 18 cases of orbital ODM described with abnormal pigmentation, 15 (83%) harbored a malenoma.

The most severe ocular complications associated with ODM are glaucoma and malignant melanoma.[44] The trabecular meshwork

and Schlemm canal are frequently involved, but frank secondary glaucoma has only occasionally been reported.[57,58,59,60,61] Increased intraocular pressure (IOP) may be seen with increased angle pigmentation and has been described with ODM in 10% to 15% of patients.[36] *(Print pagebreak 659)* However, frank glaucomatous change associated with ODM is very rare and most cases reported as glaucoma in ODM had pigmentation of the trabecular mesh but normal IOP and normal optic disk. Some authors have suggested that glaucoma, when it is seen, has not been demonstrated to be caused by ODM alone. Cronemberger et al[62] reported that there was no glaucoma in the eight eyes in which the gonioscopy revealed an intensively pigmented angle. Kitagawa et al[63] reported that ODM can cause abnormal thickening of the cornea causing a false elevation of measured IOP by tonometry.

A clear case of ODM-related glaucoma was reported by Magarasevic and Abazi[41] in a patient who developed progressive pigmentation of the trabecular mesh over several years, with increasing IOP, glaucomatous disk cupping, thinning of the nerve fiber layer, and a visual field defect. Several mechanisms for glaucoma in ODM have been proposed, including congenital glaucoma, acute angle-closure glaucoma, uveitis, and open-angle glaucoma. However, obstruction of aqueous outflow by accumulated melanocytes in an open angle is the most likely mechanism directly associated with the ODM.[60,64]

Malignant degeneration is a rare but potentially deadly complication of oculodermal melanocytosis. Dutton et al[4] recorded an incidence of 4.6% melanomas among 670 cases from the literature. Of the reported cases, only three (9.4%) occurred among Asian patients, even though this group accounted for 87% of oculodermal melanocytosis cases. Since then, approximately 86 additional cases of melanoma associated with ODM have been described, and of these, 78% were in white, 13% in black, and 9% in Asian patients. Adjusting for race, the incidence of malignancy is about 25% for whites, 1% for blacks, and 0.5% for Asians, confirming that melanoma associated with ODM is far more common in white patients and is very rare in Asian and black individuals.[4,33] Although ODM usually appears in early childhood or adolescence, cases associated with melanoma are typically in the fifth to seventh decades, with a mean age of 60 years, and men and women are equally represented.

The most common sites for malignant degeneration in ODM are the choroid (42%), orbit (18%), brain and meninges (12%), and skin (9%).[4] In several large series of choroidal melanoma, ODM was associated in 2.7% of 400 cases reported by Carreño et al[65] and in 3.0% of 7872 cases reported by Shields et al.[32] Unal et al[48] reported a case of ODM-associated melanoma of the optic nerve head and Font et al[59] described a case of melanoma involving the pigmented iris. Malignant melanoma of the brain and meningeal tissues has been noted in only a few patients,[66,67,68,69] one of which involved the pineal gland. Kojima et al[70] found a case of melanoma arising within the optic chiasm in a 37-year-old man in which melanocytosis was present in the meninges, cerebral cortex, and optic nerve.

Melanomas associated with ODM are typically of the spindle cell type, with very few having an epithelioid component.[71,72,73] Several cases of melanoma have occurred in patients with bilateral involvement.[46,66,71,74]

Differential Diagnosis

The differential diagnoses of ODM consists of a very wide variety of pigmented and vascular lesions. Such lesions include facial cafe-au-lait patches, speckled lentiginous spilus nevus, blue nevus and its variants, Mongolian spots, melanocytic nevi, congenital and acquired melanosis, dermal melanocytic hamartoma, melanoderma from B12 deficiency, and ceruloderma from chronic amiodarone usage.

Treatment

A variety of treatments have been introduced for ODM, including surgical excision with skin grafting, cryosurgery, and dermabrasion. However, in recent decades, laser technology, based on the concept of photothermolysis, has been advocated and is currently the treatment of choice.[75,76,77,78]

Q-switched lasers were introduced in 1992 and have resulted in better outcomes and less scarring than previous laser technologies.[79] The 694-nm Q-switched ruby laser (QSR) was the first applied to ODM but has largely been replaced by the 755-nm Q-switched alexandrite laser and the 1064-nm Q-switched Nd:YAG laser, which has dramatically increased the success rate and decreased the complication rate.[77] Most reports of ODM treatment with the Q-switched alexandrite and Nd:YAG lasers have shown high success rates of 71% to 97%, with low complication rates of 0% to 6.4%.[78,80,81] Permanent hypopigmentation is the most commonly reported complication of Q-switched lasers in the treatment of ODM.[82,83]

Prognosis

The pigmentation in ODM is mostly of cosmetic concern, and the use of Q-switched lasers has significantly improved the prognosis, and early treatment is associated with better results.[81] About 80% to 90% of patients can attain a satisfactory cosmetic outcome. Of greater concern is malignant change seen in 4% to 5% of patients with ODM, 93% of which are in Caucasians. Most of these involve the choroid, and patients with uveal melanoma in the setting of ODM vs no ODM show a higher rate of metastasis (48% vs 24%) and a greater mortality rate (19% vs 12%) at 10 years.[32]

Histopathology

Ito reported cutaneous histological findings from 24 patients with ODM.[5] Heavily pigmented melanocytes were most common in the upper reticular dermis, next in the middle dermis, and least often in the lower reticular dermis and subcutaneous adipose tissue (Figure 99.3). Melanocytes in the upper dermis were fusiform or stellate shaped, while cells lower in the dermis were predominantly long string- or fiber-like cells. The melanocytes' long axes were usually oriented parallel to the skin surface, but they were oriented vertically or obliquely around small blood vessels, sweat glands, sweat *(Print pagebreak 660)* ducts, sebaceous glands, and adipose tissue. The melanocytes were dispersed in the dermis, but some connected with each other through tapered cytoplasmic tips. Dermal melanocytes only occasionally formed small bundles similar to those in a blue nevus. Melanin granules in the dermal melanocytes were coarser than those in the overlying epidermis, and a large amount of cytoplasmic melanin often obscured nuclei. The epidermis was usually normal, although there were sometimes patches of hyper- and hypopigmentation limited to several epidermal ridges. Other authors have reported similar histological findings in ODM.[15,61,84,85]

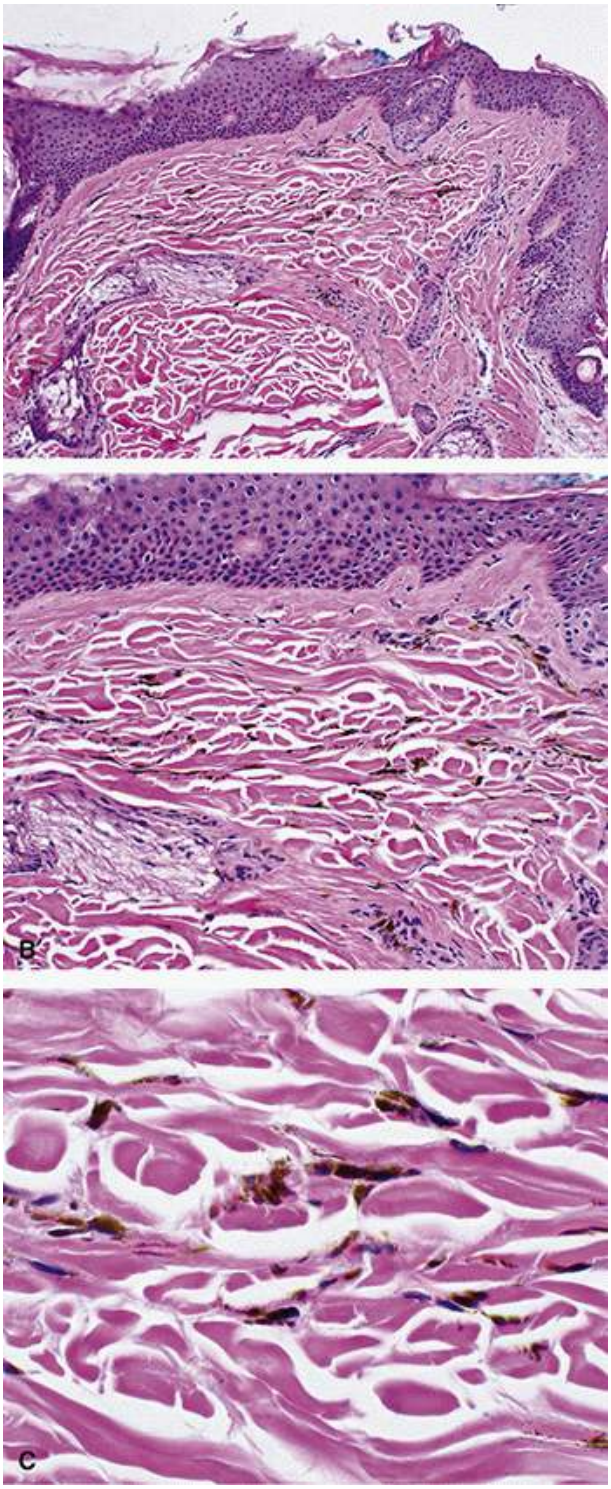

FIGURE 99.3 A, Heavily pigmented melanocytes are in the upper and mid-dermis in ODM. B, The melanocytes are spindle shaped and oriented parallel to the skin surface except around epidermal appendages. C, High magnification to show the characteristic abundant melanin within the spindle-shaped melanocytes. The dispersed melanocytes are separated by intervening collagen bundles. The dispersion of melanocytes distinguishes ODM from a blue nevus.

More recently, Hirayama and Suzuki correlated clinical appearance with histological findings in at least 3 biopsies from 40 patients with nevus of Ota.[86] They classified lesions into five histological subtypes: (1) superficial type (S) with melanocytes located in the superficial dermis, (2) deep type (De) having melanocytes in the deep dermis, (3) diffuse type (Di) with melanocytes dispersed throughout the dermis, (4) superficial dominant type (SD) with a diffuse distribution of melanocytes with a greater concentration of melanocytes in the superficial dermis, and (5) deep dominant (DD) type with a greater concentration of melanocytes in the deep dermis.[86] The ratio of the S, SD, Di, DD, and De types was approximately 3:2:3:1:1. Lesions that were brown clinically were the superficial or superficial dominant types, while bluer lesions were the diffuse, deep dominant, and deep histological types. The diffuse, deep dominant, and deep subtypes were more frequent on the eyelids, temple, and forehead, and the superficial and superficial dominant types were more common on the cheeks.

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CHAPTER 100

Pemphigus Vulgaris

Key Points

- Pemphigus vulgaris (PV) is an autoimmune disease in which autoantibodies are directed against desmosomal adhesion molecules resulting in blistering in the suprabasal layers of the cutaneous epidermis and mucosa
- Triggers of the immune response include drugs, viral infections, contact allergens, physical agents, and foods
- The etiology remains unknown, but associations have been reported with major histocompatibility complex class II antigens
- Involved mucosal surfaces include oral, pharyngeal, esophageal, and nasal bullae
- Ocular PV presents with eyelid skin erythema, erosions and ulcerated blisters, as well as bilateral hyperemic conjunctivitis, often associated with pain, stinging, irritation, pruritus, photophobia, and epiphora
- Initial management includes identification and removal of specific triggers, followed by corticosteroid therapy to reduce the inflammatory reaction
- Where conjunctival cicatrization is evident, early debridement should be performed to minimize symblepharon formation
- PV can be associated with sepsis, fluid and electrolyte imbalances, impaired thermoregulation, and cardiac and renal failure, but with systemic, corticosteroid, and immunosuppressive therapies, the mortality rate has been reduced to approximately 10%

Pemphigus is a life-threatening autoimmune disease in which autoantibodies are directed against desmosomal adhesion molecules resulting in blistering in the suprabasal layers of the cutaneous epidermis and mucosa.[1,2,3,4] The disease is classified as pemphigus vulgaris or foliaceus depending upon the histologic layer of blistering, and as paraneoplastic pemphigus.

Paraneoplastic pemphigus, mostly presenting as pemphigus vulgaris (PV) with severe mucosal involvement,[5] is often associated with lymphoproliferative neoplasms and carcinomas of the colon, lung, breast, pancreas, prostate, uterus, liver, and kidney.[5,6,7,8,9,10] It may be related to an altered immunologic state and immunologic cross-reactivity between the tumor and the skin.[2,5] Paraneoplastic pemphigus is characterized by painful erosions and ulcerations affecting the mucous membranes of the oropharynx, tongue, lips, and conjunctiva.[6,11,12] Skin lesions vary in appearance from blisters to lichenoid-like[2] and are seen most often on the head, neck, upper trunk, and proximal extremities.

Induced or triggered pemphigus is a condition in which an exogenous factor induces the onset of the disease.[2] Triggers can include drugs, viral infections, contact allergens, physical agents, and foods.[13] Viral infections, especially herpes virus infections, have been linked to pemphigus, and herpes virus DNA has been detected in lesions of some patients with PV.[2,14] Dietary factors have been implicated as triggers for pemphigus in genetically predisposed individuals, including thiol-allyl compounds present in garlic, leeks, and onions; and polyphenolic compounds present in black pepper, red chili pepper, cherry, cranberry, blackberry, red wine, and tea.[2,13] Physical agents, such as thermal burns, ultraviolet radiation, and surgical procedures have also been shown to trigger pemphigus in genetically predisposed individuals.[13,15,16,17] Contact allergens such as pesticides of the organophosphate group can serve as potential triggers.[13] Drugs capable of inducing pemphigus include non-thiol angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, calcium channel blockers, and some vaccines and interferons.[2]

PV accounts for approximately 80% of all types of pemphigus and is the most common form. It occurs more frequently in individuals of Mediterranean and Jewish descent[3,18,19] and is seen most often in the fourth or fifth decades of life. Some reports have shown a slight predilection for females at about 66%,[20,21] whereas others have shown no gender predominance.[22] The incidence of PV varies from 1 to 16 new cases per million persons per year.[23,24]

PV is typically seen in previously normal skin as a blister caused by the separation of the superficial epidermal layers from its basal layer.[2] In nearly half of cases, the oral mucosa is initially involved, but later, lesions spread to involve the skin and other mucous membranes including the pharynx, esophagus, conjunctiva, urethra, cervix, and rectum.[19,22,25,26] Bacterial infection can be seen following the sloughing of the fragile blister walls.[27,28] The disease is characterized by repeated exacerbations, fluid and protein loss, and opportunistic infections,[2] and even with treatment, these can lead to death in 10% of cases.[3,13]

Ocular PV is uncommon but well-known.[4,19,29,30,31,32,33,34,35,36,37,38,39,40,41,42] It is reported to occur in approximately 7% to 26% of pemphigus cases,[19,22,43] but ocular findings are unpredictable and their presence does not correlate with the general severity *(Print pagebreak 664)* of the disease.[2,3,4,19] Ocular involvement involves the conjunctiva in most cases (88%), the eyelid skin or margin in 67% of cases,[22] and may be unilateral or bilateral. It usually presents as chronic blepharitis and conjunctivitis,[4,19,29,42,43] associated with conjunctival injection, foreign body sensation, photophobia, dry eye, and epiphora. Inflammation, blisters, and eyelid margin mucosal papillomas can be seen.[29,30,44,45] Conjunctival bullae can be seen, but are unusual.[46] PV can rarely present with a distinct conjunctival inflammatory mass without associated typical findings such as conjunctivitis, mucous discharge, blisters, or erosions.[47] Other rare findings include cicatricial contraction of the eyelid skin or conjunctiva,[2] cobblestone-like conjunctival papillae,[48] sicca keratoconjunctivitis, eyelid ectropion or entropion, and trichiasis.[2,3,42,49,50,51]

While eye involvement has been reported as an early manifestation of PV,[4,37] most patients develop the ocular lesions 1 to 3 years after the diagnosis of PV.[19,22]

Etiology and Pathogenesis

The etiology of pemphigus remains unknown. Multiple associations have been reported and the majority of genetic studies have shown an association between PV and major histocompatibility complex class II antigens such as HLA-DR4 or HLA-DQ1.[2,52,53,54,55] The HLA class II subtypes DRB1*0402 and DQB1*0503 have been recognized in more than 95% of patients with PV.[56] Even with these genetic findings, pemphigus has been reported in only one of two monozygotic twins and only two of three siblings with identical predisposing haplotype.[2] This suggests that environmental factors may also be required for initiation of the disease and for directing its clinical course.[13]

Patients with PV have IgG1 and IgG4 antibodies against mucocutaneous desmoglein 1 and/or the exclusive mucosal desmoglein 3.[57,58,59,60,61] Desmoglein 1 and 3 are transmembrane proteins that provide the desmosome of the epidermis with the function of cell adhesion.[13,62] As a result, the blisters seen in PV result from the loss of keratinocyte and conjunctival epithelial cell cohesion.[1,14]

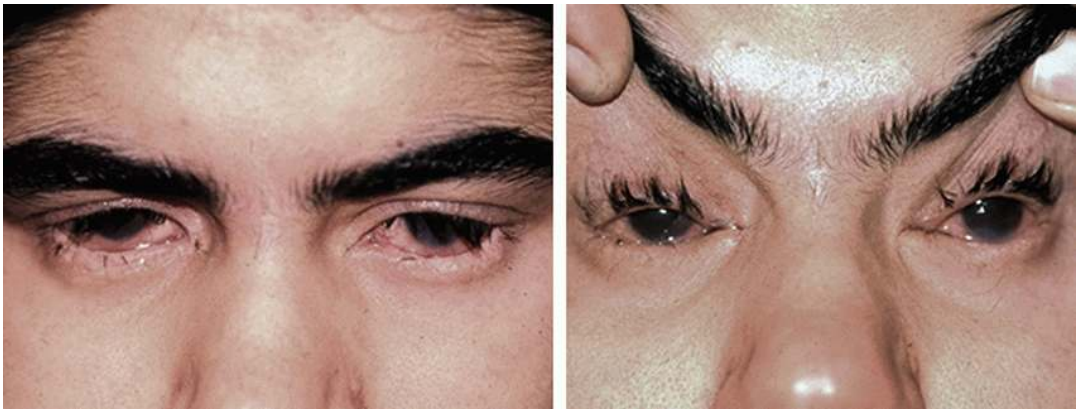

FIGURE 100.1 Bilateral hyperemic conjunctivitis in a case of pemphigus vulgaris. (Courtesy of Dr. Mohsen Kashkouli.)

Pemphigus, especially PV, has been associated with other autoimmune diseases such as myasthenia gravis, systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, pernicious anemia, scleroderma, and thyroiditis,[5,13,63,64,65,66,67,68] and with other autoimmune blistering diseases including mucous membrane pemphigoid, herpetiform dermatitis, psoriasis vulgaris, and erythema multiforme.[5,68,69] The mechanisms and significance underlying these associations are unknown.

Clinical Characteristics

The diagnosis of PV is based on a combination of clinical presentation and detection of tissue-bound and/or circulating autoantibodies. The disease usually runs a chronic relapsing course. The most common clinical finding in ocular PV is bilateral hyperemic conjunctivitis observed in 87.5% of cases (Figure 100.1).[22] Conjunctival injection can be bilateral and seen on the

palpebral or bulbar conjunctiva. Subconjunctival hemorrhage and canaliculitis are seen only rarely. Additional symptoms are pain and stinging in 71.4%, irritation and pruritus in 47.6%, photophobia in 38.1%, and epiphora in 23.9% of cases.[22] Other involved mucosal surfaces include oral, pharyngeal, esophageal, and nasal bullae, often with scales, crusts, and ulcerations. The eyelid skin is involved in about 41% of patients with ocular PV and shows erythema and madarosis, with erosions and ulcerated blisters (Figure 100.2). Eyelid skin erosions are seen both on the upper or lower eyelids and in the medial canthus in about 21% of cases.[22]

Differential Diagnosis

The differential diagnosis of PV should include other autoimmune blistering diseases, such as mucous membrane pemphigoid, bullous pemphigoid, IgA-mediated bullous dermatoses, and epidermolysis bullosa, as well as impetigo, infectious, and *(Print pagebreak 665)* inflammatory diseases. For oral lesions, the differential should also include herpetic stomatitis, aphthous ulcers, lichen planus, paraneoplastic pemphigus, erythema multiforme, lupus erythematosus, and dermatitis herpetiformis.[2,5]

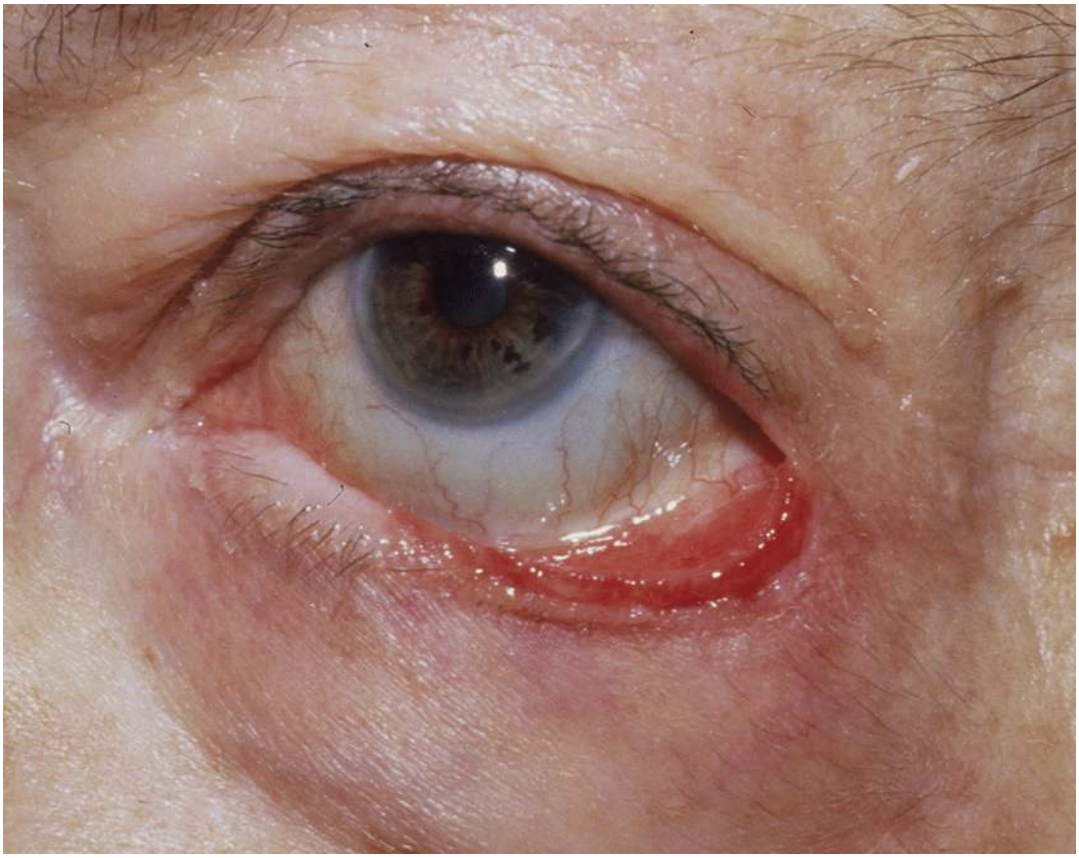

FIGURE 100.2 Pemphigus vulgaris with erosion of the eyelid margin and madarosis. (Courtesy of Dr. Gordon Klintworth.)

Treatment

In cases of PV initiated by specific triggers, identification and removal of the triggering agent is an important first step. Corticosteroid therapy is the first-line therapy for PV to reduce the inflammatory reaction,[3,11,13,19,29,70,71,72] supplemented with immunosuppressive agents, such as azathioprine and mycophenolate mofetil, for more refractory cases. Most patients respond well to these agents.[19] However, in a Danish study of 19 patients treated with prednisolone and azathioprine, the recurrence rate was 50% over a mean time of 15 weeks.[73] Intravenous immunoglobulins neutralize and slow down the production of circulating pemphigus antibodies. They are considered adjuvant therapy for pemphigus.

In cases where conjunctival cicatrization is evident, early debridement should be performed to minimize symblepharon formation.[74] A bandage contact lens may be necessary to limit corneal damage. Trichiasis and entropion are managed surgically.[3]

Biological agents such as rituximab may be helpful in cases where corticosteroids and immunosuppressive agents are not effective. In one study, rituximab plus a short course of prednisone resulted in a greater than threefold higher rate of complete

remission off prednisone therapy, and a greater than twofold decrease in the rate of moderate and severe relapse compared with standard-dose prednisone alone.[75]

For eyelid and conjunctival involvement with symptoms of severe dry eyes, artificial tears are used and punctual plugs may be helpful. Topical antibiotics can help prevent infections.[3] Conjunctival and mucosal lesions often resolve with systemic immunosuppressive therapy, but topical corticosteroids[36,76] and subconjunctival triamcinolone injection[36] can be used as adjunctive measures for eyelid erosions and conjunctival blisters. To minimize steroid use, success has been reported with topical cyclosporine.[46] Successful treatment with topical tacrolimus along with systemic immunosuppressive drugs has also been reported.[76]

Eyelid scrubs and warm compresses are used to improve eyelid margin hygiene,[3] and topical antibiotics may be included as a local treatment to prevent further bacterial infections.[77] In mild cases, topical corticosteroids plus oral tetracycline or minocycline in addition to conventional treatments may be beneficial.[13,70] In recent years, there has been a paradigm shift in the treatment of recalcitrant ocular surface diseases (OSD) including PV from the classic sequential, step-up topical therapy outlined above where synergistic therapies are sequentially added, to a combined approach where combinatorial topical therapy is given from the start.[71] This "triple play" therapy consists of (1) topical anti-inflammatory/immunosuppressive (steroid) eyedrops, (2) with immunomodulatory (pooled human immune globulin) eyedrops, and (3) tear substitute (serum) eyedrops. Preliminary results suggest this combined approach simultaneously targets several immunological pathways may be more efficacious than the standard approach.[71]

Any surgical procedure on the eyelid or conjunctiva during active disease can exacerbate the inflammatory process, so that whenever possible surgery should be deferred until the disease is inactive.[3,78,79] For trichiasis associated with PV, epilation of the eyelashes provides short-term relief. More permanent results are achieved with cryotherapy, laser ablation, or electrolysis (see Chapter 42). For eyelid malpositions including ectropion, entropion, and lagophthalmos, there are several different procedures available depending on the amount of skin and conjunctival scarring (see Chapters 16, 17, 18, 19 and 20).[80] Cicatricial lagophthalmos from symblephara and fornix shortening is managed surgically, often requiring autologous conjunctival transplantation, mucous membrane grafts, or amniotic membrane grafts.[81,82]

Ocular lubrication and antibiotic ointments should be used for corneal abrasions that may lead to infectious keratitis, ulceration, and even perforation. Where skin or conjunctival scarring results in significant lagophthalmos, a lateral tarsorrhaphy may be necessary to protect the corneal surface.

Prognosis

PV can be associated with multiple life-threatening complications such as sepsis, fluid and electrolyte imbalances, impaired thermoregulation, as well as cardiac and renal failure.[12] Without treatment, PV has a mortality rate ranging from 60% to 90%.[83] With adequate systemic treatment with corticosteroids and adjuvant immunosuppressive therapies, the mortality rate has been reduced to approximately 10%.[83] In a series of 24 patients with ocular PV, España et al[22] reported a complete clinical response to systemic treatment in 91.3% of cases, without complications on follow-up. In patients who do respond to systemic immunosuppression, blisters and erosions usually heal without significant seque *(Print pagebreak 666)* lae.[22,71,84] However, the use of high-dose corticosteroids and adjuvant steroid-sparing immunosuppressive agents do carry a risk of serious adverse events, especially infections.

Histopathology

The earliest histological change in PV, detectable before a clinical lesion appears, is intercellular edema in the lower stratum spinosum and stratum basale.[85] The basal cells become vertically elongated and narrowed, sometimes resulting in a spindle shape.[85] Clefts between the basal cells and the overlying prickle cells form next due to keratinocyte dissociation (acantholysis; Figure 100.3A).[85,86] Cleft formation results in basal cells returning to their normal shape.[85] The intercellular bridges between basal cells may rupture, leading to the lateral separation of cells and the appearance of a row of tombstones or a picket fence at the vesicle base.[86] As the cleft enlarges, individual epidermal cells lie individually or as small clumps in the clefts.[85,86] Fluid accumulation expands the clefts to form bullae whose base may be the single layer of basal cells or more than one layer of cells, especially near the middle of the bullae.[85,86] Bullae may rarely be in the mid epidermis.[85] At the periphery, bullae often taper into a suprabasal cleft, causing the edge to have an acute angle (Figure 100.3B). Approximately 50% of biopsies have bullae containing only acantholytic cells; 25% have acantholytic cells, neutrophils, and eosinophils; and 20% have acantholytic cells and neutrophils.[87] Acantholysis extends into hair follicles in one-third of biopsies, with hair follicles and sebaceous glands involved in about 15% of biopsies.[87] The bullae base may be gently undulating or have irregular upward growth of papillae lined by a single layer of epidermal cells.[85] As the bullae

age, the prickle and granular cells forming the roof degenerate until shedding as desiccated, thinned, and parakeratotic scale.[86] Epidermal regeneration begins in the bulla floor's central area, may begin before the roof ruptures or is shed, and may be uneven.[86]

Dermal inflammation is absent before bulla forming.[85] At the time of bulla formation, there is usually a mild to moderately intense inflammatory infiltrate around superficial dermal blood vessels, often containing numerous eosinophils[85] though there may be only lymphocytes or lymphocytes and neutrophils.[87] Older lesions with ruptured bullae and erosions may have more severe dermal inflammation, but eosinophils are usually few or absent.[85]

A diagnosis of PV relies on a typical light microscopic appearance and intercellular staining for immunoglobulin G (IgG) and/or C3 by direct immunofluorescence (DIF) using fluorescein-labeled antibodies.[88,89,90,91] Positive DIF staining for IgG creates a reticular pattern often termed “fishnet,” “net-like,” or “chicken-wire.” Other methods for confirming a PV diagnosis include indirect immunofluorescence staining using patient serum applied to monkey esophagus sections or an enzyme-linked immunosorbent assay (ELISA) to detect antibodies to desmoglein 3 and sometimes desmoglein 1.[90] Rare patients may have a negative DIF stain for immunoglobulins and C3 with positive indirect immunofluorescence staining for desmoglein 3.[87]

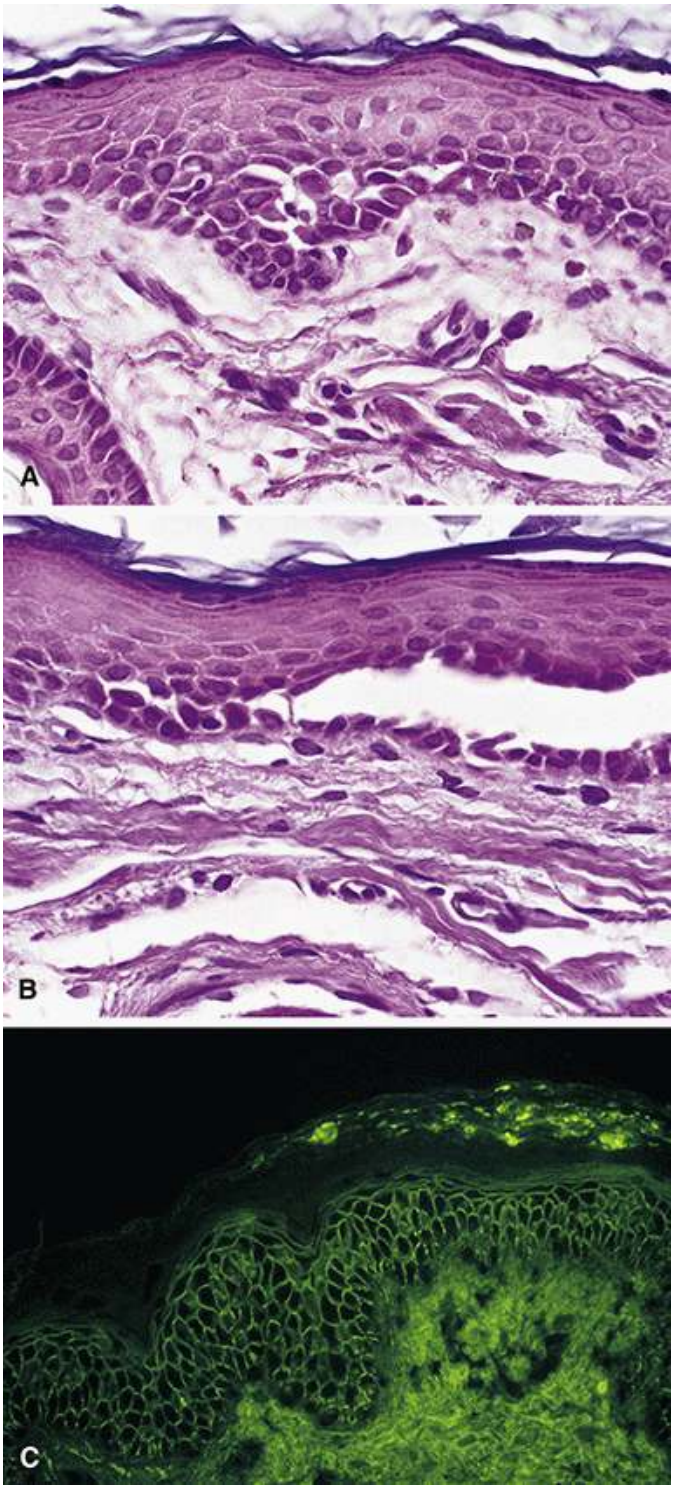

FIGURE 100.3 This biopsy from the left lower eyelid is from the patient shown in Figure 100.2. A, There is acantholysis with cleft formation between the basal cells and the overlying prickle cells. B, A suprabasal bulla with tapering at the periphery causing the edge to have an acute angle. C, Direct immunofluorescence demonstrating IgG in the intercellular regions of the epidermis.

The histological and DIF appearances of eyelid lesions in PV are similar to those in other body sites.[19] DIF staining of conjunctival biopsies has the typical intercellular staining pattern for IgG deposition.[19,30]

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CHAPTER 101

Phakomatous Choristoma

Key Points

- Phakomatous choristoma is a very rare congenital lesion
- It is believed to arise early in the embryogenesis of the eye during the optic vesicle stage as tumor cells migrate toward the region of the embryonic choroidal fissure
- Elements that eventually form the phakomatous choristoma may have been left behind in the mesenchymal tissue
- Clinically, phakomatous choristoma presents as a smooth, firm, painless, generally immobile, palpable subcutaneous mass in the inferonasal eyelid
- Surgical excision is the initial treatment of choice to rule out alternative diagnoses
- The prognosis is excellent, and recurrences have not been reported

Phakomatous choristoma (PC), sometimes referred to as "Zimmerman tumor," is a very rare congenital lesion, first described by Zimmerman in 1971.[1] Since then fewer than 30 cases have been added to the literature.[2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25]

PC generally is present at birth, but in some cases, it may not become obvious until several weeks or months later.[14,15,16,21,25] Although published cases are few, some studies reported a male predominance of about 2:[1,14,25] whereas others report no apparent sex or ethnic predilection.[16,22] The tumor occurs equally on the left and right sides, and all reported cases have been unilateral. Although phakomatous choristoma is usually an isolated abnormality, association with other congenital ocular abnormalities has been reported, including hypoplasia of the optic nerve and coloboma.[20]

Etiology and Pathogenesis

When first described, Zimmerman postulated a lenticular anlage origin for PC based on the similarity of the microscopic appearance of the epithelial components to cataractous lenses, the presence of a thick basement membrane, and the absence of mucin and sebum secretions.[1] Since then, this histogenetic origin has been confirmed in several electron microscopic and immunohistochemical studies.[4,6,7,8,10,11] It is thought that PC arises early in the embryogenesis of the eye during the optic vesicle stage as tumor cells migrate toward the region of the embryonic choroidal fissure.[6]

Because this tumor occurs primarily in the lower eyelid, Peres et al[12] argued that PC must already have been present and growing at the time the eyelids are formed during embryogenesis. However, Seregaard[14] noted that the lens is formed through a depression of the lens pit from the surface ectoderm between the 5- and 9-mm embryonic stages and that the lens vesicle remains connected to the surface by a thin stalk. After the disappearance of this stalk, the lens vesicle closes and is surrounded by the lens capsule.[26] He argued that the elements that eventually form the phakomatous choristoma have to be left behind in the mesenchymal tissue before the 9-mm stage ends.[14] Since the buds that eventually become the eyelids do not arise until after the 10-mm stage,[27] and the bony walls of the orbit also develop after the 9-mm stage, deposition of the phakomatous elements that will form the tumor must occur before either the eyelid or orbit are anatomically defined. This supports the idea that these phakomatous elements are left behind in undifferentiated mesenchymal tissue that only later will give rise to the eyelids and orbit.

Several other hypotheses have been proposed for the origin of PC. These include aberrant migration of lenticular cells toward the embryonic choroidal fissure during the optic vesicle stage in early embryogenesis, invagination of surface ectoderm into the mesoderm of the eyelid, and proliferation of native ectodermal cells that are present in the subcutaneous tissue of the inferior medial eyelid.[4,6,8,10,15,16,23]

Clinical Characteristics

Clinically, phakomatous choristoma presents as a smooth, firm, painless, palpable subcutaneous mass in the inferonasal eyelid (Figure 101.1). It is generally immobile, but with free moveable normal-appearing overlying skin. The tumor usually ranges from 10 to 17 mm in diameter.[18] Lesions may remain unchanged in size, but slow enlargement may be seen in about 50% of cases.[14] The eye is usually normal, but larger lesions can be associated with an anisometropic refractive error.

Although most cases of PC are situated inferomedially in the lower eyelid, cases have been reported in the anterior medial orbit.[9,12,14,28] When located in the orbit the globe may be slightly laterally displaced.[22] Rarely, PC may involve the inferior rectus or inferior oblique muscles.[1,3] Adulkar et al[29] described a single case of PC occurring within the corneal stroma in a 6-month-old boy. Verb et al[22] reported a case of *(Print pagebreak 670)* PC in the medial lower eyelid presenting with a nasolacrimal duct obstruction from external compression of the NLD.

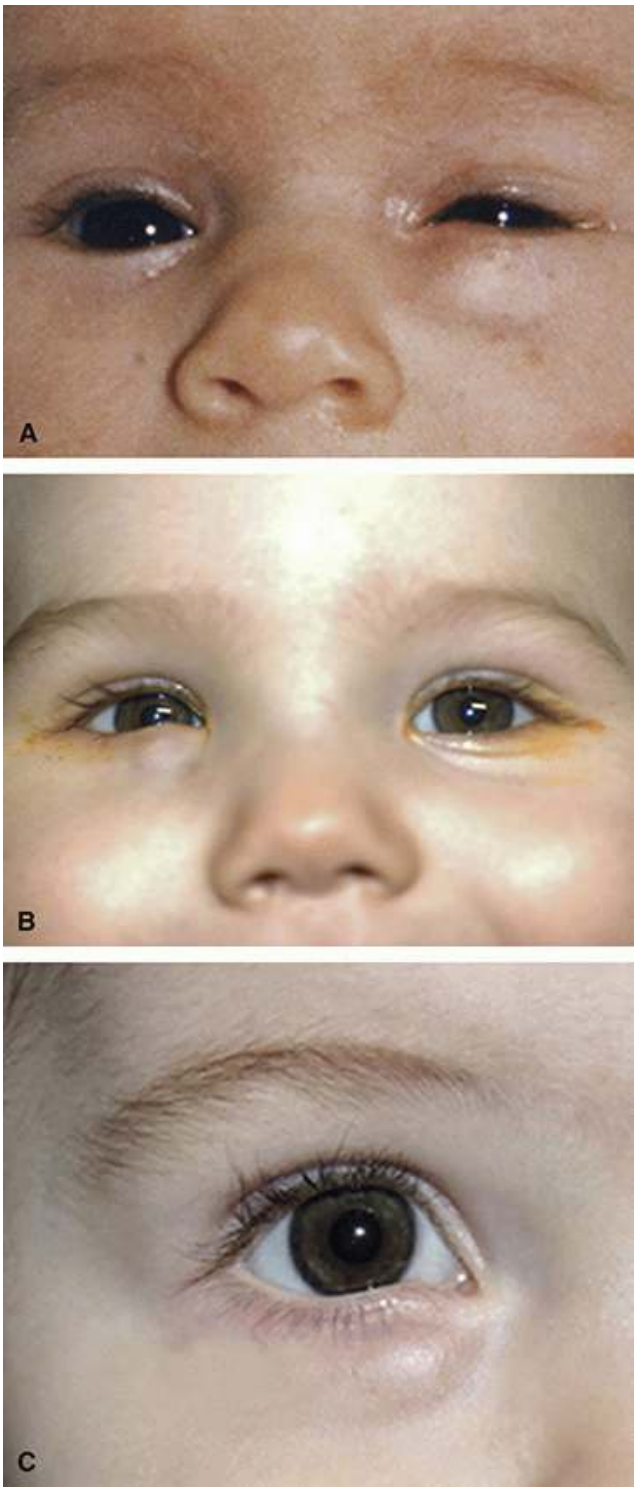

FIGURE 101.1 Phakomatous choristoma. (A, Courtesy of Dr. Stefan Seregaard. C, Reprinted with permission from Harris BF, Harris JP, Ducey PJ, et al. Phakomatous choristoma of the orbit with involvement of the inferior oblique muscle. *Ophthalmic Plast Reconstr Surg*. 2019;35:e9-e12.)

On computed tomography, PCs appear as well-circumscribed, discrete homogeneous mildly enhancing solid lesions without fat or calcification and not associated with any bony erosion.[9,11,12,13,14,22] On MRI, they have been reported to be well defined and mildly enhancing.[23,24]

Differential Diagnosis

Phakomatous choristoma is almost always clinically unsuspected and initially misdiagnosed. The most common clinical diagnosis is a dermoid cyst.[1,15,17,18,23] However, a dermoid cyst is situated superolaterally in 75% of cases, is often associated with bony erosion, is usually fluctuant, and on imaging frequently contains fat and a fluid level. Phakomatous choristoma, on the other hand, never has a fat content and is always located in an inferomedial location.

Other lesions in the differential diagnosis should include chalazion, dacryocele, dacryocystitis, infantile hemangioma, juvenile xanthogranuloma, lymphatic malformation, and ocular adnexal oncocytoma.[8,16,23] Dacryoceles generally present as a medial canthal mass below the medial canthal tendon, usually have a slight bluish discoloration,[22] and often resolve with probing and irrigation.[30] A chalazion occurs anywhere on the upper and lower eyelid, is usually fluctuant, and is often associated with blepharitis. Ocular adnexal oncocytoma is a benign tumor that occurs most commonly in the medial canthus of elderly patients, has a female predominance, and presents as a slowly growing red to tan mass.

The young age of patients with PC and the presence of a palpable mass often raise concern for malignant lesions, most importantly rhabdomyosarcoma. On MRI, malignant tumors often show heterogeneous signal intensities on T1-and T2-weighted images caused by areas of necrosis, which is not seen in PC. Also, rhabdomyosarcoma and associated cervical metastatic lymph nodes show variable heterogeneous enhancement.[31]

Treatment

Because PC is so rare and the diagnosis is not usually suspected on patient presentation, surgical excision is universally accepted as the initial treatment of choice to rule out alternative diagnoses like a dermoid cyst, dacryocele, and especially rhabdomyosarcoma and other malignancies. Complete surgical excision, preferably through a transconjunctival approach, is curative of this lesion,[3] and surgical excision is also warranted for the correction of any associated anisometropia and astigmatism. Following surgical excision, even if incomplete, no recurrence has ever been reported in the literature.[3]

Intraoperatively these lesions are often found to be adherent to adjacent structures such as the inferior tarsus, orbital septum, conjunctiva, and lateral lacrimal sac fascia,[2,16] making it more difficult to completely remove surgically.

Prognosis

In all available reported cases of phakomatous choristoma, treatment by surgical excision has been successful. There are no reports of recurrence even after incomplete surgical excision.

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Histopathology

The histological features of phakomatous choristoma of the eyelid and orbit remain unchanged since the seminal description of this lesion by Lorenz E. Zimmerman in 1971.[1] Within dense collagenous tissue are nests and irregular islands of polygonal epithelial cells having lightly eosinophilic cytoplasm and round to oval nuclei without nucleoli (Figures 101.2 and 101.3). The nests and islands of epithelial cells are surrounded by basement membrane material that stains positively with periodic acid-Schiff reagent (PAS stain), and thick strands of PAS-positive material often accumulate between cells. Swollen epithelial cells may resemble "bladder cells" ("Wedl cells") occurring in cataractous crystalline lenses, and brightly eosinophilic material resembling cataractous lens fibers forms pools within the epithelial islands. Dystrophic calcification[1,14,19] and psammoma bodies[6] may be present.

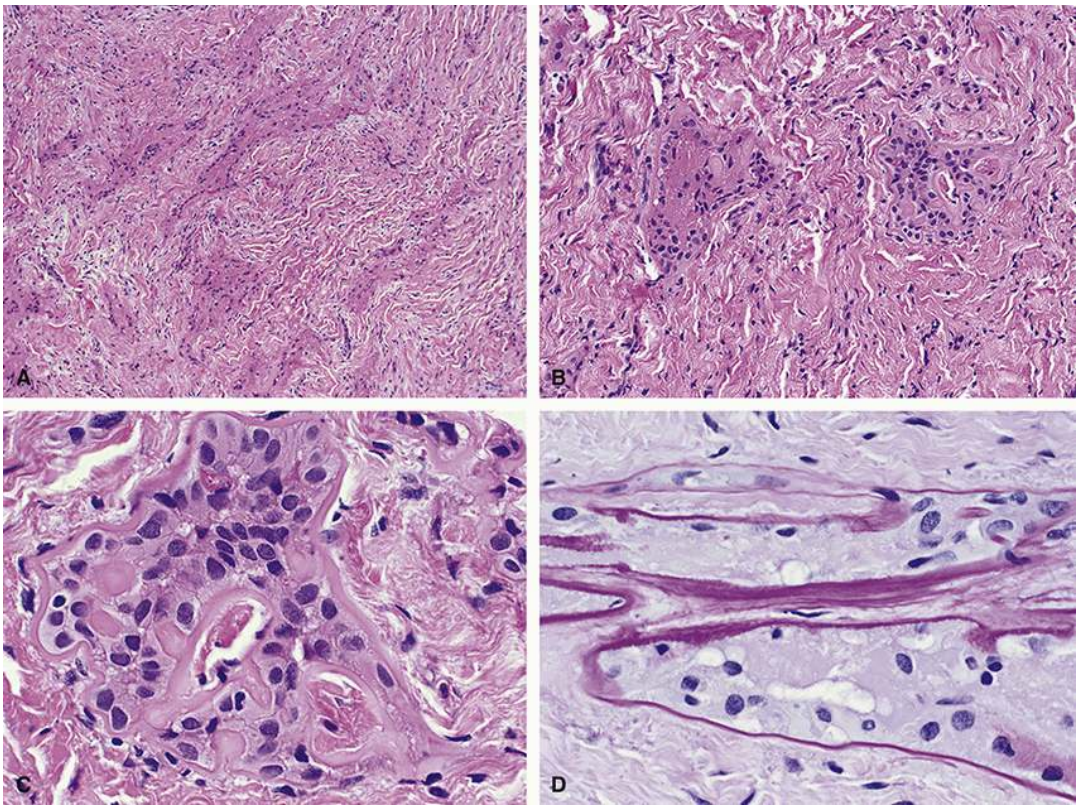

FIGURE 101.2 This phakomatous choristoma of the medial right lower eyelid of a baby boy was present from birth and excised at 3 months. A, Irregularly shaped islands of eosinophilic tumor cells are within dense collagenous tissue. B, The island of epithelial cells on the left surrounds a central zone of eosinophilic material, while the island on the right has entrapped basement membrane surrounding two small cysts. C, Higher magnification of the island on the right in (B) showing hyaline basement membrane surrounding two small cysts containing eosinophilic material with cells having pyknotic nuclei. D, Periodic acid-Schiff stain highlights a thick layer of basement membrane around the epithelial islands.

Immunohistochemical stains are not necessary for diagnosis due to the distinctive morphology by routine staining, and immunohistochemical studies have yielded variable results. Typically, the epithelial cells express S100 protein,[7,10,11,12,13,14,15,17,18] although staining may be focal and weak.[16] Epithelial cells are usually positive[10,11,12,13,14,15,16,17,18] but may rarely be negative[7] for immunoreactivity using antibodies to vimentin. Most studies have found no expression of cytokeratins by the epithelial cells, although one case had focal positivity using AE1/AE3 antibodies.[10] Neuron-specific enolase may[12,13,15] or may not[7] be expressed, while immunostaining for glial fibrillary acidic protein is either negative[13,21] or focally positive.[22] Immunoreactivity for crystallins supports a lenticular origin.[11,13]

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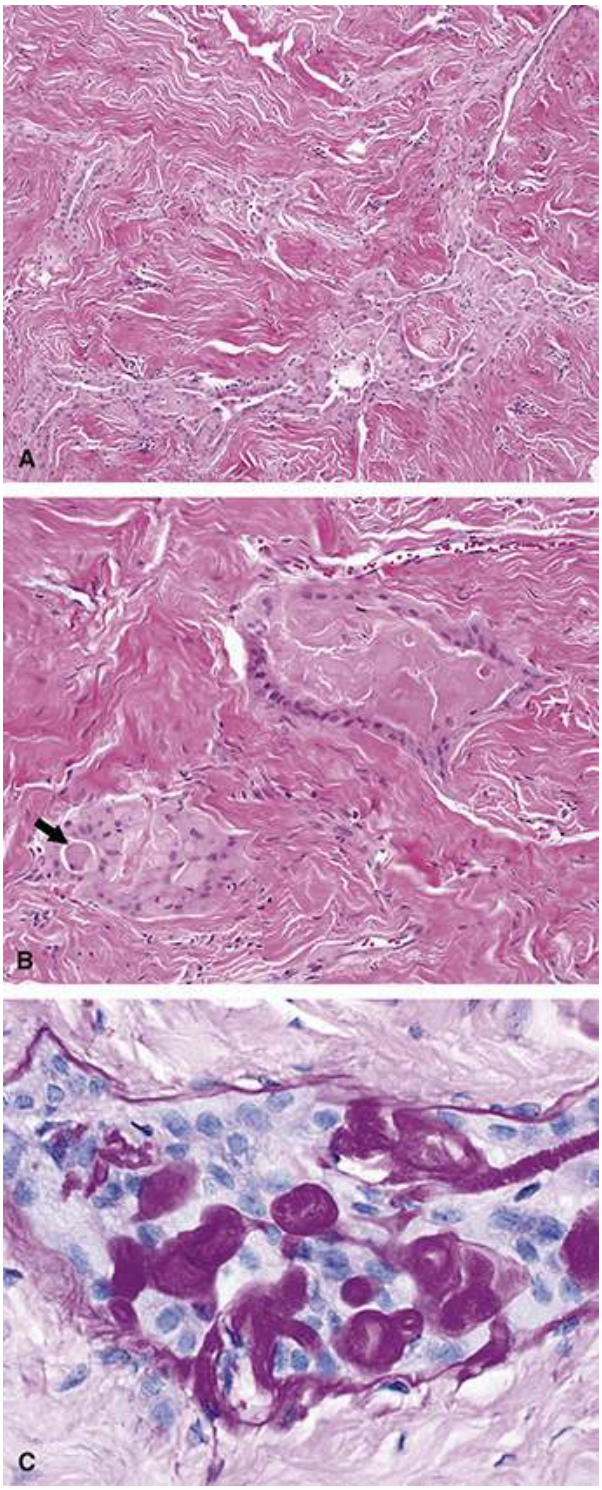

FIGURE 101.3 This phakomatous choristoma, present since birth, was removed from the preseptal medial right orbit at age 13 months due to anisometropia and eyelid deformity. A, Irregularly shaped, palely eosinophilic islands of epithelial cells are within dense, brightly eosinophilic collagenous tissue. B, Epithelial cells surround acellular eosinophilic material at the top right, while the island at the lower left has a bladder (Wedl) cell (arrow). C, Periodic acid-Schiff stain demonstrates thick ribbons of basement membrane among epithelial cells.

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CHAPTER 102

Pilomatrixoma

Key Points

- Pilomatrixoma is a benign tumor of the hair follicle
- It occurs in any hair-bearing areas of the body, most often in the skin of the head and neck
- The pathogenesis remains unknown, but it has been suggested that pilomatrixoma may develop from sequestered epidermal elements into abnormal locations during embryonic development or that it may arise from ectodermal tissue from the hair matrix
- Clinically, periorbital pilomatrixomas present as slow-growing, solitary, asymptomatic, well-circumscribed, hard, mobile cutaneous masses
- The treatment of choice is complete surgical resection, and malignant transformation is very rare
- The prognosis is generally excellent following surgical resection, and recurrences are unusual

Pilomatrixoma, also known as pilomatricoma and calcifying epithelioma of Malherbe, is a benign tumor of the hair follicle. It was initially described by Malherbe and Chenantois in 1880 as a "calcified epithelioma," believed to derive from the sebaceous gland.[1] In 1949, Lever and Griesemer[2] suggested an origin from the hair matrix cells.

Pilomatrixoma can occur in any hair-bearing area of the body, although it occurs most often in the skin of the head and neck.[3,4] In the periorbital skin it arises from the matrix cells at the base of the eyelids and the eyebrows.[5] Although it can be seen in patients from infancy to old age, it is far more common in the first 2 decades of life. Sixty percent of cases arise before the age of 10 years,[6,7,8] and 75% occur in patients 20 years or younger.[9] Some studies have reported little or no gender difference,[10,11] but most have demonstrated a clear female predominance,[12,13,14,15] with a female to male ratio of 2:1 to 3:1.[9,16,17] The most common site of occurrence is the head and neck (51.8%), followed by lesions on the extremities (37.7%) and trunk (10.5%)[7,18] and other rare sites such as the middle ear.[19] Malignant transformation is rare but has been described, with metastasis to regional lymph nodes, the lung, brain, bones, and visceral organs.[9,20,21] Familial cases have also been observed,[18,20,22] sometimes in association with systemic syndromes. Lesions are typically single, and multiple pilomatrixomas are rare.[23,24,25] When multiple lesions are seen it should raise suspicion for related systemic disorders such as myotonic dystrophy,[26] Churg-Strauss syndrome,[27] Gardner syndrome,[28] trisomy 9,[29] Rubinstein-Taybi syndrome,[30] xeroderma pigmentosum,[31] and sarcoidosis.[32]

Periocular pilomatrixoma is uncommon, but many cases have been described.[1,5,30,33,34,35,36,37,38,39,40,41] In a series of 16 periocular cases, the mean age of patients at treatment was 17 years (range, 1-74 years),[16] and there was a clear female predominance.

Etiology and Pathogenesis

The exact pathogenesis of pilomatrixoma remains unknown. Some authors have suggested that pilomatrixoma may develop from sequestered epidermal elements into abnormal locations during embryonic development.[19,42] Lever and Griesemer[2] considered pilomatrixoma to be a hamartoma, and Dubreuilh and Cazenave[43] proposed pilomatrixomas arise from ectodermal tissue consistent with their origin from the hair matrix.

Several studies have demonstrated mutations in the Wnt signaling pathway and altered protooncogene expression in basophilic and shadow cells.[38,44] Other studies have demonstrated mutations in the *CTNNB1* gene (3q22), which encodes beta-catenin,[45] a downstream effector in the Wnt signaling pathway that affects multiple cellular processes, including cell differentiation into the hair follicle and cell proliferation.[44] Mutations of this gene result in an upregulation of intracytoplasmic and intranuclear beta-catenin leading to the development of neoplasms of hair matrix differentiation.[11,44] Associations between pilomatrixoma and several

genetic diseases, such as Gardner syndrome, Rubinstein-Taybi syndrome, Sotos syndrome, myotonic dystrophy, and Turner syndrome suggest abnormalities in other cell signaling pathways as well.[11,26,46]

Clinical Characteristics

Clinically, periorbital pilomatrixomas present as slow-growing, solitary, asymptomatic, well-circumscribed, hard, mobile cutaneous masses (Figure 102.1).[12,13,14,15,47] They can be multiple in up to 4% of cases.[18,25,48] The overlying skin may be normal or show a red to blue coloration,[7,16] and rarely, there may be areas of surface ulceration (Figure 102.2).[49,50,51] Lesions can range from 4 mm to 2.5 cm. Occasionally, lesions can show rapid growth after surgical trauma.[52] About 65% involve the eyebrow (Figure 102.3), 28% the upper eyelid, 5% the lower eyelid, *(Print pagebreak 675)* and 1.5% the medial canthus.[16] About one-third show some calcification, and 1% are ossified.[53,54]

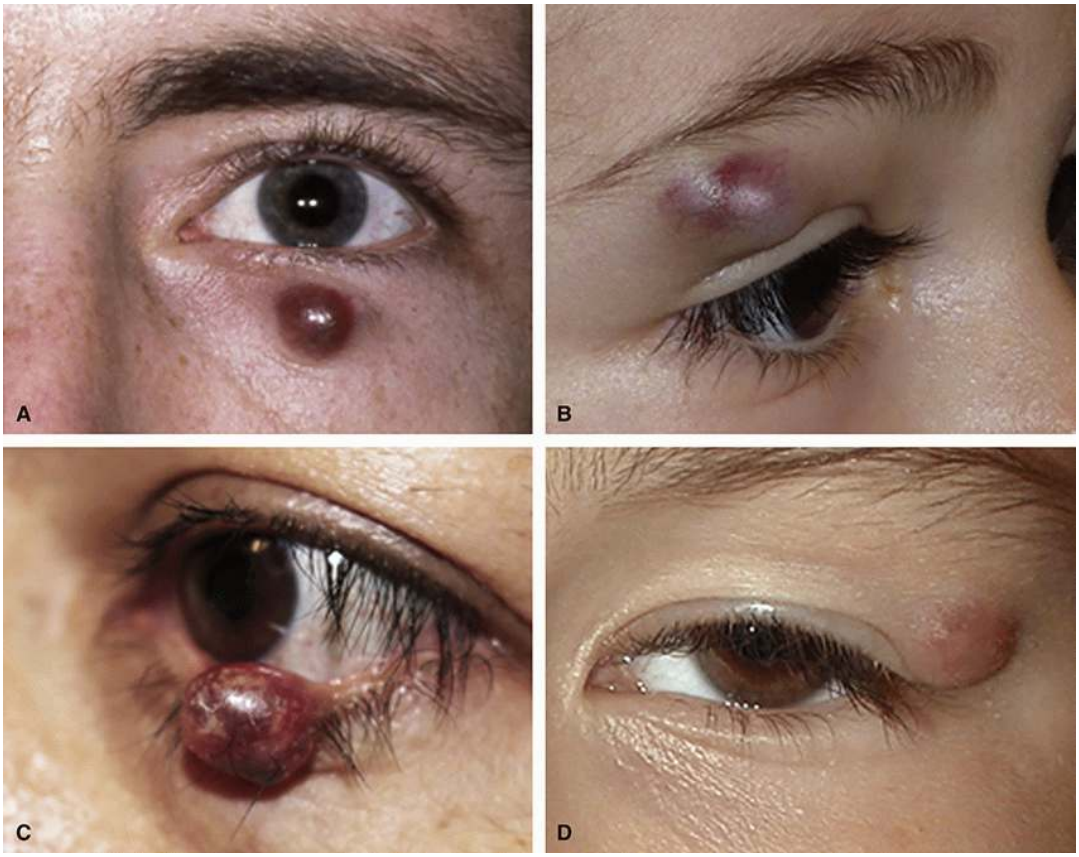

FIGURE 102.1 A-D, Solitary pilomatrixoma of the eyelids. A, (Courtesy of Dr. Charles Soparkar.) B, (Courtesy of Dr. Alan McNab.) C, (Courtesy of Dr. Nahyoung Grace Lee). D, (Courtesy of Dr. Peter Rubin.)

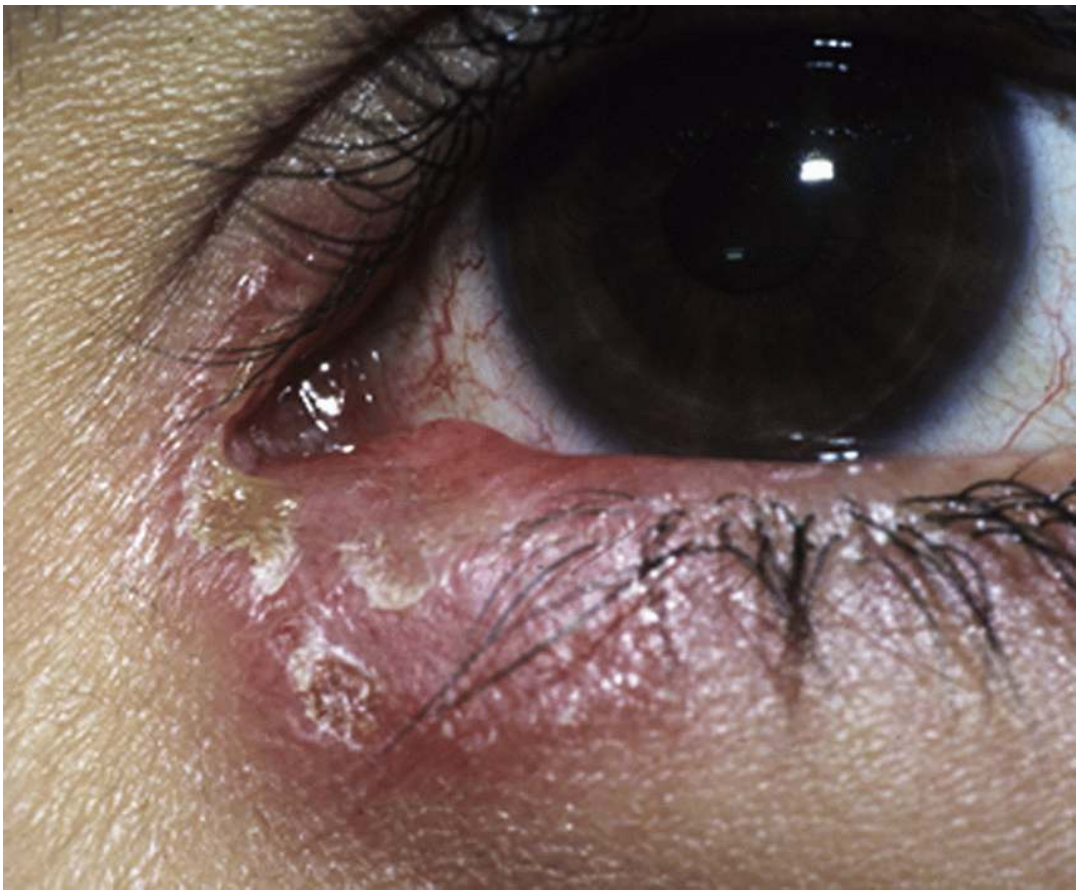

FIGURE 102.2 Pilomatrixoma of the medial lower eyelid with crusting and areas of superficial ulceration.

Differential Diagnosis

The clinical characteristics of pilomatrixoma are nonspecific and are similar to many other cutaneous lesions so that the diagnosis is usually not suspected until the tissue is examined by histopathology.[15,55,56,57] The correct diagnosis of periorbital lesions is made clinically in only 12% to 23% of cases.[16,38] The differential diagnosis includes chalazion, dermoid cyst, epidermoid cyst, trichoepithelioma, basal cell carcinoma, keratoacanthoma, papilloma, and abscess.[36,38,58,59]

Treatment

The treatment of choice for pilomatrixoma is complete surgical resection.[8,9,20,24,56,57] Recurrences and malignant transformations following surgical excision have been described *(Print pagebreak 676)* but are very rare.[23,36,38,55,60] Incomplete resection is usually followed by local recurrence.[6,20,24] In a large review, among 1797 patients with pilomatrixoma who were followed for 1 month to 7 years after surgical resection, 27 (1.5%) had recurrence at the site of excision.[11]

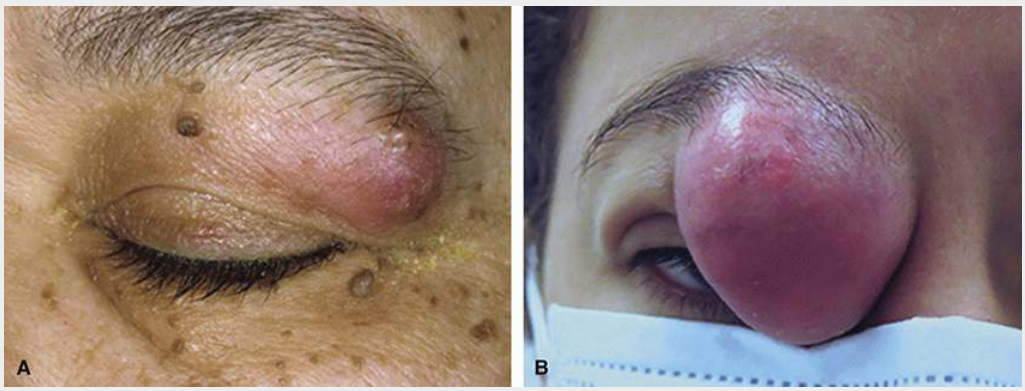

FIGURE 102.3 A and B, Pilomatrixoma of the lateral brow. B, (Courtesy of Dr. Robert Kersten.)

Prognosis

The prognosis for pilomatrixoma is generally excellent following surgical resection, and recurrences are unusual. Malignant transformation is very rare, seen more frequently in middle-aged to elderly males (76%).[12,61,62,63] The relationship between pilomatrix carcinoma and benign pilomatrixomas is incompletely understood,[61] but the histologic association between these two lesions raises the possibility the pilomatrix carcinoma arises from malignant degeneration of its benign counterpart.[61,64,65,66] In a review of 123 cases of pilomatrix carcinoma from the literature, the recurrence rate following excision was high (23%-83% depending on the extent of surgery). Metastasis occurred in 13% and the mortality rate was 7%.[61]

Histopathology

Pilomatrixoma histopathology is well described,[2,67,68,69,70] with the most thorough description being that of Forbis and Helwig.[48] Tumors are round or oval, well-circumscribed masses occurring in the dermis or dermis/subcutaneous tissue or confined to the subcutis.[48,71] Pilomatrixomas are partially or wholly surrounded by compressed collagenous connective tissue, creating the appearance of a capsule.[2,48,68] The tumors are composed of islands of basophilic cells and eosinophilic shadow (ghost) cells separated by connective tissue,[2,48,68] although basophilic cells are not identifiable in up to 45% of lesions.[48] Basophilic cells are small with hyperchromatic basophilic nuclei, a small nucleolus, scant palely eosinophilic cytoplasm, indistinct or inapparent cell borders, and moderate to abundant mitoses.[2,48] Eosinophilic shadow cells represent mummified basophilic cells and have pale pink cytoplasm, often a central unstained shadow where the nucleus was located, and distinct, although faint, cell borders.[2] Shadow cells contain melanin in 8% of pilomatrixomas.[48] Basophilic cells may form a band around masses of shadow cells or form variably sized and shaped clusters (Figure 102.4A and B).[2]

Forbis and Helwig described four fates for the basophilic cells. There may be an abrupt transition from basophilic cells to eosinophilic shadow cells, or there may be an intermediate zone of six to eight layers of transitional cells that develop progressively more eosinophilic cytoplasm while the nucleus becomes pyknotic and loses its basophilia (Figure 102.4C). The second fate is for the basophilic cells to form hyalinized shadow cells with translucent, glassy, eosinophilic material having unidentifiable cell boundaries. The third scenario is for basophilic cells to transition to squamoid cells with increased lightly eosinophilic or clear cytoplasm, occasional cells with keratohyalin granules, an enlarged nucleus with a prominent nucleolus, distinct cell boundaries, and rare intercellular bridges. Squamoid cells usually form small groups and may have associated keratin or parakeratin. The fourth fate for basophilic cells is to degenerate into amorphous debris "accompanied by hemorrhage, occasional shadow cells, and shreds of keratin."[48] A recent study showed that shadow cell differentiation from basophilic cells is a caspase-independent form of programmed cell death.[72]

Calcification is seen in from two-thirds[2] to 84%[48] of tumors. The calcification may appear as a dusting of basophilic particles or solid purple masses and tends to occur in the center of the shadow cell groups.[48] Ossification, most often at the periphery of calcified masses,[48] occurs in about 3%[13] to 21%[48] of tumors. Boniuk and Zimmerman observed ossification in 4 of 40 eyelid and eyebrow pilomatrixomas,[73] and it may occasionally be a striking feature of the tumor.[74] *(Print pagebreak 677)* Foreign-body giant cells occur in the stroma of 50%[13] to 100%[2] of tumors, usually along the edges of the shadow cell fields (Figure 102.4D).[2] The stroma between islands may feature hemosiderin in about 20% of cases.[48]

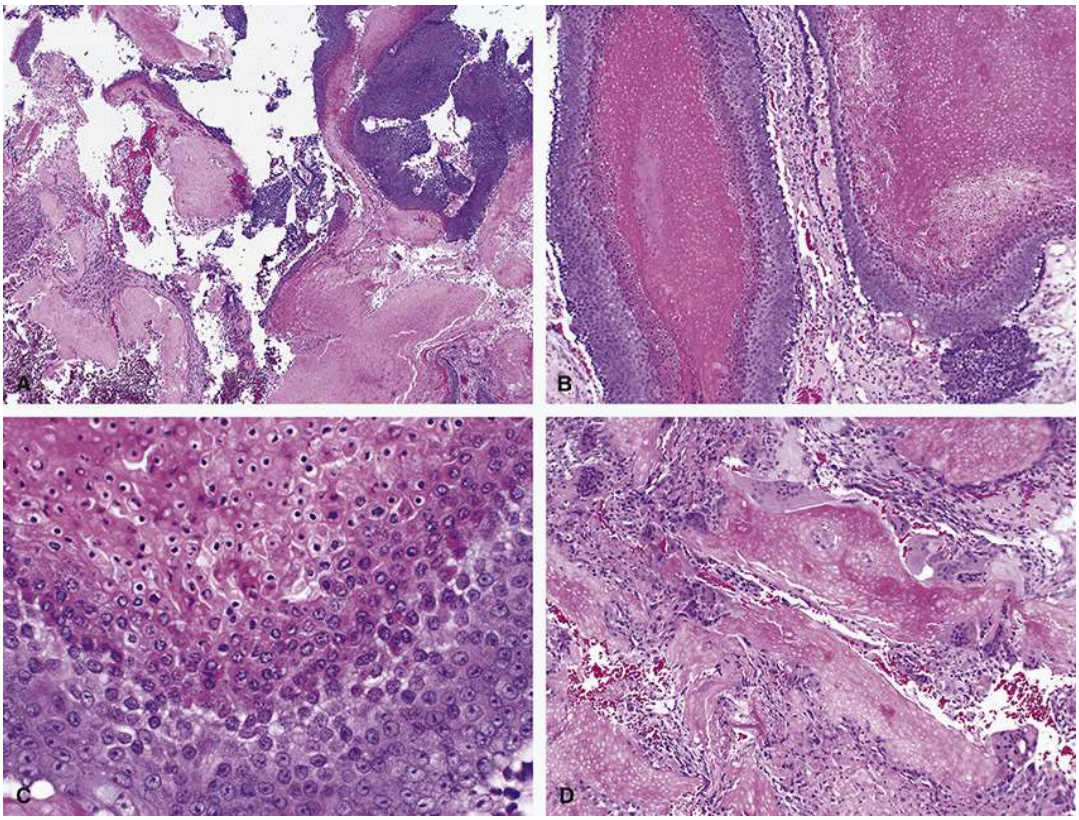

FIGURE 102.4 This pilomatrixoma developed in the left medial eyebrow of a middle-aged man. It arose over 3 months and was firm, mobile, and erythematous. The tumor fragmented during removal. A, At low magnification, the pilomatrixoma has a mixture of basophilic cells and eosinophilic shadow cells. B, Basophilic cells surround eosinophilic shadow cells. Both islands of tumor cells have an intermediate zone of transitional cells between the basophilic cells and the shadow cells. C, Transitional zone cells have progressively more eosinophilic cytoplasm and increasingly pyknotic nuclei as they move toward the center of the islands and become shadow cells. D, Pilomatrixomas often have foreign-body multinucleated giant cells, most often around the areas of shadow cells.

The variable histological appearance of pilomatrixomas led Kaddu and colleagues to postulate that pilomatrixomas evolve through four morphological stages.[70] They deem early lesions to be small cysts lined by squamoid and basaloid epithelium surrounding keratin filaments and shadow cells.[70] Large neoplasms with peripheral basophilic cells and central irregularly shaped zones of cornified masses containing shadow cells are considered fully developed lesions.[70] Early regressive lesions lack an epithelial lining but have peripheral basophilic cells foci and shadow cells surrounded by granulation tissue with multinucleated giant cells.[70] Late regressive pilomatrixomas are solid; lack basophilic and squamoid cells; have shadow cells with varying degrees of calcification, ossification, and giant cell reaction; and are embedded in thickened, hyalinized, and sclerotic collagen bundles.[70]

Pilomatrixomas in people >45 years of age resemble those in individuals <45 years of age, although atypical features may occur in patients >45 years of age.[69] Atypical features include a larger proportion of basophilic cells, with cells having cytological atypia manifest as increased variability in cell size, shape, and staining; increased mitoses with a few abnormal mitotic figures; variability in nuclear/cytoplasmic ratios; and hyperchromatic nuclei.[69] Malignant pilomatrixomas (pilomatrix carcinomas) are rare.[75,76,77] Malignant pilomatrixomas are often larger; have infiltrating borders with fascial or skeletal muscle invasion, basophilic cell predominance, nuclear pleomorphism, prominent eosinophilic nucleoli, high mitotic activity, abnormal mitotic figures, and areas of confluent necrosis; and may exhibit vascular, lymphatic, and perineural invasion.[76] Periocular pilomatrixomas resemble those at other body sites.[67,73,77]

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CHAPTER 103

Pleomorphic Adenoma (Mixed Tumor)

Key Points

- Pleomorphic adenomas arise most often in the lacrimal or salivary glands, and less commonly from ectopic periorbital lacrimal gland tissue, sweat glands of Moll, or accessory lacrimal glands of Krause and Wolfring in the eyelids
- They are characterized by translocations or intrachromosomal rearrangements with breakpoints affecting 8q12 in 50% and 12q14-15 in 10% to 15%
- Lesions are very slow-growing, small, smooth, firm, nontender, nodular masses that may be associated with madarosis and telangiectasias
- Treatment is with complete local surgical resection and eyelid reconstruction when necessary
- The prognosis is excellent, and the reported eyelid cases showed no recurrence or malignant transformation

Mixed tumor of the skin was first described by Billroth in 1859,[1] and since then the terms “chondroid syringoma,” “benign mixed tumor,” and “pleomorphic adenoma” all have been used interchangeably for this lesion. In recent years the term “pleomorphic adenoma” has been preferred for salivary gland neoplasms,[2] while mixed tumor is preferred for skin tumors.[2] Pleomorphic adenoma (PA) most often arises in the lacrimal or salivary glands.[3,4,5] Less commonly it may arise from ectopic periorbital lacrimal gland tissue, sweat glands of Moll, or accessory lacrimal glands of Krause and Wolfring in the eyelids.[6,7,8,9,10,11,12,13,14]

At birth, there are between 20 and 40 accessory lacrimal glands of Krause in the upper conjunctival fornix and 6 to 8 laterally in the lower fornix.[15,16,17] Three to four accessory lacrimal glands of Wolfring are larger and are situated at the superior border of the tarsus in the upper eyelid.[15] Accessory lacrimal glands may also be encountered in the caruncle and in the plica semilunaris[18,19,20] Although ectopic lacrimal gland tissue has frequently been reported in the orbit, eye, and eyelid,[21,22,23,24,25,26,27,28] pleomorphic adenoma arising from ectopic lacrimal glands is rare,[29,30] and even less frequent is adenoid cystic carcinoma.[13,20]

Cutaneous malignant PA, usually termed “malignant chondroid syringoma”[31] or “malignant mixed tumor,” is very rare and usually develops on the torso or extremities, but about 25% may be located on the face and scalp.[32,33] It presents most frequently as a nonulcerated, slow-growing subcutaneous or intradermal nodule.[34,35,36,37,38,39,40] In contrast to benign cutaneous PA, malignant lesions tend to occur more frequently in women, with no age preference. They can develop de novo or less commonly from incompletely resected benign PA lesions. Malignant transformation has not been reported in pleomorphic adenomas arising in the eyelid. Nevertheless, because PA of the lacrimal and salivary glands carries a small but significant risk of malignant transformation if not completely excised, it is likely that this may also be seen eventually in tumors arising in ectopic or accessory lacrimal glands.

Etiology and Pathogenesis

Benign pleomorphic adenomas of the salivary glands are characterized by translocations or intrachromosomal rearrangements with breakpoints affecting 8q12 (in 50%) and 12q14-15 (in 10%-15%).[41,42] The translocations and rearrangements result in gene fusions involving the transcription factor genes *PLAG1* and *HMGA2*.[41,42,43,44] A subset of cutaneous mixed tumors feature *PLAG1* rearrangement with aberrant nuclear expression of PLAG1 protein,[45] while other tumors have *EWSR1* rearrangement.[46] Another study showed *PLAG1* expression by epithelial cells of cutaneous mixed tumors in the absence of fusion gene transcripts detectable using a reverse transcriptase-polymerase chain reaction method.[47] Oncogenic activation of the *PLAG1* gene on 8q12 is a crucial event in the formation of pleomorphic adenomas of the salivary glands[48] and some cutaneous mixed tumors.[47] Activation mainly results from recurrent chromosomal translocations that lead to promoter substitution between *PLAG1* and several other genes,[43,49] leading to an exchange of the regulatory control elements.[48] The replacement of the *PLAG1* promoter, inactive in adult salivary glands, by a strong promoter derived from the translocation partner, leads to ectopic expression of PLAG1 in the tumor cells and presumably results in deregulation of *PLAG1* target genes, causing salivary gland tumorigenesis.[50]

Clinical Characteristics

Fewer than 50 cases of pleomorphic adenoma arising in the eyelids have been reported. Most patients at presentation are 50 to 60 years old, with a range of 12 to 84 years, and there is a strong male predilection. The right and left sides are equally affected, and the lower eyelid is involved in 55% of the reported cases. Most lesions are very slow growing over 1 to 20 years before presentation. The vast majority of tumors *(Print pagebreak 681)* are small, with 96% being equal to or less than 1 cm in diameter. Clinical examination typically show a smooth, firm, nontender, nodular mass in 88% of cases (Figures 103.1 and 103.2), with rare lesions being ulcerative or cystic. Madarosis and surface telangiectasias is seen in about 25% of cases. The caruncle can be involved in 6% of affected patients.[9,10,12,18,31,51,52,53,54,55,56,57,58,59,60,61]

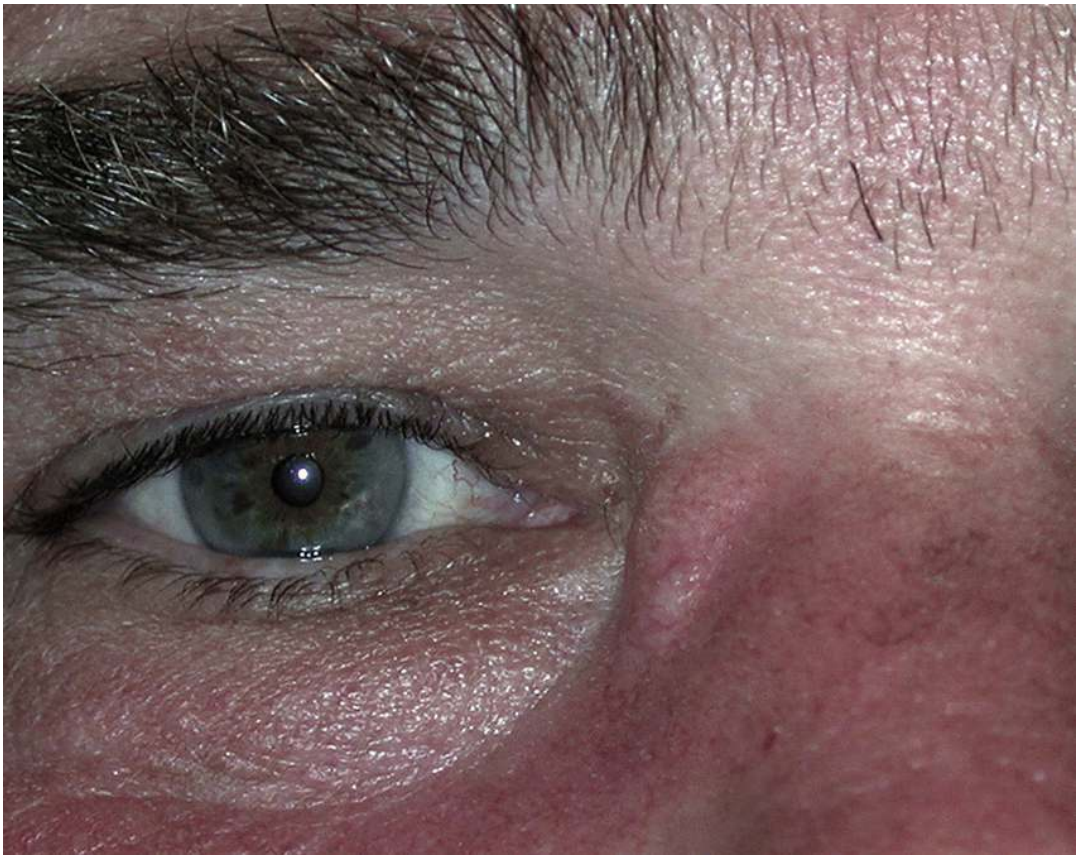

FIGURE 103.1 Pleomorphic adenoma of the medial canthus and side of the nose. (Courtesy of Dr. Alan McNab.)

Differential Diagnosis

There is no specific group of lesions that are more commonly confused with eyelid pleomorphic adenomas. The clinical differential diagnosis should include any nodular, slow-growing, periocular adnexal lesion, such as an epidermoid cyst, epidermal inclusion cyst, hidradenoma, pilomatrixoma, neurofibroma, acrospiroma, and nodular basal cell carcinoma, among others.[62]

Treatment

Pleomorphic adenoma of the eyelid is typically managed with complete local surgical resection with several millimeters of clear margin, and eyelid reconstruction as appropriate when necessary. PA is generally well circumscribed and shells out easily from the surrounding tissue.[63] However, because there is a potential low risk of malignant transformation, these patients should be monitored long term due to the possibility of local recurrence.[62,63,64,65,66,67]

Prognosis

With complete surgical excision, the prognosis for eyelid pleomorphic adenoma is excellent. Although the literature is sparse, none of the reported cases showed recurrence of tumor after follow-up intervals of 6 to 36 months.[20,68,69,70,71] Despite the lack of recurrence or malignant transformation in reported cases of eyelid PA, both have been reported for PA in other locations, so that postoperative monitoring is necessary.

Histopathology

Cutaneous mixed tumors exhibit epithelial, myoepithelial, and mesenchymal elements.[63,72,73,74,75,76,77,78,79] Hirsch and Helwig examined 188 cases of cutaneous mixed tumor.[63] The dermal tumors were circumscribed and multilobulated with fibrous septa between lobules.[63] Only two cases had a connection with the epidermis.[63] Cuboidal or polygonal epithelial cells with large uniform nuclei and abundant, homogeneous, eosinophilic cytoplasm lacked pleomorphism, cellular atypia, or "appreciable" mitotic activity.[63] Epithelial cells formed nests; tubuloalveolar structures with "gland-like elements lined with 2 or more (depending on the plane of sectioning) rows of cuboidal cells morphologically similar to those in nests of cuboidal cells"; ductal structures composed of one or two rows of cuboidal cells; and occasional keratinous cysts with the epithelial wall lined by flattened squamoid cells.[63] Tubuloalveolar and ductal structures connected by epithelial tracts formed lacelike networks.[63] A few scalp tumors had basophilic and shadow cells, similar to pilomatrixoma, together with the epithelial and matrix features of the more typical mixed tumors.[63] Homogeneous faintly basophilic chondroid matrix was most common, foamy myxoid areas were the next most common, and eosinophilic, homogenous, and hyaline matrix was the least common.[63]

At about the same time as Hirsch and Helwig's paper appeared in 1961, Headington classified seven mixed tumors into eccrine and apocrine types based on their histological features.[74] Eccrine mixed tumors were well-circumscribed and lobulated neoplasms located in the lower reticular dermis or at the junction of dermis and subcutis (the usual site of the coiled or secretory portion of eccrine glands).[74] They typically featured a homogeneous and monotonous pattern with numerous small gland-like spaces and individual cell nests evenly separated in a cartilaginous or chondroid matrix.[74] The individual glands had irregular outlines, and there were frequent small eccentric proliferations of cells creating the appearance of a "comma or eccentric handle."[74] Headington did not observe any large gland-like spaces lined by a double row of epithelium, characteristic of apocrine differentiation, in any of the four eccrine mixed tumors (Figure 103.3). The three apocrine mixed tumors were well circumscribed and lobulated, and they were also in the deep reticular dermis or at the junction of the dermis and subcutis. The tumors all had a variegated and haphazard tissue pattern similar to that of salivary gland mixed tumors.[74] "Broad sheets of squamous epithelial cells with and without intracellular bridges are interspersed in a connective tissue stroma showing varying *(Print pagebreak 682)* degrees of cartilaginous forms. Glandular spaces show marked variation in size and shape, and they may be lined by flattened cuboidal cells or by the characteristic double epithelial layer; this latter finding is considered to be the most important single diagnostic criterion. Areas of squamous and osseous metaplasia may be found. The haphazard distribution of epithelial and stromal components and the presence of typical apocrine epithelium are considered to be diagnostic."[74]

Since Headington's seminal publication, the classification of cutaneous mixed tumors into apocrine and eccrine subtypes is well established.[75,80,81] Hassab-El-Naby and coworkers examined 64 mixed tumors of the skin; none of the tumors involved the eyelids or eyebrows, and 52 (81%) were apocrine subtype.[75] A few of the apocrine tumors had follicular differentiation resembling a pilomatrixoma or sebaceous differentiation, and 25% of the tumors had an "overwhelming predominance of epithelial over stromal elements."[75] All of the eccrine mixed tumors had small glands and ductlike structures lined by a single layer of cuboidal cells with pale eosinophilic cytoplasm and round nuclei dispersed in stroma consisting mainly of chondroid or mucin.[75] Spindle-shaped and round cells similar to those forming the glands were also within the stroma.[75] Apocrine tumors showed immunohistochemical expression of S100 protein in aggregations of epithelial cells and polygonal cells arranged as solitary units, while tubules with decapitation secretion were negative for S100 protein. Carcinoembryonic antigen (CEA) and epithelial membrane antigen (EMA) were detected only in the inner layer of tubular structures and luminal secretory products. Muscle-specific actin occurred focally and weakly in some spindle-shaped stromal cells, especially in areas of fibroplasia. Gross cystic disease fluid protein-15 (GCDFP-15 [BRST-2]) was in tubules, aggregations of epithelial cells, and luminal secretions.[75] Eccrine mixed tumors had S100 protein expression in glands and ductlike structure and stromal polygonal cells; CEA in glands and ductlike structures with paraluminal accentuation; and no expression of actin, EMA, and GCDF-15 expression was seen.[75] Hassab-El-Naby et al. concluded that the immunohistochemical studies did not provide unequivocal evidence of either apocrine or eccrine differentiation.[75] A more recent study of 244 apocrine mixed tumors by Kazakov and colleagues identified 18 in the eyebrow and 9 in the eyelid.[80] The epithelial component of the 244 tumors exhibited a spectrum of metaplastic changes, including squamous, mucinous, oxyphilic, columnar, and hobnail metaplasia and clear cell change and cytoplasmic vacuolization. Myoepithelial cells had clear cell change, hyaline cells, plasmacytoid cells, spindling, and collagenous spherulosis, while the stroma had chondroid, osseous, and adipose metaplasia.[80] No eccrine mixed tumors were located in the eyebrow or eyelid in a more recent study of 50 eccrine tumors by Kazakov et al.[81]

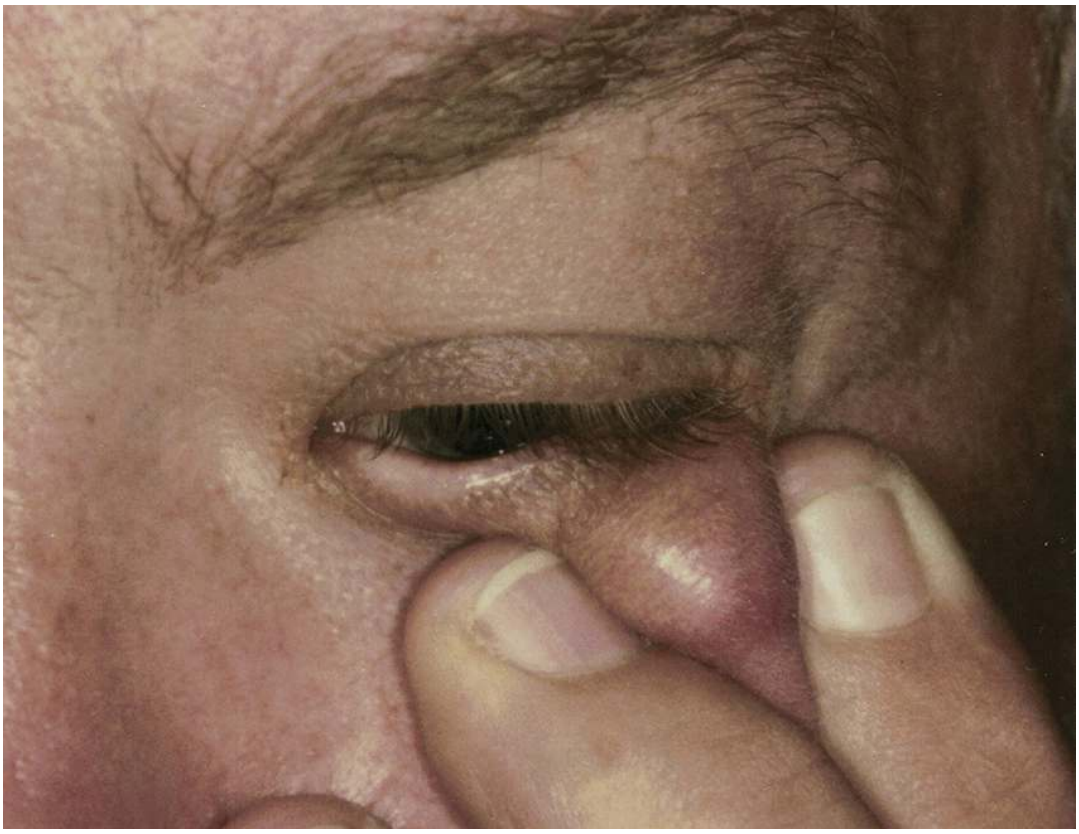

FIGURE 103.2 Benign cutaneous apocrine mixed tumor of the lateral left lower eyelid of a man in his early 40s. It was a freely movable 1.5 × 0.9 cm tumor that had been slowly growing for about 5 years and was associated with episodic eyelid swelling.

Most malignant mixed tumors (Figure 103.4) likely arise de novo since remains of benign mixed tumors are uncommon.[77] The tumors are infiltrative, sometimes have ulceration of the overlying epidermis, and are composed of neoplastic epithelial cells within a myxoid stroma. The neoplastic epithelial cells have pleomorphic hyperchromatic nuclei and may form solid aggregates, cords, or ducts.[77] There may be atypical mitotic figures.[77] The myxoid stroma may be highlighted using alcian blue stain[74] but not with periodic acid-Schiff stain.[77,82] Immunohistochemical stains, although limited in number, have shown expression of S100 protein,[82,83] CAM5.2,[84] CK7,[84] and vimentin[82] by the epithelial cells. Tumor cells may[83] or may not[77] express CEA. One malignant mixed tumor of the eyebrow has been reported,[32] and we have seen one example arising in the eyelid (Figure 103.4). In the periocular region, cutaneous extension of tumor from a lacrimal gland primary must be excluded (Figure 103.4).[84]

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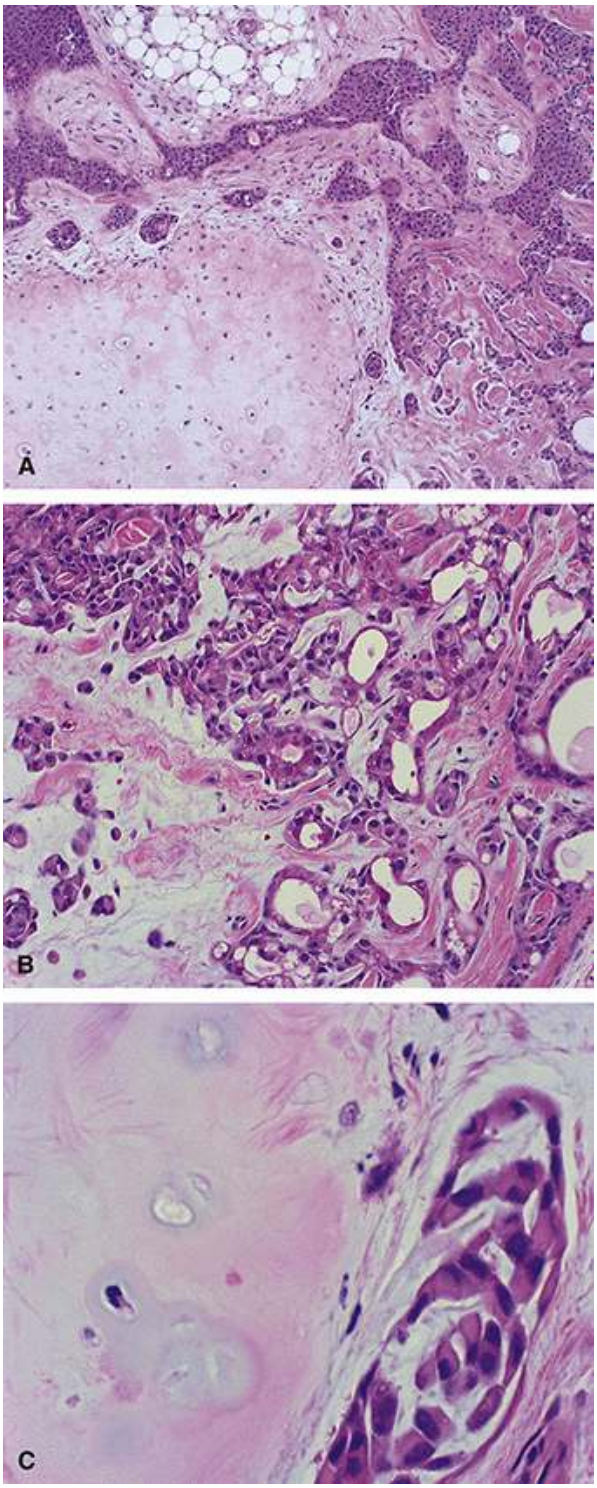

FIGURE 103.3 Benign cutaneous apocrine mixed tumor from the patient in Figure 103.2. A, Cords and tubules of epithelial cells are in a stroma having adipose (top) and chondroid (bottom) metaplasia. The stroma on the right is hyalinized and brightly eosinophilic. B, The epithelial cells formed solid cords, as well as ductlike structures. C, Chondroid metaplasia of the stroma was a prominent feature of this neoplasm.

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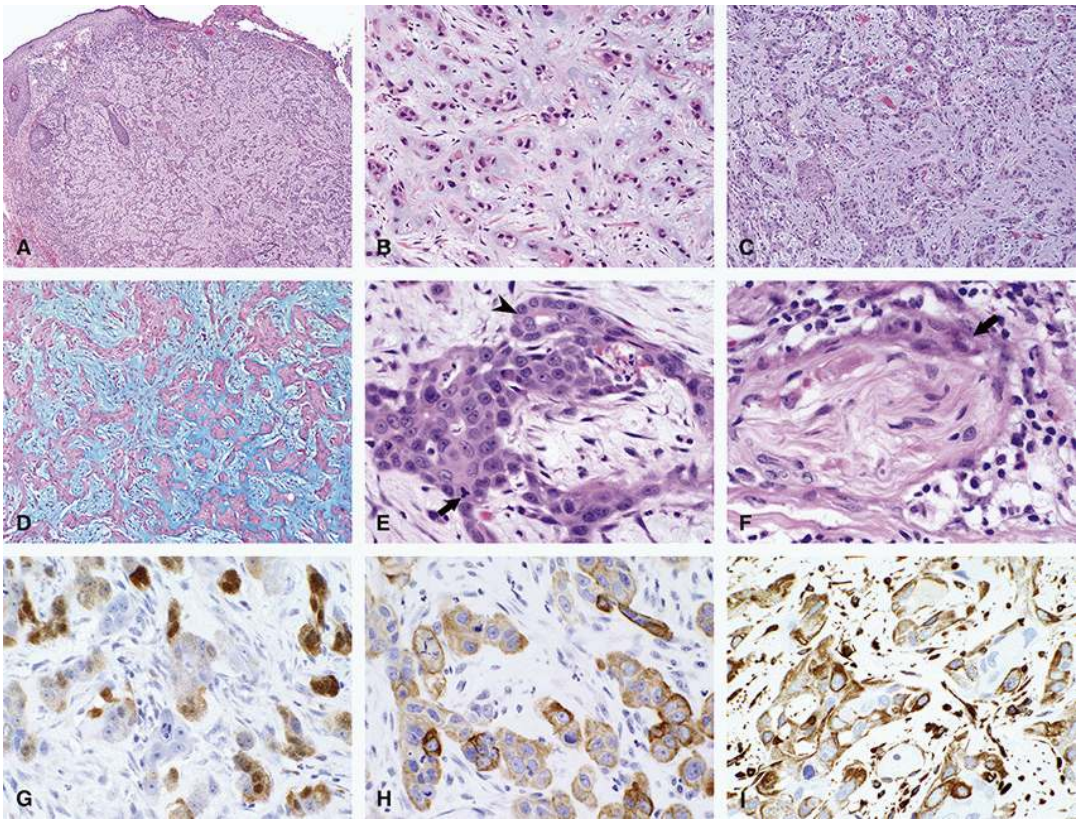

FIGURE 103.4 This malignant mixed tumor in a woman in her mid-70s involved most of the left lower eyelid and inferior anterior orbit and extended into the lateral left upper eyelid and superior anterior orbit. The tumor did not involve the lacrimal gland. A, The tumor is contiguous with the epidermis. Much of the epidermis is ulcerated, as seen on the right side of the photomicrograph. B, Nests of tumor cells were embedded in a faintly basophilic chondroid matrix focally. C, In most areas, the tumor cells formed cords, rudimentary tubules, and nests within a lightly basophilic, myxoid fibrous stroma. D, Alcian blue stain for glycosaminoglycans is strongly positive, confirming the stroma's myxoid nature. E, A rudimentary tubule is at the arrowhead. There were frequent mitoses; a tripolar mitotic figure is at the arrow. F, Perineural invasion (*arrow*) by tumor was common. G, Some tumor cells were immunoreactive using antibodies to S100 protein. The expression of S100 protein by the tumor cells varied widely from one area to another within the tumor. H, CAM5.2 antibodies, immunoreactive principally to cytokeratin 8 (Becton Dickinson Biosciences), highlighted some tumor cells. The normal epidermis lacked immunoreactivity. I, All of the tumor cells were immunoreactive using antibodies to vimentin, which also highlighted the stromal cells.

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CHAPTER 104

Poliosis

Key Points

- Poliosis is a localized patch of hypopigmented hair caused by a reduction or absence of melanin in the affected hairs
- The pathogenesis is unknown, but this condition frequently occurs in the setting of several genetic syndromes such as piebaldism, tuberous sclerosis, and Waardenburg syndrome
- It can also be associated with nongenetic, autoimmune conditions such as Vogt-Koyanagi-Harada syndrome, congenital and acquired nevi, and sarcoidosis
- The clinical presentation of eyelash poliosis may vary from one or two white lashes to involvement of the entire eyelid margin
- There is no specific treatment for poliosis, and when the eyelashes and eyebrows are involved the condition can be socially disabling
- Treatment is directed toward cosmetic improvement such as with hair dyes
- Some cases of poliosis will resolve following management of the underlying inciting condition suggesting restoration of normal immune homeostasis

Poliosis, also known as poliosis circumscripta, is defined as a localized patch of hypopigmented hair caused by a reduction or absence of melanin in the affected hairs.[1] It may affect any region of the body including the eyelashes and eyebrows. On histopathology, poliosis demonstrates a decrease or absence of melanin or melanocytes in the hair bulbs of the affected hair follicles. The adjacent epidermal melanocytes are usually not affected unless there is associated vitiligo.[2] Poliosis can occur in the setting of several genetic syndromes, either as one of their characteristic clinical manifestations or as a rare manifestation.[3] It also has been described in association with a variety of acquired inflammatory, neoplastic, and medication-induced conditions.[1]

Etiology and Pathogenesis

Poliosis and Genetic Syndromes

The exact pathogenesis of poliosis in most cases is unknown or only speculative. Possible causes are extensive, and this condition frequently occurs in the setting of several genetic syndromes.[3] Although poliosis is not specific for any of these syndromes, it may be the initial presentation even before other more characteristic manifestations appear.[4]

Piebaldism is an autosomal dominant inherited disorder that most commonly develops secondary to a mutation in the c-kit proto-oncogene on chromosome 14q12 that affects melanoblast migration, proliferation, differentiation, and survival.[5,6] It is characterized clinically by the presence of congenital poliosis and leukoderma,[7] with a white forelock and poliosis of the eyebrows and eyelashes seen in 80% to 90% of cases.[1]

Tuberous sclerosis is an autosomal dominant disorder characterized by hamartoma development in various tissues, most frequently the brain, skin, heart, kidneys, and lungs.[8] It is caused by mutations in the *TSC1* (9q34) or *TSC2* (16p13) genes resulting in activation of the mechanistic target of rapamycin (mTOR) signaling pathway. More than half of cases present with seizures, and dermatologic manifestations may be seen initially in more than 90% of affected children.[4,9] Hypopigmented skin macules are identified in infancy or early childhood in 15% to 50% of patients.[4,9] Although poliosis is not one of the diagnostic criteria, it is often present as one of the earliest signs of the disease and may precede the appearance of other manifestations.[4]

Waardenburg syndrome type I is a rare autosomal dominant disorder of neural crest cell development associated with a

heterozygous pathogenic variant in *PAX3* (2q36). It is characterized by sensorineural deafness and pigmentary abnormalities, often associated with a white forelock and possible poliosis of eyebrows and eyelashes.[3,10] Other ophthalmic manifestations may include segmental heterochromia, or hypoplastic or brilliant blue irides, and segmental choroidal hypopigmentation.[11] Depigmentation in Waardenburg syndrome is caused by the absence of melanocytes from the affected areas in the skin, hair, eyes, or ears.[10,12]

Poliosis has also been reported rarely in patients with Rubinstein-Taybi syndrome,[13,14] Marfan syndrome,[15] and neurofibromatosis type 1.[16]

Poliosis and Acquired Conditions

Vogt-Koyanagi-Harada (VKH) syndrome is a rare, nongenetic, systemic T cell-mediated autoimmune inflammatory disorder. It is characterized by bilateral uveitis that is frequently associated with neurological, auditory, and integumentary manifestations. The etiology and pathogenesis are not completely understood, but it is believed that *(Print pagebreak 688)* the clinical manifestations are caused by an autoimmune response directed against melanin-associated antigens in the target organs, such as the eye, inner ear, meninges, and skin. Accumulating evidence suggests that predisposing genetic factors, including VKH disease-specific risk factors (HLA-DR4), general risk factors for immune dysfunction (increased Expression of IL-23 Receptor [IL-23R]), environmental triggers (eg, viruses), and recently COVID-19 vaccinations, are all involved in the development of VKH disease.[17,18] The clinical manifestations of VKH include vitiligo occurring in association with poliosis, uveitis, aseptic meningitis, tinnitus, dysacusis, and alopecia.[17,18,19,20,21,22] Vitiligo, poliosis, and alopecia usually develop in the late phase of the disease, although they can manifest earlier. Periocular hair involvement is common in this disorder and usually manifests as eyelash poliosis.

Alezzandrini syndrome is a very rare disease with only a few cases reported in the literature.[23,24] The etiology is unknown but several theories involving viral or autoimmune processes have been postulated. The disease is characterized by hearing abnormalities, unilateral tapetoretinal degeneration, ipsilateral facial vitiligo, and poliosis. It is suspected that an autoimmune process destroys melanocytes.[23,24]

Vitiligo is a chronic pigmentary disorder characterized by loss of epidermal melanocytes leading to depigmented skin macules.[25] The exact cause of the loss of functional melanocytes in affected skin is not fully understood, but it is believed that a triggering event leads to a stress response in the skin that initiates an autoimmune response against melanocytes in genetically predisposed individuals.[26] Genetic predisposition is supported by the fact that 25% of patients with vitiligo have a positive family history and more than 40 gene variants have been identified in genome-wide association studies.[27] The melanocyte destruction has been attributed to several mechanisms such as autoimmune, cytotoxic, neural, and viral causes.[25] Poliosis, especially of the eyebrows, can be associated with vitiligo in up to 48% of cases, especially in patients with segmental vitiligo.[2,28,29]

Alopecia areata is a disorder characterized by poliosis resulting from an immune response leading to hair-related melanocytes destruction.[30] Poliosis is seen in about 5% of these patients, and they tend to be older with a male predominance. The white hair is believed to result from dysregulation of signaling pathways and transcription factors in the microenvironment surrounding the hair follicles or by an imbalance in the management of oxidative stress.[31,32] Selective involvement affecting pigmented hairs leaves a salt-and-pepper appearance.

Blepharitis is a common chronic inflammatory disorder affecting the eyelid margin.[33] It may be associated with several conditions such as chalazion, conjunctivitis, keratitis, rosacea, and seborrheic dermatitis. Chronic blepharitis may manifest with lid margin hypertrophy, scars, trichiasis, madarosis, and poliosis.[33]

Poliosis also has been reported to occur with both congenital and acquired nevi.[34,35] In congenital nevi, poliosis arises as the fetal melanocytes proliferate in the perifollicular area secondary to the arrest of migration from the neural crest to the hair bulbs.[1] This results in a congenital nevus in the skin with nonpigmented hairs growing out of it.[35,36] In acquired nevi, poliosis may develop circumferentially around the nevus several months after its appearance.[37,38,39,40,41] Lymphohistiocytic infiltration around nevus nests suggests that an inflammatory or autoimmune cytotoxic T cell response against the melanocytic nevi may destroy adjacent normal epidermal and follicular melanocytes producing a halo reaction and poliosis.[38,39,40]

Eyelash poliosis has been described in patients with sarcoidosis.[42] The humoral response is believed to play a role in causing hair depigmentation.[43] It has been postulated that depigmentation is the result of an autoimmune mechanism where overactivity of CD3 and increased expression of cytokines IL-1b, IL-2, IL-6, and TNF-a leads to T helper cell differentiation and subsequent activation of T cytotoxic cells and B-cells, which produce circulating antibodies against melanocytes.[44,45]

Poliosis associated with malignant neoplasms has been reported with melanoma of the scalp,[43] conjunctiva,[46] and orbit.[47] The pathogenesis of poliosis in these cases is not known, but it has been suggested that it may be related to inflammatory destruction of melanocytes in the hair follicle, apoptosis of the follicular melanocytes, or a targeted autoimmune response.[48,49] The malignant cells may initiate an immune response that cross-reacts with the normal follicular melanocytes.[43,49]

A number of drug-induced cases of poliosis have been described.[50,51,52,53] Topical prostaglandin analogs alter melanocyte tyrosinase activity in some hair follicles, reducing melanogenesis and leading to poliosis.[54,55] The white lashes are typically interspersed among normally pigmented eyelashes. The pathogenesis is uncertain, but it has been suggested that cytotoxic T cell activation leads to melanocyte destruction.[56] Topical chloramphenicol sometimes used after eyelid surgery has been associated with anterior uveitis, poliosis, and periocular vitiligo, possibly as a T cell-mediated hypersensitivity reaction against melanin or melanocytes.[57] Acitretin, a metabolite of the aromatic retinoid etretinate, is utilized in the treatment of psoriasis and has been associated with poliosis with alopecia.[51]

There are several case reports of poliosis not associated with any underlying disease. One was a 5-year-old girl with congenital macular hyperpigmentation of the nose and eyelash poliosis. The authors proposed that this represented somatic mosaicism for genes affecting pigmentation.[58] In another case, spontaneous poliosis of the eyelashes in a 68-year-old male was described as a possible rare representation of idiopathic poliosis.[37]

Clinical Presentation

The clinical presentation of eyelash poliosis may vary from one or two white lashes to involvement of the entire eyelid margin (Figure 104.1). It may involve one eyelid or all four *(Print pagebreak 689)* lids depending upon the etiology. Poliosis is usually not seen with other ocular or eyelid abnormalities, except where it is associated with a nevus, vitiligo, or malignancy. The condition can evolve rapidly over days to weeks or slowly over months to years. In rare cases, eyelash poliosis can be associated with trichomegaly with curled and brittle lashes or with trichiasis (Figure 104.2). In most cases, a history of a systemic syndrome or acquired eyelid condition as discussed above can be uncovered. However, poliosis can be the initial manifestation of some genetic disorders so that depending on the presence of other signs, a thorough evaluation may be in order.

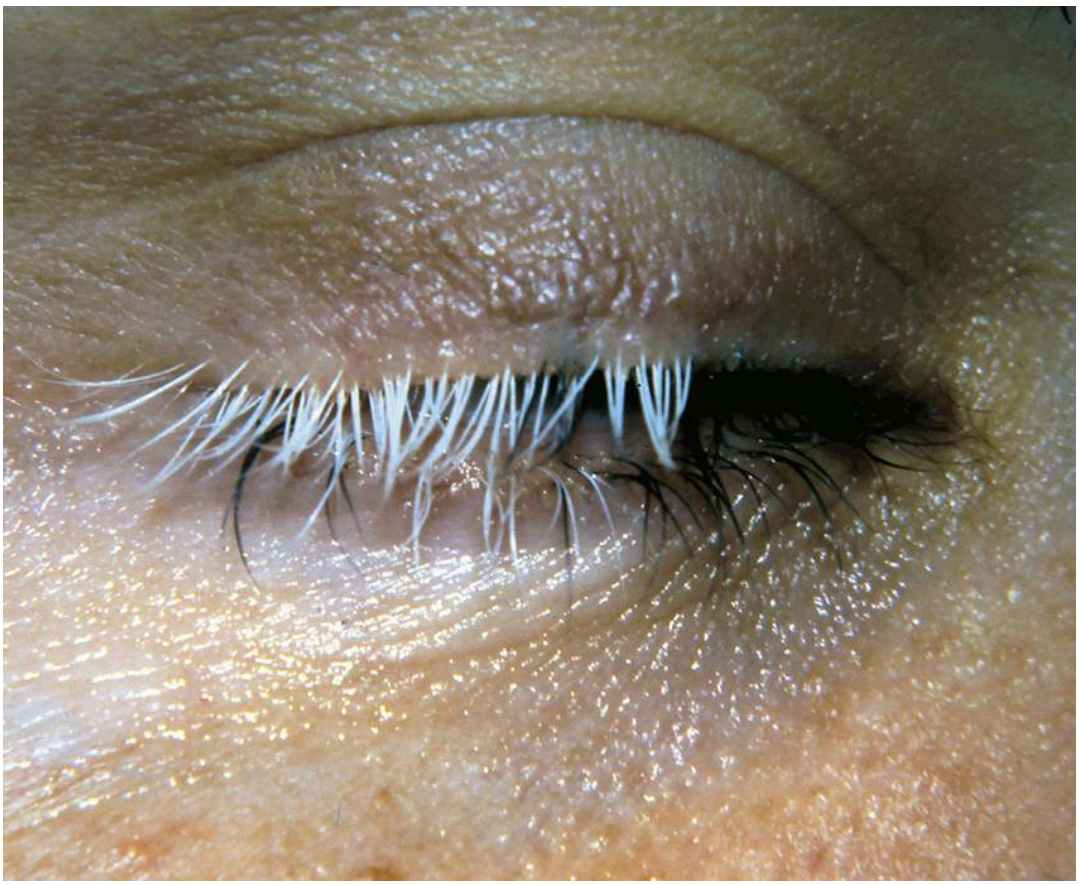

FIGURE 104.1 Poliosis associated with vitiligo. (Courtesy of Dr. Alan McNab.)

Differential Diagnosis

The differential diagnosis of poliosis includes several genetic disorders such as Griscelli syndrome, Chediak-Higashi syndrome, Hermansky-Pudlak syndrome, and oculocutaneous albinism.[1,3] However, the distribution of white hair in these syndromes is typically more diffuse than in poliosis. Another condition that can be confused with poliosis is white piedra, a mycotic infection caused by yeasts of the genus *Trichosporon* where individual hairs exhibit barely visible but palpable whitish to cream-colored,

easily detachable nodules 1 to 1.5 mm in size present over the shaft of hairs on the scalp, eyebrows, and eyelashes.[59,60,61,62]

Treatment

There is no specific treatment for poliosis. In most cases the condition is permanent, and when the eyelashes and eyebrows are involved the condition can be socially disabling. Treatment is directed toward cosmetic improvement such as with hair dyes.[63] In cases where poliosis is associated with segmental vitiligo, treatment with a 308-nm excimer laser has been reported to show 75% or more repigmentation of the white hairs.[64] A case of a halo nevus on the eyelid margin with localized poliosis of the eyelashes was treated with wedge resection of the involved region including the white eyelashes.[39]

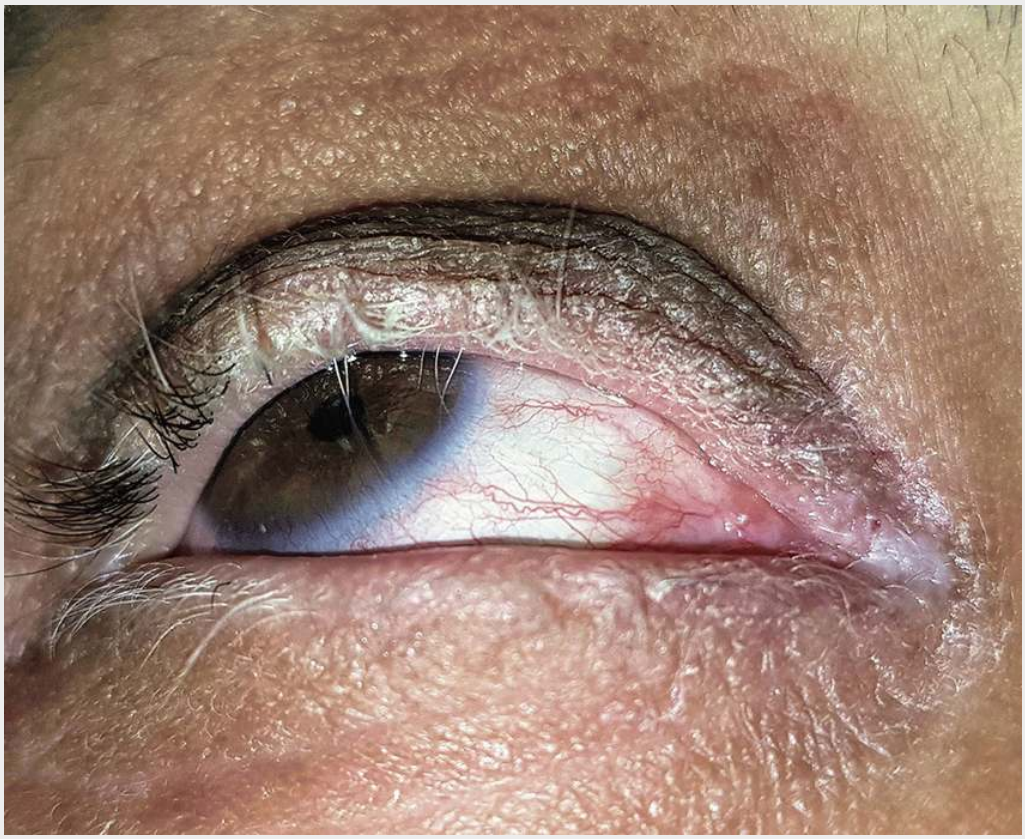

FIGURE 104.2 Poliosis associated with trichiasis. To the best of our knowledge, this association is hitherto unknown and could be accidental.

Prognosis

Some cases of poliosis will resolve following management of the underlying inciting condition. A child with intracranial ganglioglioma and brow poliosis showed resolution of the poliosis following tumor resection.[65] In a series of 22 patients with VKH disease treated with corticosteroids and cytotoxic agents, six (27%) showed reversal of the poliosis after treatment, suggesting restoration of normal immune homeostasis.[21] A case of poliosis and abnormal eyelash growth associated with cetuximab treatment for metastatic colorectal cancer was reported to resolve 1 month after cessation of drug therapy.[52]

Histopathology

There is no histopathologic description for poliosis.

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CHAPTER 105

Pseudoepitheliomatous Hyperplasia

Key Points

- Secondary pseudoepitheliomatous hyperplasia (PEH) is a benign proliferative pseudoneoplastic response to trauma, wounds, burns, radiation therapy, cryotherapy, pharmaceutical agents, and cutaneous malignancies
- Primary PEH has no clinical or histopathological evidence for a definite etiology
- Keratinocyte proliferation is likely a secondary phenomenon due to cytokine expression by activated immune cells
- Clinically, it presents as a nodule or plaque of various sizes with a rugose surface, scaling, and occasionally crusting and ulceration evolving rapidly over several days to weeks
- Surgical excision is considered the most appropriate treatment to provide a definitive diagnosis and to rule out malignancy
- The prognosis is good following surgical resection

Pseudoepitheliomatous hyperplasia (PEH) is a benign proliferative pseudoneoplastic response to trauma, wounds, burns, radiation therapy, cryotherapy, pharmaceutical agents, and cutaneous malignancies.[1,2,3,4,5,6,7,8,9] It can simulate basal cell carcinoma clinically and squamous cell carcinoma (SCC) histopathologically, which often complicates the initial diagnosis and management.[4] One case of PEH was reported to be associated with a cutaneous horn.[10]

PEH can be secondary or idiopathic.[3,5] Secondary PEH is by far the most common form, associated with a known etiology such as infectious agents, insect bites, some drugs, or cutaneous malignancies. It also has been reported after Mohs micrographic surgery[11] and following diode laser therapy.[13] In primary PEH on the other hand, there is no clinical or histopathological evidence for a definite etiology.[14] These lesions have been described under various names such as verrugoma, molluscum sebaceum, and self-healing squamous cell epithelioma.[14]

Clinically, the most important associations of PEH are with malignant cutaneous tumors such as SCC, basal cell carcinoma, melanoma, cutaneous lymphoma, pulmonary adenocarcinoma, and metastatic breast cancer.[15,16,17,18,19,20,21] This makes initial biopsy or excision necessary to uncover the underlying pathology.

Besides its cutaneous manifestations, PEH can involve the conjunctival epithelium,[22,23,24,25] where it can be associated with vernal keratoconjunctivitis,[22,25] possibly resulting from chronic inflammation exacerbated by mechanical trauma to the limbal epithelium.[23] It also has been described as a complication of cultivated limbal epithelium transplantation.[23]

PEH is frequently associated with tattoo dye. The development of PEH in response to red tattoo pigment was first reported by Sulzberger in 1937.[26] In 1959, Goldberg[27] further defined this condition as multiple verrucous papules within an area of red ink. The verrucous growth pattern is often mistaken for SCC, which is important clinically since cases of SCC have also been reported arising in tattoos.[28,29,30,31,32] Although most reported tattoo-related PEH cases were associated with the use of either red or purple dye,[33,34,35,36] occasional cases also have been seen in black, green, and blue tattoos.[30,37] While PEH has not been described associated with blepharopigmentation, granulomatous reactions have been reported.[38,39,40]

The interval between tattooing and the onset of PEH varies from several days to several years. Upon transfer of the pigment into the dermis, pigment granules are ingested by skin phagocytes and a transient inflammatory period, characterized by a foreign body reaction and fibrous tissue formation, begins and lasts about 2 weeks.[41] Later, the pigment becomes encapsulated in dense layers of connective tissue located in the papillary dermis either within fibroblasts or between collagen bundles.[41]

Etiology and Pathogenesis

The tissue of origin for PEH has been a matter of controversy. Grunwald et al proposed that PEH is not a hyperplasia of the epidermal epithelium, but rather a hyperplasia of the adnexal epithelium of the follicular infundibula,[12,42] and Tuttle et al[17] reported 25 cases of infiltrative basal cell carcinoma associated with PEH with primarily a follicular differentiation pattern. In an experimental study of PEH occurring during the healing stages of cutaneous leishmanial ulcers in mice, Akilov et al[43] showed that the epidermal proliferation mostly involved epithelial structures of the hair follicle infundibula and that there was a continuity between the pseudoepitheliomatous epithelium and preexisting follicular infundibula and the proliferating epithelium. This suggests a follicular origin for PEH. Other authors argued that the hyperplastic epithelium is of eccrine origin, based on the observation that PEH is most commonly encountered on mucosal surfaces rich in salivary glands.[44,45]

The molecular mechanisms that underlie the etiopathogenesis of PEH are unknown.[44] These lesions appear to be an epithelial response to trauma or compression or might *(Print pagebreak 693)* result from aberrant expression of trophic epidermal growth factors.[43] Several cytokines and growth factors play a role in sustaining persistent dermal inflammation and epidermal proliferation, both of which are major characteristics of PEH. The regulation of leukocyte activation and recruitment plays a major role in the production and maintenance of PEH lesions, likely through the production of TNF-α and IFN-γ. Fibroblast stimulation by TNF-α may result in increased keratinocyte growth factor production, leading to abnormal keratinocyte hyperplasia.[43] Epidermal growth factor and transforming growth factor are also involved in epidermal proliferation, differentiation, and wound healing,[46] and it has been postulated that dysregulation of these factors may be important in the development of PEH.[47,48]

Keratinocyte proliferation is likely a secondary phenomenon due to cytokine expression by activated immune cells. The development of PEH may play a role in the normal healing process of ulcers and necrotic tissue through the process of transepidermal extrusion, where removal of damaged or necrotic tissue is enveloped within the proliferating epithelium.[49] PEH may be a means of removing superficial necrotic or other abnormal material and may be a physiological response to different forms of skin damage or disease where such foreign body material is present.[43] The presence of pathogenic bacteria in cutaneous wounds has been suggested to be a possible predisposing factor of PEH formation in some patients, and in a case of Mycobacterium ulcerans, Hayman et al[50] concluded that PEH represented a mechanism for active extrusion of necrotic material containing viable mycobacteria and should be seen as part of a protective physiological response to the infection.

The pathophysiology of PEH secondary to tattoos remains uncertain. It has been hypothesized that pigment granules act as foreign bodies causing early inflammation that could result in the development of PEH.[41] Alternatively, PEH has been regarded as an autoimmune reaction where epidermal hyperplasia results from lymphocyte-derived chemokines that promote keratinocyte proliferation.[41]

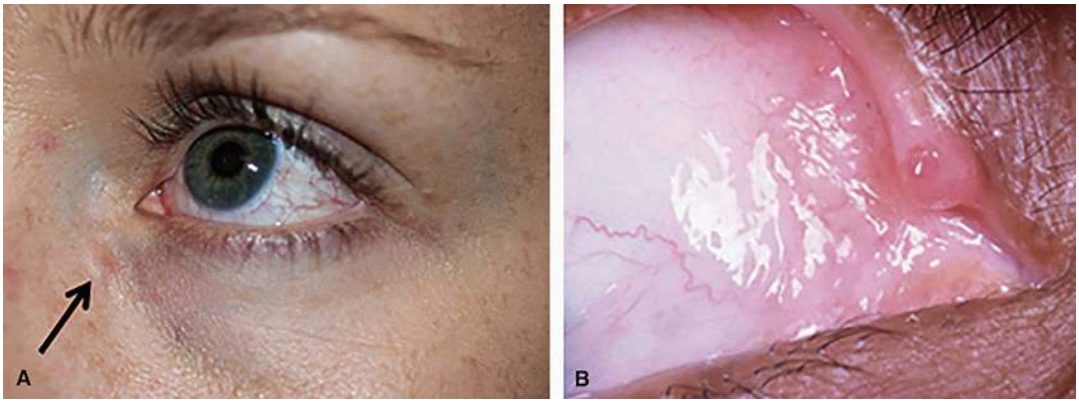

FIGURE 105.1 A, Subcutaneous nodule of pseudoepitheliomatous hyperplasia (PEH) in the medial lower eyelid. B, PEH around the superior punctum. (A, Courtesy of Dr. Suzanne Freitag. B, Reprinted with permission from Bothra N and Ali JM. Punctal pseudoepitheliomatous hyperplasia mimicking a mass lesion. *Orbit*. 2021;40(1):73-74.)

Clinical Characteristics

PEH of the head and neck can occur in patients of any age but are most prominent in the fifth and sixth decades. Clinically, they present as a nodule or plaque of various sizes with a rugose surface, scaling, and occasionally crusting and ulceration (Figure 105.1).[51] It often develops rapidly over several days to weeks. In burns, multiple dark red, soft to firm, fleshy granulomatous lesions tend to be confluent, associated with inflammation at the wound edges.[2]

On the conjunctiva, PEH presents as a white, hyperkeratotic, elevated proliferation of the conjunctival or corneal epithelium. It can be misidentified as ocular surface squamous neoplasia, especially when it arises at the corneal limbus.[24]

Differential Diagnosis

PEH can be confused with a variety of benign and malignant lesions. Squamous and basal cell carcinomas are the most frequent lesions that must be included in the differential diagnosis. When occurring on the conjunctiva, it can be confused with squamous neoplasia or nodular episcleritis.[52]

Treatment

There is no standard or optimal treatment for PEH. Because these lesions are often confused with cutaneous malignancies, surgical excision is usually considered the most appropriate treatment to provide a definitive diagnosis. Neither cryosurgery nor laser therapy has proven to be useful, and both have been associated with the development of PEH.[9,13,53] Photodynamic therapy is ineffective for the treatment of *(Print pagebreak 694)* PEH.[54] Some PEH lesions have been reported to gradually regress spontaneously over several months without treatment,[55] but given its similarity to malignant lesions in many cases, few lesions are observed conservatively.

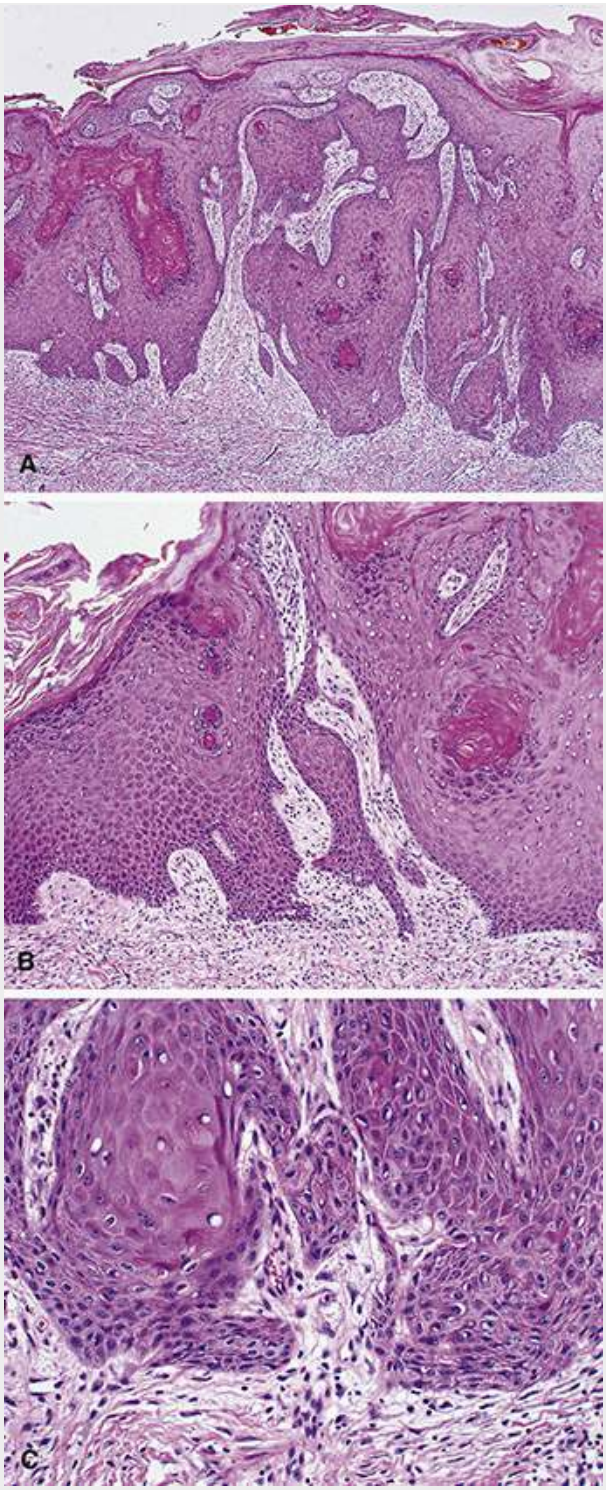

FIGURE 105.2 Cutaneous pseudoepitheliomatous hyperplasia at the site of newly formed scar from recent melanoma surgery. A, The epidermis has extensive irregular hyperplasia with anastomosing downward projections into the dermis with jagged borders and rounded or pointed bases. B, The epidermis has hyperkeratosis, and keratin pearls are in the anastomosing epidermal masses projecting into the dermis. C, There is minimal cytological atypia and foci of keratinization with brightly eosinophilic cytoplasm.

Prognosis

The prognosis for PEH is good following surgical resection for lesions associated with benign conditions such as wounds, burns, or tattoos. When PEH arises from infectious lesions or malignant tumors, the prognosis will depend upon the underlying pathology and its management.

Histopathology

Cutaneous PEH manifests as extensive irregular hyperplasia of the epidermis with downward projections of the epidermis into the dermis with jagged borders and often pointed bases (Figures 105.2 and 105.3).[51,56] The epidermis often has hypergranulosis and hyperkeratosis or parakeratosis.[51] The epidermal projections may anastomose,[56] and there may be keratinization and formation of "keratin pearls."[42,51] Hyperplastic epidermis may appear as discrete islands within the dermis.[42] PEH differs from SCC by having minimal cytological atypia, fewer mitoses, no abnormal mitotic figures, and no vascular, lymphatic, or perineural invasion.[42,51,56] Identification of an underlying pathological stimulus for PEH also helps to differentiate PEH from invasive SCC.[42]

Conjunctival PEH has thickened epithelium that may have parakeratosis or hyperkeratosis, extension of the hyperplastic epithelium into the substantia propria with jagged borders, and there may be keratin cysts and numerous *(Print pagebreak 695)* mitoses (Figure 105.4).[24,57,58] Lack of nuclear atypia differentiates conjunctival PEH from invasive SCC.[24] Extension of inflammatory cells into the hyperplastic epithelium may be seen with PEH but is rare in conjunctival SCC.[24]

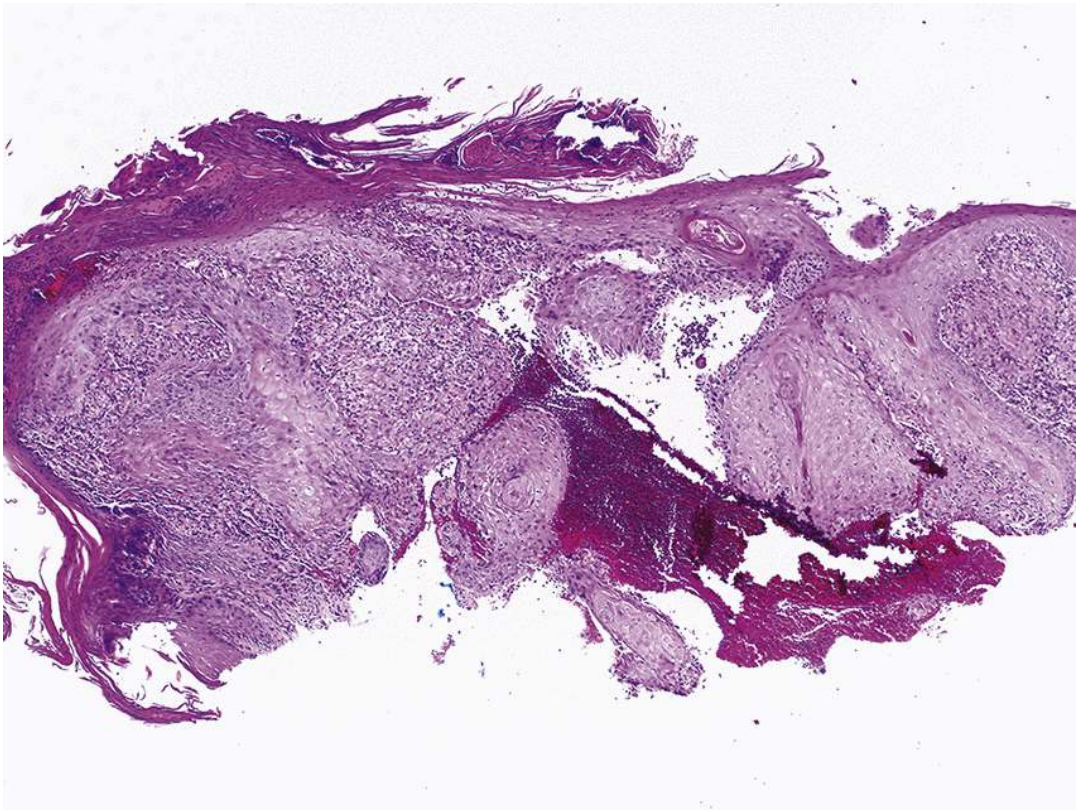

FIGURE 105.3 Pseudoepitheliomatous hyperplasia of the right upper eyelid in a man with ulcerative sarcoidosis. There is a thick layer of parakeratosis and pseudoepitheliomatous hyperplasia of the epidermis. The dermis has non-necrotizing granulomatous inflammation with a sparse lymphocytic infiltrate around discrete and coalescing granulomas. The focal hemorrhage at the base of the lesion is from the biopsy.

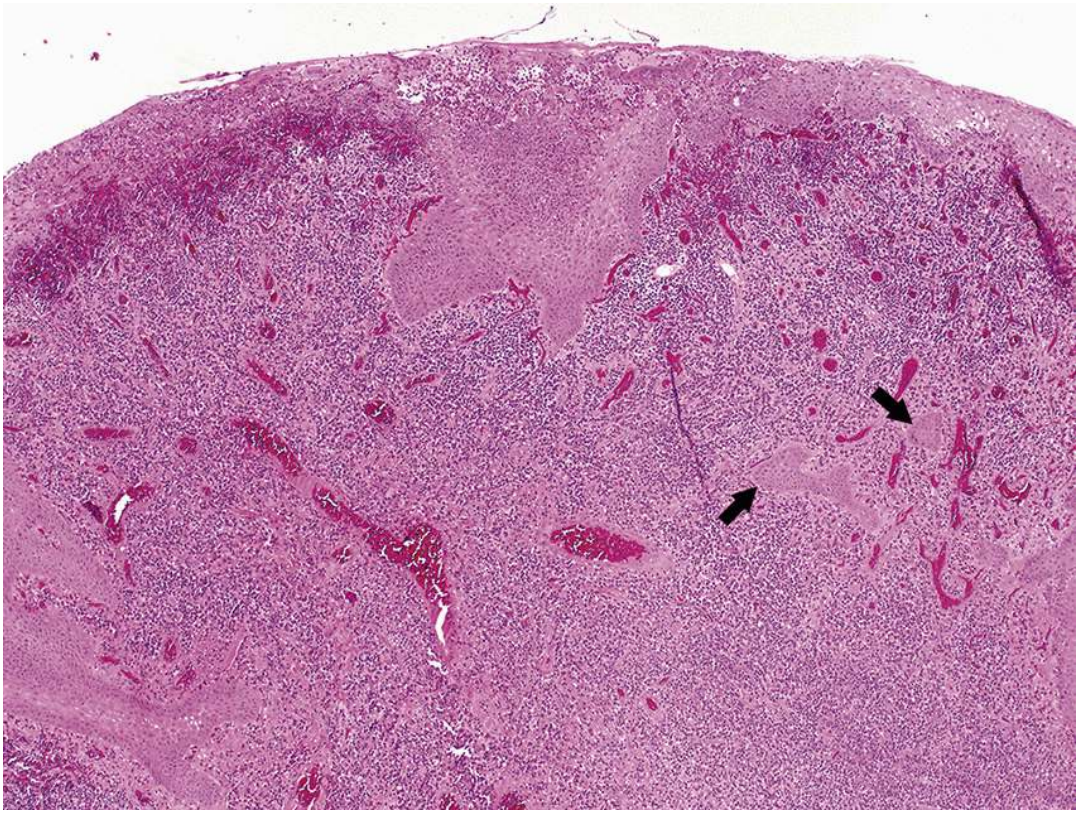

FIGURE 105.4 Pseudoepitheliomatous hyperplasia of the conjunctiva in a middle-aged man with herpes simplex virus conjunctivitis secondary to immunosuppression. There is an irregular thickening of the conjunctival epithelium with extension into markedly inflamed substantia propria. There are discrete, isolated nests of epithelium in the substantia propria (arrows).

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CHAPTER 106

Punctal Stenosis and Agenesis

Key Points

- Punctal stenosis is a condition in which the proximal external openings of the nasolacrimal drainage system on the medial eyelid margins are narrower than normal
- Punctal agenesis refers to the congenital absence of the external punctum
- Punctal stenosis can be associated with aging, inflammatory syndromes, infectious agents, drugs, and local eyelid therapies such as surgery or laser treatment
- Etiologies vary but are often related to gradual fibrotic changes and progressive occlusion of the punctum
- Patients with punctal stenosis or agenesis most commonly complain of epiphora and in some cases lower lid ectropion
- Treatment of punctal stenosis is usually with punctal dilatation, minor surgical techniques such as punctoplasty, or the placement of perforated punctal plugs or silicone stents
- In patients with eyelid laxity or frank medial ectropion associated with punctal stenosis, lower eyelid horizontal tightening should also be performed
- The prognosis of punctal stenosis is usually excellent, and most patients can achieve a patent and normally draining proximal NLD system

Acquired punctal stenosis is a condition in which the proximal external openings of the nasolacrimal drainage system on the medial eyelid margins are narrower than normal. Stenosis of the puncta may also be accompanied by canalicular stenosis.[1] In contrast to stenosis, punctal agenesis refers to a complete congenital occlusion or absence of the external punctum.

The normal anatomy of the punctum varies greatly.[2] Common textbook measurements for normal punctal diameter generally range from 0.2 to 0.5 mm.[3,4,5,6] However, in formal studies, mean punctal diameters as measured visually, by infrared imaging, or by optical coherence tomography have varied from 0.1 to 0.9 mm.[2,7,8,9,10,11,12,13,14] As a result, the concept of what constitutes punctal stenosis is unclear and there does not appear to be any standard definition of a specific size. In the widely used Kashkouli grading system for punctal stenosis,[15] grade 2 is “less than normal size,” grade 3 is “normal regular size,” and grade 4 is “small slit <2 mm” without further definition. Caesar and McNab[16] defined punctal stenosis for their study as a diameter of less than 0.3 mm or the inability to intubate the punctum with a 26 G cannula (outer diameter 0.47 mm) without dilation.

The incidence of punctal stenosis has not yet been studied, but two reports have evaluated the prevalence of the disease. Of 682 patients seen in a hospital-based population, 54.3% had an element of punctal stenosis.[17] Another study showed a prevalence of 17.3% of punctal stenosis among 621 individuals in the general population in Spain.[18] In a study from Turkey on 278 patients 65 years and older, the prevalence of punctal stenosis was 63%, of which 48.9% also had chronic blepharitis, and other associated factors included the use of glaucoma medications and lower eyelid ectropion.[19] However, among 20,102 patients with lacrimal drainage disorders in India, only 3% were diagnosed with punctal stenosis,[20] and in a study from Canada of 150 patients with epiphora, 8% were diagnosed with proximal nasolacrimal duct (NLD) (punctal or canalicular) obstruction.

Patients with significant punctal stenosis requiring treatment predominantly have been older women at a mean age of about 65 years.[1,15,16,21,22,23] The most common clinical conditions associated with punctal stenosis include blepharitis, chronic conjunctivitis, meibomian gland dysfunction, and eyelid malpositions.[1,15,16,21,22,23,24] The preponderance of associations with inflammatory conditions and histopathology suggest a common mechanism of chronic inflammation resulting in fibrosis that progressively leads to narrowing of the punctum.[25] In several studies, chronic inflammation was found on histopathology of stenotic puncta in 80% to 100% of cases.[23,26,27]

Punctal stenosis has also been associated with a very large number of other conditions, although specific etiologic relationships are not always established. These include involutional changes such as aging; inflammatory syndromes such as ocular cicatricial pemphigoid and graft vs host disease; infectious agents such as *Chlamydia trachomatis*, herpes virus, and actinomyces; topical eye drops and systemic medications such as timolol, latanoprost, betaxolol, chloramphenicol, tobramycin, mitomycin C, 5-fluorouracil, and docetaxel; and local eyelid therapies such as photodynamic therapy.[15,28,29,30,31,32,33,34] An increased association was also reported with outdoor occupational activities, but not with tobacco and alcohol consumption, or with some systemic diseases such as rosacea, allergy, or diabetes.[18,30]

Punctal dysgenesis is a general term used for maldevelopment of the lacrimal punctum. It includes everything from incomplete punctal canalization to true punctal agenesis.[35] Familial association has been reported in 36% of cases and a syndromic association in 40%.[36]

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Punctal agenesis was first documented in 1846 by Blanchet and is defined as an absence of the lacrimal punctum secondary to a defect in embryogenesis.[37] Although the epithelium of the lacrimal canaliculi makes contact with the conjunctiva in embryos at 9 to 10 weeks of gestation, the puncta remain occluded by a combination of conjunctival and canalicular epithelium until about 7 months of gestation.[38] Disruption at any point in this developmental process can lead to punctal dysgenesis.[39] One to or both puncta can be involved in one eye, but the condition can also be bilateral.[40] Epiphora is the most common presenting symptom, and a positive family history was reported in 26% of 50 patients with punctal agenesis.[40]

Incomplete punctal canalization refers to a form of punctal dysgenesis with external and internal punctal membranes.[41,42,43] In the external membrane variant, the membrane covers the external surface of the puncta simulating punctal agenesis. The internal membrane variety has a membrane just at the entrance into the punctum. Both varieties can be misdiagnosed as congenital nasolacrimal duct obstruction in pediatric patients or as punctal agenesis.[41,44] Clinical diagnosis is based on the presence of a translucent membrane with slight avascular dimpling at the site of the normal punctum.[41] Occasionally a balloon subtype can be seen with the external membrane variety where the translucent membrane is ballooned upward as a dome that merges with the tarsal conjunctiva.[42] The pathogenesis of punctal membranes is unknown but is believed to represent either failed dehiscence of the epithelium overlying the normally formed canaliculi or an incomplete canalization of the proximal-most part of the lacrimal drainage system.[42]

Etiology and Pathogenesis

Many factors have been implicated in the pathogenesis of acquired external punctal stenosis. Involutional changes associated with old age have been identified as factors causing punctal stenosis in several studies.[2,15,45] Eyelid inflammation, especially chronic blepharitis leading to gradual fibrotic changes and progressive occlusion of the punctum is also a major cause of punctal stenosis.[15,17] Dry eye syndrome has also been suggested as an etiological factor.[17] Eyelid infections such as trachoma, herpes simplex, chlamydia, actinomyces, and human papillomavirus may also be important factors.[16,28,29]

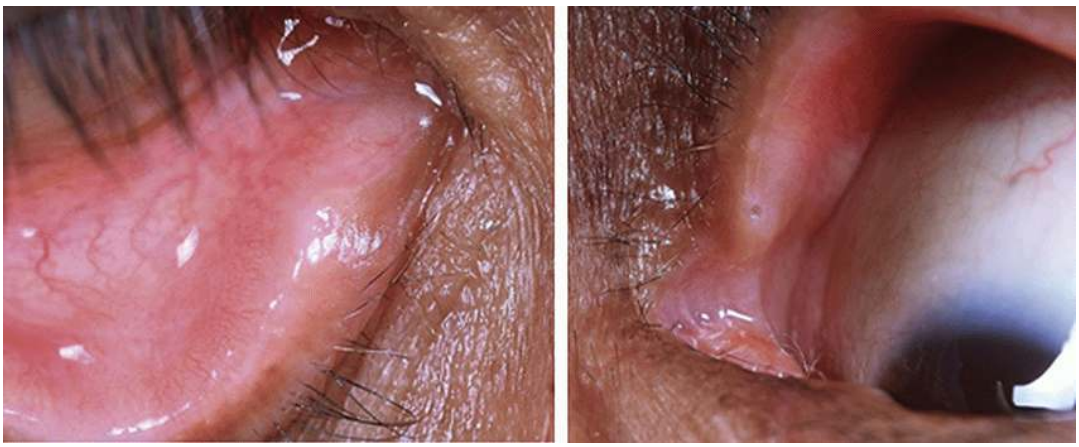

FIGURE 106.1 Lower eyelid punctal stenosis showing its small size. (Courtesy of Dr. Javed Mohammad Ali.)

Topical medications such as the antiglaucoma agents timolol, latanoprost, betaxolol, dipivefrin hydrochloride, echothiophate iodide, and pilocarpine have also been associated with punctal stenosis.[15,46] Other topical agents including prednisolone acetate, dexamethasone, phenylephrine hydrochloride, adrenaline, tobramycin, chloramphenicol, indomethacin, tropicamide, and naphazoline have also been suggested as causes of punctal stenosis.[46] Topical mitomycin C for ocular surface neoplasia has also been associated with punctal stenosis.[47,48,49] Systemic chemotherapeutic agents such as 5-fluorouracil, docetaxel, and paclitaxel

have also been associated with punctal stenosis and canalicular fibrosis.[22,32,50,51,52,53] Idoxuridine has also been thought to be a causative agent.[54]

Eyelid malpositions, particularly lower lid ectropion, can also cause punctal stenosis.[15,55,56,57,58,59] Very rare eyelid lesions including benign and malignant tumors near or around the puncta can also narrow the puncta.[56,57,58,59]

Clinical Characteristics

Patients with punctal stenosis most commonly complain of epiphora, but depending upon the degree of punctal narrowing and the association with other factors such as dry eyes, they may also be asymptomatic. While concurrent canalicular stenosis may also be present in some cases, for the most part, following dilatation and irrigation, the canalicular and lower nasolacrimal drainage systems are usually patent. The punctum is smaller than normal, usually smaller than 0.2 mm in diameter (Figure 106.1). Blepharitis is a common *(Print pagebreak 699)* associated finding, and lower eyelid malposition, such as generalized or medial ectropion, may also be noted.

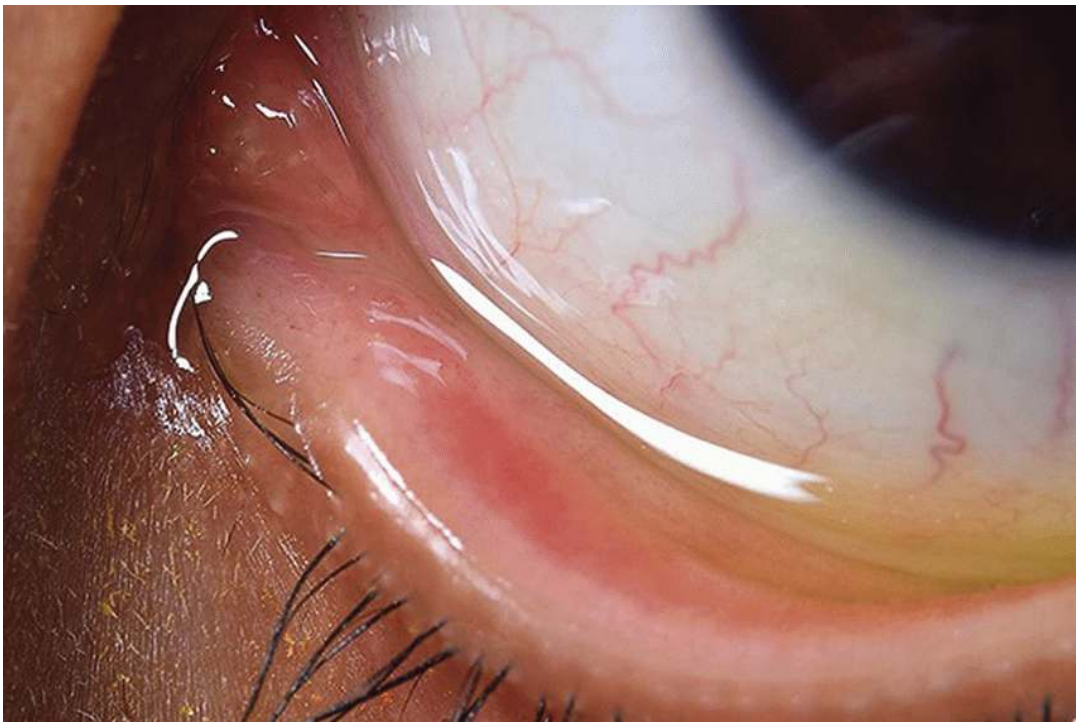

FIGURE 106.2 Punctal agenesis. (Courtesy of Dr. Javed Mohammad Ali.)

In patients with punctal dysgenesis or agenesis, the punctum is absent (Figure 106.2), epiphora is almost always, and there may be a positive family history.

Differential Diagnosis

The differential diagnosis of punctal stenosis includes a normal variant of punctal size. As previously discussed, normal puncta in asymptomatic patients may be as small as 0.1 mm, which by most evaluations might be considered “stenotic.” Benign peripunctal eyelid lesions, such as nevi, inclusion cysts, squamous papilloma, pyogenic granuloma, oncocytoma, and punctal keratinizing cyst, as well as a variety of malignant lesions can also partially or completely occlude the lacrimal punctum.[57,58,59,60,61,62,63,64]

Treatment

Several medical and surgical approaches are available for the management of punctal stenosis. In cases where punctal stenosis is associated with dry eyes or which are otherwise asymptomatic, no intervention is necessary. In patients where there is a history of topical ocular medications, cessation of the offending agent should be tried at first before proceeding with surgical intervention. Where bothersome epiphora is present, treatment may include minor surgical techniques such as punctoplasty, or the placement of reversible perforated punctal plugs or silicone stents. In patients with eyelid laxity or frank medial or

generalized ectropion associated with punctal stenosis, lower eyelid horizontal tightening should be performed with a lateral tarsal strip or alternative procedure along with any punctal procedure. Since chronic blepharitis or conjunctivitis are common associated findings, these should be managed appropriately before the correction of punctal anatomy.

Perforated punctal plugs are widely used for the management of punctal stenosis. It can be performed in an office setting where the punctum is dilated and the plug is placed in the external punctum. When left in place for several months, it may result in permanent dilation of the punctum with a reported success rate of 84.1%.[65]

Placement of a mini-Monoka silicone stent is appropriate for cases of punctal stenosis combined with canalicular stenosis. Instead of a punctoplasty, the system is dilated followed by stenting.[66] A success rate of 82% of 123 eyes with a limited follow-up of only 6 months was reported in one study.[67]

The one-snip punctoplasty was initially reported in 1853 by Bowman[68,69] using a full-length incision along the canaliculus. The technique was later modified by introducing a vertical snip along the ampulla.[70] Subsequent modifications have introduced 2, 3, and even 4 snips to accomplish enlargement of the punctum with resection of the posterior lip or ampulla wall. Success rates as high as 91% have been reported.[16,71]

In a small study of 44 eyes in 50 patients with inflammatory punctal stenosis treated with a topical antibiotic and steroid combination, evaluated with anterior segment OCT, and followed for 6 weeks, Awny et al[72] reported significant increase in punctal diameter from 228 μm to 373 μm and a significant reduction in the Munk score.

In patients with asymptomatic punctal agenesis with no epiphora or infection, observation alone is appropriate. If the underlying canalicular system is normal in cases of punctal dysgenesis, the canaliculus can be exteriorized to the conjunctival surface by membrane lysis using a punctal dilator.[73]

Prognosis

The prognosis of punctal stenosis is usually excellent, and most patients can achieve a patent and normally draining proximal NLD system following surgical punctoplasty or dilation with or without silicone stenting.

Histopathology

The normal human lacrimal punctum is funnel-shaped,[74] and nonkeratinizing stratified squamous epithelium covers its surface and inner lining.[75] The nonkeratinizing stratified squamous epithelium of the punctal surface merges with keratinizing stratified squamous epithelium of the eyelid and goblet cell-containing epithelium of the palpebral conjunctiva.[75] Dense fibrous connective tissue encircles the punctum[3,76] and contains elastic fibers[77] and the muscle of Riolan.[3]

Port and coworkers examined 30 three-snip punctoplasty specimens from 24 patients with punctal stenosis associated with one or more associated ocular conditions, including blepharitis, dry eye syndrome, or Meibomian gland dysfunction, or use of ocular medications associated with the development of punctal stenosis.[23] The authors observed chronic inflammation in 11 specimens (37%), fibrosis in 7 specimens (23%), chronic inflammation and fibrosis in 4 eyes (13%), squamous metaplasia in 3 eyes (10%), normal conjunctival mucosa in 3 eyes (10%), and *Actinomyces* species *(Print pagebreak 700)* in 2 specimens (7%).[23] In a subsequent report by Ali and colleagues, 20 punctoplasty specimens were examined by light microscopy and 6 by transmission electron microscopy.[26] The clinical characteristics of the patients were not provided.[26] "The universal histopathological and ultrastructural feature noted in the punctae was the presence of fibrosis involving the subepithelial areas of both canalicular and conjunctival epithelium."[26] Eighty percent (16/20) of the specimens exhibited chronic inflammation, and this was severe in 20%.[26] Two more recent studies examined the histopathological features of punch biopsy[25] and three-snip[78] punctoplasty specimens from patients with primary punctal stenosis. Jang et al identified subepithelial fibrosis in 83% and inflammation in 17% of the punch biopsy specimens,[25] while Eroglu et al identified fibrosis in 44%, inflammation in 23%, and fibrosis with inflammation in 26% of the three-snip punctoplasty specimens.[78] While it is tempting to conclude that fibrosis is the underlying histopathological correlate in many patients with acquired or primary punctal stenosis, it is crucial to note that none of the reports included control tissue from cadavers or orbital exenterations. Since dense fibrous tissue encircles the normal punctum, the significance of the fibrosis observed in the punctoplasty specimens requires clarification by additional studies.

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CHAPTER 107

Pyogenic Granuloma

Key Points

- Pyogenic granuloma is a reactive benign vascular proliferation that can be seen on the skin or mucous membranes
- It can involve the conjunctiva and the eyelids as a sequel to incomplete surgical or traumatic wound healing
- The pathogenesis of PG is not well understood
- *BRAF* and *RAS* mutations have been demonstrated in some patients with PG believed to drive angiogenesis by enhancing the expression of several proangiogenic and proinflammatory molecules
- Lesions appear as small lumps that progressively increase in size, usually as a pedunculated mass with an underlying stalk of connective tissue and feeder blood vessels
- Topical steroids are usually prescribed as initial treatment but the addition of topical β-blockers can result in vasoconstriction within the lesion causing inhibition of vascular growth factors thus promoting apoptosis
- If medical measures fail, surgical excision followed by cauterization of the base of the lesion is recommended
- Following medical treatment or surgical excision, pyogenic granulomas usually heal with minimal scarring

Pyogenic granuloma (PG) is a commonly occurring acquired reactive tumor-like lesion or benign vascular proliferation that can be seen on the skin and mucous membranes throughout the body. PG frequently involves the conjunctiva and the eyelids and usually occurs as a sequel to incomplete surgical or traumatic wound healing.[1,2,3,4,5,6,7,8,9] Other less commonly used synonyms include granuloma pyogenicum, reactive tissue hyperplasia, acquired capillary hemangioma (pyogenic granuloma type), or lobular capillary hemangioma.[6,9,10,11] According to the latest iteration of the ISSVA (International Society for the Study of Vascular Anomalies) classification for vascular anomalies (May 2018), the term “PG” is still retained and is used interchangeably with the “term lobular capillary hemangioma.”

Etiology and Pathogenesis

The term “pyogenic granuloma” or “granuloma pyogenicum,” which is a relic of 19th century medicine, is a misnomer.[1,2,6,9,10] Because the inflammatory component is prominent, early pathologists erroneously implicated pyogenic bacteria. There is no bacterial infection or purulent inflammatory exudate involved, which belies the “pyogenic” prefix. Nor are epithelioid or giant cells observed, which negates that “granuloma” formation is involved in the histogenesis.[9,10]

The exact pathogenetic sequence of events underlying the development of PG on the eyelid is not well understood, but the quintessential event is an injury to the conjunctival epithelium,[6,7,9,10] particularly in the setting of a transverse conjunctival wound that transects the meibomian gland orifices, which may continue to express meibomian secretions for a few days hampering epithelial healing.[6,10] Alternatively, the presence of an exogenous agent like the sharp edge of a Jones Pyrex tube would also inhibit conjunctival healing and could result in the development of PG.[10] The older theory that a pyogenic granuloma is a reaction to foreign material is unlikely.[10,12,13]

Pyogenic granulomas may be classified as a primary (idiopathic) type or secondary to an insulting factor.[9] Primary lesions may appear de novo without any apparent cause[9]; however, this is an uncommon presentation. More commonly, pyogenic granulomas develop on top of preexisting chalazia even without a history of chalazion excision, due to minor trauma to the periocular region, or at the surgical site following chalazion excision. Other scenarios include the development of PG following transconjunctival surgical approaches to the orbital floor and transconjunctival blepharoplasty.[6,7,9,10] Other surgical procedures that may also be associated with the development of PG on the bulbar conjunctiva include strabismus surgery and scleral buckling, pterygium, or stent-related trauma with dacryocystorhinostomy surgery.[9,10,14,15,16]

Recently, *BRAF* and *RAS* mutations have been demonstrated in patients with secondary PG occurring on top of port wine stains.[17,18,19] *BRAF* and *RAS* drive angiogenesis by enhancing the expression of several proangiogenic and proinflammatory molecules.[17,18] Recent evidence also suggests that a viral etiology (herpesvirus type 1, Orf virus, and/or human papillomavirus type 2) may also be implicated.[19]

Clinical Presentation

Pyogenic granulomas can occur at any age or sex, but they have a predilection for male children and young adults.[18] A history of a prior insult such as surgery or trauma is usually elicited from the patient, and in cases where PG develops after chalazion excision, this may be interpreted by the patient as recurrence of the lesion. The patient should specifically be asked about a history of remote surgical procedures, particularly scleral buckling.[6,10]

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Even when the patient denies any antecedent history, a ruptured chalazion, the presence of which may be unknown to the patient, can sometimes be felt as a palpable eyelid mass adjacent to the pyogenic granuloma upon clinical examination. Pyogenic granuloma is usually confined to the palpebral or bulbar conjunctiva. Rarely it may develop on the lid margin or the outer surface of the eyelid. It usually grows rapidly in the days to weeks after a conjunctival injury from surgery or trauma.[4] Typically, the new lesion starts as a small lump on the palpebral conjunctiva, progressively increasing in size, and may even protrude from the eyelids.[4] The shape of the lesion is variable from patient to patient.[9] It may rarely present as a sessile, broad-based lesion but more commonly presents as a pedunculated lesion with an underlying stalk of connective tissue and feeder blood vessels (Figure 107.1).[7] Lifting the tip of the granuloma off the surface of the conjunctiva usually demonstrates the peduncle.[9] Pyogenic granulomas are usually reddish and of friable consistency that may bleed on the slightest touch or even spontaneously because they receive florid blood supply from the conjunctive.[4,6,7,9]

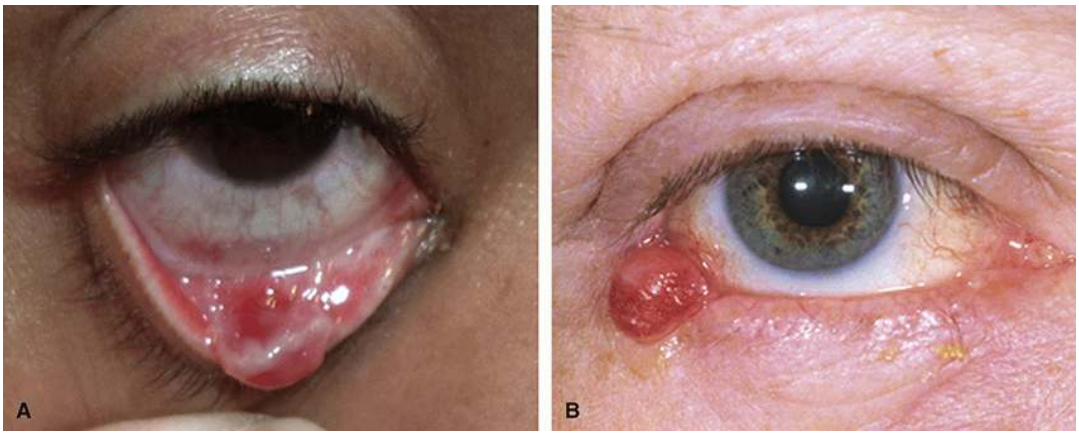

FIGURE 107.1 Pyogenic granuloma. A, Central lower eyelid palpebral conjunctiva. B, Medial lower eyelid conjunctiva.

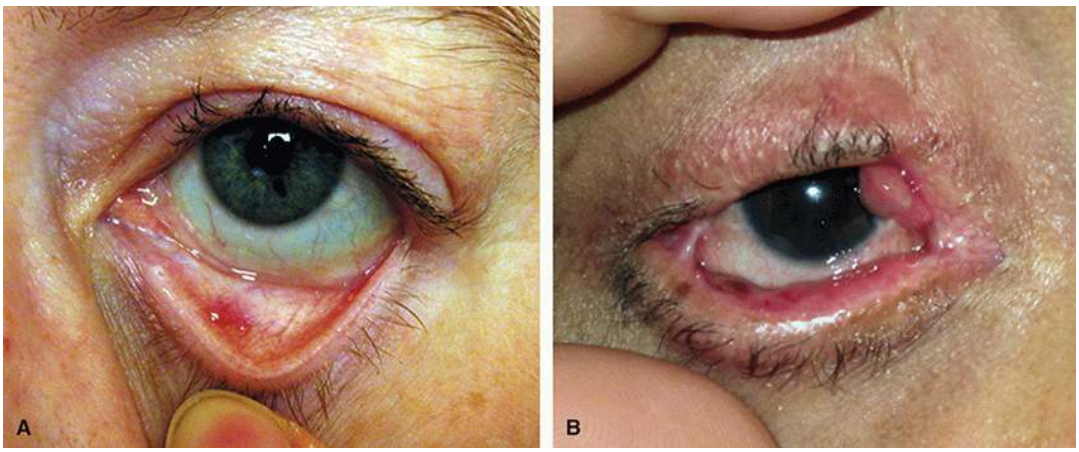

FIGURE 107.2 A, PG of the lower eyelid palpebral conjunctiva. B, Lateral upper eyelid PG from the conjunctiva associated with a traumatic defect. A, (Courtesy of Dr. Robert A. Goldberg.)

Pyogenic granulomas may also develop as an inflammatory outgrowth from the upper or lower punctum in patients with canaliculitis or after punctal plug insertion due to mechanical stress on the canalicular epithelium with attendant epithelial injury (Figure 107.2).[9,12,20] They can also be observed *(Print pagebreak 704)* in the medial canthal region following silicone intubation or after placement of a Jones Pyrex tube, or in an anophthalmic socket beneath an ocular prothesis (Figure 107.3).[12,21]

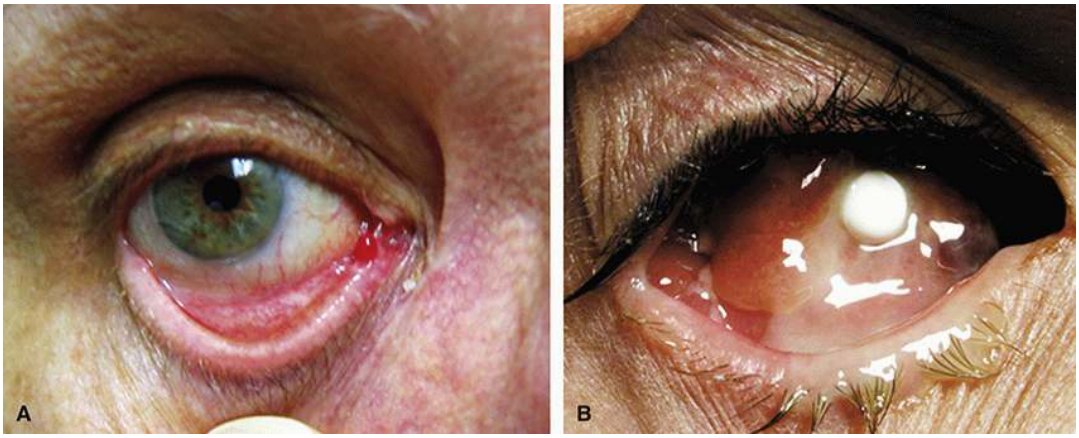

FIGURE 107.3 A, A small PG arising from the inferior punctum. B, An extensive PG in the medial canthal palpebral conjunctiva and the medial bulbar conjunctiva. B, (Courtesy of Dr. Robert A. Goldberg.)

Differential Diagnosis

Although the typical clinical picture combined with a history of chalazion excision or other conjunctival surgery or trauma easily establishes the diagnosis, pyogenic granuloma may be confused with several other entities. These include other vascular tumors of the eyelid or conjunctiva, particularly acquired or cherry angioma of the eyelid, which is considered by some authorities to be a variant of PG.[22] Other vascular tumors of the conjunctiva such as infantile hemangioma, lymphatic malformation, lymphangiectasia, Kaposi sarcoma, varix, cavernous venous malformation, racemose hemangioma, cherry angioma, glomangioma, and solitary fibrous tumor should be excluded as well.[8,18]

The differential diagnosis should also include conjunctival foreign body granulomas (teddy bear granuloma) caused by embedded synthetic fibers or eyelashes, a condition that is typically observed in the inferior fornix.[23,24,25] The color of those lesions is usually whitish yellow, which can help differentiate them from pyogenic granulomas. However, a bluish-black color can be encountered as well and may be difficult to discern from PG.[26]

Ointment granulomas, which may occur due to exposure of an open conjunctival wound to ophthalmic ointments containing petrolatum or paraffin, may also simulate a pyogenic granuloma.[27] Clinically, they present as unilateral or bilateral reddish or inflamed eyelid bumps following sutureless transconjunctival lower eyelid surgery.[27] If the diagnosis is in doubt, microscopic evaluation can help clinch the diagnosis because even in the setting of foreign body granulomas or ointment granulomas, the histopathological features are unique and distinct from a pyogenic granuloma.[23,24,25,26,27] Pyogenic granulomas may also mimic rare eyelid entities like amelanotic melanoma[18] or eyelid metastasis, which may occur with or without a detectable primary lesion.[28,29]

Treatment

Topical steroids have been routinely prescribed as initial monotherapy for the management of pyogenic granulomas. However, in recent years the options for the medical management of PG have been expanded with the addition of topical β-blockers.[30] Currently, recommended medical treatment consists of a twice-daily application of timolol 0.5% eyedrops, with or without the addition of topical steroid ointment for a minimum of 3 weeks.[3,5,11] The mechanism of action of timolol is probably similar to the role played by β-blockers in the management of infantile hemangiomas.[3,11] Vasoconstriction within the lesion causes inhibition of vascular growth factors thus promoting apoptosis.[11] Whether the addition of topical β-blockers reduces the need for surgery for a condition that was historically considered essentially surgical[10] requires further clarification in larger studies.[7,11] The role of topical timolol may clinically be more important in children with PG than in adults because it may be difficult to monitor the intraocular pressure in children receiving topical steroids alone. Moreover, if surgery is required, general anesthesia may be needed in children,[11] in contrast to adults where surgery can be performed with topical anesthetic eye drops alone.[6] *(Print pagebreak 705)* When the diagnosis of PG is in doubt, surgical excision for

histologic confirmation may be the preferred procedure of choice regardless of age.[30]

If medical measures fail, surgical excision followed by cauterization of the base of the lesion is recommended.[6,10] Because PG is essentially a vascular tumor, cautery is needed to control bleeding, but even if no cautery is used, intraoperative hemorrhage is seldom a problem and only minimal bleeding is encountered.[6] Also, cautery after surgery may reduce recurrences.[7,9] Low-dose plaque brachytherapy may also be indicated if multiple recurrences occur.[7,9] Intralesional injection of steroids at the time of surgery may also help reduce recurrences.[4]

Prognosis

Because the lesions are friable they can rarely fall off on their own.[6,10] Following medical treatment or surgical excision, pyogenic granulomas usually heal with minimal scarring; however, even after complete excision they may recur, and some patients may experience multiple recurrences especially if the initiating event is not attended to.[4,6,9,10]

Histopathology

Pyogenic granulomas may be encountered on the conjunctival surface or the epidermal surface of the eyelid, although conjunctival PGs are far more common. Conjunctival PGs represent a form of exuberant granulation tissue, usually resulting from trauma.[6,31,32,33,34,35] They feature proliferating capillaries, often with a prominent radial arrangement, extending from the base of the lesion toward the surface (Figure 107.4A). Endothelial cells are often plump and prominent.[31] The capillaries are within edematous stroma containing varying proportions of neutrophils, lymphocytes, plasma cells, and macrophages (Figure 107.4B and C).[6,31,35] The overlying epithelium may be attenuated or ulcerated.[6,31,35]

Early cutaneous pyogenic granulomas are identical histologically to granulation tissue, while mature lesions have a lobular pattern due to fibrous septa subdividing the capillary proliferation (Figure 107.5).[36] Many PGs feature an exophytic mass of proliferating capillaries in an edematous matrix superficially and a lobular pattern of proliferating capillaries in the deeper portion of the lesion.[37] Early lesions usually have eroded epidermis with a mixed inflammatory infiltrate in the edematous stroma.[36] Epidermis covers fully developed cutaneous PGs, a collarette of hyperplastic epidermis partially surrounds the base, stromal edema resolves, and inflammation is sparse.[36] Over time, there is increasing fibroplasia with diminishing capillaries until ultimate resolution into a fibroma.[36] Endothelial cells of cutaneous PGs do not express glucose transporter 1 (GLUT1).[38]

Intravenous PGs are the vascular analog of conjunctival and cutaneous PG.[39,40,41] There is a polypoid lobular *(Print pagebreak 706)* proliferation of capillaries embedded in a fibromyxoid stroma within the vessel lumen (Figure 107.6A and B).[39,40] Larger thin-walled veins, arterioles, and small arteries accompany the capillaries within the stroma.[39] A broad fibrovascular stalk connecting the lesion to the vein wall can usually be identified.[39,40] On other occasions, the lesion appears to be floating within the vessel lumen or it may completely occlude the lumen. Endothelial cells of the proliferating capillaries express CD31 (Figure 107.6C), CD34, factor VIII-related antigen, vimentin, and *Ulex europaeus* agglutinin-1 (UEA-1).[42,43] In addition to the endothelial cells, smooth muscle cells are carried from the vein wall into the fibrovascular stalk.[39] The fibromyxoid stroma of intravenous PGs contains scattered chronic inflammatory cells.[40]

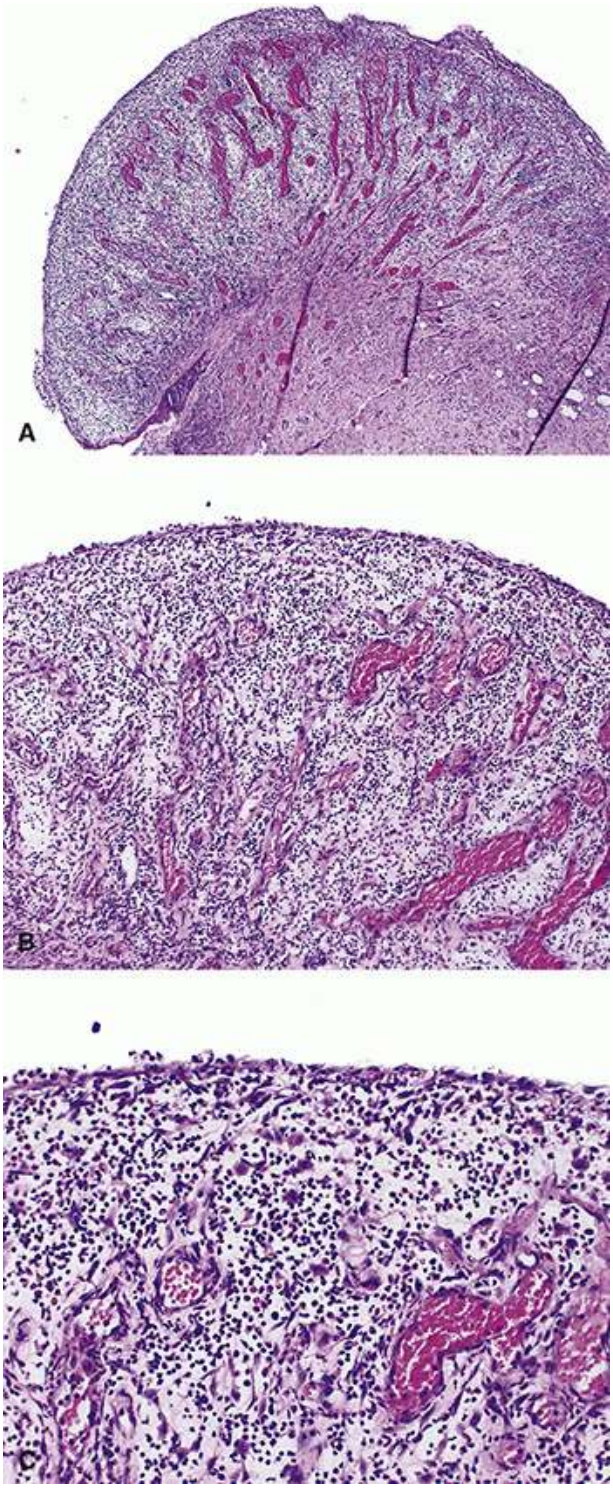

FIGURE 107.4 This conjunctival PG arose following surgery for a pterygium removal. A, At low magnification, proliferating capillaries within an edematous stroma radiate from a narrowed base toward the surface. The overlying epithelium is ulcerated, and there is focal hyperplastic epithelium creating a collarette at the lesion's base. B, Capillaries of varying caliber are within edematous stroma containing numerous leukocytes. C, The leukocytic infiltrate has a mixture of neutrophils, lymphocytes, plasma cells, and macrophages.

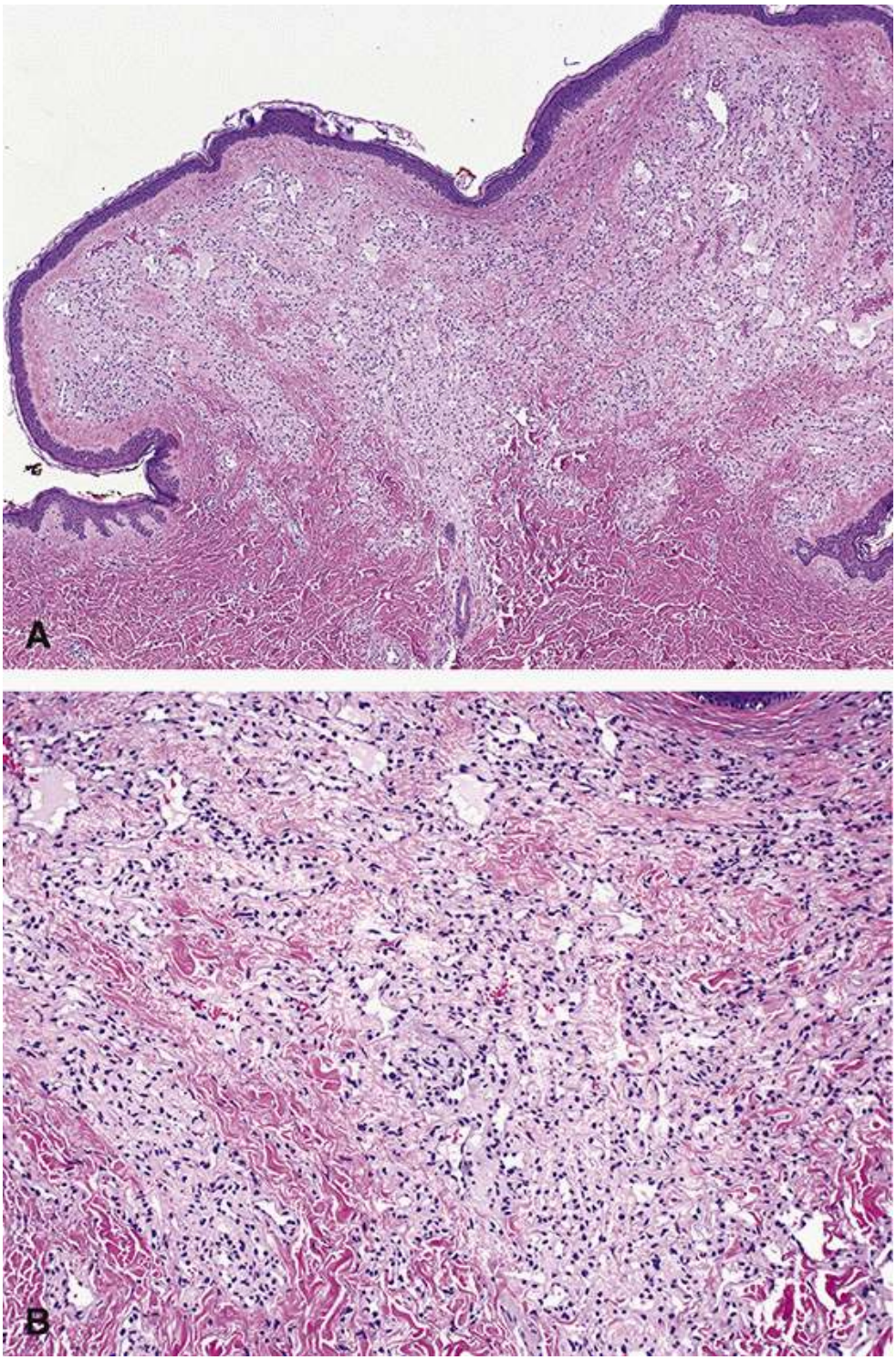

FIGURE 107.5 A, Epidermis covers this cutaneous PG, a collarette of hyperplastic epidermis surrounds the base, stromal edema is minimal, and inflammation is sparse. B, Lobules of capillaries are enmeshed in loose fibrous stroma and separated by dense fibrocollagenous septa.

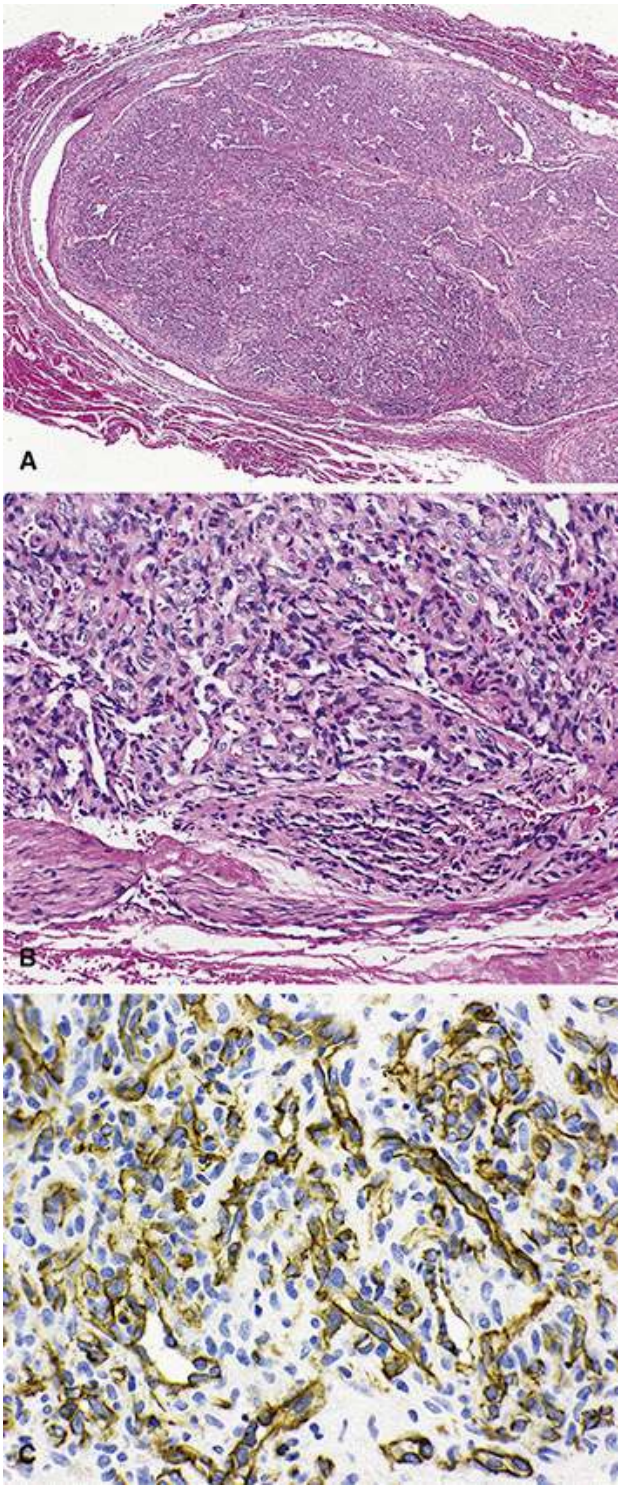

FIGURE 107.6 A, This intravenous PG arose in a vein at the left upper eyelid's lateral edge and was manifest clinically as a freely mobile subcutaneous mass. It was present clinically for 6 months before excision. B, The polypoid lesion is formed of lobules of capillaries enmeshed in fibromyxoid stroma with few chronic inflammatory cells. C, Immunohistochemical staining using antibodies to CD31 highlights the capillary endothelial cells.

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CHAPTER 108

Rhabdomyoma

Key Points

- Rhabdomyoma is a rare benign mesenchymal tumor of soft tissue originating from skeletal muscle cells
- It is usually subdivided into two major subtypes, cardiac and extracardiac, based on their sites of location
- The extracardiac type is uncommon, usually affects the soft tissues of the head and neck, and most often derives from the musculature of the third and fourth branchial arches
- They frequently involve in the larynx, pharynx, floor of the mouth, and tongue, and very rarely the eyelid
- Rhabdomyoma has been considered to be a hamartoma of striated muscle, but it may also result from chronic irritative stimulation
- Tumors usually present as a unilateral or bilateral, solitary or multifocal, smooth, mobile, firm to rubbery subcutaneous or submucosal nodule
- Treatment is with complete surgical excision, but more recently, patients have been treated successfully with sirolimus and everolimus
- The prognosis is usually very good, and recurrence after surgery is very rare

Tumors showing skeletal muscle differentiation are classified as either benign rhabdomyomas or malignant rhabdomyosarcomas. Rhabdomyomas are rare benign mesenchymal tumors of soft tissue originating from skeletal muscle cells and account for about 2% of all skeletal muscle tumors.[1,2,3] Classification is based on histologic, topographic, clinical, and immunohistochemical criteria. They are usually subdivided into two major subtypes, cardiac and extracardiac, based on their location.[4,5]

The cardiac type is more common. It is seen mostly in children and is frequently associated with phacomatoses.[6] Cardiac rhabdomyomas are considered to be hamartomatous lesions derived from embryonal myoblasts. They exhibit a fetal pattern of atrial natriuretic peptide immune reactivity and are associated with tuberous sclerosis complex in up to 60% to 96% of cases.[7]

The extracardiac type of rhabdomyoma is extremely uncommon, usually affecting the soft tissues of the head and neck with a 2:1 to 3:1 male predominance.[6,8,9] The peak age of incidence is in the fifth to sixth decades, but they can be seen in patients ranging from childhood to old age. Tumors occur in diverse anatomical sites and have been divided into subtypes based on clinical and morphological criteria[1,2,10,11,12,13]: the adult and fetal subtypes. Unlike the cardiac type, extracardiac rhabdomyomas do not have an association with tuberous sclerosis.[10]

Adult rhabdomyomas most often derive from the musculature of the third and fourth branchial arches located in the head and neck.[14,15] They frequently involve the larynx,[16] pharynx,[6] floor of the mouth,[17] and tongue.[18] Other rare locations include the cheek,[19] lower lip,[20] the tunica vaginalis of the testis,[21] the sternocleidomastoid muscle,[1,22] and the muscular wall of the stomach, even though striated muscle is normally not present in this location.[23] Adult rhabdomyoma has also very rarely been reported in the skin.[24,25,26] Only two cases of adult rhabdomyoma have been described involving the eyelid,[27,28] and six orbital cases were described involving the rectus muscles.[29,30,31,32,33,34]

The fetal type of extracardiac rhabdomyoma is the least common variety. It is seen most often in the head and neck region of young male children, less than 3 years of age.[35,36] They are classified histologically into myxoid and cellular subtypes.[11,36] The myxoid type has been described in infants during the first year of life as subcutaneous lesions in the head and neck, particularly in the preauricular and postauricular regions, and in the vulvovaginal region of middle-aged women. The cellular type occurs most often in mucosal and soft tissues of the head and neck of children, adolescents, and occasionally older male adults.[36,37,38] This type has also been reported in the stomach, retroperitoneum, upper extremity, and anus.[11,39] Two cases of fetal rhabdomyoma were

described in the eyebrow.[40,41]

Etiology and Pathogenesis

Rhabdomyoma has been considered to be a hamartoma of striated muscle because most cases are seen in children, often associated with congenital conditions.[42,43] For fetal rhabdomyoma, the pathophysiology has also been considered as a developmental malformation,[44] or even a neoplasm.[25] In a case of parapharyngeal rhabdomyoma a translocation between chromosomes 15 and 17 and an abnormality on chromosome 10 was described, suggesting a neoplastic etiology.[45] In another case of an eyelid rhabdomyoma associated with an anophthalmic socket,[27] the tumor was associated with a prosthesis, perhaps suggesting a role for a chronic irritative stimulation in the development of the tumor.

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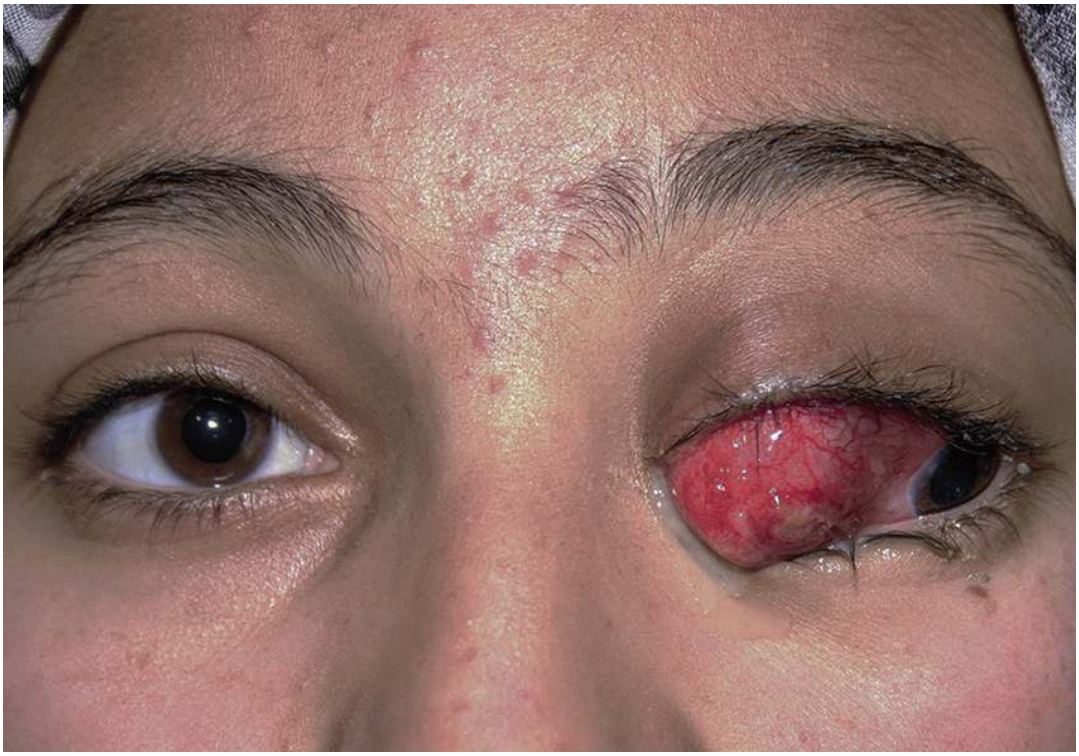

FIGURE 108.1 Submucosal rhabdomyoma of the medial canthus.

Clinical Characteristics

The clinical presentation of rhabdomyoma varies depending upon the specific location. In most cases, it presents as a slow-growing lesion that may enlarge over months to years. Tumors usually present as a unilateral or bilateral smooth, mobile, firm to rubbery subcutaneous or submucosal nodule (Figure 108.1).[20,25,27] They are generally asymptomatic initially and for long periods but may become symptomatic if adjacent structures become compressed. Pain is unusual. Tumors are usually solitary but may be multifocal with up to 10 synchronous lesions.[46,47,48] When near the surface, the lesion may appear tan or brownish and can be focally ulcerated.[27]

Differential Diagnosis

The differential diagnosis of rhabdomyoma includes a wide variety of benign and malignant lesions. In published cases, initial diagnoses have included granular cell tumors, rhabdomyosarcoma, alveolar soft part sarcoma, hibernoma, oncocytoma, crystal storing histiocytosis, schwannoma, squamous cell carcinoma, and vascular malformations.

Treatment

Treatment of extracardiac rhabdomyoma is with complete surgical excision (Figure 108.2). Recurrences are rare and patients usually do well. The outlook for patients with cardiac rhabdomyoma has been considered to be poor, resulting in death within the first 5 years of life being usual.[49] Some authors have suggested that an aggressive surgical approach to this tumor is indicated.[50] More recently, patients have been treated successfully with sirolimus and everolimus resulting in significant tumor regression.[51,52] In a study of 7 children with 24 cardiac tumors followed for 2 to 15 years, 20 underwent complete and 3 partial spontaneous regression.[5]

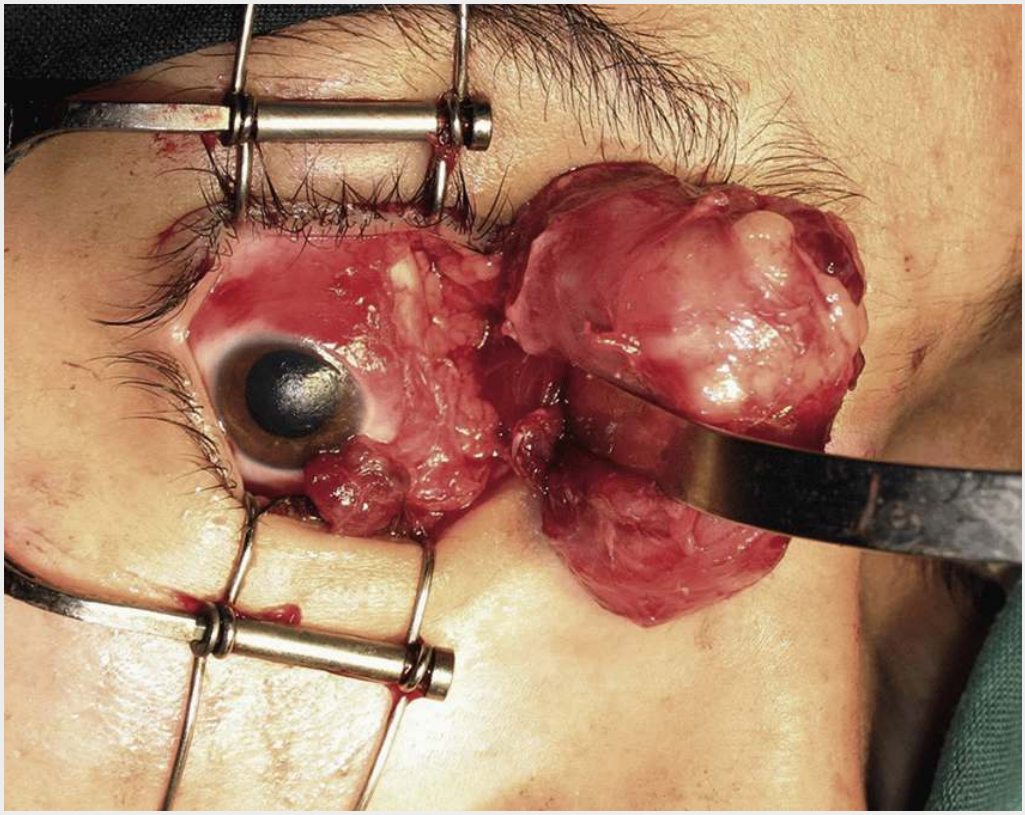

FIGURE 108.2 Surgical excision of the lesions in Figure 108.1.

Prognosis

The prognosis is usually very good, and recurrence after surgery is very rare, usually attributed to incomplete removal. No cases of malignant transformation have been reported.

Histopathology

Adult rhabdomyomas are composed of well-demarcated, unencapsulated lobules of large polygonal cells with scant intervening stroma (Figure 108.3).[10,15] Tumor cells have large amounts of eosinophilic granular cytoplasm or vacuolated cytoplasm, well-defined cytoplasmic borders, and small, round central or peripherally located nuclei with prominent nucleoli.[10,15,53] Cytoplasmic vacuoles may create a “spider web” appearance due to cytoplasmic strands between peripheral vacuoles.[10,15] Abundant cytoplasmic glycogen can be highlighted with periodic acid-Schiff stain.[10,15,53] Cytoplasmic cross-striations may be evident in hematoxylin and eosin-stained sections and accentuated using Masson trichrome or phosphotungstic acid hematoxylin stains.[15,54] The cytoplasm may also contain haphazardly arranged rod-like crystalline inclusions.[15,53] Mitoses are not seen,[10,15,53] but foci of inflammation and necrosis are identified in a minority of mucosal adult rhabdomyomas.[15] Tumor cells are immunoreactive using antibodies to muscle-specific actin, desmin, and myoglobin.[15,54] There may be focal immunoreactivity for vimentin, smooth muscle actin, S100 protein, and CD57 (Leu-7).[15]

Fetal rhabdomyomas are subdivided histologically into myxoid (classic) and intermediate (cellular) variants.[10,36] Myxoid fetal rhabdomyomas are well circumscribed but unencapsulated masses “composed of an admixture of haphazardly arranged, immature, slender skeletal muscle fibers with rare, delicate cytoplasmic cross-striations and undifferentiated round, oval to spindled, and serpentine cells in an abundant myxoid to fibromyxoid stroma.”[36] The skeletal muscle cells of myxoid fetal rhabdomyomas of the head and neck have small oval *(Print pagebreak 710)* nuclei, inconspicuous nucleoli, and scarce cross-striations.[35,36]

Undifferentiated mesenchymal cells vary from resembling small lymphocytes to large, spindle-shaped fusiform cells without myofibrils or cross-striations.[35] Mitoses are rare.[35]

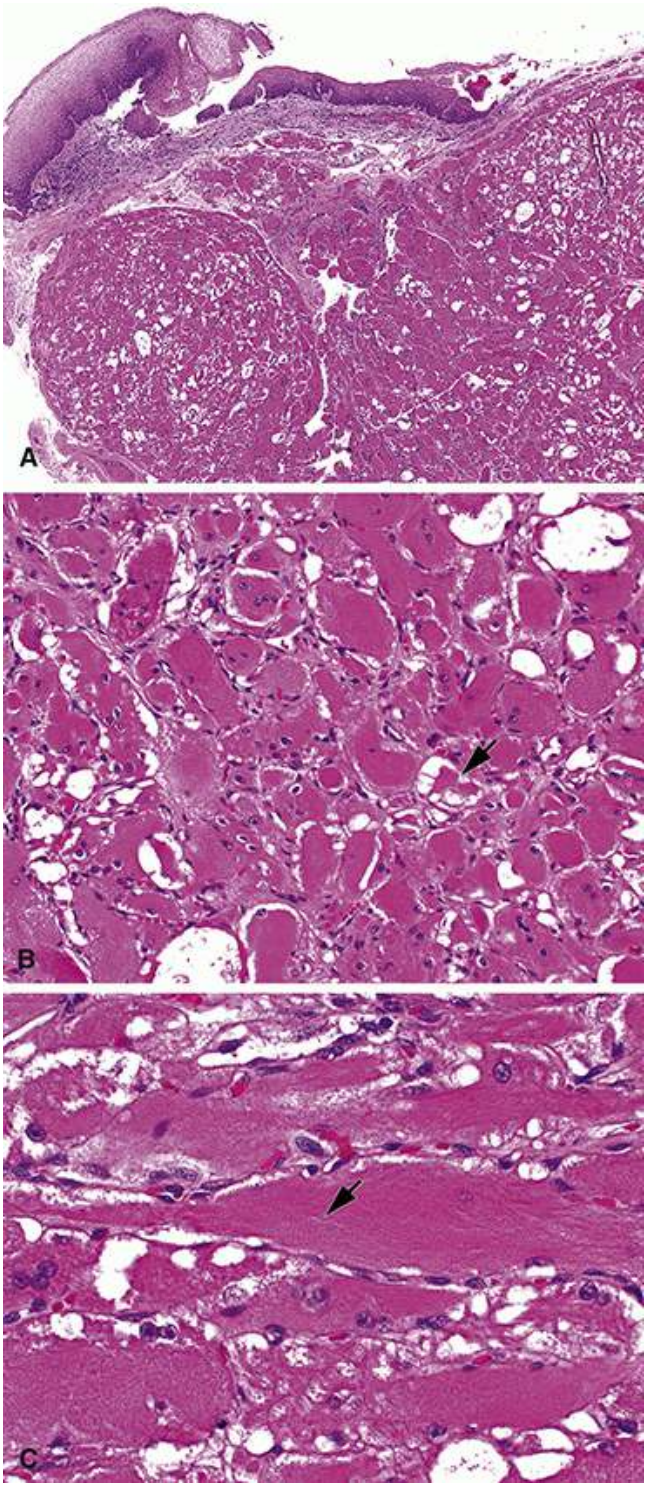

FIGURE 108.3 This adult rhabdomyoma developed in the base of the tongue of a man in his early 60s. A, Well-circumscribed lobules of tumor cells are in the submucosa. B, The tumor cells are large and round to polygonal and have eosinophilic and vacuolated cytoplasm. Round nuclei with distinct nucleoli are in the center or periphery of the cells. One cell has cytoplasmic strands between vacuoles creating a "spider web appearance" (*arrow*). There is scant stroma with blood vessels between tumor cells. C, The cells have variable vacuolation and focal cross-striations (*arrow*).

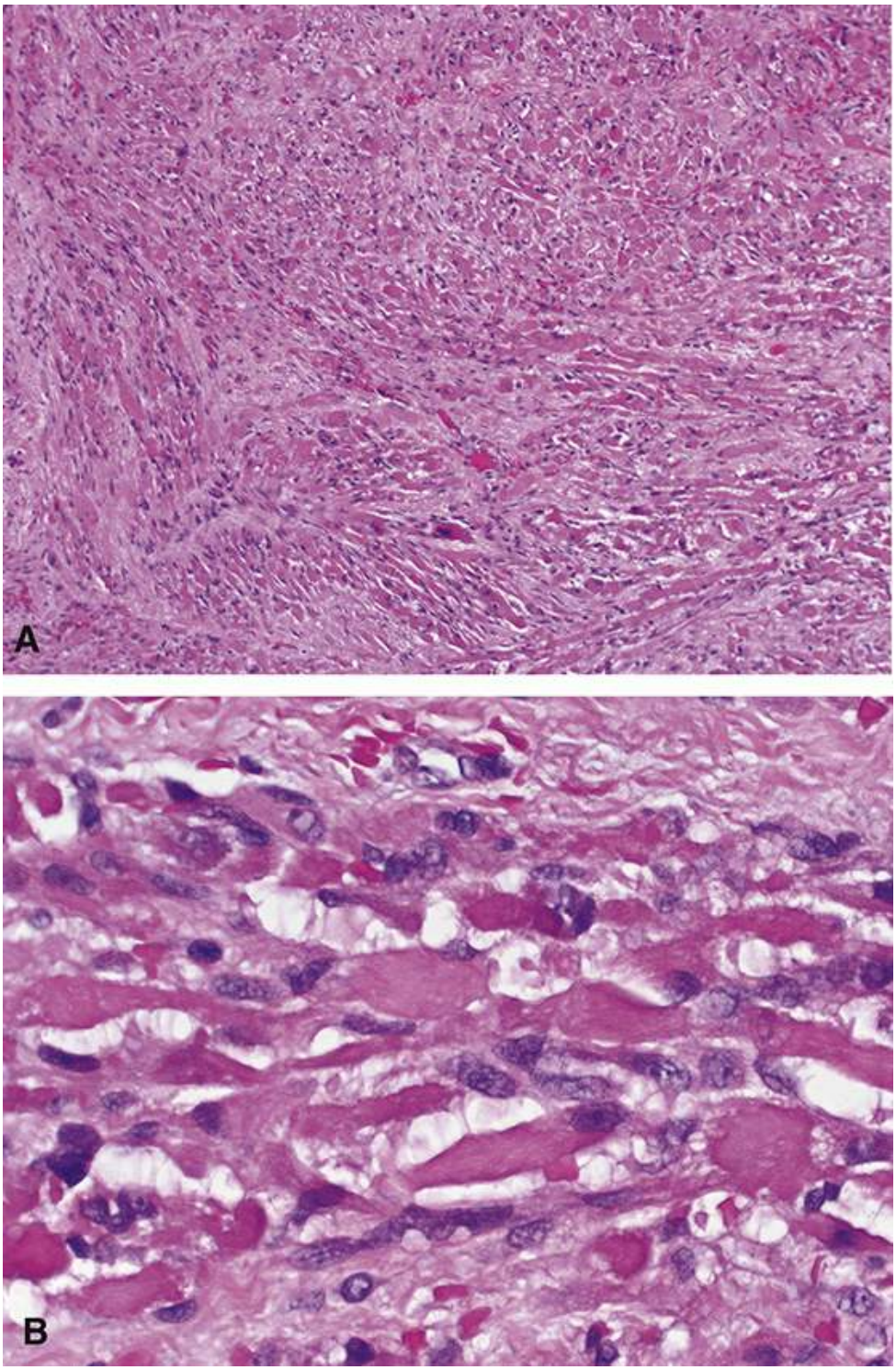

FIGURE 108.4 Intermediate fetal rhabdomyoma from the orbit of a 3-year-old boy. A, Eosinophilic tumor cells form fascicles with some sectioned longitudinally, others in cross-section. B, The tumor is a mixture of cells with scant cytoplasm and many strap cells with abundant eosinophilic cytoplasm and occasional cross-striations. There were no mitotic figures identified in the tumor.

Intermediate fetal rhabdomyomas exhibit a broad range of skeletal muscle differentiation, but most tumors have at least small foci of primitive mesenchymal cells and delicate rhabdomyoblasts.[36] Of the 16 intermediate fetal rhabdomyomas reported by Kapadia et al, 7 had differentiation ranging from primitive mesenchymal cells to large ganglion cell-like rhabdomyoblasts to strap cells having prominent cross-striations.[36] Ribbon-like rhabdomyoblasts may form sheaves or interlacing bundles.[36] Of the 16 intermediate fetal rhabdomyomas reported by Kapadia et al, 9 had maturation arrest with rhabdomyoblasts of slightly larger caliber than fetal-type muscle fibers and more abundant eosinophilic cytoplasm than in the myxoid variant of fetal rhabdomyoma (Figure 108.4).[36] Six of the cases with *(Print pagebreak 711)* maturation arrest had broad fascicles of cells that resembled a leiomyoma at low magnification.[36] Cross-striations are usually more apparent in intermediate fetal rhabdomyomas than in the myxoid variant.[36] Mitoses are uncommon, and atypical mitoses are not seen.[36] Tumor cells are immunoreactive using antibodies to muscle-specific

actin, desmin, and myoglobin, with focal or rare staining for vimentin, smooth muscle actin, S100 protein, glial fibrillary acidic protein, and CD57 (Leu-7).[36]

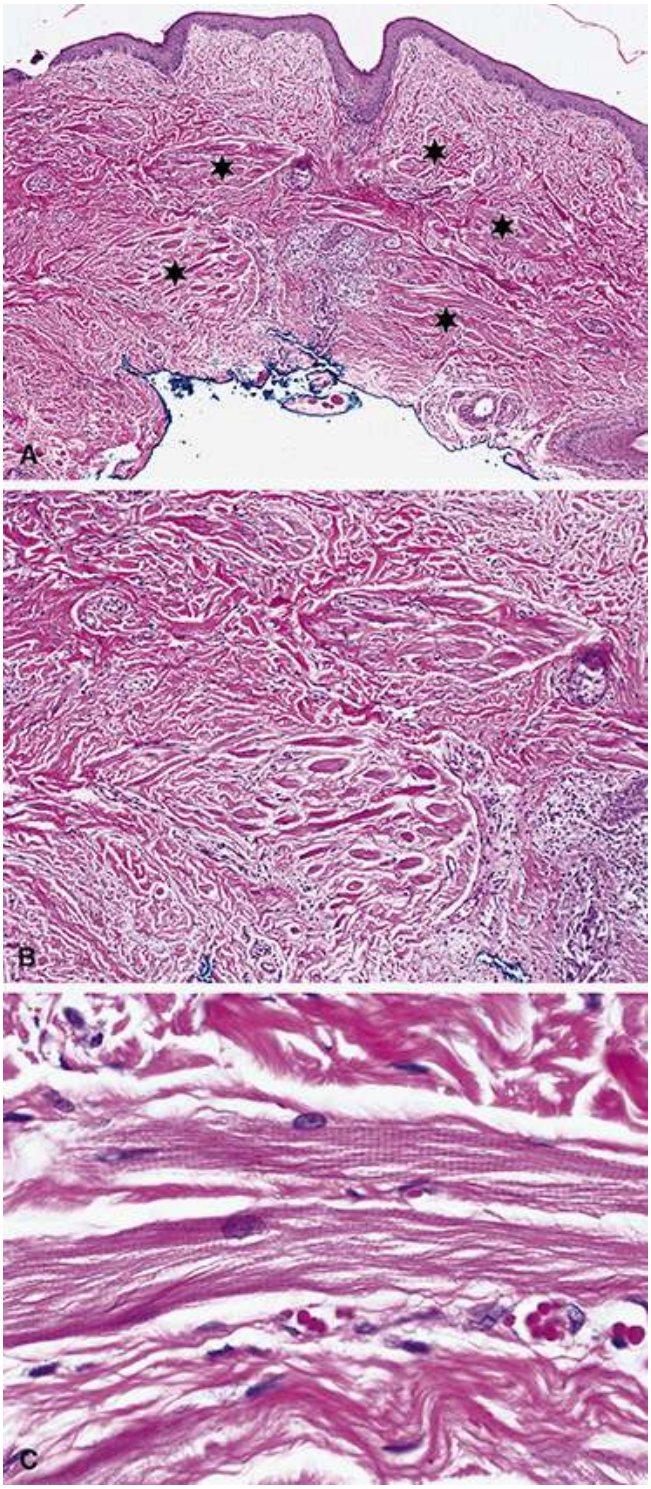

FIGURE 108.5 This skeletal muscle hamartoma (rhabdomyomatous mesenchymal hamartoma) was excised from the medial left lower eyelid of a 57-year-old woman.[57] A, Multiple striated muscle fiber bundles (★) are in the superficial to deep reticular dermis. B, Irregularly thickened collagen bundles are between and among the bundles of skeletal muscle fibers. C, Most of the myocytes have a splayed appearance with retained cross-striations.

A cutaneous lesion that may be confused with rhabdomyoma is rhabdomyomatous mesenchymal hamartoma, also termed "skeletal muscle hamartoma." These rare lesions feature single or small groups of mature skeletal muscle fibers in the dermis and subcutis, frequently in a collagenous stroma with mature adipose tissue and adnexal structures.[55] The cases reported in the adult eyelid have featured individual and bundles of disorganized well-differentiated skeletal muscle in the dermis (Figure 108.5).[56,57]

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CHAPTER 109

Rosacea

Key Points

- Rosacea is a chronic skin disorder of diverse cutaneous manifestations associated with inflammation of the face
- It is characterized by episodes of flushing of the central face, sometimes associated with telangiectasia often brought on by alcohol, spicy foods, exercise, UV light exposure, cold or hot weather, or hot water
- Phymatous rosacea manifests as marked skin thickening and irregular nodularities that are most often seen on the nose and less frequently on the forehead, eyelids, and chin
- The etiology and pathophysiology of rosacea are not completely understood, but there is evidence to support a genetic predisposition
- Ocular rosacea usually presents with conjunctival hyperemia, epiphora, burning, itching, foreign body sensation, dry eyes, photophobia, blurred vision, conjunctival telangiectasia, eyelid blepharitis, and meibomian gland dysfunction
- A careful history should attempt to uncover any identifiable factors that trigger exacerbations of the symptoms
- Treatment includes warm compresses, eyelid scrubs, oral antibiotics, correction of collagen abnormalities, topical retinoids, and intense pulsed light therapy
- Ocular rosacea is not a curable disease, and patients typically suffer significant morbidity although symptoms can often be controlled

Rosacea is a chronic skin disorder of diverse cutaneous manifestations associated with inflammation of the face.[1] It occurs in about 10% of the population, most commonly in patients over 30 years of age and those with Fitzpatrick skin types I and II.[2] Women are affected with cutaneous rosacea more frequently than men,[3,4] but ocular rosacea affects both genders equally.[3] Rosacea most commonly affects middle-aged adults, with a peak incidence between the ages of 40 and 59 years,[3] but it may sometimes be seen in early childhood and old age.[5] Approximately 30% to 40% of patients with rosacea report a family member with the condition.[6]

The diagnosis of rosacea is based on the clinical findings, but these are generally nonspecific, making the diagnosis difficult in many cases.[7,8] In 2002, the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea proposed four broad clinical subtypes of rosacea: erythematotelangiectatic, papulopustular, phymatous, and ocular.[9,10]

In erythematotelangiectatic rosacea, there are episodes of flushing of the central face, sometimes associated with telangiectasia. The redness also may involve the ears, scalp, neck, and chest, but the periocular skin is spared. Alcohol, spicy foods, exercise, cold or hot weather, and hot water may bring on these episodes.[9] Papulopustular rosacea generally presents with erythema and flushing of the central portion of the face combined with intermittent or persistent episodes of small papules and pustules. As with the erythematotelangiectatic subtype, the periocular skin is usually spared.[9] Phymatous rosacea is characterized by marked skin thickening and irregular nodularities that are most often seen on the nose (rhinophyma) and less frequently on the forehead, eyelids, and chin.[9] In ocular rosacea, ophthalmic manifestations usually occur along with the cutaneous findings, but in some cases, they may precede them by many years.[8,11] It is not clear if these different subtypes develop progressively or if they occur as discrete variants.[12,13]

Ocular rosacea usually presents with conjunctival hyperemia, epiphora, burning, itching, foreign body sensation, dry eyes, photophobia, blurred vision, conjunctival telangiectasia, eyelid blepharitis, and meibomian gland dysfunction.[8,14] The findings of ocular rosacea in children are generally similar to those seen in adults.[15] The skin findings are often absent in pediatric cases,[16,17] but when present, they follow the ocular manifestations in about 55% of cases.[18]

Etiology and Pathophysiology

The etiology and pathophysiology of rosacea are not completely understood, but there is evidence to support a genetic predisposition. This includes the increased prevalence of rosacea in some northern European populations and the association of rosacea with autoimmune disorders.[19] Gene array and polymerase chain reaction analyses indicate a defined gene profile for each of the different rosacea subtypes.[12,20] Proposed factors that may be contributory to the development of rosacea include abnormal vascular reactivity, dysregulation of the innate immune system, increased susceptibility of sensory nerves to temperature changes or spicy foods, ethanol, exercise, UV radiation, *Demodex* overgrowth on the face or small intestinal bacterial overgrowth, and pilosebaceous unit abnormalities.[4,13,21,22,23,24]

Rosacea shows great variation in clinical manifestations suggesting a possible wide range of pathophysiological mechanisms.[25] The major elements appear to be an augmentation of immune reaction and response, and neurovascular *(Print pagebreak 714)* dysregulation.[25,26] There is an upregulation of genes involved in vasoregulation and neurogenic inflammation in all subtypes of the disease.[27] The causes of transient flushing are poorly understood, but some evidence suggests it is associated with the release of antimicrobial peptides and proteases,[28] neuropeptides,[13] or transient receptor potential ion channels[29] in the induction of erythema and vasodilation. The inflammatory infiltrate present in all four subtypes is not well characterized, but in early-onset rosacea, a lymphomonocytic infiltrate consisting primarily of CD3+ T cells, with CD20+ B cells, mast cells, and dendritic cells has been described.[25,27,30]

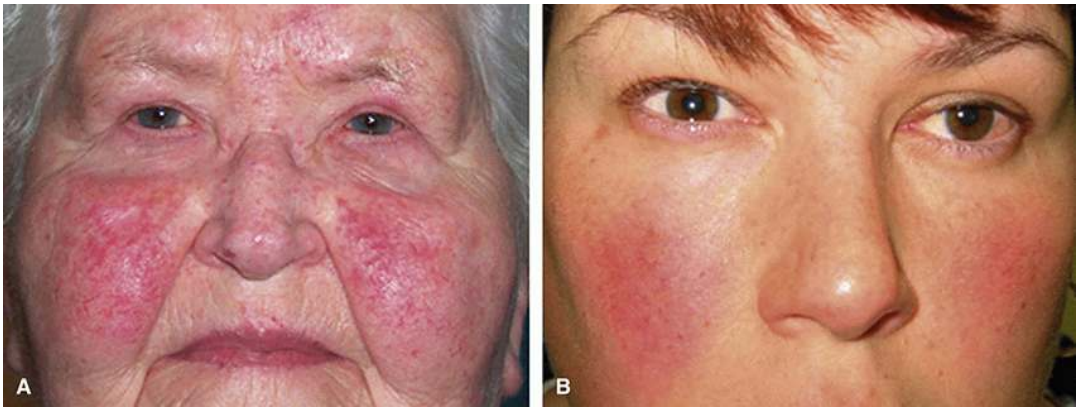

FIGURE 109.1 Rosacea primarily involving the central face with little or no simultaneous eyelid involvement. A, Facial rosacea with telangiectasis and mild erythema of the eyelids. B, Diffuse facial rosacea. A, (Courtesy of Dr. Morris Hartstein.)

Environmental factors that are known to exacerbate the disease lead to the activation of proinflammatory products and innate immune responses.[20,21] Cathelicidin, which has both vasoactive and proinflammatory actions, is elevated in the skin of patients with rosacea and has been implicated in its pathogenesis.[21,28,31]

In patients with ocular rosacea, the inflammatory basis of the disease is supported by elevated concentrations of interleukin-1a and 1b, tumor necrosis factor-alpha, and a greater activity of metalloproteinase-9 and collagenase-2 in tear fluids.[32,33,34,35] Overexpression of toll-like receptor 2 on keratinocytes may explain enhanced inflammatory responses to environmental stimuli and may be a factor in the pathogenesis of rosacea.[36] The inflammatory markers ICAM 1 and HLA-DR have also been observed to be overexpressed in conjunctival epithelial cells.[37]

Clinical Presentation

The symptoms of rosacea show episodes of exacerbations and remissions, but over time the disease usually progresses. While certain trigger factors such as sun exposure, extreme temperatures, alcohol, spicy foods, exercise, and emotional stress can worsen the symptoms, others, like smoking, appear to significantly reduce the risk of developing rosacea.[3] Facial rosacea may present with little or no simultaneous eyelid involvement[7] (Figure 109.1) More often, facial lesions include acne, sebaceous thickening with edematous papules and pustules, and thickening of the nose as rhinophymia (Figure 109.2). The eyelid inflammatory reaction results in meibomian gland dysfunction, chronic scarring of the gland orifices, and eyelid margin telangiectasias. This leads to tear film instability, epiphora, photophobia, keratitis, and blurred vision.[38,39] Other common findings include blepharitis and collarettes around the eyelashes. Patients often experience recurrent hordeola and chalazia (Figure 109.3).[7,17] Dry eye is a major finding in up to two-thirds of patients with ocular rosacea,[37,40] and pinguecula, chronic cicatricial conjunctivitis, and fibrosis have also been reported.[41,42,43]

Corneal manifestations may be seen in up to 33% of patients.[38,44] These can include superficial punctate keratitis on the lower third of the cornea and peripheral neovascularization with subepithelial infiltrates and can proceed to stromal ulceration, and even corneal

perforation.[45,46] Iritis, episcleritis, and scleritis are other potential ocular findings,[7,47] and a case of spontaneous scleral perforation has been described.[48]

Differential Diagnosis

Systemic lupus erythematosus is a skin condition that can mimic rosacea. This is a chronic inflammatory disease that has protean clinical manifestations, which include malar erythema in approximately 50% of patients. The erythema may last for hours to days and often recurs, especially with sun exposure.[49,50] Dermatomyositis is an inflammatory myopathy characterized by varying degrees of muscle weakness and skin erythema, but some patients lack muscular involvement and initially present only with skin manifestations. Macular violaceous erythema occurs most frequently in the seborrheic area of the face[51] that might be *(Print pagebreak 715) (Print pagebreak 716)* confused with the erythema seen in rosacea. Polymorphous light eruption is a common idiopathic photodermatosis with a higher prevalence in fair-skinned individuals,[52] characterized by erythematous papules, papulovesicles, and plaques on exposed skin surfaces following sun exposure.[53] Seborrheic dermatitis is a chronic skin disease characterized by a relapsing erythematous rash with well-demarcated patches, papules, or plaques seen most often on sebum-rich areas such as the face and scalp. Acne vulgaris is characterized by noninflammatory comedones and inflammatory papules, pustules, and nodules. It typically affects areas of skin with a high density of sebaceous glands such as the face, upper chest, and back.[54] Other rare conditions that have been misdiagnosed as rosacea include carcinoid syndrome with flushing of the face, neck, and upper trunk[55] and cutaneous lymphoma that can present with violaceous papules, plaques, and nodules on the face.[56]

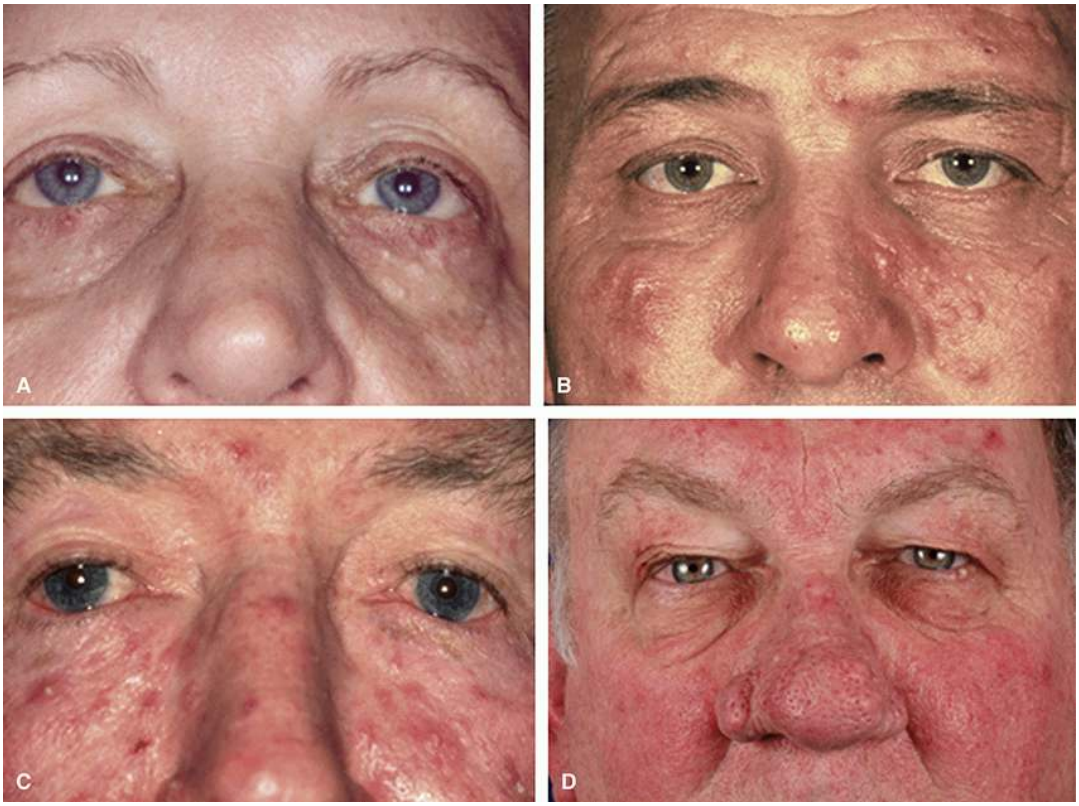

FIGURE 109.2 A, Facial and eyelid rosacea with sebaceous pustules. B and C, Facial and eyelid rosacea acne. D, Rosacea involving the face, eyelid, and forehead, with rhinophyma. C, (Courtesy of Dr. Charles Soparkar.) D, (Courtesy of Dr. Peter Rubin.)

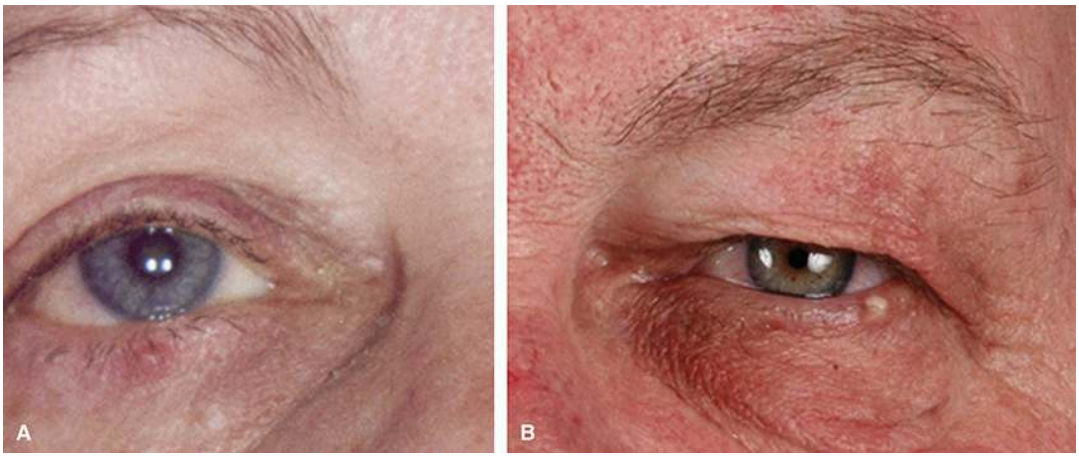

FIGURE 109.3 Eyelid rosacea with recurrent chalazia of the lower eyelids. B, (Courtesy of Dr. Peter Rubin.)

Treatment

Before the initiation of medical therapy, a careful history should attempt to uncover any identifiable factors that trigger exacerbations of the symptoms.[4,57] Identification of factors such as temperature extremes, wind, hot beverages, caffeine, exercise, spicy food, and emotional stress can help facilitate their avoidance or modulation.[58] A broad-spectrum sunscreen should be used for protection against UV light exposure. Some authors advocate the use of over-the-counter skin care products that contain a gentle cleanser designed to remove bacteria and other irritating residues, metronidazole topical gel for the treatment of inflammatory papules and pustules, and a hydrating agent to provide moisture and protect the skin barrier.[59]

More definitive initial approaches continue with conservative treatments to address the meibomian gland dysfunction and any ocular surface complications. Warm compresses, eyelid scrubs, and digital massage are used to express impacted oils and cellular debris from the meibomian glands.[60] Oral omega-3 fatty acids may help improve meibomian gland dysfunction, and artificial tears are used to improve corneal dryness.[61] Cyclosporine is an immunosuppressive agent that inhibits T cell functions, and topical cyclosporine is effective for the management of the ocular surface symptoms associated with ocular rosacea.[62]

Oral antibiotics have been used to help manage meibomian gland disease.[63] Although the mechanism by which antibiotics might influence meibomian gland function is not clear, it has been proposed that they may have an impact on matrix metalloproteinases, may effect changes in interleukins and nitric oxide, and correct collagen abnormalities.[34,35,64]

In addition to antibiotics, topical retinoids have been advocated as useful adjuncts for recalcitrant cases,[65] but recurrences are common. Retinoids inhibit comedone formation and make keratinocytes in sebaceous follicles less cohesive and easier to remove.[59]

Oxymetazoline cream is a vasoconstrictive alpha-adrenergic agonist used as a topical treatment for persistent facial erythema due to cutaneous vascular dilatation,[66] and in clinical trials, oxymetazoline resulted in a significant reduction of facial edema in patients with rosacea.[67,68]

Ivermectin has been used for some forms of rosacea because of its anti-inflammatory properties.[69] In several randomized, controlled studies, ivermectin 1% cream on the facial skin of patients with papulopustular rosacea was shown to be effective and well tolerated.[70,71] Gene expression levels for biomarkers including cathelicidin, interleukin-8, toll-like receptor-4, and human beta-defensin-3 were significantly downregulated following the use of topical ivermectin.[72]

Laser therapy for the treatment of rosacea has included the 595-nm pulsed dye laser and the dual-wavelength long-pulsed 775-nm alexandrite/1064-nm neodymium:yttrium-aluminum laser. These wavelengths are absorbed by hemoglobin, potentially eliminating cutaneous vascular lesions.[73,74] Studies have demonstrated the efficacy of laser therapy in treating telangiectasia [75] and in treating diffuse erythema in patients with rosacea.[76]

Intense pulsed light (IPL) therapy for rosacea is absorbed by telangiectatic vessels inducing coagulation and free radical vascular damage.[57] In several studies, IPL showed improvement in meibomian gland function and tear breakup time,[77,78] and others have shown improvement in erythema and telangiectasias.[79] A retrospective study demonstrated that doxycycline used in conjunction with laser or pulsed light therapy was efficacious in improving the signs and symptoms of rosacea.[80]

Surgical options are few for rosacea but may be appropriate in some cases. These include punctal occlusion for intractable dry eyes and ocular surface complications and incision and drainage of recurrent chalazia. For rhinophyma, mechanical dermabrasion, CO_2 laser resurfacing, or surgical shave procedures can provide a cosmetic improvement.

Prognosis

Ocular rosacea is not a curable disease, and patients typically suffer significant morbidity. Nevertheless, improved treatment options over the past several years have increased so that symptoms are more easily controlled. Identification and avoidance of trigger factors are important, as is routine everyday skincare. Recent investigations have expanded our options to include a variety of pharmaceutical agents, laser and IPL therapies. Strategies for the management of rosacea should be based on individual patient symptoms, as well as the psychological and psychosocial impact of the disease.[81,82]

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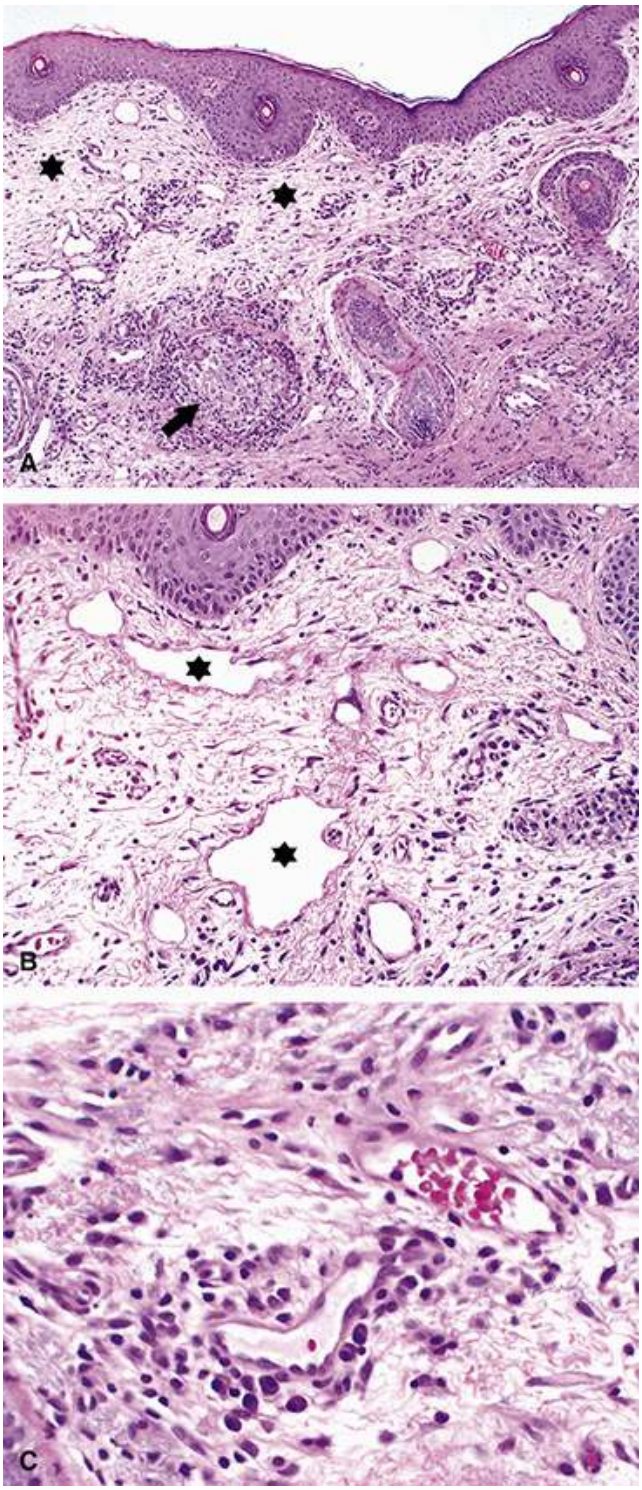

FIGURE 109.4 A man in his mid-70s with clinical rosacea had an incisional biopsy of an erythematous plaque of his right upper eyelid that was clinically suspicious for basal cell carcinoma. A, The papillary and superficial reticular dermis have telangiectatic vessels with marked edema of the papillary dermis (★). A granuloma is in the superficial reticular dermis (*arrow*). B, Markedly dilated vessels have irregular shapes, and some have a discontinuous endothelial cell lining (★). The papillary dermis is markedly edematous with separation of the collagen fibers and fibroblasts by clear edema fluid. C, Lymphohistiocytic infiltrate around a dermal blood vessel with swollen endothelial cells.

Histopathology

The histopathological findings in rosacea are variable and nonspecific.[83,84] The most common histological features are actinic (solar) elastosis,[83,84,85,86] telangiectasia (Figure 109.4A and B),[83,84,85,86] dermal edema (Figure 109.4A and B),[83,84,86] a loose lymphohistiocytic infiltrate around upper dermal blood vessels (Figure 109.4C)[83,84,86] and hair follicles,[84,86] acute folliculitis,[83,

[85] perifollicular granulomatous inflammation,[83] and *Demodex folliculorum* mites in hair follicles and sometimes in the dermis.[83,84,85,86] The actinic elastosis is usually moderate to severe,[84,85] characterized by curling, fragmentation, and aggregation of elastic fibers,[84] and more marked than in matched control specimens.[83] Vascular dilation is often prominent,[83,84] and the ectatic vessels are often irregularly shaped[84,87] with a discontinuous endothelial lining and swollen endothelial cells.[87] Perrigouard, Peltre, and Cribier found that two-thirds of the ectatic vessels with a diameter >30 µm were capillaries and venules and one-third were lymphatics.[87] None of the largest ectatic vessels were lymphatics.[87] Dermal lymphohistiocytic inflammation is usually more intense in papulopustular than erythematotelangiectatic rosacea.[83,86] A minority of rosacea biopsies have epidermal changes including parakeratosis,[83,84,86] hyperkeratosis,[83,86] acanthosis,[86] atrophy,[83] exocytosis of inflammatory cells,[86] and spongiosis.[84] Approximately 6% of biopsies have interface dermatitis.[86]

Granulomas may be found in erythematotelangiectatic[86] and papulopustular[83] rosacea and are an obligatory finding for diagnosing granulomatous rosacea (Figure 109.5).[85,88] Aroni et al identified granulomas in 48/73 (66%) of biopsies from patients with rosacea.[84] Biopsies with granulomatous inflammation had small palisaded granulomas with a concentric rim of histiocytes around degenerated collagen in 40/48 (83%) of cases, elastolytic granulomas in 20/48 (42%), and granulomas surrounding remnants of extrafollicular Demodex or destroyed follicles in 15/48 (31%) cases.[84] Sanchez and coworkers, in a study of 24 biopsies of granulomatous rosacea, classified the granulomatous inflammatory pattern as nodular (8 patients), perifollicular (3), diffuse (2), or combined perifollicular and nodular (13).[88] The different patterns of granulomatous inflammation were not specific for a particular clinical presentation; all were most common in people presenting with papules or erythematous plaques.[88] Helm and colleagues identified caseation necrosis in 11% of biopsies with granulomatous rosacea.[85]

Classic rhinophyma, clinically manifest as an enlarged nose with prominent pilosebaceous orifices and a preserved profile, has histological features of rosacea but with prominent sebaceous gland hyperplasia.[89] Severe rhinophyma, with a markedly distorted nose, has telangiectasia, dermal thickening, markedly diminished or absent pilosebaceous structures, and sclerotic collagen bundles with large amounts of mucin.[89,90]

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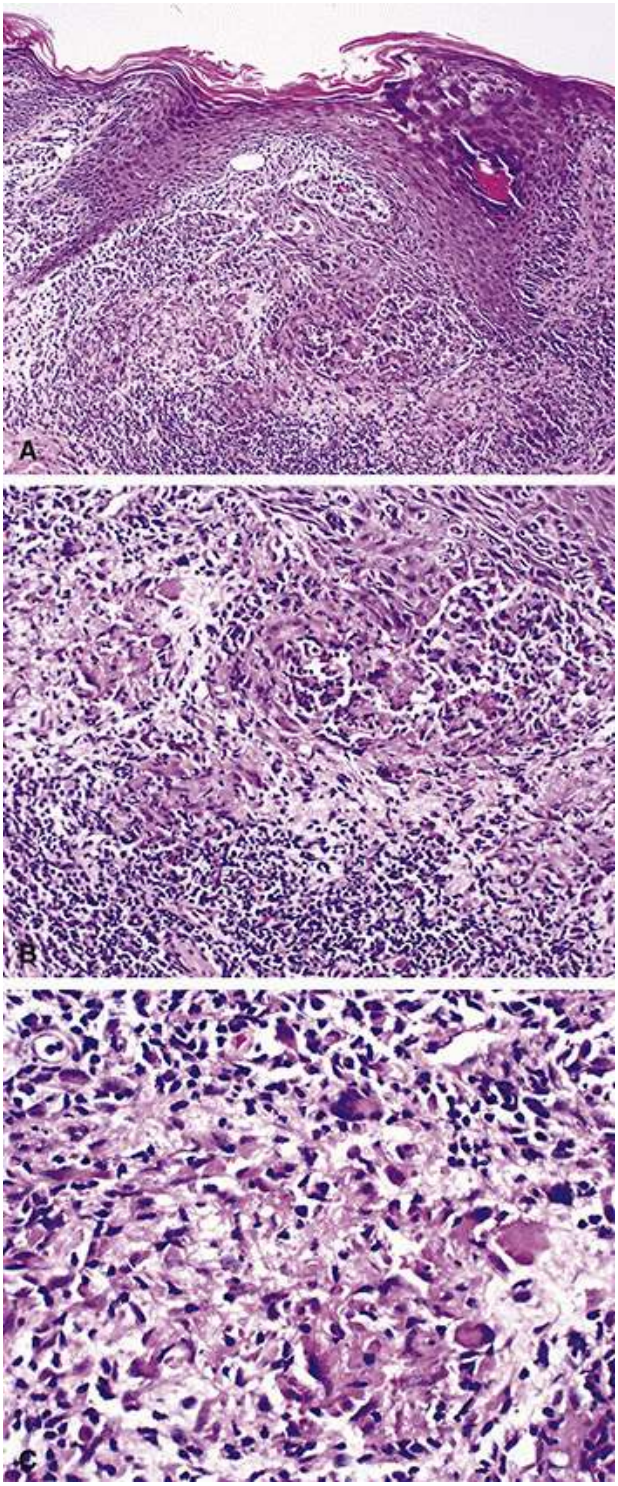

FIGURE 109.5 This man in his early 70s with chronic blepharitis had a biopsy of a hyperkeratotic area associated with madarosis. A, The epidermis is acanthotic with hyperkeratosis and parakeratosis. B, The dermis is diffusely infiltrated by lymphocytes and granulomas composed of loose aggregates of epithelioid cells with occasional multinucleated giant cells. The dermis between granulomas has a dense infiltrate of lymphocytes. C, The granulomas contain mostly epithelioid cells with a few giant cells. No fungi or acid-fast microorganisms were identified using histochemical stains. The histological findings in the biopsy are nonspecific, but the predilection for hair follicles favors granulomatous rosacea.

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CHAPTER 110

Rosai-Dorfman Disease

Key Points

- Rosai-Dorfman disease (RDD) is a rare benign non-Langerhans cell condition characterized by a nonmalignant proliferation of histiocytes
- It most commonly is confined to cervical and other lymph nodes but can involve extranodal sites in 25% to 40% of cases
- The most common extranodal sites are the skin, orbit, eyelid, upper respiratory tract, salivary glands, central nervous system, bone, and testis
- Approximately 10% of patients exhibit skin lesions, and in 3% the disease is seen solely in the skin
- The etiology remains unknown, but proposals have included a disorder of immune regulation or a response to presumed infectious agents
- Most patients present with fever, fatigue, weight loss, night sweats, joint pain, and pharyngitis associated with painless, bilateral, massive cervical lymphadenopathy
- The most common ophthalmic presentation is with a painless soft eyelid thickening or a palpable mass, eyelid retraction, blepharoptosis, proptosis, uveitis, scleritis, decreased visual acuity, serous retinal detachments, and diplopia
- Symptomatic disease is treated with surgical excision, laser ablation, radiation therapy, intralesional steroids, or isotretinoin, but results are variable and inconsistent
- RDD often runs an indolent clinical course with spontaneous regression seen in about 41% of cases
- A 7% fatality rate has been reported from renal, CNS, or pulmonary complications

Rosai-Dorfman disease (RDD) is a benign non-Langerhans cell histiocytosis. It was first described in 1969 by Juan Rosai and Ronald Dorfman as a distinct histiocytic disorder in young black males presenting with chronic, bilateral, painless, massive cervical lymphadenopathy.[1] They termed the condition “sinus histiocytosis with massive lymphadenopathy,” which has since been referred to as Rosai-Dorfman disease. A subsequent report by these authors with a larger number of patients showed that there was no racial predilection for this disease.[2]

RDD is a rare disorder characterized by a nonmalignant proliferation of histiocytes.[3] The disease is typically located in lymph node sinuses but can also occur in extranodal sites.[1,2,4,5,6] Patients typically present with chronic, painless cervical lymphadenopathy seen in 90% of cases, combined with fever, leukocytosis, increased erythrocyte sedimentation rate, and hypergammaglobulinemia.[2] Other involved nodal groups include inguinal nodes in 26%, axillary nodes in 24%, and mediastinal lymph nodes in 15%.[2] The disease classically affects children and young adults at an average age of onset of 20 years, with a slight male predominance.

Although RDD most commonly is confined to the cervical and less commonly other lymph nodes, patients with RDD present with extranodal disease in 25% to 40% of cases. The most common extranodal sites are the skin, orbit, eyelid, upper respiratory tract, salivary glands, central nervous system, bone, and testis. The simultaneous involvement of multiple extranodal sites is not unusual. Foucar et al[2] reported extranodal involvement in the skin and soft tissue (16%), sinuses and nasal cavity (16%), bone (11%), salivary glands (7%), central nervous system (7%), oral cavity (4%), kidney/genitourinary tract (3%), and the lower respiratory tract (3%). In patients with extranodal involvement, lymphadenopathy may not develop until later in the course of the disease.[2]

Approximately 10% of patients with RDD exhibit skin lesions, and in 3% the disease is seen solely in the skin.[6,7] Cutaneous lesions may range from single papules to multiple nodules and plaques. They can be seen on any part of the body but are more common in the head and neck region. Skin lesions present as pink, red, purple, brown, or yellowish nodules, papules, or plaques that

can be sessile, polypoid, or exophytic and may be solitary or multiple.[8] In contrast to classic RDD, cutaneous RDD shows a slight female predominance, with an older age of onset in the fifth decade. These patients often lack lymphadenopathy as well as most of the systemic symptoms and laboratory abnormalities seen in classic RDD.[9]

The ophthalmic sites most commonly involved are the orbit and less frequently the eyelid.[2,10,11,12,13,14,15] Some ophthalmic cases may initially present without any evidence of lymphadenopathy,[16] and many also have other sites of extranodal involvement, such as the nasal cavity or paranasal sinuses.[2,10] In a series of 113 patients with RDD, Foucar et al[10] reported that 13 (11.5%) had ophthalmic manifestations, with the orbital soft tissue as the most frequent ophthalmic site of involvement. Orbital manifestations typically present as a nontender, rubbery mass often located in the lacrimal gland and eyelid.[17] Other clinical findings include conjunctival injection, blepharoptosis, epiphora, proptosis, blurred *(Print pagebreak 722)* vision, and diplopia.[18] Rare findings can include an epibulbar mass,[19] uveitis,[10,20,21] elevated intraocular pressure,[22] and endophthalmitis.[23]

Eyelid involvement is uncommon and usually is associated with orbital lesions.[2,8,13,17,18,24,25,26,27,28] The eyelids usually show a nontender thickening, often with massive swelling, erythema, and sometimes pitting edema. Eyelid masses usually measure 1 to 3 cm in size. Patients range in age from teens to old age, with more than half in the third to fifth decades. Males are affected more commonly than females.

Etiology and Pathogenesis

The etiology of RDD remains unknown. Middel et al proposed that this disease is a disorder of immune regulation or response to presumed infectious agents that has its major manifestation as the proliferation of sinusoidal histiocytes in lymph nodes.[29] They suggested that macrophage colony-stimulating factor (M-CSF) stimulation of monocytes/macrophages leads to immune suppressive macrophages as an important mechanism for the pathogenesis of sinus histiocytosis resulting in massive lymphadenopathy. Several viral and bacterial organisms have been suggested, including varicella zoster virus, cytomegalovirus, Epstein-Barr virus, human herpesvirus 6, Salmonella, Brucella, and Klebsiella species,[2,26,30,31,32,33,34] but to date, no specific infectious agent has been identified.[35] Other proposed etiologic mechanisms include autoimmune dysfunction or an aberrant reactive response to an unspecified antigen.[26] It has also been proposed that defective Fas/FasL signaling leading to altered apoptosis may be a mechanism leading to uncontrolled histiocytic proliferation.[30]

Clinical Characteristics

Most patients with RDD present with fever, fatigue, weight loss, night sweats, joint pain, and pharyngitis associated with painless, bilateral, massive cervical lymphadenopathy. Laboratory studies show an elevated erythrocyte sedimentation rate and hypergammaglobulinemia with a reversal of the albumin-globulin ratio.[2,30] Other findings can include leukocytosis with neutrophilia, a mild normochromic normocytic or hypochromic microcytic anemia, a positive rheumatoid factor and/or antinuclear antibody, and a polyclonal elevation of IgG.[2,30,34]

RDD usually affects children and young adults with an average age at onset of approximately 20 years, with a slight male predominance of 58%.[2] Although most cases are acquired, congenital cases have been reported.

Extranodal RDD has a predilection for the head and neck but intracranial lesions are uncommon.[36] The most common ophthalmic sites of involvement are the orbit or eyelid, seen in approximately 8% to 11% of cases.[2,10] In some patients, orbital involvement may be the presenting manifestation of the disease, and approximately 20% of ophthalmic cases have no initial evidence of lymphadenopathy,[2,16] and most may be associated with other extranodal sites of involvement.[2,10]

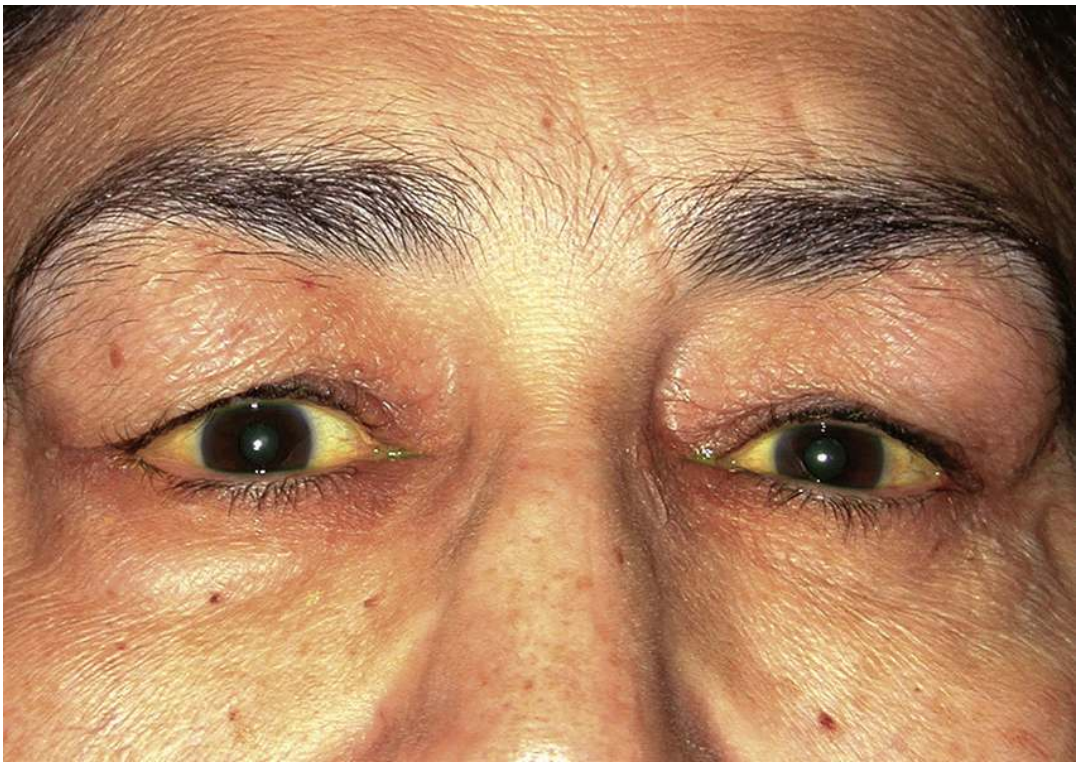

FIGURE 110.1 Rosai-Dorfman disease with bilateral upper eyelid swelling.

As mentioned previously, the most common ophthalmic presentation is with a painless soft tissue eyelid thickening and swelling (Figure 110.1) or a palpable mass, eyelid retraction, blepharoptosis, madarosis, conjunctival injection, and proptosis (Figure 110.2).[2] Other findings can include an epibulbar mass, uveitis, corneal lesions, scleritis, decreased visual acuity, serous retinal detachments, compressive optic neuropathy, limited extraocular motility, diplopia, and orbital pain.[13,14,15,20,37,38,39,40,41] Ocular involvement also has been reported with infiltration of the sclera and choroid.[37]

Differential Diagnosis

The differential diagnosis of RDD is broad due to variable clinical presentations and the large number of sites that can have extranodal involvement. RDD may mimic systemic conditions such as sarcoidosis, tuberculosis, leprosy, leukemia, granulomatosis with polyangiitis, nonspecific sinus hyperplasia, and Langerhans cell histiocytosis. Orbital RDD may clinically be misdiagnosed as an orbital inflammatory disease, juvenile xanthogranuloma, Erdheim-Chester disease, rhabdomyosarcoma, meningioma, lacrimal gland tumors, metastatic disease, lymphoma, other neoplastic tumors, and other histiocytic tumors. Definitive diagnosis is determined on histopathology, immunohistochemistry, and orbital imaging.

Treatment

There is no universally accepted treatment for RDD. Many lesions will remain relatively asymptomatic without any intervention.[42] In almost half of patients with RDD the clinical course is chronic, but with variable episodes of remission and exacerbation.[2] In a review of 80 patients with RDD from the literature, Pulsoni et al[43] reported that 50% required no treatment, and 82% of these (41% of the total) experienced complete spontaneous remission.

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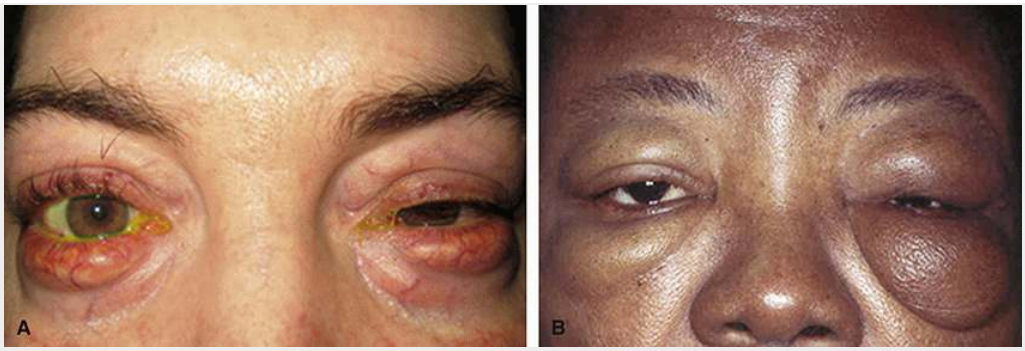

FIGURE 110.2 A, Bilateral lower eyelid thickening with telangiectatic vessels and mechanical ptosis. B, Massive edema of the eyelids with ptosis in a patient with Rosai-Dorfman disease. A, (Courtesy of Dr. Roman Shinder.) B, (Courtesy of Dr. David Jordan.)

For symptomatic or progressive disease, various treatment options have been utilized including surgical excision,[44,45] laser ablation,[46] radiation therapy,[38,47] intralesional steroids,[44,48] dapsone,[49] thalidomide,[50] and isotretinoin.[51] However, all treatments have shown variable and inconsistent results.

Complete surgical resection or debulking has provided the best results for patients with isolated, symptomatic, superficial masses or those with aesthetic or functional compromise,[13,26,37,38,44] and surgery combined with chemotherapy or radiotherapy has been advocated for cases with vital organ compression or life-threatening manifestations from nodal or extranodal involvement. Intralesional steroid injection at the time of surgery may be a useful adjunct.[52]

Chemotherapy has been advocated for cases of systemic disease with vital organ involvement[53,54] and orbital disease with compressive optic neuropathy.[37,41] But in a larger review of published cases, chemotherapy was shown to largely be ineffective.[43] Cyclosporine also has been used successfully in orbital cases.[55]

Radiotherapy is generally ineffective, with only about 33% of cases responding favorably.[44] But isolated case studies have reported good response of orbital and oral cavity involvement that were refractory to other treatments.[38]

Intralesional or systemic steroids have been reported to result in remission of orbital and systemic disease in several case reports.[26,56,57,58]

Pulsed dye laser selective photothermolysis and CO_2 laser ablation have been reported to achieve the resolution of isolated extranodal RDD.[46,59]

Prognosis

RDD often runs a lengthy, indolent clinical course.[4] Spontaneous regression is common, seen in about 41% of cases, especially in patients with localized disease.[44,60] In patients with widespread extranodal involvement, lymphadenopathy may persist for decades.[10,15,61]

While mortality is unusual, a 7% fatality rate has been reported from renal or CNS infiltration,[61] from respiratory involvement and pneumonia,[44] from a defect in immune function associated with autoimmune disease,[2,62,63,64] or from a coexistence of RDD and neoplastic diseases such as lymphoma or multiple myeloma.[2]

A poor prognosis is seen in cases of widespread systemic disease with involvement of visceral organs and those with immunological abnormalities, anemia with neutrophilia, lymphocytopenia, or an extremely high ESR.[67] Patients with an increased number of affected nodal groups and a greater number of extranodal sites also show a more unfavorable prognosis.[4]

Histopathology

The histopathological features of extranodal RDD involving the orbit[10,23] and eyelid[66] are similar to those of RDD in other extranodal[2,67,68] and cutaneous sites.[53,69,70,71,72] Orbital and eyelid RDD infiltrates typically form well-circumscribed masses surrounded by fibrous connective tissue, sometimes with satellite foci creating a lobular pattern.[10,23] Fibrosis may also be present within the RDD infiltrate, composing a majority of the excised tissue.[10] The predominant cells within the infiltrate are large histiocytes with abundant cytoplasm that may be pale staining and foamy (Figure 110.3) or brightly eosinophilic (Figures 110.4 and

110.5). Cytoplasmic borders may be poorly delineated (Figures 110.3 and 110.4) or sharply defined (Figure 110.5). Nuclei are round to oval with fine chromatin stippling and one or more small nucleoli.[10] Multinucleated histiocytes are occasionally present,[10] sometimes appearing as small, multinucleated giant cells.[23] Mitoses and cellular atypia of the histiocytes are rare.[10,23] The histocytes are accompanied by variable numbers of lymphocytes, plasma cells, scattered neutrophils, and occasionally eosinophils.[10,23] The lymphocytes may form aggregates (Figure 110.3) or follicles with germinal centers (Figure 110.4) or have a more diffuse distribution with looser aggregates (Figure 110.5). A distinctive feature of RDD, but not unique to this illness, is the presence of *(Print pagebreak 724) (Print pagebreak 725)* lymphocytes, plasma cells, or erythrocytes in the cytoplasm of occasional histiocytes,[10,23] a process termed "emperipolesis."[73] Emperipolesis in extranodal RDD is usually "much less prominent than in involved lymph nodes."[10] The histiocytes in RDD are diffusely immunoreactive for S100 protein and CD68 (Figure 110.3), which differentiates them from usual histiocytes that are positive for CD68 and negative for S100.[2] It is essential to note that S100 protein may be expressed in juvenile xanthogranuloma,[74,75] and we have seen one adult example of periocular xanthogranuloma with diffuse positivity of mononuclear and multinuclear histiocytes for CD68 and S100 protein. Thus, RDD's diagnosis requires correlating all of the histological and clinical features in a particular patient.

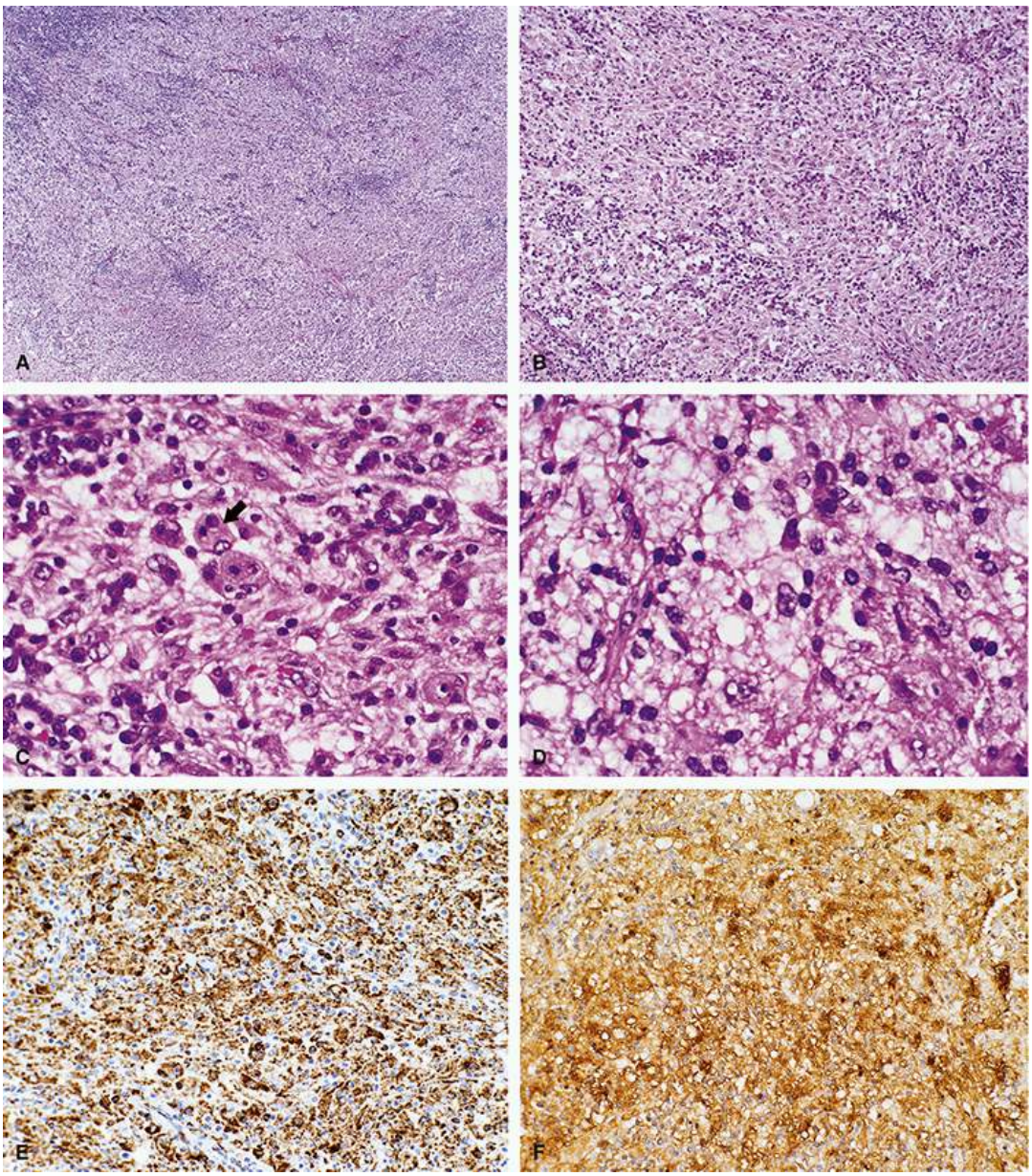

FIGURE 110.3 A-D, Rosai-Dorfman disease of the upper eyelid with predominantly pale staining, foamy histiocytes having indistinct cytoplasmic borders. There are scattered small aggregates of lymphocytes and plasma cells, as well as individual cells percolating among the histiocytes. A large histiocyte with a binucleate plasma cell and a neutrophil in its cytoplasm (emperipolesis) is in C (*arrow*). The histiocytes were all immunohistochemically positive for expression of CD68 (E) and S100 protein (F).

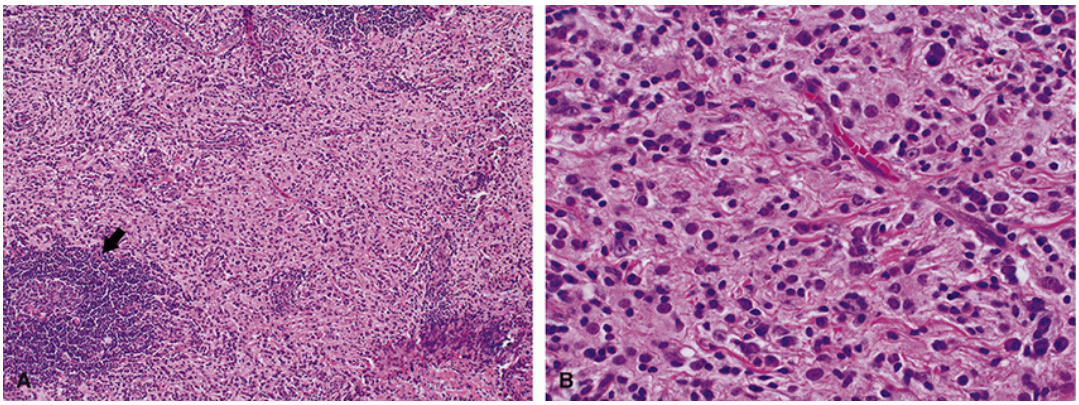

FIGURE 110.4 A and B, Rosai-Dorfman disease of the lower eyelid with histiocytes having eosinophilic, finely vacuolated cytoplasm and indistinct cytoplasmic borders. Lymphoid follicles with germinal centers are present, as seen in A (*arrow*). There is a diffuse infiltrate of lymphocytes and plasma cells among the predominating histiocytes.

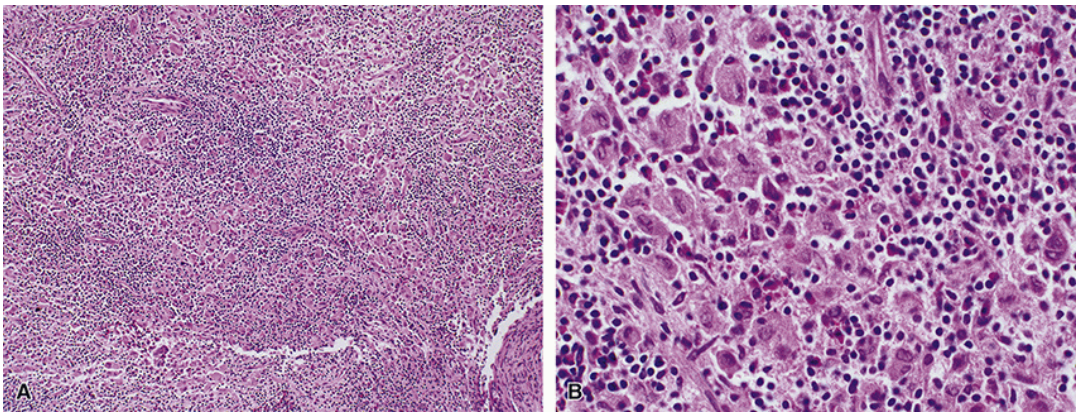

FIGURE 110.5 A and B, Rosai-Dorfman disease of the orbit featuring large, polygonal, histiocytes with eosinophilic cytoplasm and distinct cytoplasmic borders. There are numerous lymphocytes and plasma cells and scattered eosinophils among the histiocytes.

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CHAPTER 111

Sarcoidosis

Key Points

- Sarcoidosis is a multisystem inflammatory disease of unknown etiology characterized by noncaseating granulomas in the involved organs
- The most common manifestation is pulmonary involvement, but extrapulmonary manifestations include the skin, central nervous system, peripheral nervous system, liver, kidney, musculoskeletal system, heart, salivary glands, the eye, and orbit
- Sarcoid uveitis is the most common ophthalmic manifestation
- Scar sarcoidosis is a rare circumscribed form of cutaneous sarcoidosis localized in scars
- Sarcoidosis develops in genetically susceptible individuals through an alteration of the immune system in response to certain environmental, occupational, or infectious exposures
- Eyelid lesions appear as yellowish to violaceous scaling, erythematous, firm small nodules, often associated with epiphora, pruritus, eyelid thickening, madarosis, and occasionally poliosis or trichiasis
- Up to 30% of patients with clinical sarcoidosis will undergo spontaneous remission
- Oral or intralesional corticosteroids are the initial treatment of choice for the management of sarcoid lesions of the eyelid
- Sarcoidosis is thought to predominantly be a benign condition, but more than 40% of patients require treatment for many years

Sarcoidosis is a multisystem inflammatory disease of unknown etiology characterized by noncaseating granulomas in the involved organs. Signs and symptoms of the disease are not specific, and it may take months to years before the correct diagnosis is made.[1] Sarcoidosis has a female predilection. Females also present at an earlier age and show a significantly higher frequency of eye, salivary gland, and skin involvement.[2] The age at onset shows peak incidences in the 3rd and 5th decades of life, but it can also be seen in children and adults over the age of 60. The disease is more common in black individuals than white, with an incidence ratio of 2:1 to 7:1[3,4,5] and a prevalence ratio of 3:1 to 5:1.[3] Serum angiotensin converting enzyme (ACE) has been used as a major biomarker for the diagnosis of sarcoidosis. ACE is produced by the epithelioid cells of the sarcoid granuloma,[6] and serum ACE levels have been used as a reflection of the granuloma burden in this disease,[7] with a sensitivity for the diagnosis between 41% and 100% and a specificity of 83% to 99%.[8]

The most common manifestation of sarcoidosis is pulmonary involvement but extrapulmonary manifestations include the skin, central nervous system, peripheral nervous system, liver, kidney, musculoskeletal system, heart, salivary glands, eye, and orbit.[9] After the lungs, the skin is the second most common organ involved in sarcoidosis, seen in 12% to 35% of patients with systemic disease.[10,11,12,13,14,15,16] Cutaneous lesions can be the presenting manifestation of the disease in about one-third of cases.[17] Cutaneous features include maculopapular eruptions, lupus pernio, and erythema nodosum.[12] Diagnosis is based on biopsy showing the presence of noncaseating granulomas, as well as the clinical features, raised inflammatory markers, elevated serum ACE, and hilar lymphadenopathy on chest radiography.

Ocular involvement has been reported in 11% to 60% of patients with sarcoidosis.[10,18,19,20,21,22,23,24] Females are affected more than males in a ratio of 2:1.[25] The occurrence of ocular involvement was reported to be 1.8 times greater in women than in men in one study[26] but 1.25 times greater in men than in women in another.[18]

Ophthalmic manifestations can involve the anterior and posterior segments of the eye, and less commonly the orbit and lacrimal

gland (Figure 111.1).[18] Sarcoid uveitis is the most common ophthalmic manifestation, presenting with bilateral mutton-fat keratic precipitates, anterior cells and flare, iris nodules, anterior and posterior synechia, and increased intraocular pressure often associated with pain, photophobia, and conjunctival injection.[20,27] Vitritis, vasculitis, choroidal lesions, and optic neuropathy characterize posterior segment involvement. Rare and atypical ophthalmic manifestations include limbal corneal nodules, retinal pigment epithelial detachments, and solitary choroidal granulomas.[28]

Granulomatous inflammation of the conjunctiva is the second most common ophthalmic finding in sarcoidosis,[29] usually involving the palpebral surface (Figure 111.2), but less frequently the bulbar conjunctiva.[30] Multiple translucent noncaseating conjunctival granulomas can occur as the first clinical signs.[31] Lesions present as one or more white, discrete conjunctival deposits that may show redness and irritation.[32] Occasionally they can present as follicular conjunctivitis[33,34] or progress to conjunctival *(Print pagebreak 729)* scarring and symblepharon formation[35,36] that may simulate a conjunctival tumor.[37]

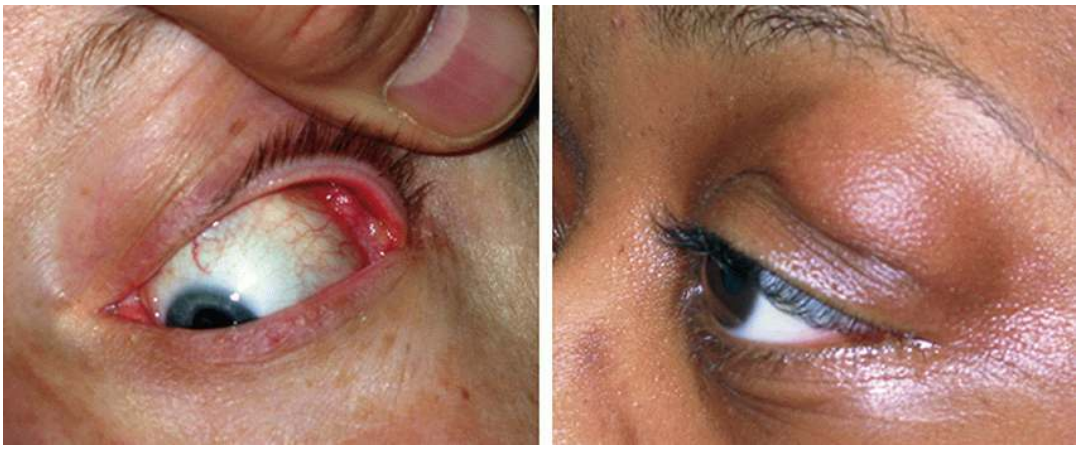

FIGURE 111.1 Lacrimal gland involvement with sarcoidosis.

The age distribution of ocular sarcoidosis in adults is bimodal, with two peaks of incidence between 20 and 30 years and 50 to 60 years.[23] The mean age at presentation of uveitis is 42 years (range 4-82),[38] and ocular findings are reported to be higher and to occur at an earlier age in patients of African descent compared with Caucasians.[39,40]

Adnexal involvement is rarely associated with intraocular inflammation.[12] In one study of 30 patients with adnexal sarcoidosis, only 3% had concomitant intraocular inflammation.[41] The incidence of eyelid involvement in adnexal sarcoidosis may be as high as 17%.[19,20,41] It is seen in adults at a mean age of 46 years (range 29-66), and with 58% occurring in males. Eyelid erythema and swelling may be the only sign,[42,43] with lesions varying in size from small papules[44] to large masses.[45] Chronic eyelid nodules may cause eyelid deformities, with extensive scarring, entropion, trichiasis, madarosis, or symblepharon (Figure 111.3).[46,47] Isolated eyelid structures such as the Müller muscle may be involved with granulomatous inflammation causing eyelid retraction.[48]

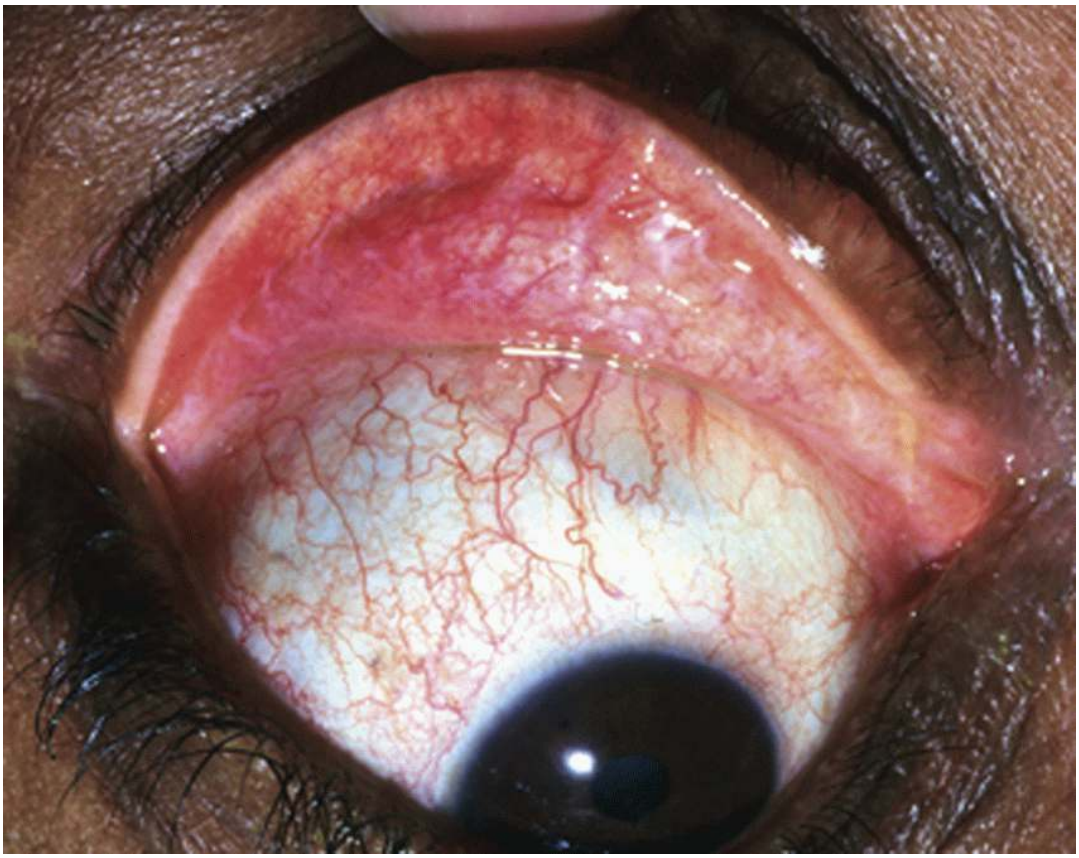

FIGURE 111.2 Sarcoid granulomatous inflammation of the upper eyelid palpebral conjunctiva.

Scar sarcoidosis is a rare circumscribed form of cutaneous sarcoidosis localized in scars that have been described in patients with systemic sarcoidosis or patients with no evidence of systemic disease.[45] However, Ingber and Klinken showed that scar sarcoidosis can be an early sign of systemic sarcoidosis.[49] It is marked by inflammatory infiltrations and bruise-like, black and blue discoloration. Scar sarcoidosis has been described following herpes zoster infections[50] and in previous scars caused by venipuncture, trauma, tattoos, and sites of previous laser surgery.[51]

Etiology and Pathogenesis

Sarcoidosis has long been recognized as a disease with a genetic background owing to its accumulated appearance in families and within twin pairs. One twin study showed an 80-fold increased risk for the development of sarcoidosis for the monozygotic twin of an affected individual.[52] Several novel predisposing genes have been identified by genome-wide association studies, including several HLA class II alleles, tumor necrosis factor (TNF) and interleukin 23 receptor (*IL23R*) genes, the butyrophilin-like 2 (*BTNL2*) gene, and the Ras-related protein Rab-23 (*RAB23*) gene. A detailed discussion of the possible predisposing genetic associations with sarcoidosis is beyond the scope of this chapter and has been extensively discussed elsewhere.[52]

Sarcoidosis likely develops in genetically susceptible individuals through an alteration of the immune system in response to certain environmental, occupational, or *(Print pagebreak 730)* infectious exposures.[53,54] A comparison of gene expression in normal lungs and lungs affected by sarcoidosis found an upregulation of T helper-1 (Th1) immune response genes in sarcoidosis and also of genes regulating macrophage-derived proteases matrix metalloprotease 12 and ADAM-like decysin-1.[55] A study of gene expression in skin lesions and normal skin of patients with sarcoidosis and the skin of normal controls found that skin lesions showed a strong Th1 profile and expression of interleukin (IL)-23 and IL23R.[56]

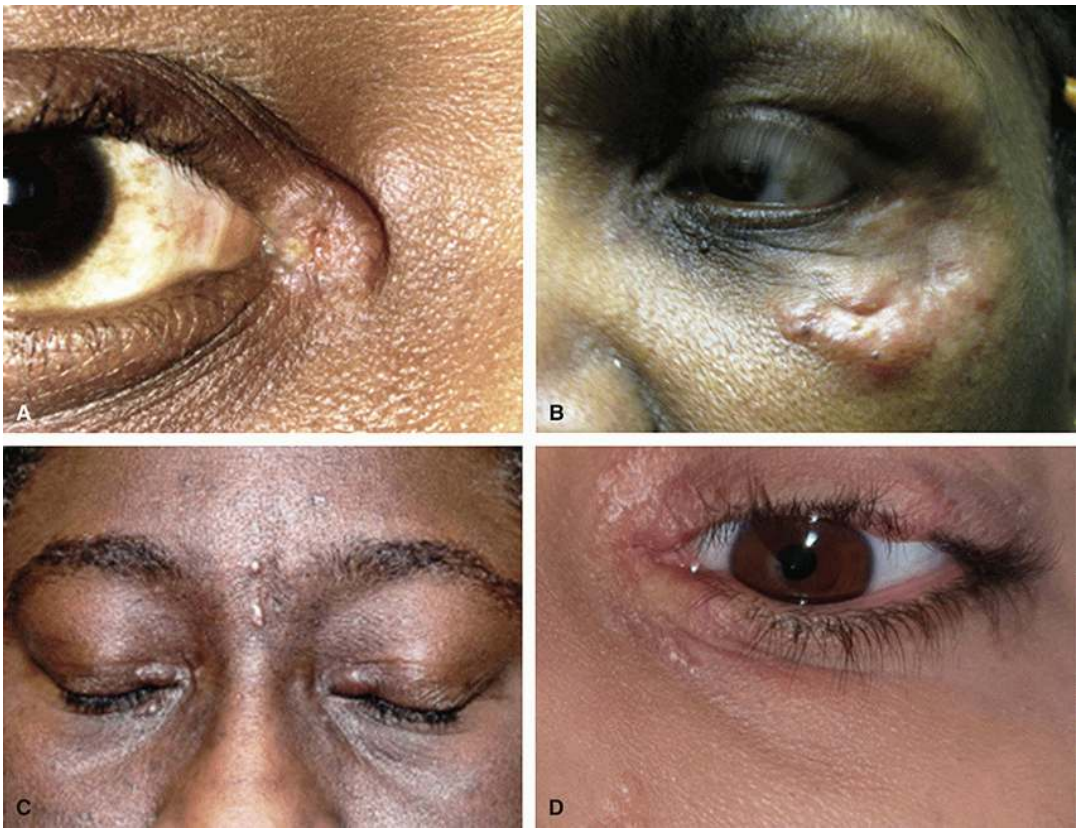

FIGURE 111.3 Papular and nodular sarcoid lesions on the eyelids.

It is believed that sarcoidosis is a granulomatous reaction to one or more inciting exogenous agents in genetically susceptible individuals.[57] Epidemiologic studies support an environmental trigger with case clustering, transmissibility by organ transplantation, and an immune response typical for nonself antigens.[58] Besides an environmental trigger and a genetically mediated immune response, additional genes and exposures can likely modify the risk for the development and severity of sarcoidosis.[59] Such modifier exposures might include smoking, which is known to decrease the risk of sarcoidosis, and photocopier toner and certain insecticides, which can increase the risk.[60,61]

Granulomas are inflammatory responses consisting of mononuclear phagocytes and their derivatives.[62] The inciting event involves the deposition of antigenic material, not yet identified, into tissues where it is phagocytosed or endocytosed by macrophages or dendritic cells,[63] is transported to the cell surface, and activates CD41 T cells.[64] The granuloma organizes through the elaboration and secretion of cytokines and chemokines.[65] The ensuing immune response leads to clinical lesions of sarcoidosis characterized by elevated IFN-g, IL-2, and IL-12. TNF alpha is a critical cytokine in this process that enhances the recruitment of macrophages into the granuloma.[66]

Clinical Characteristics

Eyelid involvement in sarcoidosis is rare. Typically, the eyelid lesions appear as yellowish to violaceous scaling and erythematous, firm small nodules, often associated with epiphora, pruritis, eyelid thickening, madarosis, and occasionally poliosis or trichiasis.[13,67], They may also appear as larger nodules,[13,16,19,67,68,69,70,71] papular eruptions,[16,44,68,69,70] lupus *(Print pagebreak 731)* pernio plaques,[16,72] or swelling of the eyelids (Figure 111.3).[44] Eyelid nodules very rarely ulcerate or become necrotic.[72] Even rarer is destructive sarcoidosis affecting the full-thickness eyelid leading to tissue loss (Figure 111.4).[46,47] Scar sarcoidosis may occasionally develop at the site of old injuries or tumor resections (Figure 111.5). Dry eyes reported in patients with eyelid sarcoidosis are attributed to infiltration of the lacrimal gland and destruction of the meibomian glands.

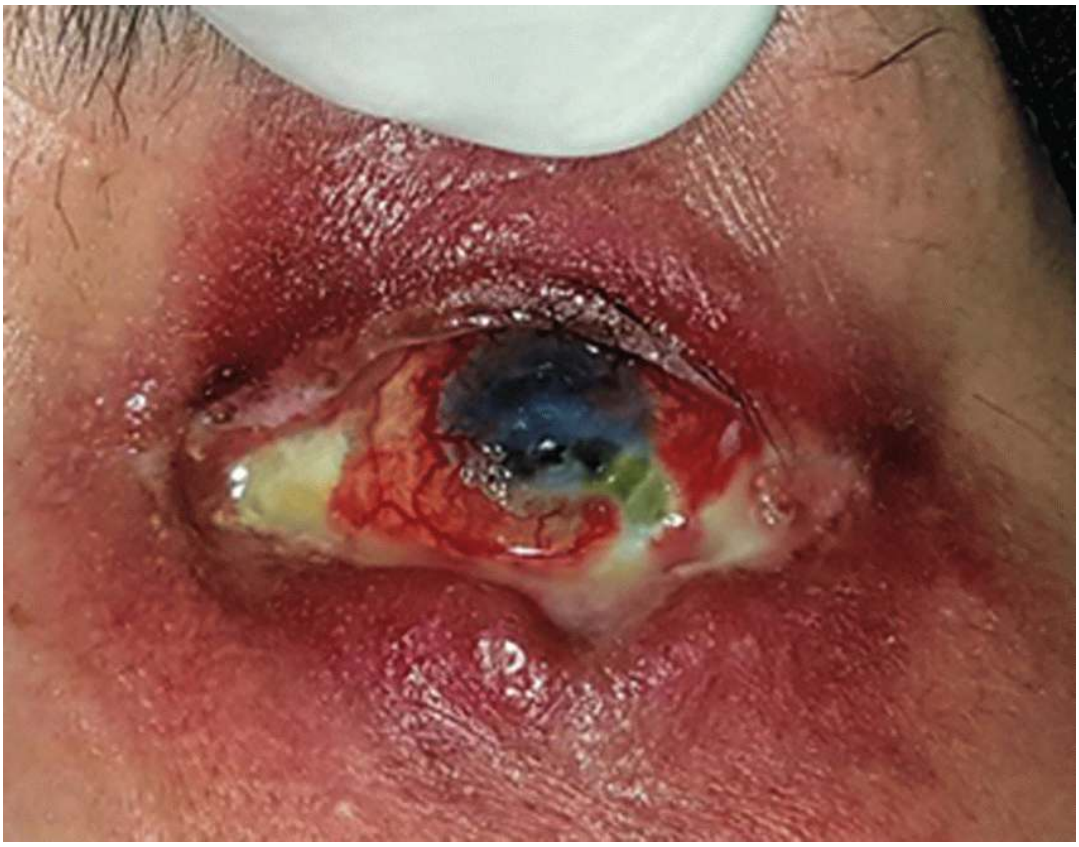

FIGURE 111.4 Necrotizing sarcoidosis with extensive tissue destruction of upper and lower eyelids.

Differential Diagnosis

The differential diagnosis of sarcoidosis includes idiopathic granulomatous inflammation, granulomatosis with polyangiitis (GPA), tuberculosis, leprosy, nontuberculous mycobacterial infection, secondary syphilis, herpes simplex, scleroderma, eosinophilic fasciitis, Behcet disease, cutaneous lupus, and fungal granulomas. The list also includes inflammatory conditions such as chalazia, cystic lesions such as epidermal cysts, various malignant and nonmalignant neoplasms, others such as xanthomas, and viral infections such as molluscum contagiosum.

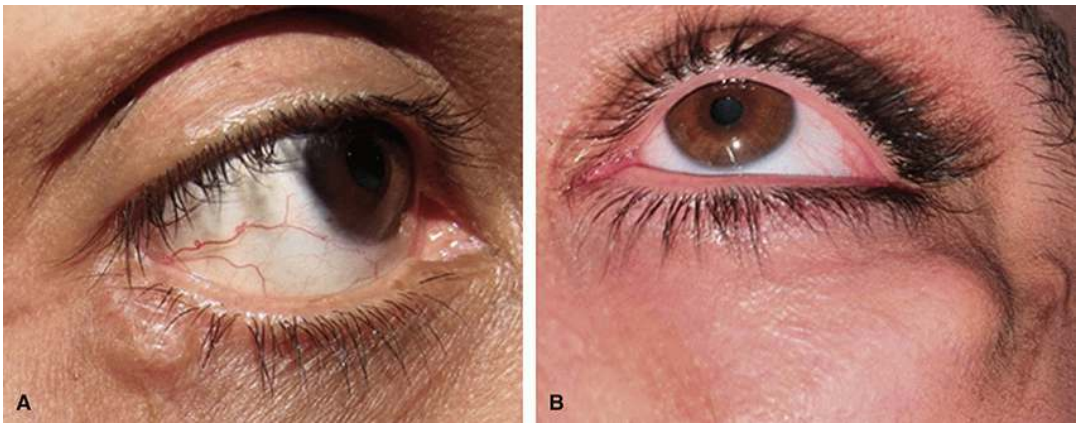

FIGURE 111.5 Scar sarcoidosis. A, Sarcoid arising in an old basal cell carcinoma scar. B, Subcutaneous sarcoidosis adjacent to an old traumatic lateral canthal scar.

Treatment

Up to 30% of patients with clinical sarcoidosis will undergo spontaneous remission.[10] Management is aimed at the relief of symptoms and minimizing the loss of function[73] and will depend on the extent of the disease, the degree of functional

impairment, and the presence or absence of systemic disease.[74] Oral corticosteroids are the initial treatment of choice for ophthalmic and active systemic sarcoidosis.[20] The use of intralesional triamcinolone in the management of sarcoid lesions of the eyelid has been reported in the literature with good effect.[45] The major risks of steroid medications include skin atrophy, dyspigmentation, and the development of telangiectasias.

In cases refractory to steroids cytotoxic agents such as methotrexate, azathioprine, leflunomide, and mycophenolate have been considered second-line therapy for sarcoidosis.[75,76,77] These agents work by inhibiting cell activation, proliferation, and migration through cytokine modulation or the generation of extracellular anti-inflammatory mediators.[78,79,80]

Tumor necrosis factor antibodies such as infliximab have also been proposed as a potential treatment for systemic and ophthalmic sarcoidosis.[81,82] These block cell activation and proliferation, inhibiting granuloma formation and promoting granuloma dissolution.[83,84] TNF antagonists also eliminate TNF-expressing cells through complement-dependent cytotoxicity and apoptosis.[85]

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Other therapies for cutaneous lesions in sarcoidosis have been reported to be useful.[64] Photodynamic therapy has yielded beneficial results, but recurrence often follows after discontinuation.[86,87,88] Ultraviolet A phototherapy also has been reported to yield improvement in skin lesions after 30 to 50 treatments,[89] but, as with photodynamic therapy, it may be associated with burning, erythema, and skin discomfort. Pulsed dye, CO_2, ruby, and potassium titanyl phosphate lasers have also been reported to give good results.[90,91,92,93,94,95] Conservative surgical excision can be used when a tissue sample is necessary for diagnosis, in some scar or subcutaneous sarcoid nodules, or in severe cases refractory to medical therapies.

Prognosis

The course of sarcoidosis is variable, and there is no reliable biomarker for prognosis. Although sarcoidosis is thought to predominantly be a benign condition, a survey of major centers found that more than 40% of patients with sarcoidosis with more than 5 years of follow-up were still receiving therapy for their disease.[96] Age, pulmonary fibrosis, and pulmonary hypertension are the major factors relating to poor prognosis in patients with chronic pulmonary sarcoidosis.[97] For eyelid lesions, the prognosis is good with oral, intralesional, or systemic steroids or cytotoxic agents, or with partial or complete surgical excision depending upon the degree of tissue destruction.

Histopathology

The histopathological feature deemed typical of sarcoidosis, including that in the skin, is the so-called naked granuloma characterized by noncaseating (nonnecrotizing) epithelioid granulomas lacking a prominent cuff of lymphocytes.[98] However, sarcoidal granulomas are a morphologic spectrum based on the evolution and duration of lesions.[98,99] Early lesions have globular masses of macrophages developing into epithelioid cells, usually without the formation of multinucleated giant cells.[98] Aging sarcoidal granulomas have epithelioid cells in a radial pattern, an increasing number of giant cells, and a fine pattern of reticulin throughout the lesion.[98] Later lesions have fibrosis beginning at the periphery that may progress inward; hyalinization may accompany the fibrosis.[98] End-stage sarcoidal lesions are hyaline fibrinoid masses.[98] In addition to varying appearances of the granulomas, the histological appearance depends on the clinical subtype of cutaneous sarcoidosis: papules, plaques and nodules, subcutaneous, scars, and infrequently seen variants such as ulcerative and verrucous.[100] Papules typically have granulomas superficially in the papillary and upper reticular dermis, and plaques have granulomas throughout the entire dermis.[100]

Ball, Kho, and Martinka reported the histological findings in 28 biopsies from 24 patients with systemic sarcoidosis.[101] They classified granulomas as naked if the lymphocyte cuff was less than 25% of the granuloma diameter, tuberculoid if the lymphocyte cuff was >25% of the granuloma's diameter, interstitial if three or more adjacent single or multinucleated histiocytes were aligned in single file between two collagen fibers, and linear if the length of the granuloma was ≥4 times their smallest diameter.[101] Of 28 biopsies, 25 (89%) had naked granulomas, and in 19 (68%), these were the only types of granulomas.[101] Four biopsies (14%) contained tuberculoid granulomas: two biopsies had only tuberculoid granulomas and two had tuberculoid and naked granulomas.[101] Five biopsies (18%) had focal interstitial granulomas, and in four, there were also naked granulomas.[101] Half of the biopsies had irregular fragments of birefringent foreign material >1 μm in diameter within granulomas, and half of these were cases of scar sarcoidosis.[101] Twelve biopsies (43%) had focal necrosis: eight had fibrinoid necrosis within granulomas, and four had focal necrobiosis of dermal collagen around granulomas.[101] Linear granulomas around small dermal nerves resembling those in tuberculoid or borderline tuberculoid granulomas were in five biopsies (18%).[101] All biopsies had multinucleated giant cells, a mixture of Langhans and foreign body types.[101] The cytoplasm of multinucleated giant cells in 15 biopsies (53%) contained asteroid bodies (stellate inclusions[98]) and/or Schaumann bodies (concentric lamellated calcifications[98]).[101] Additional histological

findings were elastophagocytosis (39% of biopsies), increased dermal mucin in or near granulomas (18% of biopsies), and lichenoid inflammation (14% of biopsies).[101] The Ball, Kho, and Martinka study amply demonstrates the variable histopathological features of cutaneous sarcoidosis and the high percentage of biopsies with naked granulomas.[101]

More recent studies have confirmed and elaborated upon the varying histological features of cutaneous sarcoidosis; Table 111.1 summarizes histopathological features abstracted from data in five papers reporting 229 biopsies.[101,102,103,104,105] Naked granulomas are present in about 80% of biopsies and tuberculoid granulomas in about 20% of biopsies. The granulomas have multinucleated giant cells in 95% of biopsies, focal fibrinoid necrosis in 15%, and foreign material in about 20% of biopsies. Granulomas may occur anywhere in the dermis and less commonly in the subcutis. About 20% of biopsies have perineural granulomas, but the invasion of nerves is not present and helps differentiate sarcoidosis from tuberculoid leprosy.[106] Approximately 20% of biopsies have epidermal changes, with epidermal atrophy being the most common finding. The only histopathological feature that correlated with the clinical disease course in a study of 41 patients was the severity of the cutaneous granulomatous infiltrate.[107] Skin biopsies exhibiting a moderate or severe granulomatous infiltrate had more severe systemic clinical manifestations, a more chronic disease course, and more generalized skin involvement.[107] Granulomas in the eyelid skin[13,44] (Figure 111.6) and conjunctiva[108] (Figure 111.7) resemble cutaneous sarcoidosis occurring elsewhere on the body.

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TABLE 111.1 Histopathological Features of Cutaneous Sarcoidosis

Feature	Ball et al,[101] *n* = 28 (Table 2)	Mangas et al,[102] *n* = 41 (Table 3)	Cardoso et al,[103] *n* = 31 (Tables 1-3)	Ishak et al,[104] *n* = 81 (Tables 3-5)	García-Colmenero et al,[105] *n* = 48 (Table 3)	Mean (range; *n*)
Granuloma Types						
Naked granulomas[a]	89% (25/28)	73% (30/41)	71% (22/31)	88% (71/81)	71% (34/48)	79% (71%-89%; *n* = 229)
Tuberculoid granulomas[a]	14% (4/28)	27% (11/41)	29% (9/31)	12% (10/81)	25% (12/48)	21% (12%-29%; *n* = 229)
Interstitial granulomas	18% (5/28)	NA	16% (5/31)	NA	NA	17% (16%-18%; *n* = 59)
Granuloma Features						
Multinucleated giant cells	100% (28/28)	90% (37/41)	97% (30/31)	90% (73/81)	96% (46/48)	95% (90%-100%; *n* = 229)
Asteroid bodies	43% (12/28)	7% (3/41)	NA	NA	2% (1/48)	17% (2%-43%; *n* = 117)
Schaumann bodies	29% (8/28)	2% (1/41)	NA	NA	NA	16% (2%-29%; *n* = 69)
Asteroid or Schaumann bodies	54% (15/28)	10% (4/41)	32% (10/31)	NA	NA	32% (10%-54%; *n* = 100)
Focal fibrinoid necrosis within granulomas	29% (8/28)	10% (4/41)	6% (2/31)	1% (1/81)	27% (13/48)	15% (1%-29%; *n* = 229)
Focal necrobiosis around granulomas	14% (4/28)	2% (1/41)	NA	NA	NA	8% (2%-14%; *n* = 69)
Focal dermal mucin within or around granulomas	18% (5/28)	2% (1/41)	NA	NA	NA	10% (2%-18%; *n* = 69)
Foreign material within granulomas	50% (14/28)	27% (11/41)	13% (4/31)	10% (8/81)	10% (5/48)	22% (10%-50%; *n* = 229)
Elastophagocytosis	39% (11/28)	NA	NA	NA	NA	
Neutrophils in or						9% (0%-25%; *n* =

around granulomas	25% (7/28)	NA	3% (1/31)	0% (0/81)	NA	140)
Plasma cells in or around granulomas	36% (10/28)	NA	3% (1/31)	52% (42/81)	NA	30% (3%-52%; *n* = 140)
Eosinophils in or around granulomas	32% (9/28)	NA	NA	5% (4/81)	NA	19% (5%-32%; *n* = 109)
Granuloma coalescence	NA	70% (29/41)	65% (20/31)	NA	NA	
Granuloma Locations						
Superficial dermis	NA	74% (31/41)	16% (5/31)	5% (4/81)	44% (21/48)	35% (5%-74%; *n* = 201)
Superficial + mid-dermis	NA	NA	29% (9/31)	11% (9/81)	NA	20% (11%-29%; *n* = 112)
Superficial + deep dermis	NA	NA	NA	80% (65/81)	NA	80% (80%; *n* = 81)
Mid + deep dermis	NA	NA	32% (10/31)	NA	NA	32% (32%; *n* = 31)
Deep dermis	NA	76% (30/41)	NA	NA	71% (34/48)	74% (71%-76%; *n* = 89)
Entire dermis	NA	NA	23% (7/31)	NA	NA	23% (23%; *n* = 31)
Subcutaneous	NA	30% (12/41)	0% (0/31)	20% (16/81)	42% (20/48)	23% (0%-42%; *n* = 201)
Subcutaneous exclusively	NA	10% (4/41)	0% (0/31)	NA	NA	5% (0%-10%; *n* = 72)
Perineural granulomas	25% (7/28)	NA	13% (4/31)	23% (15/81)	13% (6/48)	19% (13%-25%; *n* = 188)
Epidermal and Other Changes						
Epidermal atrophy	14% (4/28)	10% (4/41)	26% (8/31)	32% (26/81)	10% (5/48)	18% (10%-32%; *n* = 229)
Parakeratosis	18% (5/28)	NA	19% (6/31)	10% (8/81)	NA	16% (10%-19%; *n* = 140)
Hyperkeratosis	NA	NA	NA	NA	4% (2/48)	4% (4%; *n* = 48)
Acanthosis	NA	NA	10% (3/31)	1% (1/81)	13% (6/48)	8% (1%-13%; *n* = 160)
Pseudoepitheliomatous hyperplasia	NA	NA	3% (1/31)	NA	NA	3% (3%; *n* = 31)
Lichenoid inflammation with colloid bodies	14% (4/28)	NA	NA	NA	NA	14% (14%; *n* = 28)

n = number of biopsies; NA = not available.

[a] Naked granulomas had few lymphocytes cuffing the granulomas; tuberculoid granulomas had moderate to marked numbers of lymphocytes.

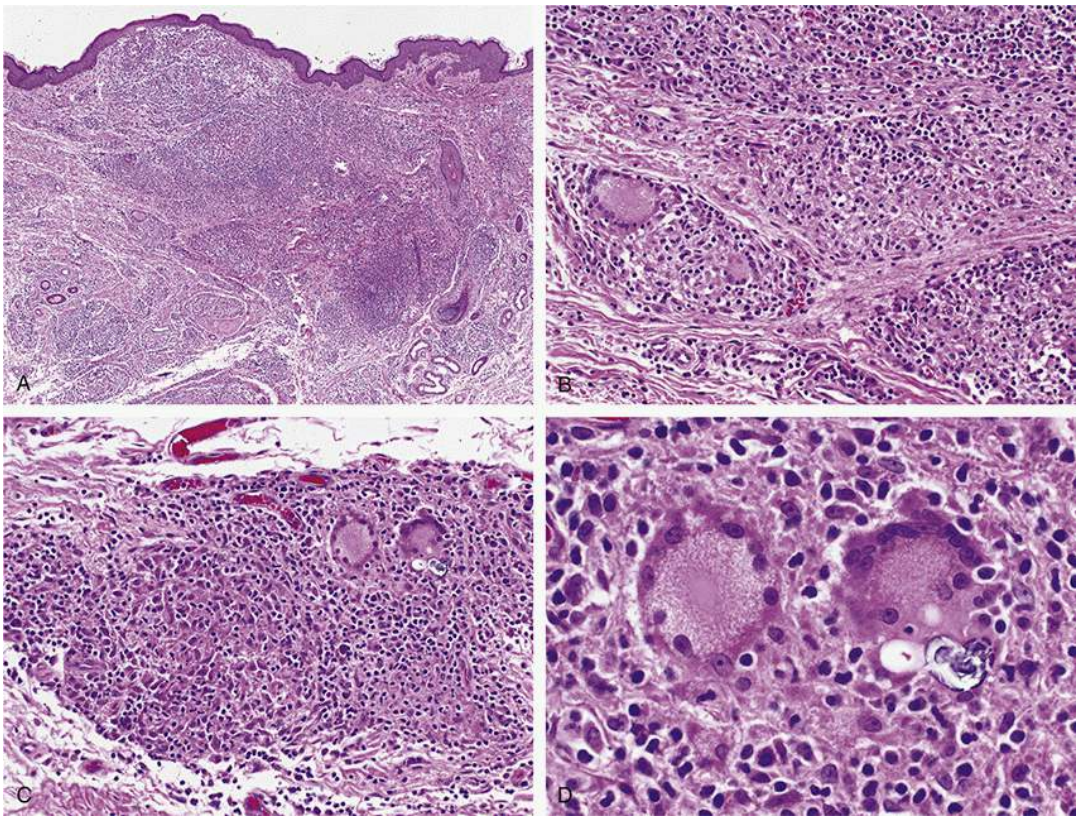

FIGURE 111.6 In his mid-20s, a man with iritis in his left eye developed an elevated, soft, mobile irregularity under the skin of the right lateral canthus with epidermal hypopigmentation. He was diagnosed with eyelid, lacrimal gland, intraocular, and pulmonary sarcoidosis. A, Numerous granulomas extend from the superficial to the deep dermis with areas of coalescence. B, Some areas have loose aggregates of epithelioid cells (top half of photomicrograph) with adjacent circumscribed, compact granulomas (bottom left and right). Epithelioid cells far outnumber lymphocytes in the granulomas. C, Coalescent epithelioid granulomas with admixed lymphocytes and two Langhans giant cells. D, Epithelioid cells and interspersed lymphocytes surround two Langhans giant cells. A basophilic Schaumann body is in the cytoplasm of one of the Langhans giant cells (right).

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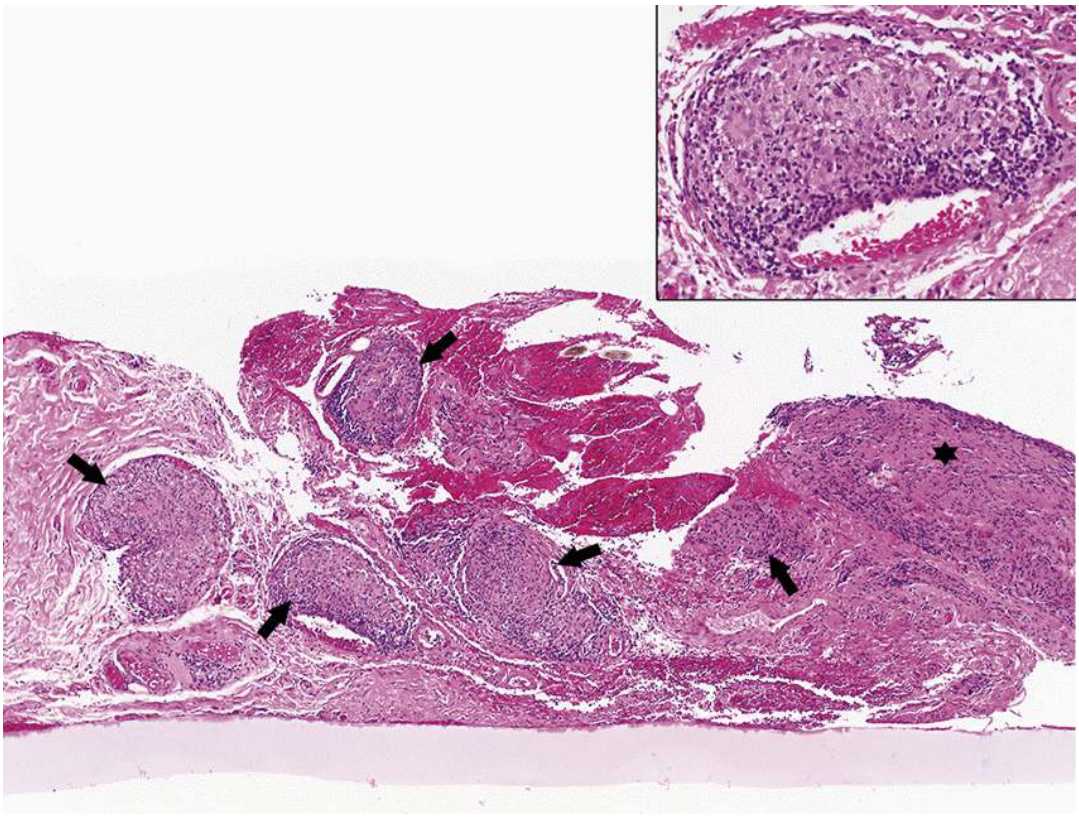

FIGURE 111.7 This conjunctival biopsy was from a woman in her late 70s with bilateral, chronic, severe conjunctivitis with minimal cicatrization. The conjunctival substantia propria contains multiple well-circumscribed granulomas (*arrows*) with focal scarring (★). The granulomas are composed of epithelioid cells, multinucleated giant cells, and a thin rim of lymphocytes (inset). Epithelium is only on the right side of the photomicrograph; most of the epithelium is artifactually detached.

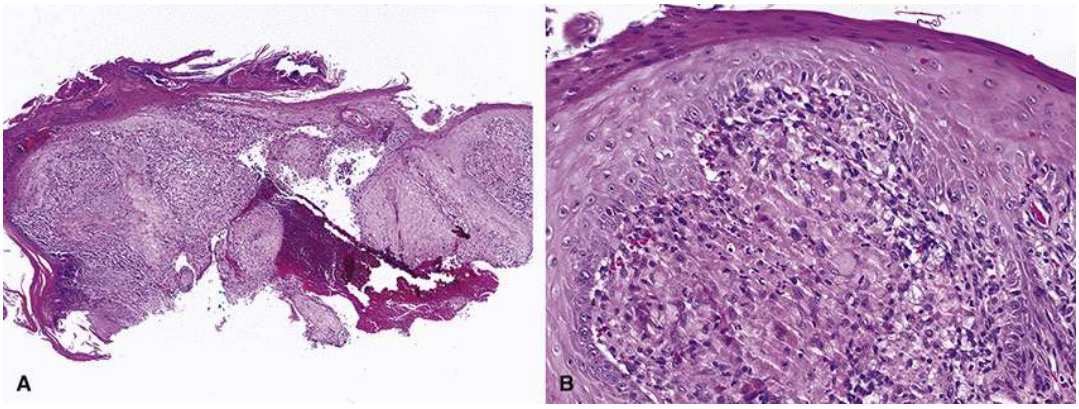

FIGURE 111.8 A man in his 30s with pulmonary and cutaneous sarcoidosis developed progressive right upper eyelid irritation, mild pain, and a 12-mm-diameter ulcer. A, The right upper eyelid lesion has healing ulceration with a thick layer of parakeratosis and pseudoepitheliomatous hyperplasia of the epidermis. B, The dermis contains nonnecrotizing granulomatous inflammation with discrete and coalescing granulomas composed of epithelioid cells and occasional multinucleated giant cells surrounded by a sparse lymphocytic infiltrate.

Subcutaneous sarcoidosis may occur with or without dermal involvement, as evident in Table 111.1. In a study of 28 patients with subcutaneous sarcoidosis, Marcoval, Penin, and Mañá reported that the 10 patients with dermal involvement had granulomas restricted to the deep reticular dermis and subcutis.[109] Fibrosis was evident in 75% (21/28) of the biopsies; the fibrosis was septal in 5, between granulomas in 4, septal and between granulomas in 3, diffuse in 3, and without a definite pattern in 6 cases.[109] Orbital sarcoidosis resembles subcutaneous sarcoidosis histopathologically.[110]

Ulcerative sarcoidosis is usually found in patients with a known history of sarcoidosis, although one review noted ulcers as the initial sign of sarcoidosis in 11 of 35 cases.[111] Ulcerative sarcoidosis occurs most commonly in adults younger than 40 years,[111,112] and there is a female and African-American preponderance.[111,112,113] It usually involves the pretibial region of the legs but has

been reported to affect the arms, trunk, face, penis, buttock, and head.[111,114] There are rare reports of ulcerative sarcoidosis of the eyelid,[47,115] and we have seen one case in our practices (Figure 111.8).

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CHAPTER 112

Schwannoma

Key Points

- Schwannoma is a benign tumor that originates from the proliferation of Schwann cells of myelinated peripheral nerve sheaths
- This tumor is usually considered to be benign, but malignant transformation has been reported
- Schwannomas can be associated with syndromic disorders such as neurofibromatosis type 2, Carney complex, and schwannomatosis
- Clinically, a schwannoma presents as a slow-growing solid, painless, round to elongated, mobile mass in the upper or lower eyelid, and rarely the lateral canthus
- Management of eyelid schwannomas is usually by complete surgical excision with clear margins
- With complete surgical excision, the prognosis is excellent and recurrence is extremely rare, but excision usually requires sacrifice of the associated nerve

Schwannoma is a benign tumor that originates from the proliferation of Schwann cells of myelinated peripheral nerve sheaths. They can arise from any nerve in the body but are located most commonly in the head and neck, followed by the flexor surfaces of the limbs and the trunk.[1] Ophthalmic occurrences are seen most often in the orbit[2] and less frequently in the conjunctiva,[3,4,5,6,7,8,9,10,11,12] uveal tract, and sclera.[13] Schwannoma in the eyelid is extremely rare with fewer than 25 cases reported in the literature to date.[14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34] Schwannomas can occur in isolation or as multi-ple lesions in some genetic syndromes.[7] The age range in the reported cases of eyelid schwannoma is 8 to 75, with a mean of about 42 years, and with no gender predilection. The size of the eyelid lesions ranges from 2 mm to 3.5 cm, with 66% being 10 mm or less in maximum diameter.

Although this tumor is usually considered to be benign, malignant transformation has been reported, and malignant schwannomas account for 5% to 6% of malignant soft tissue tumors.[35] However, no cases of malignant schwannoma have been reported in the eyelid.

Etiology and Pathogenesis

Schwannomas are among the most common peripheral nerve sheath tumors, which also include neurofibromas, perineuriomas, granular cell tumors, and malignant peripheral nerve sheath tumors.[36] They consist of a clonal population of Schwann cells, and although most cases are sporadic, some are associated with genetic syndromes such as neurofibromatosis type 2, schwannomatosis, or Carney complex. Although all three of these conditions include the development of neural tumors, their genetic bases are distinct. The most prominent feature of all three is the appearance of peripheral nervous system Schwann cell tumors.[36]

Schwannomas associated with syndromic disorders are associated with genetic mutations. Neurofibromatosis type 2 (NF2) is an autosomal dominant disorder associated with a mutation of the *NF2* gene on chromosome 22q12.[37] About 95% of patients with NF2 are affected with vestibular schwannomas, but these tumors are also found on intracranial and spinal nerves. Carney complex is a rare, autosomal dominant, multiple endocrine neoplasia and lentiginosis syndrome, and in most patients is caused by defects in the *PRKAR1 A* gene.[38,39] Schwannomatosis is an autosomal dominant condition characterized by a predisposition to develop multiple schwannomas affecting peripheral and spinal nerves and, less frequently, meningiomas.[39] It is associated with a heterozygous germline pathogenic variant in the *SMARCB1* (22q11) or *LZTR1* (22q11) genes. In patients younger than 25 years with apparent sporadic cranial schwannomas (mostly vestibular), 20% were found to have an identifiable constitutional genetic predisposition consisting of either *NF2* or *LZTR1* mutations.[40] In another study of sporadic schwannomas in adults, 38.5% were found to harbor *SMARCB1* or *NF2* mutations, without any evidence of neurofibromatosis or schwannomatosis.

Schwannomas of the eyelid were first reported by Mishra and Sharan in 1960.[41] They usually are associated with branches of the supraorbital, supratrochlear, and infraorbital nerves. In the conjunctiva, schwannomas are believed to arise from the nasociliary nerves, and also possibly from autonomic nerves that are subconjunctival in location.[10]

Occasionally, schwannomas may occur after radiation therapy.[42,43] Postradiation schwannomas can be delayed for up to 50 years following treatment.[42,44,45,46,47]

Clinical Presentation

Clinically, schwannomas present as a slow-growing solid, painless, round to elongated, mobile mass in either the upper or lower eyelid, and only rarely the lateral canthus *(Print pagebreak 740)* (Figure 112.1).[26,32] They have a smooth nodular outline, sometimes with the nerve of origin visible, and when cut they have a tan or yellow color, often with areas of hemorrhage and cystic change.[36] Rarely, eyelid schwannomas can present with upper eyelid ptosis as the presenting symptom (Figure 112.2A).[26,48] One case has been reported with inflammatory signs of eyelid swelling, erythema, and ulceration simulating a malignancy.[26] Very rarely, malignant schwannoma can involve the eyelid (Figure 112.2).

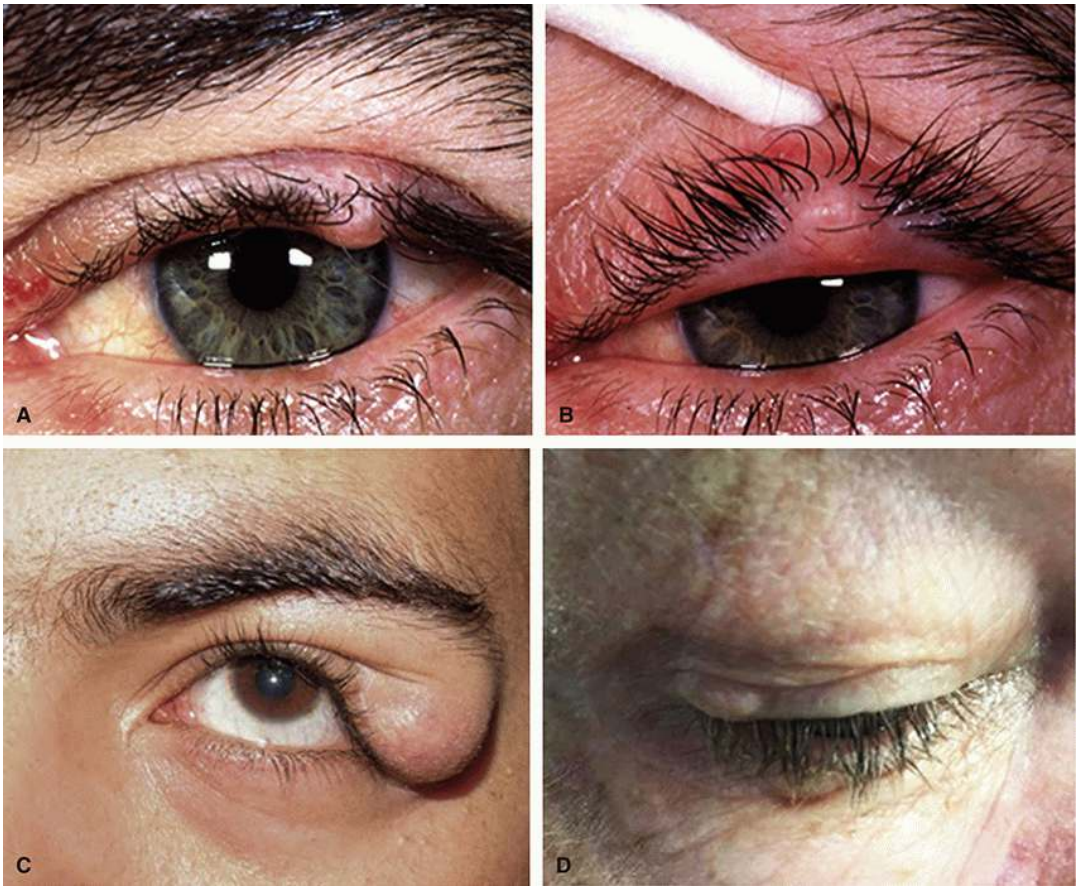

FIGURE 112.1 Smooth, solid nodular schwannomas of the eyelid. A and B, (Courtesy of Dr. David Jordan.)

Differential Diagnosis

The differential diagnosis of schwannoma includes other solid, subepidermal masses, and when on the eyelid, it can mimic an inclusion cyst, chalazion, hidrocystoma, or papilloma, or other soft-tissue and neurogenic tumors such as neurofibroma.[15,19,21,26,31,33] They can also be confused with malignant eyelid tumors such as sebaceous gland carcinoma, sweat gland tumor, and hair follicle tumor.[49] When involving the conjunctiva, the differential includes nodular scleritis, myxoma, parasitic cyst, and hemangioma.[4]

Treatment

Management of eyelid schwannomas is usually by complete surgical excision with clear margins. Incomplete removal is

associated with recurrence and sometimes more aggressive behavior with infiltration into surrounding tissue planes.[15,16,50] Preservation of nerve continuity is desirable, but this is not always possible.

Radiotherapy has not been used for eyelid schwannomas, but reports on its use for other schwannomas, such as *(Print pagebreak 741)* the facial nerve, have shown limited benefit and risks persistence of the tumor, tumor regrowth, and possible malignant degeneration.[51]

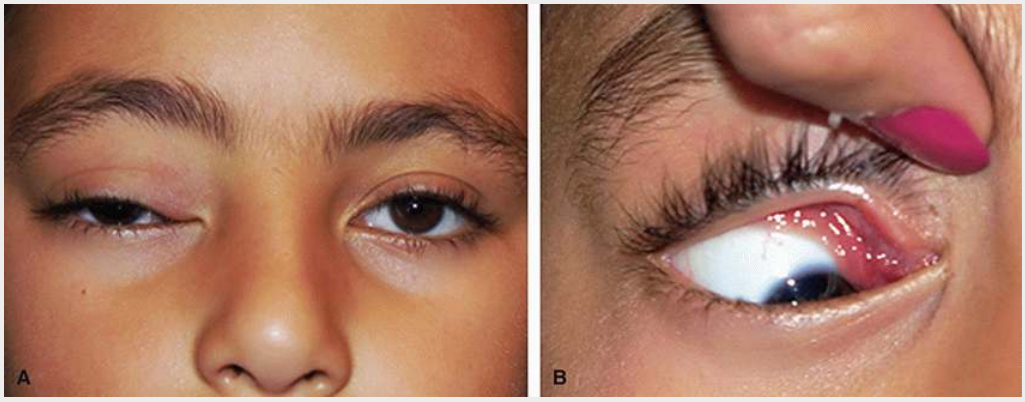

FIGURE 112.2 A rare case of malignant schwannoma of the eyelid and conjunctiva.

Prognosis

The number of reported eyelid schwannomas is too small to determine the ultimate prognosis with any form of treatment. For schwannomas elsewhere in the body, with complete surgical excision, the prognosis is excellent and recurrence is extremely rare. However, this usually requires sacrifice of the associated nerve. Recurrence of tumor can be seen where sacrifice of the nerve is not possible or not desired. In a series of 103 vestibular schwannomas treated with subtotal or near-total resection, the recurrence rate was 13.6% at a median of 41 months.[52] The decision to opt for less than a total resection is based on the intraoperative findings and the decision that more complete dissection would result in an undesired compromise of neurologic function.

Histopathology

Cutaneous schwannomas are encapsulated well-circumscribed nodules usually located in the subcutaneous fat (Figure 112.3),[53,54] although they may be in the dermis (Figure 112.4) with or without extension into the subcutis.[55] Conventional (classical) schwannomas are spindle cell tumors with varying proportions of compact areas (Antoni A areas) and loosely arranged foci (Antoni B areas).[55,56] Antoni A areas are cellular with interlacing fascicles (Figure 112.3B) of spindle-shaped Schwann cells having elongated, twisting, tapering nuclei (Figure 112.3C)[55,57] and modest amounts of eosinophilic cytoplasm without discernible cell borders.[56] The Schwann cell nuclei may align parallel to each other (palisading) separated by their eosinophilic cell processes, forming Verocay bodies (Figure 112.3C).[54,55,56,57] Antoni B tissue has a loose cobweb-like meshwork of haphazardly arranged Schwann cells in a myxoid matrix containing lipid-laden histiocytes and dilated blood vessels with thick, often hyalinized, walls.[54,55,56] Cytoplasmic nuclear inclusions and nuclear pleomorphism may be seen,[56] but mitoses are rare.[58] Longstanding ("ancient") schwannomas feature degenerative changes with nuclear atypia, sclerotic blood vessels, calcification, pseudocysts, and foci of necrosis with hemosiderin-laden macrophages (siderophages).[54,55,56] Cellular schwannomas are highly cellular, composed solely or predominantly of Antoni A tissue without Verocay bodies,[56,59] have focal mitoses[54] and Ki-67 proliferation hot spots,[56] and most often involve large nerves and nerve plexuses[56] with rare examples in the skin.[55] Other rare schwannoma variants that may occur in cutaneous tissue include plexiform schwannoma, granular cell schwannoma, collagenous spherulosis schwannoma, glandular schwannoma, epithelioid schwannoma, neuroblastic schwannoma, psammomatous melanotic schwannoma, and microcystic or reticular schwannoma.[54,55]

The neoplastic Schwann cells express vimentin, myelin basic protein, S100 protein (Figures 112.3D and 112.4D), and SOX10.[54,58] Expression of calretinin by tumor cells (Figure 112.4E) occurs in 27%[60] to 96%[61] of schwannomas and 0%[60] *(Print pagebreak 742)* to 7%[61] of neurofibromas and may assist in differentiating these tumors. Immunostaining for neurofilament protein demonstrates intratumoral axons in variable numbers and distributions in about half of sporadic[54,62] and neurofibromatosis 2-associated schwannomas.[63] Thus, demonstration of axons is unreliable as the sole basis for distinguishing schwannomas and neurofibromas when there are overlapping histological features.[62] The presence of large numbers of axons within a tumor favors the diagnosis of a solitary circumscribed neuroma.[64,65] Perineurial cells in the capsule are immunoreactive using antibodies to

epithelial membrane antigen (MUC1; Figure 112.4F).[66]

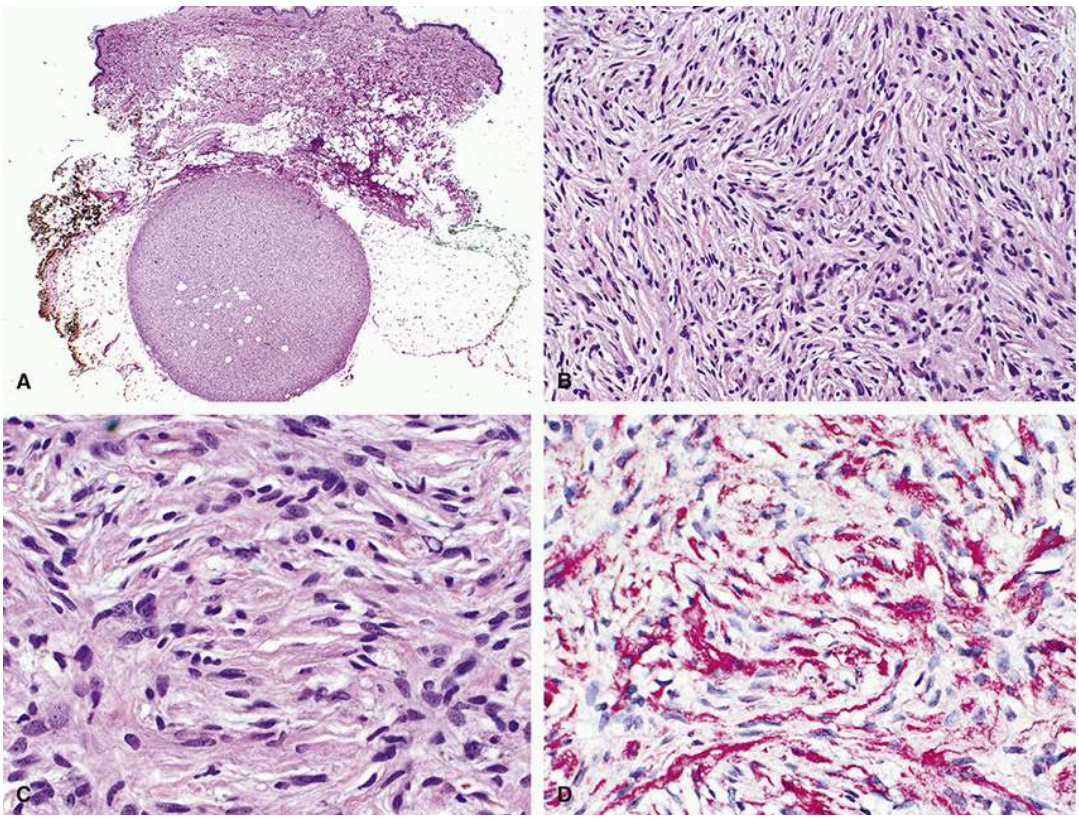

FIGURE 112.3 A, Cutaneous schwannomas are encapsulated well-circumscribed nodules usually located in the subcutaneous fat. B, This schwannoma of the left thigh is composed of interlacing fascicles of spindle-shaped Schwann cells. C, The neoplastic cells have elongated, twisting, tapering nuclei and eosinophilic cytoplasm with indiscernible cell borders. An indistinct Verocay body, formed by palisaded tumor cell nuclei with intervening eosinophilic cell processes, is in the center of the image. D, The tumor cells stain intensely and uniformly positive using antibodies to S100 protein.

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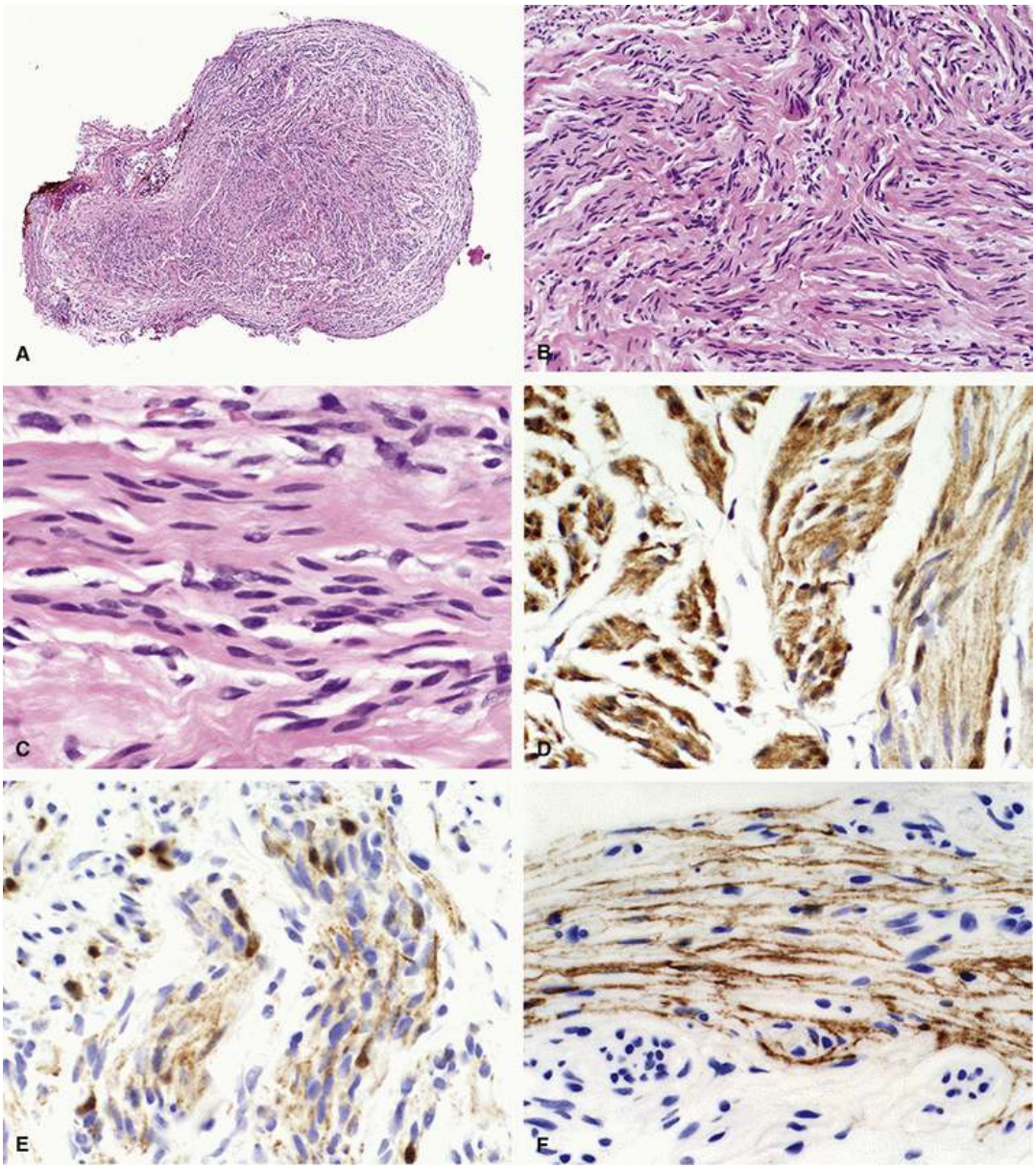

FIGURE 112.4 This schwannoma of the lateral left upper eyelid dermis presented as a 2-mm-diameter dome-shaped papule near the ciliary margin in a middle-aged woman. A, The schwannoma was encapsulated and well circumscribed. B, Interlacing fascicles of spindle-shaped Schwann cells with long, tapering, often wavy nuclei. C, Close-up photomicrograph showing tapering nuclei, lack of cytological atypia, and cytoplasmic nuclear inclusions in some of the neoplastic Schwann cells. Cell borders are not discernible. D, All of the tumor cells strongly expressed S100 protein. E, Expression of calretinin by tumor cells supports the diagnosis of schwannoma. Axons were sparse in a section stained using antibodies to neurofilament protein (not shown). F, Perineurial cells in the capsule are immunoreactive using antibodies to epithelial membrane antigen (MUC1).

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CHAPTER 113

Sebaceous Adenoma

Key Points

- Sebaceous adenoma is very rare tumor often associated with Muir Torre syndrome (MTS), a rare cancer predisposition disorder
- The cutaneous tumors associated with MTS include primarily sebaceous adenoma and sebaceous carcinoma, keratoacanthoma, basal cell carcinoma, and colorectal and genitourinary carcinoma
- Sebaceous adenoma on the eyelid can be isolated and nonsyndromic, but the potential association with Muir-Torre syndrome is critical because of the high association with internal malignancies
- Patients with Muir-Torre syndrome have mutations in DNA mismatch repair genes that are essential for the maintenance of genomic integrity
- Sebaceous neoplasms have also been reported in immunocompromised transplant patients, and those with AIDS
- They are slow-growing skin tumors that usually present as yellow papules with a predilection for the face, scalp, and eyelids
- Sebaceous adenomas are benign lesions so that treatment for most individuals can be conservative
- When lesions are bothersome, they can be removed with complete surgical excision for comfort or for cosmetic reasons
- The prognosis is excellent with very few recurrences reported

Sebaceous adenoma (SA) was first reported in 1949 by Van Walbeek[1] and was characterized as a benign tumor that presents clinically as a tan, pink, or yellow nodule or papule. It is a very rare benign tumor that is a common finding in Muir-Torre syndrome (MTS), so much so that it has been regarded as pathognomonic for that disorder.[2] However, isolated nonsyndromic cases have also been described.[3]

MTS is a rare cancer predisposition syndrome characterized by unusual cutaneous tumors and internal systemic malignancies.[4,5] The cutaneous tumors associated with MTS are primarily SA and sebaceous carcinoma, keratoacanthoma, and basal cell carcinoma.[4,5,6] Colorectal adenocarcinoma and genitourinary carcinoma are the most common types of internal malignancies, occurring in 40% and 25% of cases, respectively.[6,7]

On the eyelids, SA is exceedingly rare. Jagan et al[8] identified only 9 cases of SA (0.15%) among 5884 eyelid lesions. Nevertheless, the diagnosis of a solitary SA should raise a strong suspicion of MTS, and these patients, as well as their first-degree relatives, should undergo a systemic evaluation to exclude gastrointestinal and genitourinary malignancy.[6] These systemic malignancies may occur many years after the onset of SA so that long-term surveillance is necessary. It is therefore important to counsel all patients with an SA that there is a small increased risk of internal malignancies long after the initial diagnosis of SA.[6,9]

Sebaceous glands are found abundantly in the eyelids as glands of Zeiss and meibomian glands, and SA on the eyelids can arise from these structures. The tumors are usually small in size, measuring 5 mm or less,[10,11] although rarely they can attain a much larger size of up to 2 cm associated with rapid growth.[12] SA lesions can also rarely develop in the caruncle, which contains both conjunctival and cutaneous dermal elements.[13,14,15] Less commonly they have been reported in the bulbar conjunctiva,[16,17,18,19,20] even though sebaceous glands are normally not present in the conjunctiva.[13,14,17,21] It is unclear how a tumor of sebaceous origin can arise in the bulbar conjunctiva, but it has been suggested that this might occur from faulty migration of sebaceous gland cells from the caruncle through the nasal bulbar conjunctiva or derived from pluripotent basal cells of the conjunctival epithelium.[18] One case of an SA of the cornea has been reported. The mechanism of its development is unknown, but it was suggested to derive from pluripotential limbal epithelial stem cells that differentiated into sebaceous cells, then developed into an SA with intraepithelial

growth into the cornea.[22] Alternatively, previous trauma could have initiated the development of the SA from conjunctivalization of the cornea.

Fewer than 20 cases of SA involving the eyelid or conjunctiva have been reported.[3,9,12,17,23,24,25]

The mean patient age at diagnosis of the eyelid lesion was 54.4 years (range 23-83 years), and most patients were male (93%). The upper eyelid was predominantly involved, with rare involvement of the medial canthus.[12,24,26,27]

Etiology and Pathogenesis

Although SA on the eyelid can be isolated and nonsyndromic, the potential association with MTS is critical because of the high association with internal malignancies, *(Print pagebreak 747)* and these systemic manifestations can develop years after the appearance of the cutaneous lesion. MTS is a rare genodermatosis considered a subtype of hereditary nonpolyposis colorectal cancer. It is an autosomal dominant disorder characterized by the association of cutaneous sebaceous neoplasms and keratoacanthomas associated with a visceral malignancy, characteristically colorectal, or genitourinary carcinoma.[28] While cutaneous neoplasms usually occur after the appearance of systemic malignancies in patients with MTS, they develop before any systemic manifestations in 22% of cases.[28]

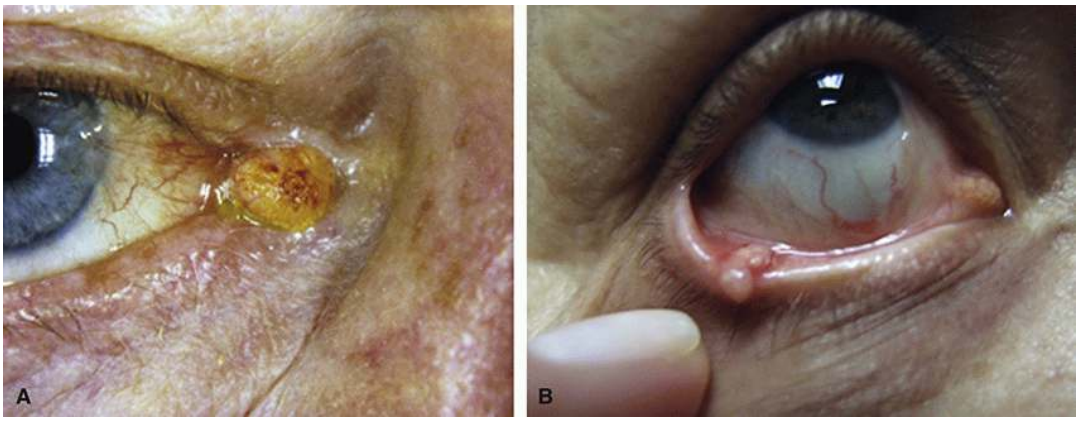

FIGURE 113.1 Sebaceous adenoma. B, (Courtesy of Dr. Suzanne Freitag.)

Patients with MTS have mutations in DNA mismatch repair genes. These genes encode MMR proteins that are essential for the maintenance of genomic integrity.[29] They normally recognize and repair erroneous insertion, deletion, and misincorporation of bases that can arise during DNA replication and recombination or in some forms of DNA damage.[30,31] There are four DNA mismatch repair genes involved in MTS that primarily include *MSH2* in more than 90% of cells and *MLH1* in less than 10%. The involvement of *MSH6* or *PMS2* is rare.[28] Patients with MTS have a germline mutation in one allele of a mismatch repair gene. With the acquisition of a somatic mutation in a second allele, mismatch repair function occurs leading to the accumulation of genetically unstable cells and increased risk of developing certain malignancies.[28] When SA is diagnosed by histopathology and immunohistochemistry is negative for MMR protein expression (*MLH2* and *MSH1*),[32,33] or the patient has a personal or family history of cancer, a workup for MTS should be conducted.[8,28]

Sebaceous neoplasms have also been reported in immunocompromised transplant patients[34] and those with AIDS.[35,36]

Clinical Characteristics

SAs are slow-growing skin tumors that usually present as yellow papules that can be mistaken for basal cell carcinoma.[29] They have a predilection for the face and scalp, particularly the eyelids due to abundant meibomian and other sebaceous glands in this region.[37] They usually are seen in older individuals with a mean age of 50 to 60 years.[10,38] Lesions associated with MTS occasionally undergo cystic change, whereas sporadic SA lesions generally do not.[39]

Eyelid SA usually present as indolent lesions that can be present for months to several years. Clinically they appear as well-circumscribed, yellowish to pink, firm, mobile nodular lesions (Figure 113.1). They may have fine papillary surface projections and telangiectasias (Figure 113.2).[40] They may rarely involve the conjunctiva (Figure 113.3) Lesions are usually less than 5 mm in diameter. Lesions can superficially look like chalazia, presenting as yellowish nodules associated with madarosis and distortion of the eyelid margin. Rarely an eyelid SA can attain several centimeters in size, with a vascular, crusted, and ulcerated surface simulating an epithelial malignancy.[12] Five cases of SA have been described presenting as a cutaneous horn, three of which showed loss of expression of mismatch repair proteins consistent with MTS.[41,42]

Differential Diagnosis

The differential diagnosis of SA includes chalazion, papilloma, sebaceous hyperplasia, seborrheic keratosis, and sebaceous and basal cell carcinoma. When on the conjunctiva, the differential should also include histiocytic, myxoid, lymphoid, lipomatous, and metastatic lesions.

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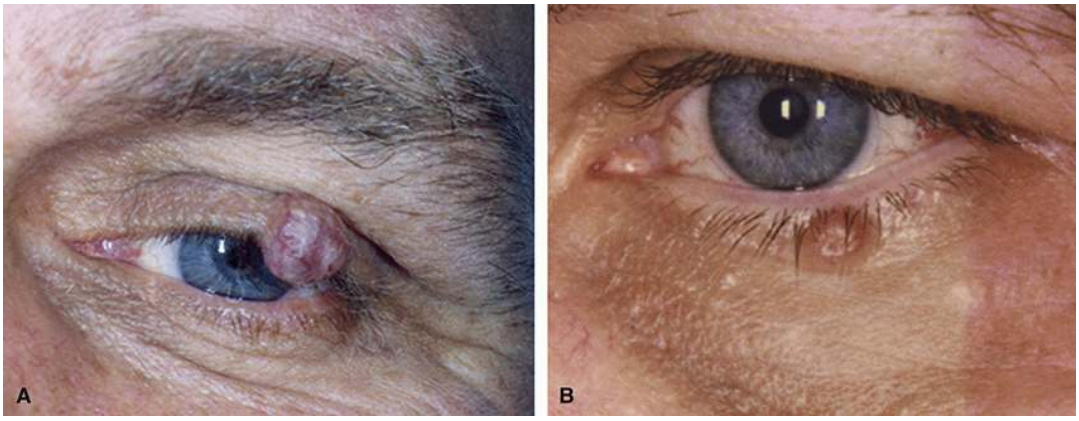

FIGURE 113.2 A, Sebaceous adenoma with fine telangiectasias. B. Sebaceous adenoma with fine filiform projections. A, (Courtesy of Dr. Bettina Meekins.)

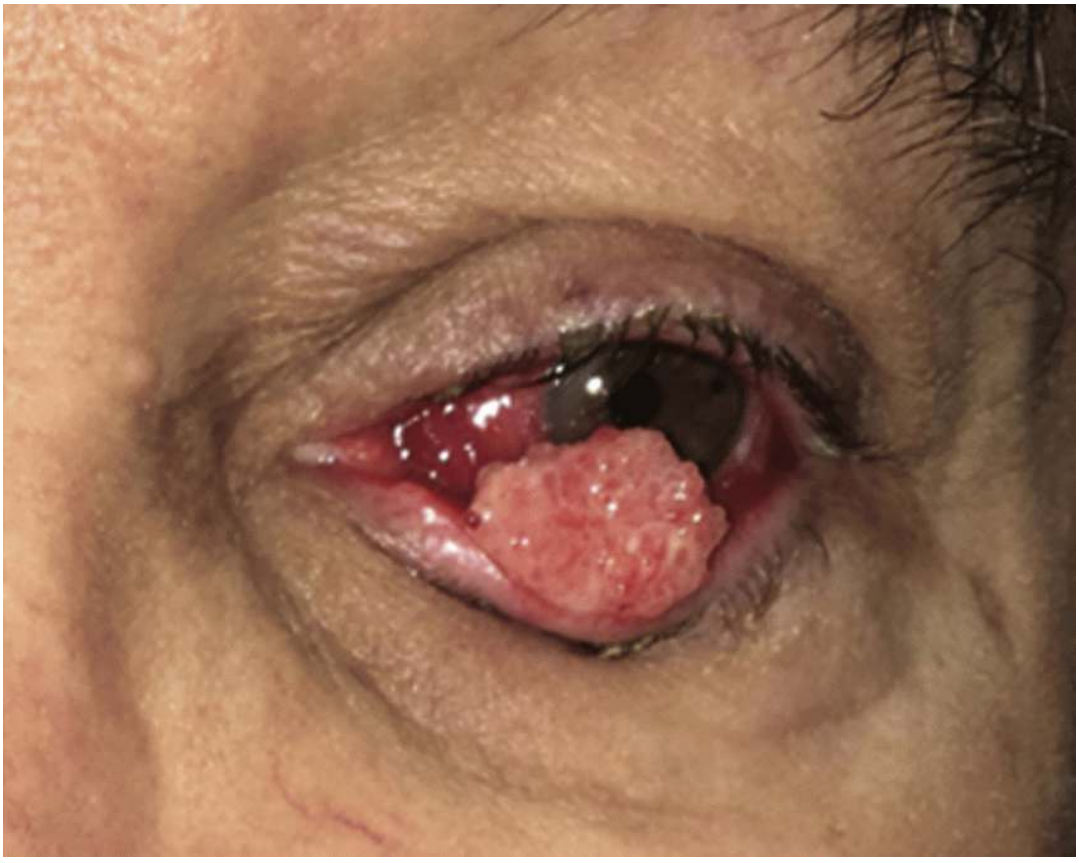

FIGURE 113.3 Large sebaceous adenoma in Muir-Torre syndrome. (Courtesy of Drs. Josiah To and Paul Phelps.)

Treatment

SAs are benign lesions so that treatment for most individuals can be conservative. When lesions are bothersome, they can be removed for patient comfort or for cosmetic reasons. When removal is indicated, the treatment of choice is complete surgical

excision. In a series of 28 cases managed surgically for which follow-up data were available, there were three documented recurrences (11%).[43] One was due to incomplete excision, but the other two lesions recurred despite apparent complete excision. Long-term follow-up should, therefore, be encouraged for possible recurrence of the cutaneous lesion. Moreover, even in patients with isolated SA, regular follow-up visits must continue since the systemic findings of MTS can develop long after the skin lesion.

Prognosis

Following complete surgical excision, the prognosis is excellent with very few recurrences reported after follow-ups of up to several years. In patients with MTS, there is a persistent risk of systemic malignancy even years after the cutaneous lesion so that long-term observation is mandatory.[44,45,46]

Histopathology

SAs of the eyelid glands of Zeiss (Figure 113.4) and caruncle (Figure 113.5) resemble those at other cutaneous sites. SAs are well-circumscribed[43,47,48] papular, nodular, or polypoid tumors[47] composed of multiple lobules of varying size and shape.[43] Tumors usually are contiguous with or replace the epidermis[43,47] but may be in the middle or deep dermis.[43,49] The epidermis may be ulcerated, form a peripheral collarette creating a keratoacanthoma-like appearance, or be hyperplastic and papillomatous.[50] The tumor lobules are separated from each other by connective tissue septa,[47] while the periphery of lobules compresses the adjacent dermal collagen, creating the appearance of a capsule.[43] The sebaceous lobules comprising the tumor have a peripheral germinative (or generative[51]) layer of small basophilic cells, then a zone of transitional cells, and finally mature *(Print pagebreak 749) (Print pagebreak 750)* sebaceous cells in the center of the lobule.[43,47,51] The germinative cells form a layer of one or more cells[50] and have large, oval to elongated deeply basophilic nuclei, little cytoplasm, and indistinct cell borders.[51] Mature sebaceous cells are larger than germinative cells, are round, have reticulated cytoplasm due to lipid droplets, and have distinct cytoplasmic borders.[43,51] Transitional cells, which lie between the germinative and mature cells, have pink cytoplasm[50] with progressively increasing amounts of lipid in their cytoplasm.[43] Mature sebaceous cells outnumber germinative cells. Histological features of SAs that correlate with MTS are cystic change, intratumoral mucin deposits, squamous metaplasia without keratoacanthoma-like changes, ulceration, and intratumoral and peritumoral lymphocytes (in the absence of epidermal ulceration).[52]

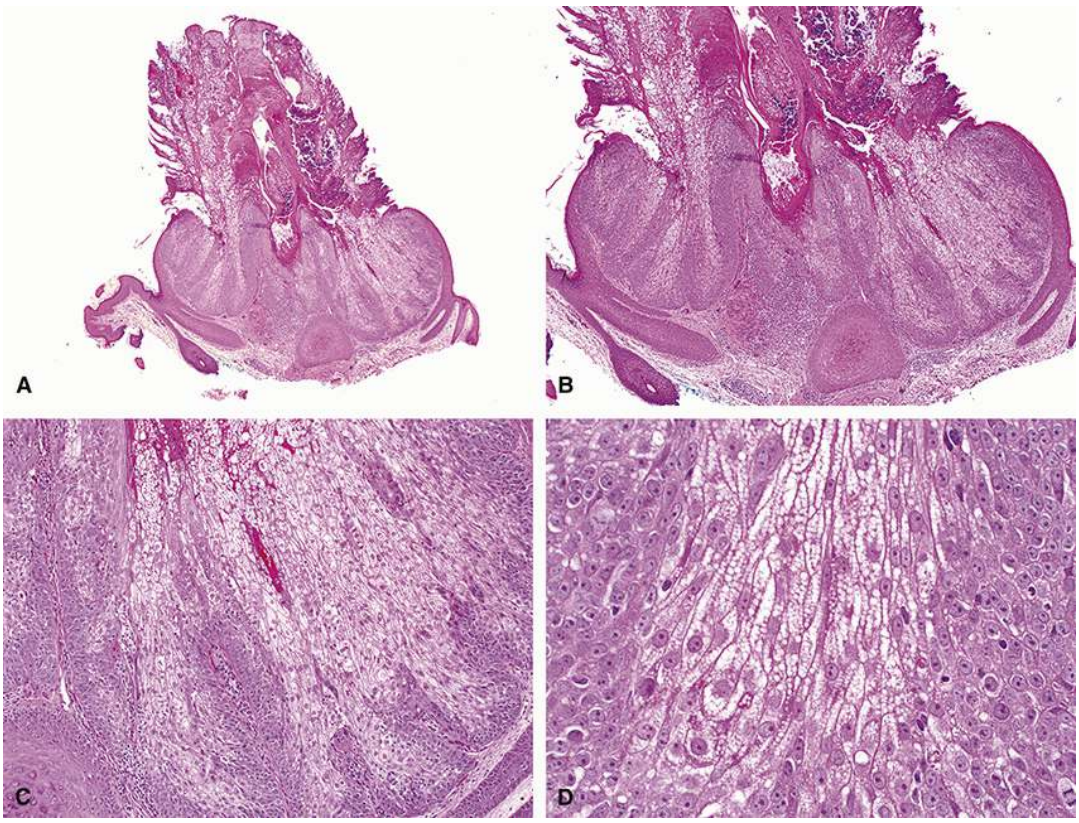

FIGURE 113.4 This sebaceous adenoma presented as a cutaneous horn of the right lower eyelid of a 60-year-old man who was subsequently diagnosed with Muir-Tore syndrome. A, The adenoma forms lobules contiguous with the epidermis and is surrounded by an epithelial collarette creating a keratoacanthoma-like appearance. The lesion's surface

has sebaceous material, foci of hemorrhage, and parakeratosis, creating the horn noted clinically. B, Mature sebaceous cells outnumber germinative cells. The overlying horn contains abundant sebaceous material released by holocrine secretion and areas of parakeratosis. C, The tumor lobules contain germinative basaloid cells, transitional cells with lightly eosinophilic cytoplasm, and mature sebaceous cells in the center of the lobules. D, The amount of cytoplasm increases and becoxmes reticulated as the germinative cells mature.

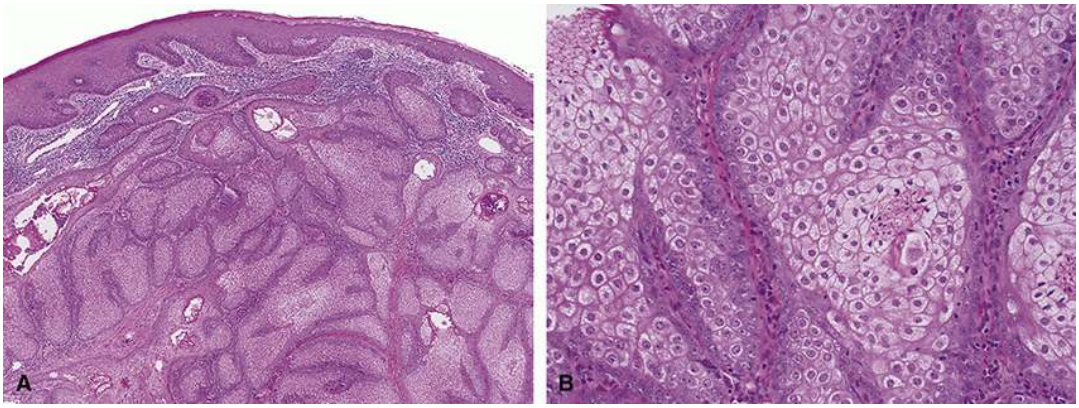

FIGURE 113.5 This sebaceous adenoma in a 67-year-old man was manifest clinically as a 5 × 5 mm pedunculated mass of the right caruncle that did not involve the right lower eyelid. A, The caruncular sebaceous adenoma has numerous lobules forming a mass that is not contiguous with the surface epithelium. B, The lobules have a one-to two-cell thick layer of germinative cells, a predominance of transitional cells with pink cytoplasm, and centrally located mature sebaceous cells with clear cytoplasm.

The differential diagnosis of SA includes sebaceous hyperplasia, sebaceoma, and sebaceous carcinoma.[50,53,54] Sebaceous hyperplasia manifests as well-differentiated sebaceous lobules usually associated with a central cystically dilated pore.[49] The hyperplastic sebaceous lobules are increased in number, are higher in the dermis than usual, are typically not much larger than expected in facial skin, and have only one or two peripheral layers of germinative cells.[49] Sebaceous hyperplasia usually has fewer germinative cells than SA and typically lacks the transitional cells that are a feature of SA.[40,49,53] Despite these descriptive differences, there is only moderate interobserver agreement among pathologists' diagnoses of sebaceous hyperplasia and SA.[54] Increased nuclear expression of survivin may assist in differentiating sebaceous hyperplasia from adenoma since adenomas have increased survivin expression.[55] Sebaceomas are well-circumscribed dermal tumors composed mainly of basaloid germinative cells (Figure 113.6).[40,49,53] Greater than 50% basaloid cells is the value usually considered as the cut-off for differentiating sebaceoma from SA,[49,53] although the number of histological sections that should be examined to determine the percentage of basaloid cells is not defined.[53] Similar to sebaceous hyperplasia, there is only moderate interobserver agreement among pathologists for diagnosing SA and sebaceoma.[54] Well-differentiated (grade 1) sebaceous carcinoma may be difficult,[40,53] if not impossible,[54] to discriminate from SA. An increased mitotic rate,[56] increased nuclear survivin expression,[55] cytological atypia,[40,53] or abnormal mitotic figures [50] favor a diagnosis of carcinoma. We concur that “If in doubt, any sebaceous tumor should be excised completely.”[53]

SAs may also arise from the eyelid meibomian glands (Figure 113.7), although reported cases are exceptionally rare.[27,57,58,59,60,61] Meibomian gland adenomas feature retained acinar organization but exhibit the loss of the normal parallel linear gland organization.[57] The sebaceous acini are generally larger than normal and have a more prominent and thicker layer of germinative cells.[57] Both of the meibomian gland SAs that we have encountered arose along the eyelid margin and were differentiated from an eyelid sebaceoma[62] by the predominance of mature sebocytes.

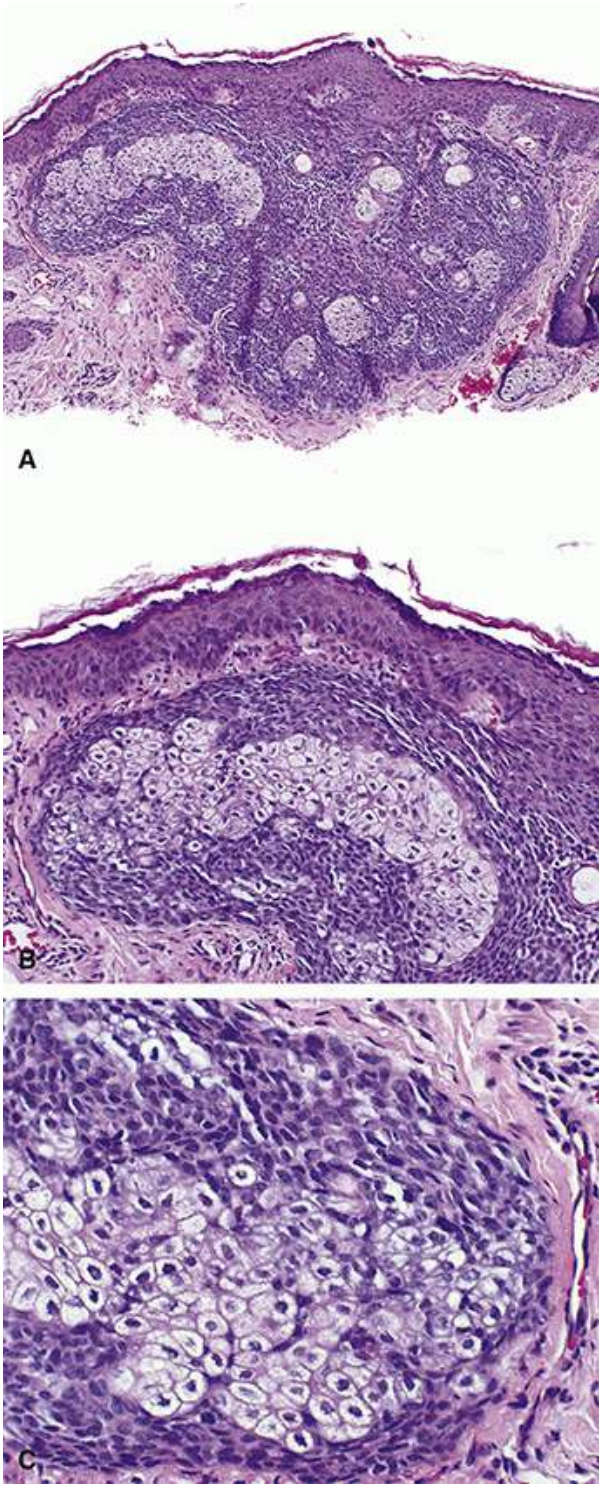

FIGURE 113.6 This sebaceoma arose in the right upper eyelid of a man in his early 50s. A, The tumor is a well-circumscribed nodule in the dermis contiguous with the epidermis. The overall predominance of basaloid (germinative) cells distinguishes sebaceoma from sebaceous adenoma. B, This tumor lobule shows continuity with the epidermis, more germinative than mature sebaceous cells, and the sharp border of the tumor and adjacent dermis. C, Maturation of germinative cells is similar to that in sebaceous adenoma.

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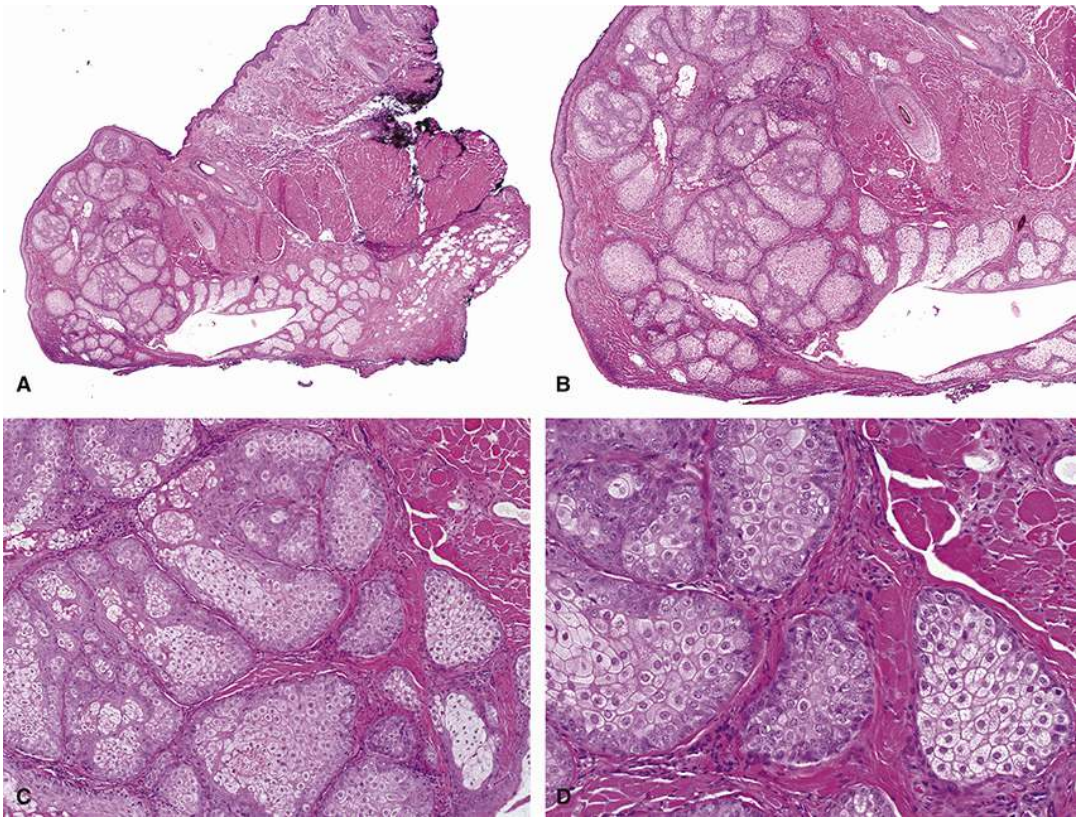

FIGURE 113.7 This meibomian gland sebaceous adenoma developed in the lateral left lower eyelid of a woman in her late 20s. It had been present for approximately 9 years, fluctuated in size, was intermittently erythematous, and itched continuously. A, The sebaceous adenoma is a nodular mass of sebaceous lobules (acini) extending anteriorly from the tarsus at the eyelid margin. The meibomian duct is dilated distal to the tumor. B, Lobules of tumor surround and compress the meibomian duct. C, The tumor lobules vary in size. The germinative layer is thicker than normal. D, The adenomatous lobules have a prominent peripheral germinative layer and abundant transitional cells with pink cytoplasm. A normal meibomian gland is at the bottom right corner of the image and has a flattened germinative cell layer surrounding mature sebaceous cells with clear reticulated cytoplasm.

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CHAPTER 114

Sebaceous Duct Cyst

Key Points

- Sebaceous duct cysts are sporadic, superficial cutaneous cysts caused by obstruction of the outflow duct of the sebaceous glands associated with the pilosebaceous follicular unit
- Steatocystoma multiplex is a benign disorder that is considered a counterpart of steatocystoma simplex and is generally inherited in an autosomal dominant fashion
- The pathogenesis of sebaceous duct cysts is unknown, but immunohistochemistry has established a relationship to the draining duct of the sebaceous gland of the pilosebaceous apparatus
- It may develop in part from obstruction of the sebaceous gland duct that involves trapping of the vellus hairs produced by a pilar unit in a cystic cavity that is connected to the epidermis by a duct that is filled with cellular debris
- Clinically, they present as well-circumscribed, asymptomatic, nontender, soft, flesh-colored or yellowish, intradermal, mobile cystic nodules that contain an oily substance composed of sebum
- When removal is desired for cosmesis or for larger symptomatic lesions, complete surgical excision, including the intact cyst wall, is the treatment of choice
- Incision and drainage is associated with a high incidence of recurrence since the wall is typically left behind
- With adequate management, the prognosis is excellent with a relatively low recurrence rate

Cysts of the cutaneous appendages can occur anywhere on the skin, with most arising from the infundibular portion of the hair follicle.[1] Other cysts arise from sweat glands or within the tarsal meibomian glands or show morphological similarities to different portions of the folliculosebaceous apparatus, and these have been described under a wide variety of different names. Ackerman et al [2] suggested that cutaneous cysts should be named based on the normal epithelial structure of those portions of the folliculosebaceous unit that the lining of the cyst most closely resembles. Based on this approach, a trichilemmal cyst is an isthmic-catagen cyst and a primary epidermal cyst is an infundibular cyst. Sebaceous duct cysts and steatocystomas most closely resemble sebaceous gland duct epithelium,[1] so that both can be grouped under the term sebaceous duct cyst.

A variety of different cysts occur on the skin. In the periorbital region, these most commonly include apocrine and eccrine hidrocystomas, intratarsal keratinous cysts, and cutaneous keratinous cysts. Among the cutaneous keratinous cysts, a large number of different labels have been applied with little consistency in usage or definition, resulting in confusion of terminology in the literature. For this book, we adopt a simple definition and divide the more common cutaneous cysts into hidrocystomas (Chapter 70), cutaneous keratinous cysts (Chapter 77), intratarsal keratinous cysts (Chapter 78), and sebaceous duct cysts, all discussed in separate chapters. Hidrocystomas arise from obstruction of sweat glands. Keratinous cysts accumulate keratin of various types within the cyst cavity and derive from the epithelium of different portions of the pilosebaceous apparatus. Sebaceous duct cysts trap sebum produced from the occlusion of apocrine sebaceous glands. In 1930, Ormsby and Finnerud[3] first recognized that the lining of steatocystomas resembles a sebaceous duct and proposed that these cysts arise by pathologic keratotic blockage of the duct at its entrance onto the skin surface. Ackerman et al[4] noted that, in the diagnosis of steatocystoma, sebaceous lobules are not necessary, arguing that cutaneous keratocyst and steatocystoma be united under the term sebaceous duct cyst.

Sebaceous duct cysts (SDCs) are superficial cutaneous cysts caused by obstruction of the outflow duct of the sebaceous glands associated with the pilosebaceous follicular unit. It has also been referred to in the literature as steatocystoma simplex and keratocyst.[5] They are nonheritable, solitary, benign adnexal lesions seen most often on the forehead, nose, scalp, neck, axillae, chest, upper limbs, back, legs, and the oral mucosa.[6,7] Males and females are affected equally, and patients range in age from the second to the eight decades.[6,7,8]

SDCs are usually found on the skin, and eyelid involvement is rare.[6,9,10,11,12,13,14,15] But since the caruncle also harbors skin elements such as hair follicles, sebaceous glands, sweat glands, and accessory glands, the caruncle may develop SDCs similar to those found in the skin.[12,16,17] A case was described of a follicular hybrid cyst of the tarsus, which included foci of pilomatricoma and some foci of steatocystoma.[18]

Steatocystoma multiplex (SM) is an uncommon benign disorder that shares similar pathological features and is considered a counterpart of steatocystoma simplex. It is seen most often on the chest and less commonly on the abdomen, upper arms, armpits, and face. Unlike steatocystoma simplex which arises as a sporadic lesion, SM is generally inherited in an autosomal dominant fashion. Lesions are thought to arise from an abnormal lining of the sebaceous duct with onset at puberty, likely due to the hormonal stimulus of the pilosebaceous unit.[19,20] The cysts are generally 2 to 4 mm firm bumps that contain an oily, yellow liquid and can sometimes contain one or more hairs.

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Etiology and Pathogenesis

The pathogenesis of SDC is unknown. Immunohistochemistry has established a relationship with the draining duct of the sebaceous gland of the pilosebaceous apparatus rather than with the epithelium of the isthmus.[21] It may develop in part from obstruction of the sebaceous gland duct. Plewig et al[22] proposed a mechanism that involves trapping of the vellus hairs produced by a pilar unit in a cystic cavity that is connected to the epidermis by a duct filled with cellular debris. It is not clear what triggers the formation of these cysts. One proposed factor is keratin 17, a protein normally expressed in hair follicles and sebaceous glands. Covello et al[23] investigated cases of both familial and sporadic steatocystomas and found missense mutations in keratin 17 helix boundary motifs in the familial cases. Analysis of the sporadic cases failed to demonstrate similar mutations, suggesting that other factors are involved.[24]

Clinical Presentation

Clinically, SDCs cannot be distinguished from other cystic lesions such as cutaneous keratinous cysts, so histopathologic examination is necessary for differentiation and diagnosis. They present as well-circumscribed, asymptomatic, nontender, soft, flesh-colored or yellowish, intradermal, mobile cystic nodules (Figure 114.1).[6,11,12] The cyst contains an oily yellow substance composed of sebum, a product of sebaceous gland secretion (Figures 114.2 and 114.3).[6] They may have been present for years before the patient seeks medical attention because of enlargement or cosmetic concerns. If the cyst ruptures, it may incite a lipogranulomatous inflammatory response with foreign body giant cells in adjacent tissues. Sebaceous lobules may be present within the cyst wall with a direct connection between the sebaceous lobules and the cyst's lining.

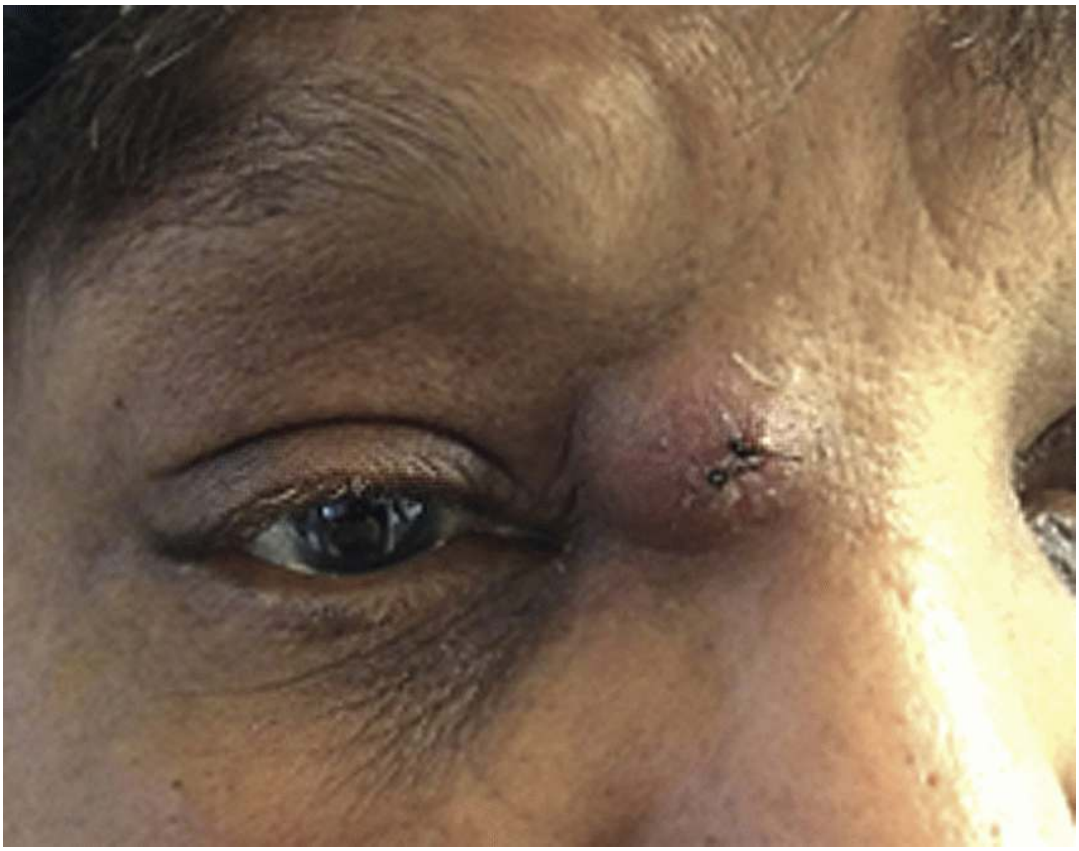

FIGURE 114.1 Sebaceous duct cyst on the medial canthus and nasal bridge. (Courtesy of Dr. Roman Shinder.)

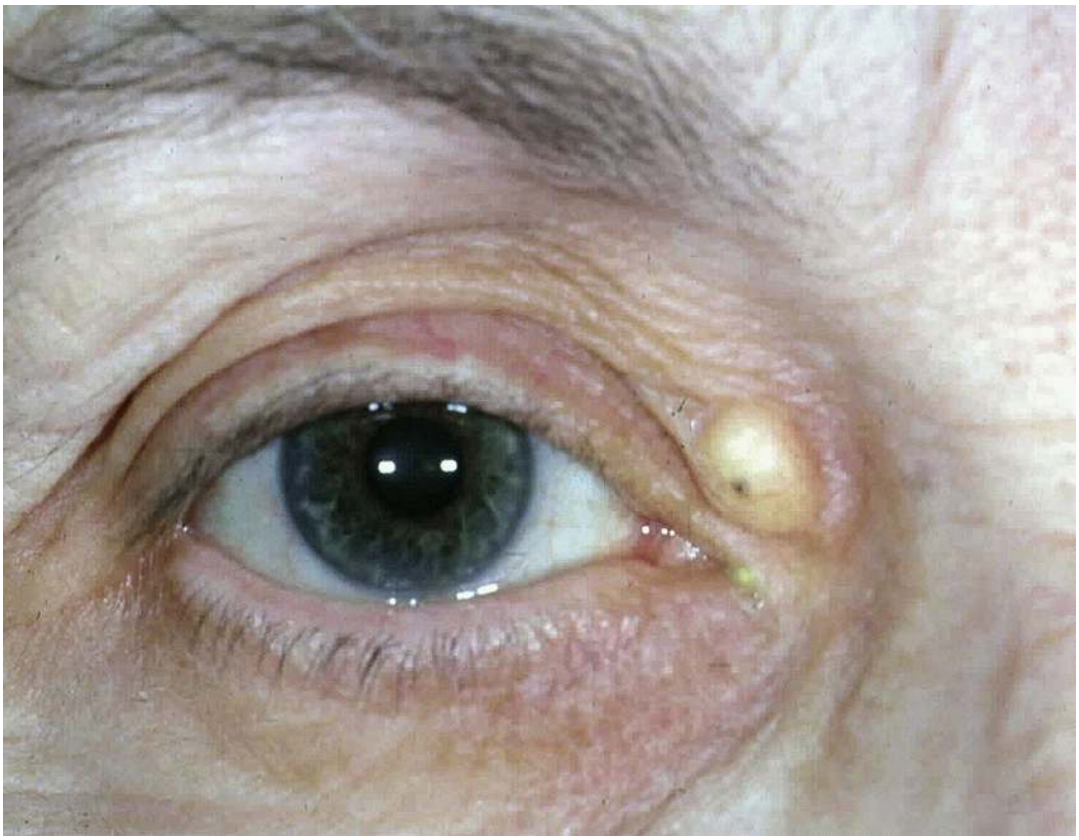

FIGURE 114.2 Small medial upper eyelid sebaceous duct cyst.

Differential Diagnosis

The differential diagnosis of SDCs includes other cystic lesions occurring on or near the eyelids. These include chalazion,

hidrocystoma, epidermoid cyst, epidermal inclusion cyst, and trichilemmal cyst, sebaceous gland hyperplasia, sebaceous gland adenoma, lipogranuloma, eruptive vellus hair cyst, and oncocytoma.[10,11,25]

Treatment

Small cysts usually do not require treatment unless requested by the patient for aesthetic reasons. When removal is desired for cosmesis or for larger symptomatic lesions, complete surgical excision including the intact cyst wall is the treatment of choice. Incision and drainage is associated with a high incidence of recurrence since the wall is left behind. In cases of active inflammation, surgery should be delayed due to a higher risk of infection, wound dehiscence, and cyst recurrence.[26] Cryosurgery,[27] radiosurgery,[28] and laser therapy[29] have also been reported with good results.[30,31]

Medical management with oral isotretinoin has been recommended for extensive lesions of SM since it also provides a reduction in the associated inflammation.[32] However, resolution may take several months and recurrence can be seen following discontinuation.[33] Oral tetracycline or topical clindamycin have been recommended for noninfectious inflammatory lesions.[33,34]

Prognosis

With adequate management, the prognosis is excellent with a relatively low recurrence rate.

Histopathology

The histological appearances of steatocystoma simplex[6] and SM [22,35] are similar. Steatocystomas are thin-walled dermal cysts with invaginations and evaginations due to fixation and loss of cyst contents (Figure 114.4A),[22] a lining of stratified *(Print pagebreak 755)* squamous epithelium varying from three to eight cells thick[35] with the absence of a granular cell layer (Figure 114.4B-D),[22,35] a wavy cyst wall with an eosinophilic crenulated luminal surface (Figure 114.4C and D),[6,22,35] and sebaceous elements within or near the cyst wall (Figure 114.4A).[6,22,35] The cyst lumen may contain keratinous material with or without vellus hairs.[35] Serial sections and three-dimensional reconstruction reveal a vellus hair follicle associated with the cyst and a ribbon-like cord or duct connecting the cyst to the epidermis.[22]

The presence of vellus hairs within a steatocystoma may cause confusion with an eruptive vellus hair cyst, which may be single or multiple lesions and may involve the eyelids.[36] Vellus hair cysts are dermal cysts lined by stratified squamous epithelium three to seven cells thick,[37] may have focal keratohyaline granules,[37] lack sebaceous elements in the wall,[38] and contain laminated and amorphous keratinous material and vellus hairs (Figure 114.5).[37,39] The epithelial lining of vellus hair cysts expresses cytokeratin 17, while that of steatocystomas expresses both cytokeratins 10 and 17.[40]

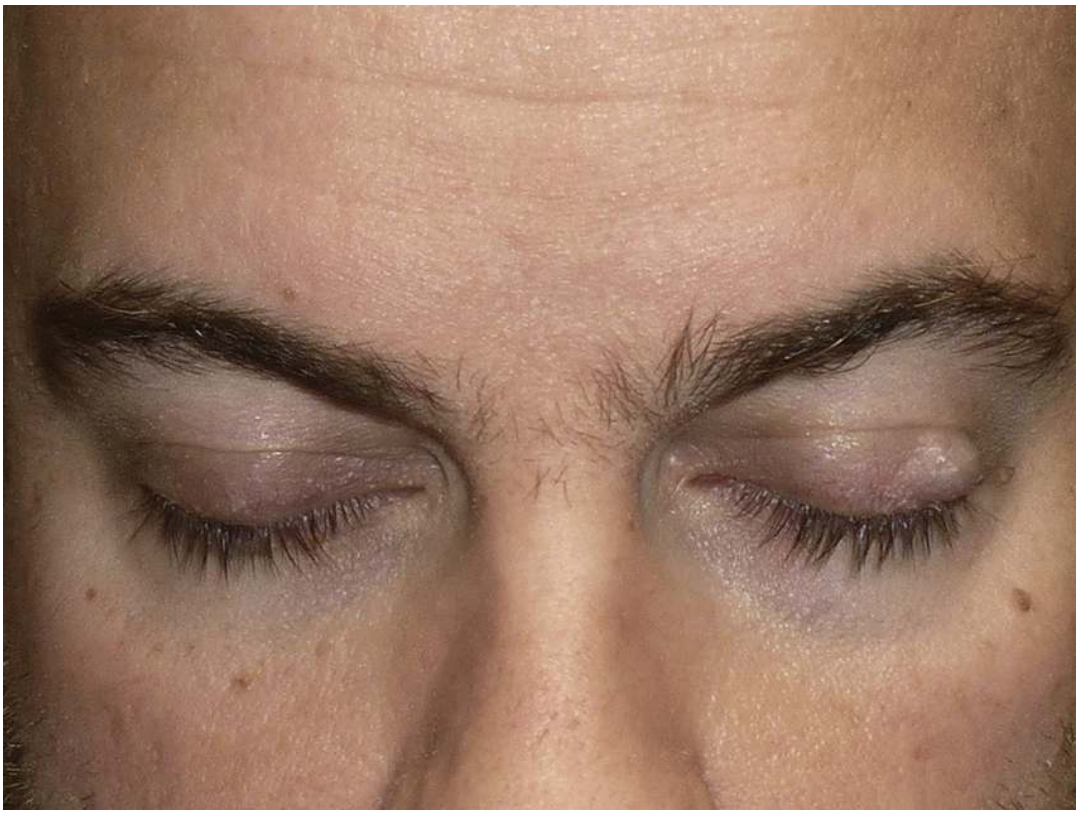

FIGURE 114.3 Steatocystoma simplex of the lateral left upper eyelid from the patient whose histopathology is in Figure 114.4.

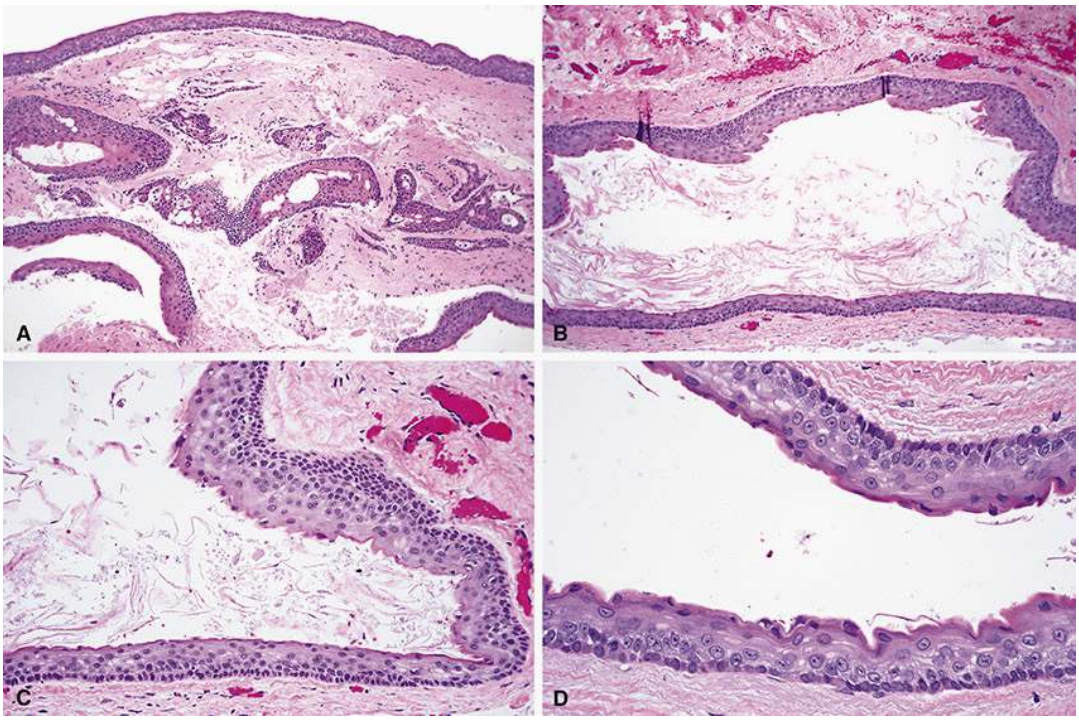

FIGURE 114.4 This steatocystoma simplex of the lateral left upper eyelid was a 7- to 8-mm-diameter cystic lesion in a man in his late 40s. It was present for 5 years, had no associated discharge or pain, and was a dark cystic lesion on slit-lamp examination. A, The cyst collapsed during sectioning causing evaginations that appear as multiple small cysts and pilosebaceous units. Sebaceous cells are in and adjacent to the cyst wall. B, The largest area of the cyst has a wavy wall, absent granular cell layer, and laminated and amorphous keratinous debris in the lumen. C, The cyst lining lacks a granular cell layer and has an eosinophilic crenulated luminal surface. Both laminated and amorphous keratinous debris is in the lumen. D, The luminal surface of the epithelial cyst lining is eosinophilic and crenulated.

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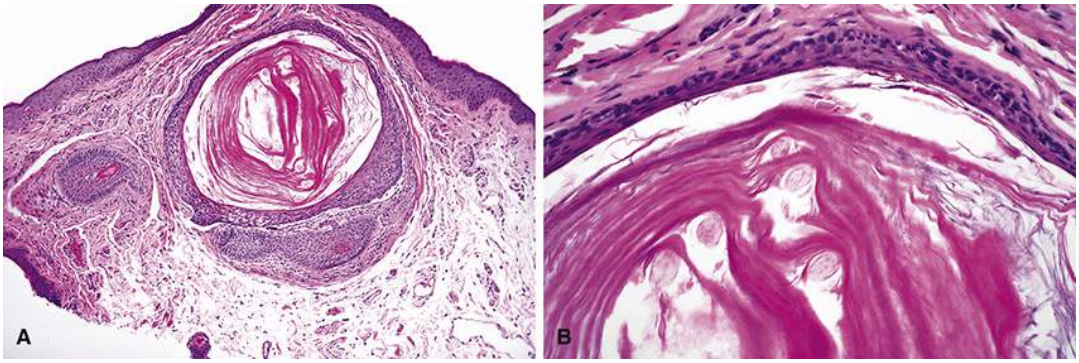

FIGURE 114.5 A vellus hair cyst developed in the right lower eyelid of a woman in her late 60s. She noted a whitish bump that increased in size over 2 to 3 months with no change in color, discharge, or pain. A, The unilocular cyst is in the dermis, is lined by stratified squamous epithelium, and is filled with laminated keratin and vellus hairs. B, The epithelial lining lacks a granular cell layer. Both laminated keratin and vellus hairs cut in cross-section are present in the lumen.

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CHAPTER 115

Seborrheic Keratosis

Key Points

- Seborrheic keratosis (SK) is the most common benign epithelial tumor and accounts for about 20% of benign epithelial neoplasms seen on the eyelid
- The pathogenesis of SK is not completely understood, but they are considered to arise in aging skin associated with UV exposure
- It does not represent reactive epidermal hyperplasia but more likely results from clonal expansion of a somatically mutated keratinocyte
- Genetic mutations have been detected in SK, showing a typical UV signature
- They present as sharply demarcated, skin-colored to darkly pigmented hyperkeratotic, slightly elevated lesions with a "stuck-on" appearance, occasionally associated with a cutaneous horn
- Treatment is generally not required, but when removal is desired for cosmetic reasons, surgical shave excision, electrodesiccation, or curettage are frequently used options
- The prognosis for seborrheic keratosis is generally very good

Seborrheic keratosis (SK) is the most common benign epithelial tumor.[1] It is estimated that about 83 million people in the United States are affected with SK, primarily middle-aged and elderly adults.[2] Lesions are seen most often on the eyelids and face, but also can be seen on the chest, back, and abdomen.[3] SK accounts for about 20% of benign epithelial neoplasms seen on the eyelid.[4,5] The occurrence of SK on the conjunctiva is very rare, with only a few cases reported.[6,7,8,9] They may be pigmented or nonpigmented, and when pigmented, they can be misdiagnosed as melanoma.

Rare cases of familial SK have been reported, including lesions presenting at a younger age. These cases tend to support a hereditary background, and somatic activating mutations of *FGFR3* have been identified in some lesions.[10,11] These mutations may be early events in the pathogenesis of a subset of SK, conferring a risk factor independent of age or ultraviolet (UV) radiation exposure.[12] However, the underlying genetic alterations in familial SK are still not clearly understood.

Dermatosis papulosa nigra has been described as a clinical variant of SK with multiple tiny lesions. It is more common in patients of African and Asian descent, and females are affected twice as often as males. Positive family history is seen in up to 85% of cases.[13] Although some authors consider this a distinct entity, the histopathology is identical to that of SK.[14,15]

The Leser-Trélat sign is the sudden appearance of multiple eruptive SKs as a paraneoplastic disorder associated with an underlying malignancy such as lung, esophageal, and nasopharyngeal carcinoma, mycosis fungoides, Sézary syndrome, and plasmacytoma.[16,17,18,19,20,21] Because of this relationship, screening for systemic cancer is recommended in cases of abrupt development of multiple pruritic SKs.

Etiology and Pathogenesis

The pathogenesis of SK is not completely understood, but they are considered to arise in aging skin associated with UV exposure. Studies have shown that some benign lesions, including SK, accumulate a number of UV-induced genomic aberrations.[22,23] SK does not represent reactive epidermal hyperplasia but more likely results from clonal expansion of a somatically mutated keratinocyte.[24] Even though SK does not have a malignant potential, more than 80% have at least one mutation, and 45% have more than one oncogenic mutation.[25]

A viral etiology involving human papillomavirus has been proposed, but this has not been substantiated in recent studies.[26,27]

Amyloid precursor protein (APP) and its downstream products are expressed more strongly in SK than in adjacent normal skin tissues, and also more strongly in UV-exposed skin compared with nonexposed skin. This suggests that overexpression of APP may promote the initiation of SK in aging, UV-damaged skin.[28]

Genetic mutations have been detected in SK, showing a typical UV signature. *FGFR3* mutations are the most frequent, detected in 48% of SK lesions, followed by the *PIK3CA* (32%), *TERT* promoter (24%), and *DPH3* promoter mutations (24%).[29] Neel et al[30] reported oncogenic mutations in the receptor tyrosine kinase/phosphatidylinositol 3-kinase/Akt signaling cascade and demonstrated that SK are sensitive to Akt inhibition. SK and squamous cell carcinoma (SCC) are both clonal tumors derived from keratinocytes, and they both have similar and overlapping genomic alterations.[31] Yet SK exhibits a benign clinical behavior and remains in situ, whereas cutaneous SCC *(Print pagebreak 759)* is locally invasive and has a small but definite malignant potential. SK is not a precursor lesion to SCC.[30] In SK there is a defect in the cornification process of epithelial differentiation, where some cells live longer than normal and undergo inappropriate intraepithelial cornification, forming so-called pseudocysts.[30] The high levels of Akt activity seem to underlie this pathological condition.

Clinical Presentation

Clinically, SKs typically present as sharply demarcated, hyperkeratotic, slightly elevated lesions with a “stuck-on” appearance (Figures 115.1 and 115.2)[32] and occasionally can be associated with a cutaneous horn.[32,33] They vary from skin-colored to darkly pigmented, and from a flat macule to an elevated nodule, and can be associated with irritation or inflammation. Irritative symptoms are frequent and lesions can become ulcerated, mimicking malignant cutaneous tumors such as basal cell carcinoma and SCC.[7,34,35] Although most SKs are 4 cm or less in diameter, giant lesions occasionally develop.[36]

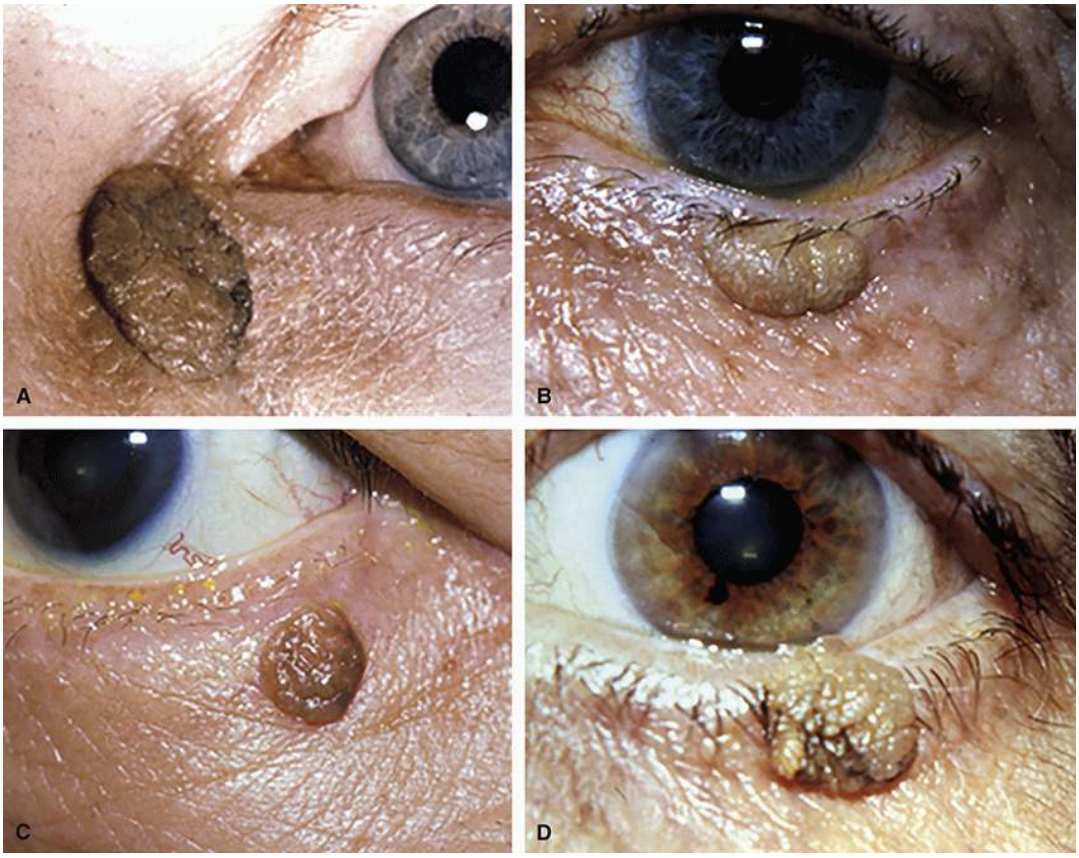

FIGURE 115.1 A-D. Sharply demarcated hyperkeratotic seborrheic keratosis. B and C, (Courtesy of Dr. Alan McNab.)

A number of dermoscopic features have been shown to characterize SK.[37,38,39] These include comedo-like openings, milia-like cysts, fissures, ridges, hairpin vessels, and multiple horn pearls.[38,40] Fissures and ridges, sometimes referred to as gyri and sulci, are thick, curved, sometimes branched lines varying from hypopigmented to brown, black, or blue that correlate with the papillomatous surface of the epidermis. Hairpin or looped vessels are two parallel vessels that form a half-looped or hairpin-like structure. They are often surrounded by a white halo and are often multiple and monomorphous in SK lesions. But they are not specific to SK and can also be observed in melanoma, SCC, basal cell carcinoma, and *(Print pagebreak 760)* other cutaneous neoplasms. Histologically, hairpin vessels correspond to enlarged capillaries of the dermal papillae.[37] Dark brown, gray, or black, round to oval clefts containing keratin plugs, called comedo-like openings, correspond to pseudohorn cysts in the epidermis that open to the surface of the lesion. Milia-like cysts are round, well-circumscribed, white to yellowish structures that correspond to intraepidermal cysts, and

multiple such cysts are characteristic of SK.

Differential Diagnosis

The differential diagnosis of SK includes melanocytic nevus, verruca vulgaris, actinic keratosis, acanthosis nigricans, pigmented basal cell carcinoma, and malignant melanoma.[41]

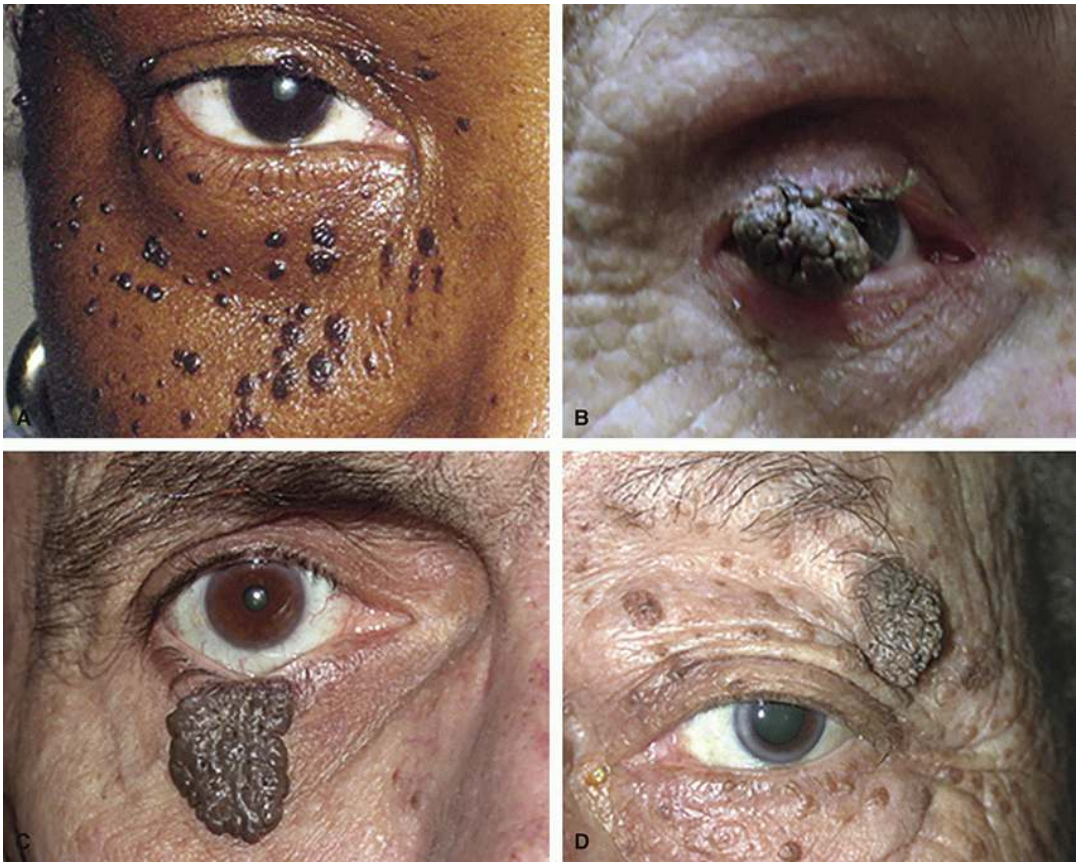

FIGURE 115.2 A, Multiple small seborrheic keratosis (SK) of the eyelids and face. B, Pigmented SK on the upper eyelid margin. C, Hyperkeratotic SK with a "stuck-on" appearance. D, Hyperkeratotic SK on the lateral brow. B, (Courtesy of Dr. Robert Kersten.) C, (Courtesy of Dr. Charles Soparkar.)

Treatment

SKs generally do not require treatment, although patients sometimes want them removed for cosmetic reasons or because they become irritated.[40,42] Surgery by shave excision, electrodesiccation, or curettage are frequently used options,[3] but recurrence and scarring are frequent sequelae. Lesions that are inflamed, bleeding, ulcerated, or excessively irritated should be biopsied or excised to rule out a malignancy.[43]

Among noninvasive therapies, cryotherapy is the most commonly employed procedure.[44] Cryosurgery is easy to use, is low cost, has a low risk of infection, requires minimal wound care, and is more effective in patients with multiple lesions. In one study, 68% of SK lesions treated with cryotherapy achieved complete healing.[45] However, cryotherapy is often associated with mild pain, scarring, *(Print pagebreak 761)* hair loss, and hyper- or hypopigmentation. A 40% solution of stabilized hydrogen peroxide in water plus alcohol (HP40) has been shown to cause oxidative damage to SK cells, leading to cell death.[46,47,48,49] Complete or nearly complete clearance was observed in up to 54% of cases treated with HP40 compared with 5% for the vehicle alone.[46] Side effects include stinging, pruritus, and hyper-or hypopigmentation.

The topical application of an aqueous solution containing nitric acid, zinc and copper salts, and organic acids (acetic, lactic, and oxalic acid) every other week for a maximum of four applications was reported to result in complete clearance in 75% of SK lesions with no relapses seen during a 6-month follow-up.[50] The successful uses of diclofenac gel, imiquimod, dobesilate, and calcitriol have also been reported for the treatment of SK in isolated case reports.[51,52,53,54]

Ablative laser therapy is also a common treatment option for SK.[55,56] Er:YAG laser therapy showed complete healing in 100% of treated lesions compared with 68% following cryotherapy.[45] Laser therapy was associated with less hyperpigmentation but more erythema than cryotherapy.[57] CO_2 laser is an alternative but carries a higher risk of scarring and pigmentary changes.[58]

Prognosis

Regardless of treatment, the prognosis for SK is generally very good, with clearance of lesions ranging from 40% to 90%. Incomplete clearance or recurrence is relatively common, and side effects such as burning, edema, and pruritus are usually minimal and temporary. Permanent adverse effects, such as hyper- and hypopigmentation seen with some therapies, are relatively infrequent, in the range of 0% to 8%.

Histopathology

SKs are well-circumscribed[3,59] benign tumors of epidermal keratinocytes, a subtype of benign acanthomas.[60] Wade and Ackerman defined three minimal criteria for the diagnosis of SK: "(1) a lesion that is exophytic and endophytic and of variable size, (2) benign epithelial hyperplasia of either basaloid cells, squamoid cells, or both, and (3) delicately laminated, amphophilically stained cornified cells massed above the general surface of the epidermis and within lesions as epithelial invaginations called pseudo-cysts of horn."[61] They considered melanin pigmentation and the absence of hypergranulosis to be less important histological findings. Hafner and Vogt distinguish horn pseudocysts from horn cysts that develop intradermally and are expelled transepidermally.[3] SKs have many histological patterns,[61] and approximately 20% of lesions had mixed histological features in the study by Roh and colleagues.[62] The World Health Organization[59] currently classifies SKs into seven histological variants, though these subtypes have no clinical significance:

1. Acanthotic (regular) type: This is the most common SK variant.[3,59,62] It is endophytic[60] with broad interdigitating columns of hyperplastic epidermis (Figure 115.3A and B),[59] especially basaloid cells,[3,61] many horn cysts[59] and pseudocysts,[3,61] and a flat base.[3,59] Hyperkeratosis and papillomatosis are slight.[60] There may be melanin pigmentation and a lichenoid or circumscribed lymphocytic infiltrate.[3]

2. Reticulated (adenoid) type: This type of SK has thin[59,60] double-rows[3] of anastomosing basaloid cells with[59,60] or without[3] horn cysts (Figure 115.3C).

3. Keratotic (papillomatous) type: This subtype features prominent hyperkeratosis with variable papillomatosis and acanthosis (Figure 115.3D and E). The hyperkeratotic and saw-tooth appearance of the epidermal surface may have a church-spire appearance (Figure 115.3D).[3] Massive hyperkeratosis may create a cutaneous horn (Figure 115.3E).

4. Pigmented type: Increased melanin pigmentation of keratinocytes and scattered melanophages in the dermis distinguish this variant (Figure 115.3F).[59]

5. Clonal type: This form has sharply delineated intraepidermal nests of benign basaloid[3] or pale[3,59] larger keratinocytes. These intraepidermal nests are referred to as the Borst-Jadassohn phenomenon; they are considered characteristic of the clonal variant of SK,[3,59] even though Mehregan and Pinkus demonstrated them in inflamed and "activated" (irritated) SKs.[63]

6. Irritated type: Irritated SKs have hyperkeratotic stratum corneum with superficial scale crust,[59] onion skin-like aggregates of eosinophilic squamous cells (squamous eddies),[3,59,61] inflammation of the dermis that may appear lichenoid,[3,59] and sometimes acantholysis, dyskeratosis, spongiosis, and apoptotic basal cells (Figure 115.3G and H).[3]

7. Macular type: Macular SKs have mild acanthosis, subtle clonal nests, and increased melanin pigmentation of the basal layer.[59] Macular SKs may be challenging to distinguish from solar lentigines.[59]

All variants of SK may have small foci of clear cells, small foci of sebaceous differentiation, or small amyloid deposits. The histopathological features of eyelid SKs are the same as those located elsewhere on the body, with the acanthotic subtype being by far the most common in our experience.

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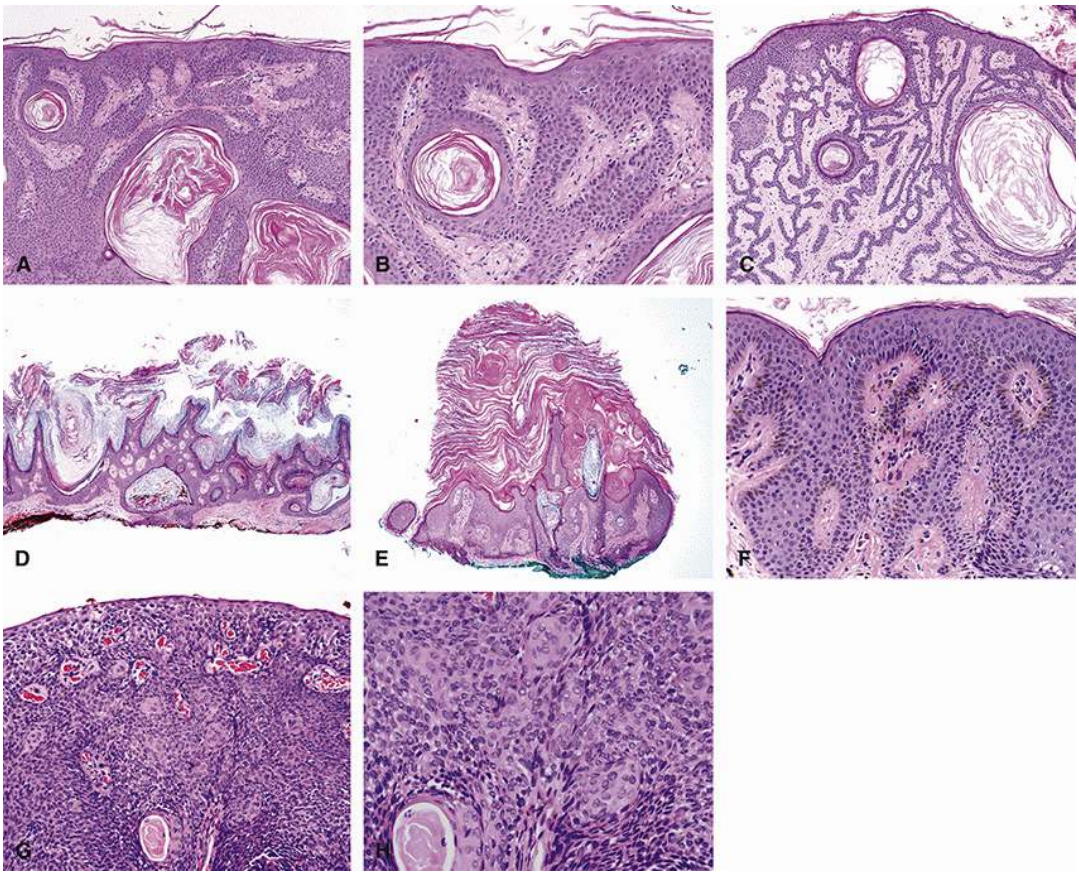

FIGURE 115.3 A and B, Acanthotic (regular) seborrheic keratosis (SK) of the left lower eyelid with broad interdigitating columns of hyperplastic epidermis and many horn cysts. C, Reticulated (adenoid) type of SK of the left lower eyelid with thin, mostly double-rows, of anastomosing basaloid cells with horn cysts. D, Keratotic (papillomatous) SK with a hyperkeratotic and saw-tooth appearing epidermal surface creating a church-spire appearance. E, This keratotic SK of the right upper eyelid had massive hyperkeratosis creating a cutaneous horn. F, Pigmented type of SK of the left lower eyelid with increased melanin pigmentation of keratinocytes. G and H, This irritated SK of the right upper eyelid had numerous aggregates of eosinophilic squamous cells (squamous eddies). The dermis, not seen in this image, had prominent chronic inflammation.

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CHAPTER 116

Solitary Fibrous Tumor

Key Points

- Solitary fibrous tumor (SFT), previously known as hemangiopericytoma, comprises a histologic spectrum of fibroblastic mesenchymal neoplasms
- The SFT group includes SFT and related lesions ranging from heterogeneous, multinodular, partially sclerotic tumors to monotonous, highly cellular ones
- The etiology remains unknown, but data support the notion that these tumors are rare spindle cell neoplasms that arise from cells of mesenchymal origin
- SFTs are associated with *NAB2-STAT6* gene fusions that arise from recurrent intrachromosomal rearrangements on chromosome 12q13
- They usually present as a painless, hard, immobile, slow-growing palpable subcutaneous mass and eyelid swelling and can cause mechanical obstruction to eyelid function, such as ectropion
- Surgical management with wide and negative resection margins and the preservation of critical surrounding organs or tissues has been the mainstay treatment
- The clinical behavior of SFT is generally benign, but recurrence can be seen and tumors considered histologically benign may behave more aggressively

Solitary fibrous tumor (SFT) comprises a histologic spectrum of fibroblastic mesenchymal neoplasms that rarely metastasize.[1] Although Wagner[2] provided the first detailed histologic description of a SFT tumor of the pleura in 1870, the lesion was only recognized as a distinct clinical entity by Klemperer and Rabin in 1931.[3] It has been recognized under several different names in the past, including benign mesothelioma, localized mesothelioma, solitary fibrous mesothelioma, pleural fibroma, submesothelial fibroma, subserosal fibroma, and localized fibrous tumor.

Hemangiopericytoma (HPC) was first described in 1942 and initially believed by Stout and Murray[4] to be a vascular tumor related to smooth muscle pericytes. However, over the years since its original description, it has become evident that HPC is simply a descriptive term to characterize a heterogeneous group of neoplasms that share a common growth pattern.[5] Three categories have been individualized within this heterogeneous group of HPC-like neoplasms. One corresponds to some non-HPC neoplasms that occasionally display HPC-like features, such as synovial sarcoma, infantile liposarcoma, and leiomyosarcoma. Another contains lesions that show evidence of myoid/pericytic differentiation such as glomangiopericytoma/myopericytoma, infantile myofibromatosis, and some sinonasal tumors.[5] The final category is the SFT group, which includes SFT and related lesions ranging from heterogeneous, multinodular, partially sclerotic tumors to monotonous, highly cellular ones.[6,7,8,9,10] Proposed variants of SFT include the fibrous variant (conventional SFT), cellular variant (conventional HPC), a fat-forming variant (lipomatous HPC), and a giant cell-rich variant (giant cell angiofibroma).[5] With the discovery of a unique fusion gene in SFT and other tumors histologically identified as HPC, these two tumor groups are now generally considered to be the same entity with the term “SFT” as the preferred name.[1,11]

SFT has an equal distribution among men and women[12,13] and occurs in adults of all ages, most commonly in the fifth and sixth decades.[12,13,14] They may be found in almost any site of the body with intrathoracic being the most common location where the pleura is most often involved, followed by lung parenchyma, mediastinum, and the diaphragm.[12,15] The most common extrapleural site is the abdomen,[6,12,16] followed by the trunk, extremities, head and neck, and intracranial sites.[17,18,19,20,21,22,23,24,25] SFT arising in the head and neck most often arises in the sinonasal tract, oral cavity, orbit, or intracranially from the meninges.[26,27,28,29,30] Primary eyelid SFT is uncommon with fewer than 40 cases reported.[10,31,32,33,34,35,36,37,38] However, the majority of the lesions involving the eyelids represent anterior extensions or coexisting eyelid lesions associated with orbital tumors.[33,39,40,41,42]

Most SFTs behave benignly, but a minority of patients will develop metastatic disease to the lungs, bones, and liver.[43] In lesions arising from the pleura, 13% to 23% are classified as malignant, whereas most extrapleural SFTs behave in a more benign fashion.[7] Larger tumor size (>10 cm), high mitotic rates, increased cellularity, pleomorphism, hemorrhage, and necrosis are predictive of a greater potential for recurrence, local invasion, and metastatic spread.[15,44]

Etiology and Pathophysiology

The etiology of SFTs remains unknown but data support the notion that these tumors are rare spindle cell neoplasms that arise from cells of mesenchymal origin.[7,45,46] In 1931, Klemperer and Rabin[3] documented the occurrence of a distinctive localized pleural-based tumor and proposed a submesothelial cell origin. Later, Stout and Murray[4] proposed a derivation from mesothelial cells based on tissue culture experiments. Since then, immunohistochemistry studies *(Print pagebreak 766)* have established a fibroblastic origin, occasionally with myofibroblastic differentiation.[8]

SFTs are associated with *NAB2-STAT6* gene fusions[47,48] that arise from recurrent intrachromosomal rearrangements on chromosome 12q13.[49] Gene expression analyses show that *NAB2-STAT6* fusions lead to altered function of the transcriptional corepressor NAB2, an important regulator of the growth response 1 transcription factor,[50] and SFTs have been shown to deregulate the expression of target genes of early growth response 1 and other developmentally important genes. The detection of this gene fusion in most cases of SFT strongly implies that this fusion gene may play a significant role in its pathogenesis.[50] Several studies have suggested that different NAB2-STAT6 fusion types may be associated with different clinicopathologic subgroups of SFT.[51] The most common fusion variant, NAB2ex4-STAT6ex2/3, corresponds to the classic pleural SFT,[52] whereas tumors with NAB2ex6-STAT6ex16/17 are found in younger patients with deep soft tissue tumors that display a more aggressive clinical behavior.[52]

Steroid hormone receptors, particularly progesterone receptors, rarely are expressed in extrapleural SFTs.[32,53] It has been proposed that progesterone may participate as a growth factor in many CD34+ neoplasms, and that progesterone receptor positivity is a feature of SFTs showing a higher proliferative activity and a trend toward recurrence.[54]

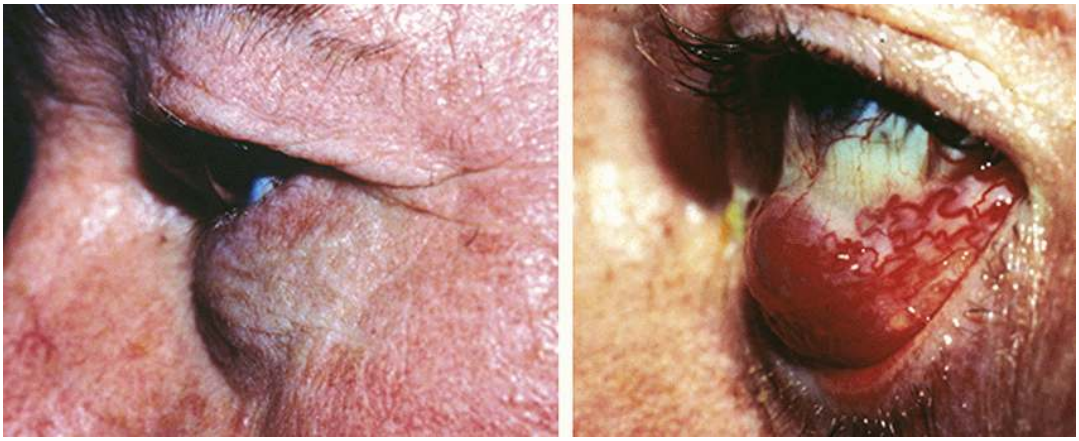

FIGURE 116.1 Solitary fibrous tumor (SFT) of the lower eyelid and conjunctiva.

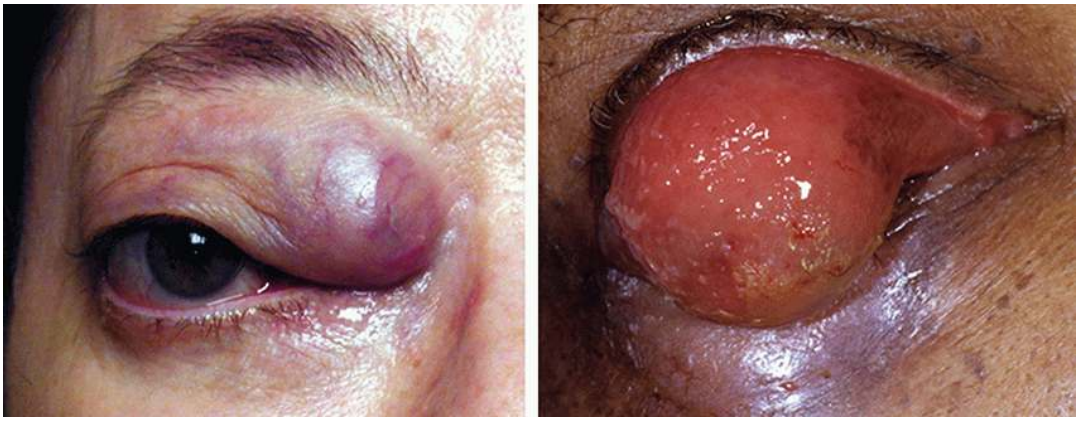

FIGURE 116.2 Solitary fibrous tumor (SFT) of the upper eyelid causing mechanical ptosis. (Courtesy of Dr. Robert A. Goldberg.)

Clinical Presentation

SFT lesions in the head and neck usually present as a painless, hard, immobile, slow-growing palpable eyelid or conjunctival mass (Figure 116.1). When present in the eyelid and periorbital region, the most frequent presenting symptoms are a palpable subcutaneous mass and eyelid swelling, and when large can cause mechanical obstruction to eyelid function, such as ectropion (Figure 116.2). Lesions involving both the eyelid and orbit are also associated with proptosis, diplopia, limited ocular motility, and occasionally decreased vision. Other rare symptoms of head and neck SFTs may include *(Print pagebreak 767)* facial swelling, bleeding, and even facial palsy. Of 18 head and neck lesions summarized by Liu et al,[55] 7 (38%) originated from the orbit, 3 (17%) from the cheek, 2 (11%) each from the masticator space and the parapharyngeal space, and 1 (6%) each from the infratemporal fossa, the maxillary, the submandibular space, and the parotid gland. Initially, 78% were clinically misdiagnosed as other lesions such as cavernous hemangioma, schwannoma, pleomorphic adenoma, granulomatous lesions, and adenolymphoma.

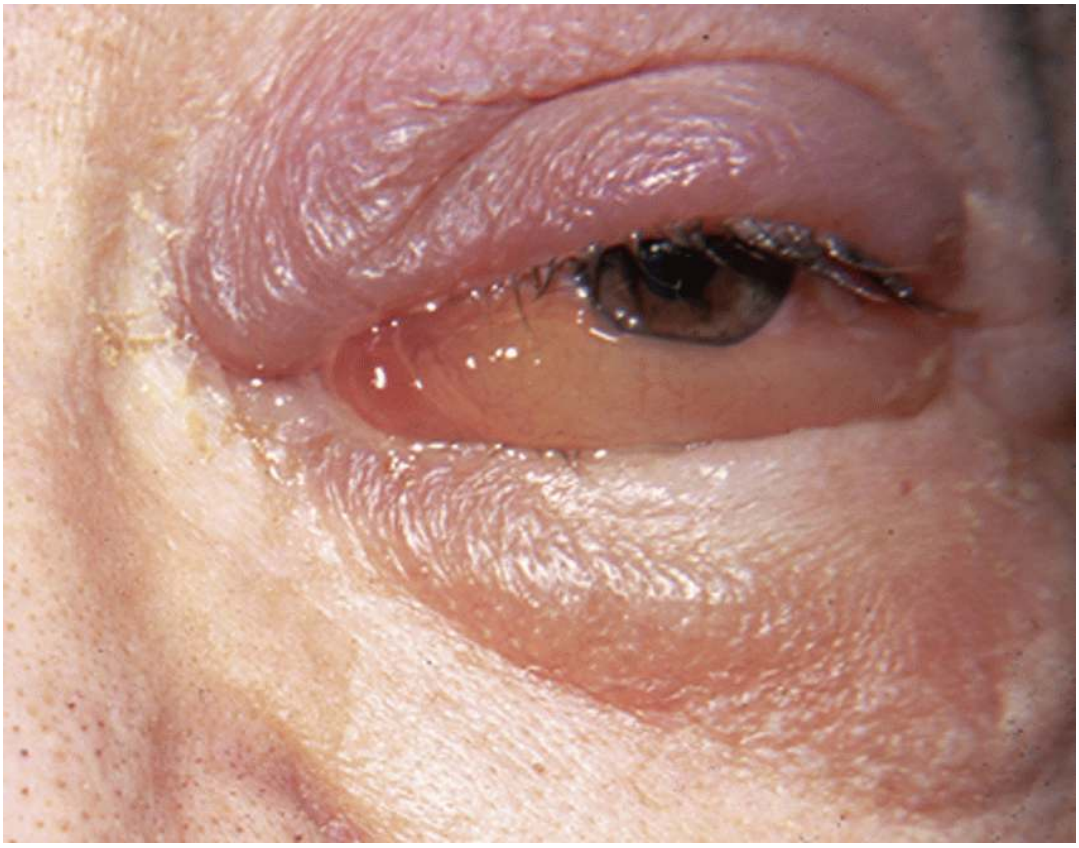

FIGURE 116.3 Solitary fibrous tumor (SFT) metastatic to the eyelid and orbit.

Higher histologic grade can be associated with recurrence and metastasis. Distant metastases have occasionally been reported.[8,56,57] In a review of 145 cases of SFT, Yamada et al[58] reported 11.8% of cases developed distant metastases, mostly associated with central nervous system (CNS) location and dedifferentiation. Rarely, SFT can metastasize to the eyelid and orbit (Figure 116.3).

Differential Diagnosis

Skin SFTs are very rare and typically present as well-circumscribed nodular lesions that can be confused with a wide variety of benign and malignant tumors. Eyelid involvement is mostly associated with orbital lesions, and neuroimaging usually shows a well-defined or less commonly diffuse mass that may be infiltrate into adjacent structures such as extraocular muscles, but the bone may be unaffected or remolded. The differential diagnosis of lesions with these characteristics is very broad and can include benign lesions such as hemangioma, schwannoma, and pleomorphic adenoma, as well as malignant tumors.

Treatment

The management of SFT usually involves a multidisciplinary team consisting of surgeons, medical oncologists, radiation oncologists, and additional ancillary support which has been shown to improve outcomes in other soft tissue sarcomas.[59,60,

[61] Surgical management has been the mainstay treatment with the goal of wide and negative resection margins and the preservation of critical surrounding organs or tissues.[6,62] After complete surgical resection, long-term follow-up has shown local recurrences as low as 8%, but this may be an underestimate since recurrence has been reported as long as 17 years following resection.[45,63] Malignant SFT tumors are more difficult to manage, with recurrence rates up to 63% even after apparent complete resection.[45]

Radiation therapy generally has not been recommended except in cases of unresectable tumors or when wide margins are not possible.[64] In a large series of intracranial STF, overall survival following surgery plus adjuvant radiotherapy compared with surgery alone was not statistically significant.[65] However, some benefit from radiotherapy has been reported in other studies, suggesting potentially improved outcomes with radiation therapy in cases of nonresectable or incomplete resection.[66,67,68,69,70]

There have been multiple retrospective studies evaluating the effectiveness of cytotoxic chemotherapy for SFTs. However, most results have shown poor results or questionable response rates.[71,72] The use of chemotherapy is best reserved for metastatic or symptomatic nonresectable SFTs. Although SFTs are relatively chemoresistant, the most effective drugs have been anthracyclines and ifosfamide, followed by gemcitabine and dacarbazine, which are commonly used in other soft tissue sarcomas.[73]

Retrospective analysis using targeted therapy with temozolomide and bevacizumab has shown a partial response in 79% of patients, stable disease in 14%, and progressive disease in 7%.[74] Antiangiogenic agents including pazopanib, sorafenib, sunitinib, regorafenib, and axitinib have also been investigated and have achieved stabilization of disease in about 50% of cases.[75,76,77,78,79]

Prognosis

Although the clinical behavior of SFT is generally benign, recurrence is not uncommon and was reported in 22.5% of 145 cases, mostly associated with CNS lesions and dedifferentiation.[57] Even tumors considered histologically benign may behave more aggressively and can demonstrate malignant behavior.[43,80] Yamada et al[57] reported metastatic disease in 11.8% of 145 cases. Even so, the overall prognosis for SFT is considered good, with 5-year survival rates between 59% and 100%, and 10-year survival rates between 40% and 89%.[13,45,62]

Poor prognostic factors include macroscopic or microscopic positive resection margins, tumor size >10 cm, more than 4 mitoses/10 HPF, increased nuclear pleomorphism, increased cellularity, tumor necrosis or hemorrhage, and the presence of malignant components.[12,13,15,81] SFT with malignant features is predictive of poorer outcomes with overall median survival ranging from 59 to 94 months. While the prognosis is usually good for most SFTs without malignant histologic features, because of the unpredictable nature of this disease, long-term follow-up of patients is mandatory.

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Histopathology

Noncutaneous SFTs are usually circumscribed, unencapsulated tumors composed of cytologically bland ovoid or spindle cells that most often lack a pattern of cellular organization (Figure 116.4).[49] The cellularity of SFTs is variable, and there may be some areas of low cellularity (Figure 116.4B) and others of higher cellularity (Figure 116.4C) within a tumor.[49] There may be sparse stroma in high cellularity areas (Figure 116.4C) and abundant collagen in low cellularity areas (Figure 116.4B).[49] The collagen may form sheets or bundles and may resemble the appearance of collagen in keloids.[49] There may be focal myxoid stroma, or it may be a prominent feature of the tumor. The tumors tend to be prominently vascularized with large, dilated, thin-walled vessels (Figure 116.4D) that may branch, creating a staghorn appearance, and small- and medium-sized vessels that may have perivascular hyalinization.[49] Morphological variants of SFTs include fat-forming (lipomatous HPC) and giant cell-rich (giant cell angiofibroma).[49] Immunohistochemical analysis is critical to confirm the diagnosis of SFT due to the wide variation in the histological appearance and overlaps with other soft tissue neoplasms.[82,83] A large majority of SFTs, including those in the skin, stain positively using antibodies to CD34, CD99, Bcl-2, and STAT6.[83] Nuclear expression of STAT6, a surrogate for detecting *NAB2-STAT6* gene fusion, is especially beneficial for discriminating SFTs from other soft tissue tumors.[82]

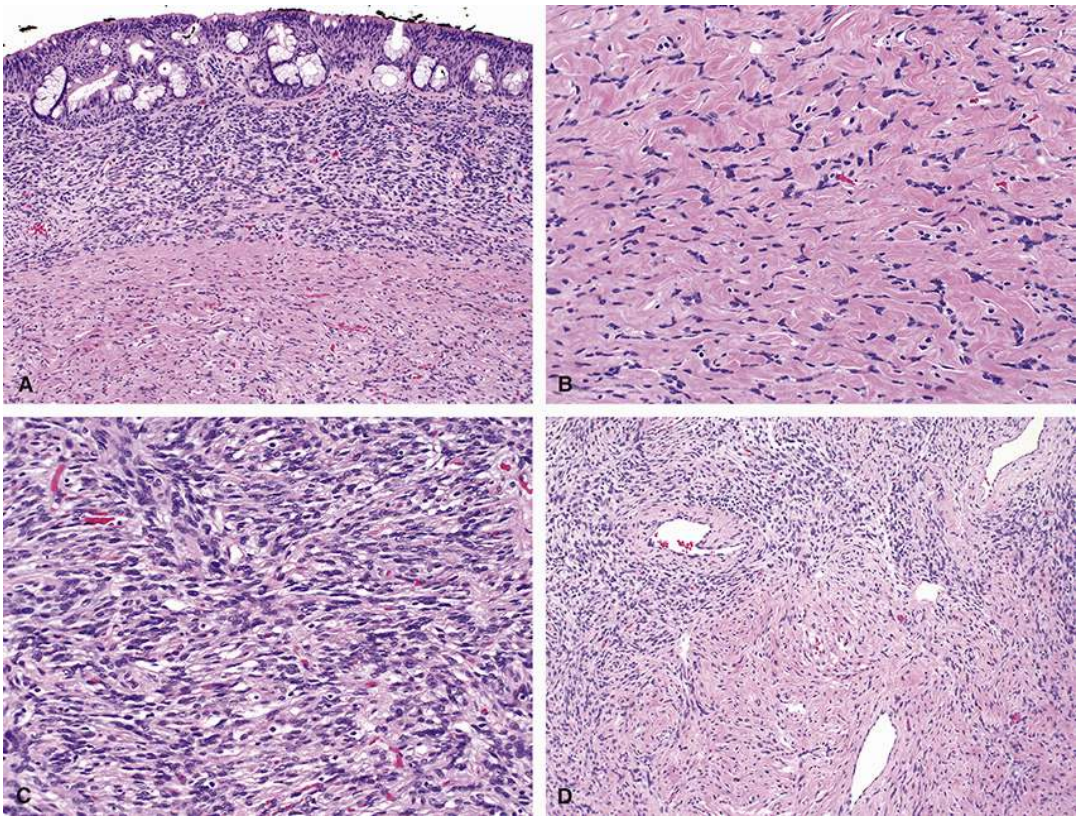

FIGURE 116.4 A man in his middle 30s developed tearing due to a solitary fibrous tumor (SFT) involving the left medial canthus and left lacrimal sac. A, SFT is present in the lacrimal sac subepithelium and extends into the adjacent connective tissue. The lacrimal sac epithelium has goblet cells individually and forming mucous glands.[87] B, The cellularity of SFTs is variable. This area of the tumor has low cellularity and abundant collagen. C, This area of the tumor has high cellularity and sparse stroma. D, The SFT has areas of prominent vascularization with large thin-walled vessels. (Reprinted with permission from Paulsen F. *The Human Nasolacrimal Ducts*. Springer; 2003:19.)

Cutaneous (superficial) SFTs involve the dermis or subcutis (Figure 116.5).[84,85] Erdag and coworkers examined 10 cutaneous SFTs, six located on the head.[84] All tumors were centered in the reticular dermis or superficial subcutis.[84] Seven tumors were circumscribed multinodular neoplasms, and three had a diffuse growth pattern.[84] Cytologically bland fusiform cells were usually haphazardly arranged, though *(Print pagebreak 769) (Print pagebreak 770)* three tumors had a vaguely fascicular pattern (Figures 116.5B and C).[84] Supporting vasculature was prominent in only five of the tumors.[84] All cases had collagenized and focally sclerotic stroma.[84] Of the 10 tumors, 8 were immunoreactive for CD34 (Figure 116.4D), and 6 were positive for CD99 (Figure 116.4E).[84] More recently, Feasel et al reported a series of 26 superficial SFTs.[85] Four tumors were in the dermis, 6 were in the dermis and subcutis, 15 were in the subcutis, and the depth was not available for one tumor.[85] Eleven of the superficial SFTs were on the head, with 2 being eyelid neoplasms.[85] Around 70% of the superficial SFTs were "in the cellular end of the spectrum with irregular fascicles of spindled cells with staghorn-like vessels and variable amounts of collagen."[85] One eyelid tumor was classified morphologically as a fat-forming giant cell angiofibroma, and the other had a focally storiform classic pattern.[85] Around 94% (17/18) of the tumors were positive for immunohistochemical expression of STAT6 (Figure 116.5F), 95% (21/22) expressed CD34, and none expressed S100 protein (0/8) or cytokeratins (0/5).[85] The one tumor that lacked STAT6 expression had classic histologic features of SFT and expressed CD34.

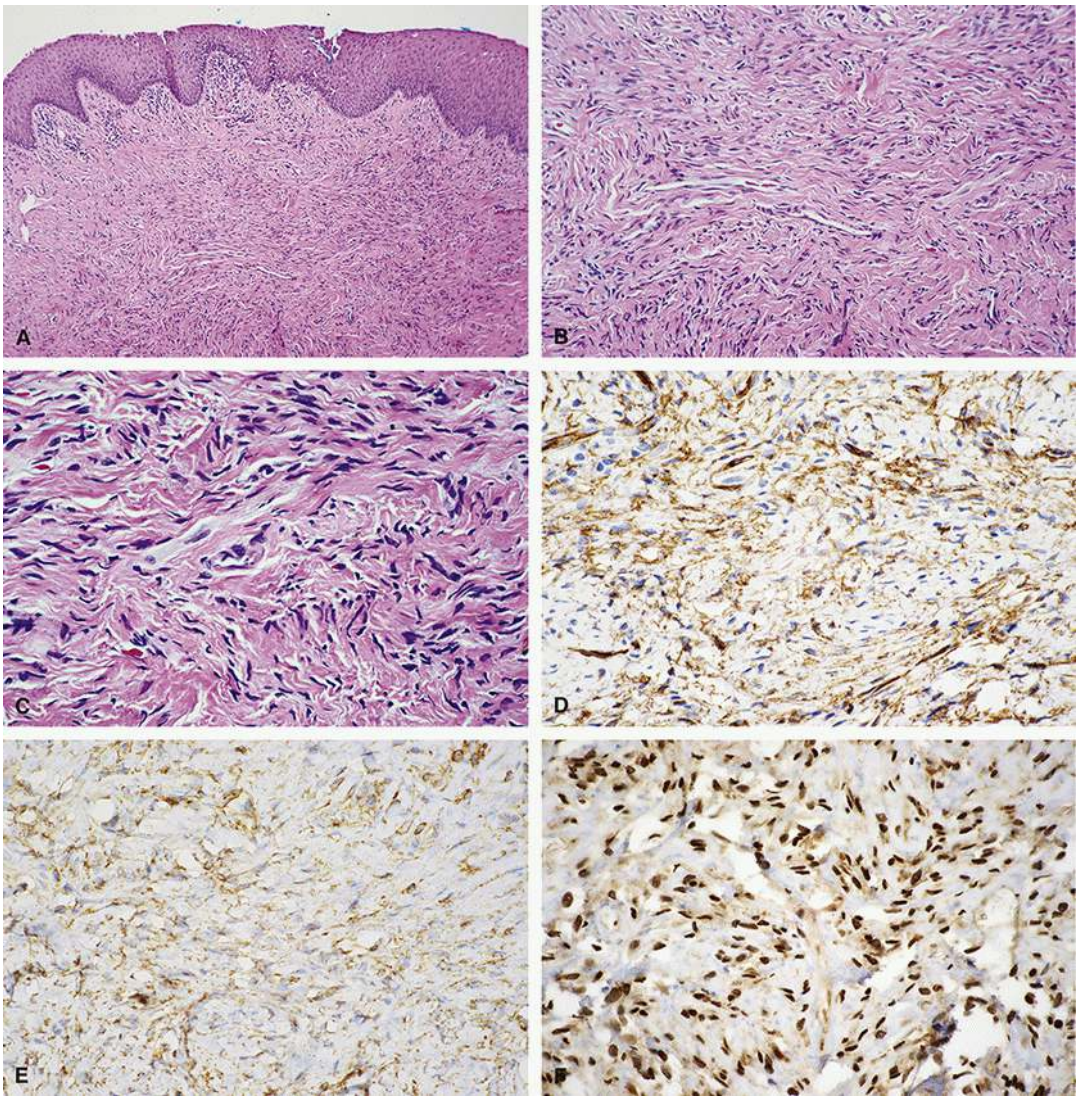

FIGURE 116.5 This solitary fibrous tumor (SFT) of the right lower eyelid mucocutaneous junction lateral to the punctum was from a woman in her late 60s. The lesion was raised, had a diameter of about 1 mm, and there was telangiectasia but no madarosis. It was present for about 1 to 2 years before biopsy during ectropion repair. A, The SFT is in the conjunctival substantia propria with a thin zone of normal connective tissue between the tumor and thickened conjunctival epithelium. B, The SFT is cellular, with spindle cells forming fascicles with interspersed stromal collagen. Some areas had many blood vessels. C, The spindle cells are cytologically bland, mitotic figures and necrosis are absent, and abundant eosinophilic collagen is present among the fascicles of spindle cells. The tumor cells exhibit cytoplasmic staining using antibodies to CD34 (D) and CD99 (E). The tumor cells did not express smooth muscle actin, S100 protein, or glial fibrillary acidic protein (not shown). F, Approximately 95% of superficial SFTs exhibit nuclear expression of STAT6.

Histological features of malignancy are infiltrative margins, hypercellularity, at least focal cellular pleomorphism, and more than four mitotic figures per 10 high-power microscopic fields.[49] In the modified risk assessment model developed by Demicco and colleagues,[86] the risk of metastasis by SFTs is based on a cumulative score of age (0 for age <55 years and 1 for age ≥55 years), mitotic activity (score 0 for <1 mitotic figure/10 HPF, 1 if 1-3 mitotic figures/10 HPF, and 2 if ≥4 mitotic figures/10 HPF), tumor size (score 0 if ≤5 cm, 1 if 5 to <10 cm, 2 if 10 to <15 cm, and 3 if ≥15 cm), and necrosis (0 if <10% necrosis and 1 if ≥10% necrosis). A cumulative score of 0 to 3 is low risk, 4 to 5 is intermediate-risk, and 6 to 7 is high risk.[86] Demicco et al found no metastases at 10 years of follow-up in patients with low-risk SFTs, a 7% 10-year metastatic risk in the intermediate-risk group, and a 49% 5-year metastatic risk for the high-risk patients.[86] Feasel and coworkers found that all (23/23) of their patients with superficial SFTs were low risk using this scheme, even two patients with malignant histology.[85] None of their seven patients with follow-up had recurrence or metastasis of their SFT with a mean follow-up of 100 months (range, 2-241 months).[85]

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CHAPTER 117

Stevens-Johnson Syndrome

Key Points

- Stevens-Johnson syndrome (SJS) is a severe T-cell-mediated, usually drug-induced, acute blistering disease of the skin
- SJS, together with toxic epidermal necrolysis, represents a wide spectrum of adverse cutaneous drug reactions
- It is an idiosyncratic reaction to drug intake where the accumulation of drug metabolites in the epidermis in genetically predisposed individuals initiates an immunologic process that causes massive keratinocyte cell death, eventually leading to full-thickness necrosis of the epidermis
- Acute conjunctivitis typically precedes or occurs concurrently with skin eruptions in more than 65% of patients with SJS
- Palpebral anomalies are mostly attributable to tarsal conjunctival scarring, which can result in entropion, trichiasis, distichiasis, ectropion, and symblepharon formation
- Studies have reported significantly better visual outcomes with topical steroid use
- Management of trichiasis and entropion is recommended in patients with frank cicatricial entropion
- The ultimate prognosis is related to how quickly the proper clinical diagnosis is established, how rapidly the causative drug can be identified and discontinued, and how aggressively appropriate treatment can be initiated

Stevens-Johnson syndrome (SJS) is a severe T-cell-mediated, usually drug-induced, acute blistering disease of the skin and at least two mucosal surfaces, which, together with toxic epidermal necrolysis (TEN) and their intermediate variety (SJS/TEN overlap), represents a spectrum of adverse cutaneous drug reactions. These conditions may be complicated with high mortality or significant long-term ocular morbidity.[1,2,3,4,5,6,7,8,9,10]

Etiology and Pathogenesis

SJS/TEN is essentially an idiosyncratic reaction to drug intake where the accumulation of drug metabolites in the epidermis in genetically predisposed individuals initiates an immunologic process that causes massive keratinocyte cell death, eventually leading to full-thickness necrosis of the epidermis.[10] The list of implicated medications exceeds 200 drugs, but the most common ones include antibiotics (sulfonamides like trimethoprim or sulfamethoxazole, beta-lactam antibiotics, tetracyclines, or quinolones), antiepileptic medications, nonsteroidal anti-inflammatory agents, antigout medications, and vaccinations.[1,2,6,10] Rarely, nonpharmaceutical factors like exposure to industrial chemicals, traditional Chinese herbal medications, infections with *Mycoplasma pneumoniae*, herpes virus, or HIV may initiate SJS/TEN.[1,2]

Regardless of the exact etiologic risk factor, the etiopathogenetic mechanisms underlying the onset of SJS/TEN complex have not yet been fully elucidated but are postulated to have both an immunologic and a genetic basis, which when acting together both lead to keratinocyte cell death by apoptosis and secondary epidermal necrosis, usually with irreversible consequences.[1,2,5] Granulysin, a powerful cytolytic protein secreted by the immune system, is hypothesized to play a decisive role underlying the massive epidermal cell death and mucous membrane pathology in SJS.[5] Genetic associations include abnormalities in the *HLA-B12* allele and several of its subgroups, the *IKZF-1* gene, as well as several other genes.[2] Because each of these different genes or HLA alleles may predispose an individual of a certain race to a specific drug and not any other,[2,5] a full review of those genetic/immune-mediated mechanisms and the various theories associated with SJS or TEN are beyond the scope of this chapter and are discussed in detail elsewhere.[2,5]

Lid margin keratinization is a chronic ocular sequela of SJS, causing progressive ocular surface damage. The exact etiopathogenesis remains elusive, but possible pathophysiologic mechanisms included loss of the mucocutaneous junction barrier leading to

epidermalization, dyskeratosis involving the meibomian gland orifices, altered lid margin microbiome, and de novo squamous metaplasia of the marginal conjunctival epithelium. Findings support a role for inflammation in the pathogenesis.[11]

Clinical Presentation

SJS/TEN is a rare disease with an annual incidence that ranges from 0.4 to 7 cases per million, but with a high mortality rate of 25% to 40% in TEN and 1% to 5% in SJS.[1,8] SJS is predominantly a disease of children and adolescents, whereas TEN may occur in all ages, although the mortality rate is higher in the elderly. Both conditions may recur (16 recurrences/1000 person-years), but recurrences tend to decline with age.[4] SJS is defined when 10% or less of the body surface area is involved, while in TEN 10% to 30% of the cutaneous surface area is involved.[2] Patients with acute SJS rarely present to the *(Print pagebreak 774)* ophthalmologist, but any bilateral conjunctivitis associated with an extremely high fever with or without oral involvement and with paronychia should alert the clinician to the possibility of SJS.[6] Acute conjunctivitis typically precedes or occurs concurrently with skin eruptions in more than 65% of patients with SJS.[6] If an ophthalmologist is consulted in the ICU later, after the diagnosis is established, 75% of these patients typically have bilateral conjunctivitis. This may progress to corneal ulceration in 25% of patients,[2] and occasionally tarsal ulceration may also be present.[6,7] Patients with SJS are often seen by an ophthalmic specialist after they have been released from the hospital, but in fact, the residual ocular side effects of SJS are frequently the most debilitating part of the disease.[2,3,4]

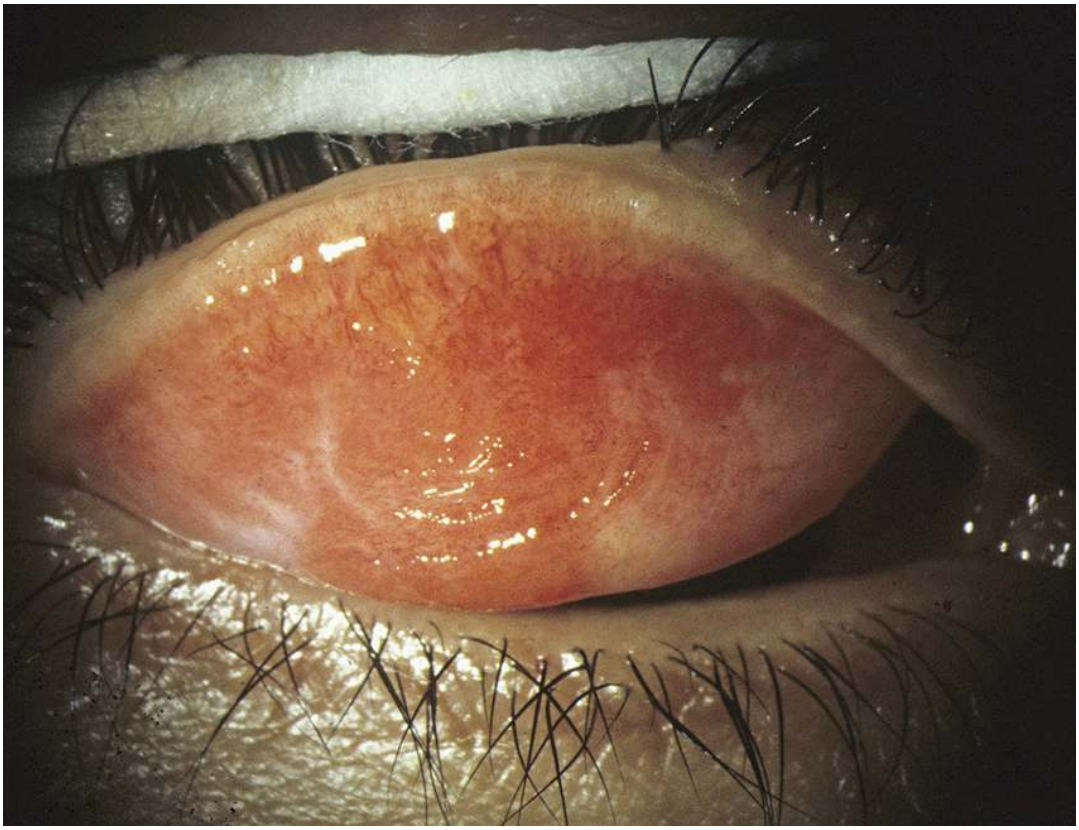

FIGURE 117.1 Hyperemia and scarring of the upper eyelid tarsal conjunctiva in SJS.

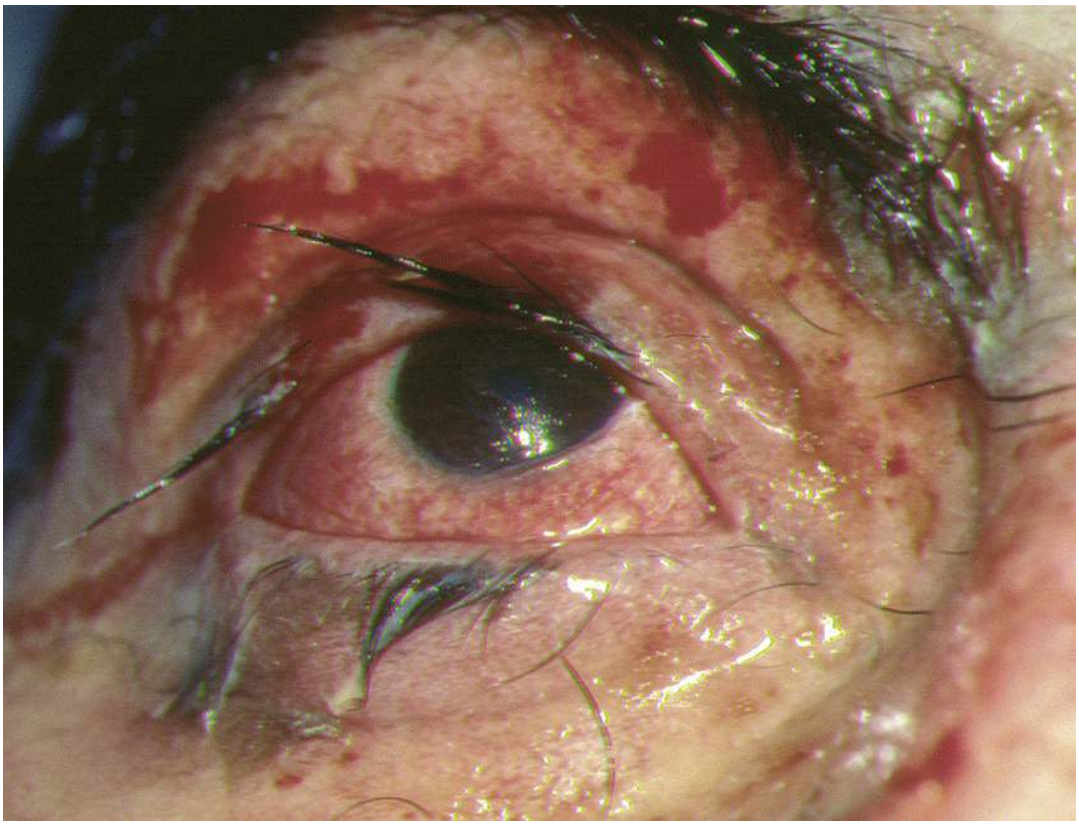

FIGURE 117.2 SJS with eyelid blisters and skin sloughing. (Courtesy of Dr. Charles Soparkar.)

Palpebral anomalies in SJS are mostly attributable to tarsal conjunctival hyperemia and scarring (Figure 117.1), which can result in entropion, trichiasis, distichiasis, or even ectropion.[10] If not removed, misdirected eyelashes, or the distichiatic ones originating from metaplastic meibomian glands, can mechanically abrade the corneal epithelium causing repeated blink-related microtrauma.[2,3,8] The exact incidence or prevalence of eyelid malpositions in SJS is difficult to conclude from the literature and varies from as low as 3% to as high as 71%.[3,8,9,10] This dramatic variability may be attributable to the lack of medical care in some rural areas, lack of standardization of diagnostic criteria for palpebral anomalies in SJS,[3] or earlier evaluation before chronic sequelae have set in.[9] More importantly, it may also be attributable to a difference in genetic backgrounds.[3] An often overlooked cause of persistent ocular inflammation in SJS/TEN is chronic irritation of the ocular surface due to lid margin keratinization.[8,9] Tarsal ulceration, which occurs in the acute phase, eventually leads to destruction of the mucocutaneous junction with subsequent keratinization of the eyelid margin that usually extends 2 to 3 mm into the tarsal conjunctiva.[8,9]

Symblepharon formation can result in lagophthalmos and extensive corneal exposure and even ankyloblepharon as late sequelae of the conjunctival ulceration observed in the acute phase.[8] Other abnormalities include eyelid erythematous macules and patches, bullae, and sloughing of skin (Figure 117.2). Severe dryness with a reduction of both the aqueous and lipid layers also is encountered frequently. This is multifactorial, occurring as a result of scarring of the lacrimal ducts, chronic reduction of lacrimal gland function, meibomian gland atrophy/orifice metaplasia, or reduction in conjunctival goblet cells.[2,3,8] In addition to the aforementioned cicatricial problems, destruction of corneal limbal stem cells combined with repeated mechanical trauma to the corneal epithelium by the trichiatic or distichiatic lashes, or by the keratinized lid margin itself, may lead to recurrent corneal abrasions, infections, corneal pannus, corneal neovascularization, and scarring. All these factors eventually lead to end-stage disease with corneal blindness[2,3] and may even progress to corneal melting and perforation.[7]

Systemically, the chronic manifestations of SJS/TEN may vary among patients, as some patients may survive their disease without apparent sequelae. However, if they do occur, chronic sequelae may include skin scarring or pigmentation; penile phimosis; vulvar adenosis; vaginal, urethral, or anal strictures; dental abnormalities; esophageal strictures; and dry mouth.[1] The psychological toll is also quite high, and these patients may become chronically afraid of becoming sick or receiving any medications or transmitting the disease to their children.[1]

Differential Diagnosis

While establishing the diagnosis of SJS may be straightforward from the history and is easy to diagnose in the chronic phase of the disease, several peculiar conditions, such as chickenpox, measles, or a herpetic infection may be confused with the acute phase of SJS. However, the presence of very high fever, oral mucosal lesions, and paronychia at the onset should raise the suspicion of SJS.[6]

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Treatment

The ophthalmologist's role in the acute management of SJS/TEN has been limited to prescribing topical medications, including antibiotics and corticosteroid preparations, as well as preservative-free lubricating agents.[3] The use of topical steroids in the acute stage is controversial,[3] but some studies have reported significantly better visual outcomes with topical steroid use.[6] Covering areas of tarsal conjunctival ulcerations with a temporary amniotic membrane graft in the acute stage of the disease may help suppress inflammation and prevent late palpebral changes and consequently corneal pathology.[3] The sloughing and inflammation of mucosal epithelium during the acute phase may lead to keratinization of the eyelid margins and scarring sequelae of the ocular surface, resulting in pain and vision loss. Amniotic membrane transplantation to the eyes and eyelids during the initial 1 to 2 weeks of the disease can decrease the chronic sequelae.[12] However, eyelid-related complications in the chronic phase of the disease after AMT can include trichiasis, distichiasis, eyelid margin keratinization, and cicatricial entropion.[13]

While eyelash epilation or a large-diameter contact lens may provide temporary relief in patients with SJS,[3] lash ablating procedures are the treatment of choice for trichiasis manifesting in SJS without frank entropion.[3] Failure to address these eyelashes will result in further morbidity to the cornea, which is already compromised by the keratinized lid margin and the limbal stem cell deficiency. Getting rid of those misdirected eyelashes rubbing against the cornea also helps eliminate the confusion about the exact cause of ocular redness, whether it is of mechanical nature from the eyelashes or due to an alternative concomitant pathology such as irritation by a keratinized eyelid margin, which should be addressed.[7,8]

Tarsal rotation procedures, like anterior lamellar reposition with a gray line split or anterior lamellar recession, are generally recommended in patients with frank cicatricial entropion.[11] However, surgeons should not overlook the fact that symblepharon formation may pose a special problem in patients with SJS.[14] While a single symblepharon band may lend itself to simple division, fornix reconstruction with a mucosal graft[14] or amniotic membrane transplantation[15,16] may be advocated for more extensive symblepharon formation.[14,15,16] As was mentioned earlier, another unique situation that is not uncommonly encountered in patients with SJS/TEN is lid margin keratinization.[7,8] Excision of the keratinized area with replacement by a mucous membrane graft helps restore the integrity of the mucocutaneous junction by creating a barrier to prevent the crossover of keratinized epithelium.[7,8] It should be borne in mind that the strip of oral mucosa should cover as much of the length of the lid margin as possible.[7] It is also important to bear in mind that the keratinization process usually extends 2 or 3 mm into the tarsal conjunctiva; therefore, the strip of oral mucosa used should have an average size of 20 × 5 mm or even more if adequate oral mucosa is available.[7] Although the oral mucosa is involved in SJS, these lesions are probably self-limiting manifesting only in the acute phase, therefore the lip is the preferred donor site.[7]

Prognosis

The ultimate prognosis for SJS/TEN is related to how quickly the proper clinical diagnosis is established, how rapidly the causative drug can be identified and discontinued, and how aggressively appropriate treatment can be initiated.

A validated severity-of-illness score for TEN and SJS, called SCORTEN, was developed by Bastuji-Garin et al to determine the variables useful as predictors of prognosis and risk of death.[17] They identified seven independent clinical and laboratory risk factors for death, and a higher score was related to a higher mortality rate. In a later report, they showed excellent performance of the SCORTEN in predicting prognosis during the first 5 days of hospitalization.[18]

In a series of 460 patients with SJS, SJS/TEN, and TEN, Sekula et al reported the mortality rates at 6 weeks of 12% for SJS, 29% for SJS/TEN, and 46% for TEN.[19] The 1-year mortality rates were 24% for SJS, 43% for SJS/TEN, and 49% for TEN. The prognosis does not seem to be affected by the type or the dose of the causative drug.[20]

Histopathology

The histopathology of SJS/TEN overlaps with those of erythema multiforme (EM), and different studies have yielded varying results.[21,22,23] Côté et al examined biopsies from 18 patients with EM and 15 with SJS.[21] Of 18 EM biopsies, 12 had a predominantly inflammatory pattern with a lichenoid infiltrate of lymphocytes and macrophages at the dermal-epidermal junction; a sparse, deep, perivascular inflammatory infiltrate; exocytosis; and a variable degree of epidermal necrosis that was predominantly in the lower epidermal layers.[21] Confluent epidermal necrosis was associated with subepidermal and intraepidermal bullae.[21] Of 15

SJS biopsies, 12 had a predominantly necrotic pattern with “intense” epidermal necrosis and minimal dermal inflammation that, if present, was sparse and localized around vessels in the superficial vascular plexus (Figure 117.3).[21] The epidermal necrosis in the SJS biopsies resulted in subepidermal separation.[21] Features that differentiated EM from SJS were more severe epidermal necrosis in SJS while EM had more significant dermal inflammation and exocytosis.[21]

Rzany and coworkers[22] examined 16 biopsies from patients with EM, 34 from patients with SJS, and 61 from patients with TEN and concluded that all were a spectrum of the epidermal variant of EM reported by Orfanos et al.[24] All biopsies had necrotic keratinocytes ranging from individual cells to confluent total epidermal necrosis, with the amount of total necrosis being higher in patients diagnosed clinically with SJS, SJS/TEN overlap, and TEN than those with EM.[22] All biopsies had basal epidermal changes varying from vacuolar change to subepidermal bullae *(Print pagebreak 776)* that was independent of the clinical diagnosis.[22] Dermal inflammation was superficial and perivascular, and the degree of inflammation was greater in EM than in SJS or TEN.[22] Extravasated erythrocytes were more common in EM than in SJS or TEN.[19] The finding by Rzany et al[22] that SJS/TEN has greater epidermal necrosis and less dermal inflammation than EM agrees with the report by Côté and colleagues.[21]

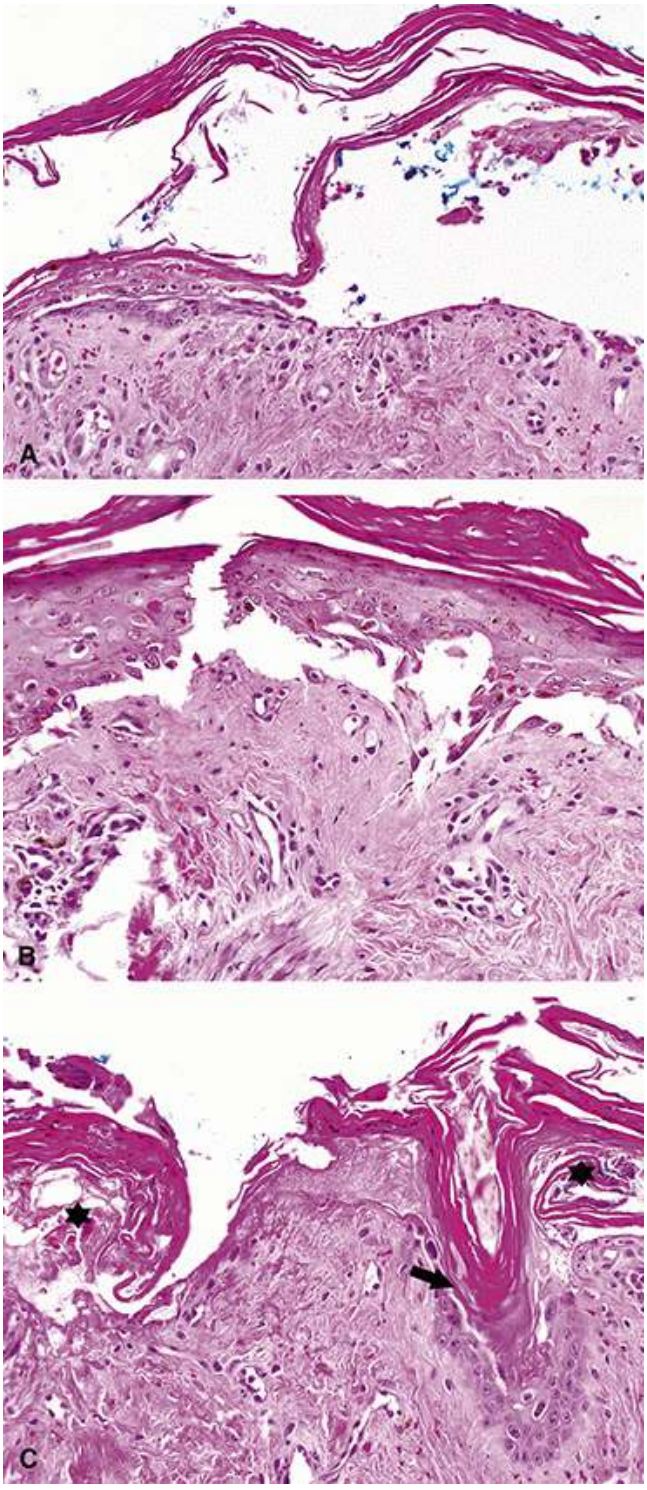

FIGURE 117.3 A, This SJS biopsy has full-thickness epidermal necrosis, a subepidermal blister, and a scant dermal inflammatory infiltrate. B, Individual hypereosinophilic necrotic keratinocytes are in this SJS biopsy, along with a subepidermal bulla and a sparse perivascular dermal inflammatory infiltrate of lymphocytes and macrophages. C, The epidermal necrosis in this SJS biopsy varies from full thickness (★) to partial thickness (*arrow*). There are subepidermal blisters and minimal dermal inflammation.

More recently, Wetter and Camilleri reported histological findings in 15 biopsies from 13 patients with SJS.[23] Epidermal necrosis was present in 8 of 13 patients (62%) and was full thickness in 6 patients (46%).[23] Basal vacuolar change occurred in 77% of patients, with moderate to severe change in 38%.[23] Subepidermal bullae were present in 77% of the patients.[23] A histological finding that differed from the reports of Côté and colleagues[21] and Rzany and coworkers[22] was that 11 of 13 patients (85%) had either a moderate (8 patients) or severe (3 patients) dermal inflammatory infiltrate of predominantly lymphocytes.

As these three studies demonstrate, there is no sharp demarcation of histological features between EM and SJS/TEN. Thus, histopathological diagnosis requires clinical correlation.

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CHAPTER 118

Subepidermal Calcinosis

Key Points

- Subepidermal calcinosis is a form of localized cutaneous soft tissue calcium deposit
- It is classified as dystrophic, metastatic, calciphylaxis, iatrogenic, and idiopathic types
- The pathogenesis is poorly understood, and of the various causes proposed, none are supported by convincing evidence
- Clear clinical characteristics are generally absent so that the diagnosis is usually made only after histopathologic examination
- Lesions appear as a round to oval; painless; yellow, white, gray, or pink; solitary; mobile; hard nodule located in the upper dermis of the skin
- The definitive treatment is not established, but complete surgical excision has been the treatment of choice in most reports
- The prognosis is excellent following surgical excision, even when the resection is incomplete

Subepidermal calcinosis (SC) is a form of soft tissue calcium deposit that was first recognized by Winer in 1952[1] and later named by Woods and Kellaway in 1963.[2] A wide variety of synonyms have been used in the literature including idiopathic calcinosis cutis, localized cutaneous calcinosis, subepidermal calcified nodule, cutaneous calculi, and solitary nodular calcification.[3,4]

SC is classified as dystrophic, metastatic, calciphylaxis, iatrogenic, and idiopathic types.[5] Dystrophic calcification is the most common form and usually occurs in association with autoimmune and other diseases that cause chronic inflammation and alterations within connective tissue.[4] Metastatic calcification is characterized by abnormal calcium and or phosphate metabolism.[4] Calciphylaxis refers to calcification in the media of small and medium-sized dermal blood vessels and subcutaneous tissues sometimes seen in end-stage renal disease.[6] Idiopathic SC occurs in otherwise healthy individuals without any associated systemic disease, abnormal laboratory studies, or history of trauma.[7,8,9,10,11,12,13]

Subepidermal calcinosis is a rare dermatological condition with only about 150 cases described in the literature. Of these, fewer than 60 cases have involved the ocular adnexa.[9,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28] Among the eyelid lesions, there is a marked male predominance of about 67%.[3] These lesions have been seen in patients aged from 3 to 90 years, but about 90% occur in patients ≤21 years of age, and the mean age at presentation is about 12 years.[5] About 42% of reported cases occurred in Caucasian, 24% in Hispanic, 21% in black, and 13% in Asian patients.[3]

Etiology and Pathogenesis

The pathogenesis of subepidermal calcinosis is poorly understood, but numerous possible etiologies have been proposed. Dystrophic calcification that forms in devitalized tissues or in preexisting lesions within the connective tissue of the dermis following trauma seems unlikely for many cases because there is no consistent history of trauma.[5,29] Calcified lesions have been associated with syringomas and milia,[20,30] especially in patients with Down syndrome,[31] but this association is rare. Nanobacterial activity has been proposed as a cause, but ultrastructural analysis of a series of dystrophic calcifying conditions of the skin failed to show any evidence of nanobacteria.[32] A hypersensitivity reaction followed by degranulation of mast cells with subsequent deposition of calcium and phosphate has also been proposed,[33,34,35] but there is little evidence to support this view. Another proposal suggested that SC might arise from calcification of sweat ducts or hair follicles.[28]

Clinical Characteristics

As a general rule, all patients with cutaneous calcification should be examined for underlying conditions, particularly serum calcium and phosphorus dysfunction, as well as rheumatologic conditions.[9] Idiopathic SC is rare, and clear clinical characteristics are generally absent so that the diagnosis is usually made only after histopathologic examination. On the eyelids, lesions are usually present for weeks to years, with 76% more than 6 months, and 27% more than 12 months.[5] Lesions appear as a round to oval, painless, solitary, mobile, hard nodule (Figure 118.1). They generally are small, being less than 5 mm in 81% of cases, but can be up to 10 mm in diameter. Nodules are located in the upper dermis of the skin, and in the eyelid, the calcification can occur along the superior border of the tarsus[5] or between the tarsus and the palpebral conjunctiva.[17] The overlying epidermis can appear verrucous, hyperkeratinized, or papillomatous and can be yellow, white, gray, or pink. There typically is no history of trauma or systemic disease. Calcium, phosphate, and parathyroid hormone levels are in the normal range. Lesions involve the upper eyelid in 63% of cases, the *(Print pagebreak 779)* medial canthus in 28%, and the lower eyelid in 9% of cases.[5] Lesions are single in 82% of cases but may be multiple in 18%.[3] When multiple, lesions can occur on several different eyelids and can be seen bilaterally.

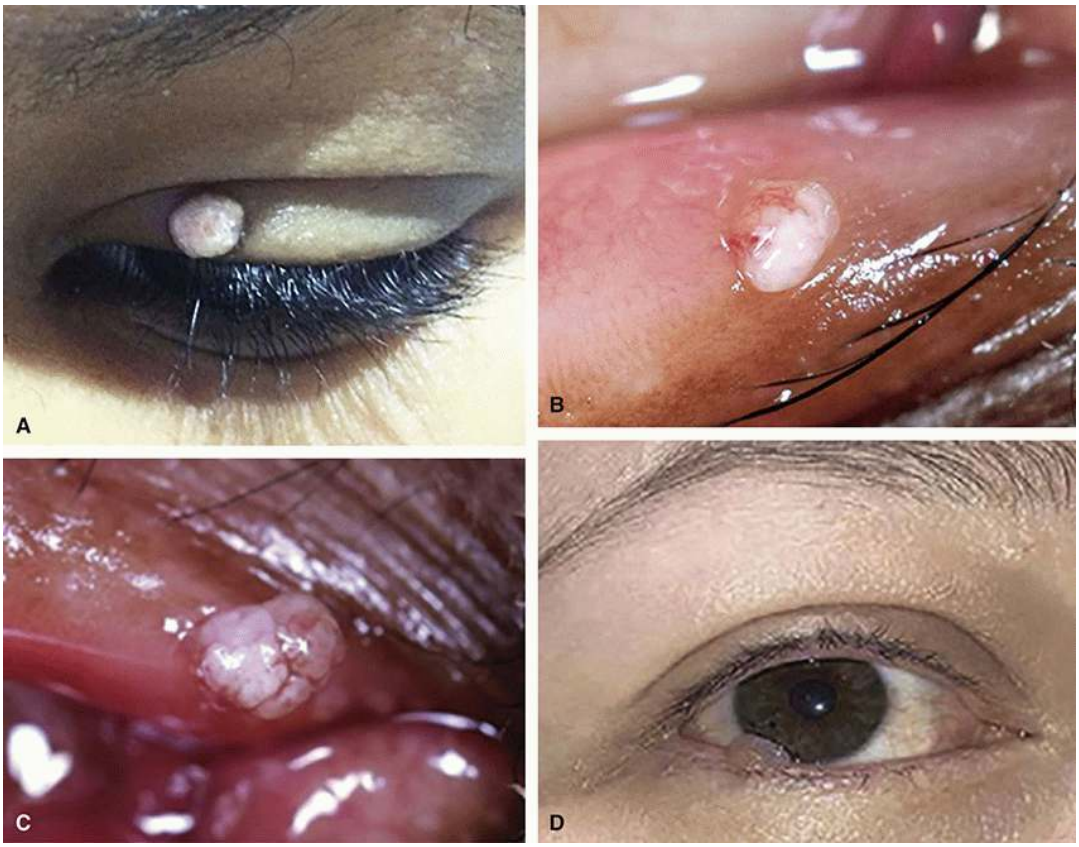

FIGURE 118.1 Calcinosis cutis. A, Papillomatous nodule on the upper eyelid. B, Small lower eyelid lesion. C, Nodular calcinosis lesion around the lower eyelid punctum. D, Calcinosis lesion on the lower eyelid margin. B and C, (Courtesy of Dr. Javed Mohammad Ali.) D, (Courtesy of Dr. Norman Charles.)

Differential Diagnosis

Subepidermal calcinosis is almost always misidentified clinically as a more common lesion. These include pilomatrixoma, warty papilloma, cutaneous horn, juvenile xanthogranuloma, chalazion, syringoma, milia, molluscum contagiosum, epidermoid cyst, seborrheic keratosis, xanthelasma, hemangioma, or sebaceous cell carcinoma.[3,9,14,19,21,22,36,37]

Treatment

Although the definitive treatment of SC is not established, complete surgical excision has been the treatment of choice in most reports.[14,15,17,19,21,22,23,37,38,39] Recurrence even after incomplete excision is rare, reported in only one of eight incompletely removed cases by Kim et al.[19] CO_2 laser ablation has been reported in several cases for multiple lesions or where surgery was deemed cosmetically inappropriate.[40,41,42] Topical and intralesional steroids have been ineffective.[21,22,37]

Prognosis

In cases of idiopathic SC, the prognosis is excellent following surgical excision, even when the resection is incomplete. Even though most eyelid cases are idiopathic with no systemic associations, any presentation of calcinosis cutis can sometimes occur with serious underlying diseases of calcium metabolism including hyperparathyroidism, renal disease, rheumatologic conditions, systemic sclerosis, and CREST (calcinosis cutis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) syndrome, and with dermatomyositis.[9]

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Histopathology

Subepidermal calcified nodules (SCNs) account for the vast majority of SC in the periocular region and appear similar to SCNs at other body sites (Figure 118.2).[9,14,18] Woods and Kellaway first defined the histological appearance of SCNs in 1963 in a review of 22 biopsies from 20 patients.[2] The age range of their patients was from birth to 56 years. All but four of the patients were below 16 years of age.[2] SCNs consisted of calcified material in the upper dermis abutting the epidermis. Larger nodules extended deeper into the dermis but never into the subcutis. Calcified material formed irregular basophilic granules 20 to 40 μm in diameter and larger masses. The granules stained more intensely than the larger deposits using periodic acid-Schiff stain. The authors identified well-preserved nuclei in occasional granules and masses, suggesting a cellular origin for the calcified deposits.[2] The overlying epidermis was verrucous, often thickened by acanthosis, and had hyperkeratosis and sometimes patchy parakeratosis. Narrow-pointed rete pegs and keratin-filled pits commonly extended far into the nodules. Early SCNs had granules in a moderately cellular stroma containing fibroblasts, macrophages, and multinucleated giant cells, often forming rings around the granules. Granules often invaginated the epidermis and were present in the keratin layer. Early lesions often contained calcified granules and large masses of calcified material composed of finely granular particles. Woods and Kellaway thought that the masses resulted from focal degeneration of the stroma with the inclusion of the granules in the degenerating area. Larger masses abutting the epidermis sometimes caused degeneration and calcification of the prickle cell layer. The calcific masses in early lesions were poorly outlined by stromal cells. Mononuclear cells and multinucleated giant cells bordered calcified masses in later lesions. The stroma of older SCNs was usually dense acellular collagen. Woods and Kellaway stated: “In this description there has been a considerable amount of interpretation of the way in which the lesions evolve. The histological appearances suggest that calcified granules in a cellular stroma form the essential lesion and that large masses may result from degeneration and calcification of the stroma.”[2]

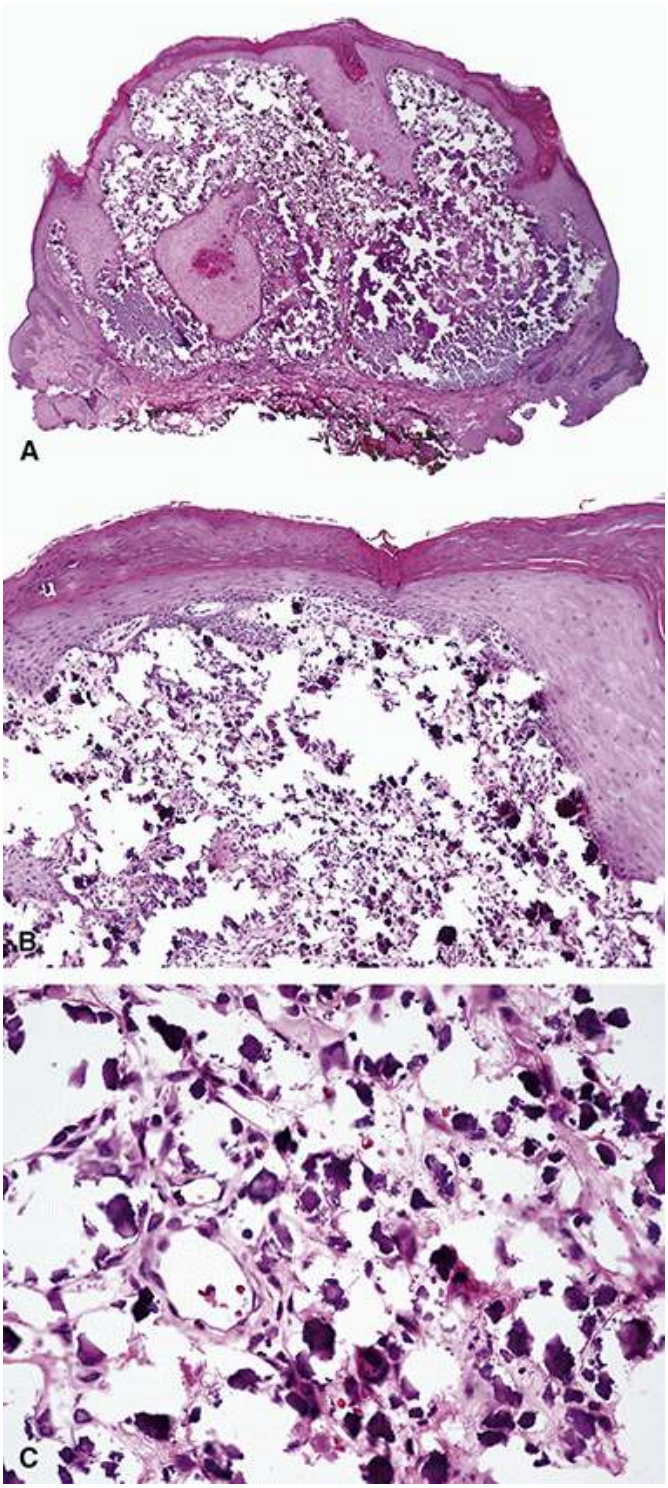

FIGURE 118.2 This subepidermal calcified nodule arose on a young girl's medial left upper eyelid (shown in Figure 118.1A). The nodule was diagnosed clinically as a pilar (trichilemmal) cyst, and it was treated with hot compresses and massage three times per day. It went entirely away after 1 week of treatment, but it then recurred at the same site with intermittent drainage and swelling. It was excised 8 months after its appearance. A, The SCN is well circumscribed in the dermis and abuts the acanthotic epidermis. Numerous clefts are present in the nodule, at least partially reflecting artifacts from the extensive calcification. B, The epidermis has prominent hyperkeratosis. There are innumerable calcific deposits, some directly in contact with the basal epidermis. C, The calcific deposits vary widely in size from punctate particles to small, irregular, but primarily round to oval deposits. Larger deposits tend to be more basophilic than the minute particles.

Evans, Blessing, and Gray confirmed and extended our knowledge of SCN histopathology by examining 21 specimens from children ranging in age from one to 17 years.[29] One specimen was from the eyelid of a 17-year-old boy. Calcium deposits were small globules or large amorphous deposits. Three specimens had mainly large deposits, 10 had small globules, and 8 had a mixture of small and large deposits. There was epidermal ulceration and transepidermal *(Print pagebreak 781)* elimination of calcium

deposits in six specimens. Based on the duration between clinical appearance and biopsy, younger lesions had a more verrucous appearance with calcium predominantly in large amorphous clumps. Older lesions featured small globular spherules of calcium. Only two specimens had a focal foreign body giant cell reaction.

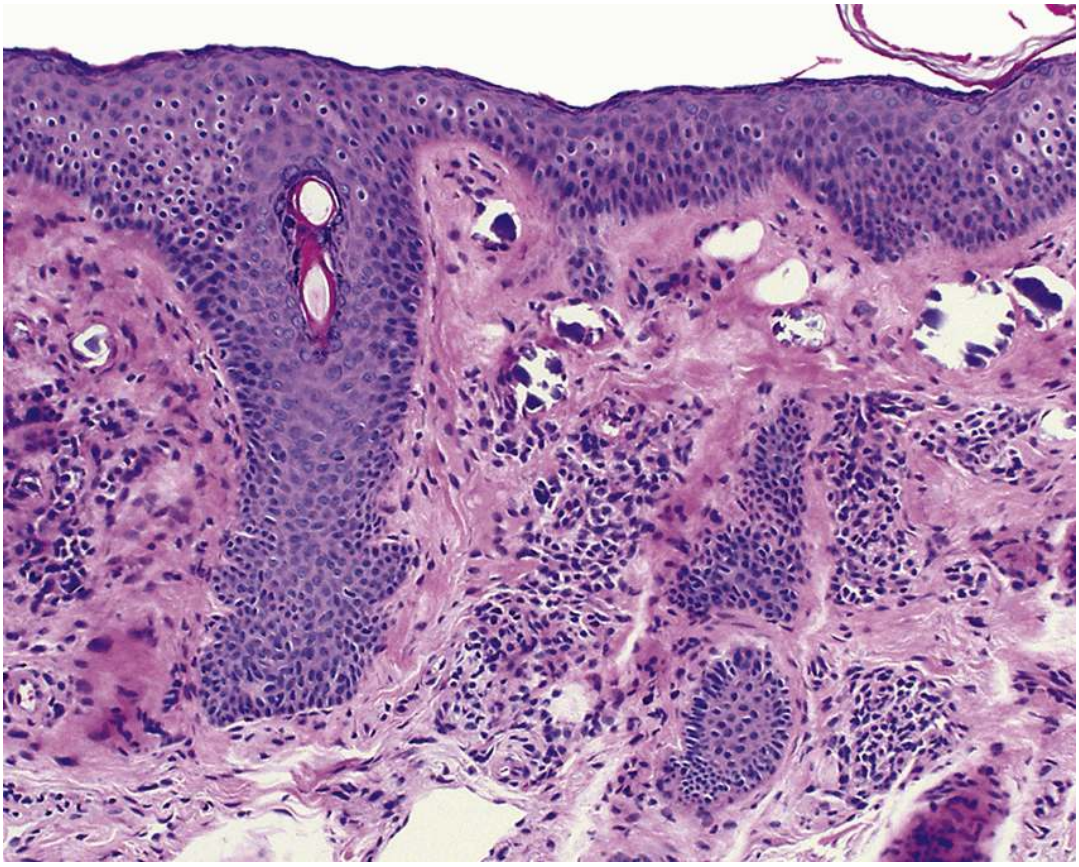

FIGURE 118.3 Subepidermal calcinosis (calcinosis cutis) developed in the medial left upper eyelid near the medial canthus of a man in his early 30s. The lesion started as a 2 × 3 mm keratotic papule thought to be a verruca vulgaris. There was no response to two cryotherapy applications, and the lesion was excised about 4 months later. Deposits of basophilic calcification in clear lacunae are in the superficial dermis and are typical of idiopathic calcinosis cutis. The empty spaces around the calcific deposits result from fragmentation and loss of deposits during histological sectioning.

More recently, AlWadani and coworkers examined 14 eyelid SCNs.[14] In three SCNs the calcific deposits were from people aged 70, 84, and 88 years, and the other 11 were from individuals ranging from 13 to 19 years old. The duration of lesions ranged from one to 228 months before the biopsy. The SCNs from younger patients were dermal nodules containing numerous small round to oval calcified bodies, while the biopsies from the older adults featured a single, large, well-demarcated deposit of amorphous calcified material. The calcific deposits of all younger individuals were surrounded by a lymphoplasmacytic inflammatory infiltrate, and 10/11 had a foreign body giant cell reaction. The SCNs from the older people lacked chronic inflammation and a foreign body reaction. The calcific bodies from all specimens stained using von Kossa's method,[14] which "demonstrates the presence of phosphates, soaps, and amorphous but not crystalline carbonates, rather than calcium itself."[43]

There are only rare reports of eyelid calcification other than cutaneous SCNs. Jun et al reported a 42-year-old woman with a papillomatous mass involving the tarsus that histologically was characterized by a large mass of amorphous calcium.[17] This mass may represent the tarsal analog of the large calcific masses noted by AlWadani and coworkers in cutaneous SCNs of older adults.[14] More recently, Charles and Belinsky reported flecks of calcium in the substantia propria between the conjunctival epithelium and an intradermal and subepithelial melanocytic nevus.[44] We have seen one example of eyelid calcification resembling that noted in the conjunctiva by Charles and Belinsky[44] (Figure 118.3).

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CHAPTER 119

Syringocystadenoma Papilliferum

Key Points

- Syringocystadenoma papilliferum (SCAP) is a benign adnexal skin tumor presenting as a proliferating lesion of apocrine, eccrine, or pluripotential appendageal cells, mostly located on the head and neck
- It is associated with nevus sebaceous of Jadassohn in 40% of cases
- Human papillomavirus (HPV) DNA and mutations in the RAS/mitogen-activated protein kinase signaling pathway have been detected in both sporadic cases and lesions arising in nevus sebaceous
- SCAP may present as a flat, flesh-colored or dark brown plaque with a smooth or raised verrucous or papillomatous surface
- Papular lesions are skin-colored to pink or reddish, and when multiple they are usually arranged in a linear configuration
- Symptoms include an enlarging mass, localized eyelid swelling, pruritus, discomfort, and bleeding
- Treatment most often is by complete surgical excision with clear margins
- The prognosis of SCAP is good following surgical excision, and recurrence is uncommon

In 1917, John Stokes described a cutaneous neoplasm on the thigh of a patient that he termed naevus syringadenomatosus papilliferus.[1] Additional early cases were added by Biberstein,[2] Reuterwall,[3] and Sachs and Lewis.[4] Since then, several hundred additional cases have been reviewed from the literature, and several large series have reviewed these cases.[5,6,7]

Syringocystadenoma papilliferum (SCAP) is a benign adnexal skin tumor presenting as a proliferating lesion of the apocrine or eccrine type of differentiation. It is located on the head and neck in 75% of cases, followed by the trunk (20%) and the extremities (5%), especially the lower limbs.[5,6,7] More than half of these tumors are present since birth,[6] although most cases present for medical attention 2 to 4 decades later.

The mean age at presentation for SCAP is 45 years with a range of 8 to 82 years.[6] In patients with a known duration of symptoms, the lesions were present for 2 to 70 years with an average of 23 years. Most lesions enlarge slowly over time, but a small number of tumors may show accelerated growth over several months. In younger patients, the lesions present as a cluster of papules or small nodules, often with a cystic component.[8]

SCAP has been associated with other benign adnexal neoplasms including tubulopapillary hidradenoma, apocrine cystadenoma, hidrocystoma, eccrine spiradenoma, apocrine adenoma, poroma folliculare, apocrine acrosyringeal keratosis, verrucous cyst, trichoepithelioma, trichilemmoma, sebaceous epithelioma, condyloma acuminatum, acanthoma, and nevus sebaceous.[9,10,11,12,13] However, most often it is associated with nevus sebaceous of Jadassohn (Chapter 96) where 40% of histologically documented cases show SCAP contiguous with a nevus sebaceous.[5,6] Cases arising from nevus sebaceous are more frequently associated with malignancy, and about 9% of SCAP is associated with basal cell carcinoma.[5,6] The well-known relationship between basal cell carcinoma and nevus sebaceus[14] suggests that the occurrence of BCC may not always be etiologically related to the SCAP but to the nevus sebaceous. However, several reports suggest that SCAP can transition to basal cell and squamous cell carcinoma.[5,15,16,17,18,19]

Syringocystadenocarcinoma papilliferum (SCACP) is a rare malignant tumor of apocrine glands that most often arises in association with SCAP.[20,21,22,23] It is typically described as a long-standing lesion, most commonly on the head and neck of middle-aged or elderly individuals.[20,24,25] Lesions usually are raised and nodular and may be associated with ulceration, secretion, or pain.[25,26] One case of SCACP of the eyelid was reported with orbital invasion, requiring orbital exenteration.[27] Verrucous carcinoma is

another tumor that has been associated with SCAP in a small number of patients.[28,29] This tumor is classified as a low-grade, extremely differentiated, squamous cell carcinoma with a propensity for localized growth and recurrence.[30]

SCAP on the eyelid is very rare. In Helwig and Hackney's series of 100 cases, only five were on the face and none involved the eyelid. Since then, fewer than 40 histopathologically documented cases on the eyelids have been reported.[9,10,11,32,33,34,35]

Etiology and Pathogenesis

Decapitation secretion of the glandular epithelium is seen in SCAP, suggesting that SCAP is of apocrine origin. However, although light microscopy suggests an apocrine origin of SCAP, immunohistochemistry and electron microscopy have yielded conflicting data, with some authors documenting eccrine characteristics in this tumor.[6,11,32,36] Several theories have been advanced to reconcile these conflicting observations and to explain the range of other neoplasms associated with SCAP. Mammino and Vidmar[6] suggested that perhaps the final answer is that SCAP develops from pluripotential *(Print pagebreak 784)* appendageal cells. An alternative theory involves the derivation of SCAP from a hybrid-type gland described as an apoeccrine gland.[37,38] This type of gland exhibits microscopic, immunohistochemical, and ultrastructural features that combine both eccrine and apocrine elements, including decapitation secretion.

Although the pathogenesis of SCAP remains unclear, in both sporadic cases and lesions arising in nevus sebaceous, the human papillomavirus (HPV) DNA and mutations in the RAS/mitogen-activated protein kinase signaling pathway have been detected. *BRAF V600E* and *HRAS* mutations are the most common molecular alterations found in sporadic SCAP. The detection rate of *HRAS* mutation has been reported in 10%-26.1% of SCAP lesions,[39,40,41] and the frequency of *BRAF* mutations reported in 40%-66.7% of cases.[39,41,42] These suggest an etiologic role in the pathogenesis of SCAP.

Human papillomavirus DNA has been reported in a small number of SCAP cases.[43,44] While features such as wart-like acanthosis and papillomatosis may be suggestive of HPV infection, clear-cut HPV-related cytomorphology has not been recognized.[39]

Clinical Presentation

SCAP has no clinically specific features so that a biopsy is usually required for diagnosis. Two different primary lesions have been described: a solitary plaque or a cluster of small papules. Plaques are usually flesh colored or dark brown and 4 cm or less in diameter. They may be flat and smooth or raised with a verrucous or papillomatous surface[5,7,8,35,45] and may be devoid of hair.[46] Papular lesions are skin colored to pink or reddish, and when multiple they are usually arranged in a linear configuration.[47,48] Some lesions have a central umbilicated depression,[8,15] which can ooze fluid. Larger lesions demonstrate a hyperkeratotic or verrucous surface, may be cystic, and tend to crust, ooze, and bleed (Figures 119.1 and 119.2). Although most lesions are painless, they may be pruritic.[6]

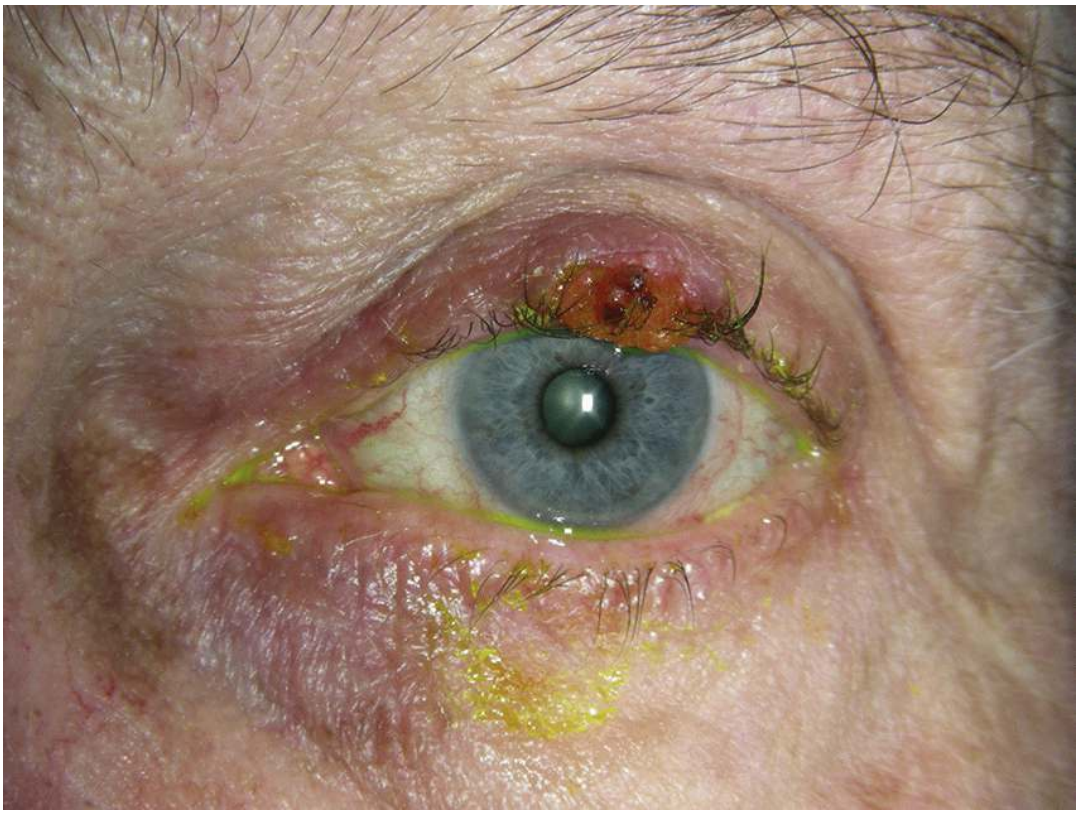

FIGURE 119.1 Syringocystadenoma papilliferum of the upper eyelid with trichiasis and madarosis. (Courtesy of Dr. Philip Custer.)

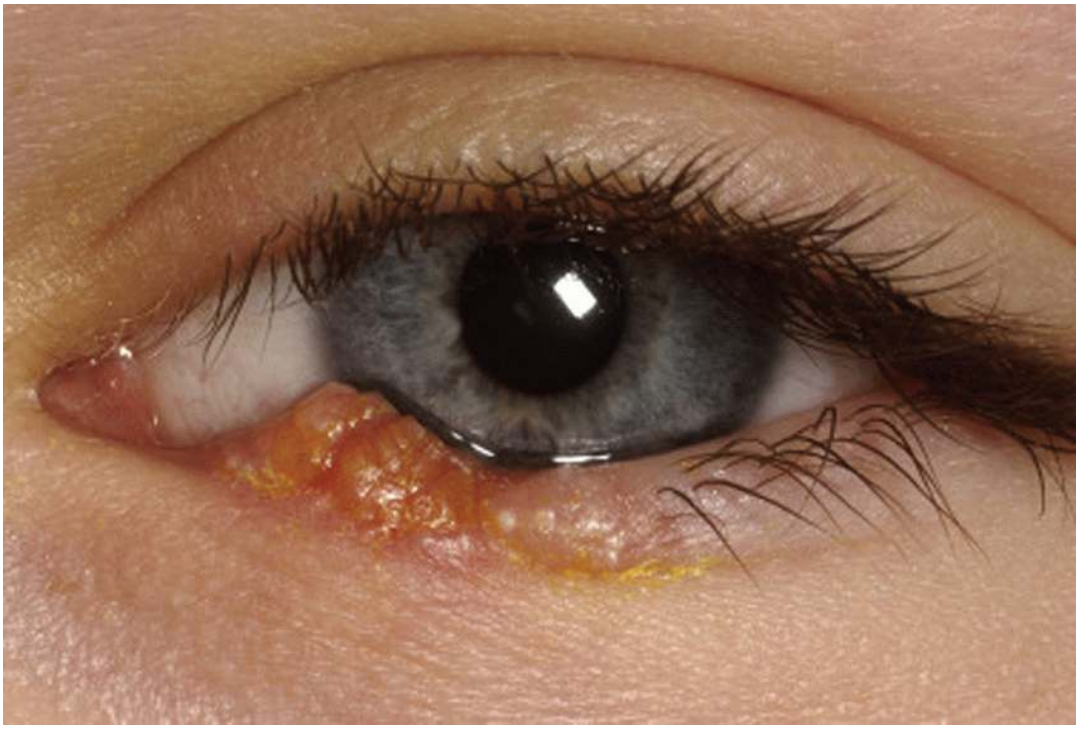

FIGURE 119.2 SCAP of the medial left lower eyelid with a rugose surface surrounding the punctum.

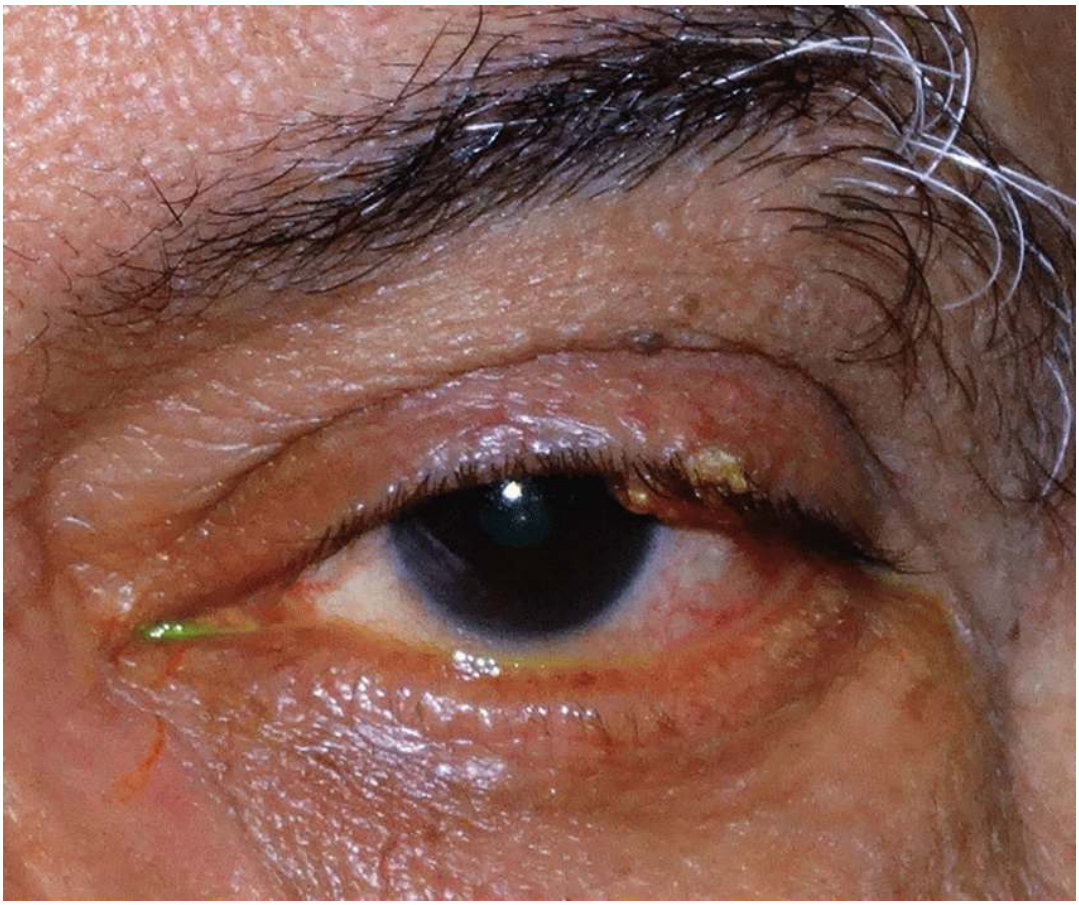

FIGURE 119.3 An elevated, yellow/tan multilobulated SCAP on the left lateral upper eyelid margin. (Courtesy of Dr. Anne Barmettler.)

Tseng et al[31] identified 26 patients with SCAP of the eyelid in the literature published between 1981 and 2015 and summarized their clinical features.[8,9,10,32,33,34,35,45,49,50] Of these 26 patients, the mean age at presentation was 43.9 years, with a range from 8 to 82. Females were affected in 62% of the cases. The duration of these lesions before presentation was between 2 months and 70 years with a mean of 24.3 years. Symptoms included an enlarging mass, localized eyelid swelling, pruritus, discomfort, and bleeding. Most cases presented as fleshy, verrucous, ulcerated, crusted, nodular, papular, or cystic lesions ranging in size between 4 and 25 mm (Figure 119.3).[31] Ten additional cases of eyelid SCAP not listed in that review or published since then show similar demographics and characteristics.[11,15,31,51,52,53,54,55]

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Differential Diagnosis

The differential diagnosis of SCAP includes other benign tumors including those with exophytic pedunculated structure and eroded surfaces. These include numerous benign lesions such as poroma, eccrine adenoma, sebaceous cyst, hidrocystoma, chalazion, verruca vulgaris, and tuberculous verruca cutis. Because of the central ulcerated crater that is often seen, the differential also includes cutaneous malignancies such as basal cell carcinoma and squamous cell carcinoma.

Treatment

The number of cases of SCAP of the eyelid is too small to establish definitive treatment recommendations. However, the recommended treatment most often is by complete surgical excision with clear margins. Incomplete excision can lead to local recurrence.[8,51] Malignant tumors can be associated with SCAP, and although SCAP transition to syringocystadenocarcinoma is exceedingly rare, it has been reported.[56] Because of the possibility of malignant association or transformation, most authors have recommended conservative surgical excision with close follow-up as the treatment of choice.[5,8,53]

In cases of SCACP, surgical resection with wide margins is recommended. Chemoradiotherapy with chemotherapy and

radiotherapy has been proposed as an alternative option.[57] In the rare event of eyelid SCACP with orbital invasion, orbital exenteration may be required.[27]

Prognosis

The prognosis of SCAP is good following surgical excision, and recurrence is uncommon. Even in cases of malignant transformation, in 20 cases reviewed from the literature only 1 showed local recurrence, 2 had progression to regional lymph nodes, and 2 developed distant metastasis.[31]

Histopathology

Helwig and Hackney reviewed 100 examples of SCAP in 1955; they opined that the distinguishing feature was “the presence of duct-like structures containing papillary processes covered by two layers of epithelial cells” (Figures 119.4 and 119.5).[5] Small flattened or cuboidal cells with scanty cytoplasm and “relatively large” round or oval nuclei formed the papillae's outer or basal cell layer.[5] The inner layer was columnar cells with oval nuclei and eosinophilic cytoplasm that was more abundant toward the luminal surface than at the base and scant lateral to the nuclei.[5] Helwig and Hackney did not see decapitation secretion in any of the 100 lesions.[5] Papillae varied in shape and size. Small papillae were formed only of epithelial cells projecting into the lumen with an occasional bridging pattern.[5] Larger papillae had a central core of connective tissue, often with a dense infiltrate of plasma cells.[5] The large ducts were usually lined by stratified squamous epithelium near the epidermal surface, transitioning to a *(Print pagebreak 786)* double-layered epithelium in the deeper aspect of the ducts.[5] Squamous-lined ducts occasionally formed cysts containing keratin.[5] The lesion's surface varied. Some SCAPs had a shallow cup-like depression composed of small papillae lined by double-layered epithelium.[5] Other SCAPs had large irregular papillary projections covered with acanthotic stratified squamous epithelium, usually with hyperkeratosis.[5] Ducts “of various sizes and contours” extended from the lesion's surface to connect with the underlying dilated ducts.[5] SCAPs varied considerably in thickness based mainly on the degree of exophytic growth.[5] Hair follicles and sebaceous glands were absent or sparse in SCAPs occurring in the absence of nevus sebaceous.[5] Eccrine sweat glands were usually present beneath the lesion.[5] Eccrine glands were sometimes dilated and occasionally cystic, with pale eosinophilic material in their lumina.[5] This histopathological description of SCAPs by Helwig and Hackney has remained chiefly unchanged,[58,59] but decapitation secretion by the inner columnar lining cells of papillae is now considered a common feature.[59]

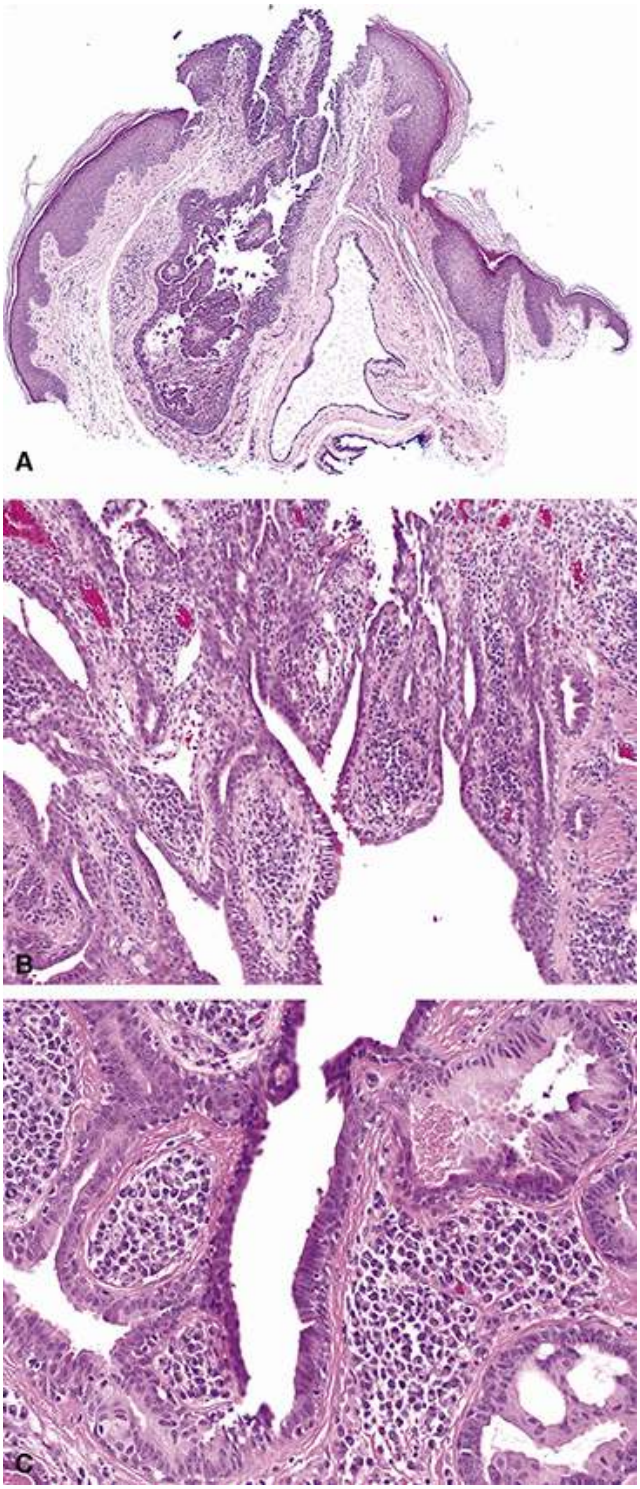

FIGURE 119.4 A, This SCAP of the neck has large irregular papillary projections covered with acanthotic stratified squamous epithelium with hyperkeratosis. A duct extends from the lesion's surface to an underlying dilated duct containing papillae. A cystically dilated eccrine duct resembling a hidrocystoma is in the dermis to the right of the SCAP. B, Numerous papillae having plasma cell-rich connective tissue cores are within the dilated duct. C, Two layers of epithelium line the papillae. The outer layer of cells is cuboidal, while the inner layer is columnar. The papillae have a dense infiltrate of plasma cells in their connective tissue cores.

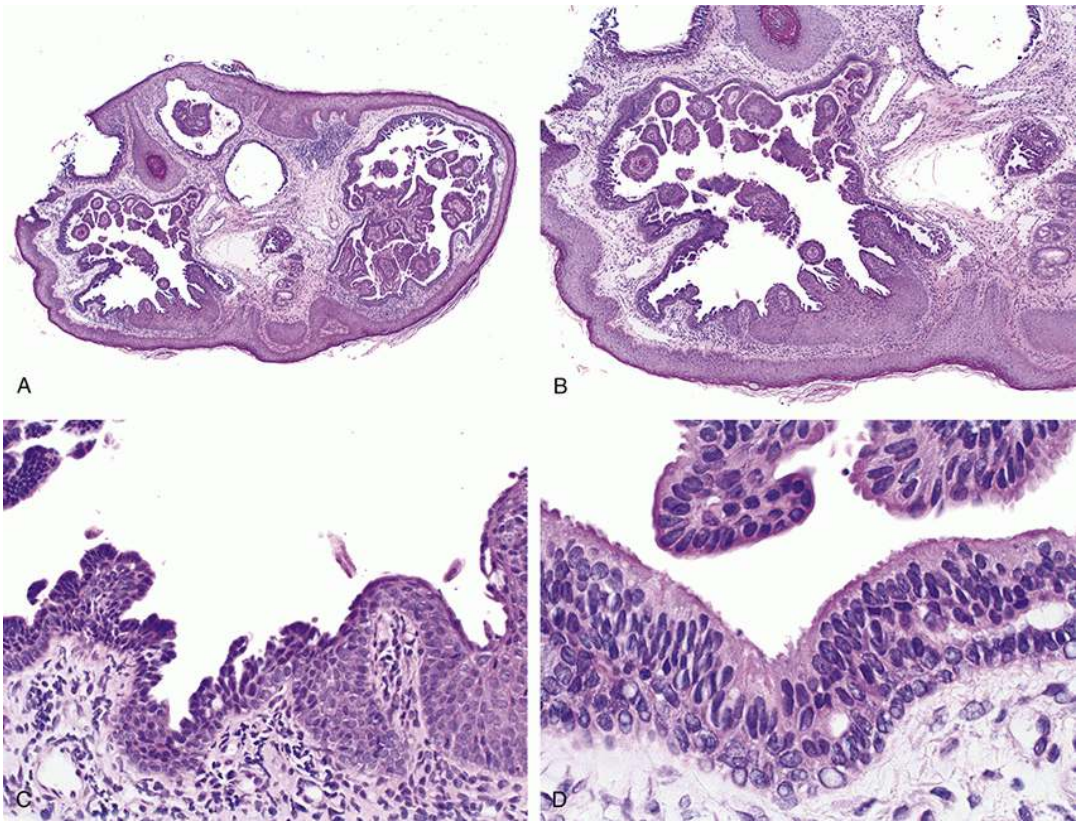

FIGURE 119.5 This SCAP from the right upper eyelid of a woman in her early 30s was present since childhood. The recent onset of irritation and bleeding prompted its removal. A, Sectioning parallel to the epidermis has resulted in epidermis surrounding the SCAP. A dilated duct connects focally to the epidermis at the top left of the photomicrograph. The dermis contains dilated ducts with many papillae. B, Dilated ducts with papillae are easily seen at higher magnification. Stratified squamous epithelium transitions to a two-layered epithelium in the dilated duct at the bottom left. C, Close-up of the transition zone between stratified squamous epithelium and the two-layered epithelium characteristic of SCAP. The fibrovascular cores of papillae are laden with plasma cells. D, The inner columnar epithelial layer of epithelium had areas of decapitation secretion typical of apocrine differentiation.

The histopathological differential diagnosis of eyelid SCAPs includes hidradenoma papilliferum,[60] apocrine cystadenomas,[61] apocrine tubular adenomas,[62,63] and SCACP.[23] Hidradenoma papilliferum has papillae with thinner connective tissue shafts and a lack of plasma cells, assisting their distinction from SCAP.[59] Apocrine cystadenomas resemble apocrine hidrocystomas but have a proliferation of the cyst lining with the formation of papillae, pseudopapillae, and cribriform areas of lining cells.[61] Apocrine cystadenomas lack the two-layer papillary epithelial lining and connection with the epidermal surface characteristic of SCAP. Tubular apocrine adenomas may be impossible to differentiate from SCAP due to overlapping histological *(Print pagebreak 787)* features.[64] SCACP differs from SCAP by having poorly delimited lateral and deep margins, cellular atypia, nuclear pleomorphism, mitotic figures, and often necrosis of isolated cells or groups of cells.[59]

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CHAPTER 120

Syringoma

Key Points

- Syringoma is a benign adnexal tumor derived from the intraepidermal eccrine duct
- It can be associated with several systemic syndromes including diabetes mellitus, Down syndrome, Brooke-Spiegler syndrome, and Nicolau-Balus syndrome
- Syringoma is classified into four clinical variants: a localized form, a familial form, a milia-like form, and a generalized form
- The pathophysiology is largely unknown but has been proposed to be a benign hyperplastic growth that arises from the intraepidermal acrosyringium portion of eccrine ducts in response to an inflammatory reaction or as a hamartoma of pluripotent stem cells
- Syringomas typically appear as 1- to 3-mm, soft to firm, skin-colored, yellowish, or translucent papules
- Treatment for cosmetic improvement can include laser ablation, electrodesiccation, cryosurgery, trichloroacetic acid, dermabrasion, and chemical peels
- Syringomas have been reported to spontaneously regress in rare cases, and improvement following treatment can range from 60% to 100%

Syringoma is a benign adnexal tumor derived from the intraepidermal eccrine duct. It may present as single or multiple papules at puberty or later in life where it affects females more frequently than males, and is seen in about 1% of the population.[1,2] Syringoma was first described by Kaposi in 1872,[3] and Darier and Jacquet later described the eruptive form as a variant.[4]

In a large series of 244 cases, Ciarloni et al[5] reported a male:female ratio of 1:3.7 and a mean age at presentation of 42 years (range 8-85). Lesions were multiple in 76% of cases, and in 29% the type was eruptive. More than half of these cases involved the face, with 36% occurring on the eyelids. Other sites included the chest (18%) and the neck (17.5%).

Several systemic syndromes have also been associated with syringoma, including diabetes mellitus, Down syndrome, Brooke-Spiegler syndrome, and Nicolau-Balus syndrome. Diabetes mellitus is associated with a clear cell variant of syringoma, consisting of nests of clear cells containing glycogen.[6,7] It is thought that elevated glucose accumulates in the skin and within the clear cells.[8] In Down syndrome, the incidence of syringomas has been reported in up to 40% of individuals and can be associated with calcinosis cutis.[9,10,11] Brooke-Spiegler syndrome is a rare autosomal dominant syndrome with cutaneous manifestations that include syringomas and trichoepitheliomas.[12] Nicolau-Balus is a rare autosomal dominant disorder consisting of atrophoderma vermiculata and syringomas.[13]

In 1987, Friedman and Butler[14] proposed a classification of syringoma consisting of four clinical variants: a localized form, a familial form, a generalized form that involved multiple eruptive syringoma lesions, and a milia-like form. Localized syringomas typically occur as isolated or multiple lesions on localized regions of the body and have been reported on the foot, penis, vulva, scalp, face, and eyelids. They usually present as small, firm dermal papules that are flesh colored to red, tan, or brown.

Syringomas can have a rare familial occurrence,[15] and a positive family history was reported in 11.5% of 61 patients with syringoma in one study.[16] Familial syringomas may be inherited as an autosomal dominant trait or result from either germline or somatic mutations.[17,18,19] The most commonly involved site for familial syringomas is the face, particularly the eyelids, followed by the trunk, and less frequently the neck.[2,20] An eruptive or generalized presentation is very rare and is most prominent on the trunk.[2,21] Milia-like syringoma is a rare variant with a white center similar to milia. Most patients with this variant are Asian with a single lesion.[22]

The incidence of syringoma in patients with Down syndrome has been reported to be 30 times greater than that in the general population,[23] with a prevalence reported to be approximately 18% to 40%.[24] While these usually are located in the periorbital region,[24] widespread eruptive syringomas associated with Down syndrome are common and have also been reported.[25,26] Milia-like syringomas associated with Down syndrome have a higher rate of calcification, which may progress to calcinosis cutis.[9,10,11,27,28,29,30] Eruptive syringoma is a rare variant, typically occurring in a generalized form.[2,18,31] They usually present at puberty or during childhood in successive crops on the chest, abdomen, neck, arms, eyelids, and upper cheeks. It has been suggested that cases of eruptive syringoma may represent a hyperplastic response to an inflammatory reaction rather than a true adnexal neoplasm.[32]

The plaque type of syringoma was first described in 1979 by Kikuchi et al[33] as another rare distinct variant that is more commonly associated with symptoms, such as pruritus. Cases have been reported on the face, neck, trunk, penis, and acral areas.[33,34,35,36,37,38] Plaque-type syringomas are more frequently misdiagnosed as malignant lesions such as morpheaform basal cell carcinoma and microcystic adnexal carcinoma from which they can be differentiated on histopathology.[34,35,38]

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Etiology and Pathogenesis

The pathophysiology of syringomas is largely unknown, but several hypotheses have been proposed for the pathogenesis of the various types.[18,21,31] One is that syringomas are benign hyperplastic growths that arise from the intraepidermal acrosyringium portion of eccrine ducts in response to an inflammatory reaction.[39,40] Another is that syringomas represent a hamartoma of pluripotent stem cells that precede the pathological process in eruptive syringomas.[32,41] An alternate hypothesis suggests that phosphorylase deficiency, resulting from hyperglycemia seen in diabetes, leads to an accumulation of glycogen in the skin and within the clear cells of syringomas.[42] Additionally, syringomas may be under hormonal influence. Some vulvar syringomas exhibit estrogen and progesterone receptors demonstrated by immunohistochemical staining.[43,44] One report showed that syringomas of the vulva exacerbated during pregnancies with regression in the periods between pregnancies.[45]

Immunohistochemistry of syringomas demonstrates the presence of eccrine straight duct CK6 and CK10, supporting previous suggestions that syringomas are tumors of the eccrine origin arising from the dermal and lower intraepidermal duct.[46] An electron microscopy study demonstrated ductal cells with numerous short microvilli, desmosomes, luminal tonofilaments, and lysosomes.[42] The histogenesis of syringomas is most likely related to eccrine ductal elements or pluripotential stem cells.

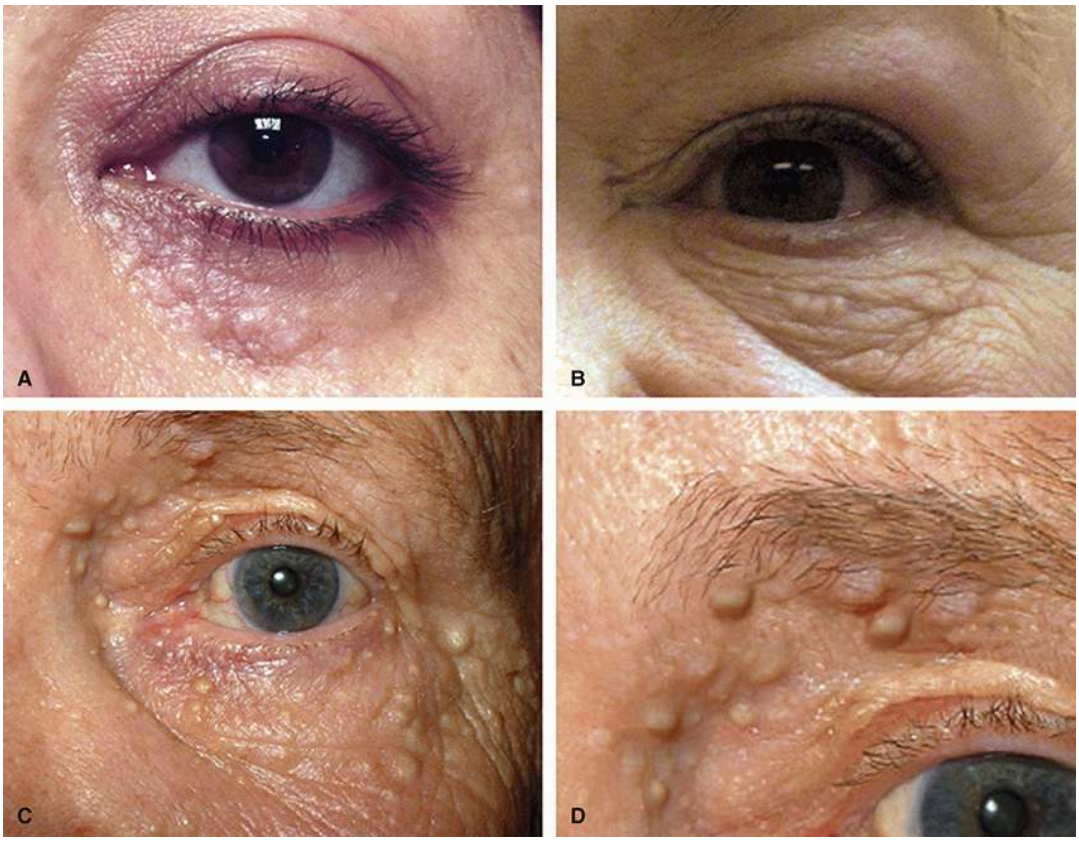

FIGURE 120.1 Syringomas of the eyelids as soft, skin-colored papules. A, (Courtesy of Dr. Robert Goldberg.)

Clinical Presentation

Syringomas typically appear as soft to firm, skin-colored, yellowish, or translucent papules 1 to 3 mm in diameter (Figure 120.1).[2,18,21,31,47] The age distribution shows a peak in the third and fifth decades.[16] Lesions most often present in the periorbital area, although they can also be found on the face, in the armpits, and on the abdomen, chest, extremities, and genitalia. Lesions usually are multiple and symmetrical in distribution, but occasionally they appear as unilateral, linear, nevoid lesions.[16,48] Syringoma usually is asymptomatic, but in rare cases, they are associated with pruritus.[49]

Eruptive syringomas may present as an asymptomatic diffuse papular rash with flesh-colored lesions 1 to 5 mm in diameter. Occasionally they may be hyperpigmented. Plaque syringomas *(Print pagebreak 791)* are usually asymptomatic, bilateral, symmetric, ill-defined flesh-colored papules that gradually enlarge and coalesce. They may be large,[50] up to 1 to 2 cm in diameter with peripheral smaller 1- to 2-mm papules. Milia-like syringomas are globoid papules, whitish to slightly erythematous in color, with small calcium deposits that may progress to calcinosis cutis.

Differential Diagnosis

Clinically, syringomas on the face can be confused with milia, trichoepithelioma, xanthelasmas, and basal cell carcinoma. Eruptive syringomas can be confused with other papular dermatoses that appear during childhood. These include common warts, acne vulgaris, lichen planus, disseminated granuloma annulare, papular sarcoidosis, sebaceous hyperplasia, eruptive xanthoma, urticaria pigmentosa, Darier disease, pseudoxanthoma elasticum, verruca plana, bowenoid papulosis, keratosis pilaris, sarcoidosis, sebaceous hyperplasia, and hidrocystoma.[51,52] Plaque-type lesions may be mistaken for microcystic adnexal carcinoma.[35,53]

Treatment

Treatment for syringoma is offered primarily for the improvement of cosmetic appearance. However, because syringomas are embedded within the dermis, complete removal is often not possible and recurrence is common.[54] Destructive options include laser ablation, electrodesiccation, cryosurgery, trichloroacetic acid, dermabrasion, and chemical peels.[2,55,56,57,58] In dark-skinned individuals, success has been reported with a combination of trichloroacetic acid and CO_2 laser ablation,[59] but laser therapy and cryosurgery may cause pigmentary changes.[15,60,61] Medical therapies have included topical retinoids with variable results.[62,63] Oral tranilast, which inhibits the release of histamine and prostaglandins from mast cells, was successfully used in one patient.[64,65] Topical atropine has been used to relieve pruritus.[54] Application of topical adelmidrol, a semisynthetic cannabinoid that may act via downregulation of mast cell activation, was beneficial in a case of giant vulvar syringoma.[66]

Prognosis

Syringomas have been reported to spontaneously regress in rare cases,[45] but in most cases, they remain stable.[1] Improvement following treatment can range from 60% to 100%, but recurrences are common.

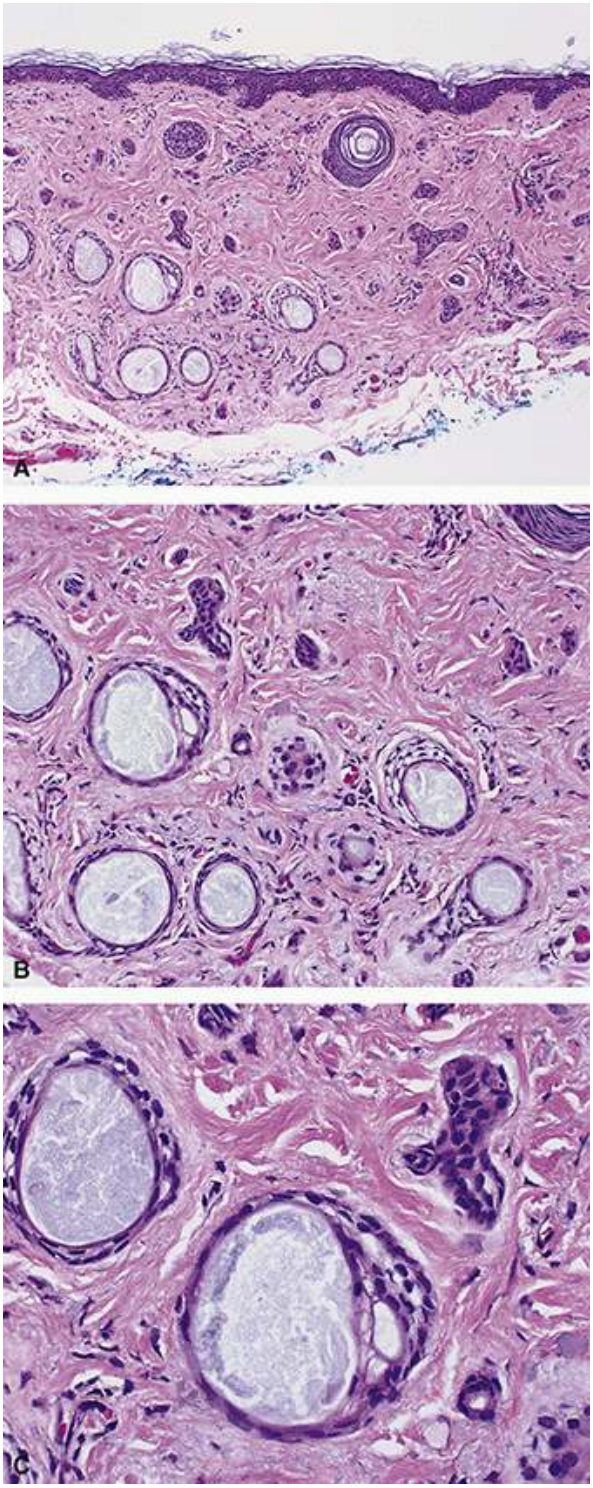

FIGURE 120.2 This conventional syringoma was one of many involving all four eyelids in a woman in her middle 50s. A, The syringoma is well circumscribed and in the mid and upper dermis without connecting to the overlying epidermis. B, The tumor is composed of small nests and ducts (tubules) embedded in a collagenous eosinophilic stroma. An epithelial strand at the end of the ductule at the bottom right creates a tadpole appearance. C, Two layers of flattened to low cuboidal cells form the ducts. The ductal lumens contain homogeneous material. Tumor cells are cytologically bland with small nuclei and eosinophilic cytoplasm.

Histopathology

The typical (conventional) syringoma (Figure 120.2) is symmetrical,[1,67] relatively well circumscribed,[1,67,68] and in the mid[67] or upper[1,68,69] dermis without connecting to the overlying epidermis.[69] Small nests, cords, and ducts (tubules)[1,67,69] *(Print pagebreak 792)* embedded in a collagenous eosinophilic stroma[67] that may appear sclerotic[21,68,70] comprise the tumor. Ducts are usually formed of two layers of flattened to cuboidal cells, and an epithelial strand at the end of a ductule may create a tadpole or

comma-like appearance.[5,40,67,68] Ductal lumens often contain homogeneous material that stains positively using periodic acid-Schiff stain and resists diastase digestion.[67] Ductal structures may predominate in some syringomas.[67,70] Tumor cells are cytologically bland with small nuclei and eosinophilic cytoplasm.[69] Mitotic figures are absent.[68] Inflammation is present in about 10% of tumors, and the overlying epidermis is acanthotic with basal layer pigmentation in about 70% of cases.[5] Mast cells may be numerous in the stroma.[67,68] Sweat glands adjacent to the tumor may be normal, abnormal, or absent.[71]

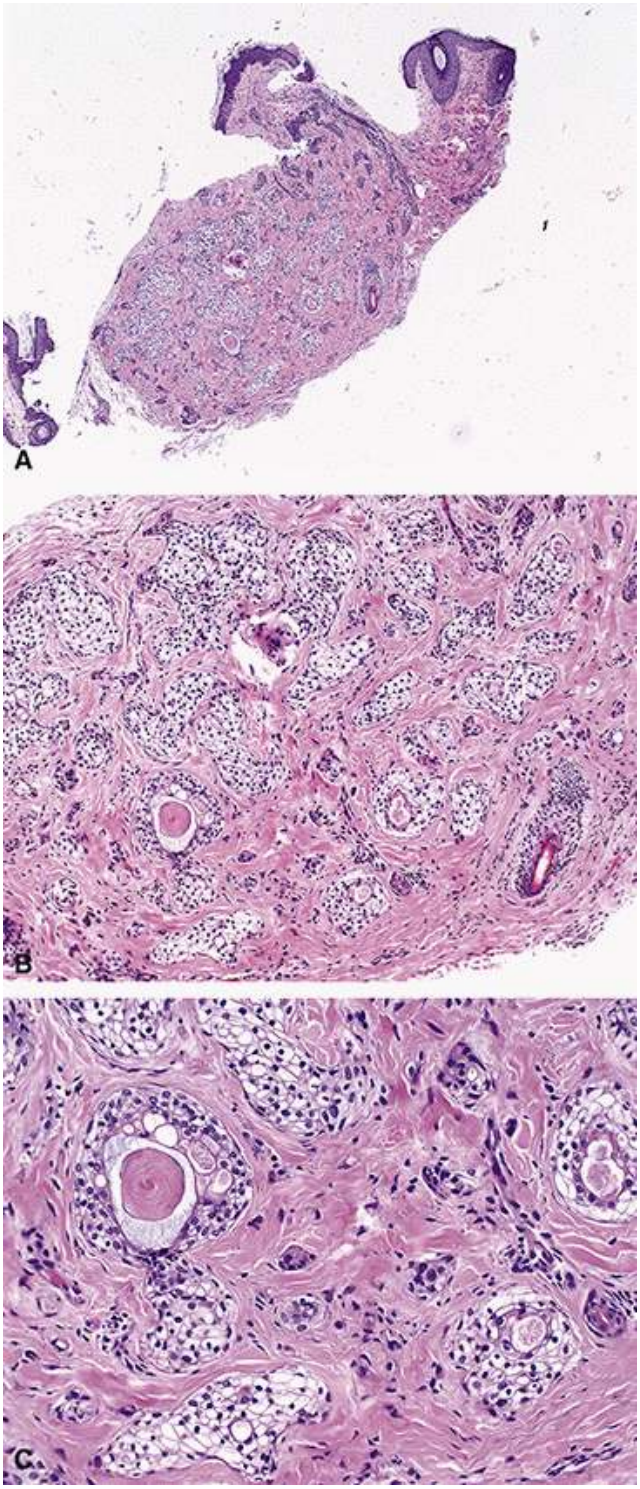

FIGURE 120.3 This clear-cell syringoma was from the right lower eyelid of a woman in her early 50s with well-controlled diabetes mellitus. She had multiple tumors of both lower eyelids. A, The syringoma is well circumscribed and mainly in the mid-dermis. The epidermis and superficial dermis near the center of the biopsy are artifactually disrupted. The tumor is difficult to see at low magnification due to the clear cytoplasm in the tumor cells. B, The tumor is composed mostly of small nests and cords with a few ducts (tubules) embedded in a collagenous eosinophilic stroma. C, Almost all of the cells have clear cytoplasm due to glycogen accumulation. Eosinophilic material is in duct lumens.

Clear cell syringomas (Figure 120.3) are composed predominantly of cells with clear cytoplasm[5,21,40,72,73] due to glycogen

accumulation[73] secondary to reduced cellular phosphorylase activity.[72] Clear cell syringomas otherwise have the same histological appearance as conventional syringomas.[40,67,72] Clear cell syringomas were 8.5% of the 244 lesions in the study by Ciarloni and colleagues, and about one-fifth of the lesions were on the eyelids.[5]

Features that help distinguish a syringoma from a microcystic adnexal carcinoma include good circumscription, confinement to the upper and mid dermis, lack of deep extension into the dermis and underlying tissues, and lack of perineural invasion.[69] In a superficial biopsy, it may not be possible to differentiate these two neoplasms.[68]

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CHAPTER 121

Trachoma

Key Points

- Trachoma is a chlamydial infection characterized by recurrent episodes of conjunctival inflammation with lymphoid follicles and, in some cases, severe papillary hypertrophy
- Chlamydial antigens are believed to induce cell-mediated immune and delayed hypersensitivity responses with the production of proinflammatory cytokines and cellular infiltration forming lymphoid follicles
- Active disease is more commonly found in children and is characterized by a chronic, recurrent follicular conjunctivitis, most prominently seen on the upper tarsal conjunctiva
- The late-stage scarring sequelae develop in later life promoted by the inflammatory process but can be seen earlier in cases of more severe disease
- Scarring can be relatively mild with only a few linear or stellate scars or severe with thick fibrotic bands, shortening of the fornix, and symblepharon formation. Contraction of the conjunctiva results in cicatricial entropion
- Antibiotic therapy, mostly tetracycline eye ointment, has been used to reduce the burden of trachoma infection
- For late-stage disease, surgical correction of trichiasis and entropion are needed to prevent corneal scarring and blindness
- Surgery for trachomatous eyelid trichiasis and entropion is associated with a significant recurrence rate and adverse outcomes from surgery include can be seen in 5% to 30% of cases

Trachoma is the third most common cause of blindness worldwide, after cataracts and glaucoma.[1] It is estimated that about 1.2 billion people live in trachoma-endemic areas in 51 countries.[2] More than 40 million people have active trachoma, 8.2 million have trachomatous trichiasis,[2] and 5.6 million are already blind from trachoma.[3] Endemic regions for trachoma involve large parts of Africa, some regions of the Middle East, the Indian subcontinent, Southeast Asia, and South America.[4] In some regions, such as Ethiopia, trachomatous inflammation may be seen in more than 30% of children.[5]

Trachoma is caused by the obligate intracellular bacterium *Chlamydia trachomatis*. Chlamydial infection usually starts in childhood,[6] characterized by recurrent episodes of conjunctival inflammation with lymphoid follicles and, in some cases, severe papillary hypertrophy.[7] Conjunctival scarring gradually develops from the repeated tissue damage.[7,8] With more severe conjunctival scarring the eyelashes become distorted and trichiatic, where they come into contact with the cornea.[8] If left untreated, loss of vision can result from corneal scarring and opacification.[9] The prevalence of active disease peaks in preschool children and declines in adulthood.[10,11,12,13,14] The prevalence of late-stage trachomatous conjunctival scarring, on the other hand, increases with age as a result of cumulative damage.[10,13] Male and female children with active trachoma are generally affected equally, but the late blinding sequelae are usually seen more frequently in females.[10,13] It has been suggested that close exposure to children in endemic countries is a risk factor for women contracting the active disease.[15]

Chlamydia is probably transmitted from an infected individual to an uninfected one. This likely occurs through direct spread from eye to eye during close contact, spread on fingers, indirect spread on fomites, and transmission by flies.[16]

Etiology and Pathogenesis

C. trachomatis is an obligate intracellular bacterium with 19 different serovars. Endemic trachoma is caused by serovars A-C,[17] whereas genital chlamydial infection is associated with serovars D-K. During its developmental cycle, *C. trachomatis* exists as reticulate bodies that are metabolically active in the intracellular stage and as elementary bodies that are the metabolically inactive extracellular form of the organism that can transfer between host cells and organisms.[18] The infectious cycle begins with the

attachment of the elementary bodies to the surface of epithelial cells, followed by endocytosis of the bacteria. Inside the host cell, within 6 to 9 hours, the elementary bodies transform into the reticulate form and replicate by binary fission.[18] Chlamydial antigens are believed to induce cell-mediated immune and delayed hypersensitivity responses with the production of proinflammatory cytokines and cellular infiltration forming lymphoid follicles. Some immune cell infiltrates have shown a phenotype suggestive of NK cells.[19] Chronic conjunctival inflammation associated with enriched expression of proinflammatory factors and altered expression of extracellular matrix regulators appear to be important factors in the development of conjunctival scarring.[20] Some reticulate bodies transform back into elementary bodies that become extracellular and can transmit the infection to another host.

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Individual and environmental risk factors that may facilitate the introduction and transmission of *C. trachomatis* into vulnerable communities probably include migration of infected individuals who transmit new strains of the bacterium into areas with crowded living conditions.[21,22] Children with active disease in areas where water is scarce, and face washing less common, often have ocular and nasal secretions that can be a source of bacterial spread.[23] Flies that feed on ocular secretions can also act as vectors for disease transmission.[24]

Clinical Characteristics

Clinically, trachoma is subdivided into early active and late-stage cicatricial disease. Active disease is more commonly found in children and is characterized by chronic, recurrent follicular conjunctivitis, most prominently seen on the upper tarsal conjunctiva. More severe cases may have papillary hypertrophy with engorgement of small vessels, surrounding edema, and inflammatory thickening of the conjunctiva.[25] Recurrent or persistent ocular infection leads to conjunctival scarring (Figure 121.1A). During the active phase the superior corneal limbus develops follicles composed of lymphocytes surrounding a reticuloendothelial cell germinal center. When these follicles heal and regress, they result in round, thinned depressions, referred to as Herbert pits, which are a characteristic and pathognomonic finding of trachoma (Figure 121.2).

The late-stage scarring sequelae develop in later life promoted by the inflammatory process but can be seen earlier in cases of more severe disease. Scarring can be relatively mild with only a few linear or stellate scars (Figure 121.1B) or severe with thick fibrotic bands, shortening of the fornix, and symblepharon formation. Contraction of the conjunctiva results in cicatricial entropion that rotates the eyelid margin toward the globe (Figure 121.3). Distortion of the eyelash follicles manifests as secondary trichiasis (Figure 121.4).

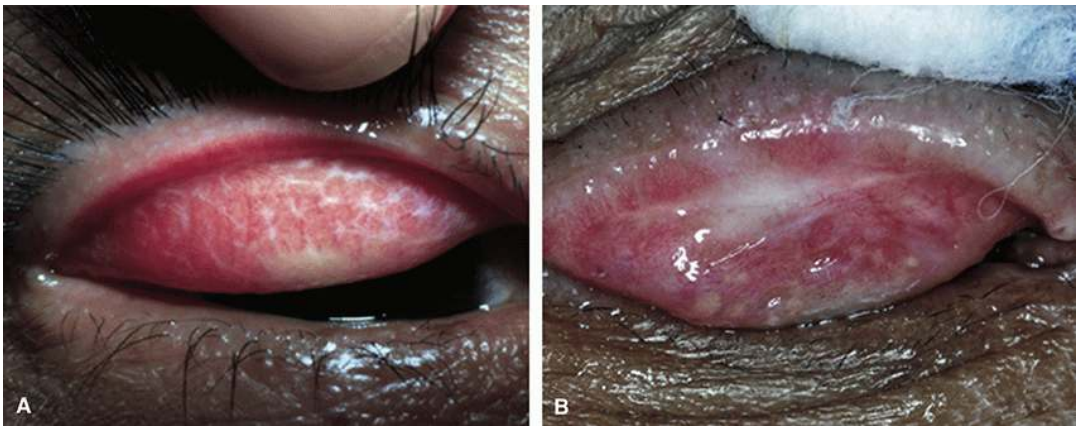

FIGURE 121.1 A, Conjunctival scarring from repeated or persistent ocular infection with *Chlamydia trachomatis*. B, Late-stage trachomatous scarring with linear von Arlt line on the superior tarsal conjunctiva and follicular conjunctivitis. A and B, (Courtesy of Dr. Antonio Augusto Cruz.)

FIGURE 121.2 Herbert pits within a pannus along the superior corneal limbus. (Courtesy of Dr. Antonio Augusto Cruz.)

In individuals infected with trachoma, progression to conjunctival scarring develops in 23% to 30% over 2 years, and there is a strong relationship between progressive scarring and an increasing number of episodes of clinical inflammation.[6] Studies have reported progression of conjunctival scarring in 47% of patients followed for 5 years[26] and 68.5% followed for 14 years.[27] The development of trachomatous trichiasis varies with the presence and degree of conjunctival scarring from less than 10% in patients followed up to 12 years[28,29] to more than 38% in cases of severe scarring over 14 years.[27]

The most severe complication of trichiasis and entropion is corneal abrasion and opacification (Figure 121.5). It *(Print pagebreak 797)* has been reported to develop in 5% to 10% of cases over 2 to 10 years,[29,30,31] but as high as 34% in cases with severe trichiasis.[32]

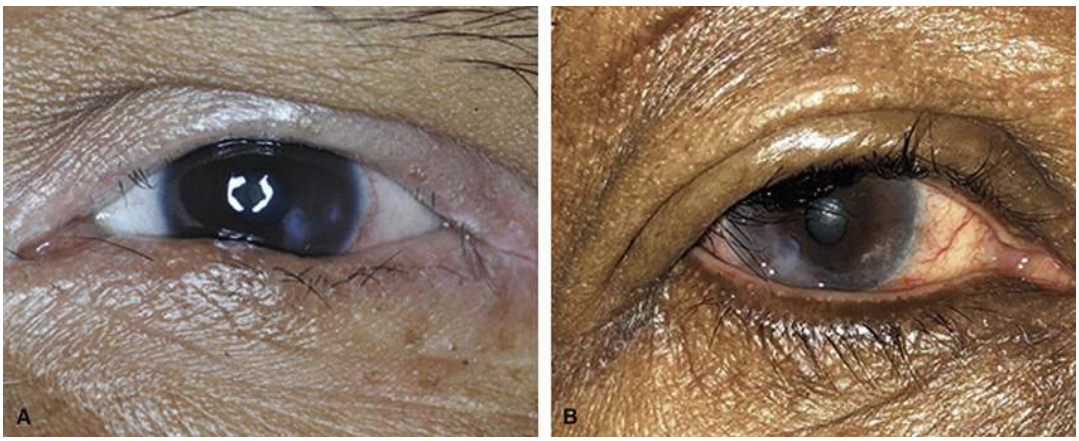

FIGURE 121.3 Upper eyelid cicatricial entropion in late-stage trachoma. A, (Courtesy of Dr. Antonio Augusto Cruz.) B, (Courtesy of Dr. Roman Shinder.)

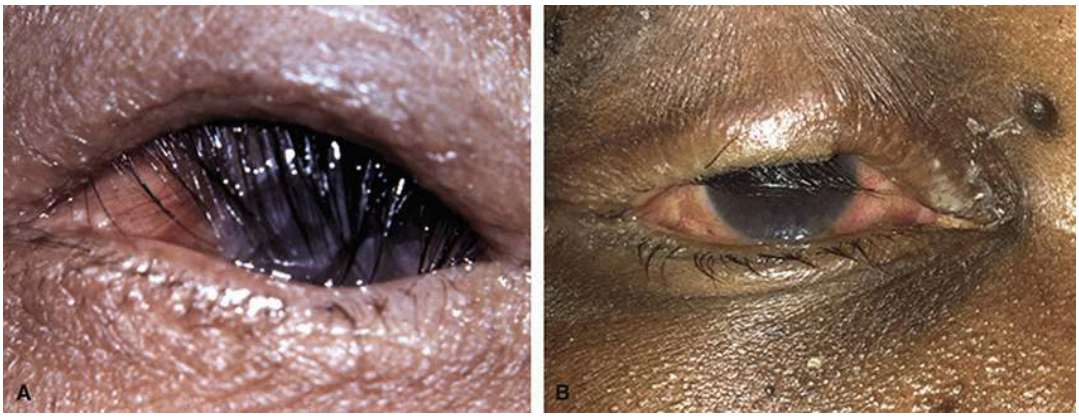

FIGURE 121.4 Secondary trichiasis of the upper eyelid in late-stage trachoma. A, (Courtesy of Dr. Alan McNab.) B, (Courtesy of Dr. Roman Shinder.)

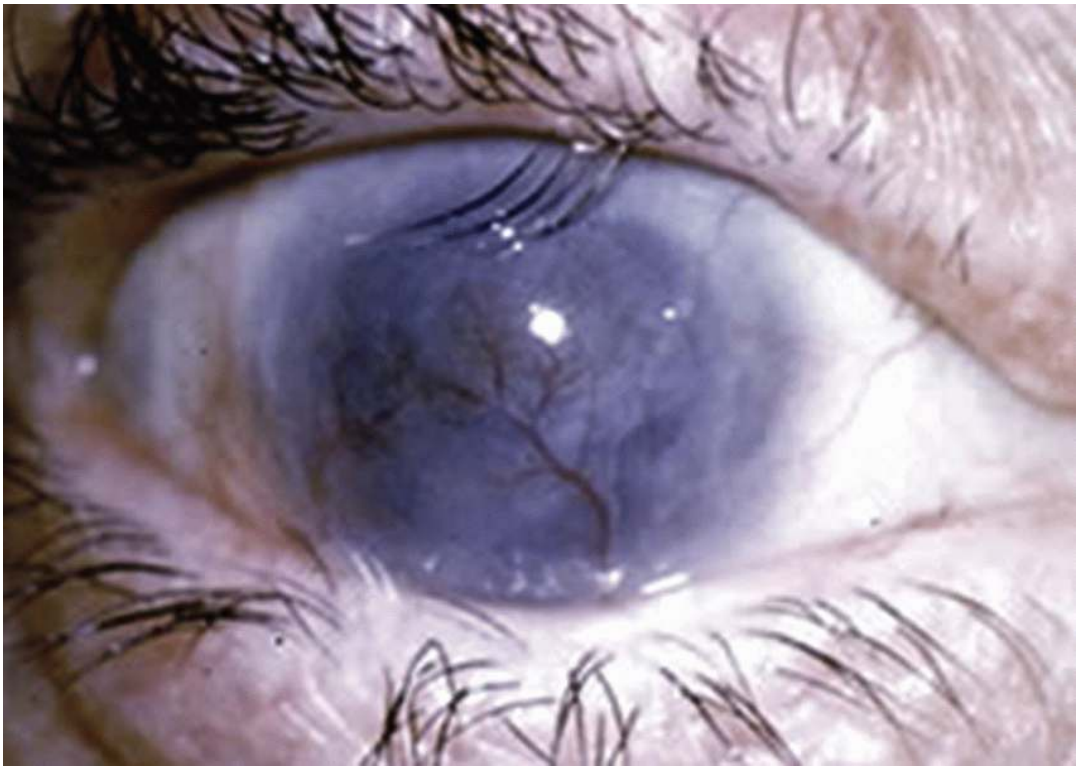

FIGURE 121.5 Corneal opacification from trachomatous entropion and trichiasis.

Differential Diagnosis

Several conditions can produce chronic follicular conjunctivitis with a similar appearance to active trachoma. These include conjunctivitis caused by viruses and bacteria, adult inclusion conjunctivitis, and infection with genital strains of *C. trachomatis*.[25] Cicatricial entropion and trichiasis can be seen with mucous membrane pemphigoid, Stevens-Johnson syndrome, systemic sclerosis, involutional changes, chemical injuries, and drugs. Epiblepharon and distichiasis are characterized by eyelash-to-ocular contact, with possible corneal abrasion and opacification.

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Treatment

Topical and systemic antibiotic therapy has been used to reduce the burden of trachoma infection, and several different antibiotics have antichlamydial activity. The most commonly used are tetracycline eye ointment applied twice a day for 6 weeks or a single oral dose of azithromycin (20 mg/kg up to a maximum dose of 1 g).[12,21,33,34,35,36,37,38] However, azithromycin is not used in infants under the age of 6 months. Since this group can be a significant reservoir of infection, it is

recommended that infants under 6 months be treated with a 6-week course of topical tetracycline.

There are about 8 million people with trachomatous trichiasis worldwide who are at risk of developing blinding corneal opacification. Surgical correction of trichiasis can usually reduce the risk of this complication. Various surgical procedures are in use, from epilation of individual trichiatic lashes to more extensive tarsal rotation procedures (see Chapter 42).[39] In countries where ophthalmologists are in short supply, trained ancillary personnel can perform simple procedures such as epilation to reduce the risk of corneal damage.[40,41] However, even with surgery, recurrence of trichiasis can be as high as 40% to 60%.[42]

Various factors may contribute to the choice of a procedure to treat trichiasis. These include preoperative disease severity, surgical technique, and current infection. Perioperative antibiotics may reduce the risk of recurrence.[43,44] Despite the high recurrence rate, there can be some improvement in vision following surgery.[39,43]

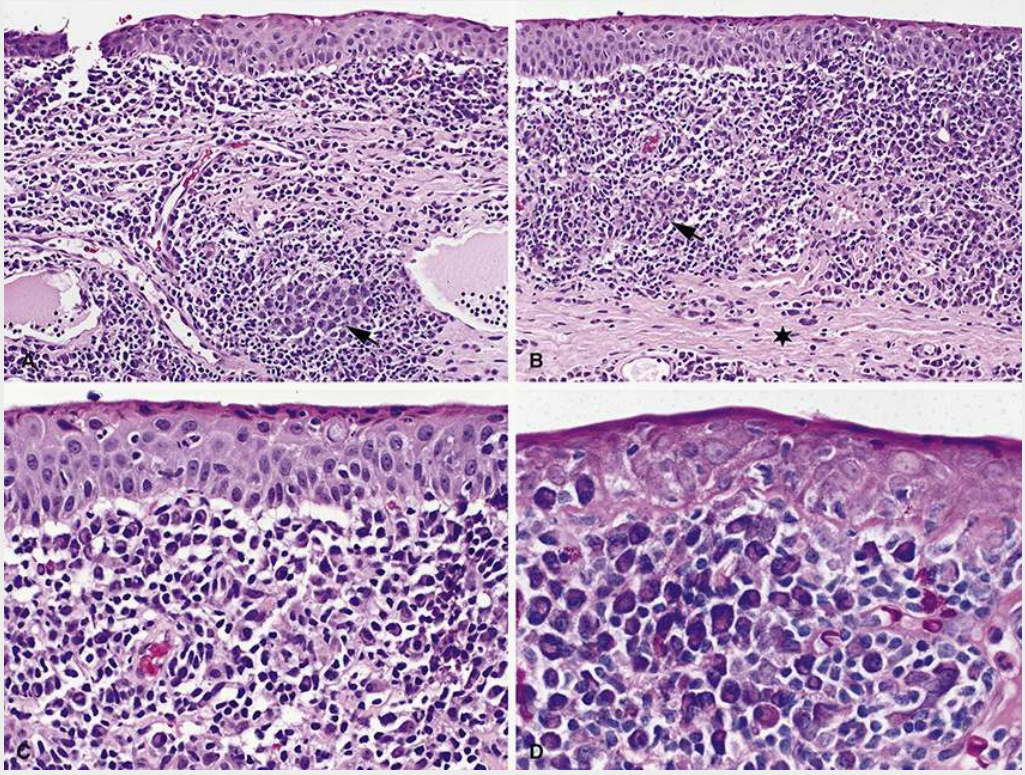

FIGURE 121.6 This biopsy was from the right inferior fornix of a young woman with bilateral chronic follicular conjunctivitis, confirmed as *Chlamydia trachomatis* infection using the cobas CT/NG v2.0 Test (Roche Diagnostics). A, A band of chronic (mononuclear) inflammatory cells is beneath the epithelium, and a follicle is present in the deeper substantia propria (*arrow*). The follicle center cells are large, pale, activated B lymphocytes with admixed macrophages and some T cells.[54] B, In this biopsy area, there is a band of dense subepithelial mononuclear inflammation with a vague follicle (*arrow*). A band of fibrosis is beneath the inflammation (★). C, The epithelium is superficially keratinized, and there is a marked reduction in the number of goblet cells customarily found at this location.[56] The inflammatory infiltrate contains numerous plasma cells along with lymphocytes and macrophages. D, Giemsa stain highlights the numerous plasma cells, including several in the epidermis (*arrows*). A few eosinophils are also present (*arrowheads*).

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Prognosis

Surgery for trachomatous trichiasis is associated with a significant recurrence rate and may have to be repeated to prevent corneal damage.[42,45,46,47,48] Adverse outcomes from surgery include eyelid contour abnormalities and granuloma formation, which occur in 5% to 30% of cases.[40,45,47,49,50] Several clinical trials reported unfavorable surgical outcomes to be associated with surgical quality, type of procedure, and preoperative disease severity.[45,47,49] Management of unfavorable surgical outcomes is often challenging and usually requires more advanced surgical skills.

Histopathology

The histopathology of trachoma was reviewed in exquisite detail by Sir Stewart Duke-Elder.[51] The earliest changes are found in the palpebral conjunctiva near the fornix and include epithelial hyperplasia with lymphocytic infiltration, the formation of epithelial crypts with collections of neutrophils, and flattening of the superficial epithelial cells with nuclear degeneration, exfoliation, and chlamydial inclusion bodies.[51] The epithelial changes progress with the formation of papillae and pseudoglands.[51] In chronic trachoma, the epithelium becomes attenuated and ultimately develops squamous metaplasia ("epidermalization") with prickle cell and horny layers[51] and loss of goblet cells.[52]

The earliest changes in the substantia propria are capillary dilation with diffuse infiltration by lymphocytes, plasma cells, and macrophages (Figure 121.6).[51] The inflammatory infiltrate increases in intensity over time with the formation of lymphoid follicles.[51] Lymphoid follicles are characteristic of trachoma,[51,53,54,55] but they are not invariably present.[51] Macrophages predominate in fully developed follicles, and there are usually large macrophages containing phagocytosed nuclear debris (phagocytic cells of Leber).[51] "In the submucosa, the general cellular infiltration eventually contains, in addition to the preponderating lymphocytes, elements such as eosinophils and mast cells in considerable numbers especially deep in the tissues, plasma cells in enormous numbers especially under the epithelium, wandering through it and into the discharge, an occasional large macrophage, and relatively few polymorphs, usually aggregated in heaps and usually associated with secondary infection."[51] Scarring of the substantia propria progresses over time, the histological correlate of the cicatrization noted clinically.[51,52] Diagnosis of *C. trachomatis* infection can be confirmed using cultures or nucleic acid amplification techniques of ocular swabs.[9]

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CHAPTER 121

Trachoma

Key Points

- Trachoma is a chlamydial infection characterized by recurrent episodes of conjunctival inflammation with lymphoid follicles and, in some cases, severe papillary hypertrophy
- Chlamydial antigens are believed to induce cell-mediated immune and delayed hypersensitivity responses with the production of proinflammatory cytokines and cellular infiltration forming lymphoid follicles
- Active disease is more commonly found in children and is characterized by a chronic, recurrent follicular conjunctivitis, most prominently seen on the upper tarsal conjunctiva
- The late-stage scarring sequelae develop in later life promoted by the inflammatory process but can be seen earlier in cases of more severe disease
- Scarring can be relatively mild with only a few linear or stellate scars or severe with thick fibrotic bands, shortening of the fornix, and symblepharon formation. Contraction of the conjunctiva results in cicatricial entropion
- Antibiotic therapy, mostly tetracycline eye ointment, has been used to reduce the burden of trachoma infection
- For late-stage disease, surgical correction of trichiasis and entropion are needed to prevent corneal scarring and blindness
- Surgery for trachomatous eyelid trichiasis and entropion is associated with a significant recurrence rate and adverse outcomes from surgery include can be seen in 5% to 30% of cases

Trachoma is the third most common cause of blindness worldwide, after cataracts and glaucoma.[1] It is estimated that about 1.2 billion people live in trachoma-endemic areas in 51 countries.[2] More than 40 million people have active trachoma, 8.2 million have trachomatous trichiasis,[2] and 5.6 million are already blind from trachoma.[3] Endemic regions for trachoma involve large parts of Africa, some regions of the Middle East, the Indian subcontinent, Southeast Asia, and South America.[4] In some regions, such as Ethiopia, trachomatous inflammation may be seen in more than 30% of children.[5]

Trachoma is caused by the obligate intracellular bacterium *Chlamydia trachomatis*. Chlamydial infection usually starts in childhood,[6] characterized by recurrent episodes of conjunctival inflammation with lymphoid follicles and, in some cases, severe papillary hypertrophy.[7] Conjunctival scarring gradually develops from the repeated tissue damage.[7,8] With more severe conjunctival scarring the eyelashes become distorted and trichiatic, where they come into contact with the cornea.[8] If left untreated, loss of vision can result from corneal scarring and opacification.[9] The prevalence of active disease peaks in preschool children and declines in adulthood.[10,11,12,13,14] The prevalence of late-stage trachomatous conjunctival scarring, on the other hand, increases with age as a result of cumulative damage.[10,13] Male and female children with active trachoma are generally affected equally, but the late blinding sequelae are usually seen more frequently in females.[10,13] It has been suggested that close exposure to children in endemic countries is a risk factor for women contracting the active disease.[15]

Chlamydia is probably transmitted from an infected individual to an uninfected one. This likely occurs through direct spread from eye to eye during close contact, spread on fingers, indirect spread on fomites, and transmission by flies.[16]

Etiology and Pathogenesis

C. trachomatis is an obligate intracellular bacterium with 19 different serovars. Endemic trachoma is caused by serovars A-C,[17] whereas genital chlamydial infection is associated with serovars D-K. During its developmental cycle, *C. trachomatis* exists as reticulate bodies that are metabolically active in the intracellular stage and as elementary bodies that are the metabolically inactive extracellular form of the organism that can transfer between host cells and organisms.[18] The infectious cycle begins with the

attachment of the elementary bodies to the surface of epithelial cells, followed by endocytosis of the bacteria. Inside the host cell, within 6 to 9 hours, the elementary bodies transform into the reticulate form and replicate by binary fission.[18] Chlamydial antigens are believed to induce cell-mediated immune and delayed hypersensitivity responses with the production of proinflammatory cytokines and cellular infiltration forming lymphoid follicles. Some immune cell infiltrates have shown a phenotype suggestive of NK cells.[19] Chronic conjunctival inflammation associated with enriched expression of proinflammatory factors and altered expression of extracellular matrix regulators appear to be important factors in the development of conjunctival scarring.[20] Some reticulate bodies transform back into elementary bodies that become extracellular and can transmit the infection to another host.

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Individual and environmental risk factors that may facilitate the introduction and transmission of *C. trachomatis* into vulnerable communities probably include migration of infected individuals who transmit new strains of the bacterium into areas with crowded living conditions.[21,22] Children with active disease in areas where water is scarce, and face washing less common, often have ocular and nasal secretions that can be a source of bacterial spread.[23] Flies that feed on ocular secretions can also act as vectors for disease transmission.[24]

Clinical Characteristics

Clinically, trachoma is subdivided into early active and late-stage cicatricial disease. Active disease is more commonly found in children and is characterized by chronic, recurrent follicular conjunctivitis, most prominently seen on the upper tarsal conjunctiva. More severe cases may have papillary hypertrophy with engorgement of small vessels, surrounding edema, and inflammatory thickening of the conjunctiva.[25] Recurrent or persistent ocular infection leads to conjunctival scarring (Figure 121.1A). During the active phase the superior corneal limbus develops follicles composed of lymphocytes surrounding a reticuloendothelial cell germinal center. When these follicles heal and regress, they result in round, thinned depressions, referred to as Herbert pits, which are a characteristic and pathognomonic finding of trachoma (Figure 121.2).

The late-stage scarring sequelae develop in later life promoted by the inflammatory process but can be seen earlier in cases of more severe disease. Scarring can be relatively mild with only a few linear or stellate scars (Figure 121.1B) or severe with thick fibrotic bands, shortening of the fornix, and symblepharon formation. Contraction of the conjunctiva results in cicatricial entropion that rotates the eyelid margin toward the globe (Figure 121.3). Distortion of the eyelash follicles manifests as secondary trichiasis (Figure 121.4).

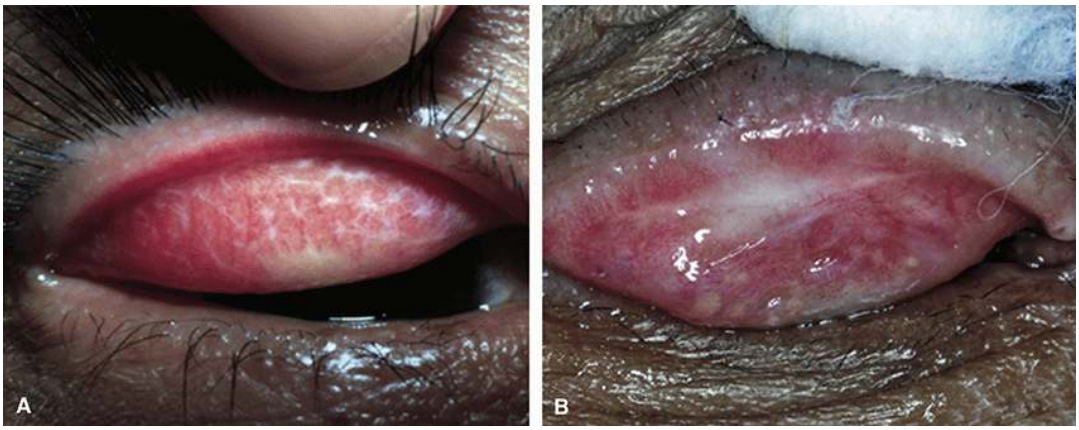

FIGURE 121.1 A, Conjunctival scarring from repeated or persistent ocular infection with *Chlamydia trachomatis*. B, Late-stage trachomatous scarring with linear von Arlt line on the superior tarsal conjunctiva and follicular conjunctivitis. A and B, (Courtesy of Dr. Antonio Augusto Cruz.)

FIGURE 121.2 Herbert pits within a pannus along the superior corneal limbus. (Courtesy of Dr. Antonio Augusto Cruz.)

In individuals infected with trachoma, progression to conjunctival scarring develops in 23% to 30% over 2 years, and there is a strong relationship between progressive scarring and an increasing number of episodes of clinical inflammation.[6] Studies have reported progression of conjunctival scarring in 47% of patients followed for 5 years[26] and 68.5% followed for 14 years.[27] The development of trachomatous trichiasis varies with the presence and degree of conjunctival scarring from less than 10% in patients followed up to 12 years[28,29] to more than 38% in cases of severe scarring over 14 years.[27]

The most severe complication of trichiasis and entropion is corneal abrasion and opacification (Figure 121.5). It *(Print pagebreak 797)* has been reported to develop in 5% to 10% of cases over 2 to 10 years,[29,30,31] but as high as 34% in cases with severe trichiasis.[32]

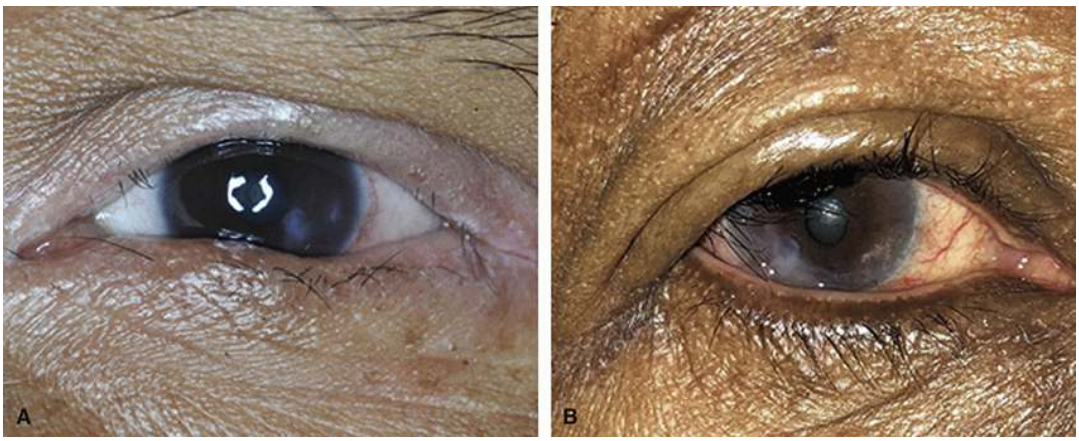

FIGURE 121.3 Upper eyelid cicatricial entropion in late-stage trachoma. A, (Courtesy of Dr. Antonio Augusto Cruz.) B, (Courtesy of Dr. Roman Shinder.)

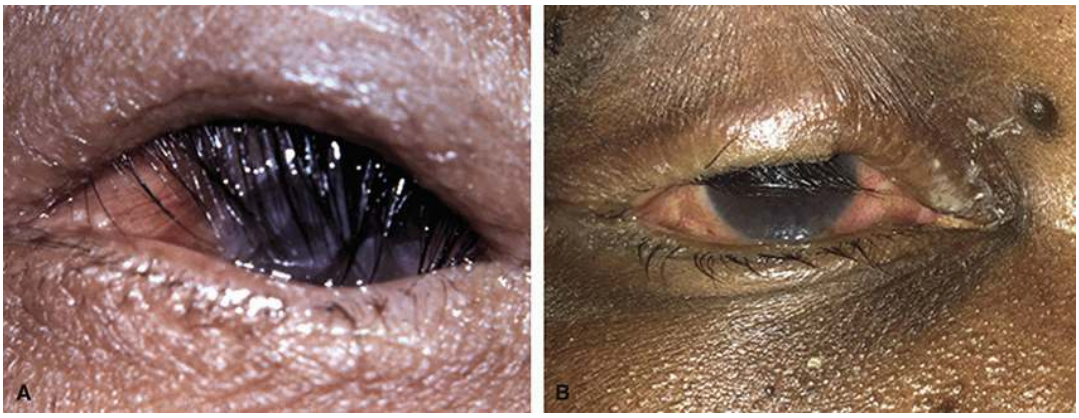

FIGURE 121.4 Secondary trichiasis of the upper eyelid in late-stage trachoma. A, (Courtesy of Dr. Alan McNab.) B, (Courtesy of Dr. Roman Shinder.)

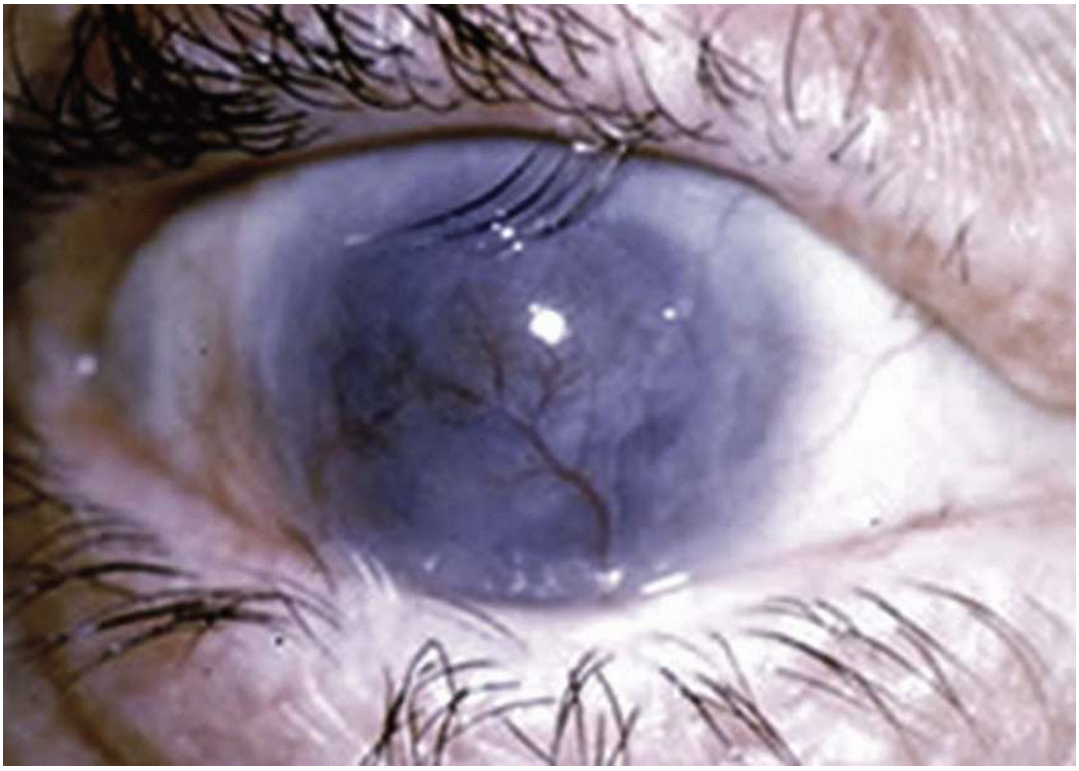

FIGURE 121.5 Corneal opacification from trachomatous entropion and trichiasis.

Differential Diagnosis

Several conditions can produce chronic follicular conjunctivitis with a similar appearance to active trachoma. These include conjunctivitis caused by viruses and bacteria, adult inclusion conjunctivitis, and infection with genital strains of *C. trachomatis*.[25] Cicatricial entropion and trichiasis can be seen with mucous membrane pemphigoid, Stevens-Johnson syndrome, systemic sclerosis, involutional changes, chemical injuries, and drugs. Epiblepharon and distichiasis are characterized by eyelash-to-ocular contact, with possible corneal abrasion and opacification.

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Treatment

Topical and systemic antibiotic therapy has been used to reduce the burden of trachoma infection, and several different antibiotics have antichlamydial activity. The most commonly used are tetracycline eye ointment applied twice a day for 6 weeks or a single oral dose of azithromycin (20 mg/kg up to a maximum dose of 1 g).[12,21,33,34,35,36,37,38] However, azithromycin is not used in infants under the age of 6 months. Since this group can be a significant reservoir of infection, it is

recommended that infants under 6 months be treated with a 6-week course of topical tetracycline.

There are about 8 million people with trachomatous trichiasis worldwide who are at risk of developing blinding corneal opacification. Surgical correction of trichiasis can usually reduce the risk of this complication. Various surgical procedures are in use, from epilation of individual trichiatic lashes to more extensive tarsal rotation procedures (see Chapter 42).[39] In countries where ophthalmologists are in short supply, trained ancillary personnel can perform simple procedures such as epilation to reduce the risk of corneal damage.[40,41] However, even with surgery, recurrence of trichiasis can be as high as 40% to 60%.[42]

Various factors may contribute to the choice of a procedure to treat trichiasis. These include preoperative disease severity, surgical technique, and current infection. Perioperative antibiotics may reduce the risk of recurrence.[43,44] Despite the high recurrence rate, there can be some improvement in vision following surgery.[39,43]

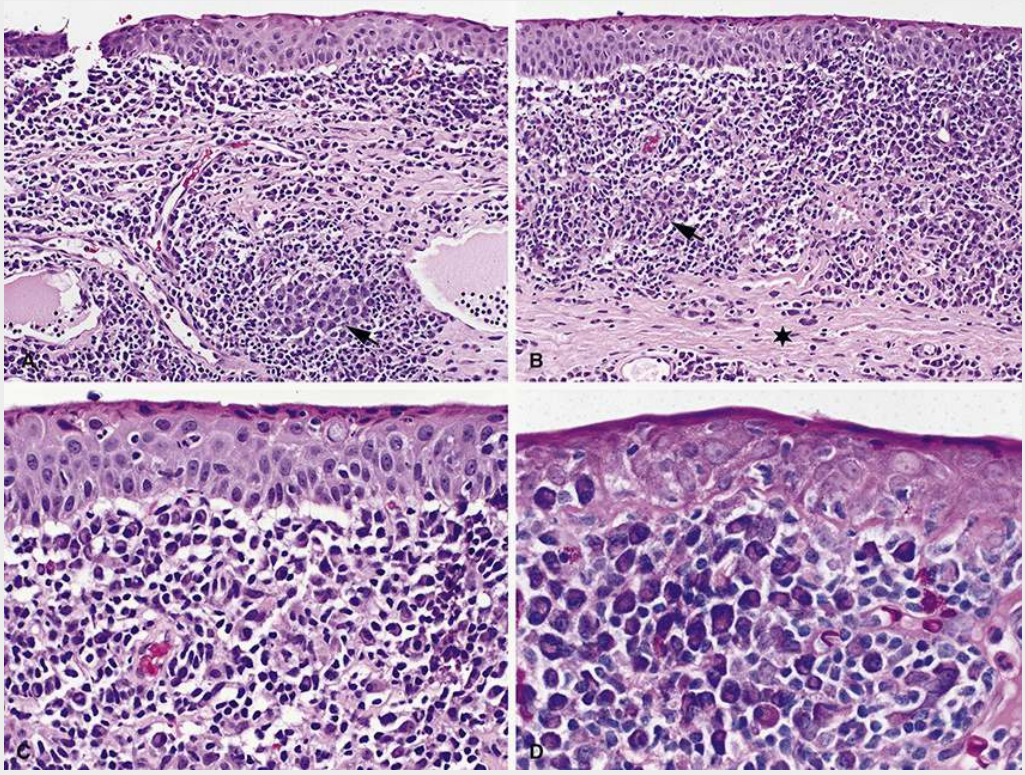

FIGURE 121.6 This biopsy was from the right inferior fornix of a young woman with bilateral chronic follicular conjunctivitis, confirmed as *Chlamydia trachomatis* infection using the cobas CT/NG v2.0 Test (Roche Diagnostics). A, A band of chronic (mononuclear) inflammatory cells is beneath the epithelium, and a follicle is present in the deeper substantia propria (*arrow*). The follicle center cells are large, pale, activated B lymphocytes with admixed macrophages and some T cells.[54] B, In this biopsy area, there is a band of dense subepithelial mononuclear inflammation with a vague follicle (*arrow*). A band of fibrosis is beneath the inflammation (★). C, The epithelium is superficially keratinized, and there is a marked reduction in the number of goblet cells customarily found at this location.[56] The inflammatory infiltrate contains numerous plasma cells along with lymphocytes and macrophages. D, Giemsa stain highlights the numerous plasma cells, including several in the epidermis (*arrows*). A few eosinophils are also present (*arrowheads*).

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Prognosis

Surgery for trachomatous trichiasis is associated with a significant recurrence rate and may have to be repeated to prevent corneal damage.[42,45,46,47,48] Adverse outcomes from surgery include eyelid contour abnormalities and granuloma formation, which occur in 5% to 30% of cases.[40,45,47,49,50] Several clinical trials reported unfavorable surgical outcomes to be associated with surgical quality, type of procedure, and preoperative disease severity.[45,47,49] Management of unfavorable surgical outcomes is often challenging and usually requires more advanced surgical skills.

Histopathology

The histopathology of trachoma was reviewed in exquisite detail by Sir Stewart Duke-Elder.[51] The earliest changes are found in the palpebral conjunctiva near the fornix and include epithelial hyperplasia with lymphocytic infiltration, the formation of epithelial crypts with collections of neutrophils, and flattening of the superficial epithelial cells with nuclear degeneration, exfoliation, and chlamydial inclusion bodies.[51] The epithelial changes progress with the formation of papillae and pseudoglands.[51] In chronic trachoma, the epithelium becomes attenuated and ultimately develops squamous metaplasia ("epidermalization") with prickle cell and horny layers[51] and loss of goblet cells.[52]

The earliest changes in the substantia propria are capillary dilation with diffuse infiltration by lymphocytes, plasma cells, and macrophages (Figure 121.6).[51] The inflammatory infiltrate increases in intensity over time with the formation of lymphoid follicles.[51] Lymphoid follicles are characteristic of trachoma,[51,53,54,55] but they are not invariably present.[51] Macrophages predominate in fully developed follicles, and there are usually large macrophages containing phagocytosed nuclear debris (phagocytic cells of Leber).[51] "In the submucosa, the general cellular infiltration eventually contains, in addition to the preponderating lymphocytes, elements such as eosinophils and mast cells in considerable numbers especially deep in the tissues, plasma cells in enormous numbers especially under the epithelium, wandering through it and into the discharge, an occasional large macrophage, and relatively few polymorphs, usually aggregated in heaps and usually associated with secondary infection."[51] Scarring of the substantia propria progresses over time, the histological correlate of the cicatrization noted clinically.[51,52] Diagnosis of *C. trachomatis* infection can be confirmed using cultures or nucleic acid amplification techniques of ocular swabs.[9]

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CHAPTER 123

Xanthelasma Palpebrarum

Key Points

- Xanthelasma is a condition characterized by the development of flat yellowish papules or plaques near the medial canthal region in the upper or lower eyelids or both
- About half of the patients who develop xanthelasma have a primary lipid disorder or secondary hyperlipidemia
- Secondary hyperlipidemia is seen with pregnancy, obesity, diabetes mellitus, hypothyroidism, nephrotic syndrome, or cholestasis
- The exact etiology is unknown, but trauma and inflammation can alter vascular permeability and may be a factor in the pathogenesis
- Xanthelasma typically presents as bilateral, symmetrical, flat or slightly elevated, soft, yellowish papules or plaques in the periorbital region, which usually grow over time
- Xanthelasma should be differentiated from some cutaneous histiocytic disorders that may present with xanthelasma-like lesions, including necrobiotic xanthogranuloma, Erdheim-Chester disease, adult-onset asthma and periocular xanthogranuloma (AAPOX), and to a lesser extent juvenile xanthogranuloma
- If there is any abnormality in the lipid profile, medical management is advised in the form of lifestyle change and lipid-lowering drugs (statins)
- Lipid-lowering drugs may have little effect on xanthelasma that have already developed and may be associated with ptosis
- In the absence of lipid abnormalities, surgical excision is usually offered for cosmetic improvement
- Surgical excision of xanthelasma directly involving the medial canthal region should be carried out conservatively
- The recurrence rate is high regardless of the method of treatment; however, the depth of the lesion is an important prognostic factor, the deeper the lesion involvement (dermal or underlying muscle) the higher the possibility of recurrence

Xanthelasma palpebrarum (XP) is a lesion characterized by localized infiltrates of lipid-laden macrophages appearing on various areas of the skin or in visceral organs[1] and is the most common cutaneous xanthoma occurring in the eyelids. It is usually found in the superficial and middle dermal layers of the skin but can extend into the underlying muscle in some cases. One case of XP has been described located within the orbicularis muscle with no cutaneous involvement.[2] Lesions are characterized by yellowish papules that occur more commonly near the medial canthus of the upper and lower eyelids. They are usually symmetrical from one side to the other, may be multiple, and occur more commonly in women than in men. It is a benign condition that usually does not cause functional problems but is of cosmetic concern to most patients.

The prevalence of xanthelasma is estimated at 4%,[3,4] with an incidence of 1.1% in women and 0.3% in men.[5,6] The age of onset can range from teens to old age but typically peaks in the fourth and fifth decades. In about 50% of cases, XP is associated with underlying hyperlipidemia,[5] and it has been suggested that a presentation in patients younger than 40 years should prompt screening to rule out inherited disorders of lipoprotein metabolism.[7] Patients with XP associated with familial hyperlipidemia syndromes may also have concomitant xanthomas, such as xanthoma tuberosum or xanthoma tendinosum.[8]

Etiology and Pathophysiology

About 52% of patients who develop xanthelasma have a lipid disorder.[9] Primary lipid disorders include familial hypercholesterolemia (hyperlipidemia type IIa), familial combined hyperlipidemia (hyperlipidemia type IIb), and familial hypertriglyceridemia (hyperlipidemia type IV). Secondary hyperlipidemia may be seen with pregnancy, obesity, diabetes mellitus, hypothyroidism, nephrotic syndrome, and cholestasis.[10,11,12,13] Some medications, such as estrogens, prednisolone, cyclosporine, tamoxifen, oral retinoids, and protease inhibitors can also cause secondary hyperlipidemia.[14,15,16] XP has also been reported in patients who previously had erythroderma,[17] generalized cutaneous inflammatory dermatoses,[18] or contact dermatitis.[19]

The exact etiology of XP is not clear. Trauma and inflammation can alter vascular permeability, and it has been demonstrated experimentally that the rate of capillary leakage of low-density lipoprotein (LDL) is increased in areas exposed to friction and constant movement.[20,21] This suggests that trauma, inflammatory cells, and mediators may be a factor in the pathogenesis of XP.[3,5]

The dermis of the eyelid is thin and vascular-rich, and pulsatile blood pressure, as well as local heat, may increase dermal capillary pressure during repeated blinking. This may play a role in the rate of lipid leakage and subsequent deposition in the eyelid by allowing lipoproteins to enter the dermis where they become oxidized by free radicals or ultraviolet *(Print pagebreak 808)* light, phagocytosed by dermal cells, and transformed into xanthoma cells.[5,22,23] These cells have a perivascular arrangement, suggesting that their stored lipid might originate from plasma lipids. Cholesterol entering cells along the capillary walls is mostly LDL, suggesting that the accumulated cholesterol is derived from blood.[21] These cells form foamy histiocytes causing inflammation and fibrosis in surrounding tissues. The yellowish cholesterol-rich foam cells accumulate in the skin, resulting in the clinical findings of xanthelasma.[24]

The inciting events leading to the formation of xanthelasma remain obscure. However, the inflammatory environment surrounding their formation is similar to that seen in the early stages of the formation of cardiac atherosclerotic plaques,[25] and it has even been suggested that XP may be a predictor of ischemic heart disease, myocardial infarction, or systemic atherosclerosis.[4,26] Atheromagenesis is believed primarily to be an inflammatory process, driven by oxidized LDL and elevated iNOS, COX, metallopeptidase, and MPO levels. These result in the recruitment of blood monocytes to the vessel wall, monocyte activation, and transformation into lipidized macrophages, or “foam cells” that accumulate cholesterol.[27,28,29]

Xanthelasmas do not develop in most patients with hypercholesterolemia, suggesting that other factors may contribute to the pathogenesis.[5] In vitro lipogenesis studies have shown in situ synthesis of all major lipid groups in xanthoma tissue in both hyperlipidemic as well as normolipidemic patients.[5,20] Impaired cholesterol removal from the tissues resulting in decreased levels of high-density lipoprotein (HDL) may also play a role in the formation of xanthelasma.[5,20]

A xanthelasma-like reaction has been reported as a complication of filler injections.[30,31] The mechanism of macrophage lipid accumulation and foam cell formation in patients with no lipid abnormalities before filler injection is not understood. However, it has been proposed that hyaluronic acid injections may bind extravasated LDL lipoprotein and that the LDL-glycosaminoglycan complex becomes internalized by macrophages and histiocytes more avidly than does native LDL, resulting in xanthelasma formation.[32]

Clinical Presentation

XP typically presents as bilateral, symmetrical, flat or slightly elevated, soft, yellowish papules or plaques in the periorbital region, and they usually grow over time (Figure 123.1). Occasionally they can appear darker red or even brown[1] and can be semisolid or rarely even calcareous (Figure 123.2A). In patients with hypercholesterolemia, lesions tend to be more nodular and tendinous (Figure 123.2B).[5] Less commonly, lesions can be seen on the neck, trunk, shoulders, and axillae.[5]

XP lesions most commonly occur near the medial canthal portion of the eyelids, more frequently on the upper lid.[33] They typically present in middle-aged and older individuals and are seen more frequently in females.[1,6] Lesions progress slowly and do not regress without treatment. When very large on the upper eyelid, they may cause mechanical ptosis (Figure 123.3).[34]

About 50% of individuals with xanthelasma have a lipid disorder, so that evaluation of the serum lipid profile is recommended in most cases. The cholesterol and triglyceride levels may be elevated, and the HDL level is often reduced.

Differential Diagnosis

The differential diagnosis of XP includes necrobiotic xanthogranuloma, orbital lipogranuloma, juvenile xanthogranuloma, Erdheim-Chester disease, granulomatosis with polyangiitis, lipoid proteinosis, primary systemic amyloidosis, necrobiosis lipoidica, sarcoidosis, atypical lymphoid infiltrate, syringoma, microcystic adnexal carcinoma, milia, sebaceous hyperplasia, steatocystoma multiplex, trichoepithelioma, and apocrine hidrocystoma.

Treatment

The choice of treatment depends on the size of the lesion and the patient's lipid status. If there is any abnormality in the lipid profile, medical management is recommended before treatment of the lesions. In patients with elevated cholesterol and triglycerides, initial treatment involves changes in lifestyle and taking medications to lower serum lipids. Even though a low-fat diet and statins are often recommended, they have little effect on the xanthelasmas once they develop.

In the absence of lipid abnormalities, removal of the lesions is usually offered for cosmetic improvement. When the size is small, this can be performed by laser therapy, radiofrequency ablation, cryosurgery, or trichloroacetic acid (TCA) chemical peel. Systemic interleukin-1 blockade and cyclosporine-A therapy have also been reported to achieve good results.[15,35] However, when the size is large, surgical excision is usually a more appropriate option.[33,36]

TCA is a destructive topical chemical peel therapy that is applied in concentrations of about 50% to 70% in one or more applications.[37,38] Good to excellent results in cosmetic improvement have been reported in up to 80% of patients,[39] although recurrence may be seen in 25% to 35%.[38,40] Postinflammatory hyperpigmentation has been reported in 9% to 12.5%,[38] and hypopigmentation at a frequency of 22% to 33%.[39]

In rare cases, TCA may be associated with extension of the lesion, suggested to occur as a Koebner phenomenon.[41] The Koebner phenomenon, also called the isomorphic response, refers to the appearance of new lesions along a site of injury. It can be seen with a variety of conditions such as lichen planus, warts, molluscum contagiosum, psoriasis, lichen nitidus, and the systemic form of juvenile rheumatoid arthritis.

Probucol is a bisphenol antioxidant with antilipidemic activity. It inhibits the oxidation of LDL and lowers the level of cholesterol in the bloodstream by increasing the rate of LDL catabolism.[42] Several studies have shown regression of xanthelasma after oral probucol therapy.[43,44]

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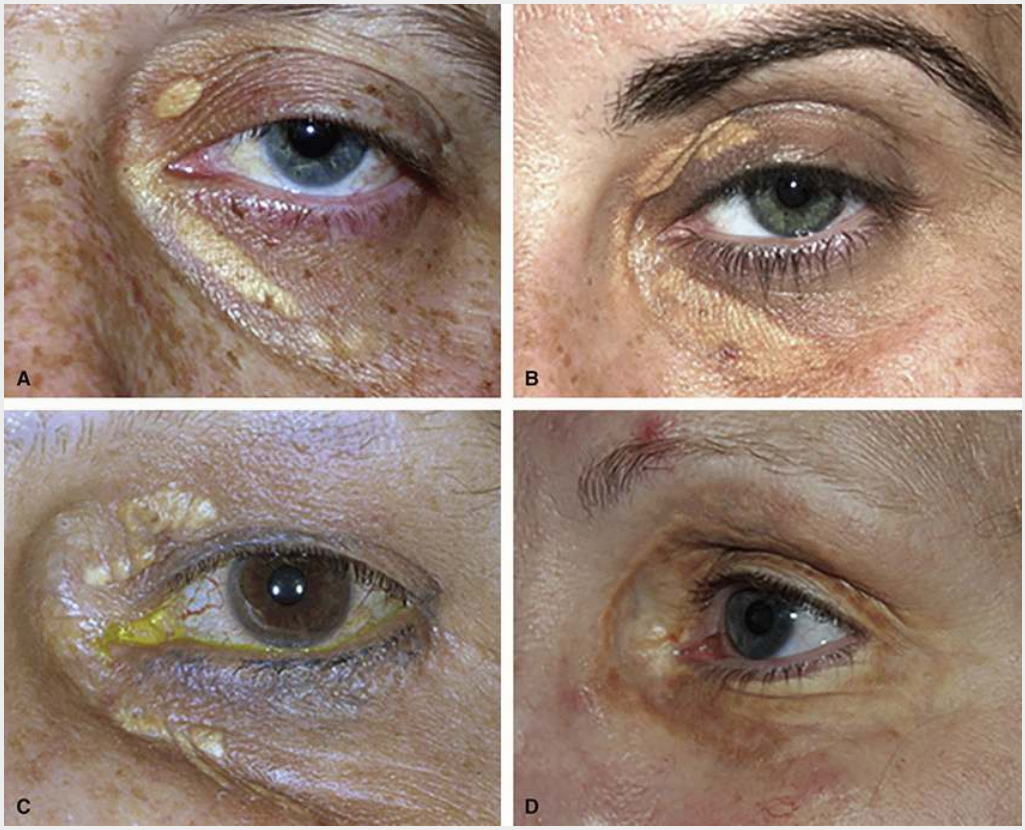

FIGURE 123.1 A-D, Xanthelasma palpebrarum involving the upper and lower eyelids and medial canthus.

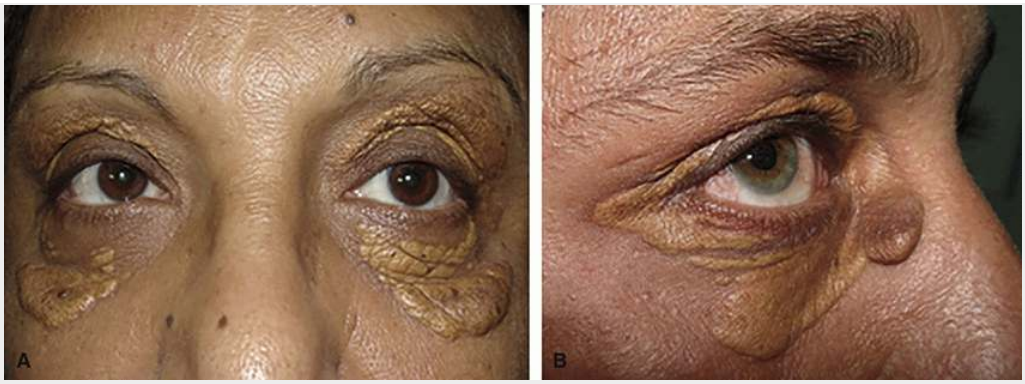

FIGURE 123.2 A, Xanthelasma appearing as bilateral brown firm lesions. B, Periorbital xanthelasma with a nodular mass on the medial canthus in a patient with hypercholesterolemia.

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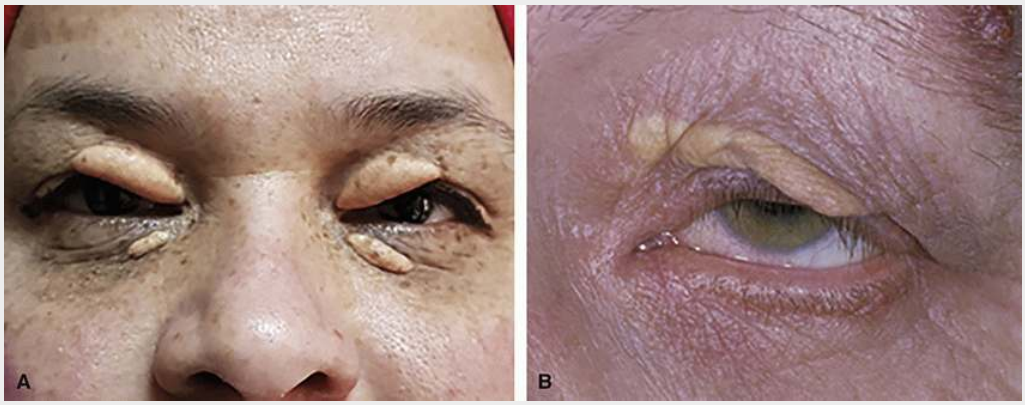

FIGURE 123.3 A and B, Large upper eyelid xanthelasma causing mechanical ptosis.

Alirocumab is a monoclonal antibody approved for anticholesterol therapy through inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9), which plays an important role in the regulation of cholesterol homeostasis. It is used primarily in the treatment of hypercholesterolemia. Rapid resolution of XP, associated with the lowering of LDL cholesterol concentrations, was reported after treatment with alirocumab.[45]

Radiofrequency (RF) ablation of XP has been reported to achieve cosmetic improvement in more than 75% of cases.[46] Although RF ablation can achieve improvement scores similar to those with TCA and with fewer treatment sessions, it is associated with more scarring and pigmentation.[47]

Laser ablation for the treatment of XP results in the destruction of perivascular foam cells and coagulation of dermal vessels in the stratum corneum leading to blockage of further lipid leakage into the surrounding tissues.[48] Various lasers, including carbon dioxide, argon, erbium, and pulsed dye lasers have been used.[49,50,51,52,53] CO_2 is considered the gold standard, and treatment of XP has resulted in excellent initial resolution in the majority of cases with little or no scarring.[54,55,56]

Cryosurgery is an outpatient procedure that is safe, relatively painless, and effective for the treatment of small XP. The results are usually cosmetically acceptable, and it is associated with few complications. However, it usually requires multiple sessions, and postinflammatory hypopigmentation can be seen.[57]

Surgical excision for the treatment of XP is widely used and often yields excellent cosmetic outcomes. It is particularly preferred in cases of deep dermal or underlying muscle involvement. For smaller upper eyelid lesions, simple surgical excision is enough, however, for larger lesions involving a significant portion of the eyelid or the eyelid plus the medial canthus, excision can be combined with local flaps or grafts. Lee et al.[9] classified periocular XP into four grades according to the location and extent of the lesion. Grade I involves only the upper eyelid; grade II involves the upper eyelid and medial canthus; grade III involves the medial canthus and the medial portions of both upper and lower eyelids; grade IV diffusely involves the medial and lateral portions of the upper and lower eyelid. Among 95 cases managed with either surgical excision alone, or excision combined with local flaps or grafts for larger lesions, recurrence was reported in 3.1% of patients at 12 months regardless of the grade.[9] However, in other reports, the incidence of recurrence has been reported to be up to 40% after primary surgical excision, 60% after secondary excision, and 80% after excision for bilateral upper and lower eyelid

involvement.[58] Regardless of the extent of surgery, slight scarring, dyspigmentation, and ectropion are possible complications.[59,60,61] Care should be taken when excising large xanthelasmas involving the upper and lower eyelids if they coalesce or join each other in the medial canthal region. Total excision of these lesions may result in cicatrix formation and shortening in the medial canthus and could result in the development of cicatricial canthal webs or medial canthal webbing. This may be difficult to correct because available skin in the medial canthus is already in short supply and is relatively fixed in position to the skin of the bridge of the nose. Lesions confined to the upper or lower eyelids usually have ample and more mobile skin so that a more generous excision may be permissible.[62,63]

Prognosis The recurrence rate of xanthelasma is high regardless of the method of treatment. Depth of the lesion is important, and those involving the deeper dermis or underlying muscle may be associated with higher rates of recurrence.[58] For patients with lipid disorders like hyperlipidemia, liver diseases, diabetes, and thyroid disorders, it is important to treat the underlying medical condition and to control hyperlipidemia. However, the prolonged use of some lipid-lowering drugs may be associated with the development of ptosis (anti-cholesterol-associated ptosis) due to statin-induced myositis.[64]

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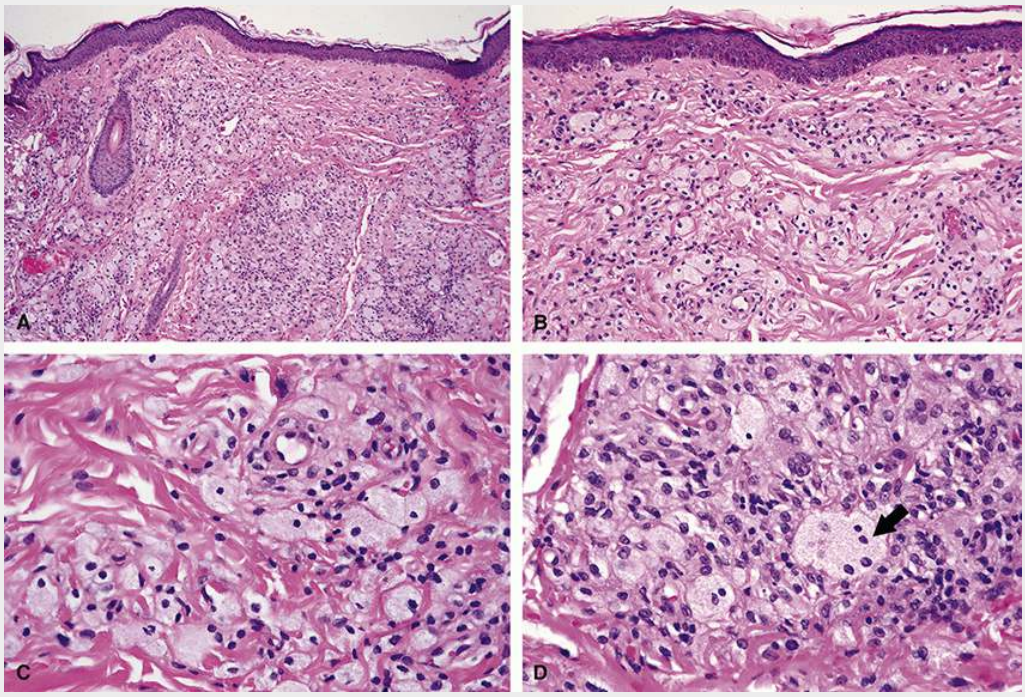

FIGURE 123.4 A, Typical xanthelasma with clusters of vacuolated, lipid-laden macrophages (foam cells) in the papillary and upper reticular dermis forming nodules separated by dermal connective tissue with scattered individual foam cells. B, Foam cells have a perivascular predilection, although they are usually present as individual cells and small clusters between the larger aggregates of perivascular foam cells. Lymphocytes and nonxanthomatous macrophages are common but often inconspicuous. C, Lipid vacuoles within the macrophages create a finely reticular, pale-staining cytoplasm. D, Xanthelasma may have occasional multinucleated foam cells (arrow), but Touton giant cells are rare.

Histopathology

The earliest stage of XP involves increasing macrophages and lymphocytes in the dermis, predominantly around small veins and the subpapillary venous plexus.[65,66] The macrophages imbibe lipids that have passed through the vessels, resulting in xanthelasma's characteristic feature: collections of vacuolated, lipid-laden macrophages (foam cells) around blood vessels in the papillary and upper reticular dermis (Figure 123.4).[65,66,67,68,69] Although often inconspicuous, the foam cells are accompanied by small numbers of lymphocytes, nonxanthomatous macrophages, and mast cells.[65,67,69,70] Xanthelasmas may have foreign-body or Touton giant cells,[65,66,69,71,72] although these are uncommon and rarely Touton giant cells.[72] Fibrosis is usually minimal,[73,74] although it may accompany regression of older lesions.[66,67] Histological diagnosis of XP does not pose a problem in patients with a typical clinical appearance. In patients lacking typical clinical features, other xanthomatous lesions such as Rosai-Dorfman disease (sinus histiocytosis with massive lymphadenopathy), Erdheim-Chester disease, or xanthogranulomas must be excluded.[75]

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CHAPTER 124

Xanthogranuloma and Histiocytoses

Key Points

- The pathogenesis of xanthogranulomas is unknown, but it is believed that they arise from a reactive, metabolic, or inflammatory process that results in the proliferation of free tissue macrophages
- Xanthogranulomas were previously classified in 1987 as class II histiocytosis (non-Langerhans cell histiocytosis)
- The updated classification of 2016 reclassified all cutaneous manifestations of histiocytic disorders under the C group (cutaneous and mucocutaneous manifestations)
- The C group is further divided into the xanthogranuloma (XG) family and non-XG family
- The xanthogranuloma family consists of juvenile xanthogranuloma (JXG) and adult xanthogranuloma (AXG)
- The nonxanthogranuloma family includes cutaneous Rosai-Dorfman disease and necrobiotic xanthogranuloma (NXG)
- Juvenile xanthogranuloma (JXG) is the most common variant of non-Langerhans xanthogranuloma disease
- Eyelid lesions vary according to the specific disease, but they are either nodular skin lesions or xanthelasmas and they may become necrotic in NXG
- Systemic manifestations are relatively uncommon in the xanthogranuloma family, but they vary according to the type
- Systemic manifestations are more frequent in Erdheim-Chester disease and Rosai-Dorfman disease
- The cutaneous lesions should be differentiated from xanthelasma, molluscum contagiosum, hemangioma, or neurofibroma
- Treatment consists of surgical excision/debulking, radiotherapy, or systemic immunosuppression
- Fatalities are rare in conditions like juvenile xanthogranuloma, while other conditions like Erdheim-Chester disease carry a poor prognosis

Xanthogranulomatous diseases of the eyelids and orbit represent a group of non-Langerhans cell histiocytic granulomatous disorders characterized histologically by the presence of foamy histiocytes, Touton giant cells, lymphocytes, plasma cells, and varying degrees of necrosis or necrobiosis and fibrosis.[1,2] They are all similar in their cell types but differ significantly in clinical presentation and prognosis, varying from benign and self-limited disorders to systemically aggressive conditions with potentially fatal outcomes. Although distinct clinical syndromes involving xanthogranulomatous inflammation have been described, there is an overlap of some clinical findings, so that all of these diseases may represent segments of a pathophysiological continuum. The most important of these syndromes include juvenile xanthogranuloma (JXG), which primarily affects children, and at least four other adult syndromes.

Adult xanthogranulomatous diseases involving ocular adnexal or orbital tissues are rare and are often associated with other systemic manifestations. The four most commonly identified syndromes in this group are based on specific systemic associations. These are adult-onset xanthogranuloma (AOX), adult-onset asthma and periocular xanthogranuloma (AAPOX), necrobiotic xanthogranuloma (NXG), and Erdheim-Chester disease (ECD).[1,3] In their review of 137 cases of adult xanthogranulomatous disease of the orbit and adnexa, Sivak-Callcott et al. identified 8 cases of AOX (5.8%), 21 AAPOX (15.3%), 72 NBX (52.6%), and 36 ECD (26.3%).[1]

Rosai-Dorfman disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy, is another rare non-Langerhans cell reactive histiocytic disorder with periorbital cutaneous and orbital manifestations.[4,5] The clinical course can vary from benign and self-limited to persistent and recurrent. It classically presents with massive neck lymphadenopathy in children and young adults

at a mean age of 20 years,[4,6] with a slight male predominance and a greater incidence among individuals of West African and Caribbean descent.[4,6]

The first classification of histiocytosis, published in 1987 by the Working Group of the Histiocyte Society, consisted of three categories (Langerhans cell, non-Langerhans cell, and malignant histiocytosis). In this older classification, the family of xanthogranulomatous diseases was grouped under the rubric of non-Langerhans cell histiocytic disorders. However, in light of recent insights, the Langerhans/non-Langerhans dichotomy noted in the prior classification system has become questionable. As a result, the histiocytosis society proposed a revised classification in 2016 that subclassified histiocytic disorders into five groups: (1) The L group (Langerhans-related including ECD, and extracutaneous JXG); (2) the C group (cutaneous and mucocutaneous), which is divided into the xanthogranuloma (XG) family (JXG, AAPOX, AOX), and non-XG family that includes cutaneous RDD and NXG; (3) the M group (malignant histiocytoses); (4) the R group (RDD); and the H group (hemophagocytic lymphohistiocytosis and macrophage activation syndrome).[7]

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When any of these conditions is present in the orbit and periorbita, there is a significant clinical and ultrastructural overlap. Because all of these conditions are closely related and fall under the rubric of histiocytosis, in this chapter we discuss NXG, ECD, and RDD, in addition to disease conditions belonging to the xanthogranuloma family (JXG, AAPOX, AOX). A more detailed description of RDD is in Chapter 110.

Etiology and Pathogenesis

Xanthogranulomatous disease is a non-Langerhans (type II [older classification], C group [new classification]), histiocytosis that is characterized by a proliferation of histiocytes. These histiocytes originate from bone marrow stem cells where they mature into monocytes.[8] They then differentiate into one of two pathways, the mononuclear-phagocytic system or the dendritic cell system.[9] The mononuclear-phagocytic system consists of phagocytic monocytes as well as free and fixed tissue macrophages.[8] The dendritic cell system includes follicular cells of the lymph nodes and Langerhans cells in the skin. Both of these cell types function as antigen-presenting cells.[8] Although the pathogenesis of xanthogranulomatous diseases is not clearly understood, it is believed that they arise from a reactive proliferation of free tissue macrophages. The inciting factors remain elusive, but some evidence suggests a possible relation to virus infection. In a case of an infant with JXG, involvement of the salivary gland was associated with cytomegalovirus infection.[10] In another case of oral JXG, cytomegalovirus antigens in the histiocytes were identified by immunohistochemistry.[11] In addition, several patients with JXG have been shown to have chromosomal instability within the lesions and peripheral blood cells.[12] It is unclear if these chromosomal abnormalities represent a fundamental genetic defect or just aberrations resulting from a cellular response to external factors such as viral infections.

The differences or variations in the pathogenesis of specific subtypes of xanthogranulomatous disease are poorly understood. The pathogenesis of JXG is unknown, but it is presumed to develop after unknown infectious or physical stimuli that then provoke a granulomatous histiocytic reaction. The reactive lesion is derived from monocytes or macrophages in response to unknown etiologic physical or infectious agents.[13,14,15] Although the pathophysiologic relationship is not understood, JXG has been associated with juvenile chronic myelogenous leukemia, juvenile myelomonocytic leukemia, and neurofibromatosis.[16] Other diseases associated with JXG include urticaria pigmentosa, insulin-dependent diabetes mellitus, aquagenic pruritus, and even cytomegalovirus infection.[17]

In NXG, an association with paraproteinemia is well known, and this immunoglobulin monoclonal gammopathy is present in at least 80% of cases. The paraprotein may serve as the primary inciting factor or act as a cofactor that facilitates a giant cell granulomatous reaction.[18] To date, however, the precise pathogenesis of NXG and the other adult orbital xanthogranulomas is unknown.

The pathogenesis of ECD is speculated to be associated with a T-helper 1 (Th1) immune response. Patients with ECD have high levels of IFN-α, interleukin-6, IL-7, IL-12, and monocyte chemoattractant protein-1, supporting the idea of an inflammatory condition.[19,20,21] An oncogenic etiology has also been suggested because of the detection of a mutation in the BRAF proto-oncogene that has been identified in 40% to 80% of patients with ECD.[22,23] The mutation causes the amino acid substitution of glutamic acid for valine at position 600 of the BRAF protein (V600E). The BRAFV600E mutation is usually detectable in biopsies and in circulating monocytes from patients with ECD, demonstrating that ECD is a clonal disease.[22] It has been shown that patients with ECD treated with the selective BRAFV600E inhibitor, vemurafenib, showed dramatic clinical and radiographic improvement.[24]

NXG originates from the mononuclear-phagocytic system, which consists of phagocytic monocytes and free and fixed tissue macrophages. The specific pathogenesis is not known, but it has been postulated to occur secondary to a reactive proliferation of free tissue macrophages. Possible causes for this proliferation include induction by a virus, paraproteinemia, immunoglobulin or lipid-Ig complex deposition, *Borrelia* species infection, or chromosomal instability.[2]

The cause of RDD is unknown, but autoimmune diseases and viruses such as human herpesvirus 6 or Epstein-Barr virus have been proposed as possible sources.[7,25,26] The pathogenesis involves recruitment of monocytes from the peripheral blood to lymph nodes or extranodal sites, and these are then transformed into RDD histiocytes.[25] Emperipolesis, a process whereby histiocytes phagocytize intact lymphocytes or plasma cells, is characteristic of RDD and distinguishes it from other cutaneous xanthogranulomatous diseases.[6,7] These histiocytes can release cytokines, such as tumor necrosis factor-α, which result in fever and other systemic symptoms.[25]

Clinical Presentation

JXG is a childhood form of xanthogranulomatous disorders[27] and is the most common variant of non-Langerhans xanthogranuloma disease. It is most commonly found in early childhood with 5% to 17% of cases occurring shortly after birth and 75% within the first 9 months of life.[15] In children, there is a slight predilection to affect males in a ratio of 1.1:1 to 1.4:1,[28] but in adults, there is no sex prevalence. About 10% of cases may appear in adulthood.[29] In up to 90% of patients, JXG manifests with nodular cutaneous lesions that clinically appear as a well-defined papule or nodule mainly affecting the head and neck.[30] Eyelid lesions most often are solitary, firm, and asymptomatic and range in size from 5 mm to 2 cm (Figure 124.1).[27,31] Initially lesions appear pink to red, but in later stages, they tend to acquire a brownish-yellow color and may develop telangiectasias.[15] The most common site of extracutaneous involvement is a solitary mass in the subcutis or deep soft tissues, but various organs may be involved.[15,32] *(Print pagebreak 816)* Eye involvement is usually unilateral and commonly presents with an asymptomatic iris tumor, red eye, uveitis, or heterochromia iridis.[15] The iris is most often involved and can be associated with spontaneous intraocular hemorrhages, glaucoma, and blindness.[33]

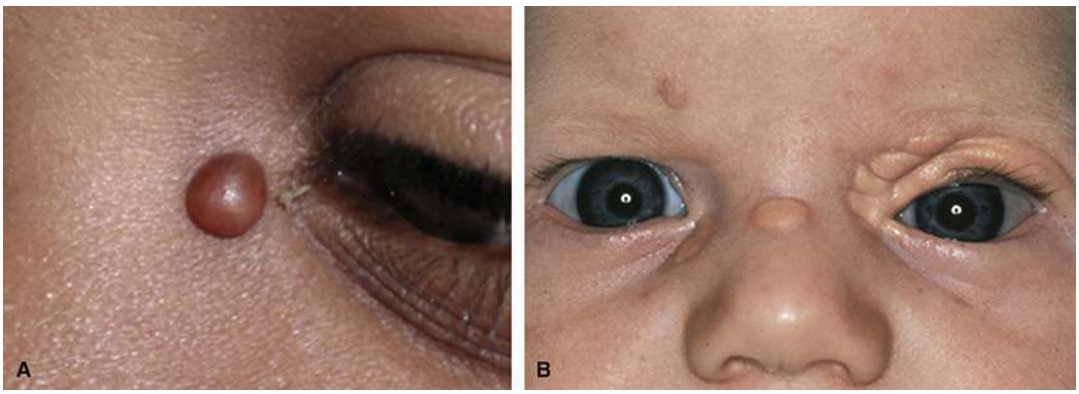

FIGURE 124.1 A and B, Juvenile xanthogranuloma nodules on the eyelids. A, (Courtesy of Dr. Brian Brazzo.) B, (Courtesy of Dr. David Lyon.)

Systemic manifestations may develop in 4% of children with JXG and 5% to 10% overall. This may involve muscles, liver, lung, pericardium, and spleen.[15,33] The central nervous system is involved in 1% to 2 % of systemic cases,[17,34] mostly manifesting with multiple intracerebral lesions and/or leptomeningeal involvement with seizures,[35] diabetes insipidus,[36] or ocular disturbance.[37] As mentioned above, JXG rarely may be associated with childhood leukemia[27,38] and neurofibromatosis type 1.[39]

AOX is the least common form and is sometimes referred to as late-onset JXG. It affects patients from teens to the ninth decade, with a median age at onset of 35 years.[32] There is no significant gender preference, and it occurs mostly without significant systemic involvement.[1] AOX lesions involve the eyelids and periorbital skin in 50% of cases and are located in the orbit in 50%.[1] Cutaneous lesions occur predominantly in the head and neck region and are similar to those of JXG, although the nodules are often larger. They generally present as bilateral isolated or diffuse yellowish lesions on swollen eyelids (Figures 124.2 and 124.3). They involute spontaneously in about 54% of cases.[40] In rare reports, both AOX and AAPOX have been associated with IgG4-related disease.[41,42,43]

AAPOX was described by Jakobiec et al. in 1993.[44] It is associated with late-onset asthma that often precedes the periocular lesions by several years.[41] Bilateral preseptal cutaneous or anterior orbital xanthomatous lesions affect adults aged between 20 and 70 years. Males are affected more frequently than females at a ratio of 2:1. Simultaneous involvement of conjunctiva has also been reported.[45] In addition to asthma, paraproteinemia and lymphadenopathy are found in 35% to 40% of patients, suggesting an underlying disorder of B cell proliferation.[1]

AAPOX presents with progressive bilateral yellow or orange, indurated xanthomatous periocular masses. The anterior orbit and lacrimal gland are often infiltrated, but intraconal involvement is very rare.[1,41] Visual function can be impaired by eyelid occlusion from mechanical ptosis or diplopia from infiltration into extraocular muscles.[44] Although this variant is usually limited to the

periocular region, mandibular gland infiltration has been described,[44] as has diffuse cervical, hilar, and inguinal adenopathy.[41] No internal organ involvement has been reported.

NXG usually involves the periorbital region, trunk, and proximal extremities. It affects men and women equally in their sixth decade of life.[46] Lesions initially may resemble xanthelasmas, but gradually increase in number and size to become indurated yellowish plaques, 0.5-5 cm in diameter, that tend to ulcerate (Figure 124.4). Ocular manifestations include skin nodules and plaques, conjunctivitis, scleritis, keratitis, anterior uveitis, and orbital infiltration with extraocular limitation. Eyelid function can become compromised with mechanical ptosis and lagophthalmos, and corneal exposure has resulted in perforation with loss of the eye.[47] NXG can be associated with hypocomplementemia and cryoglobulinemia, and with monoclonal paraproteinemia in 80% of cases. It has also been associated with multiple myeloma, non-Hodgkin lymphoma, and other hematologic dyscrasias in 25% to 30% of cases,[48] so that NXG is a more life-threatening subtype of xanthogranuloma.[1,44]

ECD is a rare infiltrative xanthogranulomatous disease.[49] The disease usually becomes apparent in adulthood between 40 and 60 years of age with a median age at diagnosis of 53 years,[50] but a few cases have been described in the pediatric population.[51] The male to female ratio is 3:1.[52] The diagnosis is made on a combination of clinical presentation and imaging features and is confirmed on histopathology. The clinical picture of ECD may vary from indolent focal disease to multiorgan involvement with a fatal outcome. Radiological characteristics are pathognomonic and skeletal involvement occurs in more than 95% of patients. Bone *(Print pagebreak 817)* pain may be the presenting symptom in 50% of cases,[53,54] and the distal ends of the femurs and proximal and distal tibia are the most frequently involved sites.[50] More than 50% of cases have other extraskeletal and internal organ involvement such as diabetes insipidus, progressive lung disease, and renal failure.[55] In about half of the patients the central nervous system is involved.[50] Cardiovascular manifestations are the major cause of death in patients with ECD, and about 60% of patients die due to a cardiac complication.[56] Orbital and periorbital lesions result in proptosis, papilledema, and nodular skin lesions. Xanthelasmas are the most frequent skin lesions in ECD, present in about 30% of patients, and are indistinguishable from those found in JXG.[57] Orbital infiltration is often bilateral and manifests as exophthalmos in about 25% of patients with ECD. Occasionally it is associated with retro-orbital pain, diplopia, or visual impairment from optic nerve compression.[57]

FIGURE 124.2 A-D, Adult-onset xanthogranuloma. C, (Courtesy of Dr. Charles Soparkar.)

RDD usually presents with fever, elevated erythrocyte sedimentation rate, leukocytosis, weight loss, malaise, sweats, anemia, and hypergammaglobulinemia (see Chapter 110).[4,6,7] Although the lymph nodes are the most common sites of involvement, extranodal involvement is seen in 25% to 43% of cases.[58,59] Extranodal disease tends to affect older individuals, and these patients show a higher tendency for a chronic relapsing course.[60] The skin is a common site for extranodal involvement, and occasionally the skin can be the only involved site.[58] Cutaneous lesions typically are red to red-brown[7] and can include infiltrated erythematous, yellowish xanthelasma-like papules, ulcerated nodules, subcutaneous masses, and rosacea-like lesions affecting the face or less commonly other parts of the body.[59,61,62] Orbital lesions may cause proptosis, blepharoptosis, uveitis, impaired extraocular

motility, and diplopia and decreased vision.[61]

Differential Diagnosis

The clinical differential diagnosis of JXG includes xanthoma, molluscum contagiosum, hemangioma, and neurofibroma, although all of these have features that help to distinguish them, such as the absence of lipid abnormalities in xanthomas, a dome shape with central umbilication in molluscum, *(Print pagebreak 818) (Print pagebreak 819)* and café-au-lait spots in most patients with neurofibromas. Lesions with at least partially similar histopathologic features include Langerhans cell histiocytosis, benign fibrous histiocytoma, xanthomas, and reticulohistiocytoma.

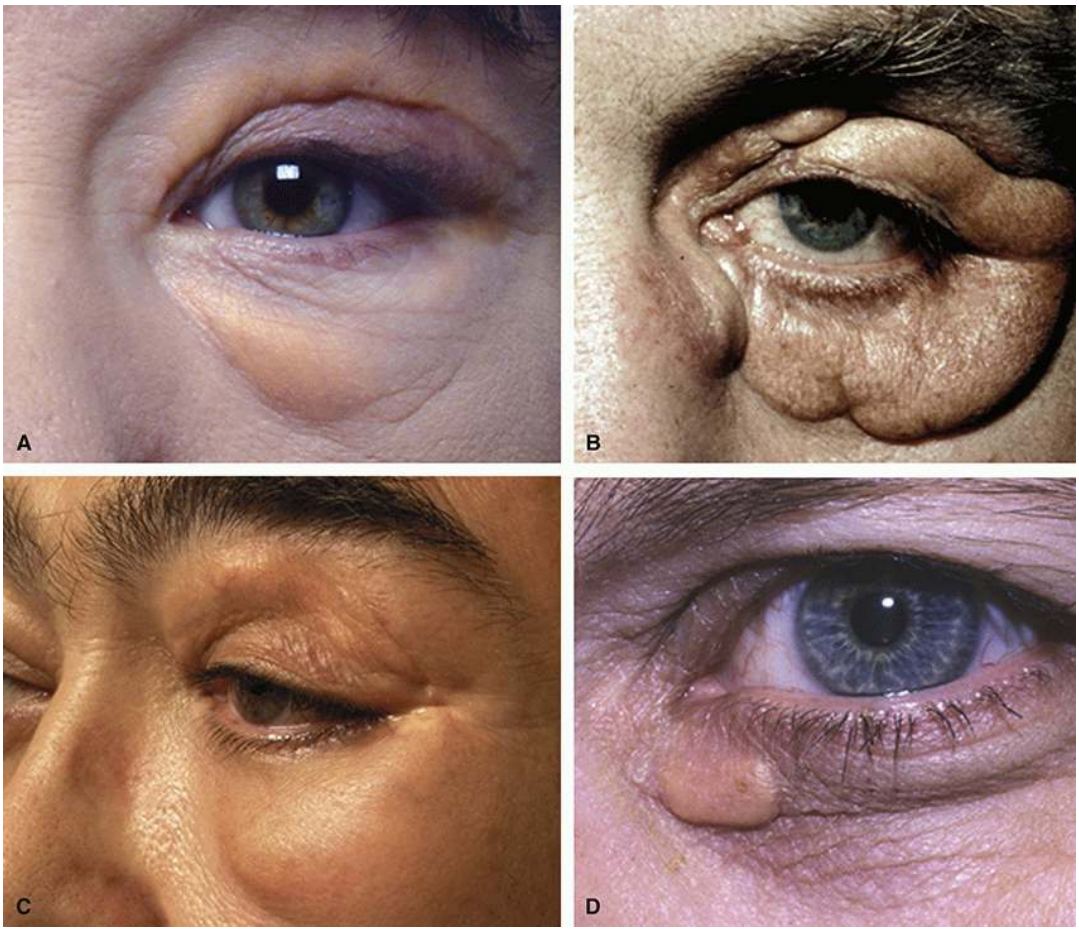

FIGURE 124.3 A-D, Adult-onset xanthogranuloma. A, (Courtesy of Dr. Robert Goldberg.) B, (Courtesy of Dr. Robert Machemer.) C, (Courtesy of Dr. Charles Soparkar.)

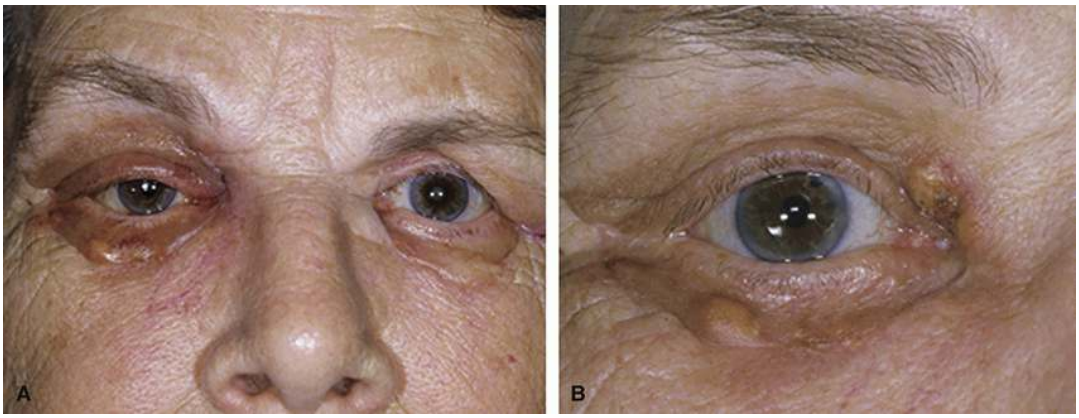

FIGURE 124.4 Necrobiotic xanthogranuloma. A, Bilateral granulomas with orbital involvement and secondary ptosis of the right eye. B, Close-up view of the right eye of the patient in 1A.

The clinical differential diagnosis of AOX includes xanthelasma, thyroid disease, sarcoidosis, allergic granulomatosis, JXG, papular

xanthoma, xanthoma disseminatum, AAPOX, NXG, and ECD.

There are a number of conditions that show symptoms and signs similar to those of ECD. These include histiocytosis X, multiple sclerosis, amyloidosis, neurosarcoidosis, metabolic diseases, mucopolysaccharidosis, Paget disease, Ormond disease, granulomatosis with polyangiitis, Whipple disease, Gaucher disease, RDD, chronic recurrent multifocal osteomyelitis, Takayasu arteritis, primary hypophysitis, cerebrotendinous xanthomatosis, cancers, and mycobacterial infections.[63]

Treatment

Xanthogranuloma diseases are very rare, so there is no agreement on the most effective treatments. Various treatments have been applied, including surgical excision or debulking,[64,65] but surgical excision is often followed by disease recurrence and scarring.[44,66] Radiotherapy has been used in some cases, but with variable results.[46,66,67]
Systemic immunosuppression and/or chemotherapy is another option,[68,69,70,71,72] but the disease often recurs after corticosteroid withdrawal. Intralesional steroid injections may be useful for isolated eyelid lesions, but there is a risk of central retinal artery occlusion, ophthalmic artery occlusion, glaucoma, eyelid necrosis, and subcutaneous fat atrophy.[73] The BRAF inhibitors, Infliximab and Vemurafenib, have been used for patients whose histiocytes contain the V600-BRAF mutation and may be considered for patients whose response to IFN-α is unsatisfactory.[24,74,75] Local and systemic proinflammatory cytokines and chemokines seem to be responsible for the recruitment and activation of histiocytes into lesions,[19,20,21] so that blockade of Th1-induced proinflammatory cytokines may be an effective therapeutic option.[19,20,76,77] Treatment of RDD varies widely depending on the disease course. Up to half of affected patients may have spontaneous resolution, making aggressive initial therapy undesirable.[2] Surgical intervention may be necessary if the airway is threatened. Corticosteroids have been helpful in some cases, but the benefit decreases after cessation.[78] Other modalities including radiotherapy, chemotherapy, and interferon are of uncertain benefit.[79] Methotrexate alone or in combination with other therapies has been helpful in some cases.[80]

Prognosis

ECD is the most severe form of the xanthogranulomatous diseases because it is associated with internal organ and bone infiltration, retroperitoneal fibrosis, severe lung disease, pericardial and pleural effusions, cardiomyopathy, central neural system lesions, and diabetes insipidus.[81] A fatal outcome is frequent despite aggressive treatment.[1,54] With INF-α treatment, the prognosis improves, with a 5-year survival rate of 70%.[82] This is a chronic condition for which there is no cure, and the goal of treatment is to prolong survival and improve the quality of life. That requires patient support. Management requires a multidisciplinary approach.

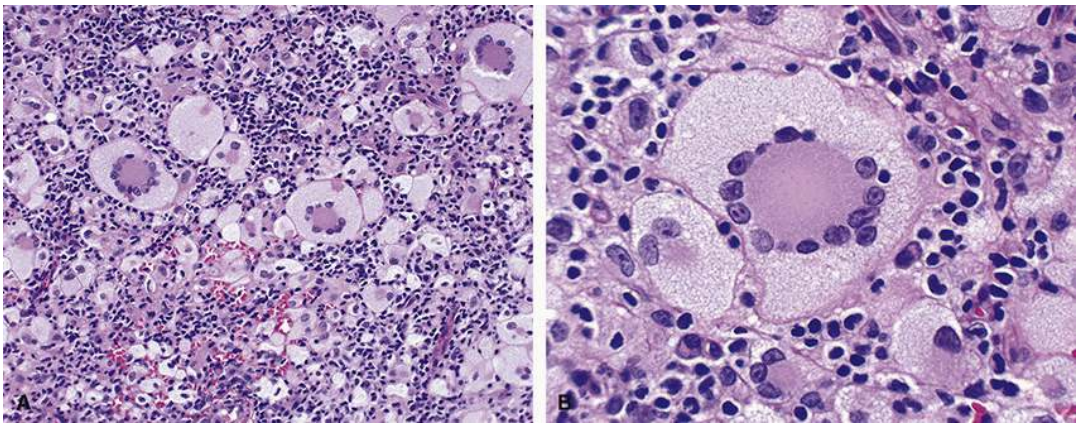

FIGURE 124.5 A, Juvenile xanthogranuloma with lipid-laden macrophages (foam cells), Touton giant cells, and numerous interspersed lymphocytes. B, Touton giant cells have a ring of nuclei surrounding eosinophilic nonvacuolated cytoplasm centrally and lipid-filled foamy cytoplasm peripherally.

Histopathology

Cutaneous JXGs are usually solitary lesions extending from just beneath the epidermis into the reticular dermis (Figure 124.5).[83,84] Lesions vary from sheets of nonxanthomatous histiocytes without Touton giant cells to the classic appearance *(Print pagebreak 820)* of foamy histiocytes mixed with Touton giant cells, lymphocytes, and scattered eosinophils.[13,83,84,85,86] Due to the variable

histological appearance, Janssen and Harms classified JXG into early JXG (≈27% of cases), classic JXG (≈47%), transitional (late) JXG (≈16%), and combined JXG (≈10%).[84] Early JXG has small- to intermediate-sized mononuclear histiocytes forming a sheet-like dermal infiltrate.[84] The histiocytes in early JXG have pale, eosinophilic cytoplasm with sparse, if any, lipid vacuoles.[84] Touton giant cells[87,88] are generally absent or few in early JXG.[84] Classic JXG has histiocytes with more abundant and vacuolated cytoplasm (xanthoma cells) and giant cells that may be foreign-body type, Touton, or Langhans type.[84] Approximately 15% of classic JXG lesions lack giant cells, most have 2 to 20 giant cells per high power field (HPF), and about 15% have >60 giant cells/HPF.[84] Janssen and Harms observed emperipolesis of lymphocytes by multinuclear giant cells in two of 68 cases of classic JXG.[84] Transitional JXGs show predominantly spindle-shaped cells with a storiform pattern with foci of foam cells and giant cells.[84] Combined JXG, as the name implies, has more than one histological pattern side by side. The histiocytes in JXG immunohistochemically express the macrophage markers CD68,[87] fascin,[85] Ki-M1P,[84,86] and CD163[85] and lack expression of CD1a,[84,85] distinguishing them from Langerhans cell histiocytoses. S100 protein was detected immunohistochemically in 7/123 cases examined by Janssen and Harms, with the positive staining in scattered cells, less than 5% of those in the lesion.[84] Kraus and coworkers cautioned against using S100 positivity to exclude a diagnosis of JXG since 8/27 JXG cases had immunoreactivity for S100 protein using a polyclonal antibody, and 6 of those cases were also immunoreactive using a monoclonal anti-S100 antibody.[85]

Cutaneous AOX resembles JXG histologically and immunohistochemically, although giant cells are more prominent in AOX.[86] Periocular AOX often accompanies orbital AOX,[89,90] and the histiocytic infiltrate extends deeply into the subcutaneous tissue and orbicularis muscle.[1] Periocular AOX features xanthoma cells, foreign-body and Touton giant cells, and lymphocytes that may be diffusely distributed, aggregated, or in lymphoid follicles (Figure 124.6).[1,89,91,92] We have seen only one example of a localized eyelid AOX similar to early JXG with only mild lipid accumulation in the histiocytes.

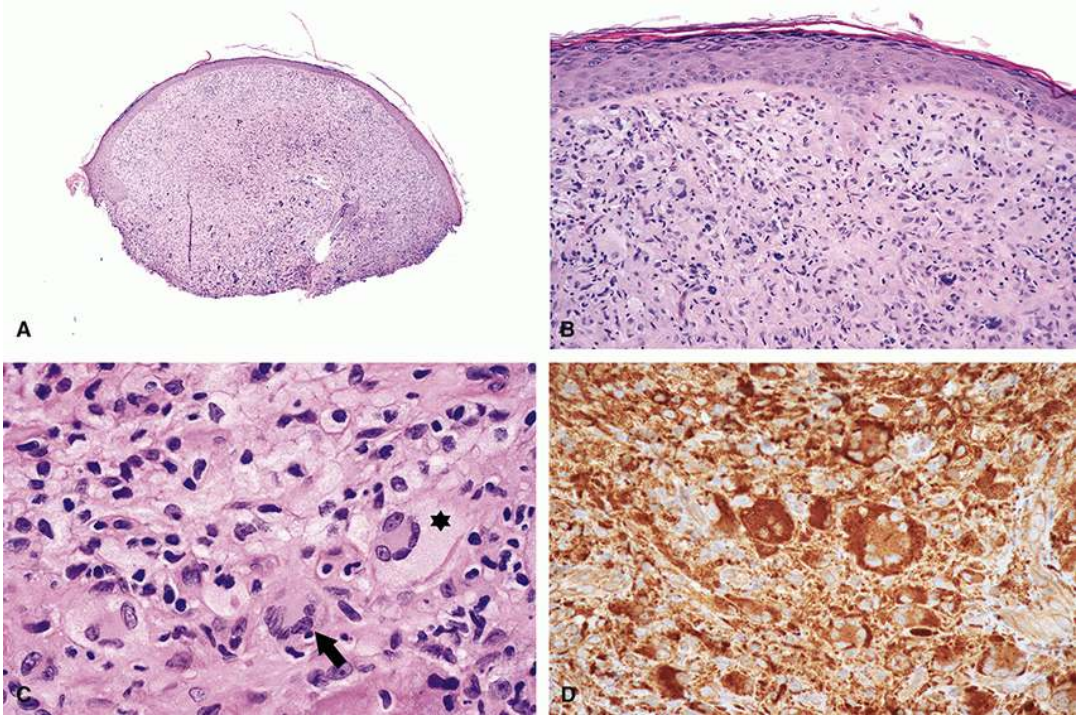

FIGURE 124.6 A, This adult-onset xanthogranuloma presented as a left lower eyelid dome-shaped nodule. B, A thin band of collagen separates the epidermis from the dermal infiltrate containing foam cells, numerous giant cells, and occasional lymphocytes. C, Both Touton (★) and foreign-body (arrow) giant cells were present in the dermal infiltrate. D, All of the mononuclear and multinuclear foam cells expressed CD68.

(Print pagebreak 821)

AAPOXs have sheets of xanthoma cells with Touton and foreign-body giant cells, lymphocytes, and a few plasma cells infiltrating the dermis, orbicularis muscle, and subcutaneous tissues, usually with involvement of the anterior orbit.[44,92,93,94] Lymphoid follicles are present in most lesions,[44,92,93,94] and two of the cases reported by Jakobiec and colleagues[44] had eosinophilia that was perivascular and interstitial in one patient and around lymphoid follicles in the other. None of the histological changes are distinctive enough to allow differentiation of AAPOX from other periocular xanthogranulomatous processes.[1,44,92]

NXG manifests as palisading xanthogranulomas with zones or bands of necrobiosis ("degeneration of the interstitial collagen, reflective either of necrosis or of hyalin homogenization with effacement of the normal tinctorial properties"[44]) in the middle dermis and subcutis (Figure 124.7).[46,95,96] There are sheets of histiocytes, foam cells, foreign-body, and Touton giant cells, and

lymphocytes that may form aggregates or nodules.[46,95,96] The foreign-body giant cells are often atypical with irregular size and shape, hyperchromatic nuclei, and clumping or polarization of nuclei to one end of the cell.[46,96] Cholesterol clefts are in the areas of necrobiosis in about 25% to 30% of biopsies.[95,96] Proposed diagnostic criteria for NXG include two major and two minor criteria, with "both major criteria and at least one minor criterion required for diagnosis, applicable only in the absence of a foreign body, infection, or other identifiable cause."[97] Major diagnostic criteria are "1. Cutaneous papules, plaques, and/or nodules, most often yellow or orange color; and 2. Histopathological features demonstrating palisading granulomas with lymphoplasmacytic infiltrate and zones of necrobiosis. Characteristic features that are variably present include cholesterol clefts and/or giant cells (Touton or foreign body)."[97] Minor diagnostic criteria are "1. Paraproteinemia, most often IgG-κ plasma cell dyscrasia, and/or other associated lymphoproliferative disorder; and 2. Periorbital distribution of cutaneous lesions."[97]

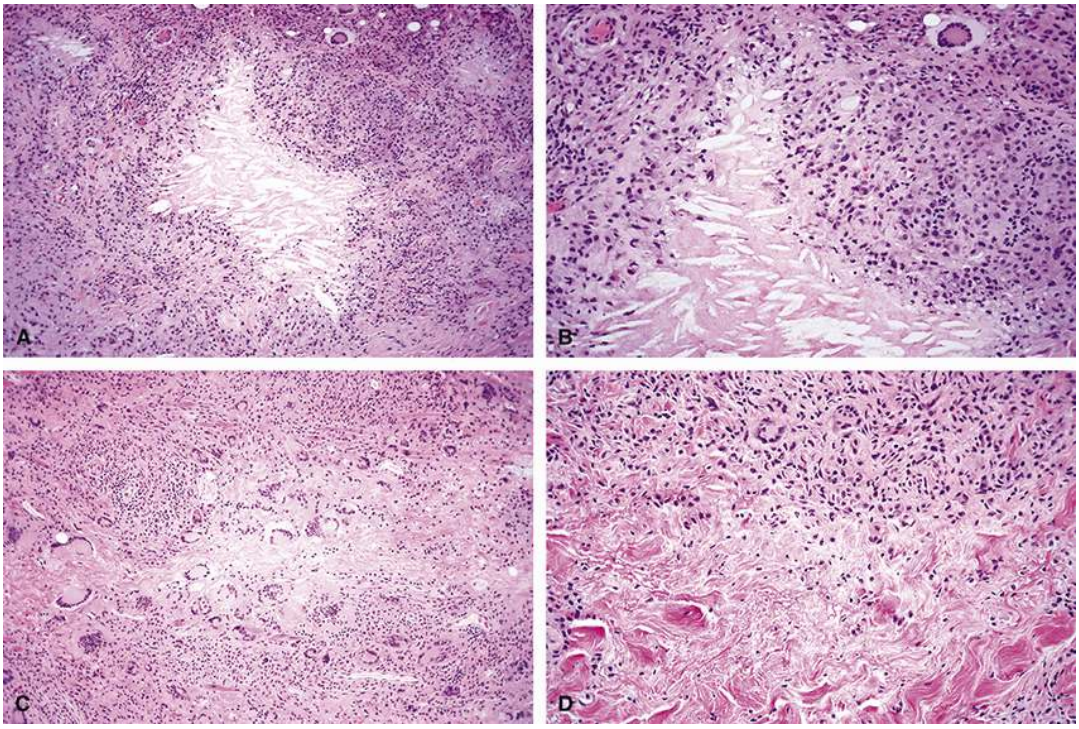

FIGURE 124.7 A and B, Necrobiotic xanthogranuloma with macrophages, foam cells, Touton giant cells, and lymphocytes surrounding necrobiotic tissue having numerous cholesterol clefts. C and D, Necrobiotic xanthogranuloma with macrophages, foam cells, Touton and foreign-body giant cells, and lymphocytes surrounding bands of necrobiotic collagen without cholesterol clefts.

The histology of cutaneous ECD is variable.[98,99,100] Approximately 25% of patients with ECD have xanthelasma-like lesions (XLLs) with foamy histiocytes, multinucleated cells, and Touton giant cells.[98] The XLLs of ECD differed significantly from xanthelasma palpebrarum by extending deeper into the reticular dermis, having more Touton giant cells, and having less fibrosis.[98] Many Touton giant cells were evident in 7/7 of the XLLs but only 1/14 classic xanthelasmas.[98] More than 30% of the foam cells were immunoreactive *(Print pagebreak 822)* using antibodies to factor XIIIa in all XLLs of ECD but only 3/14 classic xanthelasmas.[98] The *BRAF* ^{V600E} mutation was present in all 10 XLLs.[98] Kobic et al.[99] identified cutaneous lesions in 15 of 71 patients with ECD, 8 of which were XLLs and 5 subcutaneous nodules having deep dermal and pannicular xanthogranulomatous infiltration of epithelioid and foamy histiocytes with scattered lymphocytes and occasional Touton giant cells.[99] One patient had a granuloma annular-like lesion.[99] Ozkawa and coworkers reported histological findings from 19 skin biopsies in 7 patients.[100] Ten biopsies had small aggregates of xanthomatous histiocytes in the dermis with Touton giant cells, two lesions had a neutrophilic infiltrate with microabscesses, and four had histiocytes in an interstitial and perivascular pattern.[100] There was a varying degree of stromal fibrosis in the skin lesions.[100] Orbital ECD exhibits nodular to diffuse sheets of foamy histiocytes, variable numbers of dispersed and/or aggregated lymphocytes and plasma cells, and sclerotic bands separating the histiocytes (Figure 124.8).[100]

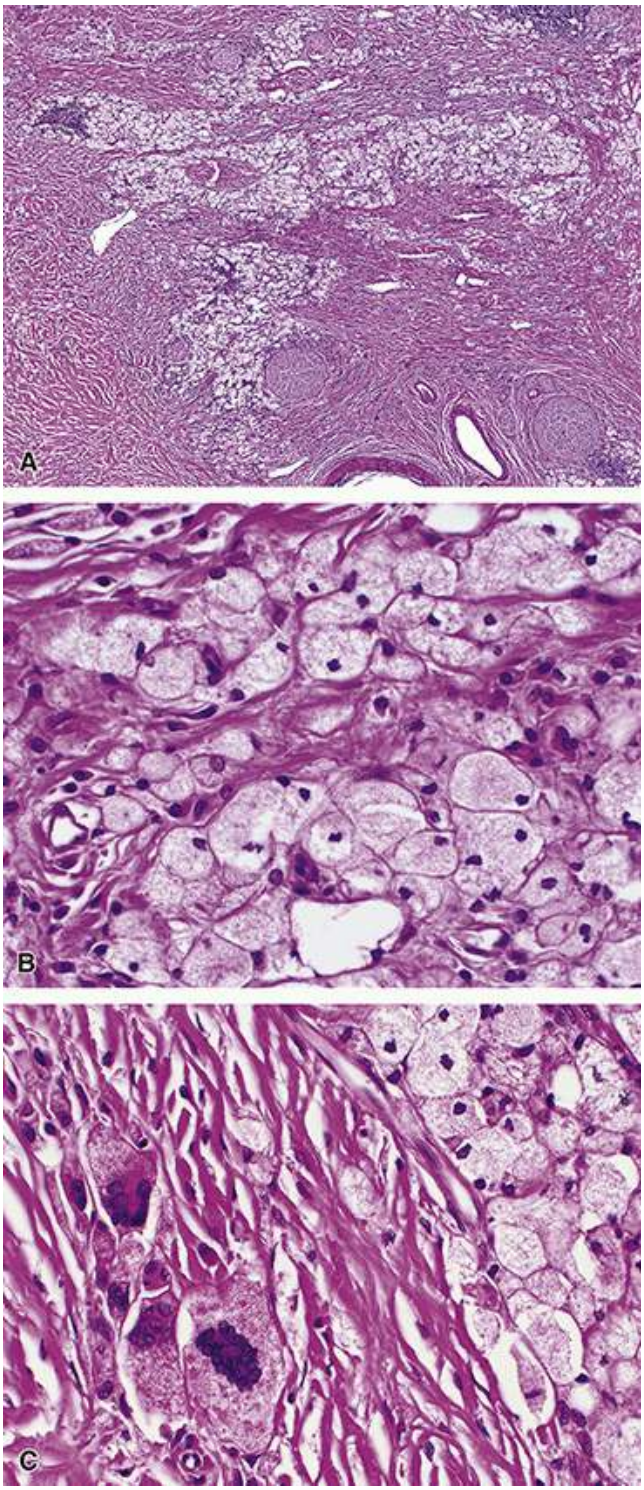

FIGURE 124.8 A, Orbital Erdheim-Chester disease showing islands of pale-staining foam cells separated by whorls of dense fibrosis. Several lymphoid aggregates are also evident. B, The foam cells are histologically similar to those in juvenile and adult xanthogranuloma and xanthelasma. C, High magnification showing Touton giant cells separated from foam cells by dense fibrous tissue.

Chapter 110 provides a detailed description of the histopathology of RDD. Briefly, cutaneous RDD has dermal or dermal and subcutaneous infiltration of large, S100+ histiocytes mixed with plasma cells, lymphocytes, and neutrophils.[101,102,103,104] Leukocytes within the cytoplasm of the histiocytes (emperipolesis[105]) is a constant feature of RDD, but it is less common in extranodal than nodal RDD.[6]

As can be seen from the above descriptions, there is a significant overlap in the histopathological features of the xanthogranulomatous processes affecting the periocular tissues. Diagnosis requires correlating clinical and histological features, and even then, a definitive diagnosis may not be possible for these rare lesions.

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CHAPTER 125

Xeroderma Pigmentosum

Key Points

- Xeroderma pigmentosum (XP) is an autosomal recessive hereditary disease
- It is a congenital sensitization of the skin to ultraviolet radiation, due to a defect in normal nucleotide excision and repair pathways involved in repairing the DNA damaged by ultraviolet radiation
- More than 90% of patients with XP may have nonmalignant ocular manifestations including photophobia, blepharospasm, conjunctivitis, corneal neovascularization, dry eye, keratitis and corneal scarring, ectropion due to skin atrophy, blepharitis, conjunctival melanosis, or cataracts
- The risk of developing cancer in these patients is extremely high, and malignant and premalignant conditions include conjunctival intraepithelial neoplasia, squamous cell carcinoma, basal cell carcinoma, malignant melanoma, or keratoacanthoma
- Neurologic manifestations are seen in approximately 25% of patients
- There is no cure for XP, although a complete and consistent UV radiation protection is paramount
- Localized ocular surface tumors can be treated by surgical excision with cryotherapy to the remaining conjunctival margins; however, diffuse lesions are more difficult to treat
- With early diagnosis, appropriate protection from sunlight, and timely surveillance and management of cutaneous and ocular complications, the prognosis is generally good

Xeroderma pigmentosum (XP) is a rare autosomal recessive disorder. The worldwide prevalence is variable, affecting one per million population in the United States, 2.3 per million in Western Europe, and 45 per million in Japan.[1,2,3] Higher frequencies have also been reported in North Africa and the Middle East.[1,2,4,5,6,7]

XP was first described in 1874 by Hebra and Kaposi[8] based on four patients having thin, parchment-like dry skin, with wrinkling of the epidermis, checkered pigmentation, dilatations of blood vessels, and skin contraction. They also mentioned a red, fissured tumor that had developed on the skin within 1 year. The disease was further defined in later reports where neurologic abnormalities were described in some patients.[9] In 1932, de Sanctis and Cacchione described three brothers from the same family with features of XP and mental deficiency, associated with dwarfism, gonadal hypoplasia, and progressive neurologic degeneration beginning at 2 years of age.[10]

As early as 1926, the disease was recognized as a congenital sensitization of the skin to ultraviolet (UV) radiation,[10,11] and subsequent investigations confirmed the role of UV radiation in its pathogenesis.[12] Cleaver[13] described defective DNA repair in cultured skin fibroblasts, and other studies showed that XP cells were not able to eliminate UV photoproducts or to repair areas of UV-damaged DNA.[14,15,16,17,18]

In 1971, a variant of XP was described with normal DNA repair mechanisms and normal UV sensitivity.[19,20,21,22,23] Patients with the XP variant (XPV) retain a normal nucleotide excision repair (NER) pathway but have a defect in *POLH,* which encodes the protein DNA polymerase *eta* required to replicate DNA containing unrepaired damage.[20] While mostly uncommon, XPV may comprise as much as 25% of the patients with XP in Japan.[6,24,25] Patients with XPV may have a clinical presentation distinct from those with NER-deficient XP and may display a delayed onset of symptoms and lack of neurologic findings, and show disease with variable severity.[6,24,26] Patients with XPV typically do not sunburn or present with severe sunlight sensitivity. They tend to be spared the neurologic findings seen in many NER-deficient patients,[6,24,26] and also often have a better prognosis and longer life expectancy.[24] There are reports of patients with XPV having their first skin cancer as early as 7 years of age[26] to as late as 71 years.[6] In one study, up to 40% of patients with XPV developed melanoma, and most had nonmelanoma skin cancers.[24,26]

There are eight XP complementation groups, corresponding to eight genes involved in the repair of UV-induced damage in DNA. The first seven genetic groups of XP (A through G) are related to defects of genes in the NER system that are required to remove UV damage from the DNA. The eighth genetic group, XP-variant, is related to an abnormality in transcription that is required to replicate DNA containing unrepaired damage. These genetic defects are responsible for the wide variability in clinical features both between and within XP groups.[27,28,29,30,31,32,33,34,35] Patients with XP from complementation groups C, E, and V (where TC-NER is preserved) have normal sunburn reactions and do not develop manifest neurodegeneration,[36] but they have an earlier age of onset of first skin cancer. However, patients with XP from complementation groups A, B, D, F, and G (where TC-NER is impaired) have severe and exaggerated sunburn reactions on minimal sun exposure and suffer neurodegeneration.[36]

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The diagnosis of XP is made largely on clinical presentation and manifestations. These include acute sunburn reaction from birth, early lentiginosis, or onset of skin cancers at a very young age[4] and can be confirmed by cellular tests for defective DNA repair.

Etiology and Pathogenesis

UV light is the most mutagenic component of sunlight.[37] Solar UV radiation is grouped into three ranges of wavelength: UVC (200-280 nm), UVB (280-320 nm), and UVA (320-400 nm) light.[38] UVB and UVA can pass through the Earth's ozone layer, and UVA contributes 95% of the total UV energy that reaches the surface.[39] Moreover, the wavelengths of UVA can penetrate more deeply into exposed skin, where they can initiate cell damage.[39,40,41]

UV-induced mutagenesis is characterized by a high frequency of transition mutations at dipyrimidine sequences containing cytosine,[42] resulting in dipyrimidine DNA photoproducts. In XP, unrepaired DNA segments lead to errors during replication, incorporating the wrong nucleotides in regions of UV damage. In addition, UVA photons induce photosensitization reactions that form reactive oxygen species that cause DNA damage,[43,44,45,46,47] by oxidation, single- and double-stranded breaks, and cross-links between DNA and proteins.[48,49,50]

UV-damaged DNA bases are repaired by the NER system. This involves two distinct pathways. The global genome repair (GG-NER) pathway recognizes damage in DNA that is not being transcribed and is capable of repairing photodimers in chromatin of different compaction levels and different functional states. The transcription-coupled repair (TC-NER) pathway recognizes when RNA polymerase stops in transcriptionally active genes and enables quick resumption of UV-inhibited transcription by efficient repair of the photodimers.[51] Mutations affecting individual components of these subpathways result in clinical syndromes. Defects in the GG-NER components (seen in XPC and XPE types) usually lead to pure XP with no neurologic abnormalities. Defects in TC-NER lead to XP with severe neurologic abnormalities.

The repair of UV-induced DNA damage involves several steps.[52] The UV-induced nucleic acid-based photoproducts serve as a substrate for DNA repair that is mediated by the transcription-coupled and global genome NER repair pathways.[51] These lead to unwinding of the DNA helix in the region of damage, excision of small fragments of the damaged genome, and repair by DNA synthesis pathways that involve DNA polymerase and ligases.

Clinical Characteristics

The clinical manifestations of XP are seen most commonly in sun-exposed areas of the skin and mucous membranes. Some patients show a relatively normal response to sun exposure, but about 60% have an exaggerated response to UV exposure with pronounced burning and blistering even with minimal exposure to sunlight. All affected patients develop freckle-like pigmentary changes in skin areas exposed to the sun and eventually develop poikiloderma, which consists of areas of hyperpigmentation and hypopigmentation, skin atrophy, and telangiectasias (Figure 125.1). This freckling pigmentation usually appears before the age of 2 years.

More than 90% of patients with XP may have ocular manifestations including photophobia and secondary blepharospasm, conjunctivitis (51%), corneal neovascularization (44%), dry eye (38%), keratitis and corneal scarring (26%), ectropion from atrophic skin (25%), blepharitis (23%), conjunctival melanosis (20%), and cataracts (14%).[1,53,54] Other findings may include pterygium, pinguecula, loss of lashes, Bowman layer breaks, ciliary body hamartoma, macular edema, chorioretinal adhesions, pigmentary retinal degeneration with pigment migration, cystoid degeneration, gliosis, drusen, and optic nerve atrophy.[53,55] In the iris, iritis, stromal atrophy, pigment abnormalities, and, rarely, melanoma have all been described.[56] The posterior ocular segment is protected from UV damage by the cornea and lens so that fundus abnormalities are not common. Nevertheless, choroidal melanoma can rarely develop.[57]

Malignant lesions are a common finding in patients with XP, but the reported frequencies of occurrence vary widely. Brooks et al reported ocular surface neoplasia in 10% of 87 patients with XP in the United States,[53] whereas Kaliki et al[58] found 72% of 120

patients with XP in India with ocular surface cancers. Nevertheless, the risk of developing cancer in these patients is extremely high. The mechanism of carcinogenesis appears to be the same in XP and the general population, but the age of onset of these tumors in patients with XP is in the first to second decades, compared with the sixth and seventh decades in the general population.

Compared with the general population, patients with XP under age 20 years have a 10,000-fold increase in the frequency of nonmelanoma skin cancer, a 2000-fold increase in melanomas, a 1000-fold increase in cancer of the sun-exposed tissues of the eye, and a 100,000-fold increase in tongue cancers.[59,60] About 80% of nonmelanoma cancers occur on the face, head, and neck.[59] In contrast, more than 45% of melanomas in patients with XP occur on the extremities. In the report by Kaliki et al,[58] among 120 patients with XP, 72% had conjunctival or corneal tumors of which squamous cell carcinoma was the most common (41%) and 44% were bilateral. Eyelid tumors were seen in 13% of patients, of which 50% were basal cell carcinomas and 7% were bilateral.

Intraepithelial neoplasia (CIN) is a premalignant lesion of the conjunctiva that is seen in patients with XP and may vary from mild to severe depending on the depth of conjunctival epithelial dysplasia.[1,61] Invasive cancers affecting the ocular surface and adnexa include squamous cell carcinoma, basal cell carcinoma, and malignant melanoma. Other less common skin tumors include keratoacanthoma and fibrosarcoma.[1] Angiosarcoma of the tongue has also been reported.[62] The median age for the first appearance of *(Print pagebreak 828)* skin cancer is 9 years (age range of 1-32 years) for nonmelanocytic skin cancer and 22 years for melanoma (age range 2-47 years).[60] Patients with XP also have a 50-fold increased risk of developing brain tumors, such as medulloblastoma, glioblastoma, spinal cord astrocytoma, and schwannoma.[52]

Neurologic manifestations are seen in approximately 25% of patients and do not occur in all XP types. It is most commonly associated with XPA, XPB, XPD, XPF, and XPG and rarely with XPC and XPE.[52,60,63] Defects include microcephaly, diminished or absent deep tendon reflexes, ataxia, cortical atrophy and ventricular dilatation, progressive sensorineural hearing loss, and progressive cognitive impairment.[60] DeSanctis-Cacchione syndrome is a rare form of XP characterized by severe neurologic disease with dwarfism and immature sexual development.

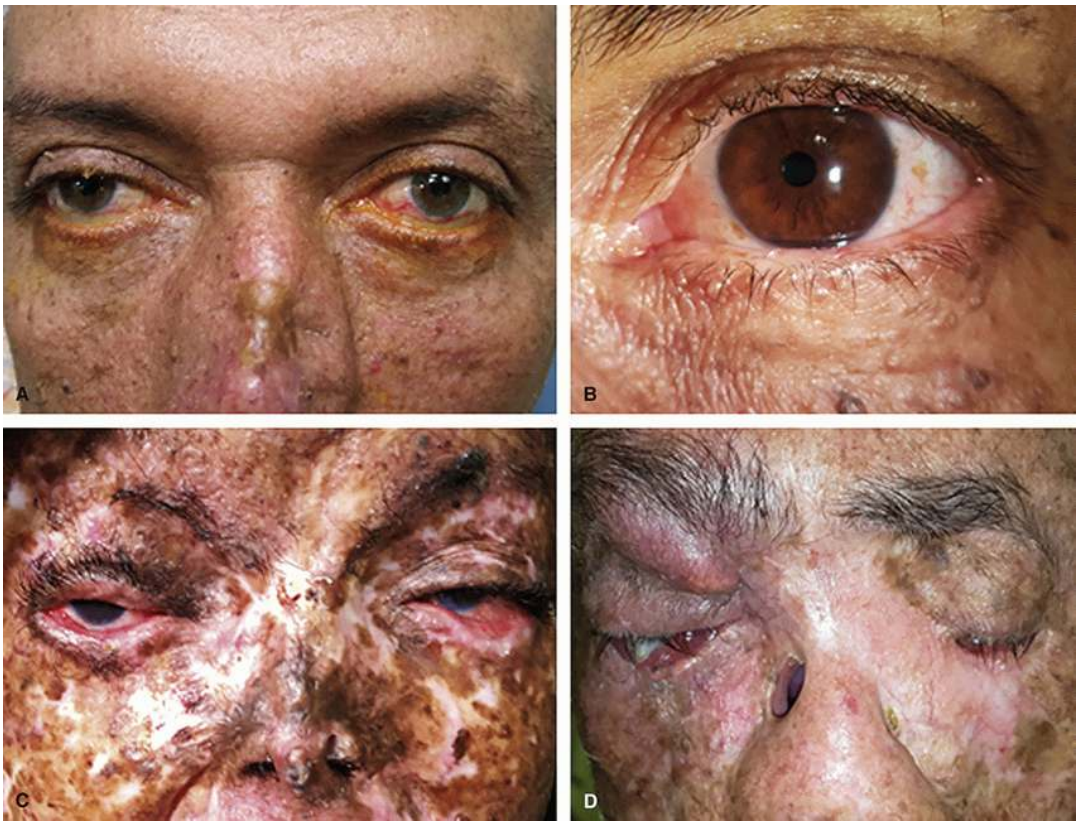

FIGURE 125.1 A-D, Xeroderma pigmentosum involving the eyelids and face. (Courtesy of Dr. Maria Claudia Schellini.)

Differential Diagnosis

The classic clinical features of XP distinguish it from other diseases that superficially can appear similar. These include other solar dermatoses such as solar urticarial and polymorphic light eruption.[4] Cockayne syndrome is a rare genetic disorder affecting children from birth to 1 year and is characterized by a prematurely aged face, growth disorders, intellectual deficits, and decreased vision and hearing, but it is not associated with pigmentary changes and results from different DNA repair defects. Rare genetic disorders with

lentiginous pigmentary changes include Peutz-Jeghers syndrome, a hereditary cancer syndrome with increased risk for a wide variety of malignancies most commonly gastrointestinal, and also gynecologic cancers in females and testicular cancer in males. Leopard syndrome is another rare genetic disorder characterized by multiple lentigines, cardiac conduction defects, growth retardation, and sensorineural deafness. Carney Complex is an autosomal dominant disorder with lentiginoses and multiple endocrine neoplasms. But in these disorders, the pigmentary abnormalities are not associated with UV exposure.

Common freckles may appear similar to the lentiginoses of XP, but their presence is limited to the face and does not extend to the neck, the dorsum of the hand, and the upper chest, and patients do not have photosensitivity.[64] *(Print pagebreak 829)* Dyschromatosis symmetrica hereditaria is an autosomal dominant disorder mainly affecting patients from East Asia, in whom skin areas develop mixed hyper- and hypopigmentation on the face, as well as the dorsum of the hands and feet. Several patients have also been described with mental deterioration. Erythropoietic protoporphyria is another autosomal dominant inherited disease characterized by loss of function of ferrochelatase, an enzyme of the heme biosynthesis process. Acute reactions such as edema, erythema, and blistering occur on the skin after sun exposure leaving a small scar.

Treatment

There is currently no cure for xeroderma pigmentosum. Complete and consistent UV radiation protection is of major importance in reducing the risk of severe sunburn and the occurrence of skin cancers. These include layered clothing, the use of sunscreen, and eye protection with UV-absorbing sunglasses and artificial tears.[65,66] Systemic retinoid treatment may also offer some benefit in reducing the number of skin cancers.[67] Early resection of premalignant and malignant lesions is important for survival.

Localized ocular surface tumors can be treated by surgical excision with cryotherapy to the remaining conjunctival margins.[68] Topical chemotherapy with 0.04% Mitomycin C has been used as monotherapy for treatment or as adjuvant therapy following surgical excision.[69] Diffuse lesions are more difficult to treat and are associated with a higher rate of recurrence.[70,71] Malignant limbal tumors have been removed with iridocyclectomy, and rare cases of extensive disease may require enucleation.[72] XP-associated neoplasia of the eyelids and ocular surface have been treated with subconjunctival injections of pegylated interferon-alpha 2b and topical mitomycin C with promising results.[73] Iris tumors have been managed with local excision, plaque radiotherapy, or enucleation.[74]

Premalignant skin lesions such as actinic keratosis can be treated by freezing with liquid nitrogen or topical applications of 5-fluorouracil. For malignant skin tumors, surgical extirpation with negative surgical margins is the appropriate standard, followed by eyelid reconstruction as needed. Patients should be encouraged to undergo regular skin surveys by a dermatologist every 3 to 6 months to examine for the presence of new premalignant or malignant neoplasms.

There is no useful therapy for the neurodegeneration seen in XP, and rehabilitation is offered for motor impairment and intellectual disabilities. Hearing loss often affects children of school age, so that hearing tests should be carried out at regular intervals and a hearing aid device prescribed early if indicated.

Because XP is a hereditary disease, genetic counseling should be given to all patients with XP and their parents. Genetic analysis can be conducted by polymerase chain reaction-restriction fragment length polymorphism for XPA, or by a sequence of all exons for other XP types.

Prognosis

Once the diagnosis of XP is made, the strict requirement for protection from sunlight and the limitations of going outdoors during the day often has a significant effect on the quality of life for both patients and their families. Patients with neurological symptoms experience a significant functional disability that may require lifelong rehabilitation and care. Patients can sometimes experience choking and dysphagia from vocal cord paralysis and larynx dystonia.

The frequent occurrence of skin cancers requires constant surveillance and treatment, often with surgery whenever indicated. Death from skin malignant tumors is not common because of the early diagnosis of XP in most cases, and in one large series of 120 patients from India followed over a mean of 61 months, only 2% developed regional lymph node involvement and 1% died from distant metastasis.[58]

With early diagnosis, appropriate protection from sunlight, and timely surveillance and management of cutaneous and ocular complications, the prognosis is generally good.

Histopathology

The nonneoplastic cutaneous histopathological manifestations of XP were characterized in the late 1800s and early 1900s.[75,76,77,78,79,80,81] Unna provided detailed histological findings from skin biopsies of two brothers with XP, although biopsies were not available for the initial stage of "erythrodermia."[75] During the second stage of the disease, manifest clinically as "small, brown, freckled pigmentation, with persistent roughness of the surface," Unna noted dense melanin pigmentation at angles of the rete pegs (ridges) and in small areas of the basal prickle cells elsewhere. In the least pigmented spots, melanin was present in basal cells with scattered intercellular streaks of melanin in the upper stratum spinosum (prickle cell layer) and smaller intercellular streaks in the stratum granulosum (granular cell layer) and stratum corneum (horny layer). The prickle cell layer was not widened overall, but the rete pegs were more numerous and broader than normal.[75] The granular cell layer was two to three rows thicker than normal, and the horny layer was "much thickened" with "distinct hyperkeratosis."[75] There was a diffuse widening of the papillary dermis by dilated veins having swollen endothelial cells.[75] Brayton noted a similar prominence of melanin accumulation in the lower layers of the rete pegs.[82]

Unna described the third or "acme" stage of XP as clinically having "white or mother-of-pearl spots" without pigment or blood vessels located between pigmented spots that have increased in number, size, and color.[75] Dilated veins *(Print pagebreak 830)* (telangiectasias) often surrounded the white spots.[75] Unna histologically noted increased thickening of the horny layer, further thickening of the granular cell layer in most areas, and deformation of the prickle cell layer with marked accumulation of melanin in the basal prickle cells. There was thinning of the prickle cell layer to only two to three cells at the sites of most abundant melanin. Areas of maximum epithelial pigmentary change had associated abnormalities in the papillary dermis and upper half of the "cutis": there was thickened papillary dermis having "active multiplication of the connective tissue cells, which are usually smaller, spherical, and show little protoplasm."[75] Melanin permeated the papillary dermis and cutis, both extracellularly and within the connective tissue cells, appearing as a black network.[75] Unna reported, "Several of the small, warty spots before me show a striking collection of cells and pigment in the papillary body and in the upper half of the cutis, so that these parts are three to four times thicker than the neighborhood, and the epidermis is arched over them."[75] Dilated lymphatics were within the pigmented cellular masses.[75] The white spots had broad prickle, granular, and horny layers without overall epidermal atrophy, and there was "almost complete" absence of dermal papillae with diminished capillaries.[75] The reticular dermis was sclerotic, resembling that in scleroderma. Pollitzer[77] and Councilman and Magrath[78] also noted sclerotic dermis. The telangiectasias observed clinically corresponded to dilated veins surrounding the areas of capillary loss,[75] as also recorded by Pollitzer.[77] Follicular and sebaceous gland atrophy were present only in areas of dermal sclerosis.[75,77]

Montgomery and Reuter examined the histopathological features in skin biopsies from a 32-year-old woman with a mild case of XP.[80] A pigmented macule had hyperkeratosis and marked atrophy of the prickle cell layer, especially over the dermal papillae, with areas of stratum corneum overlying a pigmented basal layer.[80] Rete pegs featured marked irregular proliferation of pigmented basal cells with extension deep into the dermis.[80] The papillary dermis contained "many large chromatophores" (presumably melanophages) and melanin-laden fibroblasts.[80] Epidermis adjacent to the macule had hyperkeratosis, mild intracellular edema of the basal and prickle cells, normal stratum granulosum, and normal melanin pigmentation.[80] The authors opined that the diagnostic histopathologic features of XP are a "relative and absolute hyperkeratosis; a varying degree of atrophy of the prickle cell layer, especially over the papillary bodies; irregular proliferation and prolongation of the rete ridges; intracellular edema of the cells of the epidermis, with pyknosis or karyorrhexis resulting therefrom; edema of the papillary bodies and upper part of the cutis, with resultant narrowing of the rete ridges; some dilation of the superficial vessels; a varying degree of perivascular infiltrate; a spotted melanin pigmentation of the epidermis, and in the upper part of the cutis, chromatophores laden with pigment."[80] Lynch observed similar changes in the skin from a 7-year-old child with XP and that parakeratosis occurred 24 hours after exposure to radiation.[81]

Malignant tumors in patients with XP do not differ from those in people not afflicted with the disease (Figure 125.2),[75,76,77,78,80,81,83,84,85,86] and the reader is referred to other chapters for a description of those lesions.

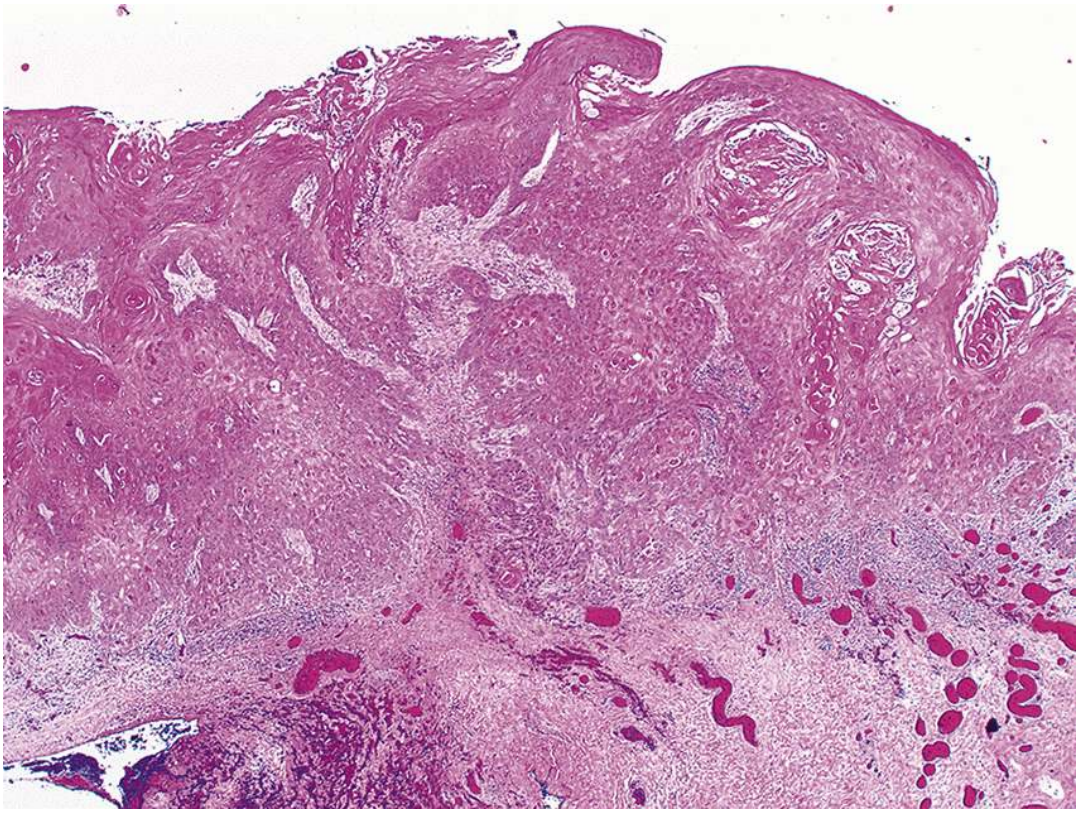

FIGURE 125.2 Invasive squamous cell carcinoma of the conjunctiva in a child with XP. The tumor is histologically the same as invasive squamous cell carcinoma of the conjunctiva in individuals without XP. (Photomicrograph prepared from a histological slide distributed by Dr. Fausto Rodriguez at the 2012 meeting of the Eastern Ophthalmic Pathology Society.)

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CHAPTER 126

Adenoid Cystic Carcinoma

Key Points

- Adenoid cystic carcinoma (ACC) is an epithelial tumor that occurs primarily in the major salivary and lacrimal glands, and the skin can be involved secondarily through direct or perineural invasion or as a site of distant metastasis
- Primary cutaneous adenoid cystic carcinoma (PCACC) is a rare form mostly seen on the scalp and chest
- Eyelid PCACC has a propensity for middle-aged to elderly males and occurs equally in the upper and lower eyelids
- PCACC can arise from accessory glands in the conjunctiva and cutaneous accessory lacrimal glands of Krauss and Wolfring
- It has a predilection for older individuals, is slow growing, usually over months to years, and is locally aggressive with a tendency for perineural invasion
- Perineural invasion is found in more than 60% of cases
- The recommended treatment for PCACC is wide local excision with tumor-free margins established on permanent histologic sections
- Local recurrence is seen in up to 59%, and metastases in 17% of cases

Adenoid cystic carcinoma (ACC) is an epithelial tumor that occurs primarily in the major salivary and lacrimal glands. It is also seen rarely in other sites including the esophagus, bronchus, lungs, breast, vulva, cervix, and prostate.[1,2,3,4,5,6] The skin can be involved secondarily through direct or perineural invasion or as a site of distant metastasis.[7] A rare form of primary cutaneous adenoid cystic carcinoma (PCACC) was first described in 1975 by Boggio,[8,9] and since then just over 100 cases have been reported in the literature,[10,11,12] where it most often arises on the scalp in 40% and the chest in 18% of cases.[13] To date only about 12 cases involving the eyelid have been reported.[14,15,16] Eyelid PCACC has a propensity for middle-aged to elderly males and occurs equally in the upper and lower eyelids. An epidemiologic study using the Surveillance, Epidemiology, and End Results (SEER) program found 152 cases of PCACC diagnosed in the United States between 1976 and 2005, with an annual incidence of 0.23 cases per 1,000,000 population.[17]

Etiology and Pathogenesis

PCACC can arise from accessory glands in the conjunctiva and cutaneous accessory lacrimal glands of Krauss and Wolfring.[11] It is usually considered to originate from eccrine glands, but this tumor can occur in the ear canal, where there are no eccrine glands.[18] Some pathologic data indicate a more likely apocrine origin.[19]

Stenman et al described a t(6;9)(q22-23;p23-24) *MYB-NFIB* translocation in salivary gland and breast ACCs.[20,21,22] Additional studies showed that this chromosomal aberration in ACCs arises from other gland-bearing tissues, including the skin.[23] This translocation results in a fusion of the two transcription factor genes *MYB* and *NFIB* with activation of *MYB*. The *MYB* gene is amplified in carcinomas of the esophagus, colon, and breast, and North et al described the *MYB-NFIB* fusion product in 9 of 10 PCACC tumors.[23]

Clinical Presentation

PCACC preferentially affects older individuals with a median age of 60 years and a range from teens to old age. It is slow growing, usually over months to years, and is locally aggressive with a tendency for perineural invasion. They present as asymptomatic, flesh-colored, nontender, firm, indurated, and well-circumscribed nodules, often associated with madarosis (Figure 126.1). They may be

associated with eyelid edema, ectropion, or ptosis. Eyelid cases involve males more frequently than females, with an equal distribution between upper and lower eyelids, and range in diameter from 3 to 25 mm. The mean duration between the onset of disease and the final diagnosis is about 10 years.[12] Most reported cases were initially misdiagnosed as a chalazion, and the diagnosis of PCACC was established only on histopathology.[1,24,25]

PCACC is known to be locally aggressive and prone to metastasis. However, sentinel lymph node involvement may or may not be found on initial examination.[1,2] Perineural invasion (PNI) has been reported in more than 60% of cases, and recurrence after excision due to PNI has been observed in up to 59% of cases.[1,12,26]

Differential Diagnosis

Primary cutaneous adenoid cystic carcinoma of the eyelid most commonly mimics a chalazion. It may also simulate other benign lesions including syringoma, cylindroma, *(Print pagebreak 836)* apocrine cystadenoma, clear cell hidradenoma, and spiradenoma. It is also sometimes confused with other malignant tumors such as sebaceous carcinoma, adenoid basal cell carcinoma, other sweat gland tumors such as adenocarcinoma of Moll glands, polymorphous sweat gland carcinoma, and apocrine cribriform carcinoma.[16,27,28,29,30]

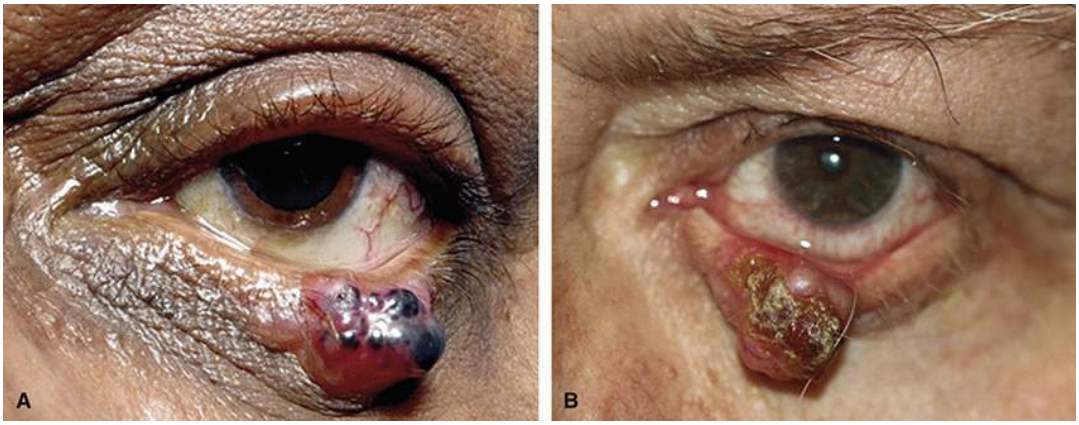

FIGURE 126.1 A and B, Indurated, nodular adenoid cystic carcinoma of the lower eyelids with madarosis.

Treatment

The recommended treatment for PCACC is wide local excision with tumor-free margins established on permanent histologic sections. Mohs surgery is felt to have greater sensitivity in the detection of PNI.[13,26,31,32,33] For tumors that exhibit PNI, Mohs surgery has been shown to result in lower rates of recurrence.[3,34]

Data are limited with regard to adjuvant radiotherapy, but some authors have advocated this modality to reduce local recurrence. When PNI is encountered in the surgical specimen, postoperative radiation therapy may be indicated to decrease the risk of local recurrence.[35] Radiation therapy in the periocular region must be carefully planned because of the risk of ocular damage. The total dose of radiation for PNI is usually in the range of 50 to 60 Gy.[25] Chemotherapy and radiotherapy remain the recommended therapeutic options in cases where total removal is not possible.[1,26]

Prognosis

Local recurrence is seen in up to 59%, and metastases in 17% of cases.[36] Both often appear many months or even decades after the initial surgery. Thus, long-term follow-up is warranted and should be performed in these patients.

PNI is found in more than 60% of cases[2,26,36] and is an important mode of tumor spread resulting in the high reported local recurrence rates. The interval from surgical excision to recurrence ranges from 4 months to 40 years.[26] Cases with multiple recurrences after standard local excision have also been reported.[26] Regional lymph node metastasis from primary cutaneous ACC can occur.[2,37,38,39,40] Distant metastasis represents a rare and late event primarily to the lungs, and less commonly to the liver and brain.[4,41,42,43]

Histopathology

PCACCs are poorly demarcated infiltrative tumors of the dermis and/or subcutaneous tissue (Figure 126.2A) with a predilection for PNI.[44,45,46] Basaloid tumor cells form cribriform, tubular, and solid patterns of varying shapes and sizes (Figure 126.2B-D), identical to those in salivary gland and lacrimal gland ACCs (Figure 126.3A and B).[44] The individual tumor cells are small to medium sized with scanty cytoplasm, hyperchromatic to vesicular nuclei, and variably sized nucleoli.[44] Mitotic activity is low, and tumor necrosis is rare.[45,46] Bilayered ducts and pseudocysts are the diagnostic features of PCACCs.[46] Pseudocysts contain lightly basophilic to lightly eosinophilic mucin (Figure 126.2C) that can be highlighted using alcian blue stain at pH2.5.[36,46] Most PCACCs are histologic grade 1 of 3, with grade 1 tumors having no solid areas, bland cytology, and few or no mitoses; grade 2 tumors having <30% solid area, more cytological atypia than grade 1; and grade 3 tumors having >30% solid areas, necrosis may be present, cellular atypia is increased, and mitoses are present.[36] The stroma is most often paucicellular and hyalinized, but it may have myoid change or fibrosis. Pathological staging of eyelid PCACC is similar to that of other eyelid malignant neoplasms.[47]

The immunohistochemical profile of PCACCs is the same as that of ACCs arising in the salivary and lacrimal glands.[44] Tumor cells stain positively for cytokeratins AE1/AE3, cytokeratin (CK) 7, and using CAM5.2 antibodies against CK8,[48] while staining for CK5/6 and podoplanin (D2-40) is variable.[44,45,46] If true ducts are present, the luminal cells express epithelial membrane antigen, carcinoembryonic antigen, and CK15, and myoepithelial cells stain for smooth muscle *(Print pagebreak 837) (Print pagebreak 838)* actin, p63, and calponin.[46] SOX10 is expressed in the nuclei of both basaloid and myoepithelial cells. Tumors diffusely stain for CD117, and most tumors express MYB.[46] Eyelid PCACC cannot be differentiated histologically from metastasis of a visceral ACC or direct extension from a lacrimal gland ACC (Figure 126.3A and B), which rely on clinical correlation. Primary cutaneous malignancies that require differentiation from PCACC are adenoid basal cell carcinoma and cribriform carcinoma. Adenoid basal cell carcinomas have peripheral palisading of tumor cells, lack true ducts, have at least focal areas of conventional basal cell carcinoma, and exhibit stromal cleft (retraction) artifact.[44,46] Cribriform carcinoma, also known as cribriform apocrine carcinoma, has more eosinophilic tumor cells; lacks myoepithelial cells, mucinous pseudocysts, and an infiltrative growth pattern; has focal solid areas; and exhibits thin, thread-like, intraluminal bridges.[44,46] Spirademonas may occasionally have areas resembling ACC but can be distinguished from PCACC by areas of typical spiradenoma with a dual cell population and lack of cytological atypia, mitoses, and PNI.[44]

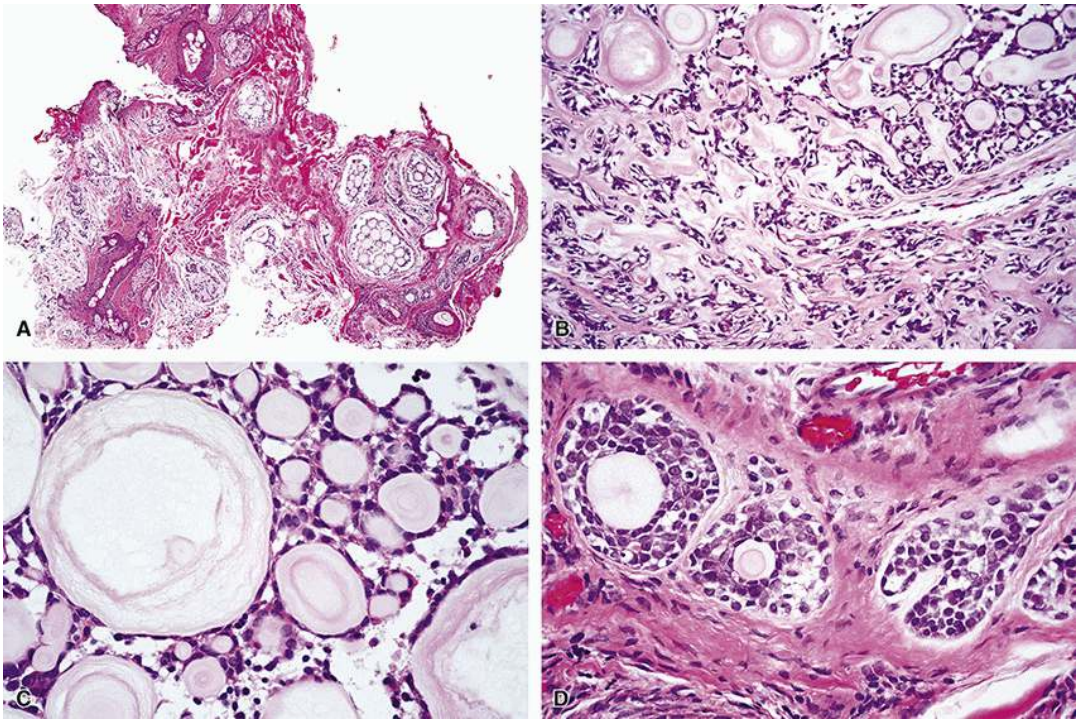

FIGURE 126.2 This adenoid cystic carcinoma arose in the left upper eyelid of a man in his mid-30s. A, Tumor infiltrated the dermis and orbicularis oculi. B, The tumor cells formed tubules (bottom of image) or a cribriform pattern with pseudocysts containing lightly eosinophilic mucin. C, Higher magnification showing tumor cells with hyperchromatic nuclei and scant eosinophilic cytoplasm having a cribriform pattern with pseudocysts. D, In another area of the tumor (bottom right of Figure 126.2A), the tumor cells are multilayered and form pseudocysts or solid islands. (Photomicrographs were prepared from a slide distributed by Dr. Ahmed Hidayat at the 1994 meeting of the Eastern Ophthalmic Pathology Society.)

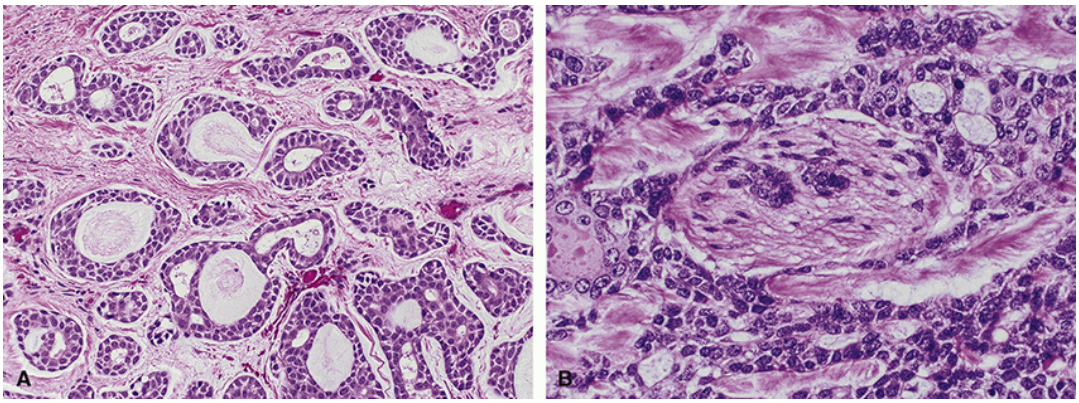

FIGURE 126.3 A, This lacrimal gland adenoid cystic carcinoma infiltrated adjacent connective tissues and surrounded and infiltrated a nerve (B) located in the center of this photomicrograph.

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CHAPTER 127

Angiosarcoma

Key Points

- Angiosarcoma is a rare aggressive malignant tumor of vascular origin
- About 62% occur in the head and neck region, more common in men in the 6th to 8th decades
- The pathogenesis is poorly understood, and the tumor may originate from vascular or lymphatic endothelium
- It usually presents as single or multiple benign-appearing bruise-like macules or nodules, often associated with erythema, chronic edema, or cellulitis
- They are often misdiagnosed as more common lesions such as basal cell carcinoma or pyogenic granuloma
- The role of surgery alone as initial treatment has decreased to less than 20%, over the past several decades, and positive margins are common even after wide resection
- Radiotherapy combined with surgery offers the best chance for long-term tumor control
- The ultimate prognosis remains poor with a mean 5-year survival of 33.5%

Angiosarcoma is a rare, aggressive malignant tumor of vascular origin that may originate anywhere in the body. It represents 1 in 10,000 cases of malignant neoplasms and accounts for 1% to 2% of all soft tissue sarcomas. About 62% occur in the head and neck region most often in men over the age of 55 years,[1,2,3] with a mean age at presentation of 71 years.[4] The eyelids are affected less often,[5,6,7] and orbital involvement is very rare.[8]

Etiology and Pathogenesis

The pathogenesis of angiosarcoma is poorly understood. The tumor may originate from vascular or lymphatic endothelium or both.[9] In most cases, it develops de novo without predisposing conditions, although its predilection for sundamaged skin of the head and neck suggests a role for solar damage.[5] It has been reported to develop 5 to 10 years following radiation therapy for preexisting lesions,[10,11,12] at sites of chronic lymphedema in Stewart-Treves syndrome,[8,13] and after exposure to some imaging contrast agents and insecticides.[4,8,14] Four cases of angiosarcoma arising from malignant transformation of benign/vascular malformations have been described.[15] Angiosarcoma has also been associated with xeroderma pigmentosum in six reported cases, possibly related to the nucleotide excision repair defect resulting in defective repair of DNA damaged by ultraviolet and ionizing radiations.[16,17,18,19] Since angiosarcomas are endothelial-cell tumors, it has been suggested that angiogenic factors might be associated with their pathogenesis, which could allow for novel targeted treatment. VEGF and its receptors are overexpressed in angiosarcomas at higher concentrations than in benign vascular or normal tissue controls.[20]

The cytogenetics of angiosarcomas shows a wide range of nonspecific chromosomal abnormalities including trisomy 5; deletions on chromosome 7p; abnormalities on chromosomes 8, 20, and 22; and loss of chromosome Y.[20] No consistent genetic abnormalities are found in cutaneous angiosarcoma, but some cases have mutations in *TP53*, *PTPRB, PLCG1, CDKN2A,* or *MYC*. *NUP160-SLC43A3* gene fusion occurs in 36% of cases.[21]

Clinical Presentation

Angiosarcomas usually present as single or multiple benign-appearing bruise-like macules or nodules, often associated with erythema, chronic edema, cellulitis, or even as a hematoma.[22,23,24,25,26] Occasionally, they may appear as rosacea-like lesions and can simulate localized bacterial or fungal infections.[27] When on the eyelid, they may be violaceous, yellow, or flesh colored; may bleed intermittently; and occasionally are associated with pain (Figure 127.1). Demirci and Christanson[28] reviewed 22 published

cases of eyelid angiosarcoma and noted that 38% presented as an erythematous nodule, 25% as a violaceous maculopapular lesion, 13% as a yellow plaque or infiltrative lesion, and 13% as a yellow nodule. Tumors may be more extensive into deeper tissues, beneath a relatively less conspicuous surface lesion.[29]

When more advanced, angiosarcomas can become very large, elevated, and even ulcerated (Figure 127.2).[30] Because of their variable appearance, definitive diagnosis is often delayed up to 18 months.[29] They are often misdiagnosed as more common lesions such as basal cell carcinoma or pyogenic granuloma.[4] They characteristically spread widely through the skin and soft tissue of the head and neck region, and eyelid tumors may extend into the orbit in about 4% of cases.[29,31]

Differential Diagnosis

The differential diagnosis includes ecchymosis, hemangioma, Kaposi sarcoma, xanthelasma, contact dermatitis, lupus-related lesions, intravascular papillary endothelial hyperplasia, angiolymphoid hyperplasia with eosinophilia, and focal infections.

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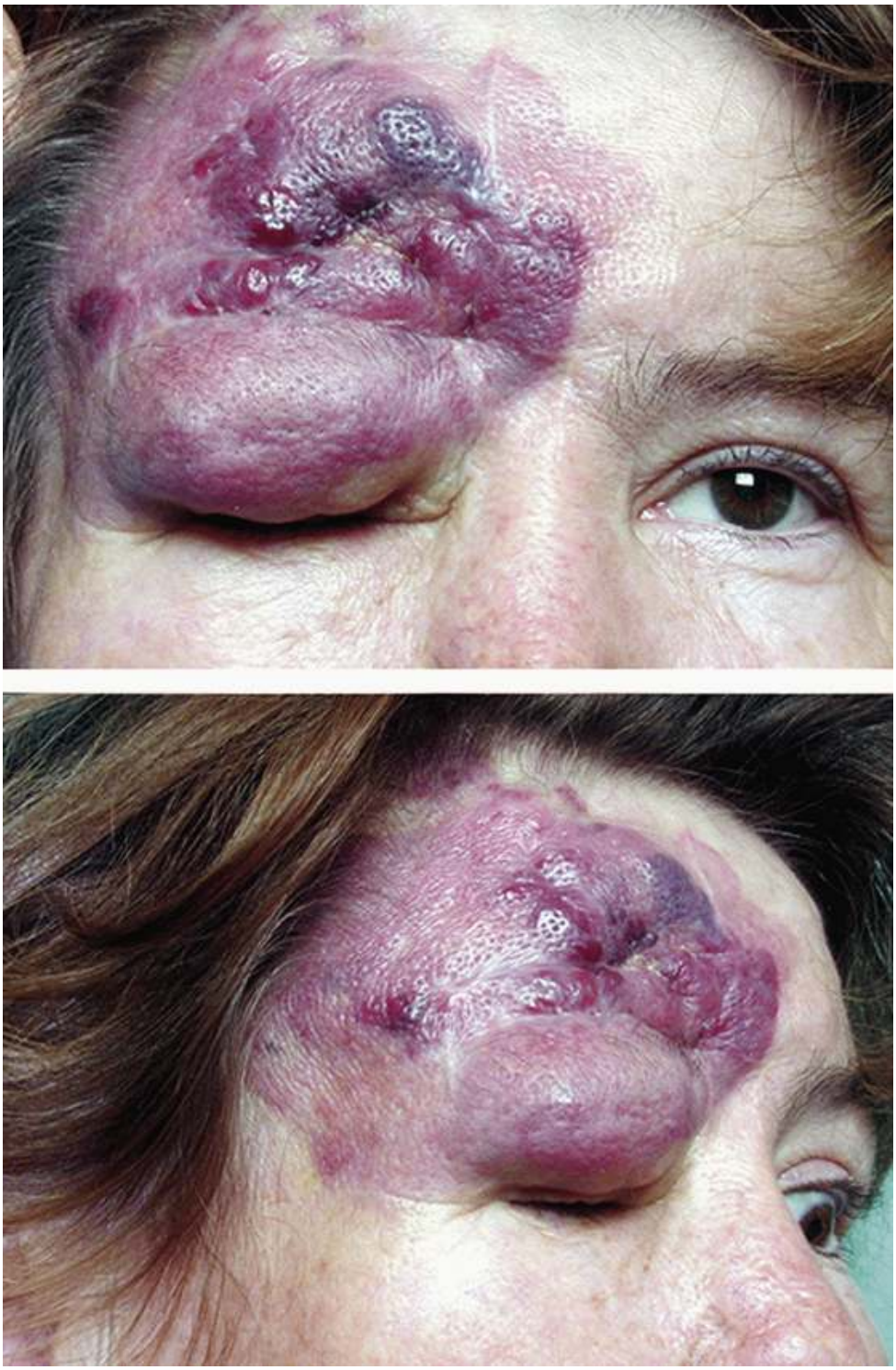

FIGURE 127.1 Extensive angiosarcoma of the forehead and upper eyelid. (Courtesy of Dr. Robert Goldberg.)

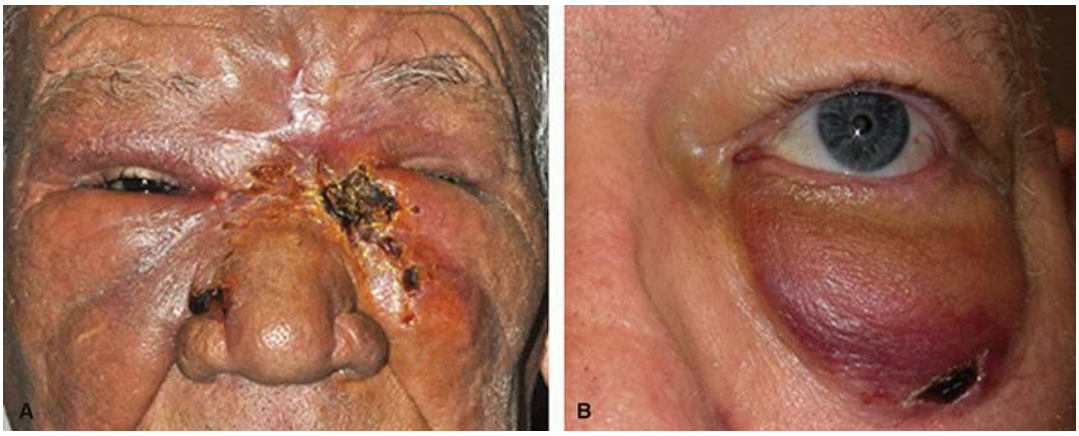

FIGURE 127.2 A, Tumor of the nasal bridge, left lower eyelid, and cheek. B, Angiosarcoma in the lower eyelid with hemorrhage and ulceration. A, (Courtesy of Dr. Antonio Augusto Cruz.) B, (Courtesy of Dr. Philip Custer.)

Treatment

The treatment of angiosarcoma remains without any accepted standard guidelines. Local surgical excision was the mainstay of therapy several decades ago. However, the role of surgery as the initial treatment modality has decreased significantly over the past 30 to 40 years, from 80% to less than 20%.[32] It is common to see positive microscopic margins even after wide surgical resection. Pawlik et al[33] reported that, among 18 patients with a clinical estimate of tumor size <5 cm (stage T1), 11 (38%) were >5 cm (stage T2) after histopathologic evaluation of margins. Also, when the eyelids and especially the medial canthus are involved, complete surgical removal may not be possible. As a result, surgery is now usually combined with electron-beam radiotherapy.[33]

Angiosarcomas have been treated with wide-field radiotherapy at doses >50 Gy. Although radiation therapy alone is generally thought to be an inadequate treatment for curative intent, Ogawa et al[34] reported that, among 25 patients who received radiation monotherapy alone, 79% who received >70 Gy achieved local control, whereas only 27% who received <70 Gy achieved similar control. A study by Scott et al[35] of 41 patients treated with radiation therapy recommended at least 60 to 65 Gy for the postoperative tumor bed after surgery and 70 to 75 Gy for patients who receive radiation monotherapy. However, current opinion is that radiotherapy combined with surgery offers the best chance for long-term tumor control.[36] Mark et al[4] reported better survival after 32 months when surgery was combined with radiotherapy, compared with surgery without radiotherapy. In difficult cases where complete surgical excision is not possible, radiotherapy alone may be the only reasonable alternative, but this usually results in only a partial response.

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The role of chemotherapy remains undefined. While it has been shown in some studies to improve local tumor control,[32] chemotherapy does not appear to change overall survival.[32,37,38,39] Chemoradiation is a newer option employing chemotherapy with taxanes combined with radiotherapy without surgery. This has been reported to achieve a 5-year survival of 56% compared with 8% for conventional surgery and radiotherapy.[40]

Eyelid angiosarcoma has been treated with intravenous recombinant interleukin-2 (rIL-2) into the external carotid or facial arteries and intralesionally through a catheter-port system into the lesion.[41] IL-2 is an activator of lymphokine-activated killer T cells that damage vascular endothelial cells causing lysis. Angiosarcoma cells have been shown to be sensitive to lymphokine-activated killer cells in a mouse model.[42] IL-2 has been reported to be effective either as monotherapy in cases of recurrent tumor or in combination with radiotherapy or chemotherapy.[43,44]

Cutaneous angiosarcomas show high levels of PD-L1 expression, making them potential candidates for targeted immune checkpoint inhibitor therapy.[45] Emerging data suggests that immune checkpoint blockade may be efficacious against some types of angiosarcomas, especially head and neck cutaneous tumors. In one study of 35 patients with a histologically confirmed angiosarcoma treated with immune checkpoint blockade, a durable clinical benefit, defined as a progression-free survival (PFS) of ≥16 weeks, was seen in 13/35 (37%).[46] Analysis showed that responsive tumors were more likely to be on the head and neck, and to have a higher tumor mutational burden, greater upregulation of angiogenesis, inflammatory response, and KRAS signaling pathways, as well as higher levels of cytotoxic T cells, dendritic cells, and natural killer cells.

Prognosis

Despite various available treatment options, long-term survival with angiosarcoma remains poor.[47] In a meta-analysis of prognostic factors, Shin et al[47] evaluated 10 studies with a total of 379 patients and found a mean 5-year survival of 33.5% (11.1% to 53.8%), with major negative risk factors being age >70 years, tumor size >5 cm, tumor site, and resection margin status. In a Surveillance, Epidemiology, and End Results Program (SEER) analysis of 1250 patients with primary head and neck angiosarcomas, of which 93.5% were cutaneous, the overall and disease-specific 5-year survivals were 26.5% and 48.3%, respectively.[47] Older age, increased tumor size, and the presence of distant disease were independent predictors of poor overall survival, while lower histologic grade and surgery did not improve survival when other risk factors were controlled.[47]

The results of wide-margin surgery alone have not been favorable for survival, with reported recurrence rates of 26% to 100%, the higher percentages possibly due to more advanced staging at the time of treatment.[48,49] Multifocal lesions with skip lesions require wide surgical margins of 3 to 5 cm, and because of the often delayed diagnosis, subclinical metastases may be fairly common. Tumor spread is by hematogenous dissemination and is often present at the time of diagnosis. Metastases to the cervical lymph nodes, lung, liver, and bone occur in approximately one-third of patients.[50,51] The overall prognosis for life is relatively poor, with reported 5-year survival rates of 9% to 54%.[52,53] Eyelid tumors may have a lower metastatic potential and a somewhat better prognosis.[31]

Positive prognostic factors include early detection, small size <5 cm, negative surgical margins, absence of metastases, and the presence of inflammatory infiltrate.[4,54,55,56,57]

Histopathology

The appearance of cutaneous angiosarcomas varies widely, depending mostly on the degree of differentiation.[30,58,59,60,61] Tumors are usually graded from I to IV with grade I being well differentiated, II moderately differentiated, III poorly differentiated, and IV undifferentiated.[57] However, differentiation is not a component of tumor staging since all cutaneous angiosarcomas are considered aggressive tumors.[58,62] Angiosarcomas isolated to the eyelid, which is much less common than those involving the eyelid and other structures, tend to be well differentiated.[31]

Well-differentiated cutaneous angiosarcomas feature anastomosing dilated vascular channels with inconspicuous endothelial cells (Figure 127.3A). Well-differentiated tumors are distinguished from hemangiomas by their architecture, with dissection through dermal collagen, fascia, and subcutaneous adipose tissue, along with isolation of adnexal structures in a network of vessels. Papalas and coworkers found that neoplastic blood vessels surrounding adnexal structures were a helpful clue in diagnosing well-differentiated angiosarcomas of the eyelid.[31] Moderately differentiated angiosarcomas have more irregular anastomosing vascular channels with more prominent and cytologically atypical endothelial cells (Figure 127.3B). Poorly differentiated tumors have sheets of pleomorphic mitotically active cells with poorly defined vascular channels (Figure 127.3C). Immunohistochemical stains using antibodies to CD31 (Figure 127.3D) and ERG (erythroblast transformation-specific transcription factor) are particularly useful for confirming the diagnosis of poorly differentiated or undifferentiated angiosarcomas,[61,63] although staining for ERG is less specific than that for CD31.[64] Immunohistochemistry is also useful in diagnosing other variants such as epithelioid, clear cell, foam cell, signet ring, and granular cell angiosarcomas. It is critical to remember, however, that none of the immunostains are specific for angiosarcomas.[61] Positive immunohistochemical staining using antibodies to CAMTA1 or demonstration of *WWTR1-CAMTA1* gene fusion is found in 85% to 90% of epithelioid hemangioendotheliomas, a tumor that is less aggressive and more sensitive to chemotherapy than angiosarcoma.[65]

The differential diagnosis of cutaneous angiosarcoma is broad, depends on the degree of differentiation and tumor *(Print pagebreak 843)* variant, and was reviewed in an excellent update by Shustef and colleagues.[61] Milman et al reported a well-differentiated angiosarcoma of the eyelid mimicking a hobnail hemangioendothelioma, emphasizing the challenge in diagnosing some well-differentiated tumors.[66]

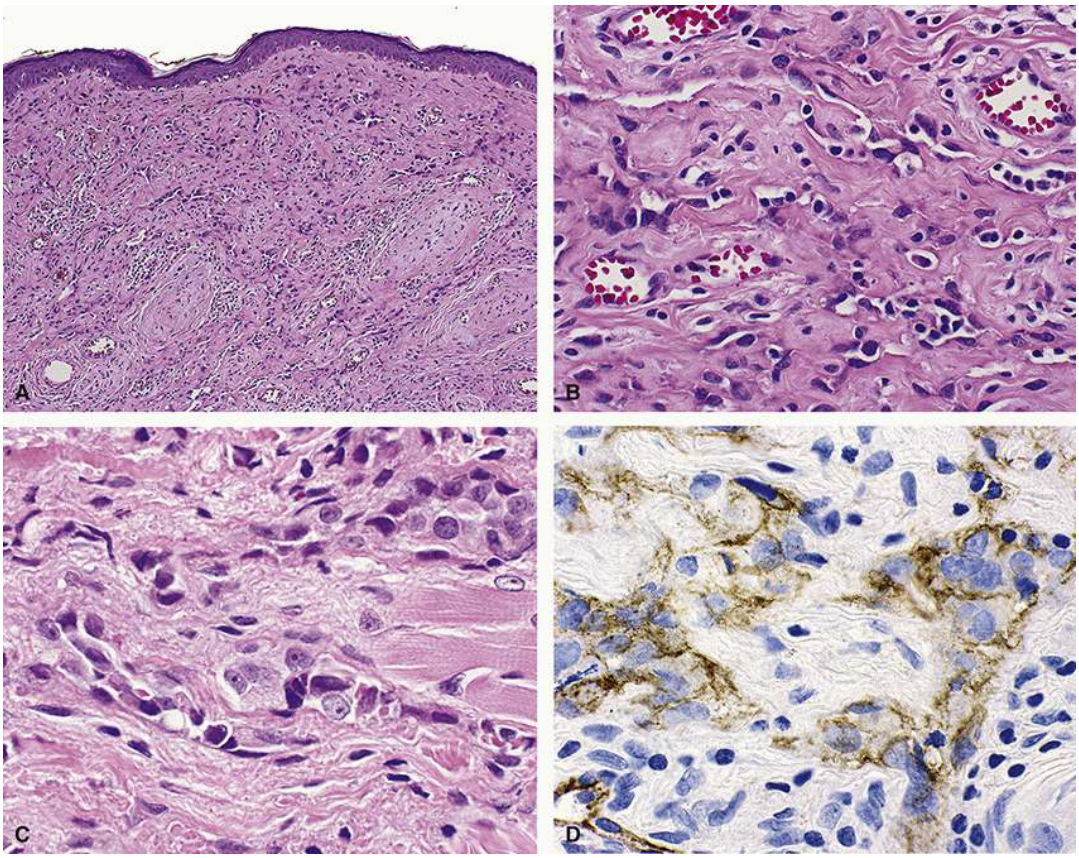

FIGURE 127.3 This angiosarcoma arose in the left lower eyelid of a woman in her middle 50s. There were multiple tumor recurrences, followed by tumor metastatic to cervical lymph nodes. A, Irregular vascular channels, some lined with plump endothelial cells, dissect through the eyelid dermis (hematoxylin and eosin). B, Plump, pleomorphic endothelial cells are evident at higher magnification. Some of the endothelial cells line slit-like spaces, while others line spaces containing erythrocytes (hematoxylin and eosin). C, Vascular channels are hard to identify in poorly differentiated angiosarcoma. D, Immunohistochemical staining using antibodies to CD31 is useful for confirming a diagnosis of angiosarcoma, especially in poorly differentiated tumors. (D, Reprinted with permission from Dutton JJ, Gayre GS, Proia AD. Diagnostic atlas of common eyelid diseases. *Inform Healthcare*; 2007.)

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CHAPTER 128

Basal Cell Carcinoma

Key Points

- Basal cell carcinoma (BCC) is the most common malignant neoplasm of the skin, and in the eyelids it accounts for about 80% to 85% of all malignant cutaneous tumors
- It occurs more commonly in fair-skinned adults, with a peak incidence between the 5th to the 8th decades of life
- Ultraviolet sunlight exposure-driven mutagenesis is believed to be the major risk factor for BCC causing inappropriate activation of the hedgehog signaling pathway
- Nodular BCC presents as an indolent, firm, indurated, elevated lesion with smooth rolled, pearly, shiny borders, and fine telangiectasias are seen around the borders
- The morpheaform or sclerosing subtype is more aggressive and presents as an infiltrative, locally destructive lesion with ill-defined margins
- Treatment is primarily with wide surgical excision with clear margins
- Targeted inhibition of the sonic hedgehog pathway now offers a promising treatment option in selected patients
- The prognosis depends upon the histologic type, anatomic location, and the size of the lesion
- Metastatic potential is reported but is very low

Basal cell carcinoma (BCC) was first mentioned in the literature by Arthur Jacob in 1827 and referred to as “ulcus rodens.”[1] The tumor was clinically described later as a malignant, locally invasive, destructive cancer by Krompecher in 1900.[2]

BCC is the most common malignant neoplasm of the skin, and in the eyelids, it accounts for about 80% to 85% of all malignant cutaneous tumors. It arises from keratinocyte precursor cells of the interfollicular epithelium where it undergoes mutagenesis.[3,4] Basal cell carcinoma occurs more commonly in fair-skinned adults, with a peak incidence between the 5th to the 8th decades of life. The incidence has been increasing in the United States, Europe, and Australia.[5,6,7,8] In 1996, it was estimated that more than two million individuals were affected annually in the United States, with a lifetime risk of at least 20% to 30%.[9] In 2012, the age-adjusted rate of treatment procedures for BCC in the United States was 3280 per 100,000 Medicare beneficiaries.[5] BCC can be seen in younger individuals, particularly those who have predisposing genetic syndromes. However, tumors have been described in healthy young individuals with no predisposing factors. While this is a true malignant tumor, it only rarely metastasizes to distant sites. When neglected, periorbital BCC can be very destructive locally and can invade adjacent structures such as the orbit and paranasal sinuses.

Etiology and Pathogenesis

Ultraviolet sunlight exposure-driven mutagenesis is believed to be the major risk factor for BCC. Sporadic BCCs arise from long-term resident keratinocyte progenitor cells of the interfollicular epidermis and upper infundibulum that undergo mutagenesis, mostly ultraviolet (UV) induced.[3,10] Most cases of BCC are UV exposure-induced and 76% have UV signature mutations.[11] Daylight UV induces a characteristic UV-specific DNA mutation occurring preferentially at methyl-CpG sites, seen after exposure to both UVA and UVB, but not UVC.[12]

Focal trauma, scars, previous ionizing irradiation, and systemic immunosuppression are other factors that can predispose to the development of eyelid BCC. Age is an independent risk factor, and the incidence doubles between the ages of 40 and 70 years.[13] Cigarette smoking is not believed to be a factor in men but has been implicated as a predisposing factor in women.[14] The most important risk factors for the development of BCC include light skin pigmentation, freckling in childhood, and a history of severe

sunburn.[15] Other factors include occupational UV exposure and the presence of actinic cheilitis, actinic keratosis, and solar lentigo.[16] Chronic infection of the pilosebaceous follicle by the mite *Demodex folliculorum* has also been suggested as a causative factor.[17]

Most BCCs show inappropriate activation of the hedgehog signaling pathway. The sonic hedgehog protein is necessary for the embryonic development of neural, musculoskeletal, hematopoietic, and skin tissue, and for adult tissue homeostasis. A mutation in the hedgehog pathway may lead to sonic hedgehog protein binding to the transmembrane receptor Patched (Ptc), encoded by a tumor suppressor gene (*PTCH-1*) that normally inhibits the downstream transmembrane receptor, smoothened (Smo).[18] Reversal of this inhibition leads to the release of cytoplasmic sequestration of the transcription factor glioma-associated oncogene homolog 1 (Gli1), allowing it to enter the nucleus to induce gene transcription.[19] This results in cellular proliferation and tumorigenesis.

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Clinical Presentation

Most cases of BCC occur in individuals between 40 and 80 years of age, with a mean of about 60 years. There may be a slight predilection for males. Solitary lesions most commonly appear on the sun-exposed skin of the face. The lower eyelid is involved in about two-thirds of cases, and the upper eyelid is rarely involved, likely due to protection from sun exposure by the brows. Tumors are typically painless, associated with hair loss, and grow slowly over many months to years before diagnosis.

There are several different clinical variations seen on the eyelids. These include nodular, noduloulcerative, pigmented, cystic, superficial, and morpheaform or sclerotic forms.[20,21,22] The nodular form is the most common, accounting for 50% to 80% of all BCCs,[15], and has a predilection for sun-exposed areas in the head and neck. Clinical appearance varies greatly but usually presents as an indolent, firm, indurated, elevated lesion with smooth rolled, pearly, shiny borders (Figure 128.1). Fine telangiectasias are seen around the borders. When located near the eyelid margin, distortion or loss of cilia may be seen. Central ulceration is a common finding, often filled with crusty exudate. The ulcerated lesion may bleed easily. Pigmentation is a rare variant seen in up to 5% to 6% of cases and may be difficult to distinguish clinically from malignant melanoma (Figure 128.2).

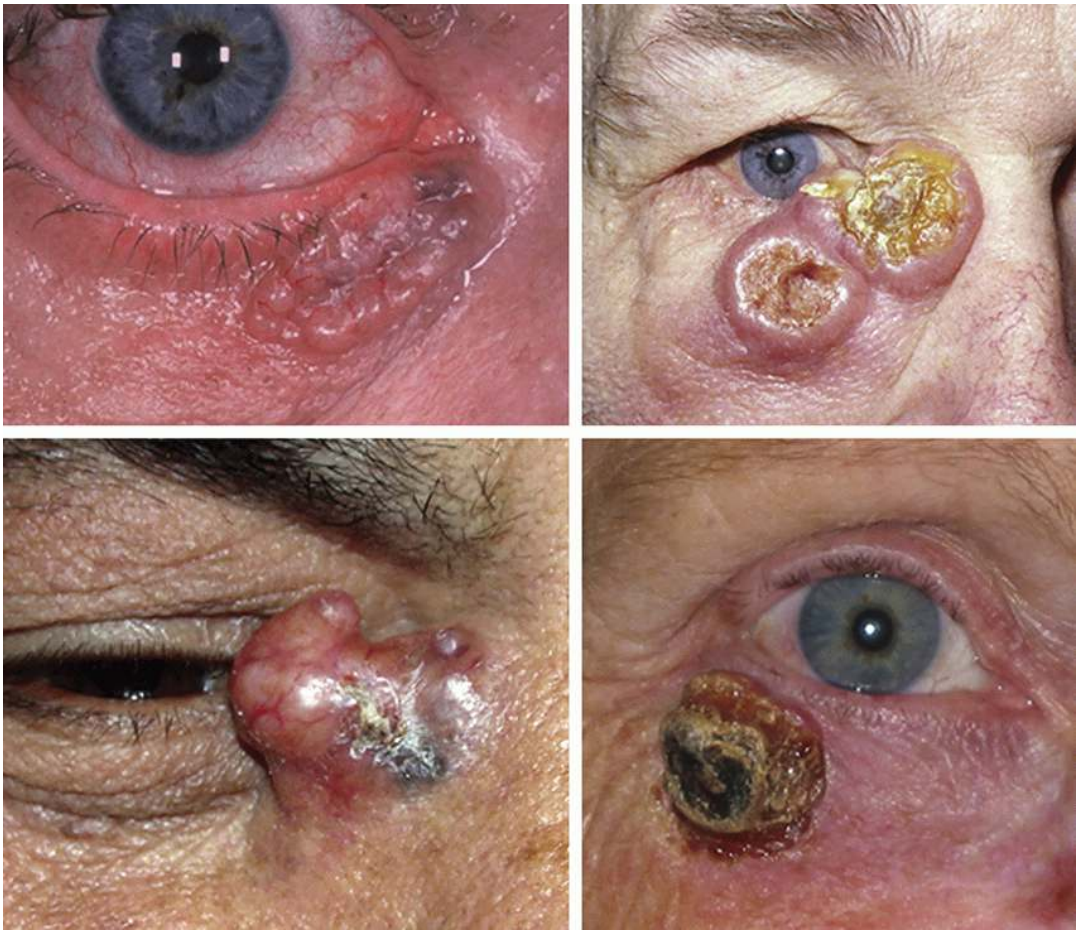

FIGURE 128.1 Nodular basal cell carcinoma.

The superficial subtype accounts for approximately 10% to 30% of BCCs and is the second most common type. Some studies have shown a younger average age of onset for this subtype and a relatively higher incidence in females.[23] Superficial BCCs present as a

thin, well-circumscribed, erythematous plaque or patch with scales (Figure 128.3) and may have central clearing and narrow rolled borders. They occur most commonly on sun-unexposed or intermittently *(Print pagebreak 848)* exposed areas of the trunk[10] but can be seen less commonly on the head and neck. Like the nodular subtype, they rarely can be pigmented.

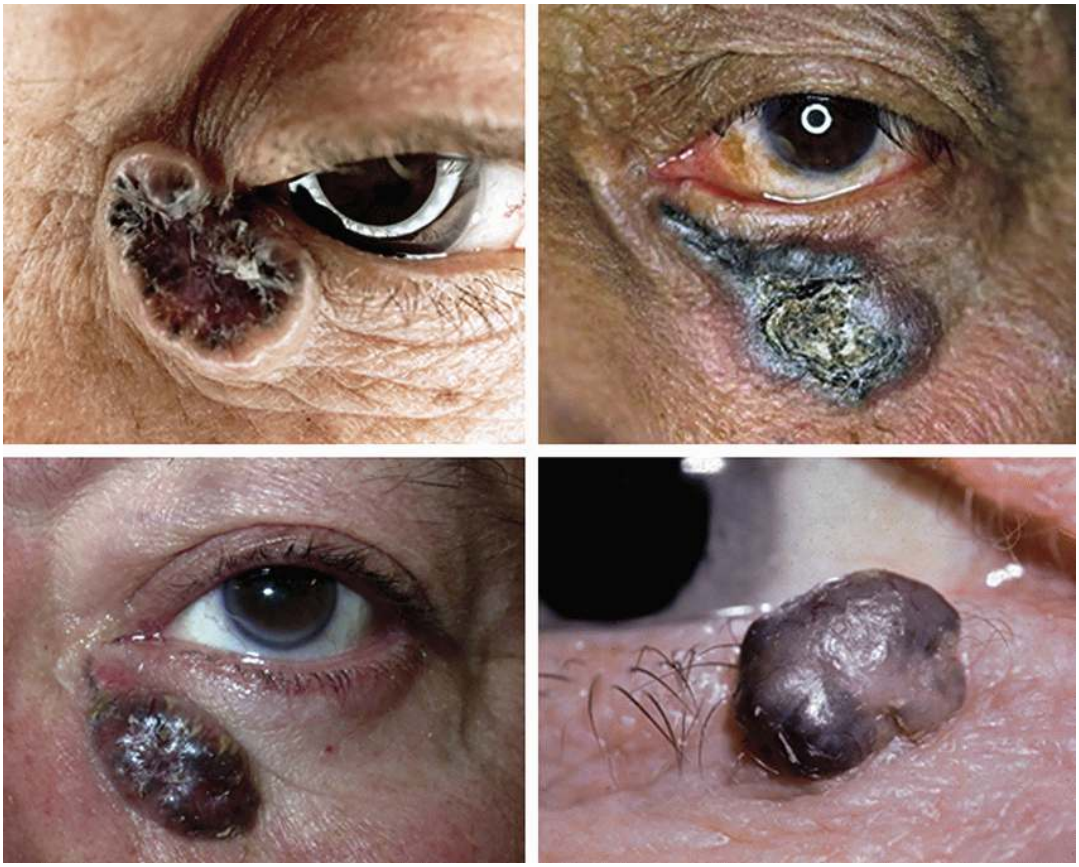

FIGURE 128.2 Pigmented basal cell carcinoma.

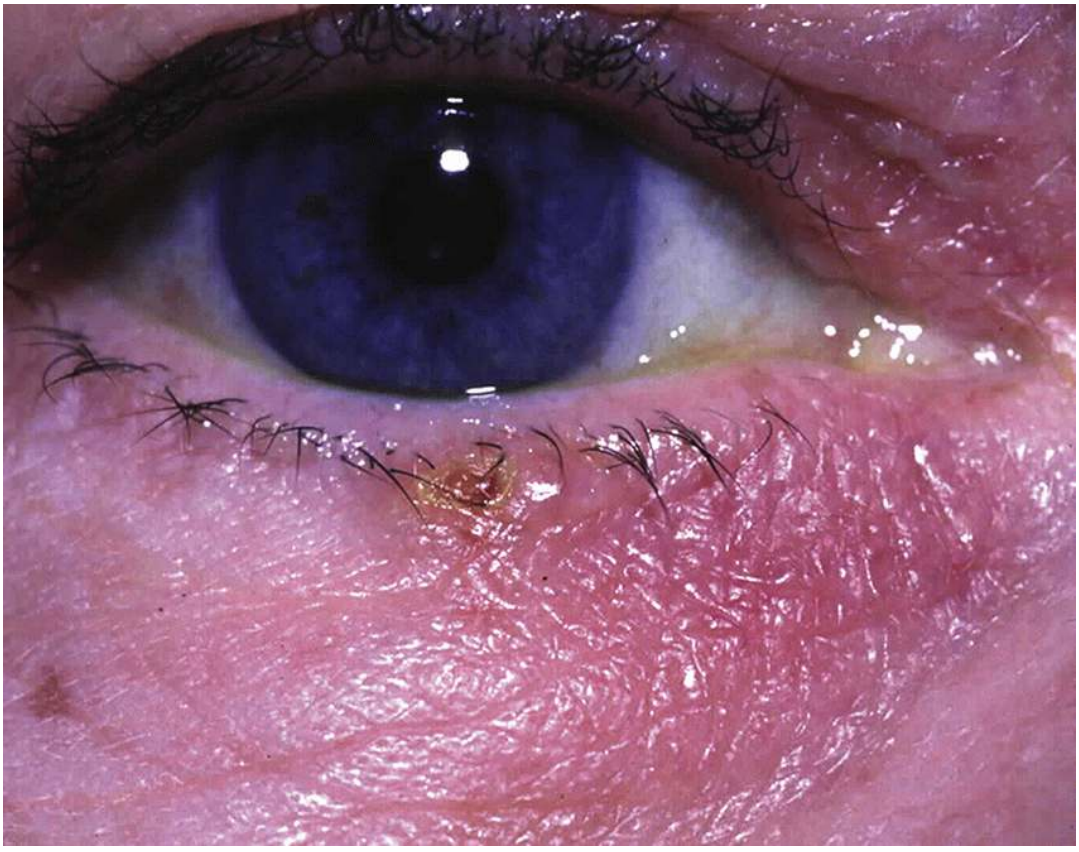

FIGURE 128.3 Flat superficial basal cell carcinoma with erythema, fine scales, and a small area of ulceration.

The morpheaform or sclerosing subtype is less common, comprising less than 10% of BCCs. Among 13,457 BCCs diagnosed at a single center, Scrivener et al found the morpheaform subtype in 6.2% of cases, of which 94.8% occurred on the head.[24] This form of BCC is more aggressive, with a greater potential for recurrence and for metastatic spread. Clinically, it appears as a pale, infiltrative, and locally destructive lesion with ill-defined margins (Figure 128.4). Neglected or recurrent tumors can be locally invasive where they may extend into the lacrimal drainage system, orbit, paranasal sinuses, and even the cranial cavity (Figure 128.4). Orbital invasion generally produces displacement of the globe, and motility restriction, and less commonly proptosis (Figure 128.5).

The basosquamous subtype is more aggressive in clinical behavior and has histologic features of both basal cell and *(Print pagebreak 849)* squamous cell carcinomas. It is a rare subtype representing less than 2% of all BCCs. It has nonspecific clinical features differentiating it from other subtypes, and the diagnosis is made primarily on biopsy. Because of its higher recurrence rate and metastatic potential, early diagnosis and treatment are essential.

Differential Diagnosis

The clinical differential diagnosis for BCC is very broad and includes numerous malignant and benign lesions. Confusing lesions include dermatofibroma, trichoblastoma, trichofolliculoma, sebaceous carcinoma, squamous cell carcinoma, keratoacanthoma, Merkel cell carcinoma, microcystic adnexal carcinoma, and metastatic carcinoma. Immunohistochemistry can help differentiate BCC from its mimics.[25] Pigmented BCC may be confused clinically with a melanocytic nevus, melanoma, and seborrheic keratosis. Cystic BCC can mimic an eccrine or apocrine hidrocystoma.

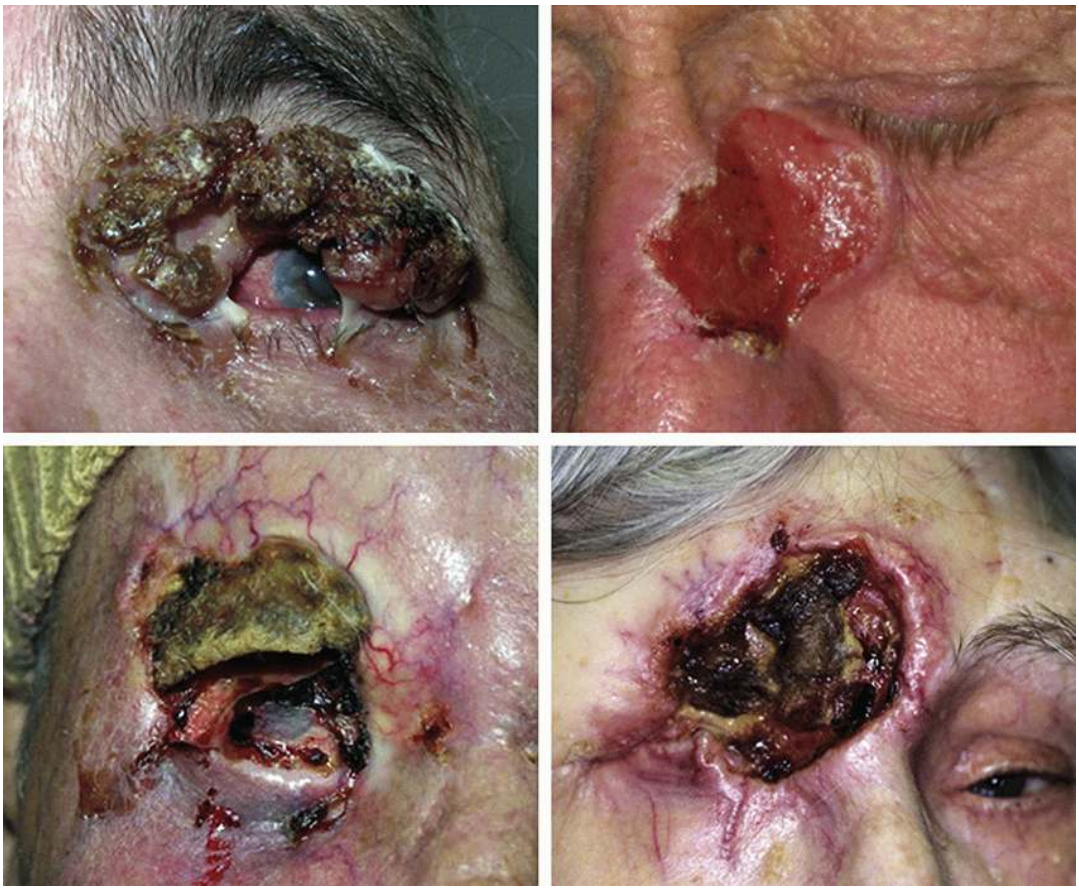

FIGURE 128.4 Infiltrative morpheaform basal cell carcinoma.

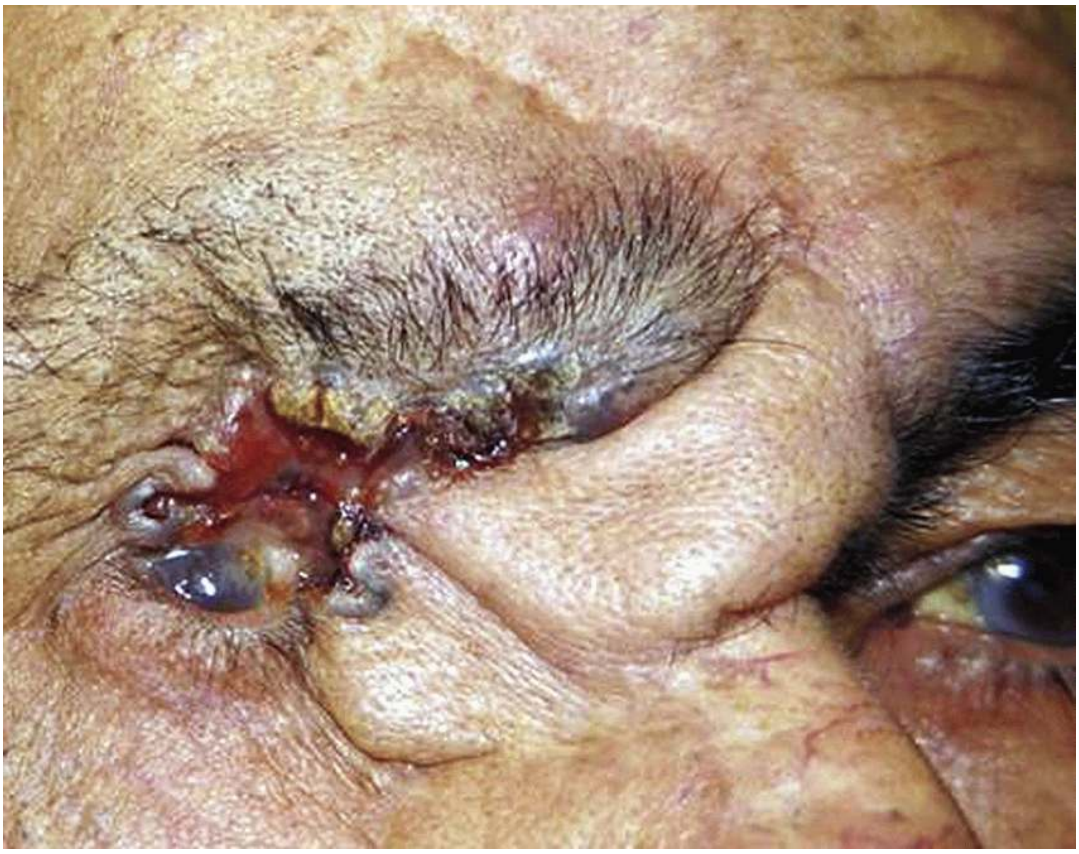

FIGURE 128.5 Medial canthal basal cell carcinoma with orbital invasion.

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Treatment

For eyelid BCC lesions where the diagnosis is uncertain, an incisional biopsy is indicated. This will allow a firm histologic diagnosis and allow for preoperative planning of resection and subsequent reconstruction. For smaller, low-risk tumors, surgical excision with a 4-mm margin is the treatment of choice. The goal should be to achieve complete tumor eradication to prevent a recurrence, local destruction, and possible metastatic spread. Resection should include frozen-section control of margins, preferably by Mohs microsurgery. Small, nonmarginal defects can heal by spontaneous granulation with acceptable aesthetic results. Larger defects are repaired by primary layered closure or with more complex reconstructions using myocutaneous flaps and grafts. A wide variety of reconstructive techniques are available depending upon the size and location of the defect and the specific tissues involved.[26]

Radiotherapy can be used as adjunctive therapy to surgical excision or in combination with orbital exenteration in cases of high-risk aggressive BCC with perineural invasion. It can also be used for patients who are not suitable surgical candidates. The use of radiotherapy remains controversial for smaller low-risk tumors, but some studies have shown good tumor control in many cases.[27] Radiotherapy has some potential side effects including dry eye; cataract; punctal, and lacrimal duct stenosis; neovascular glaucoma; and radiation retinopathy.

Electrodissection and curettage use mechanical debridement and electrocoagulation to remove the visible tumor. This technique does not allow for histologic assessment of margins so that it is more prone to leaving some tumors untreated. Complications include loss of eyelashes and some visible scarring following spontaneous granulation of the wound.

Cryosurgery is an alternative option, and some studies have reported high 5-year cure rates. Cosmetic outcomes tend to be inferior to surgery, and the technique generally is contraindicated in hair-bearing areas.

Photodynamic therapy (PDT) is an alternative treatment for BCC. Methyl aminolevulinate or aminolevulinic acid is used as the photosensitizing agent. Activation of the photosensitizer by visible light creates cytotoxic oxygen species and free radicals, which selectively destroy rapidly proliferating cells. A recent meta-analysis concluded that PDT is a useful method for the treatment of BCC that is similar in efficiency to cryosurgery and pharmacologic treatment such as with imiquimod. While it is less effective than surgical excision, PDT results in better cosmetic outcomes.[28]

For patients in whom surgery is not possible or is declined, topical immunotherapy has emerged as an alternative treatment for periocular BCC. Imiquimod is an immune modulator that stimulates innate immunity and induces apoptosis in tumor cells. For nodular BCC a topical 5% cream once a day for 8 to 16 weeks is applied. Clinical remission and histological clearance of the tumor have been reported in 80% to 100% of patients at follow-up periods of up to 2 years.[29,30,31]

Given the role of hedgehog signaling in the pathogenesis of BCC, targeted inhibition of the sonic hedgehog pathway now offers a promising treatment option for patients with advanced or recurrent disease not amenable to local resection. Vismodegib is a small-molecule compound that selectively inhibits the transmembrane receptor SMO. Early studies have shown this to be an effective treatment option for locally recurrent cases that have failed surgery, for metastatic BCC, and for advanced cases not amenable to surgery or radiotherapy. Vismodegib has been shown to have manageable side effects in most patients.[32,33,34,35,36,37] Neoadjuvant vismodegib therapy has been used followed by eye preserving surgery.[33] Sonidegib, another SMO antagonist, also has been approved for similar indications and carries a toxicity profile comparable with that of vismodegib.[38]

Prognosis

The prognosis for BCC depends upon the histologic type, anatomic location, and the size of the lesion. For nodular lesions, the prognosis is very good following complete surgical excision. With incomplete removal, the tumor can invade adjacent tissues along paths of least resistance. Destruction of muscle, cartilage, and bone can be associated with aggressive recurrences, leading to a poor prognosis. Orbital invasion is rare but is more common with lesions in the medial canthus. With local infiltrative growth patterns, the prognosis is significantly reduced and is associated with multiple recurrences. Recurrence rates average from 4% to 9% for lesions followed less than 5 years or more than 5 years, respectively.[39] However, the overall mortality rate is low, less than 1%. Spontaneous regression was reported in 25 of 400 (6%) BCCs, and another 56 (14%) showed foci of regression within the tumor.

BCCs rarely metastasize. The reported rate has been 0.0028% to 0.55%,[40] but a more recent study reported a rate of 1%.[41] Dissemination to regional or distant sites may occur via lymphatic spread (100%), hematologic spread (25%), or local subcutaneous routes. About 75% of tumors that metastasize are of the morpheaform type and usually involve the regional lymph nodes, lungs, bone, skin, liver, and spleen.[42] In one literature review of 100 cases of BCC with regional metastasis (N = 50) or distant metastasis (N = 50), the median survival for patients with regional metastases was 87 months and for distant metastasis it was 24 months.[43]

Predisposing Genetic Syndromes

Nevoid Basal Cell Carcinoma Syndrome

The basal cell nevus syndrome is also known as Gorlin-Goltz syndrome or Goltz syndrome. It is a rare, autosomal-dominant syndrome, more common in males, and involves both ectoderm and mesoderm tissues.[44,45] The clinical manifestations were originally reported simultaneously by Jarisch[46] and by White, both in 1894.[47] It was later classified as a syndrome with multiple manifestations.[20] The condition is characterized by multiple basal *(Print pagebreak 851)* cell carcinomas, odontogenic keratocysts, palmar and/or plantar pits, ectopic calcifications of the falx cerebri, and skeletal abnormalities such as bifid ribs and sometimes other tumors such as medulloblastoma and meningioma (Figure 128.6).[48] Other less common ocular abnormalities include congenital cataracts, uveal and optic nerve coloboma, strabismus, nystagmus, and microphthalmos. It is estimated that the prevalence is approximately 1 in 60,000 to 1 in 250,000, depending upon geographic locality and ethnicity. About 0.7% of patients with BCC may have this syndrome. The incidence is greater in regions with higher ultraviolet sunlight exposure, and tumors are more commonly seen in sun-exposed areas such as the face, chest, and back. The syndrome may be more common in young adults presenting with periocular BCCs.[49]

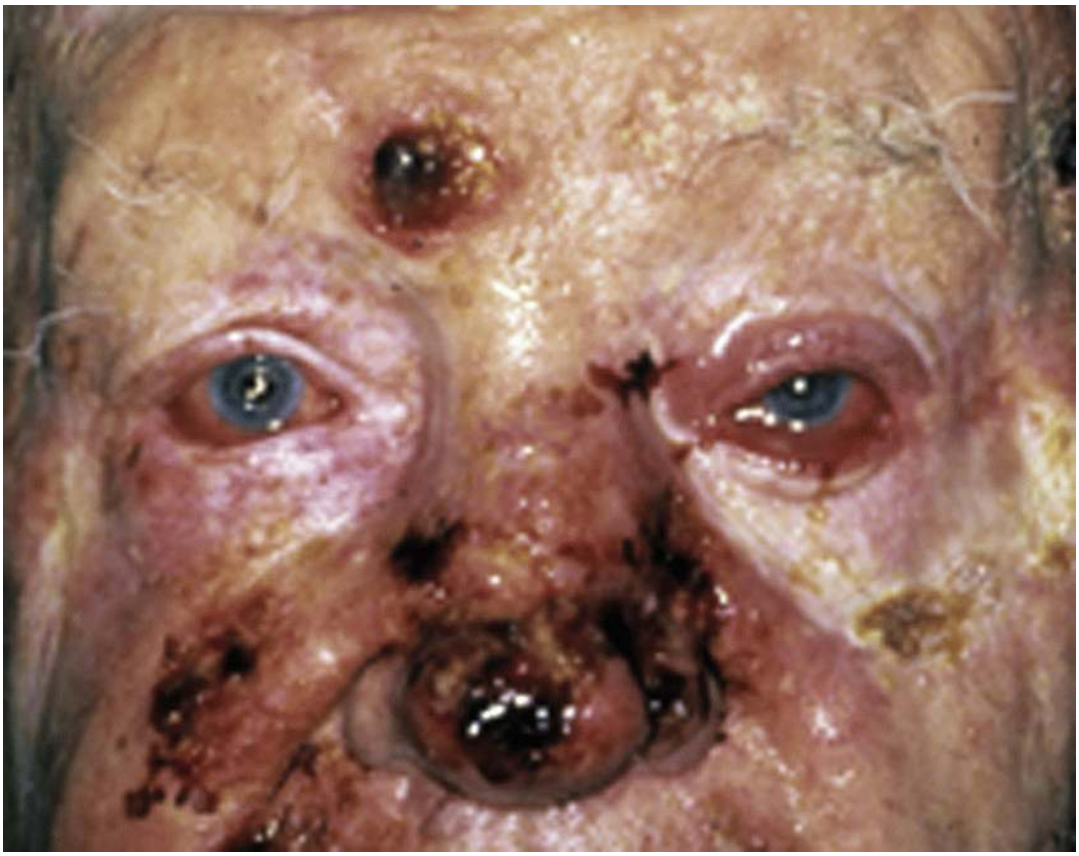

FIGURE 128.6 Nevoid basal cell carcinoma (Gorlin-Goltz) syndrome.

A gene believed to be responsible for this disorder has been mapped to chromosome 9q23.3-q31 that encodes the patched gene (*PTCH-1*) which translates into the transmembrane receptor protein for the secreted molecule Sonic Hedgehog in the Hedgehog signaling pathway responsible for the regulation of development and tumor suppression.[50,51] Patients may have a few to 1000 or more BCCs that vary in size from 1 to 10 mm in diameter. They may be skin colored and pedunculated or nodular, or even ulcerated. The mainstay of management of the BCCs associated with basal cell nevoid syndrome is surgical excision, preferably by Mohs microsurgery. Adjunctive therapies often include cryosurgery or electrodesiccation. PDT for diffuse BCCs has been used, but this is limited to smaller thin tumors less than 2 mm in thickness. Vismodegib has shown some promise in achieving tumor regression.[52]

Bazex-Dupre-Christol Syndrome

This is a very rare X-linked dominant disorder characterized by diffuse hypotrichosis, follicular atrophoderma, and basal cell carcinomas.[53] Milia cysts, trichoepitheliomas, hypohidrosis, and facial hyperpigmentation may also be seen. BCCs usually develop in the face during the first decade of life.

Xeroderma Pigmentosum

Xeroderma pigmentosum (Chapter 125) is a group of inherited autosomal recessive tumor predisposition disorders characterized by impaired DNA repair and hypersensitivity to UV-induced mutagenesis. It is characterized by photosensitivity of sun-exposed skin, premature skin aging, development of cutaneous neoplasms including BCC, photophobia, and pigmentary changes. Extracutaneous manifestations include keratosis, corneal opacification, ectropion, hearing loss, and microcephaly.[54] Patients have a 1000-fold increased risk of cutaneous malignancies compared with normal individuals. Tumors begin to develop at a median age of 8.5 years.[53]

Nevus Sebaceous of Jadassohn

Nevus sebaceous (Chapter 96) is a congenital hamartomatous malformation of the pilosebaceous follicular unit that includes both surface epithelial and adnexal structures. It primarily occurs on the scalp, head, and neck region and is usually clinically apparent at birth. In childhood, the epithelium is relatively normal with immature pilosebaceous units and alopecia. In adults, epidermal hyperplasia is seen and secondary neoplasms develop in 8.5% to 22.5% of cases.[55,56] About 80% of secondary neoplasms are benign, most commonly trichoblastoma. BCC is the most common malignant neoplasm but is quite rare, seen in only 1% to 5% of

cases.

Histopathology

Basal cell carcinomas are classified into histological subtypes by their architectural pattern, which correlates with the risk of recurrence.[10,57,58,59,60,61,62] Mixed patterns are common, occurring in from 10% to 15%[60] to ≈40%[58] of biopsies, and "can be reported as such."[60] Bonner et al reported a mixed pattern in 12.4% of 97 eyelid BCCs.[63] Superficial and infiltrative patterns tend to be located at the lateral or deep margins of the tumor,[60] leading to the upstaging of 7% to 31% of BCC subtypes at the time of definitive surgery.[64]

The WHO sorts BCCs into lower and higher risk patterns.[62] Low-risk architectural patterns of BCC are:

1. *Nodular BCC*: Nodular BCC, also known as nodulocystic BCC,[61] accounted for 35 of 51 (68.6%) eyelid BCCs reported by Salomon and colleagues,[65] which is similar to our experience (Figure 128.7A and B). Nodular BCCs often show an origin from the overlying epidermis[66] and feature discrete, variably shaped, large, or small nests of basaloid cells (basophilic tumor cells with hyperchromatic nuclei and little cytoplasm), often interconnected, in the papillary and reticular dermis.[61,66] Along the periphery of the tumor lobules, the cells are usually *(Print pagebreak 852) (Print pagebreak 853)* arranged radially with their long axes parallel to each other, creating so-called peripheral palisading.[62] Tumor cells in the center of the islands have randomly arranged nuclei, often with interspersed apoptotic tumor cells.[62] Mitoses are numerous.[67] Uncommon cases of nodular BCC have adnexal tumor-like features such as shadow cells (hair matrix differentiation), clear cells (trichilemmal differentiation), sebocytes (sebaceous differentiation), or tubular structures (ductal and glandular [sebaceous, apocrine] differentiation).[68] Stroma surrounding the tumor is often myxoid (mucinous)[61] and artifactually shrinks away from the tumor islands during histological processing, creating thin clefts (retraction artifact).[61,62] Clefts and mucinous matrix help to distinguish poorly differentiated basal cell carcinoma from poorly differentiated squamous cell carcinoma. Some BCCs have stromal keloidal-type collagen,[62] calcification,[61] thickened basement membrane,[68] or fibrocyte-rich collagen resembling a perifollicular adventitial sheath.[68] Small amyloid deposits are present in about half of BCCs but are evident in routine hematoxylin and eosin-stained sections in only about 10% of tumors.[69] Variants of nodular BCC include keratotic BCC with mature keratinization in the center of tumor islands, nodulocystic or cystic BCC with cystic degeneration of tumor islands, and adenoid BCC with cribriform nests (Figure 128.7C).[62]

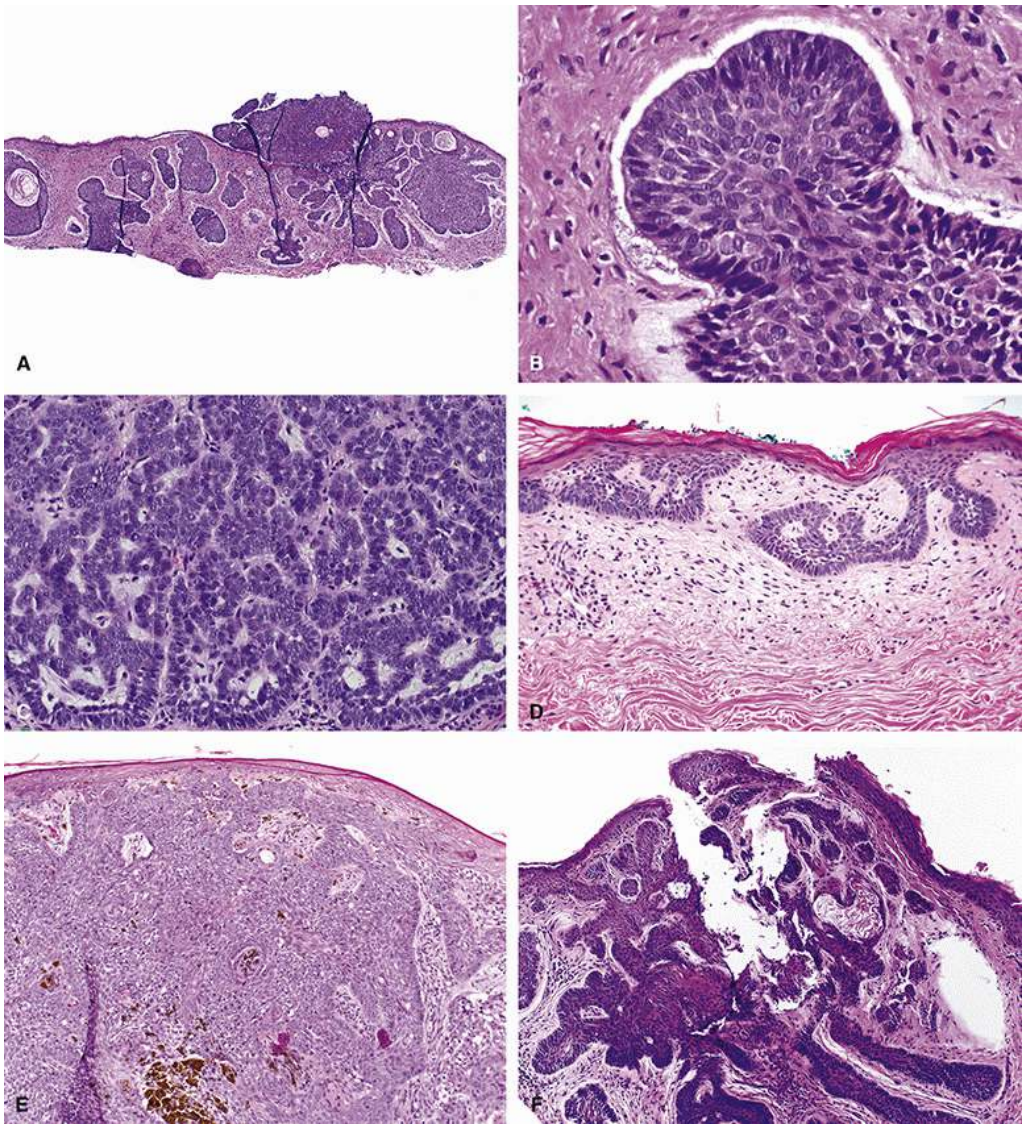

FIGURE 128.7 Histopathology of low-risk basal cell carcinoma subtypes. A, *Nodular BCC* of the left lower eyelid with discrete and interconnecting, variably shaped, large and smaller nests of basaloid cells (basophilic tumor cells with hyperchromatic nuclei and little cytoplasm) in the papillary and reticular dermis. B, Same *nodular BCC* as in A, showing peripheral radially arranged cells with their long axes parallel to each other, creating so-called peripheral palisading. The stroma surrounding the tumor lobule is mildly myxoid and artifactually shrank away from the tumor island during histological processing, creating a narrow cleft (retraction artifact). C, *Adenoid variant of nodular BCC* of the medial left lower eyelid. This tumor area has peripheral cribriform nests; other areas had solid islands of basaloid tumor cells typical of nodular BCC. D, *Superficial BCC* with basaloid tumor cells projecting from the epidermis forming lobules in the papillary dermis with an axis parallel to the epidermal surface. E, *Pigmented BCC* of the left lower eyelid with prominent melanin pigmentation. The architecture is otherwise typical of nodular BCC. F, This *infundibulocystic BCC* of the left upper eyelid was one of many 1-to 2-mm-diameter lesions involving all four eyelids in a young child with nevoid basal cell carcinoma (Gorlin-Goltz) syndrome. The tumor is sharply circumscribed, has a single infundibular cyst-like structure, central squamoid (eosinophilic) cells, and peripheral palisading. The large gap in the tumor is an artifact from sectioning the small tumor.

2. *Superficial BCC*: This BCC variant has basaloid tumor cells projecting from the epidermis or the sides of hair follicles, forming lobules in the papillary dermis with an axis parallel to the epidermal surface (Figure 128.7D).[61,62] The stroma around the tumor is myxoid, and there are typically clefts around the tumor islands.[61,62] Salomon and coworkers reported 5 of 51 eyelid BCCs were superficial type (9.8%).[65] Superficial BCC represented 13.6% of 1292 BCCs excised by Mohs surgery in Australia between 1993 and 1999; 73 cases involved the lower eyelid, 8 the upper eyelid, and 86 the medial canthus.[71] 3. *Pigmented BCC*: Pigmented BCCs have a nodular or superficial BCC pattern but differ by increased dendritic melanocytes within tumor islands.[71] In several large studies, pigmented BCCs accounted for 3.7%,[65] 5.1%,[72] and 9%[73] of eyelid BCCs. Basal cell melanization and melanophages contribute to the pigmentation of eyelid pigmented BCCs (Figure 128.7E).[72]

3. *Infundibulocystic BCC*: This rare BCC variant differs from other BCCs by occurring only on the face, small size (usually <5 mm in diameter), sharp circumscription, clefts within the connective tissue, absent ulceration, and follicular differentiation manifest as infundibular cyst-like structures.[74,75] The infundibular cyst-like structures are few in early lesions and many in larger tumors.[76] Infundibulocystic BCCs of the eyelids, although rare,[77] are a common form of BCC in nevoid basal cell carcinoma syndrome (Figure 128.7F).[78]

4. *Fibroepithelial BCC*: This BCC variant, also known as fibroepithelioma of Pinkus, has elongated, anastomosing cords of basaloid cells extending downward from the epidermis surrounding fibrotic stroma.[62] These lesions are most common on the intergluteal cleft and trunk.[61,62] They have not been reported on the eyelid to our knowledge.

High-risk BCC subtypes are:

1. *Micronodular BCC*: These tumors have small (more than 50% of nodules <0.15 mm in diameter)[62,79] discrete nodules of BCC widely scattered throughout the dermis and/or subcutis (Figure 128.8A).[61,62] The tumor nodules are often asymmetrically distributed[61] with infiltrative peripheral and deep borders.[62] A thin rim of myxoid or collagenous stroma[61] surrounds tumor micronodules dispersed in the normal dermis.[62] Retraction artifact is uncommon.[61] To minimize interobserver disagreements, the diagnosis of micronodular BCC should be restricted to tumors "with an irregular/tentacular, infiltrative deep or peripheral edge (an irregular interface at the deep or peripheral margins of the tumour with its adjacent stroma) composed predominantly (ie, >50%) of small discrete nodules (<0.15 mm in diameter)."[79] Micronodular BCCs were 9.8% of eyelid BCCs in the Salomon and coworkers study[65] and 5.2% of periocular BCCs in the 1993 to 1999 Australian Mohs registry report (33% lower eyelid, 5% upper eyelid, and 62% medial canthus).[70]

2. *Infiltrating BCC*: Infiltrating (infiltrative) BCCs (Figure 128.8B) have variably sized and shaped nests of basaloid tumor cells in the dermis that is often fibrotic.[62] The tumor islands are usually >5 to 8 cells thick,[61,62] angulated,[61] have occasional foci of retraction artifact,[61] and there are frequent mitoses and individual cell necrosis.[61] Infiltrating BCCs have irregular infiltrating margins,[61,62] approximately one-third have a nodular component,[61] and perineural invasion was present in 4.7% of infiltrating BCCs in an Australian Mohs registry between 1993 and 2002.[80] Infiltrating BCCs were 34.8% of periocular BCCs in the Australian 1993 to 1999 Mohs registry (54% lower eyelid, 4% upper eyelid, and 42% medial canthus).[70] The frequency of infiltrative BCCs in the Australian Mohs registry study may be skewed by selective referral of patients for Mohs surgery since Salomon et al noted only 4 of 51 eyelid BCCs (7.8%) were infiltrative.[65]

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3. *Sclerosing/morpheic BCC*: This form of BCC, also termed morpheaform BCC,[61] has thin cords of basaloid tumor cells compressed in a dense collagenous stroma (Figure 128.8C).[61] The tumor cords are one to five cells thick,[61,62] but typically one to two cells thick.[61] Individual cell necrosis and mitoses are common,[61] retraction artifact from the stroma is uncommon,[61,62] and the tumors are deeply infiltrative with tumor tentacles extending into the adjacent tissue.[62] Of the 1292 periocular BCCs in the 1993 to 1999 Australian Mohs registry, 4.1% were sclerosing/morpheic BCC, with all but one involving the lower eyelid or medial canthus.[70] In another Australian Mohs registry study, perineural invasion occurred in 8.3% of cases.[80]

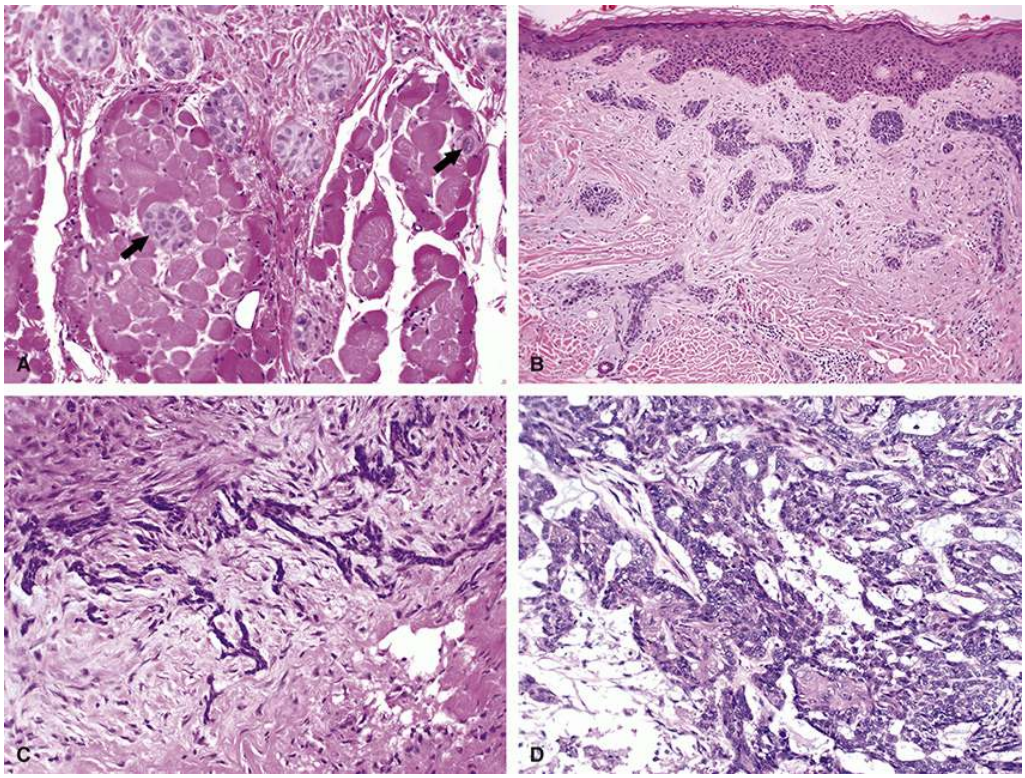

FIGURE 128.8 Histopathology of high-risk basal cell carcinoma subtypes. A, *Micronodular BCC* of the right upper eyelid with small nests of tumor in the deep reticular dermis and infiltrating the orbicularis oculi muscle (*arrows*). The larger tumor micronodule surrounded by orbicularis oculi muscle fibers is 0.05 mm in diameter. The anterior eyelid dermis contained typical nodular BCC with the micronodular subtype at the lateral and deep edges of the tumor. B, *Infiltrating BCC* with variably sized and shaped nests of basaloid tumor cells in the dermis surrounded by myxoid fibrotic stroma. Many of the tumor islands are angulated, and most are >5 to 8 cells thick. C, *Sclerosing/morpheic BCC* of the right medial canthus demonstrating thin cords of basaloid tumor cells surrounded by dense collagenous stroma. The tumor cords are 1 to 3 cells thick in this tumor. BCC also involved the glabella, and there was extensive perineural invasion. D, *Basosquamous carcinoma* involving the right lower eyelid and face with extension into the orbit. This area is a mixture of adenoid BCC and squamous cell carcinoma (SCC; cells with pink cytoplasm). Other areas of the tumor had a mixture of nodular BCC and SCC with areas of transition.

4. *Basosquamous carcinoma*: Basosquamous carcinoma, also referred to as metatypical BCC, has histological features of BCC and squamous cell carcinoma and transition zones between the two (Figure 128.8D).[61,62] Atypical squamous cells have abundant eosinophilic cytoplasm and may be focal or more widespread throughout the tumor.[62] About 10% of basosquamous carcinomas have perineural invasion.[62] The basaloid cells express epithelial cell adhesion molecule (Ber-EP4 antibody), while the squamous cells express epithelial membrane antigen.[62] Basosquamous carcinoma differs from keratotic BCC by the presence of malignant squamous epithelium and the absence of mature squamous pearls.[62] There are only a few reports of basosquamous carcinoma of the eyelid,[70,81,82] but periocular involvement is more common, although still far less frequent than nodular BCC.[83] There were 20 basosquamous carcinomas out of 1292 cases (1.6%) of periocular BCC in the Australian Mohs surgery registry between 1993 and 1999.[70] Nine of the basosquamous carcinoma arose in the lower eyelid, and 11 were in the medial canthus.[70]

5. *BCC with sarcomatoid differentiation*: This variant has BCC admixed with sarcomatous stroma that may be pleomorphic undifferentiated sarcoma, osteosarcoma, chondrosarcoma, leiomyosarcoma, and/or rhabdomyosarcoma.[62] We are aware of only one report of an eyelid BCC with sarcomatoid (osteosarcoma) differentiation.[84]

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Adnexal tumors, squamous cell carcinoma, and sebaceous carcinoma are tumors that must be distinguished from BCC.[25] In the eyelid, trichoepitheliomas are the most common adnexal mimic of BCCs in our experience. Stanoszek, Wang, and Harms, in their excellent review,[25] discuss histological and immunohistochemical features that differentiate adnexal neoplasms from BCC. We discuss immunohistochemical characteristics that separate poorly differentiated BCC from squamous and sebaceous carcinomas in Chapter 144 (Sebaceous Carcinoma).

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CHAPTER 129

Cutaneous T-Cell Lymphoma

Key Points

- Primary cutaneous T-cell lymphoma is a heterogeneous group of non-Hodgkin lymphomas that is responsible for two-thirds of all cutaneous lymphomas
- The most common forms are mycosis fungoides, which primarily involves the skin, and Sézary syndrome, which involves the skin and blood
- The etiology remains unknown, but genetic, environmental, and infectious agents have been implicated as possible risk factors
- Chromosomal abnormalities, including loss at 10q and abnormalities in *p15, p16,* and *p53* tumor suppressor genes have also been described, especially in advanced stages of the disease
- In the eyelids, it usually presents with localized cutaneous patches or plaques with flaking blepharitis, and eyelid thickening that advances to skin tumors, erythroderma, and extensive node or visceral involvement
- Other ophthalmic findings include conjunctival injection, episcleral infiltrates, punctate keratitis, stromal opacification and melts, retina infiltrates, vascular occlusions, and optic neuropathy
- Treatment is primarily palliative with topical therapies to improve quality of life that can include BCNU (corticosteroids, nitrogen mustard, carmustine), topical bexarotene gel, imiquimod, interferon alpha, receptor-targeted cytotoxic fusion proteins, radiotherapy, total skin electron beam radiotherapy, and phototherapy
- Patients with limited patch or plaque-stage disease have a 10-year disease-specific survival reported as 97% to 98%
- In cases with more advanced tumor stage disease and lymph node involvement, the disease-specific survival is reduced to 42%

Primary cutaneous T-cell lymphoma (CTCL) encompasses a heterogeneous group of non-Hodgkin lymphomas (NHL), which are responsible for two-thirds of all cutaneous lymphomas. Mycosis fungoides (MF), also known as Alibert-Bazin syndrome, is the most common variant of CTCL, accounting for over half of all cases. It was first described in 1806 by the French physician Baron Jean-Louis Alibert[1] as mycotic-like plaques in the early phases of the disease and mushroom-like tumors that can be seen late in the disease.[2,3]

While MF is the most common cutaneous lymphoma, it is still a relatively rare, extranodal, non-Hodgkin lymphoma that consists of a proliferation of helper T cells that exhibit an affinity for the epidermis.[4] It most often presents in individuals aged 45 to 60 years but occasionally has been seen in children and adolescents.[2,5,6,7] It is more common in black than in white or Asian patients and twice as frequent in men as in women. According to the Surveillance, Epidemiology and End Results (SEER) program of the United States National Cancer Institute, the incidence of MF is estimated at 5.6 per million persons, and this has remained constant for the past 2 decades.[8]

MF has been classified by its clinical presentation as a patch, plaque, or tumor.[9]
Patch or plaque lesions have a predilection for non-sun-exposed areas of the skin, although any area of the skin may be affected.[10] They are frequently misdiagnosed as chronic contact dermatitis, atopic dermatitis, or psoriasis and may show areas of hypopigmentation or hyperpigmentation, atrophy, and petechiae.[10]

The behavior and prognosis of primary cutaneous lymphomas are often different from histologically similar systemic non-Hodgkin lymphomas that secondarily involve the skin so that they are classified as separate entities by the European Organization for Research and Treatment of Cancer and the World Health Organization.[11,12] MF has been divided into several subtypes with

slightly different clinical characteristics and different prognostic implications. Classical MF runs an indolent clinical course and usually progresses slowly over years or even decades as a patch or plaque. The skin lesions tend to occur in sun-protected areas and may progress from patches and plaques to tumors that often show ulceration.[13] Regional lymph nodes and visceral organs may become involved in later stages of the disease.

In addition to the classical Alibert-Bazin type of MF, a long list of clinical and/or histologic variants have been reported. Bullous, hyperpigmented, and hypopigmented MF clinically behave in a similar fashion to that of classical MF. They are, therefore, not considered as separate entities. Folliculotropic MF and pagetoid reticulosis, on the other hand, do have distinctive clinicopathologic characteristics and, usually, are considered to be distinct variants. Folliculotropic MF is a localized form of CTCL characterized by the presence of folliculotropic infiltrates and lymphomatous changes around hair follicles and most commonly involves the head and neck.[14] It occurs more often in adults but is seen occasionally in children and adolescents, and men are more often affected than women.

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Lesions may present as groups of follicular papules, acneiform lesions, indurated plaques, or tumors and may be associated with alopecia.[15,16] Pagetoid reticulosis is characterized by the presence of localized patches or plaques, with a proliferation of intraepidermal neoplastic T cells.[11,17,18] Lesions generally present as a slowly progressive solitary psoriasiform or hyperkeratotic patch or plaque, usually localized on the extremities, and have a relatively good prognosis. A newer variant is papular mycosis fungoides characterized by the presence of papules in the absence of the usual patches and plaques. This variant has a relatively nonaggressive behavior and a good prognosis.[19,20]

Sézary syndrome (SS) is a variety of T-cell cutaneous lymphoma that develops most frequently in men during their fifth decade of life and progresses rapidly.[3] It has an annual incidence rate of about 1/10,000,000 and represents about 3% of all cutaneous lymphomas. It affects the skin of the entire body as a scaling erythroderma and infiltration. SS is also known as red man syndrome because the skin is usually bright red. Alopecia, palmoplantar keratoderma, nail onychodystrophy, and lower eyelid ectropion may also be present. Neoplastic T cells (Sézary cells) are located in the skin, enlarged lymph nodes, and in the peripheral blood. The disease can advance to involve the liver, spleen, and bone marrow.

Etiology and Pathogenesis

The etiology of MF remains unknown, but genetic, environmental, and infectious agents have been implicated as possible risk factors in initiating lymphocyte activation.[21,22] Clonal T-cell receptor gene rearrangements have been found in most cases of classic MF. Chromosomal abnormalities, including loss at 10q and abnormalities in *p15, p16,* and *p53* tumor suppressor genes have also been described, especially in advanced stages of the disease.[13,23] MF has been observed related to mature CD4+ memory cells, and a hypothesis of persistent antigen stimulation leading to a breakdown in immune surveillance and eventually malignancy has been proposed as an initial event.[24]

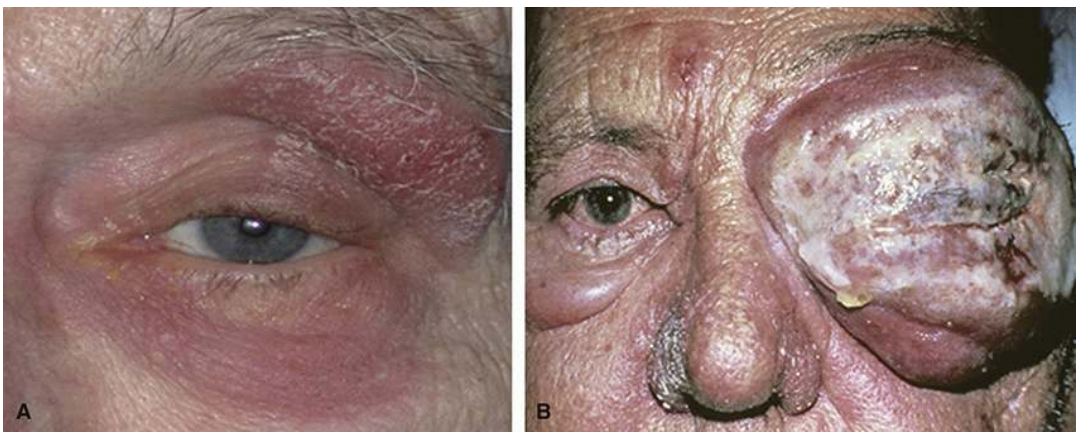

FIGURE 129.1 A, Early manifestation of mycosis fungoides as erythematous induration of the eyelids. B, Late-stage tumorous mycosis fungoides. A, (Courtesy of Dr. Bita Esmaeli.)

Malignant T cells in MF arise from skin-homing T cells, and the tumor microenvironment is critically involved in supporting tumor growth.[25] Cytokine expression and functional variations in the immune system have been seen in the various stages of MF. Early-stage disease expresses a Th1 type helper T-cell cytokine pattern, which limits the disease to the skin. With progression to late stages, there is a shift from Th1 to a Th2 type helper T-cell profile,[26,27,28,29] and this cytokine shift may promote malignant lymphocyte proliferation.[25] In addition, resident skin T cells express various chemokine receptors, which are necessary for

migration into the skin.[30,31]

SS has been linked to a wide range of chromosomal anomalies, particularly rearrangements in the 6q23-27 region that lead to alterations in the *MYB* proto-oncogene and the interleukin-22 receptor subunit alpha-2 gene (*IL22RA2*). However, the etiology remains unknown.

Clinical Presentation

The diagnosis of mycosis fungoides is usually difficult, especially in early stages, and often requires multiple biopsies for confirmation because of its clinical similarity to other conditions.[32,33,34] Erythematous plaques are usually the initial manifestation, similar to other mild skin disorders such as eczema, atopic dermatitis, psoriasis, and pityriasis lichenoides (Figure 129.1A). As the disease progresses, infiltrative lesions appear, and in the late stage, tumorous lesions develop (Figure 129.1B) and metastasis to lymph nodes and distant organs may follow.

MF is more common in males at a median age at diagnosis of 55 years.[35] Blacks are almost twice as likely to develop *(Print pagebreak 859)* MF compared with whites and Asians.[36] In the eyelid, the disease usually presents with localized cutaneous patches and/or plaques in the early stages. More advanced stages include erythroderma and extensive node or visceral involvement. Flaking blepharitis is a common finding, followed by eyelid thickening with eyelash and eyebrow flaking. The most frequent complaints are burning, impaired vision, redness, itching, and crusting of the eyelids and eyebrows.[37] Other findings include conjunctival injection; episcleral infiltrates; punctate keratitis with stromal opacification, melts, and subepithelial infiltrates; retina, choroid, and vitreous infiltrates; uveitis and vascular occlusions; and optic nerve infiltration and neuropathy.[38,39,40,41,42,43,44,45,46] Nonspecific manifestations include dry eyes, cataracts, glaucoma, and peripheral nerve palsy, among others.

The frequency of ophthalmic involvement in mycosis fungoides is not well established. Among 30 patients described by Stenson and Ramsay,[47] 11 (36.7%) had ophthalmologic manifestations. Most common were dry eyes (37%), ectropion (33%), and eyelid tumors (27%), with conjunctival tumors, keratitis, uveitis, and optic atrophy all reported in 10% of cases or less. Leib et al[37] described 17 cases of MF, and the eyelids were the most frequently affected region (76%), characterized by seborrheic blepharoconjunctivitis, cicatricial ectropion, meibomiantitis, chalazion, and madarosis. Cook et al[48] assessed 42 cases of cutaneous T-cell lymphoma and reported that ectropion was the most prevalent condition, seen in 40.4% of cases.

The disease usually follows a protracted course, through three stages: patch, plaque, and tumor. In some cases the disease may not advance to other stages,[49] but up to one-third of cases it will progress to a more aggressive form with infiltration or tumors, and in some cases can develop with erythroderma.[32,34,50]

In SS, the cutaneous involvement is characterized by reddened, thickened, peeling, and painful skin patches, plaques, and tumors all over the body (Figure 129.2). Sézary cells are also found in the blood and lymph nodes.

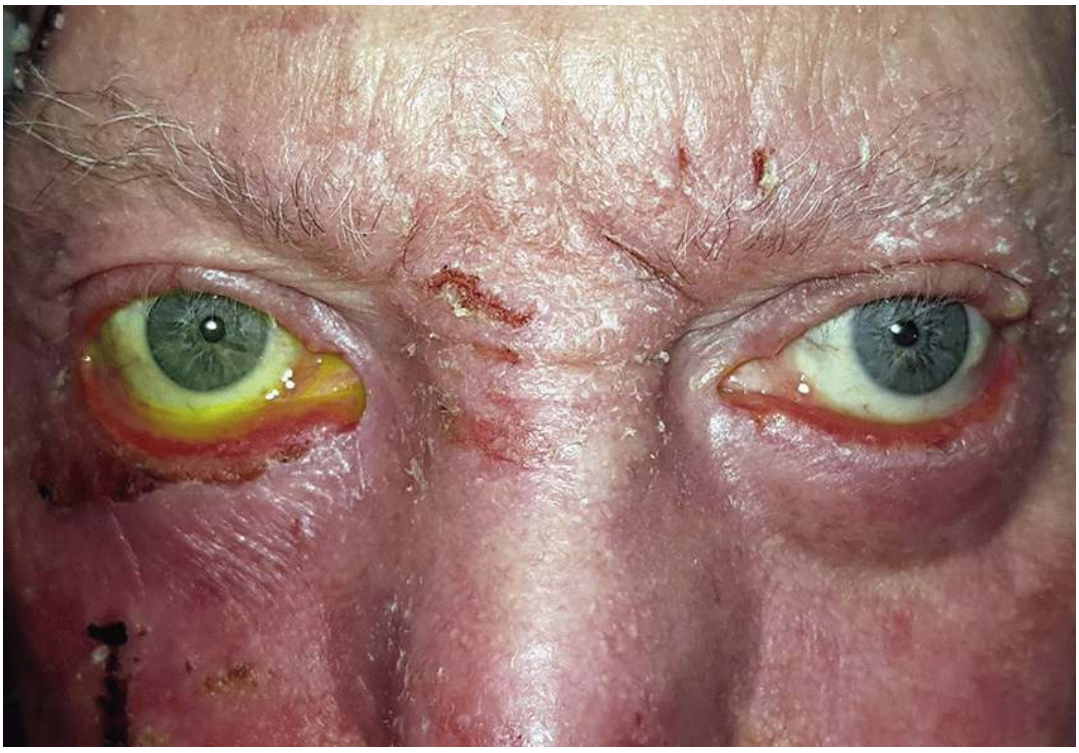

FIGURE 129.2 T-cell cutaneous lymphoma in Sézary syndrome. (Courtesy of Dr. Timothy Sullivan.)

Differential Diagnosis

MF is easily confused with other more common skin disorders. The differential diagnosis includes eczema, psoriasis, drug reactions, atopic and contact dermatitis, pityriasis lichenoides, and other lymphomas.

Treatment

MF usually runs an indolent, uncontrollable course, and treatment is primarily palliative.[32,34,50] The only treatment that can cure the disease is a bone marrow transplant, which is rarely used.[51,52] When MF is confined to the skin, skin-directed therapies are preferred. These include topical BCNU (corticosteroids, nitrogen mustard, carmustine), topical bexarotene gel (retinoid), imiquimod cream, interferon alpha and other cytokines, receptor-targeted cytotoxic fusion proteins, radiotherapy, total skin electron beam radiotherapy, and phototherapy.[53,54,55,56,57] However, the role of these treatments, as single-agent therapies or in combination with others, remains unclear.

The benefit of skin-directed therapies in preventing MF progression is not clear,[53] and these approaches have been used principally to improve quality of life,[58] to help control pruritus and pain, and to improve physical appearance. However, there is no firm evidence that more aggressive topical therapies prolong survival. In one randomized controlled clinical trial, parenteral chemotherapy combined with external beam irradiation was compared with topical treatment. There was a higher rate of complete response in the systemic group (38%) compared with the topical group (18%), but there was no significant difference in the disease-free or overall survival rates after a median follow-up period of 75 months.[59]

Emollients are frequently prescribed for patients with MF, and their use may reduce pruritus and scaling. They reduce transepidermal water loss and can reduce corneocyte loss and alter the lipid barrier.[58,60] Emollients may also be of some value as moisturizers, which may be a useful adjunctive therapy alongside other topical therapies. Topical corticosteroids are frequently used as palliation for patients with patches or plaques. Zackheim et al[61] reviewed 79 patients with early-stage MF and reported a partial or complete response rate of 94% in T1 stage tumors and 82% in T2 stage tumors. But the response durations were not prolonged, and recurrences were common following discontinuation of the topical steroids.

Bexarotene gel is an antineoplastic agent that selectively activates retinoid X receptors to induce cell differentiation and apoptosis. It has been used in patients with MF where other topical therapies have not been effective. In several clinical trials, the overall response rate was 54% to 63%.[62,63] Although not evaluated in clinical trials, imiquimod 5%,[64,65,66,67] 5-fluorouracil cream,[68] topical methotrexate-laurocapram,[69] and topical alkylating agents like chlormethine gel (also referred to as mechlorethamine)[70] have been reported to be beneficial in case reports and small case series.

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Phototherapy with broadband UVB light and psoralen plus ultraviolet A light photochemotherapy (PUVA) is frequently used in the management of MF and has been reported to result in a high complete remission rate.[71,72,73] MF is extremely radiosensitive, and radiotherapy has been used for all stages of the disease.[74,75,76] Localized radiotherapy is often employed as palliation for isolated plaques and tumors, and this may be performed in combination with other skin-directed therapies.[53,77]

Chemotherapy is generally used in more advanced cases or where there are widespread cutaneous tumors refractory to skin-targeted therapies. The main goals of systemic treatment are long-term disease control, effective symptom management, and control of life-threatening complications.[78] Numerous systemic chemotherapy agents have been used, but they have not provided long-term disease control.[79] Chemotherapy is reserved for the treatment of patients with advanced disease and relapses after previous therapy.[80], It may also be considered for patients with aggressive disease, bulky nodes, and visceral involvement.[81]

There are many other systemic therapies available that are beyond the scope of this chapter. They are comprehensively discussed by Alpdogan et al.[82]

Prognosis

The prognosis of patients with MF depends on the stage of the disease and the presence of any extracutaneous involvement.[6,83] Patients with a limited patch or plaque-stage MF do not have a reduced life expectancy compared with age-matched controls, and the 10-year disease-specific survival is reported as 97% to 98%.[54] But since the disease is not usually cured, the expected quality of life is poor from painful, itchy, and disfiguring lesions.[84] However, for patients with more advanced tumor stage disease and lymph node involvement, the disease-specific survival is reduced to 42%.[6,83] Patients in the most advanced stages with bulky tumors, diffuse lymphadenopathy, elevated lactic dehydrogenase, high circulating tumor burden, and visceral disease have a very poor survival, regardless of systemic therapy.[85,86,87]

The prognosis for SS is poor. The disease is not felt to be curable, and the median survival of patients is approximately 5 years.

Histopathology

The histopathological features of eyelid T-cell lymphomas depend on its subtype.[11,88,89,90,91] The frequency of eyelid involvement by T-cell lymphoma and its subtypes is uncertain. In Svendsen and Heegaard's review of 199 published cases of primary eyelid lymphoma, 44% were of T-cell origin.[92] Of the T-cell lymphomas, 29% were mycosis fungoides, 14% were cutaneous anaplastic large-cell lymphoma (C-ALCL), and 14% were extranodal natural killer/T-cell lymphoma, with a smattering of many other subtypes.[92] The published reports are biased, as evidenced by the data for 86 patients from seven international eye centers seen between 1980 through 2015.[93] T-cell lymphomas accounted for 15 (17%) of the 86 patients with eyelid lymphoma.[93] The subtypes of eyelid T-cell lymphoma were mycosis fungoides (eight patients [53%]), peripheral T-cell lymphoma (two patients [13%]), lymphomatoid papulosis (two patients [13%]), C-ALCL (one patient [7%]), systemic ALCL (one patient [7%]), and systemic T-cell lymphoma, not otherwise specified (one patient [7%]).[93] Of the patients with mycosis fungoides, one (13%) had primary disease involving the eyelid and seven (88%) had relapsed disease.[93]

Mycosis fungoides is an epidermotropic CTCL featuring small to medium-sized T lymphocytes with cerebriform nuclei.[94] MF exists as a classic form that progresses through patch, plaque, and tumor stages,[94] as well as folliculotropic MF, granulomatous slack skin, and pagetoid reticulosis variants.[32,95] The patch stage of classic MF (Figure 129.3) has a superficial dermal band-like, patchy lichenoid, perivascular, or periadnexal infiltrate of mostly lymphocytes and macrophages, with a few small to medium-sized atypical lymphocytes having cerebriform nuclei.[32,94,96] The atypical lymphocytes are usually in the lower epidermis and may be single, form small clusters, or be arranged linearly.[32,94] Approximately one-fifth of biopsies have intraepidermal collections of atypical lymphocytes (“Pautrier microabscesses”).[96] The intraepidermal atypical lymphocytes may have a clear cytoplasmic rim (halo cells) that assists in diagnosing patch stage MF.[32,94] Other histological changes in patch-stage MF are focal parakeratosis and papillary dermal fibrosis with coarse collagen bundles.[32,96] Classic MF plaques (Figure 129.4) have more prominent dermal inflammation and more epidermotropism and Pautrier microabscesses than the patch stage.[32,94] The tumor stage of MF (Figure 129.5) has a dense, diffuse, nodular infiltrate of atypical lymphocytes with pleomorphic and hyperchromatic nuclei and prominent nucleoli.[32,94] Epidermotropism and Pautrier abscesses may be absent in the tumor stage of MF.[32,94] “The typical phenotype is positivity for CD2, CD3, TCRβ chain, CD5, and CD4 and negativity for CD8 and TCRγ chain. Cases with a cytotoxic phenotype (ie, positivity for CD8 and/or TCRγ chain) are well-recognized.”[94] T-cell receptor gene rearrangement analysis facilitates diagnosis of early MF infiltrates.[94] The histopathological features of SS are similar to the patch and plaque stages of MF, although the infiltrate is often more monotonous and epidermotropism may be absent.[89,97]

Cutaneous anaplastic large cell lymphoma (Figure 129.6) is a form of primary cutaneous CD30+ T-cell lymphoproliferative disorder[89,98] having a diffuse dermal infiltrate of large anaplastic tumor cells with or without epidermotropism.[89,90,98] The tumorous lymphocytes have round, oval, or irregularly shaped nuclei, prominent nucleoli, and abundant cytoplasm.[89,90,98] Ulceration is frequent.[89] “The neoplastic cells show an activated CD4+ T-cell phenotype, with variable loss of CD2, CD5, CD7, and CD3 and frequent expression of cytotoxic proteins (granzyme B, TIA1, and perforin). Some cases may have a CD4-/CD8+ or CD4+/CD8+ T-cell phenotype. CD30 is by definition expressed by a majority (>75%) of the neoplastic cells.”[98]

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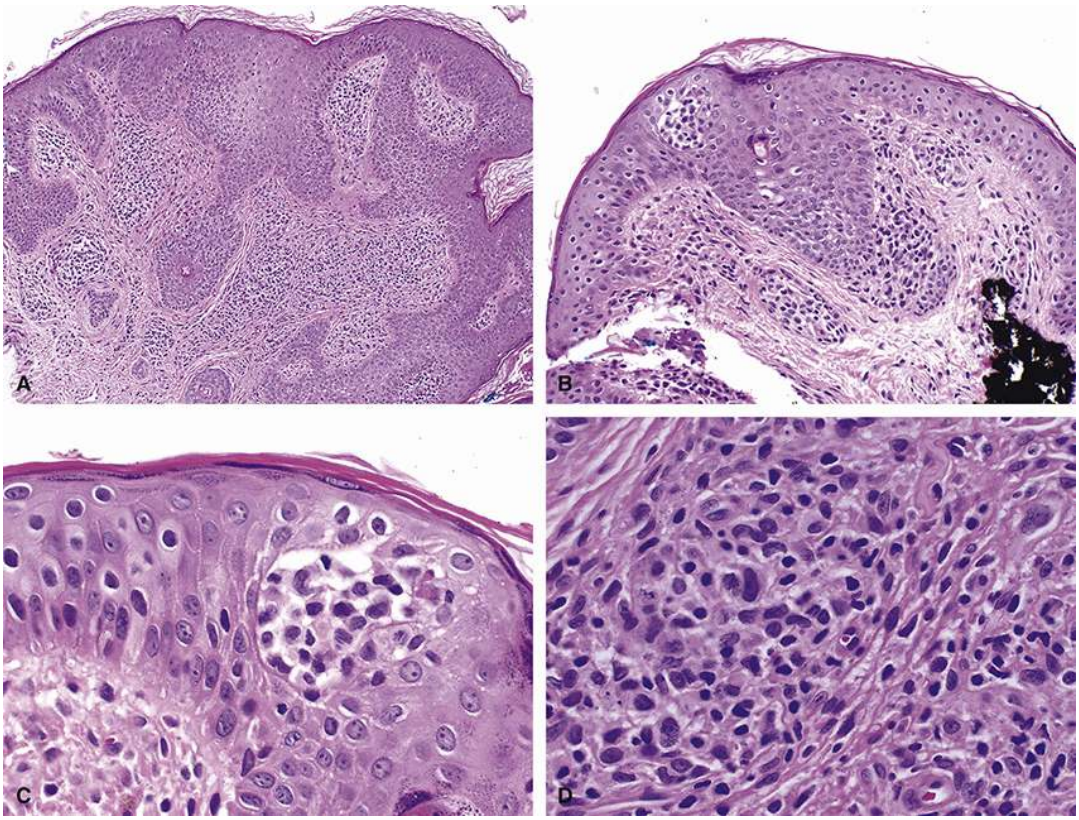

FIGURE 129.3 A man in his late 50s, clinically in remission from CTCL, developed an itchy, faint erythematous patch under his left eyelid. A, The epidermis is acanthotic, and there is a papillary and reticular dermal perivascular infiltrate of lymphocytes and macrophages in this patch-stage MF. B, The papillary dermis has a perifollicular and perivascular infiltrate of macrophages and lymphocytes and one collection of atypical lymphocytes in the epidermis (Pautrier microabscess). The black at the bottom right is ink used for orienting the biopsy. C, Atypical lymphocytes with pleomorphic convoluted (cerebriform) nuclei form the Pautrier microabscess. D, The dermal infiltrate contains scattered atypical lymphocytes with irregular nuclear configurations.

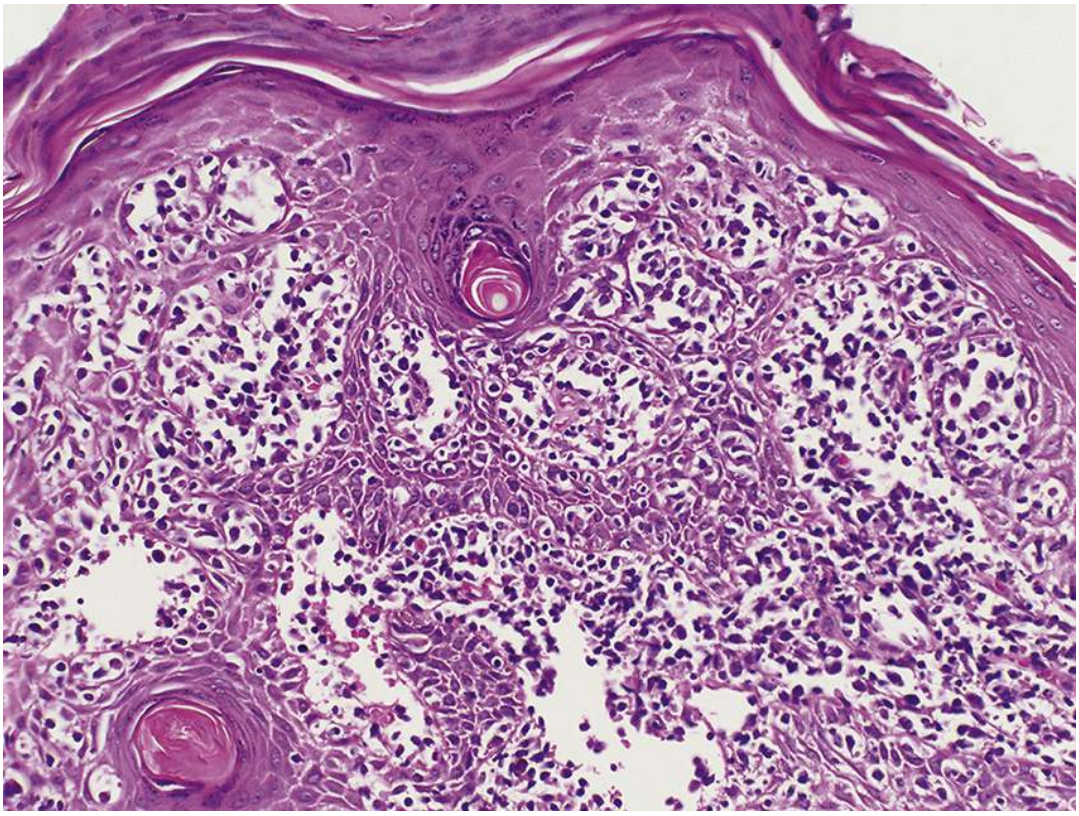

FIGURE 129.4 A woman in her upper 30s with a 1-year history of CTCL developed an erythematous, scaly plaque on

her left upper eyelid. This plaque-stage MF has a dense papillary dermal infiltrate of atypical lymphocytes with extensive epidermotropism and numerous Pautrier microabscesses. Many of the individual lymphocytes in the basal epidermis have clear cytoplasmic rims (halo cells). The lymphocytes were CD3+, CD4+, and CD5+.

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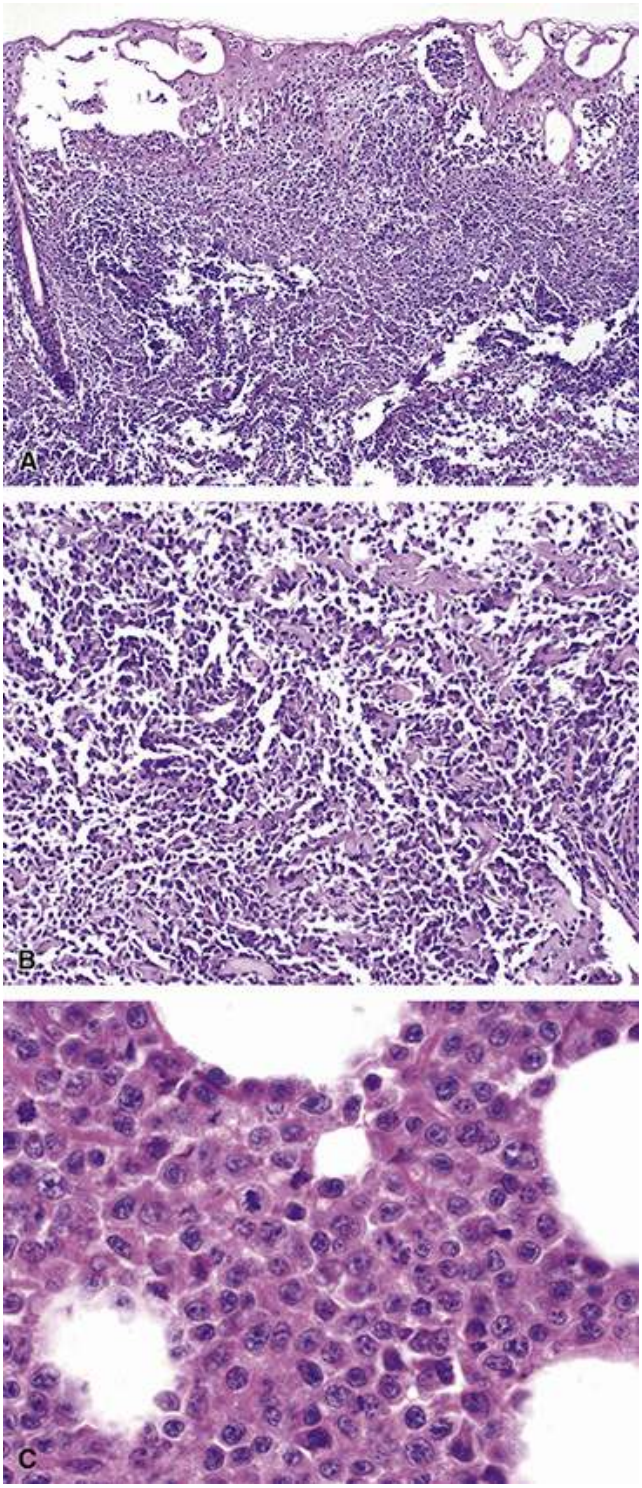

FIGURE 129.5 This biopsy is from the lower eyelid of the MF tumor shown in Figure 129.1B. A, Atypical lymphocytes extensively infiltrate the epidermis and efface the dermis. B, Only a few bands of collagen are present in the dermis among the diffuse infiltrate of atypical lymphocytes. C, Sheets of atypical lymphocytes extensively replace the subcutaneous adipose tissue. Some of the atypical lymphocytes feature cerebriform nuclei, others have prominent nucleoli, and a mitotic figure is near the center of the photomicrograph.

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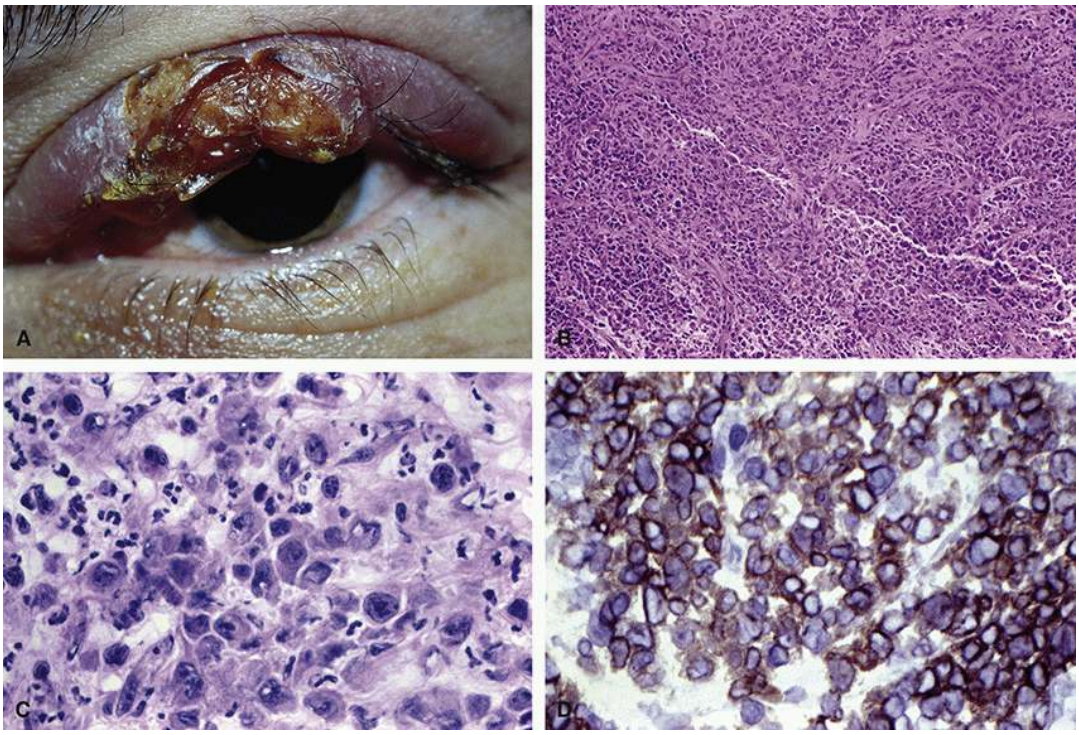

FIGURE 129.6 A, A man in his middle 30s developed an ulcerated 2-cm-diameter lesion of his left upper eyelid over 2 months. B, The dermis has a diffuse infiltrate of mostly large lymphocytes with fewer intermixed small lymphocytes and neutrophils. C, The large lymphocytes are anaplastic with irregularly shaped nuclei, large nucleoli, and a moderate amount of amphophilic cytoplasm. There are neutrophils between the lymphoma cells. D, The large anaplastic lymphocytes express CD30 on their cell membrane. The CD30+ anaplastic lymphocytes also expressed CD4 (T helper lymphocyte marker). They were negative for the expression of B-lymphocyte markers CD19 and CD22. There was no evidence of systemic lymphoma, and he received chemotherapy and radiotherapy and had resolution of his eyelid disease with no recurrence after 10 years.

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CHAPTER 130

Dermatofibrosarcoma Protuberans

Key Points

- Dermatofibrosarcoma protuberans is a fibroblastic cutaneous sarcoma that represents the most common dermal sarcoma
- It has a very low metastatic potential but has a tendency for local recurrence when incompletely resected
- It typically arises within the dermis and subcutaneous fat and runs an indolent, low-grade course
- Cases have been associated with tattoos and areas of previous trauma and radiation exposure
- Lesions present as an asymptomatic, skin-colored to red-brown, slowly growing, indurated, superficial soft tissue plaque
- The mainstay of treatment is surgical resection with negative margins
- The prognosis is generally very good if the tumor is widely excised

Dermatofibrosarcoma protuberans (DFSP) is a fibroblastic cutaneous sarcoma that represents the most common dermal sarcoma.[1] It generally runs an indolent course and is associated with a high cure rate when completely resected.[2] The classic form of DFSP has a very low metastatic potential but has a tendency for local recurrence when incompletely resected. However, this tumor may undergo a fibrosarcomatous transformation in 5% to 15% of cases, and this is associated with an increased risk of metastases, of about 10% to 15%.[3] The presence of transformed fibrosarcomatous features can often be detected in the primary tumor, but in some cases, it is identified only in relapsed tumors.[3,4] DFSP was first established as a distinct disease by Darier and Ferrand in 1924.[5] The term dermatofibrosarcoma protuberans was coined in 1925 by Hoffman,[6] and in 1962 Taylor and Helwig emphasized its histopathologic findings.[7]

DFSP is an indolent, low-grade cutaneous soft tissue sarcoma that typically arises within the dermis and subcutaneous fat, and in some cases infiltrates deeper into muscle and fascia.[8] Rarely, this tumor can arise within subcutaneous fat, either without involvement of the dermis or with only minimal dermal involvement.[8] It represents less than 0.1% of all malignancies, less than 5% of adult soft tissue sarcomas, about 18% of all cutaneous soft tissue sarcomas,[9] and fewer than 1% of all malignant tumors of the head and neck.[10,11] It has an incidence of 0.8 to 4.2 cases per million persons per year.[12,13]

DFSP is a soft tissue sarcoma that usually originates from the dermis of the skin. It rarely metastasizes (less than 5%), but there is a high propensity for local recurrence, often associated with significant morbidity.[14] The tumor can be locally aggressive when it extends into deeper subcutaneous layers.[15]

This tumor usually occurs in the third to sixth decades of life, but it has also been reported in infants, children, and adolescents, with pediatric patients accounting for about 6% of cases.[16,17] Males are affected slightly more frequently than females (about 57%),[18,19] and blacks have an incidence that is almost double that reported among Caucasians.[20]

DFSP occasionally exhibits fibrosarcomatous transformation (DFSP-FS), seen in 7% to 16% of cases.[18,21] In these instances, it exhibits a more aggressive course, shows an increased capacity for hematogenous dissemination, and is associated with a risk of metastasis of about 10%.[22,23,24,25] The main sites for DFSP-FS metastasis are the lungs, bones, soft tissue, and brain.[26,27] Clinically, DFSP-FS is indistinguishable from classic DFSP and requires histopathology for differentiation.[28]

Etiology and Pathogenesis

The etiology of DFSP remains unknown. Cases have been associated with tattoos,[29,30] and can occur in areas of previous trauma such as vaccination scars, central venous lines, and burn scars, and have been associated with tanning bed use.[31,32,33,34] Postradiation DFSP has been reported in seven cases.[35,36,37,38,39,40]

The histogenesis of DFSP remains controversial and has been attributed to fibroblastic, myofibroblastic, and neural origins. Dominguez-Malagon et al[41] presented ultrastructural evidence supporting a dendritic dermal cell origin. DFSP is characterized by the chromosomal translocation t(17;22) (q22;q13) between chromosomes 17 and 22. This translocation is present in more than 90% of DFSP and is thought to be a key factor in its pathogenesis. This leads to the fusion of the genes encoding for platelet-derived growth factor-beta polypeptide (*PDGFB*) and collagen type 1A1 gene (*COL1A1*). The resulting fusion gene upregulates PDGFB, resulting in overproduction of PDGF and leading to cellular proliferation and tumor formation.[1,42]

Molecular profiling in a small number of cases (five DFSP and five DFSP with FS transformation) indicated that the FS progression was sustained by a transcriptional reprogramming, paralleled by a loss of genomic material from a nontranslocated chromosome 22q, and occasional loss of the short arm of chromosome 22.[22]

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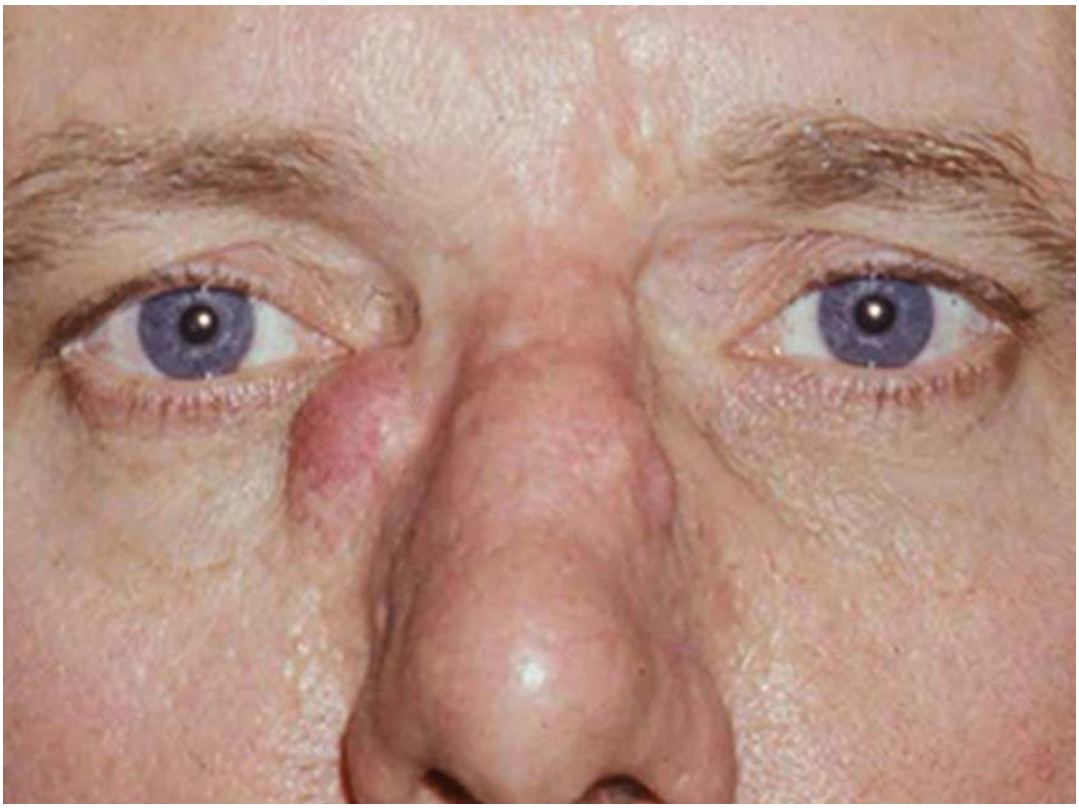

FIGURE 130.1 Subcutaneous nodule of dermatofibrosarcoma in the medial lower eyelid and medial canthus. (Courtesy of Drs. John Holds and Scott Fosko.)

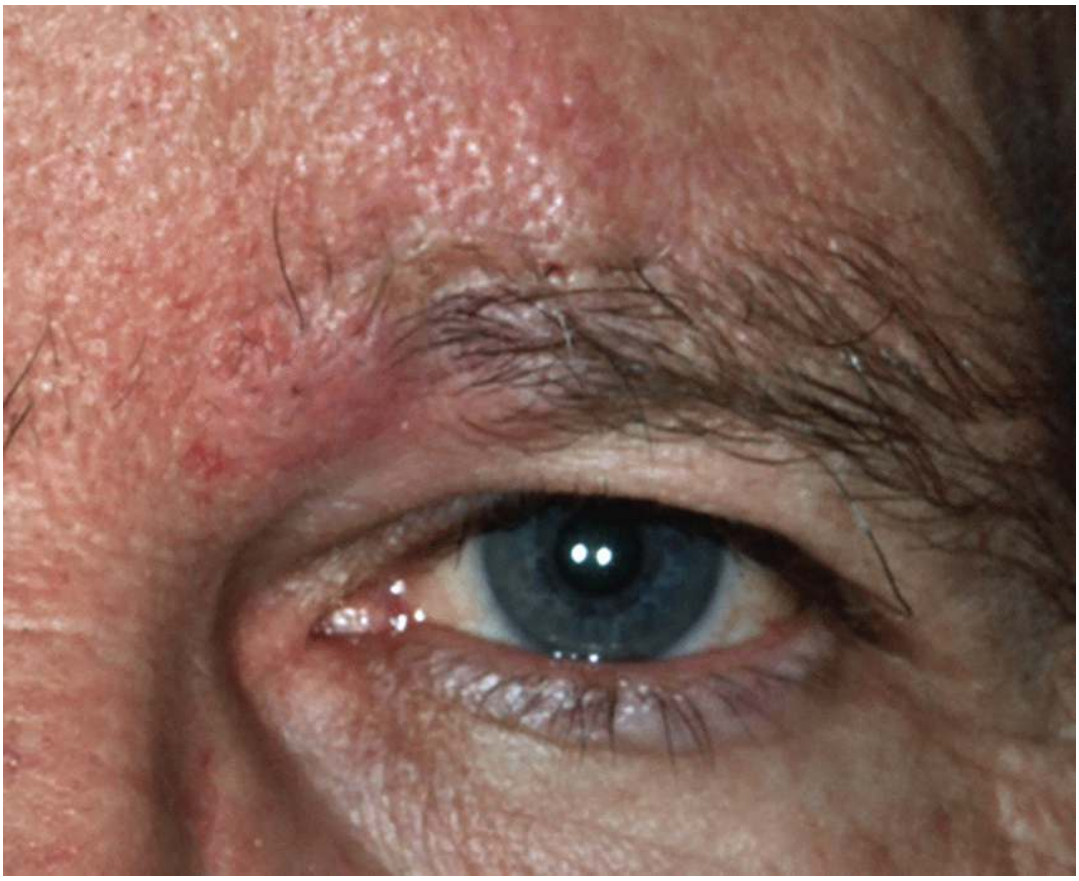

FIGURE 130.2 DFS of the medial brow. (Courtesy of Dr. Jurij Bilyk.)

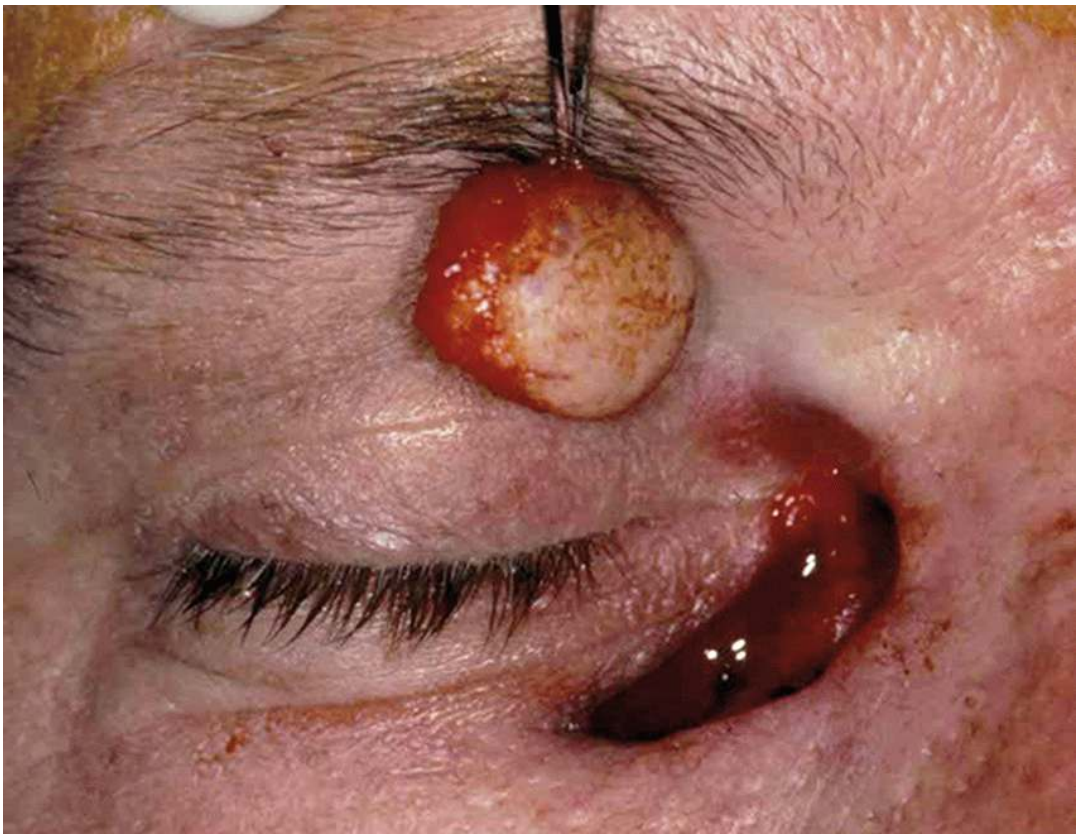

FIGURE 130.3 Surgical excision of the lesion in Figure 130.1 showing the subcutaneous location. (Courtesy of Drs. John Holds and Scott Fosko.)

Clinical Presentation

DFSP usually presents as an asymptomatic, skin-colored to red-brown, slowly growing, indurated, superficial soft tissue plaque that eventually develops single or multiple raised violaceus nodules in early to middle adult life (Figures 130.1 and 130.2). Tumors are usually firm, and hemorrhages or cystic degeneration may be seen. A pigmented variant (known as Bednar tumor) is seen in less than 5% of cases. Necrosis is rare and suggests the possibility of high-grade transformation.[43]

The mean duration of symptoms before presentation is 2 to 3 years but can range from a few months to as much as 60 years.[44] The most common sites of occurrence are the trunk (40%-60%), proximal extremities (20%-40%), and head and neck (10%-15%).[18,45,46]

Most lesions remain localized within the dermis and subcutaneous tissue (Figure 130.3), but recurrent or long-standing tumors can invade more deeply into the fascia, muscle, periosteum, and even bone. In the early growth phase, tumors are fixed to the overlying skin without involvement of deeper tissues, but later they can begin a rapid growth phase where they can infiltrate into deeper fascial planes. Rapid tumor enlargement often reflects fibrosarcomatous transformation.[47]

Differential Diagnosis

The differential diagnosis for DFSP is extensive and includes neurofibroma, schwannoma, solitary fibrous tumor, dermatofibroma, leiomyoma, keloid, desmoid tumor, nodular fasciitis, sarcoidosis, malignant melanoma, morpheaform basal cell carcinoma, Kaposi sarcoma, and fibrosarcoma.[12]

Treatment

The mainstay of treatment for DFSP is surgical resection. When complete excision is accomplished with negative margins, a cure without recurrence can be achieved. However, excision with conservative margins of 1 to 1.5 cm can lead to unacceptable tumor control, with published local recurrence rates varying from 26% to 60%.[45,48,49,50,51,52] To improve local control after surgery, many authors have recommended wide excision with a 2 cm or greater margin of resection. In cases where the resection margin was larger than 2 cm, the mean local recurrence rate was reported to be 18%.[52]

Wide resection margins of 2 cm or more are impractical or impossible for most eyelid lesions without sacrificing vital structures. Mohs micrographic surgery (MMS) is an alternative approach in such cases where preservation of cosmesis and function are a priority. MMS has been shown to achieve tumor clearance with smaller margins of resection and greater preservation of healthy tissue than with conventional surgery.[53,54] Recurrence rates of 0% to 8% have been reported with MMS over follow-up intervals of 38 to 60 months.[55,56,57,58]

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The role of radiotherapy alone as the primary treatment for DFSP remains unclear. As an adjuvant treatment along with surgery, the difference in local recurrence is not significant compared with surgery alone. However, in a recent meta-analysis, there was a positive trend in the direction of a positive benefit.[59] Nevertheless, radiotherapy in doses of 50 to 60 Gy as an adjuvant to surgical resection should be considered if margins are positive and further resection is not possible, or where wide excision alone would result in major cosmetic or functional deficits.[60]

Systemic cytotoxic therapy for locally advanced or metastatic DFSP plays a limited role in treatment. The most common regimens include doxorubicin and ifosfamide, and case reports using methotrexate and vinblastine or vincristine, actinomycin, and cyclophosphamide have shown little to no effect in treating DFSP.[61] Overall, there is a minimal role for conventional chemotherapy, and clinical outcomes have been poor.[52]

Molecular targeted therapy based on identification of the t(17;22) translocation prompted the use of tyrosine kinase inhibitors for the treatment of DFSP.[62,63,64] Imatinib mesylate, an oral tyrosine kinase inhibitor, has been used for recurrent, unresectable, and metastatic DFSP in adults. This agent competitively inhibits ATP binding to the PDGF-beta receptor, a tyrosine kinase, slowing down kinase activity, thus limiting tumor growth and promoting apoptosis. Patients with the t(17;22) translocation show a greater response to imatinib mesylate, and the majority of such patients show a favorable response to therapy. In a meta-analysis of nine studies involving advanced or metastatic DFSP, complete response to imatinib was reported in 5.2%, partial response in 55.2%, stable disease in 27.6%, and progression in 9.2%.[65] Sorafenib, a BRAF and vascular endothelial growth factor receptor inhibitor, was reported to show a dramatic response in the treatment of a DFSP that failed all previous treatments, with no recurrences over a 6 month follow-up interval.[66]

Prognosis

The prognosis of DFSP is generally very good if the tumor is widely excised with negative margins.[48] The 2- and 5-year survival rates have been reported as 97% and 92%.[49,67] In a retrospective analysis of 5249 patients diagnosed with DFSP during 2003 to 2012 from the National Cancer Database for patients, the mortality rate was 3.1% over an average of 51.4 months of follow-up.[68]

DFSP with fibrosarcomatous transformation has been reported to have a higher rate of local recurrence, distant metastases, and death.[24] Hoesly et al[23] reported a 42% recurrence-free survival rate at 5 years. Other studies reported local recurrence rates of 36% and metastatic rates of 13%, both of which are greater than in the classic form of DFSP.[25]

Histopathology

DFSP is histologically subclassified by the World Health Organization into classic (conventional) DFSP, giant cell fibroblastoma, myxoid DFSP, pigmented DFSP (Bednar tumor), myoid DFSP, and fibrosarcomatous DFSP.[69] Other variants include atrophic DFSP, giant cell DFSP, granular cell DFSP, and sclerotic DFSP.[70,71]

The early nonprotuberant stage of classic DFSP has scattered elongated spindle cells in the upper dermis with a thin layer of normal papillary dermis between the tumor and overlying epidermis (grenz zone).[70] Protuberant DFSP lesions have uniform (monomorphic) spindle cells in the dermis that usually "extend into the subcutaneous fat or deeper" (Figure 130.4A, C).[7] Subcutaneous fat infiltration usually creates a lace-like or honeycomb pattern.[69] Tumor cell nuclei are elongated with minimal pleomorphism or hyperchromasia, the cytoplasm is scanty and moderately eosinophilic, and cell borders are ill-defined.[72] Mitotic figures are infrequent.[7,72] Taylor and Helwig noted, "the striking architectural characteristic was the disposition of tumor cells around a central 'hub', producing a pattern resembling the spokes of a wheel or whirligig. This cartwheel pattern was present in every lesion and usually dominated the microscopic picture" (Figure 130.4B, C)[7] Tumors are most cellular centrally, becoming less cellular peripherally, "where the cells appeared more mature and were associated with collagen. The lesions invariably blend into the adjacent normal corium despite the gross appearance of circumscription."[7] Centrally located tumor cells are plumper with rounder nuclei than the peripheral cells that tend to resemble typical fibroblasts.[7] Tumor cells may surround, but they do not invade skin appendages.[72] The epidermis overlying the tumor is usually thinned with flattened rete ridges,[7,72] and about 75% of tumors have a grenz zone of sparing in the upper dermis.[72] Tumor cells typically have strong and diffuse staining of their cytoplasm using antibodies to CD34 (Figure 130.4D).[1,70] The tumor cells can variably express CD99, and there may be focal expression of smooth muscle actin and epithelial membrane antigen.[1] Expression of factor XIIIa, S-100 protein, melan A (MART-1), and podoplanin are typically absent.[1] In cases where the diagnosis of DFSP is unclear, detection of the fusion gene *COL1A1-PDGFB* using fluorescent in situ hybridization confirms the diagnosis.[73] However, this fusion gene is absent in about 10% of cases, so failure to detect it does not rule out a diagnosis of DFSP.[73]

Fibrosarcomatous DFSP accounts for about 10% to 20% of DFSP cases, with the proportion of fibrosarcoma ranging from 5% to >75% of the tumor area.[71] The fibrosarcomatous areas have a fascicular or herringbone pattern, hypercellularity, atypical cytological features, increased mitotic activity, and focal or complete loss of CD34 expression.[69,71] The fibrosarcomatous area should be assigned a histological grade.[73,74]

Giant cell fibroblastomas occur most commonly in childhood[69,75] and accounted for 5 of 28 childhood DFSPs in a French Federation of Cancer Centers Sarcoma Group study.[17] Giant cell fibroblastomas are "characteristically hypocellular, consisting of loosely textured fascicles of slender wavy spindle cells set in an abundant and well-vascularized collagenous to *(Print pagebreak 869)* myxoid extracellular matrix."[17] A variable number of pleomorphic mononucleated and multinucleated giant cells are mixed with the tumor spindle cells or spread throughout the tumor.[17] Hybrid tumors with classic DFSP and giant cell fibroblastoma areas were 4 of the 28 childhood DFSPs in the French Federation of Cancer Centers Sarcoma Group study.[17]

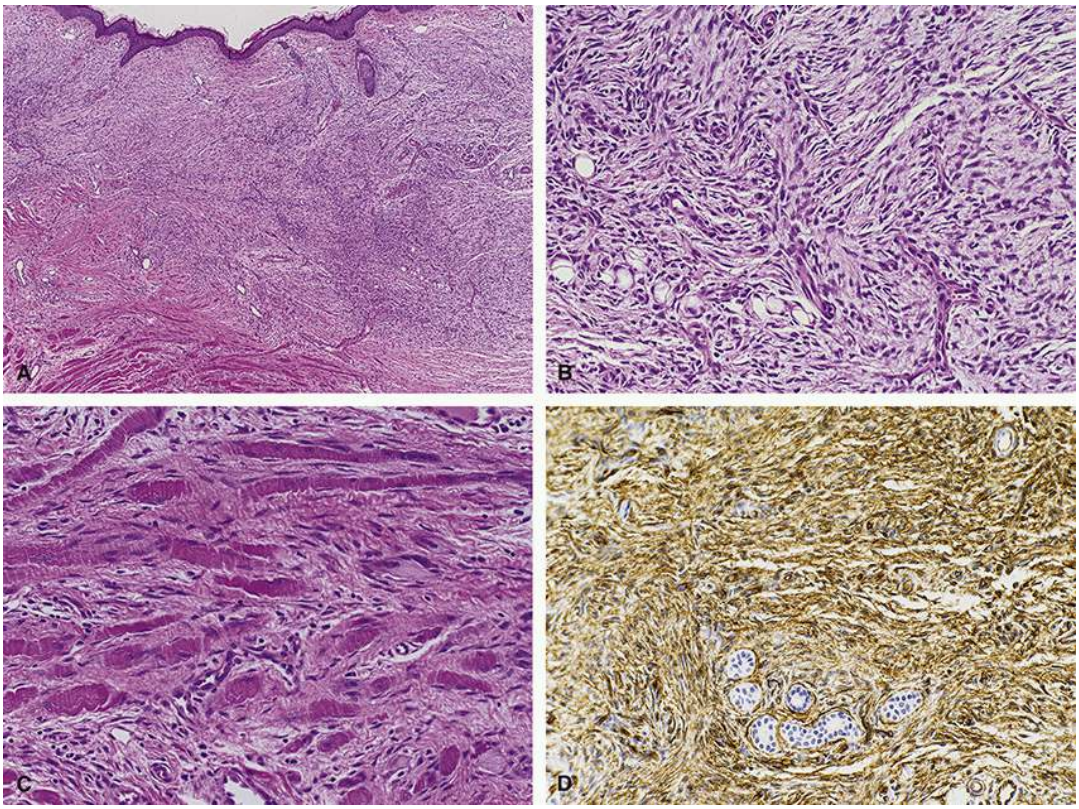

FIGURE 130.4 This classic dermatofibrosarcoma protuberans involved the left forehead and eyebrow of a child. A, The dermis has a proliferation of spindle-shaped tumor cells resulting in a blue hue compared with the underlying eosinophilic frontalis muscle. B, The tumor cells have a storiform (cartwheel) architecture typical of DFSP. The individual tumor cells have a uniform appearance without mitotic figures. C, Tumor cells infiltrate the frontalis muscle. D, The tumor cells are diffusely and strongly positive for CD34 expression. Tumor cells surround but do not infiltrate the eccrine glands near the bottom of the photomicrograph.

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CHAPTER 131

Fibrosarcoma

Key Points

- Fibrosarcoma (FS) is a highly malignant tumor of fibrous tissue
- These tumors predominantly arise from tendons and fascia of deep soft tissues, most often in the extremities, trunk, head, and neck
- The infantile type is classified as a tumor of intermediate malignancy that rarely metastasizes
- The adults type is a very malignant tumor with a high metastatic potential
- The etiology has not been identified, but genetic mutations and predisposing factors, such as scar tissues, former burns, foreign material, and radiotherapy, may be influential
- It usually presents as a painless, firm, spherical, sharply demarcated mass
- Treatment is with wide surgical resection, and for larger deep tumors radiation therapy after surgical resection
- The prognosis is poor with an overall 5-year survival rate of 40% to 60%, and the 10-year survival rate is 60% for low-grade and 30% for high-grade tumors, respectively

Fibrosarcoma (FS) is a highly malignant tumor of fibrous tissue. These tumors predominantly arise from tendons and fascia of deep soft tissues and most often involve soft tissues of the extremities, trunk, head, and neck. There have been reports of FS in visceral organs and retroperitoneum, but these have been questioned and it has been suggested that they represent other malignant lesions.[1] FS can occur inside bones as a primary tumor, and the periosteum also can be a site of origin.[2] Areas of preexisting bone injury or radiotherapy may give rise to secondary FS tumors.[3]

Two types of FS have been distinguished, an infantile/congenital type (IFS), and an adult type. FS in adults is classified as a highly malignant tumor with high metastatic potential. While this was previously believed to be the most common malignant soft-tissue sarcoma in adults,[1] more recent data show that FS accounts for only 3.6% of all adult sarcomas.[4]
Adult FSs mainly arise in middle-aged and older individuals between the ages of 25 and 80 years, with a median of 50 years,[1] and may be slightly more common in males.[5]

Several clinically, morphologically, and genetically distinct subtypes of adult FS have been recognized.[1] Low-grade fibromyxoid sarcoma occurs most often in young adults but can affect children in about 20% of cases.[6,7,8,9] It most commonly involves the deep soft tissues of the extremities and has a low risk of metastasis of approximately 15%. Sclerosing epithelioid FS has been considered to represent a distinct variant of FS, but some data suggest a link between this variant and low-grade fibromyxoid sarcoma.[10,11,12,13] It may exhibit aggressive behavior, metastatic spread, and a mortality rate of 25% to 57%.[12]

The infantile type of FS is classified by the World Health Organization as a tumor of intermediate malignancy that rarely metastasizes. It represents about 5% to 10% of all sarcomas in infants younger than 1 year.[14,15,16,17,18,19] The incidence in the United States is estimated to be five new cases per million infants. Infantile fibrosarcoma (IFS) is similar to adult FS histologically, but these two tumors differ in that *ETV6-NTRK3* gene fusion expression is present in IFS but absent in adult FS.[20]

FS can develop in the eyelid and orbit either as a primary lesion or as a secondary malignancy in children with retinoblastoma, with or without a history of radiotherapy.[21]

Etiology and Pathogenesis

A definitive etiology for FS has not been identified, but some genetic mutations and other predisposing factors, such as scar tissues,

former burns, foreign material, and radiotherapy, may be influential.[22,23,24] Adult FS has been reported to show multiple nonspecific numerical and structural chromosomal abnormalities, including complex karyotypes, unbalanced translocations, deletions, and inversion.[25,26] However, there do not appear to be any characteristic chromosomal changes.

IFS is associated with the characteristic t(12;15) (p13;q26) translocation encoding a novel fusion protein (ETV6-NTRK3) containing the protein-protein interaction domain of ETV6 and the tyrosine kinase domain of NTRK3. This results in an active fusion oncoprotein that is capable of transforming cultured fibroblasts.[20] This translocation does not occur in adult-type FS. Trisomy of chromosomes 8, 11, 17, and 20 are also frequent findings in IFS.[27]

Clinical Presentation

FS mainly arises in regions of deep connective tissue rich in collagen. The adult type is seen predominantly in the lower extremities, particularly around the thighs, knees, arms, and trunk.[28] Occurrence in the head or neck is less common. The tumor usually presents as a painless, firm, spherical, sharply demarcated mass (Figures 131.1 and 131.2).[29] Deep-seated *(Print pagebreak 873)* lesions become symptomatic when surrounding tissues are compressed.

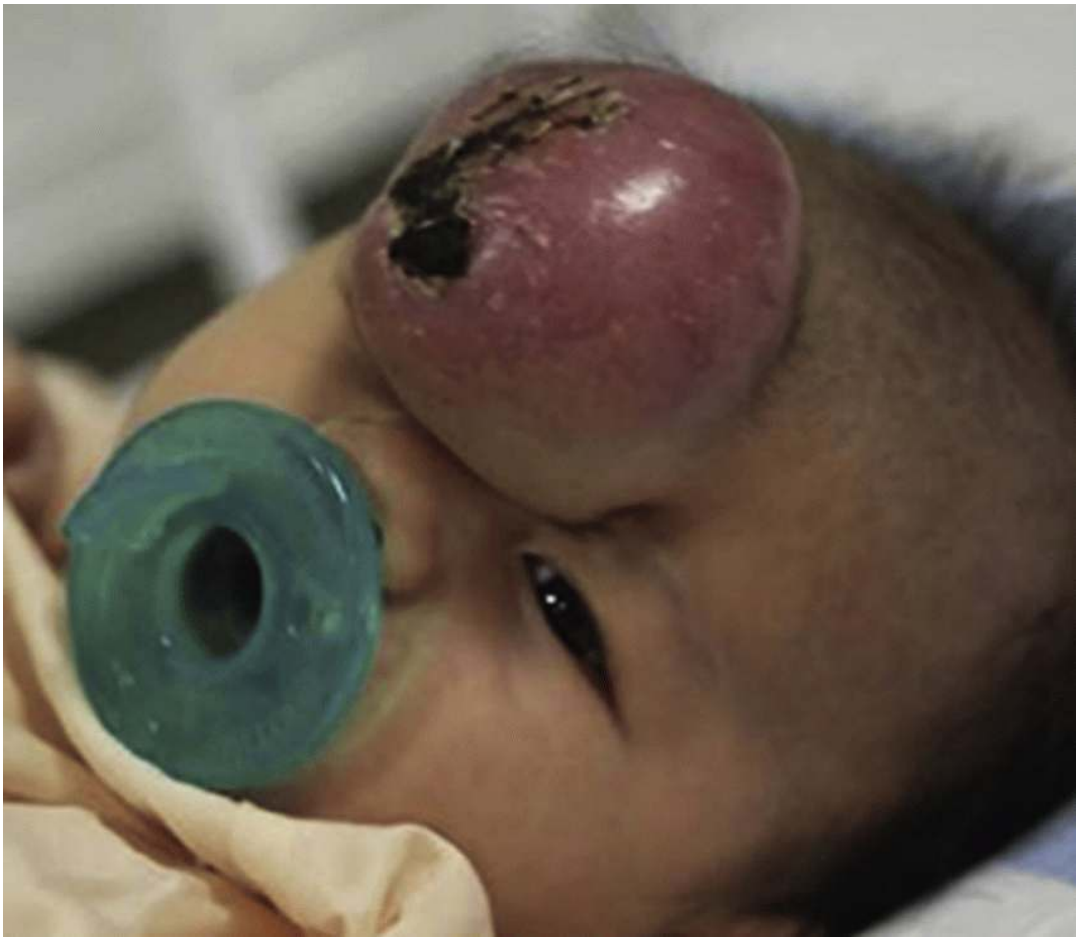

FIGURE 131.1 Infant with a 5-cm nonpulsatile congenital fibrosarcoma of the glabella. (Reprinted with permission from Elsevier; Nicholas RG, Brennan TE. Congenital infantile fibrosarcoma of the glabella: Nuances of achieving surgical cure without cosmetic or functional deformity. Int J Pediatr Otolaryngol 2019;117:110-114.)

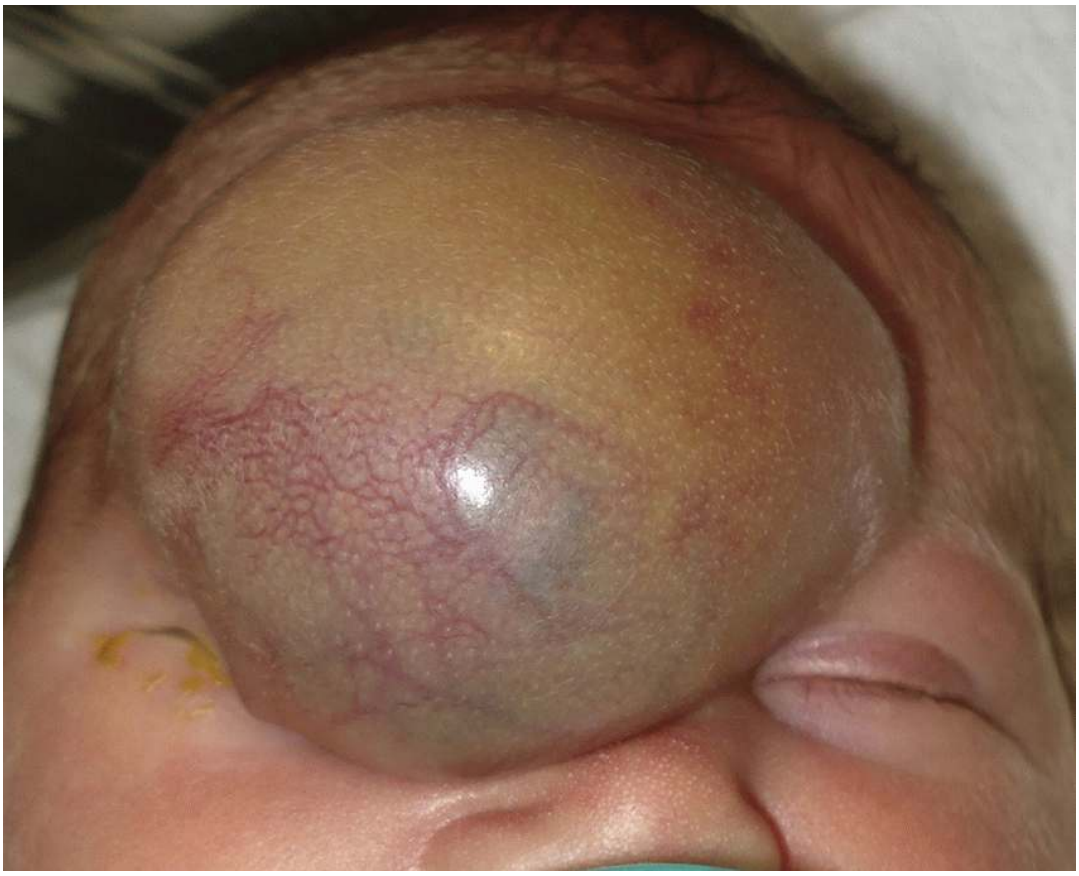

FIGURE 131.2 A massive fibrosarcoma of the eyelids, glabella, and forehead in an infant. (Courtesy of Dr. Peter Dolman.)

IFS affects infants and young children. About 30% to 40% of cases present at birth,[30] and it is rarely seen after the age of 2 years. Clinical presentation is a painless, localized, rapidly growing tumor, involving the upper and lower extremities in 60% of cases.[31] However, lesions on the abdomen and retroperitoneum have also been reported. The head and neck are involved in 10% of cases,[31] but occurrence on the eyelids is extremely rare.[32] The tumor is usually highly vascularized and occasionally causes ulceration of the overlying skin.[33] IFS occurs more commonly in males, with a male to female ratio of 3:2.

Differential Diagnosis

The presentation of FS is nonspecific, and the diagnosis is usually one of exclusion.[22] Clinically it can be confused with a wide variety of benign lesions and other sarcomas. Because of the highly vascular nature of these lesions, IFS may be confused with vascular tumors or malformations.[34] Immunohistochemical and molecular techniques help differentiate the various subtypes of FS, which otherwise can be very similar in morphology and clinical manifestations. Other spindle-type tumors such as the monophasic fibrous synovial sarcoma, malignant peripheral nerve sheath tumor, solitary fibrous tumor, aggressive fibromatosis, spindle-cell types of angiosarcoma, rhabdomyosarcoma, leiomyosarcoma, and epithelioid sarcoma must be distinguished from FS.[1,3,29,34]

Treatment

Treatment of localized FS of the eyelid consists of wide surgical resection. In cases with extension into the orbital, exenteration may be necessary.[21] For larger deep tumors radiation therapy after surgical resection is often recommended. Adjuvant chemotherapy for soft-tissue sarcomas remains controversial[28,35] and is not considered a standard treatment for these tumors except in patients with advanced disease. The response of FS to chemotherapy is generally not good, partly due to drug coresistance against vincristine, actinomycin D, vinblastine, and etoposide.[36] First-line chemotherapy in patients with advanced-stage FSs is based on anthracyclines such as doxorubicin. Improvement of overall survival rate has been seen in only 4% to 11% of patients with sarcoma treated with chemotherapy.

Prognosis

Poor prognostic factors for FS include high histologic grade, significant necrosis of greater than 50%, a high number of mitotic figures, increased cellularity, larger size, and deep localized tumors.[29,37] Histopathological grade is considered to be the most important prognostic indicator,[38,39] and patients with high-grade FS have a greater risk for metastases. About 80% of adult-type FSs are high-grade malignancies.[5] However, regardless of grade, the overall 5-year survival rate is only about 40% to 60%.[5,29,37] The 10-year survival rate is 60% for low-grade and 30% for high-grade tumors, respectively.[22]

Metastatic spread is seen in 9% to 63% of patients with adult-type FS.[40] The lungs and bones of the axial skeleton are the major sites of metastatic spread. In a small number of cases, regional lymph node involvement can also be seen.[2,40] IFS carries a more favorable prognosis with a 5-year overall survival rate of about 89%.[19,20] Tumor-associated *(Print pagebreak 874)* mortality is associated with larger tumor size and location in the head and neck and other locations where complete excision might not always be possible.[33]

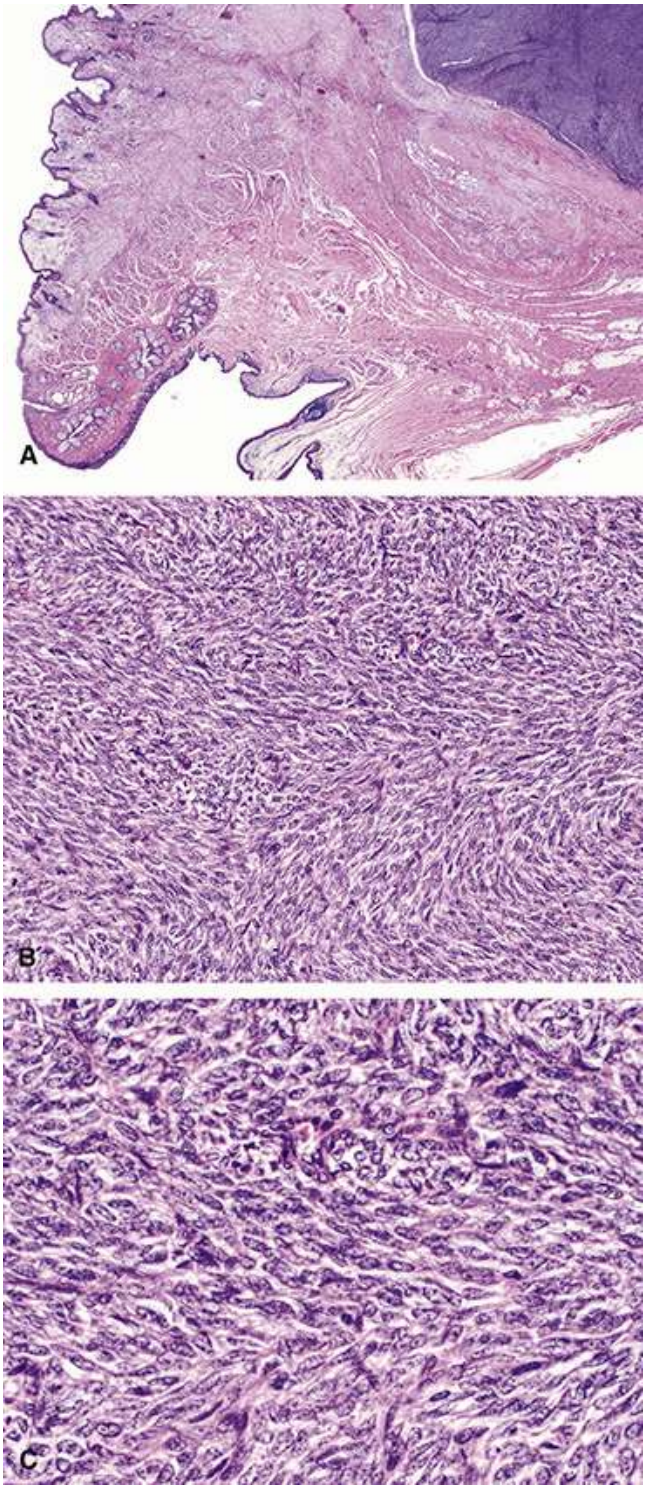

FIGURE 131.3 This fibrosarcoma arose in the right orbit of a 7-year-old boy and recurred 8 years following excision. The recurrent tumor was 25 × 28 × 17 mm and extended into the lower eyelid. A, At scanning magnification, the tumor extends anterior to the orbital septum. B, The tumor is composed of interlacing fascicles of spindle-shaped cells, creating a herringbone pattern. C, The tumor cells are spindle shaped and have oval nuclei, minimal cytoplasm, and indistinct cytoplasmic borders. There are scattered hyperchromatic nuclei. (Photomicrographs were prepared from a slide distributed by Dr. Ahmed A. Hidayat at the 1984 meeting of the Eastern Ophthalmic Pathology Society.)

Histopathology

The diagnosis of FS is one of exclusion.[1,41,42] IFSs are most commonly a cellular neoplasm with monomorphic spindle to oval cells arranged randomly or in a herringbone pattern (Figure 131.3).[43] Tumor cells have scant cytoplasm and slightly angulated nuclei, and the stroma ranges from collagenous to myxoid.[43] IFSs often have a hemangiopericytoma-like vascular pattern.[43] Mitoses may be infrequent to numerous, atypical mitotic figures are absent, and the tumors infiltrate adjacent tissues.[43] IFSs have a nonspecific immunohistochemical staining profile, but the diagnosis can be supported by demonstrating *ETV6-NTRK3* gene fusions or other gene rearrangements, including *NTRK1*, *BRAF*, and *MET*.[43]

Adult FSs are formed of relatively monomorphic spindle cells[1,42,44] "characteristically arranged in long, sweeping fascicles that may be angled in a chevron-like or herringbone pattern."[44] Tumor cells have tapering hyperchromatic nuclei, variably prominent nucleoli, and scant cytoplasm.[44] Variable numbers of mitoses are present, and the amount of interstitial collagen ranges from a delicate intercellular network to zones of keloid-like sclerosis.[42,44] There is no diagnostic immunohistochemical or molecular profile for adult FS, but immunohistochemistry and molecular analyses help exclude other soft-tissue tumors.[42,44]

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CHAPTER 132

Kaposi Sarcoma

Key Points

- Kaposi sarcoma (KS) is a low-grade, multicentric, vascular neoplasm
- Classic KS occurs in elderly men of southern European ancestry, typically on the lower extremities
- Endemic KS predominates in young black HIV-negative sub-Saharan African men
- Iatrogenic KS occurs in patients with solid-organ transplantation on immunosuppression therapy
- Epidemic KS is the most common type, seen with AIDS
- The pathogenesis remains controversial, but viral infection is thought to be the major factor
- Eyelids and conjunctival lesions present as solitary or multifocal, painless, reddish or violaceous, flat to elevated macules, papules, or nodules
- Surgical excision and radiotherapy are appropriate for isolated lesions, chemotherapy and immunomodulation for systemic disease, and highly active antiretroviral therapy (HAART) for AIDS-related KS
- The prognosis is favorable for patients with KS lesions limited to the skin, but the mortality rate in patients with visceral involvement is high

Kaposi sarcoma (KS) is a low-grade, multicentric, vascular neoplasm that was first described by Moriz Kaposi in 1872.[1] It is widely accepted that KS occurs in four clinical forms: classic, African endemic, epidemic, and idiopathic (transplant, immunocompromised-related).[2,3] Classic KS is an indolent disease that most often occurs on the lower extremities of men of southern Mediterranean, eastern European, or Middle Eastern descent in the sixth decade of life.[4,5] Risk factors associated with this form include never smoking, diabetes, and oral corticosteroid use.[6] The male:female ratio is about 17:1, and the clinical course is usually mild, with only rare involvement of visceral organs.[7,8]

African endemic KS is a subtype that predominates in sub-Saharan Africa and is typically seen in young black HIV-negative men 25 to 40 years of age.[9] There was a dramatic increase in KS since the onset of the HIV epidemic in Africa so that now it is the most common cancer among males and the second most common among females in Africa.[10] Clinical manifestations vary from indolent to aggressive and lethal. There are four subtypes of endemic KS recognized: benign nodular, locally aggressive, disseminated, and lymphadenopathic. Lymphadenopathic is the most aggressive form, seen most often in African children aged 1 to 5 years.[11]

Iatrogenic or posttransplantation, immunosuppressed-related KS occurs in patients following solid-organ transplantations treated with immunosuppression, or those on chronic immunosuppression for autoimmune disease.[12,13,14,15,16] Risk factors include male sex, nonwhite race, lung transplant, HLA-B mismatch, and older age at the time of transplant. The incidence is highest within the first year after transplantation.[17] Lesions are primarily limited to cutaneous involvement. Corticosteroids and cyclosporine A are the more common agents involved. Maintaining immunosuppression might be necessary for transplant patients to prevent organ rejection, but this can lead to further progression of iatrogenic KS. However, restoring immune defenses by reducing or discontinuing immunosuppression can often induce spontaneous tumor remission.[18]

The epidemic form of KS is the most common subtype, associated with the acquired immunodeficiency syndrome (AIDS), and is the most aggressive form of the disease. It frequently occurs in multiple locations involving the skin, mucous membranes, lymph nodes, and visceral organs including the gastrointestinal and pulmonary tracts.[19] Before the 1980s, KS was a very rare tumor occurring primarily in the classic and iatrogenic forms. But since that time, the occurrence of KS has significantly increased, primarily as the AIDS-related epidemic form. Up to 30% of patients with HIV not taking highly active antiretroviral therapy (HAART) will develop KS.[20] Since the appearance of the epidemic form of KS, there have been sporadic case reports of this tumor

in middle-aged HIV-seronegative homosexual males who have no evidence of immunodeficiency.[21,22,23,24] Clinical presentation in this group is similar to classic KS but occurs at a younger age. As with the classic form, cutaneous involvement usually involves the lower limbs, arms, genitals, and trunk. Also like the classic form, KS in this HIV-negative group runs an indolent course. This form has sometimes been recognized as a distinct subtype termed "nonepidemic KS."[19] A high percentage of patients with nonepidemic KS are positive for human herpesvirus-8 (HHV-8).[25,26,27]

Etiology and Pathogenesis

Infectious agents are known to contribute to the development of many human cancers.[18] Although the exact pathogenesis of KS remains controversial, a viral infection is thought to be a major factor. In 1994, Chang et al[26] first linked the etiology of *(Print pagebreak 877)* KS to a herpes-like virus (also known as human herpesvirus 8 [HHV-8]), where the viral genome was identified in approximately 90% of HIV-positive patients with KS. It was subsequently also found in classic Kaposi lesions of Mediterranean patients,[28,29] in KS lesions in HIV-negative individuals,[30] and in KS of bone marrow and organ transplant patients.[29] HHV-8 has also been identified in KS of the eyelid and conjunctiva.[31,32]

This virus belongs to the gamma-herpesvirus subgroup of Rhadinoviruses,[33] of which the best-known type is the Epstein-Barr virus. A high HHV-8 infection rate is found in Central and Southern Africa, with intermediate rates in the Mediterranean and Eastern European countries, and in some ethnic groups. These are locations and groups associated with the classic and endemic forms of KS. Infection is transmitted mainly by saliva, sexual contact, blood transfusion, or organ donor contamination and is thought to precede the development of KS. HHV-8 interferes with many normal cell functions and requires cofactors like cytokines or specific proteins to cause KS.[34] Although HHV-8 appears to be a promoting factor in pathogenesis, environmental and other cofactors such as inflammation and genetic or iatrogenic immune suppression are probably also required for disease development.[35]

KS is characterized by abnormal neoangiogenesis, inflammation, and the proliferation of tumor cells of endothelial cell origin, but the origin of the endothelial cell remains elusive.[36] The exact mechanism through which HHV-8 participates in oncogenesis is not completely understood, but some studies have identified HHV-8 viral oncogenes that may contribute to tumor development.[37] During the primary infection, HHV-8 induces interleukin-6 (IL-6) by modulating multiple mitogen-activated protein kinase pathways.[38] IL-6 is a proinflammatory cytokine secreted by cells including T cells, macrophages, and fibroblasts in response to trauma or pathogens. It induces *STAT3* (signal transducers and activators of transcription 3) gene activation, resulting in oncogene expression.[39,40]

It has been suggested that, after infecting endothelial cells, HHV-8 activates the mTOR pathway, alters the cells to undergo mesenchymal differentiation, and promotes aberrant angiogenesis.[33] Through immune suppression and inflammation, the HHV-8-infected cells proliferate. Expression of latency-associated nuclear antigen causes binding of p53 and suppresses apoptosis.[33,41] The nuclear factor kappa B signaling pathway, a regulator of innate immunity, is activated by HHV-8 and upregulates VEGF and bFGF resulting in neoangiogenesis.[41]

KS can also occur concomitantly with other HHV-8-associated diseases such as primary effusion lymphoma, multicentric Castleman disease, or KSHV-inflammatory cytokine syndrome.[42] Primary effusion lymphoma is a large cell non-Hodgkin lymphoma seen most commonly in body cavities and occasionally in extracavitary regions.[43] Clinically, it presents without a solid tumor mass but with lymphomatous effusions of the pleural, peritoneal, and pericardial cavities. The condition is usually associated with HHV-8 infections in immunocompromised individuals.[43] Castleman disease is a heterogeneous group of disorders, divided into unicentric and multicentric forms associated with enlarged lymph nodes, fever, night sweats, and nausea. The multicentric form is associated with KS and HHV-8 infection, often in the setting of HIV infection.[44] KSHV-inflammatory cytokine syndrome (KICS) is a systemic illness that typically occurs in association with KS.[45] Unlike most KS, KICS shares mechanisms of viral pathophysiology with KSHV-associated multicentric Castleman disease.

Clinical Characteristics

KS can present as a slow-growing localized lesion or as widespread systemic involvement. Most commonly, it involves the skin of the lower legs, genitalia, oral mucosa, and face, but it can also occur in the digestive tract, lymph nodes, bones, lungs, and liver.[46,47] Pulmonary involvement is the most common visceral manifestation and can be found in 47% of patients with AIDS KS at autopsy.[48] Visceral involvement of the gastrointestinal tract and lungs manifests with nausea, vomiting, weight loss, cough, hemoptysis, and pleural effusion.[49] Lymphatic spread can occur with resultant edema and palpable lymph nodes.[50]

The incidence of KS increased significantly after the onset of HIV infection in the 1980s, and ocular adnexal KS tumors were seen in about 20% of patients with KS.[35] Before HAART, ophthalmic manifestations were seen in 20% to 30% of patients with HIV/AIDS,[51] but now the prevalence is reported at 0.4% to 3.4%.[52,53] The eyelids and conjunctiva are typically involved equally, but with conjunctival lesions, the most common area of involvement is in the lower fornix.[35]

More than 300 cases of KS involving the eyelids and conjunctiva have been mentioned in the literature since 1984.[32,35,54,55,56,57,58,59,60,61,62,63,64,65,66,67] Although most ophthalmic cases are of the endemic type, several cases of classic KS of the eyelid or conjunctiva have been reported.[54,60,68,69] Where data were available from these reports, 85% to 90% of affected patients were male with a mean age at presentation of 39 years, and a range from infancy to beyond the ninth decade. The duration from the initial appearance of lesions to clinical presentation ranged from 3 weeks to 3 years, with most being 12 months or less. More than 50% of eyelid cases may be associated with disseminated systemic disease involving the oral cavity, pharynx, gastrointestinal tract, lower extremities, and regional lymph nodes. Eight cases were reported to involve bilateral eyelids. When ocular manifestations are present, KS may involve the skin of the eyelids; the bulbar, tarsal, and forniceal conjunctiva; plica semilunaris; and caruncle.

KS lesions on the eyelids generally present as solitary or multifocal, painless, flat to elevated macules, papules, or nodules, ranging in size from 5 mm to 1.5 cm[51] (Figure 132.1). Lesions vary in color from red and purple to dark brown in older lesions.[70] They usually are surrounded by tortuous dilated vessels and can be associated with eyelid edema, trichiasis, ptosis, and ectropion. Lesions can be sessile or pedunculated[66] and may occasionally become necrotic, with bleeding and pain.

Isolated conjunctival lesions are rare, and although they usually occur late in AIDS, there are reported cases presenting as an initial manifestation of AIDS.[64,71,72,73] Conjunctival KS lesions may be small and nodular or diffuse, elevated, and globular (Figure 132.2). Rare cases of orbital involvement have also been reported.[67,74,75]

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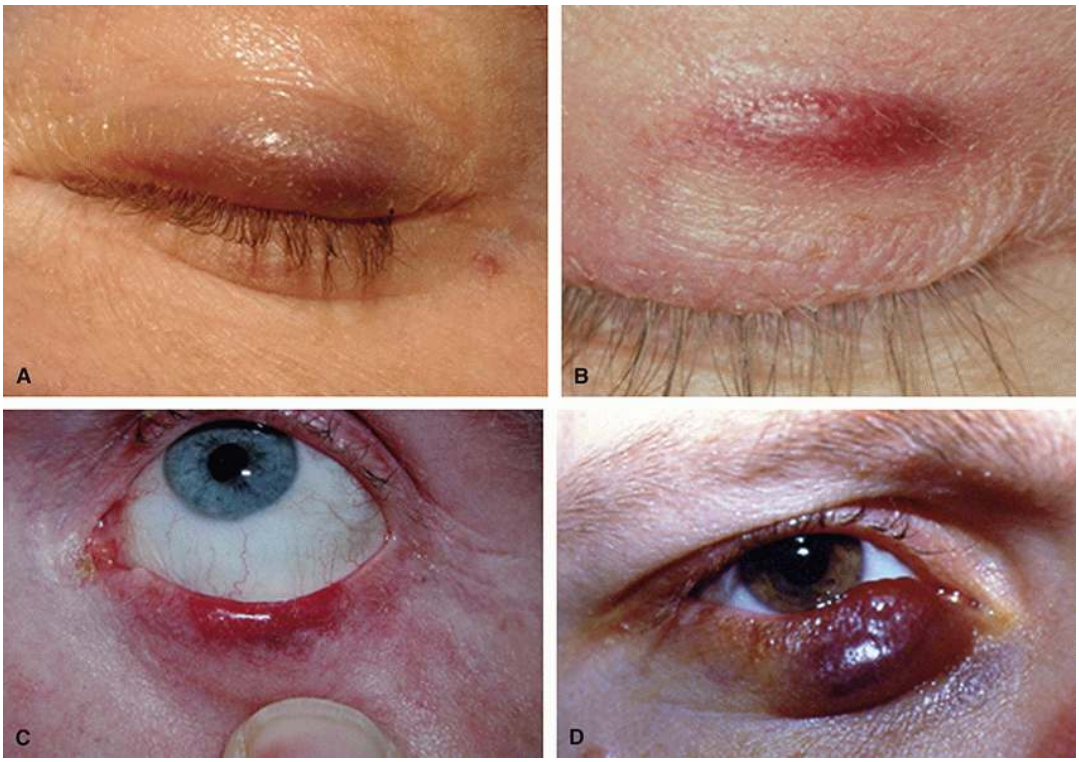

FIGURE 132.1 A-D, Kaposi sarcoma involving the eyelid skin. (A and C, Courtesy of Dr. Timothy Sullivan; D, Courtesy of Dr. Thomas Johnson.)

Differential Diagnosis

KS lesions may mimic benign lesions such as inflammatory dermatoses, pyogenic granuloma, foreign body granuloma, chalazion, hordeolum, chronic subconjunctival hemorrhage, melanocytic nevus, cavernous hemangioma, and dermatofibroma. It is also commonly mistaken for other neoplasms including angiosarcoma, malignant melanoma, or Merkel cell tumor. A biopsy is necessary to confirm the diagnosis.

Treatment

There is no cure for KS. Treatment goals include palliation of symptoms, prevention of progression and visceral organ

compromise, and in some cases cosmetic improvement. For epidemic HIV-related KS, combined antiretroviral therapy (cART) usually allows regression and prolonged stabilization of lesions, especially with mild forms of the disease.[76] A recent report suggested that patients with HIV on cART with sustained HIV viral control and restored CD4 T cell counts might develop a more limited form of KS, with restricted and less inflammatory skin lesions.[42,77]

For each of the other epidemiologic forms of KS, treatment options are similar and include conventional surgery, cryotherapy, laser therapy, intralesional injections of vinblastine or bleomycin, interferon-α (INF-α), radiotherapy, and systemic chemotherapy with liposomal daunorubicin or paclitaxel.[54] Local therapy is preferred for isolated KS lesions, whereas systemic treatment is indicated for widespread tumor dissemination, marked symptomatic edema, rapidly progressive disease, visceral involvement, and KS recurrence not responsive to local therapy. Although liposomal anthracyclines and taxanes are the mainstays of systemic cytotoxic therapy, novel therapies, including INF-α, thalidomide, antiherpes therapy, imatinib, and matrix metalloproteinase inhibitors, have been attempted with some success.

In AIDS-related KS with localized disease, therapy includes surgical excision, radiotherapy, cryotherapy, or intralesional INF-α injections.[57,78,79,80,81,82] The introduction of HAART in 1991 significantly altered the epidemiology and disease course of KS in HIV-infected patients.[76] Chemotherapy is combined with HAART in patients with more extensive, rapidly progressive disease, visceral involvement, or absence of improvement with HAART alone.[81]

Radiotherapy is an effective treatment modality for localized skin and mucosal lesions,[81] resulting in remission rates of 90% or greater with fractionated doses of 24 to 35 Gy.[58,70,83,84,85,86,87,88,89,90] Although the dose needs to be tailored for each patient, greater *(Print pagebreak 879)* doses are associated with a higher response rate, a lower incidence of residual pigmentation, and a longer duration of tumor control.[61] However, eyelid and conjunctival KS seem to be more radiosensitive than those in other sites, and lower fractionated and even single doses have been recommended. Ghabrial et al[58] reported a complete response rate of 32% and a partial response rate of 68% in the treatment of 31 eyelid and conjunctival KS after a single radiation dose of 800 cGy.

FIGURE 132.2 A-C, Kaposi sarcoma involving the conjunctiva. (B, Courtesy of Dr. Roman Shinder; C, Courtesy of Dr. Timothy Sullivan.)

Chemotherapy in combination with doxorubicin, bleomycin, and vincristine is indicated for disseminated disease. Several studies have shown that intravenous pegylated-liposomal doxorubicin is more effective and less toxic and is more effective than antiretroviral therapy alone when used as first-line systemic chemotherapy,[91] with a partial or complete response rate of 46% compared with 25% for standard chemotherapy alone.[92] With the addition of HAART, a complete or partial response rate was reported in 78% of patients.[93]

Successful treatment of classic KS with taxanes has been reported.[94,95] These agents have significant antiangiogenic activities in vivo by downregulating Bcl-2-induced antiapoptotic effects, blocking the growth, migration, and invasion of KS cells.[96] Paclitaxel, a cytotoxic taxane, has become a second-line treatment agent for patients with KS recurrent or refractory to chemotherapy.[97,98,99] This has achieved 45% to 59% partial or complete response rates, but with higher levels of toxicity.

INF-α is a less toxic alternative. Interferons are low-molecular-weight glycoproteins with antiviral and antineoplastic properties that bind to cell surface receptors causing upregulation of tumor-specific antigens and adhesion molecules. Studies have reported regression of KS with systemic INF-α in up to 45% of patients.[80,81,82] However, the side effects are significant. The pegylated formulations show greater efficacy and less toxicity compared with nonpegylated forms.[81] Topical or intralesional IFN has also been used for conjunctival and adnexal KS.[82]

Immunotherapy is aimed at reversing the anergy of immune cells induced by the tumor and its microenvironment, to kill tumor cells.[41] This restoration of immune function is based on the blockade of immune checkpoints by monoclonal antibodies. Ipilimumab blocks CTLA-4; nivolumab and pembrolizumab block PD-1; and atezolizumab blocks PD-L1. Recent reports demonstrated a positive response of KS to checkpoint inhibition therapy after 3 to 6 months in a majority of cases, with approximately 60% of partial responses, 10% of complete remissions, and 30% of stable diseases.[98,99]

For small localized eyelid KS tumors, surgical excision, with or without adjunctive cryotherapy, has been reported to provide long-term regression.[57,63]

Prognosis

The prognosis of KS in both transplant recipients and HIV-infected patients predominantly depends on the extent of disease, rate of tumor growth, and the patient's immune status. Both forms of KS have a variable prognosis that may depend on CD4 cell count and the presence of associated opportunistic infections. In patients with iatrogenic KS, the prognosis also depends on their underlying medical status and their ability to undergo a reduction in immunosuppression. A worse prognosis is usually found in patients with visceral organ involvement, particularly the lungs.[41]

Patients with KS lesions limited to the skin without systemic involvement have more favorable outcomes compared with the high mortality rate seen in patients with visceral involvement.[100] In patients with epidemic KS that is rapidly *(Print pagebreak 880)* progressive or with visceral involvement, the prognosis is good with HAART combined with liposomal chemotherapy.

Histopathology

The histopathological features of the four clinical forms of KS are similar.[101,102] Typical (usual) KS progresses through patch, plaque, and nodular stages with different histological features.[101,103] The patch stage is the earliest evolutionary stage of KS and has a subtle endothelial proliferation with irregular, often jagged, vascular channels within the dermis.[103] The vessels are thin walled, lined by flattened inconspicuous endothelial cells; some have perivascular lymphocytes and plasma cells; and there may be extravasated erythrocytes and hemosiderin-laden macrophages (“siderophages”).[103] The neovascular spaces have a predilection for the vicinity of native dermal blood vessels and cutaneous appendages.[103] The plaque and nodular stages of KS are more cellular with haphazardly intersecting fascicles of spindle cells and poorly defined, slit-like vessels within the dermis that may extend into the subcutis (Figure 132.3).[101,103] There is a background of chronic inflammation rich in plasma cells, extravasated erythrocytes, and siderophages.[101,103] There may be intracellular or extracellular small, eosinophilic hyaline globules that are positive using periodic acid-Schiff stain and resist diastase digestion.[102] These globules are most often seen in the nodular stage of KS and are thought to represent degenerated erythrocytes.[102,103] Mild cytological atypia and occasional mitoses may be present.[101,103] KS lesional cells are immunoreactive for HHV-8-associated latent nuclear antigen, CD31, CD34, and podoplanin (recognized by D2-40 antibodies).[101] Factor VIII-related antigen (von Willebrand factor) is expressed by the endothelial cells of the best-differentiated vessels and variably by the spindle cells.[102] There are numerous histological variants of KS, but these are much less common than typical KS lesions.[101,102,103,104,105]

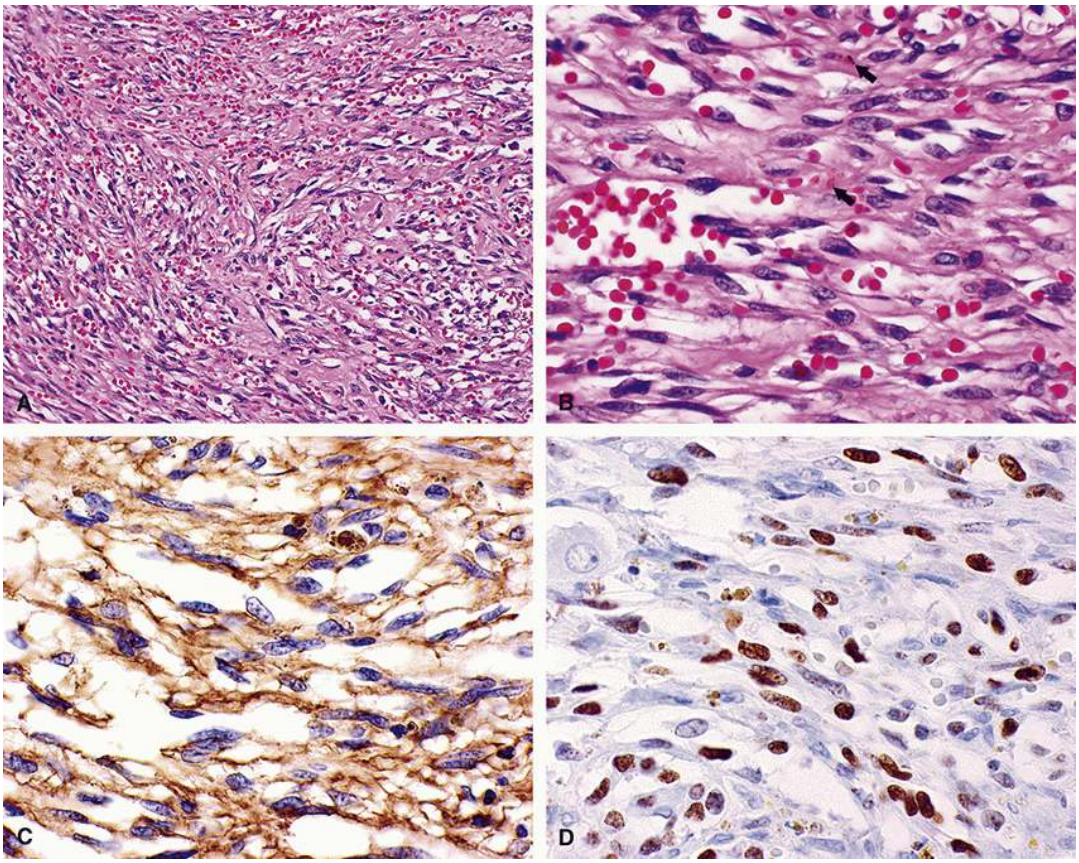

FIGURE 132.3 A man in his middle 40s developed Kaposi sarcoma due to chronic immunosuppression following orthotopic solid organ transplantation. The chest and abdominal skin had many KS nodules, with the largest being 2.1 cm in diameter. Innumerable nodules of Kaposi sarcoma were in both lungs and in the stomach and jejunum walls. A, Interlacing fascicles of spindle cells with slit-like vascular channels form the plaques and nodules of Kaposi sarcoma. B, Erythrocytes are present in the slit-like vessels, and there are a few macrophages with intracellular hemosiderin granules (arrows). C, Tumor cells uniformly express factor VIII-related antigen (von Willebrand factor). D, Most tumor cells express human herpesvirus-8 (HHV-8) latent nuclear antigen.

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CHAPTER 133

Leukemia Cutis

Key Points

- Leukemia is a cancer of myelogenous and lymphatic precursor blood-forming cells, and with infiltration of the epidermis, dermis, and subcutis it results in extramedullary lesions such as cutaneous leukemia cutis
- Leukemia cutis (LC) is seen most often with acute myelocytic leukemia
- In the periorbital region, LC presents as eyelid edema, with rubbery pink, violet, or red papules or nodules
- Extramedullary leukemia is a manifestation of current or impending systemic disease, so that treatment should anticipate systemic involvement
- Surgery is not effective, and periocular radiotherapy can have significant ocular complications
- Systemic chemotherapy is recommended for systemic disease

Leukemia is a cancer of myelogenous and lymphatic precursor blood-forming cells. These leukemic blast cells develop in the bone marrow and spread into the circulation. Several types of leukemia are based on whether the disease is acute or chronic, and whether it involves myeloid cells or lymphoid cells. According to the Surveillance, Epidemiology, and End Results (SEER) Program database, the estimated number of new cases of leukemia in the United States in 2022 is 60,650, or 5 3.2% of all new cancers. Of these, the estimated number of tumor-related deaths will be 24,000. The age-adjusted incidence is 12.9/100,000 population.[1]

Peripheral circulating leukemic cells possess the ability to leave the circulation and pass through soft tissues as a cellular infiltration, resulting in extramedullary leukemia. Myeloid sarcoma (MS), also known as chloroma or granulocytic sarcoma, is an extramedullary form of acute myeloid leukemia (AML) that can infiltrate soft tissues, bone, periosteum, and lymph nodes.[2,3,4,5] Because several variants of AML are not of granulocytic lineage, the term myeloid sarcoma is preferred over granulocytic sarcoma.[6] When the infiltration of neoplastic leukocytes is limited to the epidermis, dermis, and subcutis, and when this results in clinical cutaneous lesions, it is often referred to as leukemia cutis (LC). The latter is mostly seen with AML and acute lymphocytic leukemia (ALL), where it can occur in up to 10% of cases, but it can also be seen less commonly with other leukemia subtypes. In pediatric patients with acute leukemia, Russo et al identified specific orbital and ocular lesions (papilledema, Roth spots, leukemic hypopyon, optic nerve infiltration, exophthalmos, optic pallor, retinal infiltration, vitreal opacities) in 16.1% of 180 patients.[7] Orbital and ocular lesions occurred in 66.6% (10/15) of children with AML and 11.5% (19/159) with ALL.[7] The eyelid skin is very thin, and it has been suggested that this may predispose the patient to leukemic infiltrates.[8] Cutaneous infiltrates may develop during therapy for systemic leukemia or may signify relapse. Rarely, extramedullary cutaneous MS by a leukemic infiltrate may be the initial manifestation of disease, where it occurs in the absence of peripheral blood or bone marrow involvement by leukemia, a condition referred to as aleukemic leukemia.[9] Approximately one-third of patients with adult MS are cases of de novo aleukemic disease, with the skin being the most common site of involvement.[10,11]

In the periorbital region, the orbit is the most common site for MS, followed in frequency by the conjunctiva and eyelid.[12,13,14,15,16,17,18] It has been suggested that the higher frequency of cutaneous lesions in AML is a reflection of the more aggressive behavior of AML.[19] Bilaterality is reported in about 10% of cases. Many of the reported cases of orbital, conjunctival, or eyelid MS are lesions presenting as the initial manifestation of the disease, preceding the development of systemic leukemia.[6]

MS is reported in 2.5% to 21.2% of patients with AML[20,21] and can occur before, concurrent with, or following the onset of systemic bone marrow leukemia. Isolated MS may occur in the absence of leukemia, and these patients are often misdiagnosed with lymphoma.[22,23] MS can also develop during a relapse or after allogeneic hematopoietic cell transplantation.[24,25]

LC is much less common than MS, occurring in about 3% of patients with AML,[26] and is even less frequent in chronic leukemias.[27] Certain subtypes of AML are more commonly associated with skin infiltration, the most frequent associations being with acute myelomonocytic and monocytic differentiation with involvement in up to 50% of patients.[26,28,29] The incidence of LC may be

higher in children, particularly infants with myeloid leukemia.[30]

Leukemia is a cancer of myelogenous and lymphatic precursor blood-forming cells. In most patients, LC occurs after a diagnosis of leukemia has been established.[31] However, LC can develop before the onset of systemic leukemia, and most of these patients eventually will develop AML. The cutaneous lesions produced by different leukemia subtypes may *(Print pagebreak 885)* develop distinctly different morphologies over the course of the disease.[19,32] The most commonly involved anatomic locations are the lower extremities, followed by the upper extremities, back, trunk, and face.[33] Interestingly, LC may have a predilection for sites of previous or current inflammation.[34]

Etiology and Pathogenesis

There is no one cause of leukemia, and both genetic and environmental factors likely play a role. Most forms contain genetic or chromosomal alterations such as translocations, deletions, and inversions that block cellular differentiation or that promote the cellular proliferation of precursor lymphoid cells. AML is the most common congenital leukemia, and the most frequent chromosomal abnormalities are t(15:17) (q22;q12), t(8;21) (q22;q22), and inv (16) (p13;q22) rearrangements. Germline chromosomal abnormalities have been correlated with the prognosis of some leukemias such as AML.[35] ALL is the most common leukemia in children under the age of 15 years. The most common cytogenetic abnormalities are reciprocal translocations, t(12;21) in children and t(9;12) in adults. CML is more common in adults with a translocation between chromosomes 9 and 22, whereas in CLL the most common abnormality is del 13q14-23.1.[36]

Human T-cell leukemia virus type 1 (HTLV-1) was the first retrovirus discovered that caused human disease, and it has since been shown to cause adult T-cell leukemia (ATL), in addition to a form of myelopathy, and uveitis.[37] A genetic susceptibility was established because patients with some genetic syndromes, such as Bloom syndrome, neurofibromatosis, Fanconi anemia, ataxia telangiectasia, and trisomy 21, have a high risk of leukemia.[38] The role of other infectious agents has also been suspected in the pathogenesis of leukemia.[39,40] It is not clear how viruses could play a role in the development of leukemia, but theories include a direct transforming mechanism[41] or the result of abnormal immunological responses to congenital, neonatal, or postneonatal infections that promote secondary genetic or immunological alterations.[42]

Infants and young children with Down syndrome have a 500-fold increased risk of developing acute megakaryoblastic leukemia.[43,44] Acquired mutations of *GATA-1*, a gene responsible for megakaryocytic differentiation, are detected in the leukemia cells of these patients.[45]

Clinical Presentation

Approximately 50 cases of eyelid leukemia have been reported. Females were represented slightly more commonly than males (55% vs 45%). All ages have been affected from 10 weeks to 80 years, with a mean of 37 years.[15] The duration of symptoms until final diagnosis ranged from 10 days to 36 months, with a mean of about 8 months. All forms of leukemia can be involved, with the most common being acute myelogenous leukemia, ATL, and chronic lymphocytic leukemia.[15] Other forms that have rarely involved the eyelid include ALL, T-cell prolymphocytic leukemia, acute megakaryocytic leukemia, aleukemic leukemia, chronic myelogenous leukemia, and T-cell large granular lymphocyte leukemia.

The most common presenting symptoms and signs are one or more exophytic eyelid masses,[14,15] eyelid edema, conjunctival injection, and chemosis[19] (Figure 133.1). Fleshy pink, blue-violet, or red-brown papules or nodules are the most frequent lesions,[28,30] followed by infiltrated plaques, generalized cutaneous eruptions, and erythroderma. The nodules are typically firm or rubbery in consistency and can sometimes become purpuric.[17] Pain is rare, as is ocular involvement with uveitis, scleritis, and retinal flame hemorrhages, but lesions can frequently be asymptomatic.[46] Concurrent orbital involvement can be seen in some cases.[36] Many patients have no prior history of systemic leukemia, so that initial misdiagnosis is common. With a high index of suspicion, tissue biopsy, and appropriate histology, immunohistochemistry, and flow cytometry, will lead to a diagnosis.[15]

Differential Diagnosis

The differential diagnosis for cutaneous leukemic infiltrates is similar to that for lymphoma. These include other nonmelanoma malignancies, such as basal cell and squamous cell carcinoma, dermatofibrosarcoma, and metastatic lesions. It can also be mistaken for a variety of benign lesions such as reactive lymphoid hyperplasia, rosacea, *Herpes zoster*, erythema nodosum, and pyoderma gangrenosum. In addition, since common findings in eyelid LC are edema and chemosis, the differential diagnosis should include medication-induced hypersensitivity reaction, allergic contact dermatitis, angioedema, interstitial granulomatous dermatitis, allergic rhinitis, hyperthyroidism, Fabry disease, systemic lupus erythematosus, lymphatic obstruction, and orbital cellulitis.

Treatment

Since extramedullary leukemia is likely to be a manifestation of current or impending systemic disease, treatment should anticipate systemic involvement. Treatment depends on the location of the disease and whether it is the initial manifestation or a recurrence. In one study of MS,[22]
25% (4/16) of patients did not go on to develop acute systemic leukemia during a follow-up period of 3.5 to 16 years. Two of these four patients did not have any cytogenetic abnormalities and, given the wide variety of known anomalies in MS and AML, the authors suggested that, in some variants, no or certain cytogenetic abnormalities might confer a better prognosis and if present might spare some patients chemotherapy or radiotherapy.

Studies have demonstrated the effectiveness of systemic chemotherapy for primary MS, and this is currently the recommended therapy.[47,48,49] Systemic chemotherapy has been shown to decrease the rate of progression to acute leukemia and to increase survival time.[50]

Radiotherapy for isolated MS carries some potential toxicity depending upon the tumor location. It has also been shown to be associated with a high rate of progression to AML after a short nonleukemic period.[51] Also, Tsimberidou *(Print pagebreak 886)* et al reported that combined chemotherapy and radiotherapy for nonleukemic MS had a lower failure-free survival rate than chemotherapy alone,[52] and other studies showed that radiotherapy had no added effect on survival.[50,53]

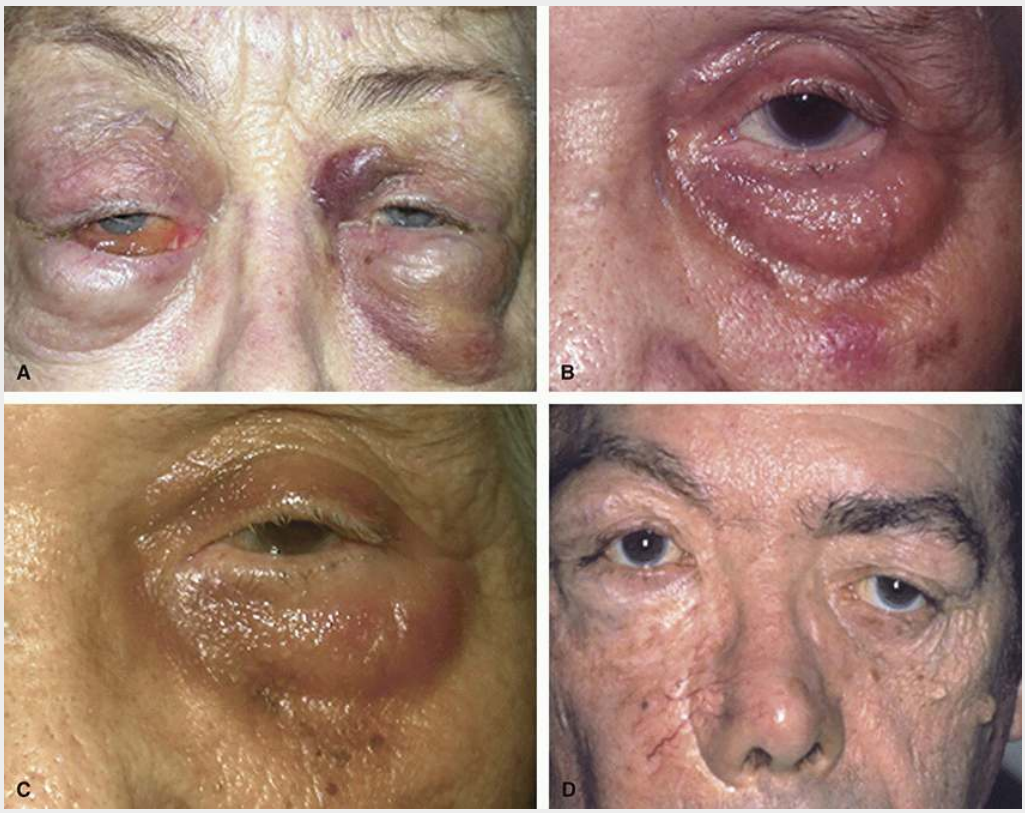

FIGURE 133.1 Leukemia cutis involving the eyelids. (A, B, & C, Courtesy of Dr. Charles Soparkar.)

Surgery for MS is even less effective, and patients frequently relapse or progress to systemic disease.[54] Patients treated with surgery alone without any systemic treatment have been shown to progress to AML sooner.[51] Surgery alone is not considered an effective treatment for primary MS, and surgery should be considered only in acute situations where rapid tumor debulking and symptomatic relief is needed.[47]

Prognosis

The presence of skin involvement with AML has been suggested to be an indication of aggressive disease with a poor outcome and shortened survival.[31,55] However, more recent studies on patients with AML did not find that the presence of cutaneous involvement was associated with a statistically significant worse response to treatment or a reduced survival rate.[26,52,53] For patients with extramedullary MS or LC disease, treatment outcome depends in part on whether it occurs alone in an otherwise

nonleukemic patient or is associated with systemic AML. Event-free survival and overall survival were found to be better in patients with isolated MS compared with those also having AML. In nonleukemic cases of MS, the 2-year event-free survival rate was reported at 32% and the overall survival rate at 43%, compared with 18% and 29%, respectively, in cases of MS with AML.[48] While most cases of nonleukemic isolated MS will develop acute leukemia, those who do not develop leukemia seem to have a better prognosis.[56]

Histopathology

LC infiltrates may be perivascular and/or periadnexal, diffuse interstitial, or form nodules in the dermis and subcutis.[57,58,59] The cellular appearance of the leukemic infiltrate reflects the underlying form of leukemia (Figure 133.2) and requires immunophenotyping to render a more specific *(Print pagebreak 887)* diagnosis.[57,58,60,61] The immunophenotype of the leukemic cells in the skin is not always concordant with that of leukemic bone marrow cells,[60] so final diagnosis should correlate bone marrow and skin findings. In biopsies of aleukemic LC, several algorithms assist in rendering an immunohistochemical diagnosis.[58,60]

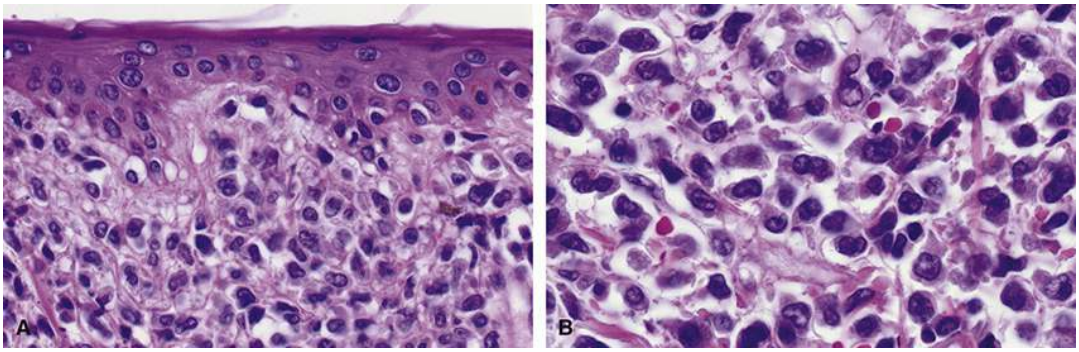

FIGURE 133.2 A man in his late 30s with acute myeloid leukemia, probable M5a (acute monoblastic leukemia) by cytogenetic analysis, developed numerous papules on his legs and papules and nodules on his abdomen. This biopsy is from an abdominal skin nodule. A, The leukemic cells form a sheet in the dermis with only a few in the zone immediately beneath the epidermis. B, The leukemic cells have mostly oval nuclei with irregular borders, fine chromatin, an occasional prominent nucleolus and scant to small amounts of faintly basophilic cytoplasm.

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CHAPTER 134

Liposarcoma

Key Points

- Liposarcoma (LPS) is the most common soft tissue sarcoma in adults
- In the periorbital region, liposarcomas may present in the orbit or on the eyelid
- They originate from primitive mesenchymal cells rather than from mature fat cells and usually develop in deep structures
- They usually present as a firm, mobile, nodular to lobulated, painless mass with well-defined to indistinct margins
- Complete wide surgical excision is considered the treatment of choice
- Incomplete surgical excision is associated with a high local recurrence rate of 80%
- Radiotherapy is ineffective, and results of chemotherapy are inconsistent
- The histologic subtype is an important prognostic indicator. Well-differentiated and myxoid LPS are low-grade lesions with 5-year survival rates of 83% to 100%; pleomorphic LPS is more aggressive, with a 20% to 60% 5-year survival rate

Liposarcoma (LPS) is a malignancy first described by Virchow in 1857.[1] It is the most common soft tissue sarcoma, accounting for 15% to 25% of all soft tissue malignancies in adults.[2] Most are located in the lower extremities, the retroperitoneum, and the mesenteric region of middle-aged individuals. LPS is uncommon in the head and neck area where it represents only approximately 1% of all sarcomas.[3,4,5] In the head and neck, liposarcomas have been reported in the neck, larynx, lip, oral cavity, cheek, larynx, thyroid gland, tongue, parapharyngeal region, temporal and frontoparietal regions, eyelid, and orbit.[6,7,8,9]

According to the 2020 World Health Organization classification scheme, there are five subtypes of liposarcoma: atypical lipomatous tumor/well-differentiated liposarcoma, dedifferentiated liposarcoma (DDLPS), myxoid liposarcoma, pleomorphic liposarcoma, and the exceptionally rare myxoid pleomorphic liposarcoma.[10] Goldblum, Folpe, and Weiss[2] advocated classifying liposarcomas into three large groups: well-differentiated/dedifferentiated (54%-64%; including spindle cell, atypical, inflammatory, and sclerosing subtypes), myxoid (25%-35%), and pleomorphic (8%-10%).[2,8,10,11,12] Generally, the well-differentiated and myxoid types behave as low-grade tumors and are more likely to occur in the head and neck.[13] The well-differentiated variety can undergo dedifferentiation, where it behaves more aggressively. The pleomorphic and round cell types demonstrate a more aggressive, high-grade behavior.[11]

Most liposarcomas are seen in adults, with a median age of 57 years, a predominance in males of about 76.5%, and 82% occur in white individuals.[13] The well-differentiated subtype is reported to occur in slightly older individuals and myxoid and pleomorphic subtypes in younger patients.[14]

In the periorbital region, liposarcomas may present in the orbit or on the eyelid. Primary orbital tumors have been reported in fewer than 50 cases, with the most common types being myxoid and well-differentiated subtypes.[15,16] Occasionally, orbital LPS can present initially as an eyelid mass.[9] Primary liposarcoma of the eyelid, on the other hand, is extremely rare, with only three cases reported in the literature.[17,18,19]

Etiology and Pathogenesis

Liposarcoma is thought to originate from primitive mesenchymal cells rather than from mature fat cells, and it usually develops in deep structures, whereas benign lipomas generally arise within subcutaneous and submucous tissues.

The classification scheme of LPS reflects distinct chromosomal aberrations in each category. About 90% of well-differentiated and dedifferentiated lesions have amplified chromosomal sequences of the 12q13-15 region, which carry the oncogenes *MDM2, CDK4,* and *HMGA2*.[20] In myxoid liposarcomas, 95% carry a translocation of t(12;16) (q13;p11) involving the *DDIT3 (CHOP)* and *FUS* genes.[21,22] Pleomorphic LPSs are high-grade malignancies that show complex karyotypes often with the loss of the tumor suppressor genes *P53* and *Rb*.[20]

Clinical Presentation

LPSs are slow-growing tumors. On clinical examination, they usually present as a firm, mobile, nodular to lobulated, painless mass with well-defined to indistinct margins. Lesions can be present for months to many years, and they are usually not associated with regional lymphadenopathy. In the head and neck, they are most commonly located in the subcutaneous connective tissue of the face, neck, and scalp, with relatively rare occurrences in the oral cavity and salivary glands.[13]

LPS of the eyelid is exceedingly rare and presents as a soft to firm, mobile subcutaneous mass (Figure 134.1). Only three cases in the eyelid have been reported.[17,18,19] One was a 67-year-old Chinese man who presented with a left lower *(Print pagebreak 890)* eyelid mass that had been present for 11 years. After a long period of slow growth, the lesion rapidly enlarged over 2 months.[17] On presentation, the subcutaneous mass was mobile, 60 mm in diameter with indistinct margins, and was initially diagnosed as a lipoma or neurofibroma. On histopathology, it was diagnosed as a well-differentiated LPS. Another case was a 25-year-old man, with a slowly growing left eyelid mass for 2 years.[18] It also was a well-differentiated LPS. The third case was an 11-year-old girl with a small left upper lid round cell LPS.[19] Despite multimodal therapy, the tumor recurred, and the child died from widespread metastases to the central nervous system and soft tissues.

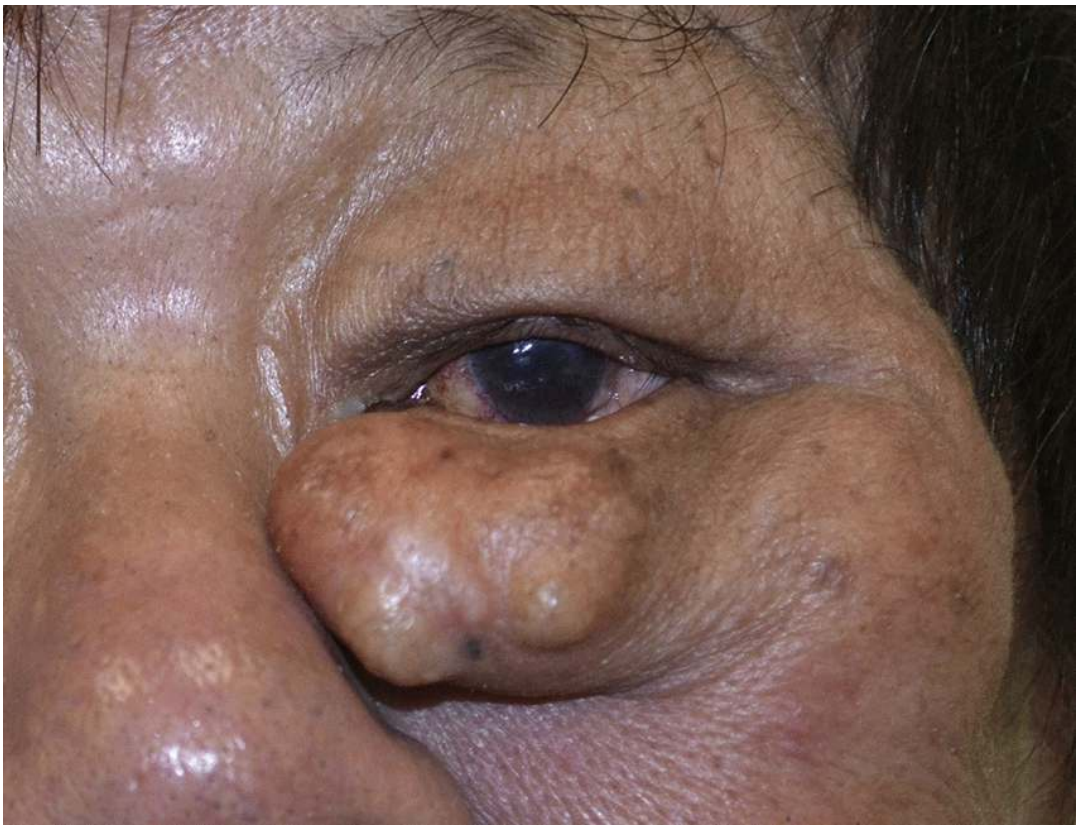

FIGURE 134.1 A large, lobular subcutaneous liposarcoma of the lower eyelid. (Courtesy of Dr. Santha Amrith.)

Differential Diagnosis

Clinically liposarcoma can be misdiagnosed as a cyst or benign soft tissue neoplasms, such as lipoma and neurofibroma, as well as other malignant tumors including dermatofibrosarcoma protuberans, low-grade malignant peripheral nerve sheath tumor, low-grade sarcoma, and low-grade myxofibrosarcoma.

Treatment

The treatment of liposarcoma is related to the tumor histologic type and grade.[4] Well-differentiated LPSs tend to recur locally (45%) but do not metastasize without dedifferentiation.[23] Myxoid and dedifferentiated LPSs rarely metastasize, but they are more locally invasive and show a greater tendency to recur compared with the well-differentiated type. Pleomorphic and round cell liposarcomas are more aggressive with higher recurrence rates (70%-100%) and a 5-year survival rate of 50% to 60%.[4,24] The anatomic location also influences potential treatment options, and for head and neck LPS, the survival rate is better than for those at most other locations.[4]

Complete wide surgical excision is considered the treatment of choice for LPS. In a review of 22 cases with sufficient documentation, McCulloch et al[24] reported that, with incomplete surgical excision, the local recurrence was 80% at 2 years, compared with a rate of 17% at 5 years with complete excision. Local recurrence may occur many years after surgical excision so that long-term follow-up is necessary.[25]

Radiotherapy does not appear to be very effective in the management of LPS,[24] and its value has been controversial. Some studies reported no benefit with radiotherapy added to surgery,[26] whereas others reported reduced recurrence and improved survival with radiotherapy combined with surgery.[23,27] Radiotherapy is especially recommended for high-grade tumors, surgical resections with positive margins, larger tumors, and sites where complete surgical excision may not be possible.[5] More recently, several authors have proposed that postoperative adjuvant radiation might delay or prevent local recurrence.[14,28,29]

The use of chemotherapy is variable since the various subgroups of LPS differ in chemosensitivity, with pleomorphic most sensitive and well-differentiated/dedifferentiated relatively resistant. In a study of 105 patients with liposarcoma, chemotherapy with doxorubicin, ifosfamide, docetaxel, gemcitabine, and/or trabectedin, complete response was seen in 3.8%, partial response in 32.4%, stable disease in 30.5%, and progressive disease in 30.5%, and the median overall survival was 16.3 months.[30] In a study of high-risk surgically resected soft tissue sarcomas treated with adjuvant doxorubicin and ifosfamide combined with radiotherapy, the 5-year overall survival was 76.1% compared with 50% for adjuvant radiotherapy alone,[31] suggesting a possible survival benefit for the addition of adjuvant chemotherapy. Another study of 16,370 patients with stage III soft tissue sarcomas treated with adjuvant chemotherapy showed increased survival compared with those who did not receive chemotherapy.[32] However, a large randomized trial of adjuvant chemotherapy (doxorubicin and ifosfamide) in 351 patients with macroscopically resected soft tissue sarcoma showed no benefit from chemotherapy in terms of local control, relapse-free survival, or overall survival.[33,34]

The vast majority of well-differentiated and dedifferentiated LPSs have cytogenetic abnormalities of supernumerary rings and giant chromosomes, which frequently contain amplifications in the long arm of chromosome 12 containing the oncogenes cyclin-dependent kinase 4 (*CDK4*) and murine double minute-2 (*MDM2*).[35] Palbociclib is an oral inhibitor of CDK4 and CDK6 that prevents downstream phosphorylation of the retinoblastoma protein.[36] In a phase II trial, patients with advanced well-differentiated and dedifferentiated LPSs treated with palbociclib achieved a 57.2% progression-free survival (PFS) at 12 weeks and a median PFS of 17.9 weeks.[37] This is not as good a response as with targeted therapy for other soft tissue sarcomas. Recently, a retrospective analysis of efficacy endpoints and outcomes among patients treated with palbociclib monotherapy in a large volume sarcoma center demonstrated that there was no *(Print pagebreak 891)* clear benefit from treatment, and few patients achieved prolonged tumor control.[20]

The role of adjuvant and neoadjuvant chemotherapy for soft tissue sarcomas has been studied in various trials on patients with high-risk tumors. Doxorubicin remains the first-line standard for systemic treatment of liposarcoma, and multiagent therapy with ifosfamide may improve response rates. The response rates are only 12% to 25% with median PFS periods of 5 to 7 months, but there has been no significant benefit in terms of overall survival.[38,39,40,41,42]

Prognosis

The histological subtype of liposarcoma is the most important prognostic factor related to its clinical behavior. Well-differentiated and myxoid LPS are considered low-grade lesions that rarely metastasize and have 5-year survival rates of 83% to 100%.[12,43] However, they tend to recur locally in approximately 40% to 60% of cases.[24,44,45] The pleomorphic subtype is more aggressive, with a 20% to 60% 5-year survival rate.[44,46,47] DDLPS is a malignant neoplasm showing a transition from atypical or well-differentiated LPS to a nonlipogenic sarcoma.[48] It behaves aggressively, with a local recurrence rate of 41% and a 5-year survival rate of 44%.[44]

Local recurrence is related to tumor location and the difficulty in obtaining adequate surgical margins in some regions. Patients with microscopically positive margins have a significantly lower survival rate.

Histopathology

Primary liposarcomas arising in the dermis or subcutaneous tissue are exceptionally rare,[49,50,51,52,53] and most liposarcomas of the skin are extensions from a deeper location.[54] Of 318 head and neck liposarcomas in the Surveillance, Epidemiology, and Results (SEER) Program of the National Cancer Institute between 1973 and 2009, only 13 (4.1%) were primary skin tumors.[13] Pleomorphic liposarcomas are the most commonly reported superficial liposarcoma subtype,[49,50] although all subtypes may occur.[49,50,51,52,53]

There are three main morphological subtypes of atypical lipomatous tumor/well-differentiated liposarcomas (ALT/WDLPSs): adipocytic (lipoma-like), sclerosing, and inflammatory.[55] Tumors may be composed of more than one subtype.[55] Adipocytic ALT/WDLPSs are formed of mature adipocytes that have more cell size variation than in benign lipomas, along with nuclear atypia in adipocytes or stromal spindle cells (Figure 134.2).[55] Lipoblasts range from none to many.[55] Sclerosing ALT/WDLPSs have scattered hyperchromatic bizarre stromal cells within a fibrillary stroma, multivacuolated lipoblasts can be observed, and fibrous areas may overshadow lipogenic areas.[55] Inflammatory ALT/WDLPSs are distinguished by a chronic inflammatory infiltrate predominating over the adipocytic component of the tumor.[55] *(Print pagebreak 892)* Most ALT/WDLPS have nuclear expression of MDM2 proto-oncogene and/or CDK4 (cyclin-dependent kinase 4) using immunohistochemical staining or *MDM2* and/or *CDK2* gene amplification.[55]

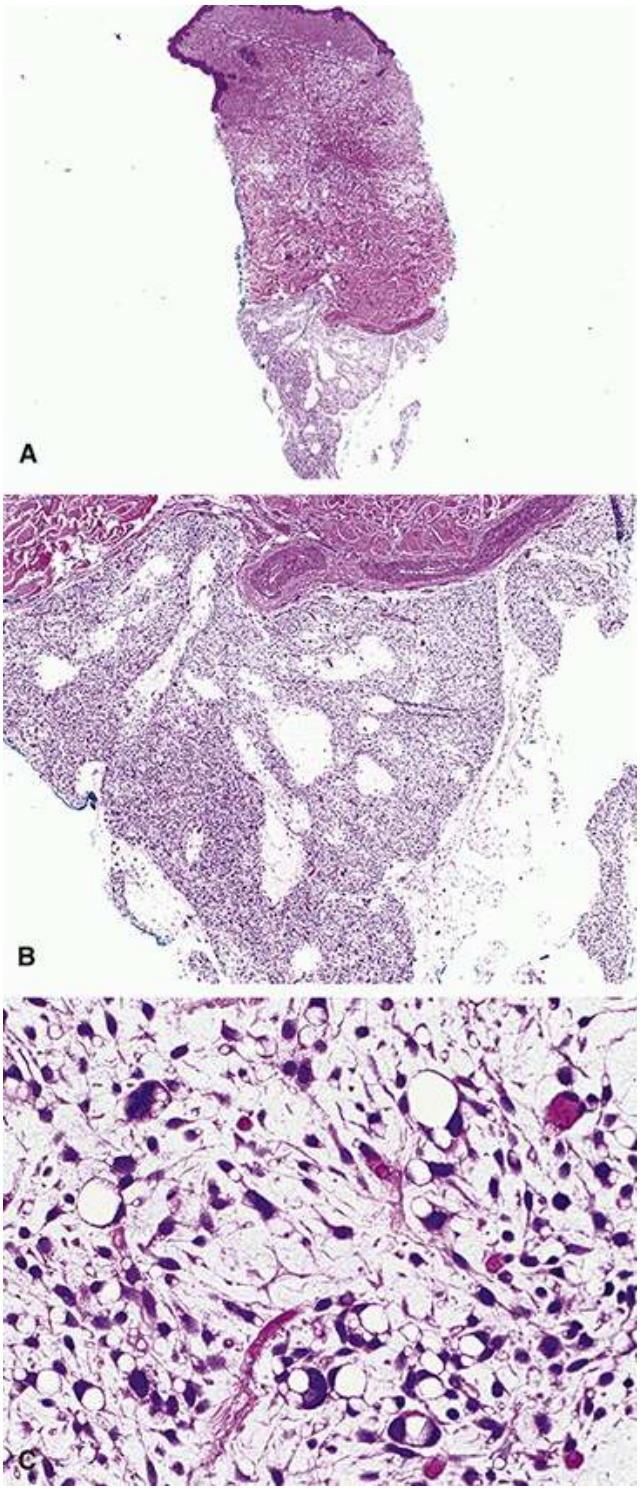

FIGURE 134.2 A, This punch biopsy of the back shows a liposarcoma in the subcutaneous tissue that arose at the site of prior radiation therapy. B, Lobules of tumor cells have a lightly basophilic myxoid stroma. C, The tumor cells are pleomorphic adipocytes with admixed lipoblasts. In a subsequent wide local excision, liposarcoma extended from the superficial dermis to the deep subcutis and had predominantly myxoid features.

DDLPS features a transition from ALT/WDLPS to nonlipogenic sarcoma, usually high grade.[56] Transition is usually abrupt, and dedifferentiated areas are most often undifferentiated pleomorphic sarcoma or intermediate- to high-grade myxofibrosarcoma.[56] DDLPSs almost invariably exhibit diffuse nuclear expression of MDM2 and/or CDK4.[56]

Myxoid liposarcomas (MLPSs) are moderately cellular, lobulated tumors with a patternless array of small, ovoid cells without morphological adipocytic differentiation and variable numbers of small lipoblasts.[57] Cellularity is increased peripherally.[57] The tumors have abundant myxoid (lightly basophilic) stroma with an arborizing capillary network.[57] Most MLPSs have a t(12;16)(q13;p11) translocation that generates a *FUS-DDIT3* fusion transcript, which can be detected using molecular techniques.[57]

Pleomorphic liposarcomas have infiltrative borders and "a varying proportion of pleomorphic lipoblasts in a background of high-grade, usually pleomorphic, undifferentiated sarcoma."[58] Identification of lipoblasts is required for diagnosis, but their numbers vary widely between tumors and within areas of a tumor.[58] Approximately one-half of pleomorphic liposarcomas have intermediate- to high-grade myxofibrosarcoma-like areas containing pleomorphic lipoblasts.[58] Pleomorphic liposarcomas lack MDM2 amplification, and this helps distinguish them from DDLPS.[58]

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CHAPTER 135

Lymphoma

Key Points

- Lymphoma is a malignant neoplasm originating from clonal proliferations of monoclonal B cell, T cell, and natural killer cell lymphocytes
- The ocular adnexa is involved in 2% of extranodal lymphomas, and 5% of these are located in the eyelid
- The majority of eyelid lymphomas are non-Hodgkin B-cell lymphomas
- They are associated with several chronic inflammatory disorders, such as chronic infection by *Helicobacter pylori* in the stomach, and unique genetic abnormalities have been seen in each specific subtype
- Most eyelid lymphomas extend from the orbit or conjunctiva; primary eyelid lymphoma typically involves the anterior lamella or preseptal tissues of the skin, subcutaneous tissue, and orbicularis oculi muscle
- Symptoms include painless eyelid swelling, epiphora, irritation or pain, ptosis, chemosis, ectropion, and a palpable mass
- Treatment of primary cutaneous lymphoma can be with surgery, radiotherapy, or chemotherapy depending upon the subtype and extent of the disease
- Prognosis varies and depends on the stage at presentation, tumor histology, primary or secondary status, and whether the tumor is unilateral or bilateral

Lymphoma is a malignant neoplasm originating from clonal proliferations of white blood cells, including monoclonal B cell, T cell, and natural killer (NK) cell lymphocytes. Lymphomas are usually divided into several broad types, Hodgkin and non-Hodgkin. Hodgkin lymphomas (HLs) are uncommon, and the classic form accounts for about 90% of HLs. It arises from a large, abnormal, multinucleated transformed type of B-cell lymphocyte called Reed-Sternberg cell. HLs rarely involve the periorbital region. Non-Hodgkin lymphomas (NHLs) are far more common. They constitute a large heterogeneous group of tumors mostly consisting of B-cell lymphomas (80%), and less frequently T-cell lymphomas (14%) or NK-cell lymphomas (6%), and all can occur in the eyelid.[1]

Based on the US Surveillance, Epidemiology, and End Results (SEER) database, it is estimated that in 2022 there will be 80,470 new cases of NHL and 20,250 tumor related deaths. Less than 5% of these will be primary cutaneous lymphomas. The incidence of primary cutaneous lymphoma has been increasing, and the condition occurs with an incidence of about four per million persons per year,[2,3,4] and cutaneous B-cell lymphomas make up about 25% to 30% of these. The majority of primary cutaneous lymphomas are cutaneous T-cell lymphomas. The highest incidence rates are among males, non-Hispanic whites, and adults over the age of 50 years.[5]

Lymphomas can occur within lymph nodes or extranodally in a variety of soft tissues. Those involving the ocular adnexa constitute about 2% of all extranodal lymphomas, and 5% of ocular adnexal lymphomas are located in the eyelid.[1,6] The majority of eyelid lymphomas are non-Hodgkin B-cell lymphomas, including extranodal marginal-zone lymphoma (EMZL), follicular center cell lymphoma (FCL), and diffuse large B-cell lymphomas (DLBCL), and follicular lymphomas (FCL).[7,8,9,10,11] Less common B-cell lymphoma subtypes in the eyelid include lymphoplasmacytic lymphoma/immunocytoma, plasmocytoma, and immunoblastic lymphoma in decreasing freque ncy.[8,9,12,13] Burkitt lymphoma very rarely involves the ocular adnexa in children.[14,15] The nonendemic form can also occur in adults, typically associated with acquired immunodeficiency syndrome and other forms of immunosuppression.[13,16]

Adnexal lymphomas of non-B-cell type are uncommon, representing approximately 1% to 3% of all ocular adnexal lymphomas.[8,12,17] The majority of non-B-cell lymphomas represent secondary manifestations of a systemic T-cell lymphoma, or they occur as an eyelid extension of mycosis fungoides (MF).[17,18,19] Very few cases of primary T-cell lymphomas of the ocular adnexa have been

reported in the literature,[17,20,21,22,23] although it has been debated whether some of these represent true clonal T-cell proliferations.[24]

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (EMZL-MALT) represents 8% of all NHLs.[25] It is the second most common primary cutaneous B-cell lymphoma in the skin, and the eyelid is the third most common site for MALT-type lymphomas (12%) after the gastrointestinal tract (70%), and the lung (14%).[25] It comprises about 75% of all ocular adnexal lymphomas of which 46% occur in the orbit, 35% in the lacrimal gland, 10% in the conjunctiva, and 8% in the eyelid.[26]

EMZL is an indolent lymphoma that accounts for approximately 25% of patients with cutaneous lymphoma.[2] The median age at presentation is 50 to 53 years, with a range of 6 to 93 years, and it occurs more commonly in men than in women.[27,28,29]

FCL is another indolent subtype comprising 60% of primary cutaneous B-cell lymphomas. Patients present at a *(Print pagebreak 895)* median age of 50 years, and it is slightly more common in men than in women. DLBCL, leg type, comprises 10% to 20% of primary cutaneous B-cell lymphomas and usually presents at a median age of 70 to 75 years.[2,30] DLBCL is more common in females, and Asians and Pacific Islanders are at increased risk of developing this subtype.[31]

Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma. It originates in the peripheral skin-tropic memory T-lymphocytes.[32,33] The incidence is about six cases per million population, it is more common in adults over the age of 50 years, there is a slight male predominance, and it is more common in blacks than in Caucasians and Asians (Chapter 129).[34] Sézary syndrome is a related condition in which malignant T cells are present in the blood in addition to skin involvement. It is unclear if this represents an advanced form of MF or a distinct disease.

Etiology and Pathogenesis

Extranodal marginal zone lymphoma (MALT lymphoma) originates from the marginal zone B cells of the mucosa-associated lymphoid tissue. These lymphomas occur at diverse anatomic sites and have been associated with several chronic inflammatory disorders, such as chronic infection by *Helicobacter pylori* in the stomach, *Borrelia burgdorferi* in the skin,[35] *Chlamydia psittaci* in the ocular adnexa,[36,37,38] and *Campylobacter jejuni* in the small intestine.[39] Evidence suggests that genetic abnormalities and antigenic drive in MALT lymphoma involve dysregulation of the molecular pathways that regulate nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB),[40] a small family of inducible transcription factors that control transcription of DNA, cytokine production, and cell survival. Recently, a Chinese study on ocular adnexal MALT lymphoma patients showed novel mutations in the *IGLL5* gene in 24% of patients, and mutations of *MSH6*, *DIS3*, *FAT1*, and *TMEM127* in 10%.[40] The exact function of the IGLL5 gene is not known at present, but it encodes a protein that plays a critical role in B-cell development.[40]

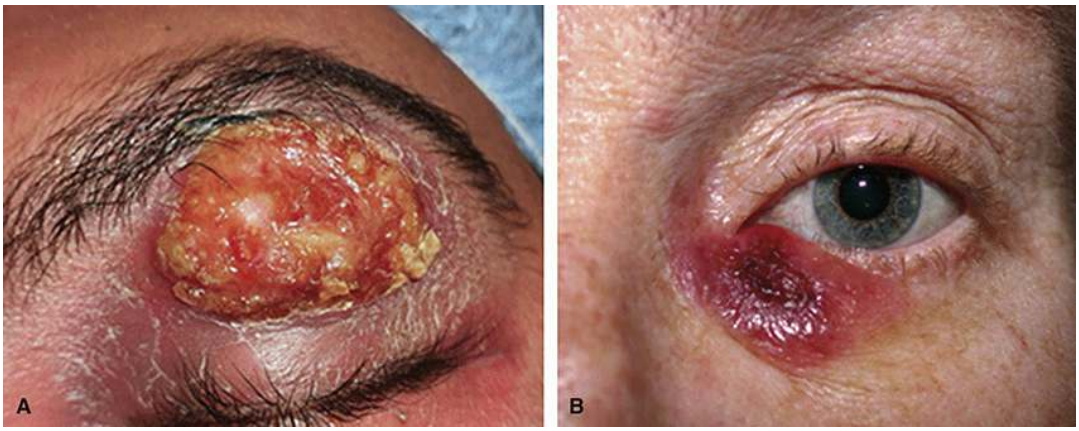

FIGURE 135.1 Superficial cutaneous lymphoma of the eyelids. B, (Courtesy of Dr. Jurij Bilyk.)

Genetic abnormalities in lymphomas are unique to each specific subtype. In mantle cell lymphoma (MCL), t(11;14) (q13;q32) translocation and (11)(q21;q23) deletion have been described in more than 95% of tumors.[41,42] It leads to overexpression of nuclear cyclin D1, and its upregulation leads to cell cycle progression.[43] Genetic abnormalities in EMZL include trisomy 3 and 18, as well as the translocations t(11;18) (q21;q21), t(1;14)(p22;q32), t(14;18)(q32;q21), and t(3;14) (p14.1;q32).[44] Most of these translocations induce the upregulation of proteins that lead to the activation of nuclear factor κB.[44] The translocation t(14;18) (q32.3;q21.3) is seen in 34% of DLBCL[45] and in 85% of FCL. This translocation leads to upregulation of the *BCL2* oncogene and prevents apoptosis.[45]

In MF, there is a clonal expansion of CD4-positive cells that often lack normal T-cell antigens such as CD7, CD5, or CD2.[46] These cells are attracted to the skin by keratinocytes and accumulate in the dermis.

Clinical Presentation

Most lymphomas of the eyelid are secondary extensions from the orbit or conjunctiva and can invade all tissue layers. Primary lymphoma in the eyelid typically involves the anterior lamella or preseptal tissues of the skin, subcutaneous tissue, and the orbicularis oculi muscle (Figure 135.1). In this location primary lymphoma is rare, accounting for only 1% to 2% of NHL.[47]

Of ocular adnexal lymphomas, 41% occur in the orbit, 31% in the conjunctiva (Figure 135.2), 18% in the lacrimal gland, and 10% in the eyelid.[48] The distribution of subtypes for eyelid lymphomas is reported as EMZL (35%-55%), FCL (15%-25%), DLBCL (15%-20%), MCL (8%-12%), and MF (9%).[48] This is in contrast to orbital lymphoma where FCL and DLBCL predominate at 63% and 50%, respectively, and in the conjunctiva where EMZL-MALT lymphoma and DLBCL predominate at 41% and 38%, respectively.[48] Eyelid and orbital adnexal lymphomas generally affect males more than females (60%-80%), except for EMZL, which has *(Print pagebreak 896)* been reported to predominate in females in 60% to 70%.[7,48] Although the disease can be seen at any age, most periocular lymphomas occur in older patients, in the 6th to 8th decades of life. Except for MF, which is typically bilateral, more than 70% of other subtypes in the ocular adnexa occur unilaterally. The AJCC T stage is T3 in the 8th edition, which now stages these tumors according to the anatomic extent of disease.[49]

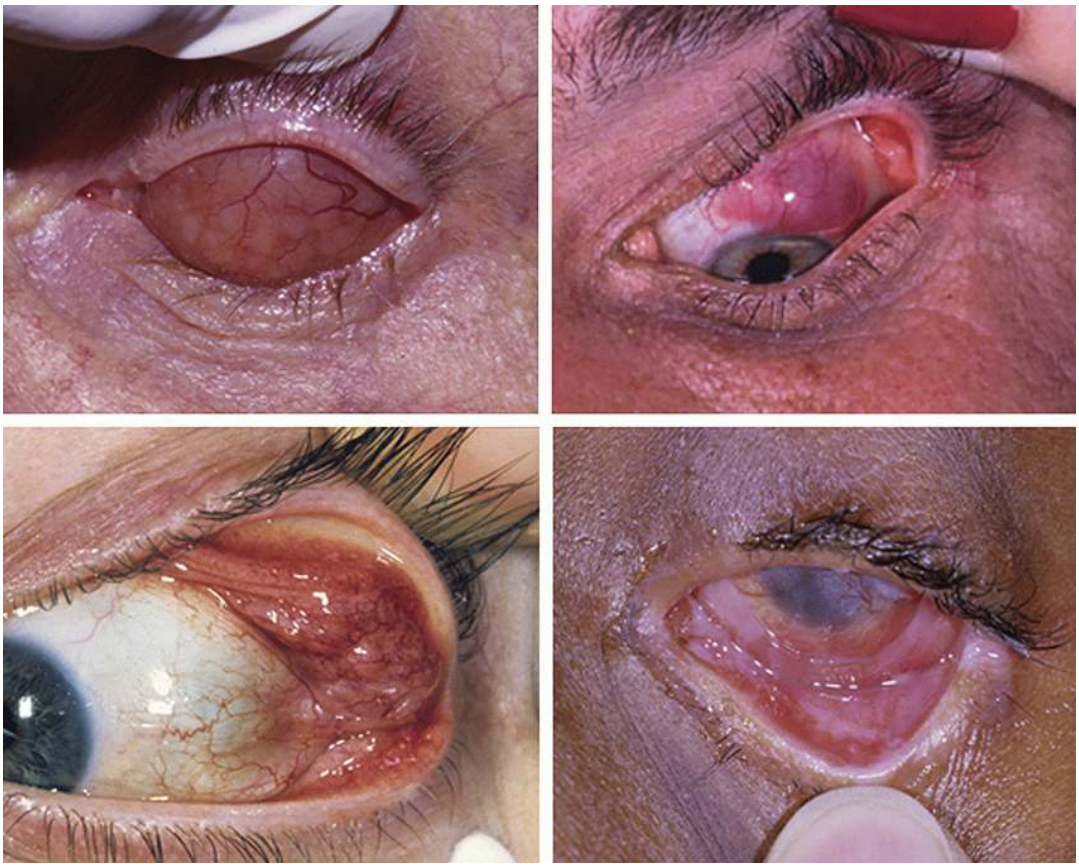

FIGURE 135.2 Lymphoma involving the conjunctiva.

The clinical signs and symptoms are usually nonspecific depending upon the size and location of the tumor and on the specific subtype. Low-grade tumors (EMZL and FCL) typically have a more indolent course and therefore may remain unrecognized for many years. High-grade lesions (DLBCL and MCL) are more aggressive and show rapid growth. EMZL usually presents as a solitary, red to violaceous, indurated plaque or nodule that may be surrounded by annular or diffuse erythema.[25,27,50] Presenting symptoms and signs include painless, nonulcerative eyelid swelling (28%-67%), epiphora (15%), irritation or pain (2%-22%), upper eyelid ptosis (5%-25%), erythema (14%-38%), a palpable mass (30%-60%), chemosis (10%-22%), and eyelid margin malposition (0%-63%) (Figure 135.3).[7,48,51] Patients may present with a single lesion (28%-58%) or multiple lesions (24%%-72%) and are otherwise asymptomatic.[27,28,52] Tumor may spread posteriorly into the orbit in up to 60% of cases and to the lacrimal sac in up to 10%.[7]

The clinical presentation of MF varies depending upon the disease stage. The earliest patch stage is a single or multiple lesion, which is an erythematous brown scaly patch that may show some atrophy. This is followed by a plaque stage, which is larger, annular, elevated lesions with cellular infiltration. The final phase is the erythematous popular or nodular tumor stage. As the lesions progress, so does the risk or lymph node and visceral organ involvement.

Differential Diagnosis

The differential diagnosis for cutaneous lymphoma is extensive given the various presentations of both B-cell and T-cell lymphoma subtypes. From case reports in the literature, lymphomas can be mistaken for other cutaneous nonmelanoma malignancies, such as basal cell and squamous cell carcinoma, and dermatofibrosarcoma, as well as metastatic lesions. Benign lesions include reactive lymphoid *(Print pagebreak 897)* hyperplasia, inflammatory dermatoses, and autoimmune inflammatory lesions, rosacea, discoid lupus erythematosus, *Herpes zoster*, cellulitis, erythema nodosum, pyoderma gangrenosum, dermatomyositis, lymphadenitis, and even sebaceous cyst. For MF, the differential diagnosis includes atopic dermatitis, drug eruptions, psoriasis, and other lymphomas.

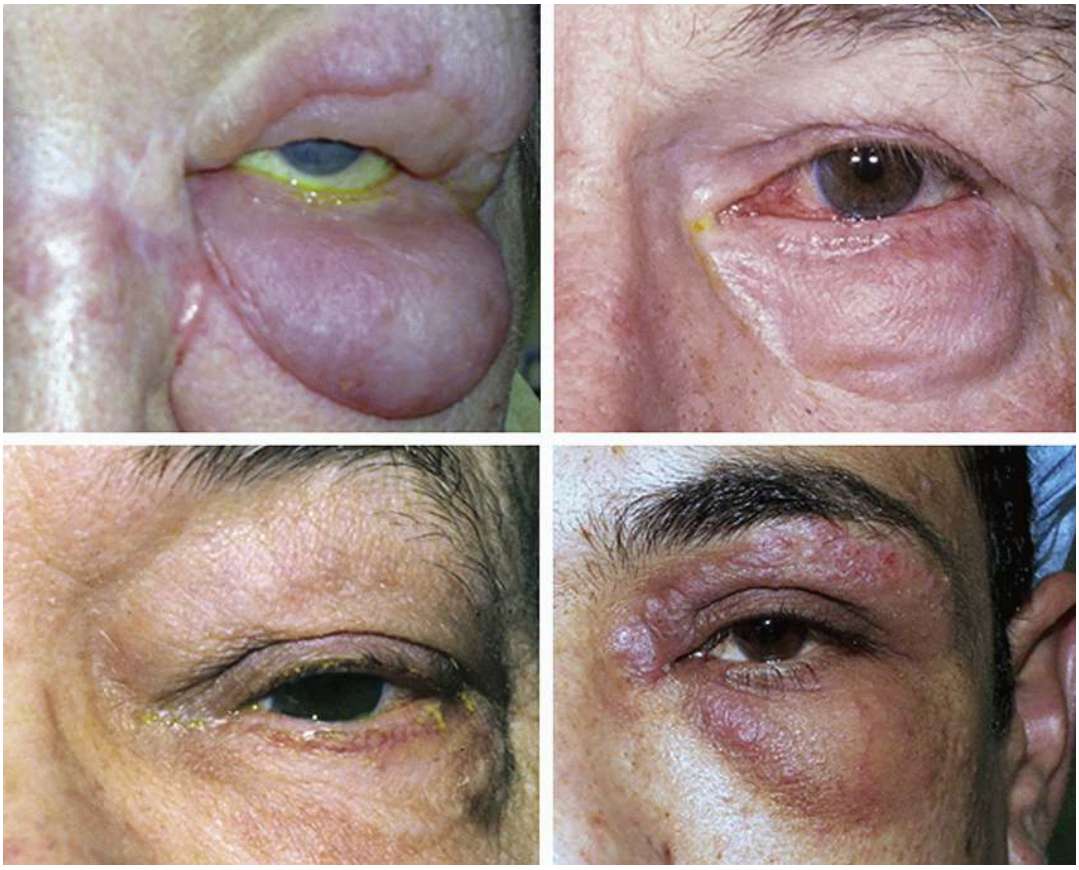

FIGURE 135.3 Cutaneous lymphoma manifesting as eyelid edema and palpable mass.

Treatment

Treatment of primary cutaneous lymphoma can be with surgery, radiotherapy, or chemotherapy or combinations depending upon the subtype and extent of disease. In patients with stage IE ocular adnexal lymphomas (single extralymphatic site with no nodal involvement) and IIE (contiguous extralymphatic extension from a nodal site on the same side), localized external beam radiotherapy is considered the therapy of choice.[52,53,54,55,56,57,58] Radiotherapy has been shown to give a high rate of local tumor control that ranges from 80% to 100%.[59,60,61,62,63] Zinzani et al[64] reported local control with radiotherapy of 98% for FCL, 95% for EMZL, and 82% for DLBCL.

For ocular adnexal lymphoma with disseminated disease, systemic chemotherapy is required. Most regimens are based upon the CHOP scheme.[65,66,67] Combined radiotherapy and chemotherapy is used in cases where the tumors are vision threatening and cannot be completely resected.[7]

Immunotherapy has been utilized to treat lymphoma with good results and few side effects. Rituximab is a monoclonal antibody that binds to the CD20 antigen[68] and makes B cells more susceptible to chemotherapy.[69] Treatment with rituximab has been described for EMZL, MCL, and DLBCL of the eyelid with a low percentage of tumor recurrence.[70,71] Combination multiagent chemotherapy combined with rituximab may be appropriate for patients with more aggressive DLBCL who tend to be elderly and sometimes too frail for chemotherapy alone.[35,72,73,74] Observation alone for low-grade EMZL has been advocated especially in older patients or those with significant comorbidities.[75,76] Studies have shown that, in a significant

number of cases (57%) followed for 5 to 10 years, no therapy was required, and more than half of conjunctival lesions regressed spontaneously.

Prognosis

Disease stage at presentation, tumor histology, primary or secondary status, and whether the tumor was unilateral or bilateral are major determinants of prognosis.[77] One study found *(Print pagebreak 898)* that women with periocular lymphoma had a worse prognosis.[48] For patients with periocular lymphoma, those with the EMZL-MALT and FCL subtypes have the best prognosis with a 5-year disease-specific survival (DSS) of 88%, whereas those with DLBCL and MCL have the worst prognosis with 5-year DSS of 21% and 50%, respectively.[7] MF generally shows a good prognosis with a DSS of 86%. Primary periocular lymphomas tend to have a better prognosis than secondary lesions (84% vs 64%).[7]

Local tumor control is generally excellent for all subtypes with almost all forms of treatment, ranging from 82% to 98% with radiotherapy, 76% to 86% with chemotherapy, and 97% to 100% with surgery.[64] While the prognosis for life with low-grade lymphomas is excellent, recurrence rates tend to be high, reported at 46% to 66% for EMZL and FCL and 80% to 100% for the DLBCL and MCL subtypes.[7] EMZL rarely exhibits extracutaneous spread,[27,78] although node dissemination and large cell transformation have been reported.[27] Nevertheless, the disease remains in the skin in a vast majority of patients (90.2%).[64]

The prognosis for FCL is generally excellent, with a 5-year DSS rate of 95%, although the recurrence rate can be 30%, and 10% may progress to extracutaneous involvement. DLBCL is associated with a DSS rate of 50% to 70%. Negative prognostic factors include location on the leg, multiple lesions, and age greater than 75 years.[7,35,79]

Histopathology

Eyelid skin biopsies with lymphoma are rare. Deprez and Uffer had no example of lymphoma in their study of 5504 cases of eyelid skin tumors,[80] while Svendsen and Heegaard identified 199 cases of primary eyelid lymphoma reported over a span of "more than 50 years."[7] Both B-cell and T-cell lymphomas may occur as primary cutaneous processes[81,82,83,84,85,86] or spread secondarily to the skin, and the histopathology reflects the specific entity. Primary cutaneous lymphomas are classified using the 2018 update to the World Health Organization-European Organization for Research and Treatment of Cancer guideline.[81] Kempf and Mitteldorf[83] outlined histopathological features that help guide the diagnosis and choice of immunohistochemical stains:

1. *Epidermotropic infiltrates* are most common in cutaneous T-cell lymphomas (CTCLs).
2. *Nodular and diffuse dermal infiltrates* occur in progressive CTCLs, peripheral T-cell lymphoma, and cutaneous B-cell lymphomas (CBCLs).
3. A *subcutaneous growth pattern* occurs in subcutaneous panniculitis-like T-cell lymphoma and subcutaneous γ/δ T-cell lymphoma and rarely with other forms of CTCL and CBCL.
4. *Angiocentric and angiodestructive infiltrates* are a feature of aggressive T- and T-/natural killer (NK)-cell lymphomas, nasal type, and cutaneous γ/δ T-cell lymphoma. They may be seen less commonly with lymphomatoid papulosis and the angioinvasive variant of primary cutaneous anaplastic large-cell lymphoma.
5. *Intravascular growth* is characteristic of intravascular T-and B-cell lymphomas.

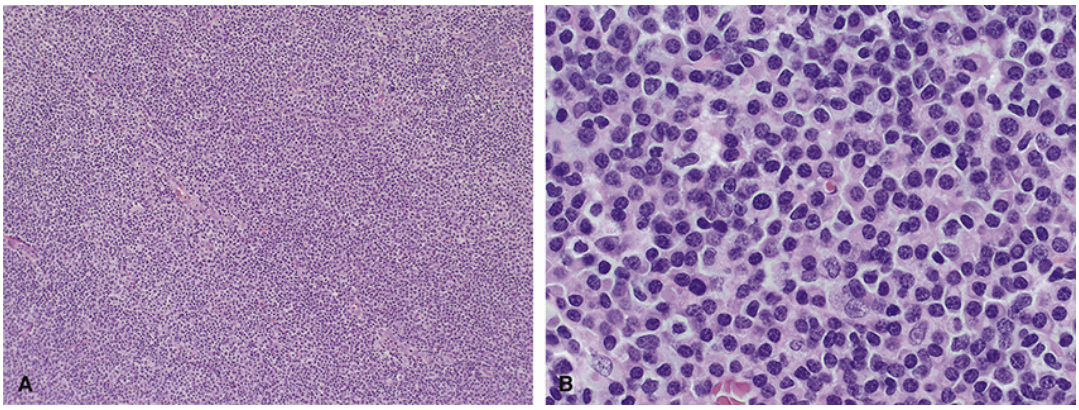

FIGURE 135.4 A woman in her early 70s developed a nodule in her right upper eyelid. Following the biopsy diagnosis of lymphoplasmacytic lymphoma (immunocytoma), radiotherapy resulted in the complete resolution of her eyelid tumor. A, The dermis has a diffuse infiltrate of small and medium-sized lymphocytes, plasmacytoid lymphocytes, and a few plasma cells. B, A majority of the cells are plasmacytoid lymphocytes resembling a plasmacytoma. Lymphoplasmacytoid lymphocyte cells expressed CD20 and kappa light chains. Uniform expression of CD20 helps differentiate lymphoplasmacytic lymphomas from plasmacytomas, which are usually negative for CD20 or have expression by only a small subset of the cells.[88] (Reprinted with permission from McKenna RW, Kyle RA, Kuehl WM, et al. Plasma cell neoplasms. In, Swerdlow SH, Campo E, Harris NL, et al, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Revised*. 4th ed. International Agency for Research on Cancer; 2017:241-258.)

In Svendsen and Heegaard's review of 199 primary eyelid lymphomas, there were 56% B-cell and 44% T-cell lymphomas.[7] The most common B-cell lymphomas were low-grade extranodal marginal zone lymphoma (14% of cases) and high-grade diffuse large B-cell lymphoma (9%).[7] Lymphoplasmacytic lymphoma (Figure 135.4) accounted for approximately 3% of *(Print pagebreak 899)* primary eyelid lymphomas.[7] MF (Chapter 129; Figures 129.3, 129.4, 129.5) was the most frequent T-cell lymphoma (13% of cases), followed by low-grade primary cutaneous anaplastic large-cell lymphoma (6%; Figure 129.6).[7] Secondary involvement of the eyelid by systemic lymphomas accounted for 18 of 264 consecutive lymphoproliferative lesions at Erasmus Medical Center between 1987 and 2016.[87] MCL was the most frequent systemic lymphoma involving the eyelid (four cases), followed by chronic lymphocytic leukemia/small lymphocytic lymphoma (three cases), follicular lymphoma (two cases; Figure 135.5), and diffuse large B-cell lymphoma (two cases).[87]

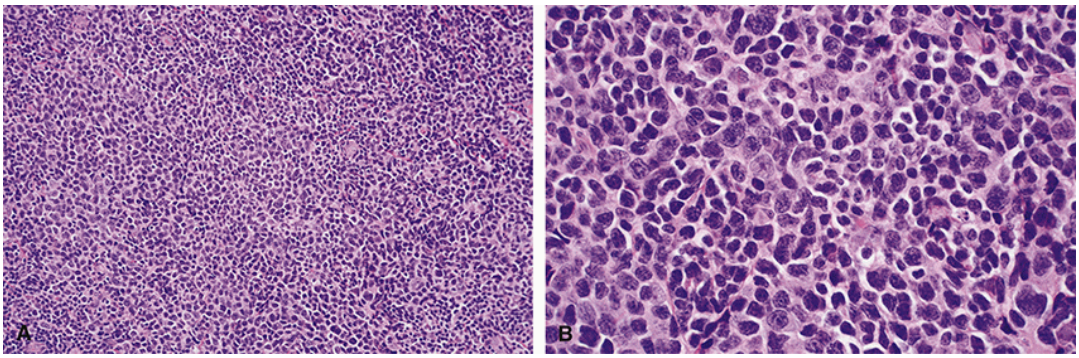

FIGURE 135.5 A man in his middle 70s with a history of follicular lymphoma developed firm periocular swelling around his left eye. A, This biopsy of the left lower eyelid has a dense lymphoid infiltrate in the dermis with a vaguely follicular appearance manifest as the central area of lymphocytes being paler than the surrounding lymphocytes. B, The vaguely defined follicle center is composed of small cleaved cells with occasional larger centroblast-like cells. The immunophenotype was characteristic of follicular lymphoma,[89] and a monoclonal B-cell population was detected by immunoglobulin heavy chain polymerase chain reaction analysis. (Reprinted with permission from Jaffe ES, Harris NL, Swerdlow SH, et al. Follicular lymphoma. In, Swerdlow SH, Campo E, Harris NL, et al, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Revised*. 4th ed. International Agency for Research on Cancer; 2017:266-277.)

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CHAPTER 136

Malignant Melanoma

Key Points

- Cutaneous malignant melanoma is an invasive tumor of malignant melanocytes
- On the eyelid, malignant melanoma accounts for about 1% of all eyelid malignancies
- On the eyelids, the nodular and lentigo maligna melanoma types are the most common
- UV light in the pathogenesis of melanoma is well established
- Approximately 50% of all cutaneous melanomas harbor *BRAF* and less commonly *NRAS* mutations
- Cutaneous melanomas usually appear as asymmetric lesions with irregular borders, uneven distribution of color, diameters over 6 mm, and a history of growth
- The treatment of choice is complete surgical excision with wide tumor-free margins
- Radiotherapy is rarely used as a primary treatment but is used as an adjuvant therapy in cases of advanced nodal or primary disease following surgical resection
- Cutaneous melanoma accounts for two-thirds of all deaths from skin cancer. Early diagnosis and treatment are critical to improved outcomes

Cutaneous malignant melanoma is an invasive tumor of malignant melanocytes. Worldwide, it is the 12th most common cancer and has an estimated age-standardized incidence rate of 3.0 per 100,000 population.[1] The incidence varies in different populations, with the highest rates reported in Australia and New Zealand and the lowest rates in South-Central and South-Eastern Asia. The annual incidence is increasing and is estimated to continue to increase due to the increasing lifespan and aging of the population.[2] While it accounts for only a small percentage of skin cancers, malignant melanoma is responsible for the majority of skin cancer-related deaths.[3] On the eyelid, malignant melanoma accounts for about 1% of all eyelid malignancies, with an annual incidence of 0.6 per million white residents over the age of 20 years.[3]

Cutaneous melanoma has been classified into subtypes recognized by the World Health Organization (WHO)[4] and less common variants.[5] The four major subtypes and their relative incidences are superficial spreading melanoma (30%-60%), lentigo maligna melanoma (10%-40%), nodular melanoma (15%-35%), and acral lentiginous melanoma (5%-10%).[5] More recently (2018), the WHO has classified melanomas into melanomas arising in sun-exposed skin and those arising at sun-shielded sites or those without known etiological associations with ultraviolet (UV) radiation exposure.[4] Melanomas arising in sun-exposed skin are subdivided into those with low- or high-cumulative sun damage (CSD), as assessed by grading the degree of solar elastosis in a skin biopsy.[4] Melanomas arising in sun-exposed skin are (1) low-CSD melanoma/superficial spreading melanoma; (2) high-CSD melanoma/lentigo maligna melanoma; and (3) desmoplastic melanoma.[4] Melanoma arising at sun-shielded sites or those without known etiological associations with UV radiation exposure are malignant Spitz tumor, acral melanoma, mucosal melanoma, melanoma arising in a congenital nevus, melanoma arising in blue nevus, and uveal melanoma.[4]

Superficial spreading, lentigo maligna, nodular, and desmoplastic melanoma are the most common subtypes of eyelid cutaneous melanoma (Figures 136.1 and 136.2).[6,7] In a review of clinical series of eyelid skin melanomas between 1990 and 2018, there were 297 invasive melanomas with approximately 35% superficial spreading, 31% lentigo maligna melanoma, 19% nodular, and 16% other melanomas.[7] An analysis of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database between 1975 and 2016 identified 2257 patients with primary melanoma of the eyelid region, with 1380 in situ melanomas (61.1%) and 877 invasive melanomas (38.9%).[7] In situ melanomas were 53.6% lentigo maligna, 3.2% superficial spreading melanoma, and 43.2% unknown subtype.[7] The major subtypes of invasive melanomas were 20.9% lentigo maligna melanoma, 20.0% superficial spreading, 8.1% nodular, 2.1% desmoplastic, 1.7% spindle, and 45.4% unknown subtype.[7] Eyelid skin melanomas can arise from

congenital nevi, cutaneous moles, and excessive sun exposure. They are far more common in Caucasians,[7] in those with a history of chronic sun exposure and severe sunburns, and in patients with dysplastic nevus syndrome. Eyelid lesions can be primary tumors or less commonly represent tumor extension from the conjunctiva, metastasis from a distant primary site, or even a metastasis from the contralateral choroid.[8,9,10] The diagnosis of cutaneous melanoma may be difficult due to variability in its appearance. The clinical suspicion for lesions later histologically confirmed to be melanomas has been reported at between 15% and 57% and even lower for amelanotic variants.[11,12] Approximately 80% of eyelid melanomas occur on the lower eyelid.[13] Eyelid cutaneous melanoma may rarely extend posteriorly into the orbit.[14]

The amelanotic variant of cutaneous melanoma is a rare form characterized by the clinical absence of pigmentation. *(Print pagebreak 903)* Because of this, it is often diagnosed late. The incidence of amelanotic melanoma has been estimated at approximately 2% to 8% of all melanoma cases,[15] but in a series of 24 patients with eyelid skin melanoma, Garner et al reported that 50% were amelanotic.[16] Any of the four histopathological subtypes can be amelanotic. In general, amelanotic melanomas may present as erythematous macules or plaques or have a scaly appearance.[17,18,19] They may also resemble inflammatory lesions such as eczema, psoriasis, rosacea, and contact dermatitis[17,20,21] or a variety of benign neoplasms such as nevi, hemangiomas, and seborrheic keratosis. Some lesions may mimic more common malignant tumors such as basal cell carcinoma or Bowen disease.[21,22,23] There are no specific clinical criteria for diagnosing eyelid amelanotic melanomas,[22] but dermatoscopy findings are helpful by showing diagnostic vascular patterns such as serpentine, irregular linear, pinpoint, and hairpin vessels.[24,25]

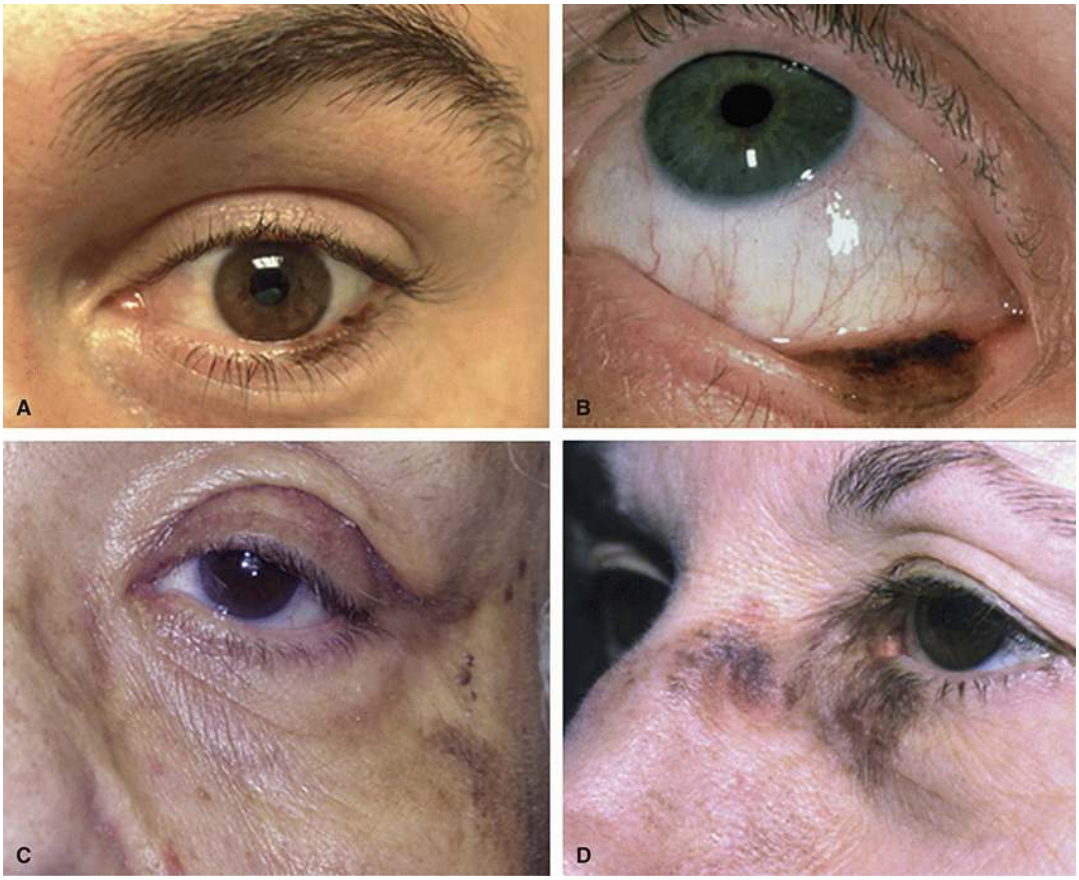

FIGURE 136.1 Lentigo maligna. A, Flat, irregular pigmented lesion along the lateral eyelid mucocutaneous border. B, Irregular, variably pigmented conjunctival lentigo maligna on the eyelid margin and palpebral conjunctiva. C, Lightly pigmented, multicentric macules and small nodules at the lateral canthus and lateral cheek. D, Very diffuse, variably pigmented flat lesion on the medial canthus, lower eyelid, and nasal bridge. (A, Courtesy of Dr. Robert Kersten.)

Conjunctival melanoma is distinct from cutaneous eyelid melanoma, but anatomically the posterior lamellae of the eyelids and the caruncle are conjunctival tissue, so any discussion of eyelid melanoma must include conjunctival lesions. Malignant melanoma of the conjunctiva is rare compared with uveal or cutaneous melanoma.[26] Its incidence has been reported as 0.2 to 0.8 per million population in non-Hispanic Caucasians,[27] with lower incidences in Hispanics, Blacks, Asians, and Native Americans.[28] As with cutaneous melanoma, its rate has been increasing, and for Caucasian men in the United States, the age-adjusted incidence rate increased by 295% from 1973 to 1999.[29] It is a potentially lethal tumor with an average 10-year mortality rate of 30%.[27] These tumors occur primarily in the fourth to seventh decades of life, but rare cases have been described in children.[30] The perilimbal bulbar conjunctiva is the area most commonly involved, although these tumors can occur on any conjunctival surface, including the eyelid and caruncle. In a recent multicenter international study of 288 patients with conjunctival melanoma, the melanoma involved the bulbar conjunctiva in 83.5% of eyes and was nonbulbar in 16.5% of eyes.[31]

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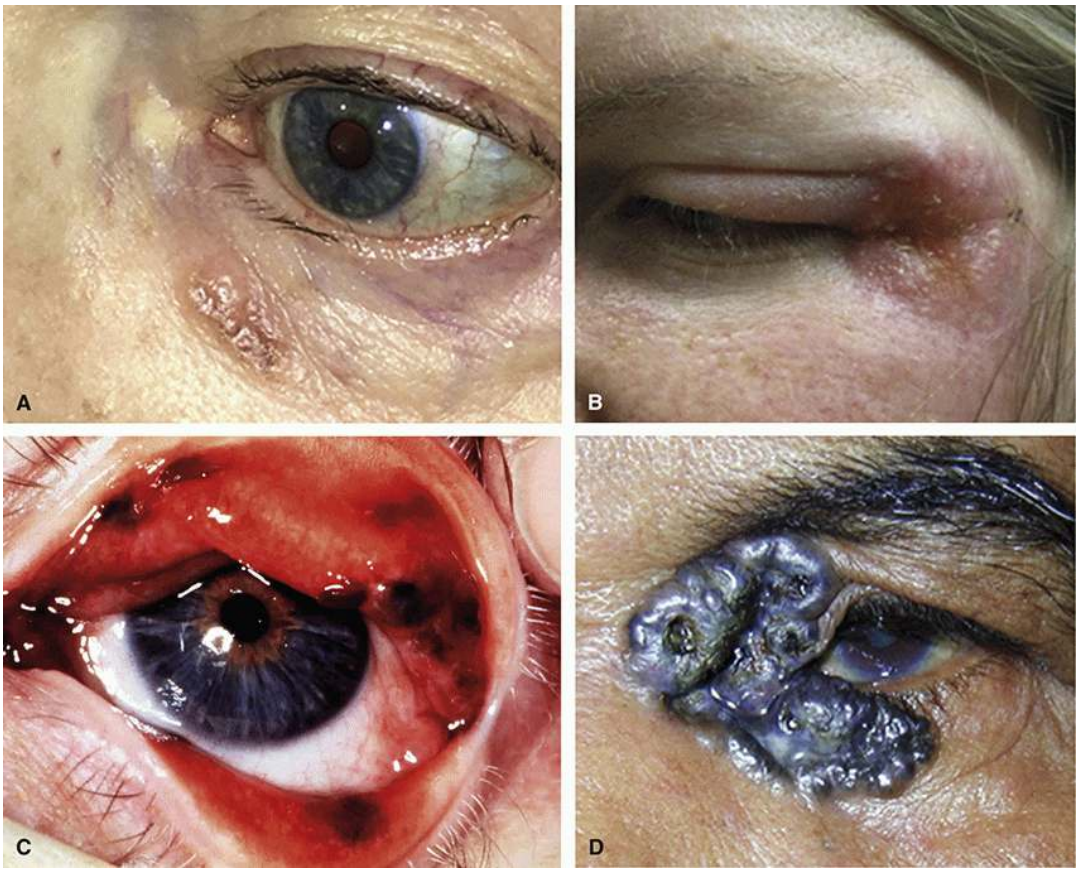

FIGURE 136.2 Spectrum of presentations of eyelid and conjunctival melanoma. A, Desmoplastic melanoma arising in a melanocytic nevus. B, Amelanotic melanoma of the lateral canthus. C, Multiple nodules of melanoma in the caruncle and palpebral conjunctiva arising in areas of PAM. D, Deeply pigmented melanoma involving the upper and lower eyelids and medial canthus. (B, Courtesy of Dr. Bita Esmaeli.)

Conjunctival melanoma can arise de novo (19%), from a preexisting conjunctival nevus (7%), or from primary acquired melanosis (PAM) with atypia (74%).[32,33,34] As with cutaneous melanomas, they may be amelanotic, where they can resemble other lesions such as squamous cell carcinomas, lymphoid hyperplasia, or pterygia.

Etiology and Pathogenesis

Cutaneous melanoma has a high burden of oncogenic mutations, most of which display an UV light signature.[35,36] The role of UV light in the pathogenesis of melanoma is well established, and the frequency of melanoma in Caucasian populations correlates with latitude, and by implication, with sunlight intensity.[13]

Approximately 50% of all cutaneous melanomas harbor *BRAF* and less commonly *NRAS* mutations[37] that contribute to oncogenesis by driving uncontrolled growth, suppressing apoptosis, and leading to melanoma invasion.[38,39] Both *BRAF* and *NRAS* mutations occur as early events in oncogenesis, but neither alone seems sufficient to trigger malignant transformation.[13] Also, about 35% of melanoma cell lines demonstrate deletions or mutations in the *PTEN* gene,[40] and loss of function of the PTEN enzyme results in increased mitogenic signaling involved in cell proliferation, apoptosis, and immune activation.

Other factors involved in the pathogenesis of cutaneous melanomas have been suggested, but studies vary in research designs, protocols, and patient populations so that further research is needed. However, oxidative stress is involved in several chronic diseases and the progression of some cancers, including melanomas.[41] Reactive oxygen species interact with inflammatory and immune processes and may participate in the melanogenic process.[41] Dietary factors may also affect the development of melanoma, particularly citrus fruits and alcohol through enhancement of UV-induced apoptosis and increased photosensitivity.[42]

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Clinical Presentation

Primary cutaneous melanoma evolves from a lesion of aberrant melanocytes with cytological atypia limited to the basal layers of the epidermis, as lentigo maligna, a form of melanoma in situ.[7] These lesions typically appear clinically as flat to slightly elevated, irregular papules or plaques with variable pigmentation (Figures 136.1).[7] They grow slowly over years or even dacades, often changing in color and morphology. Lentigo maligna progresses to early invasive melanoma as lentigo maligna melanoma with cellular invasion into the papillary dermis, and then to more advanced deeply invasive malanoma with the potential for hematogenous and lymphatic spread.

In the eyelids, melanoma is more frequently seen in the lower eyelid (56.8%), followed by the upper eyelid (13.3%), lateral canthus (10.3%), and medial cnathus (2.2%).[7]

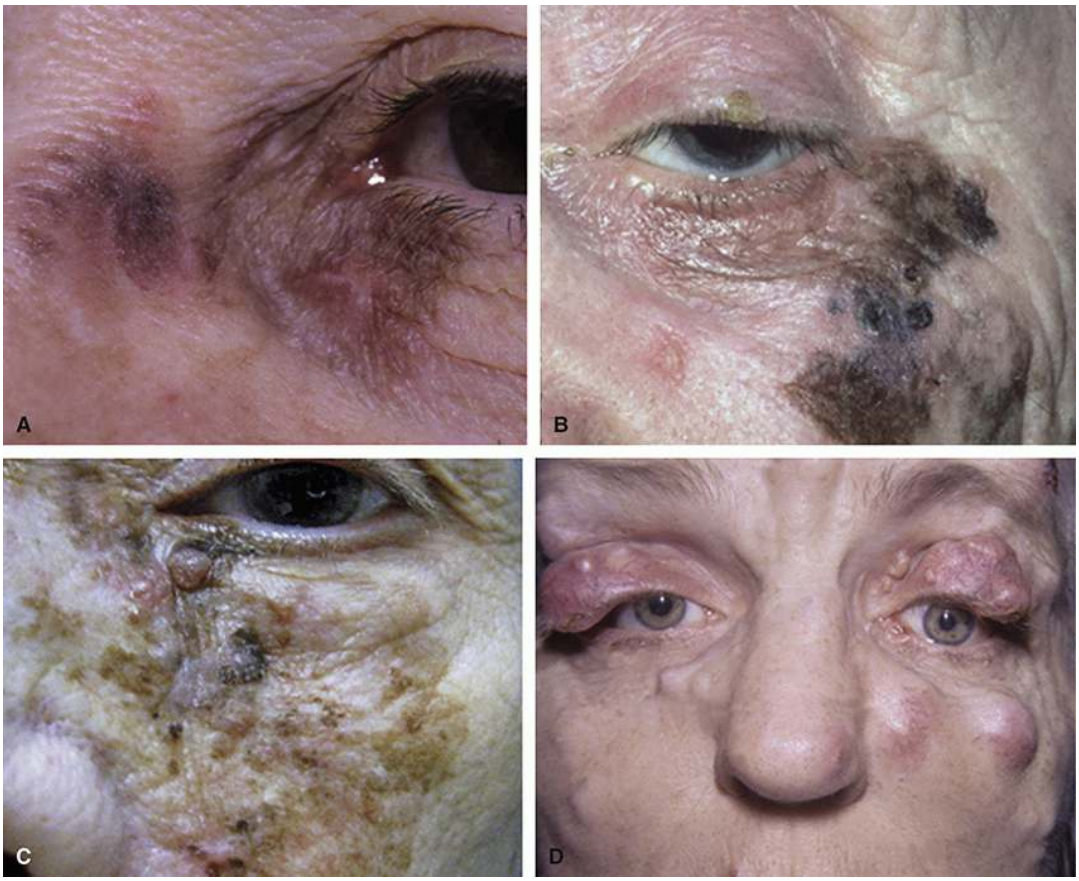

FIGURE 136.3 Melanoma involving the eyelid and adjacent areas of the face. A, Diffuse melanoma on the nose and lower eyelid. B, Multicentric melanoma at the lateral canthus and adjacent cheek. C, Widespread diffuse lightly pigmented melanoma of the lower eyelid and cheek. D, Multiple nodules of metastatic cutaneous melanoma in the eyelids, forehead, and face. (C, Courtesy of Dr. Bita Esmaeli.)

Clinically, cutaneous melanomas usually appear as asymmetric lesions with irregular borders, uneven distribution of color, diameters over 6 mm, and a history of growth. They may show ameboid projections, eccentric expansion, and notching of the borders. Superficial spreading melanoma presents as a pigmented lesion that is flat to mildly elevated. It may go through a period of relatively flat horizontal growth but eventually tends to become elevated and nodular. Nodular melanomas present as a pigmented or amelanotic bulky irregular growth that rapidly increases in size and may be associated with ulceration and bleeding (Figure 136.2). On the eyelids, melanomas may involve the eyelid skin, mucocutaneous border, and adjacent areas of the face (Figure 136.3).

Acquired pigmented lesions on the periocular skin of middle-aged and elderly patients should raise the possibility of in situ melanoma (lentigo maligna) (Figure 136.1).[43,44] These usually begin as a lightly pigmented macule that slowly enlarges over *(Print pagebreak 906)* several years or even decades. As many as 50% of these lesions may show histologic evidence of invasive lentigo maligna melanoma,[45,46] and the risk increases with continued growth.

Clinical diagnosis of eyelid melanoma is often difficult, and although in-person visual inspection greatly increases diagnostic accuracy compared with image-based evaluations, visual inspection alone is not entirely adequate. Diagnostic accuracy can be enhanced with ancillary tests such as dermoscopy,[47] reflectance confocal microscopy, impedance spectroscopy, and digital

epiluminescence microscopy.[48,49,50,51] Each of these techniques has advantages over clinical observation alone, but all also have limitations and are not widely available. Conjunctival melanoma typically presents as a nontender flat to nodular pigmented lesion, often associated with increased vascularity, prominent feeder vessels, and progressive thickening (Figures 136.2C and 136.4).[52,53] They may be associated with hemorrhage and bloody tears, and areas of ulceration. As with cutaneous and uveal melanoma, they may also be amelanotic.

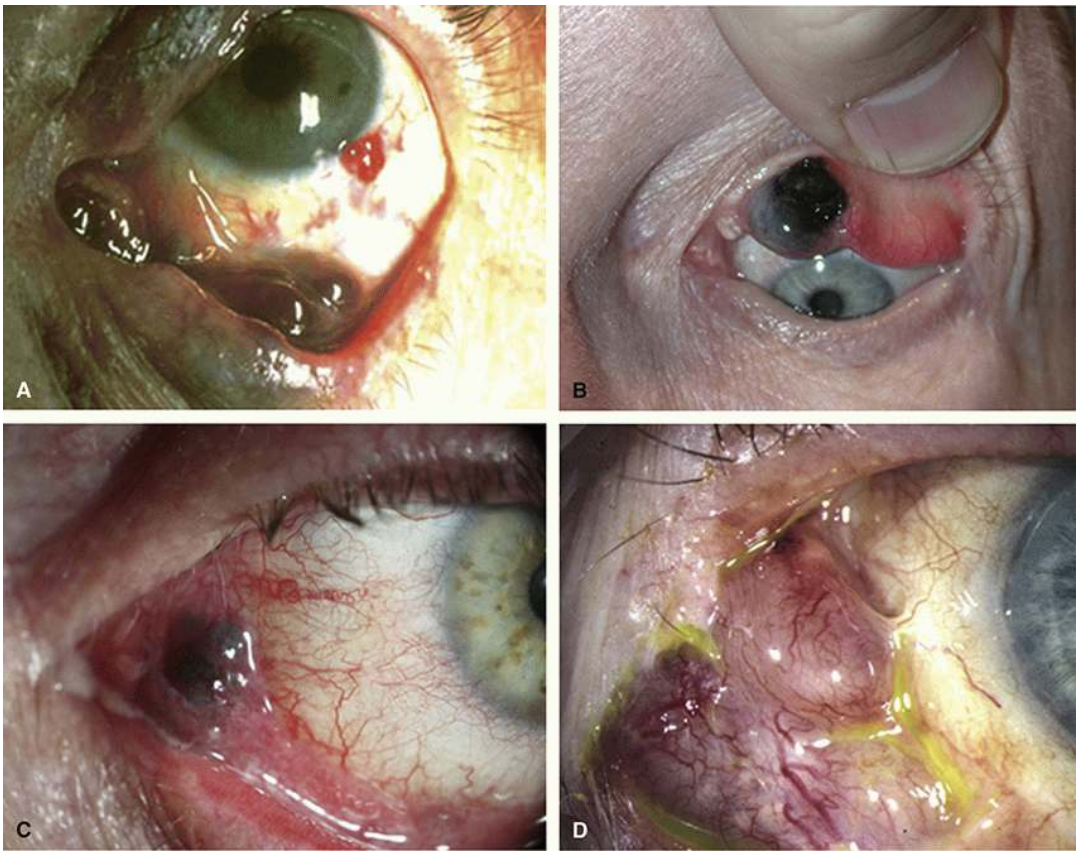

FIGURE 136.4 Conjunctival melanoma. A, Nodular melanoma of the lower eyelid palpebral conjunctiva. B, Deeply pigmented melanoma in the upper eyelid palpebral conjunctiva. C, Small nodular melanoma arising in the caruncle with surrounding vascular congestion. D, Extensive amelanotic melanoma arising in the caruncle and adjacent lower eyelid. (B, Courtesy of Dr. Bita Esmaeli.)

Differential Diagnosis

The differential diagnosis for cutaneous melanoma includes nonmalignant pigmented melanocytic nevi, pigmented basal cell carcinoma, pigmented actinic keratosis, pigmented seborrheic keratosis, dysplastic nevi, apocrine hidrocystoma, varix, hemangioma, inflammatory dermatosis, and ocular argyrosis. For conjunctival melanoma, several other clinical entities are included in the differential diagnosis. Most common are conjunctival melanocytic nevi, especially those that show growth, which can be seen in about 8% of such nevi.[54] Other lesions in the differential should include melanosis oculi, oculodermal melanocytosis, sclerouveal staphyloma, foreign body, polymerized epinephrine, nerve loop of Axenfeld, amyloidosis, ochronosis, pigmented epithelial tumors such as papilloma and squamous cell carcinoma, and pigmented pinguecula.[27,55]

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Treatment

The treatment of choice for periocular melanoma is complete surgical excision with wide tumor-free margins confirmed histologically. Studies have shown that a margin less than 1 cm is associated with a poorer prognosis than those with 1 to 2 cm margins.[56,57,58] However, for eyelid lesions, a 1 to 2 cm margin is usually not possible. In such cases, Mohs micrographic surgery is recommended, especially with the use of MART-1 or other immunostains.[59,60,61,62] In addition to surgery, regional lymph nodes should be evaluated, and a metastatic evaluation performed for all patients.

Radiotherapy for head and neck melanoma is rarely used as primary treatment but is used principally as adjuvant therapy in

advanced nodal or primary disease cases following surgical resection and lymph node dissection.[63] It is also used for the palliation of distant metastases. Radiotherapy to the primary tumor site can be considered for patients who are medically precluded from surgery, cases where surgical morbidity is considered to be high, or for surgically resected tumors with persistent positive margins and where further resection is not possible.[63] When radiotherapy is used as postoperative therapy following primary surgery, excellent local and regional control can be obtained with acceptable toxicity, but there is little added benefit for the development of metastasis and overall survival.[64]

During the past decade, innovative treatment options for metastatic melanoma have been introduced based on tumor biology, oncogenic mutations, and immune surveillance, and these have improved treatment responses and survival.[65,66,67,68] These options include immune checkpoint inhibitors that inhibit the activity of regulatory T cells and enhance effector T cell function to promote an antitumor immune response.[65] Approximately 50% of cutaneous melanomas contain an oncogenic *V600-BRAF* mutation that activates the MAPK/ERK signaling pathway.[38,69] Inhibitors of mutated *BRAF*, such as vemurafenib and dabrafenib, either alone or combined with MEK inhibitors, have significantly benefited patients with mutated *BRAF* metastatic melanoma.[66,70,71]

Treatment of conjunctival melanoma usually involves wide surgical excision with 3 to 5 mm margins without direct manipulation of the tumor.[72,73] The underlying Tenon capsule is included to the level of bare sclera, and the sclera can be treated with absolute alcohol or mitomycin C. The residual conjunctival margins are then treated with double freeze-thaw cryotherapy.[74] Some authors advocate treatment with CO_2 laser,[75] or radiotherapy with external beam or proton beam, or with brachytherapy using iodine, strontium, or ruthenium plaques.[76,77] In advanced cases invading into the orbit, exenteration of the orbital contents may be the only life-saving option if there is no systemic spread of the tumor.[33] Iodine-125 brachytherapy has been recommended as an alternative to exenteration in some cases.[78]

Prognosis

Cutaneous malignant melanoma accounts for two-thirds of all deaths from skin cancer.[79] As with most tumors, early diagnosis and treatment are critical to improved outcomes. Prognosis and metastatic potential are linked to the thickness of the tumor and depth of invasion, and poor prognosis for tumors of the eyelid is correlated with a Breslow depth greater than 1.5 mm (Clark level 4).[79] Lesions with a depth less than 0.75 mm have a 5-year survival rate of 98%, while lesions greater than 4 mm have a less than 50% survival rate. This is particularly true in cases where clinical characteristics typically used for the diagnosis of melanoma, such as pigmentation, are absent. In addition, melanomas involving the eyelid margin may have a poorer prognosis.[12,80]

In a meta-analysis of treatment options for metastatic cutaneous melanoma, Pasquali et al[81] concluded that compared to chemotherapy, biochemotherapy (chemotherapy plus cytokines), immune checkpoint inhibitors, and *BRAF* inhibitors all improve progression-free survival, with variable benefit for overall survival, and in some cases increased toxicity. For conjunctival melanoma, the 1-, 5-, and 10-year tumor-related mortality rates were 3.8%, 30.5%, and 37.4% in 57 Chinese patients.[32] Jain et al reported that 1, 5, and 10-year cumulative mortality rates varied according to clinical and pathological stages in an international multicenter study of 288 patients.[82] The cumulative rates of mortality at 1, 5, and 10 years were 0%, 2.5%, and 15.2%, respectively, for patients with cT1 tumors and 0%, 28.6%, and 43.6% for cT2 tumors.[82] cT3 tumors had 1- and 5-year cumulative mortality rates of 21.1% and 31.6%, respectively.[82]

Histopathology

The histological features of cutaneous eyelid melanomas are similar to those of other cutaneous melanomas.[83] Lentigo maligna, the in situ precursor lesion of lentigo maligna melanoma, has two patterns.[84] Classic lentigo maligna has a broad, contiguous proliferation of uniformly atypical melanocytes that may be nevoid or epithelioid along the dermoepidermal junction.[84] A few irregularly distributed nests of atypical melanocytes may hang down from the dermoepidermal junction in a drop-like pattern (Figure 136.5A).[84] The second pattern of lentigo maligna, termed nevoid or dysplastic nevus-like lentigo maligna, has more nests of tumor cells, and some nests may bridge adjacent elongated rete ridges.[84] Lentigo maligna has little pagetoid spread of tumor cells into the more superficial epidermis.[85] The epidermis often has thinning and loss of rete ridges.[84] Lentigo malignant melanoma features the epidermal changes of lentigo maligna with tumor invading into the dermis, which has severe solar elastosis. Immunohistochemical staining using antibodies to MART-1 (melan-A) or SOX10 helps demonstrate the confluence of the atypical basal melanocytes (Figure 136.5B). Superficial spreading melanoma (low-CSD melanoma) is characterized by a proliferation of atypical melanocytes, singly and in nests, within all levels of the epidermis.[85,86] The atypical melanocytes may be confined to the epidermis (in situ melanoma), or they may be associated with tumor cells invading the dermis. The tumor cells may be epithelioid, nevus cell-like, or spindle-shaped.[85] The degree of melanin pigmentation is highly variable, with some tumors having *(Print pagebreak 908) (Print pagebreak 909)* little pigment (Figure 136.5C) and others being heavily pigmented (Figure 136.5D). Nodular

melanomas are invasive dermal tumors with little or no intraepidermal atypical melanocytes extending laterally to the invasive tumor.[85,86] The epidermis may form a collarette around the dermal tumor.[87] Nodular malignant melanoma is commonly composed of round to oval epithelioid cells with varying amounts of melanin pigment.[85] Desmoplastic melanomas are paucicellular dermal-based tumors formed by strands of elongated spindle-shaped tumor cells surrounded by fine, sclerotic, or mature collagen bundles (Figure 136.5E).[85,88] The epidermis over the tumor may have lentigo maligna or atypical melanocytic proliferation, but about half of desmoplastic melanomas have little or no overlying junctional melanocytic change.[88] Neurotropism is present in about 30% of desmoplastic melanomas.[88] Desmoplastic melanomas usually lack expression of HMB-45 and MART-1, but they are positive for S100 protein (Figure 136.5F) and SOX10, which assists in distinguishing these tumors from other spindle cell neoplasms.[77] Pathological staging of cutaneous eyelid melanomas is the same as for melanomas at other sites.[89] The most important predictors for survival in patients with eyelid skin melanoma are age ≥75 years, T4 stage, the presence of lymph node metastasis, and nodular melanoma subtype.[90]

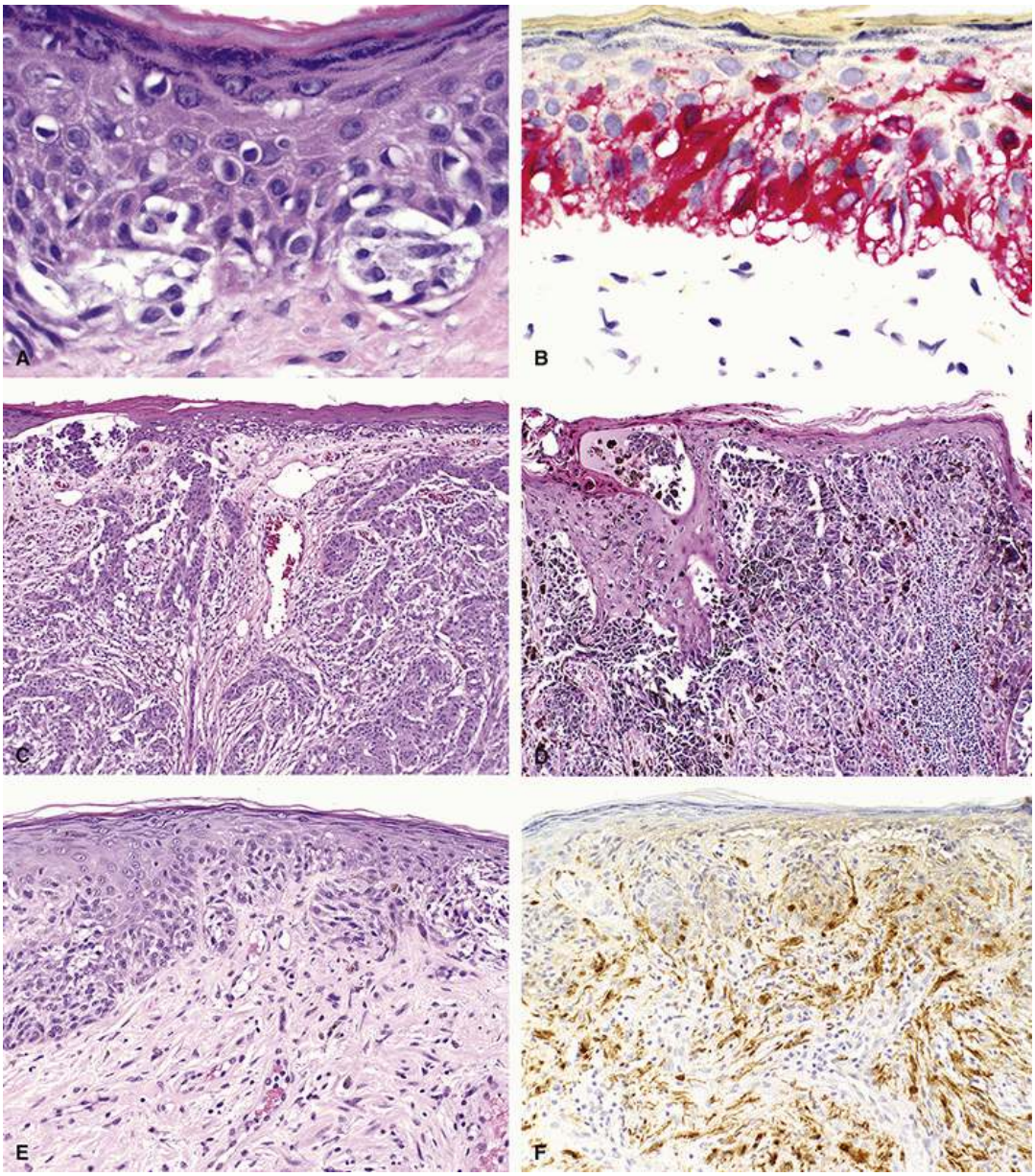

FIGURE 136.5 A, This example of lentigo maligna, the in situ precursor lesion of lentigo maligna melanoma, has the classic pattern with a broad, contiguous proliferation of atypical epithelioid melanocytes along the dermoepidermal junction with a few nests of atypical melanocytes hanging down from the dermoepidermal junction in a drop-like pattern. B, Antibodies to the melanocyte marker MART-1 highlight the contiguous atypical melanocytes along the dermoepidermal junction in the lentigo maligna. C, This invasive superficial spreading melanoma has scant melanin pigmentation. The epidermis over the invasive tumor has intraepidermal melanoma with tumor nests and areas of confluent melanoma cells along the dermoepidermal junction with pagetoid spread into the more superficial epidermis. D, This superficial spreading melanoma is heavily pigmented, making the pagetoid spread in the epidermis readily apparent. E, This desmoplastic melanoma of the right lower eyelid shows a paucicellular dermal tumor composed of spindle-shaped cells with intervening collagen bundles and occasional lymphocytes and macrophages. The epidermis

over the tumor has a lentigo maligna melanocytic proliferation. F, The desmoplastic melanoma cells stain strongly using antibodies to S100 protein.

Melanomas of the palpebral and forniceal conjunctiva are rare, and tumors may be in situ or invasive.[91] The terminology for intraepithelial melanocytic proliferations is in flux since the classification of these lesions as "primary acquired melanosis (PAM) of the conjunctiva" in the early 1980s and the subsequent demonstration that the risk for progression to melanoma depends on the degree of cytological atypia.[92,93] At Wills Eye Hospital, PAM without atypia "was defined as pigmentation of the conjunctival epithelium with or without benign melanocytic hyperplasia, PAM with atypia was characterized by the presence of atypical melanocytic hyperplasia, PAM with mild atypia was defined as atypical melanocytes confined to the basal layer of the epithelium, and PAM with severe atypia was defined as atypical melanocytic hyperplasia that extended into the more superficial nonbasal portion of the epithelium in a pagetoid fashion and/or contained epithelioid cells."[94] None of the cases of PAM without atypia or PAM with mild atypia progressed to melanoma. In contrast, 13% of patients with PAM with severe atypia developed melanoma out of 112 patients with a follow-up of at least 3 years.[94]

The WHO currently classifies intraepithelial melanocytic proliferations as conjunctival melanocytic intraepithelial neoplasia/PAM in *Classification of Skin Tumours*, 4th Edition[95] and conjunctival melanocytic intraepithelial neoplasia in *Classification of Tumours of the Eye*, 4th Edition.[96] Grading of conjunctival melanocytic cytological atypia as mild, moderate, or severe is similar to that for skin and other mucosal sites.[95] Conjunctival melanocytic intraepithelial neoplasia grading employs a scoring system from 1 to 10 based on the extent of atypical melanocytes' horizontal and vertical epithelial involvement and their degree of cytological atypia.[96] The classification systems for conjunctival intraepithelial melanocytic neoplasms correlate as follows, as adapted from Table 1.02 in the *WHO Classification of Tumours of the Eye*, 4th Edition[96]:

Primary acquired melanosis grade, modified to include melanoma in situ	**Conjunctival melanocytic intraepithelial neoplasia (C-MIN) score**	**WHO proposed simplified terminology**
PAM without atypia	C-MIN score = 1	Low-grade conjunctival melanocytic intraepithelial lesion
PAM with mild atypia	C-MIN score = 2	Low-grade conjunctival melanocytic intraepithelial lesion
PAM with moderate atypia	C-MIN score = 3	High-grade conjunctival melanocytic intraepithelial lesion
PAM with severe atypia (atypical melanocytes in ≤75% of epithelial thickness)	C-MIN score = 4-5	High-grade conjunctival melanocytic intraepithelial lesion
Melanoma in situ (atypical melanocytes in >75% of epithelial thickness)	C-MIN score > 5	Melanoma in situ

We support the proposed simplified WHO terminology since it will standardize terminology and facilitate clinical management. *WHO Classification of Tumours of the Eye*, *4th Edition*, provides excellent illustrations and descriptions for grading radial and vertical spread and cytological atypia of conjunctival melanocytes.[96] An example of conjunctival melanoma in situ is shown in Figure 136.5A.

In a study of 382 consecutive patients with conjunctival melanoma by Shields and coworkers, the tumor arose from PAM in 74% of patients, from a preexisting nevus in 7%, and de novo in 19% of patients.[97] Conjunctival melanomas have nests (Figure 136.6B) or sheets (Figure 136.6C) of atypical melanocytes[98] that may be polyhedral, epithelioid, spindle shape, or a combination of these.[99] Melanin pigmentation is variable, with spindle cells usually being less pigmented than polyhedral or epithelioid melanoma cells.[99] Neoplastic cells express melanocytic markers such as S100 protein, MART-1 (melan-A), HMB-45, and melanocyte-inducing transcription factor (MITF; also termed microphthalmia-associated transcription factor).[98] Pathological staging incorporates tumor location, tumor thickness, and local invasion.[100]

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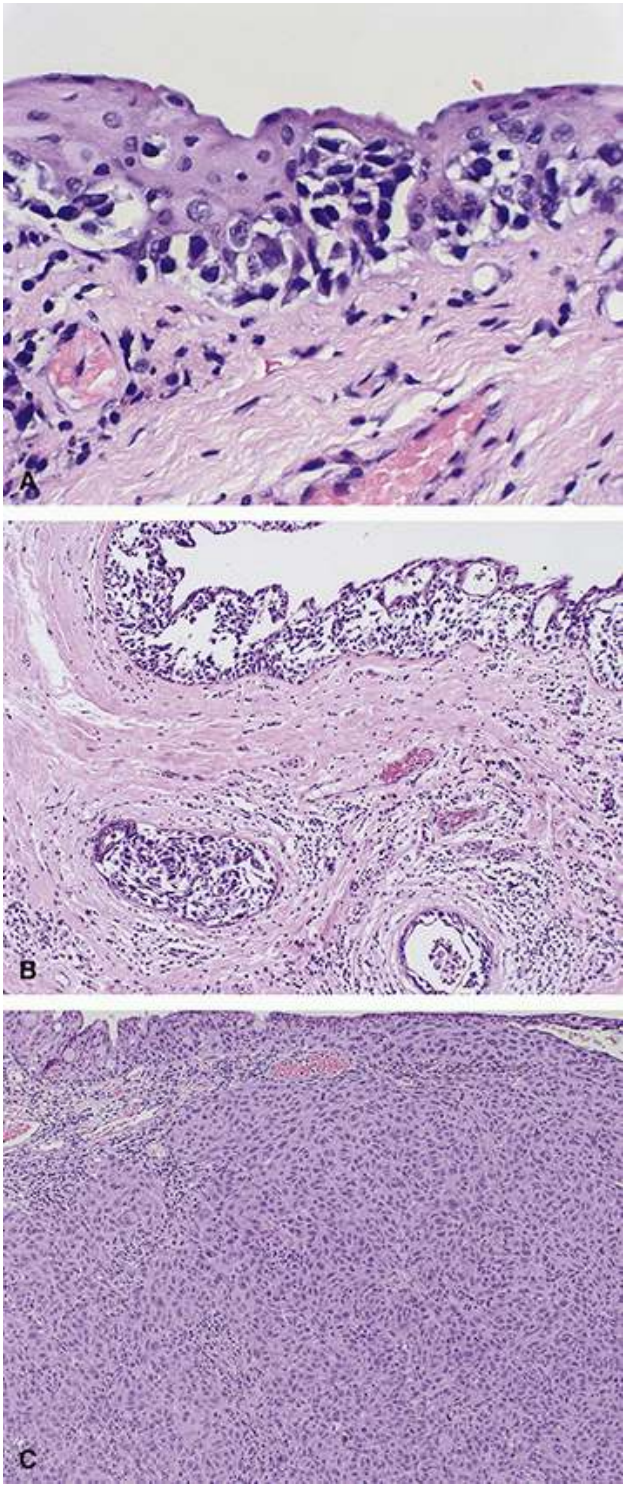

FIGURE 136.6 A, Conjunctival melanoma in situ features cytologically atypical melanocytes extending through >75% of the epithelial thickness. B, This invasive melanoma of the right superior fornix has two nests of invasive melanoma in the stroma beneath epithelium replaced by in situ melanoma. The invasive melanoma cells are predominantly spindle-shaped, and the nest on the right is cystic. C, This invasive melanoma of the left lower eyelid conjunctiva arose in association with in situ melanoma. The sheet of epithelioid melanoma cells is amelanotic.

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CHAPTER 137

Merkel Cell Carcinoma

Key Points

- Merkel cell carcinoma (MCC) is a rare, aggressive, cutaneous neuroendocrine malignancy
- The majority of MCC tumors occur on the face and head, but only 5% to 10% involve the eyelids and the periocular region
- The pathophysiology of MCC is controversial, but the tumor is likely derived from a population of cells that represents earlier stages in the Merkel cell differentiation pathway
- Ultraviolet exposure is considered a major risk factor for MCC
- Tumors typically present near the eyelid margin as a rapidly expanding, painless, indurated, erythematous, violaceous, solitary dermal nodule with dilated telangiectatic blood vessels and loss of eyelashes
- Wide local surgical excision is currently the standard of care
- The prognosis for all body sites combined is relatively poor with local recurrence seen in about one-third of patients and one-half of patients developing distant metastases

In 1875, Friedrich Merkel first described clear, oval, nondendritic cells located in the basal layer of the epidermis around hair follicles and in the mucosa, with neuroendocrine features.[1] It was not until 1972 that an undifferentiated neuroendocrine tumor found in the skin was initially described by Cyril Toker as trabecular cell carcinoma of the skin.[2] But later, he speculated that the cellular origin of this cancer was Merkel cells and the tumor was renamed Merkel cell carcinoma (MCC). The exact origin of Merkel cells remains unsettled, but they are thought to have characteristics of both epithelial and neuroendocrine origins and to arise from a common pluripotential precursor.[3,4,5]

MCC is a rare, aggressive, cutaneous neuroendocrine malignancy. The highest worldwide incidence is found in Australia at 1.6 cases per 100,000 population.[6] While the incidence is very low, it has increased over the last several decades, with an annual increase of about 8%.[7] In the United States, about 1500 new cases of MCC are diagnosed each year, with a male preponderance of about 60%.

MCC is extremely uncommon in younger patients, with only 12% younger than 60 years of age.[8] The median age at diagnosis is about 75 years old, and the incidence increases rapidly with advancing age, suggesting an accumulation of oncogenic factors.[9] The incidence is also increased in immunocompromised individuals with AIDS or those who have undergone organ transplantation.[10,11] The risk is higher among persons of European ancestry, and the incidence is inversely related to latitude suggesting its occurrence is related to a deficiency of protective melanin in the skin. Patients with MCC have a higher risk of other sun exposure-related skin tumors and also have an increased risk for multiple myeloma, non-Hodgkin lymphoma, and chronic lymphocytic leukemia.[12]

The majority of MCC tumors are present on the face and head. Only 5% to 10% involve the eyelids and the periocular region,[13] of which only about 100 cases have been reported to date. These tumors are characterized by rapid progression, a high rate of recurrence after surgical resection, and early regional and metastatic spread.[14,15]

This carcinoma has been referred to under several different names in the published literature including Toker tumor, cutaneous neoplasm of Merkel cells, neuroendocrine carcinoma of the skin, and primary undifferentiated carcinoma of the skin. Campill et al[16] proposed that primary cutaneous neuroendocrine carcinoma best describes the relevant identifying characteristics of this tumor, but this has not gained general usage.

Two patterns of clinical presentation have been recognized.[17] The first pattern includes Merkel cell polyomavirus-positive tumors (MCPyV+) and represents about 80% of cases. These arise in a slightly younger population and present as benign-appearing flesh-

colored to violaceous dome-shaped nodules on the limbs and head and neck. The second pattern is MCV-negative (MCPyV-) tumors seen more frequently in patients with tumors in sun-damaged skin of the head and neck, often associated with other nonmelanoma skin cancers.

Etiology and Pathogenesis

Identifying the cell type from which any cancer arises is important for understanding the mechanisms of tumor origin and conceivably in discovering therapeutic interventions. The etiology of MCC is controversial: while evidence for the cell of origin is lacking, MCC cells do have some similarities to benign Merkel cells in both immunophenotype and ultrastructure, though normal Merkel cells are not most densely present in the same areas where MCC is most common.[18,19] Most investigators do not consider mature Merkel cells to be the cell of origin for MCC.[20] Rather, MCCs are more likely to be derived from a population that represents earlier stages in the Merkel cell differentiation pathway.[21] In addition, polyomavirus-negative MCCs have ultraviolet mutational signatures that are not present in papillomavirus-positive MCCs, suggesting that these two tumor types might arise from distinct cells of origin.[22]

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Although Merkel cells are found in the epidermis, MCC arises predominantly in the dermis.[23] Despite the similarities between Merkel cells and MCC, there is evidence against the belief that MCC originates from epidermal Merkel cells. This includes the observation that MCC is localized in the dermis, lacks the neuroendocrine peptides typical of normal Merkel cells, and the frequent presence of neurofilament proteins (NFPs).[24] The most accepted hypothesis is that MCC originates from a common precursor cell of keratinocytes and Merkel cells.[24,25]

In 2008, a novel virus, named Merkel cell polyomavirus (MCPyV), was identified in MCC tissue and can be detected in 80% of all MCC samples.[26,27,28,29,30] This virus has been tentatively linked to the pathogenesis of some MCC. The oncogenic potentials of this virus are attributed to two of its proteins, large T-antigen that regulates cell cycle transit and small t-antigen that activates cap-dependent translation critical for cancer cell growth. These have been shown to transform cells in vitro and induce tumors in an animal model.[30]

There are significant differences between MCPyV-positive and MCPyV-negative MCCs in cellular morphology, as well as in chromosomal alterations, activating mutations, and inactivation of tumor suppressor genes.[21] This adds to the speculation that MCC may arise from multiple cells of origin. Jankowski et al[31] discussed the expression of early B cell lineage markers in 80% of MCC that are also MCPyV-positive. They hypothesized that MCC may be a heterogeneous entity with separate subtypes: a pluripotent dermal epidermal stem cell-derived MCPyV-negative MCC with epidermal tropism (20%) and an MCPyV-positive MCC possibly originating from precursor B cells (80%). However, in a review of recent studies on cancer genomics, mouse genetics, and virology experiments, Sunshine and Jahchan[22] concluded that MCPyV-positive MCCs originate from mesodermal dermal fibroblasts, and MCPyV-negative MCCs arise from ectodermal epidermal keratinocytes.

Ultraviolet exposure is considered a major risk factor for MCC. The frequency of MCC is higher at lower latitudes and is significantly lower in patients of non-white ethnicities. This tumor has a predilection for sun-exposed areas of the skin and is more common in light-skinned individuals. Australia currently has the highest reported incidence of MCC with a higher percentage of MCPyV-negative MCCs, possibly reflecting a higher risk of ultraviolet exposure.[32,33]

Immunosuppressive status is another known risk factor with organ transplant recipients and acquired immune deficiency syndrome patients disproportionately affected.[34] A significantly increased risk of MCC has been observed among patients with a history of previous hematologic and cutaneous malignancies.[35,36] MCC was also observed in patients with a history of breast cancer, but a significant association between the two entities has not been established.[36,37]

Clinical Presentation

MCC is more common in the head and neck where it accounts for about 40% to 50% of all such lesions.[14,38] About 10% involve the eyelid or periocular region.[24] The diagnosis is challenging due to its variable appearance. Tumors typically present as an asymptomatic, rapidly expanding, painless, indurated, solitary dermal nodule near the eyelid margin (Figure 137.1). The color is erythematous to deeply violaceous, with dilated telangiectatic blood vessels and minimal to significant loss of eyelashes.[34] The upper eyelid is more commonly involved than the lower eyelid, representing about 80% of all eyelid MCC. The overlying epidermis is usually intact,[24] but ulceration may occasionally be present (Figure 137.2).

The involvement of regional lymph nodes is present in up to two-thirds of patients with MCC. The rate of sentinel lymph node involvement is correlated with greater tumor diameter and thickness, those with a higher mitotic rate, and tumors with infiltrative

growth patterns. Pfieffer et al[39] found that 68% of patients with MCC > 2 cm had positive sentinel lymph nodes, whereas only 23% of patients with tumors < 1 cm had positive nodes.

Multiple lesions are exceedingly rare and there is one case report of a recurrent lesion in the lower lid associated with a second lesion on the ipsilateral upper lid 1 year after initial presentation and surgical excision.[40] Thakur S et al[41] described a patient with MCCs involving the bilateral upper eyelids.

Differential Diagnosis

As many as 56% of MCCs are initially thought to be clinically benign.[42,43] They are most commonly mistaken for chalazion, eccrine cyst, keratoacanthoma, dermatofibroma, and lipoma leading to delayed diagnosis and treatment.[41,44,45,46] It is also often mistaken for other more common nonmelanoma malignancies such as basal cell, squamous cell, and sebaceous cell carcinomas, as well as lymphoma, and metastatic neuroendocrine tumors.[15] The diagnosis is usually made following a biopsy and relies heavily on immunohistochemistry.[42] Once confirmed, further evaluation should include a total body evaluation with a PET/CT scan since MCC is highly avid for FDG (18 fluorodeoxyglucose).[7] As for all tumors, AJCC staging should be determined.

Treatment

Given the high tendency of MCC to recur locally, wide local surgical excision is currently the standard of care. The recommendation for the optimal minimum normal tissue margins elsewhere in the body is 3 cm. However, such margins do not apply to eyelid lesions. Atamney et al[7] employed excision of eyelid tumors with 5-mm margins, along with intraoperative biopsy samples confirmed by frozen section to be free of tumor cells. Other studies have confirmed that a margin width of 5 mm may be reasonable for local control of eyelid of periocular lesions, particularly for lesions <2 cm.[15,45] MCC is very radiosensitive and radiotherapy is commonly used as an adjuvant modality for patients at risk for recurrence or for patients not suitable for primary surgical resection.[47] Although postoperative radiotherapy has been associated with improved local and regional control, improvement in disease-specific survival has been variable.[47] *(Print pagebreak 915)* After appropriate postsurgical healing, adjuvant radiotherapy targeting the tumor bed for patients with localized MCC, for those with narrow resection margins, and for immunosuppressed patients, has been recommended by the National Comprehensive Cancer Network (NCCN). Fractionated radiotherapy at 50 to 66 Gy is recommended depending on whether the resection margins are negative or positive.[47]

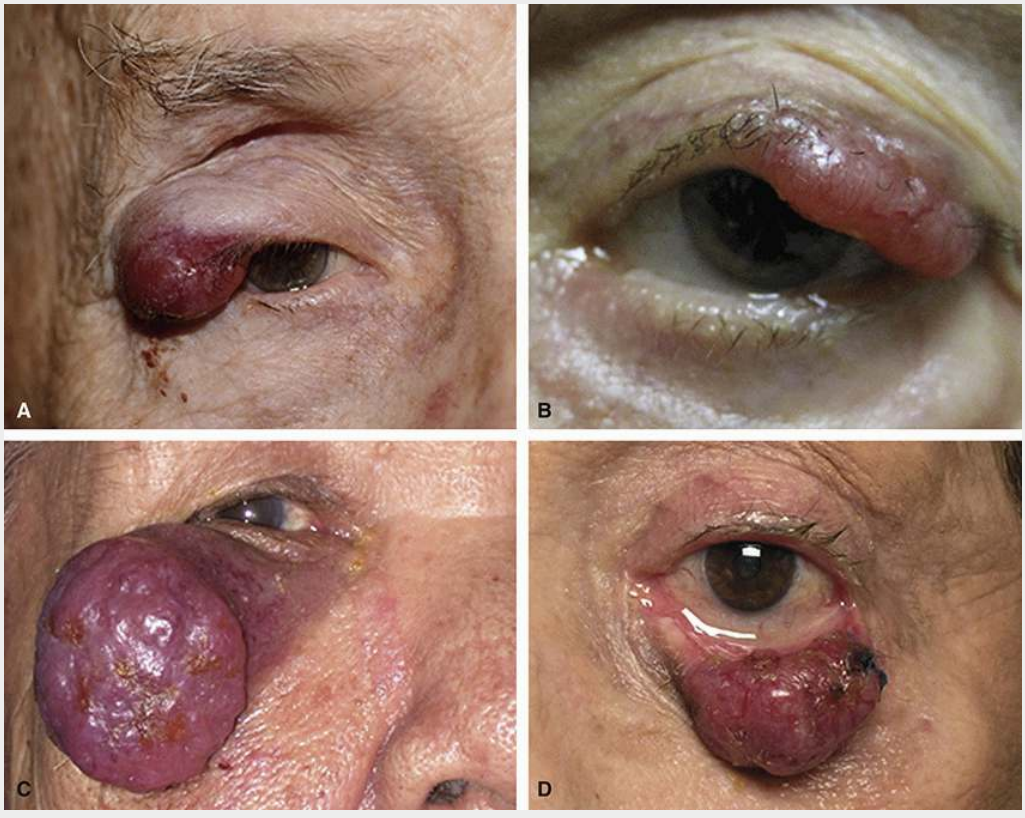

FIGURE 137.1 Nodular Merkel cell carcinoma involving the eyelid margins. (A, Courtesy of Dr. Robert

Kersten. B and C, Courtesy of Dr. Bita Esmaeli. D, Courtesy of Dr. Robert Goldberg.)

Because MCC has a propensity for early invasion of dermal lymphatics, surgical excision of the primary lesion may not be adequate for the prevention of local and regional recurrence and metastases even with adequate margins. Esmaeli et al[48] reported the first case of a positive sentinel lymph node biopsy (SLNB) in a patient with MCC of the eyelid. They suggested that SNLB may allow for the detection of subclinical nodal metastases and therefore allow for a more prompt institution of adjuvant therapy. Because MCC is highly radiosensitive, many authors have recommended adding adjuvant radiation therapy to the primary site and to the draining nodes as standard of care in addition to surgery. This is especially relevant in the eyelids where surgical margins are necessarily limited, and local recurrence may have significant visual consequences. A recent study by Lamberti et al demonstrated that radiotherapy was associated with improved overall survival not just in patients with node-positive MCC (N+), but also in node-negative patients (N0), and even in nonmetastatic MCC (M0).[49] This study found that radiotherapy was interdependently associated with a 25%, 27%, and 26% reduction in the risk of death in M0, N0, and N+ respectively. However, there was no survival benefit in T4 tumors.[49] Also, in a meta-analysis of 1254 MCC patients comparing surgery alone to surgery with adjuvant radiotherapy at all anatomic sites, the use of surgery plus local radiotherapy decreased the risk of local and regional recurrence.[50]

When palpable lymphadenopathy or positive SLNB is present at the initial presentation, lymph node dissection may be useful as the first-line treatment for micrometastatic disease.[15] If this is unacceptable to the patient, then radiotherapy can be considered. The use of chemotherapy for MCC is inconclusive and available data are limited. Chemotherapy currently has no established role for localized or regional disease, but in patients with distant metastatic disease, palliation including chemotherapy may be appropriate and provides overall response rates *(Print pagebreak 916)* of approximately 70%.[51] Combination chemotherapy is more effective when two or more drugs are given concurrently.[52,53] Cisplatin plus etoposide, cyclophosphamide plus doxorubicin plus vincristine, or cyclophosphamide plus epirubicin plus vincristine are the most commonly used regimens.[25] The response rate is 70%, with a complete response in 35%.[54] However, the disease often recurs within a few months.

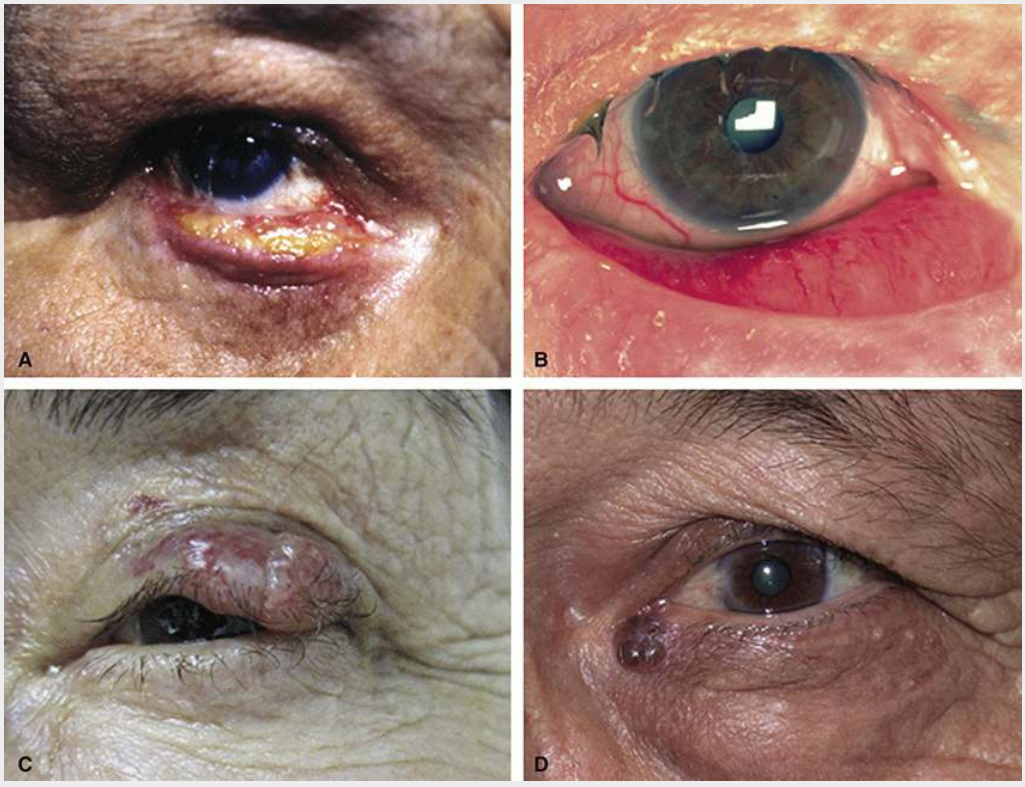

FIGURE 137.2 A, Ulcerated Merkel cell carcinoma on the eyelid margin. B, Diffuse infiltration of the lower eyelid and conjunctiva. C, Upper eyelid marginal Merkel cell carcinoma. D, Subcutaneous lower eyelid Merkel cell carcinoma. (A, Courtesy of Dr. Charles Soparkar. B, Courtesy of Dr. Robert Goldberg. C, Courtesy of Dr. Bita Esmaeli. D, Courtesy of Dr. Charles Soparkar.)

Insights into the pathogenesis of MCC have led to several clinical trials on the use of immunotherapy.[55] Recently, immune checkpoint inhibitors have shown very good durable responses, leading to the approval of a programmed death-ligand 1 inhibitor, Avelumab, for these patients.[56] In a clinical trial using Avelumab as first-line treatment for MCC patients with metastatic or locally advanced disease, objective response was achieved in 31.8% of cases, with a favorable toxicity profile, and an overall survival of 31% at 42 months.[47] However, despite initial successes, more than 50% of patients with MCC do

not benefit from PD-1 pathway blockade in any persistent fashion.[57]

Prognosis

The overall prognosis for Merkel cell tumor for all sites combined is relatively poor. Local recurrences are seen in about one-third of patients, usually within 1 year. Two-thirds have regional lymph node metastases, mostly within 18 months. More than one-half of patients develop distant metastases, usually within 2 years.[24,47]

Except for malignant melanoma, MCC is the second most common cause of skin cancer deaths in the United States with 5-year overall survival rates of 70% to 90%, 39% to 64%, and 18% to 30% for local, regional, and distant metastases, respectively.[39,58,59,60] The mortality rate within 2 years of diagnosis is 28% to 40%, with a median survival time of 6.8 months.[61,62,63]

Spontaneous regression of MCC tumors has been reported in more than 40 cases.[63,64,65] All cases were followed up to 18 months from diagnostic biopsy, and the regressions occurred rapidly over 1 to 3 months. Most *(Print pagebreak 917)* cases resulted in a cure over follow-up intervals of 1 to 15 years, although recurrence in regional lymph nodes has been reported.[66,67] Although the pathogenesis of the regression phenomenon has not yet been elucidated, it has been proposed that biopsy of the tumor may serve as the triggering mechanism by activating a T cell immune response.[68,69] Connelly et al[70] estimated the incidence of regression to be 1.67%.

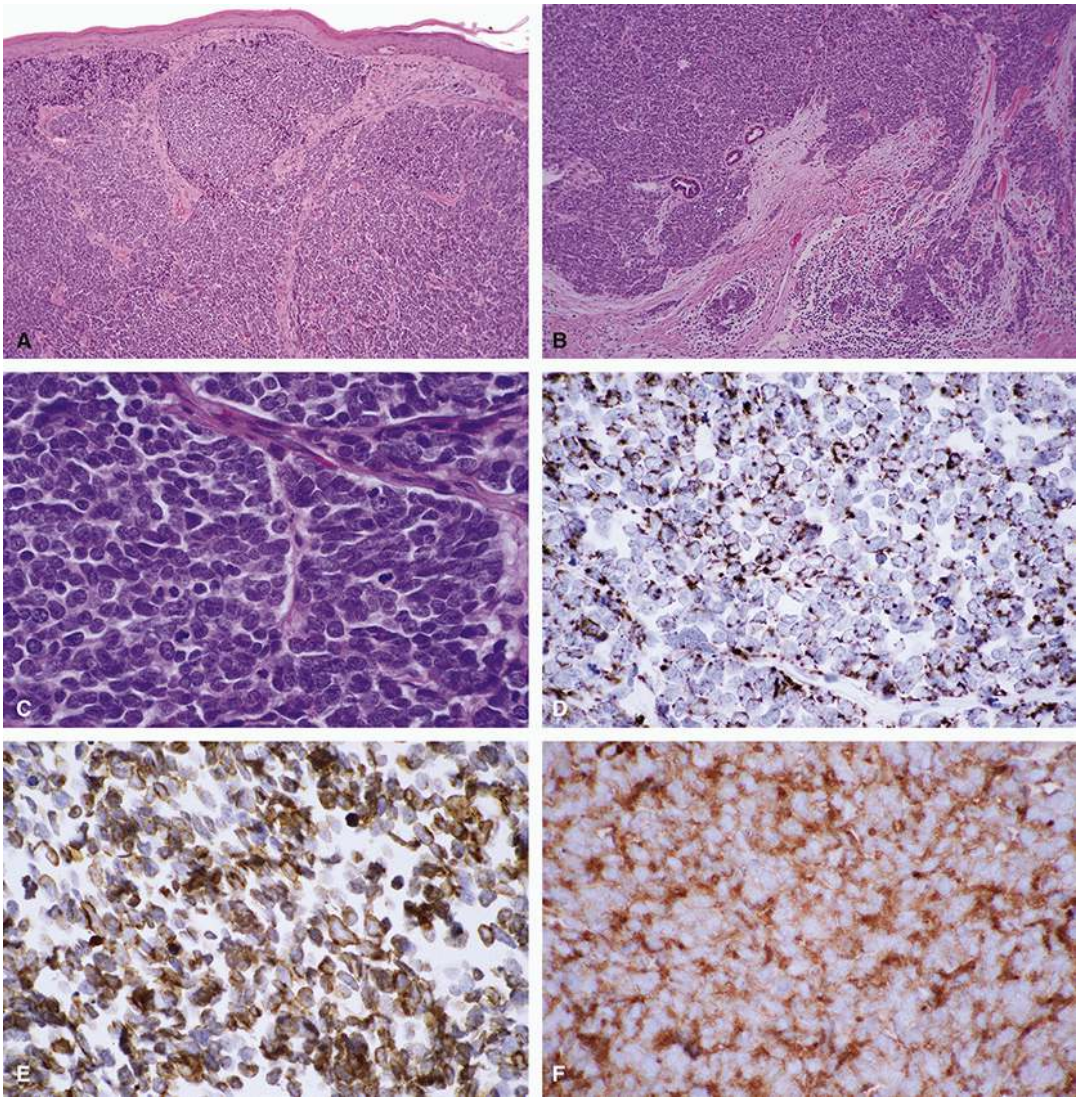

FIGURE 137.3 This Merkel cell carcinoma of the left cheek was located in the dermis of a man in his middle 70s. A, A narrow zone of normal dermis separates the anastomosing nodules of tumor from the overlying epidermis. B, Sheets of tumor cells form the nodules. The edges of the tumor are infiltrative into the adjacent dermis. C, The tumor cells are discohesive, intermediate size, and mostly round to oval. The chromatin is finely granular, and nucleoli are not apparent. The tumor cells are immunoreactive using broad-spectrum antibodies to cytokeratins (AE1/AE3; D), CK20

(E), and synaptophysin (F).

Histopathology

MCCs are dermal and/or subcutaneous tumors.[71,72,73,74] They are composed of cells that may be small, intermediate size, or large, with intermediate cell type MCC most common.[73] Epidermal involvement is uncommon,[58,74] with most MCCs having a zone of normal dermis between the epidermis and tumor (Figure 137.3A).[71] Tumor cells may form anastomosing *(Print pagebreak 918)* trabeculae (trabecular pattern) or diffuse noncohesive sheets reminiscent of lymphoma (solid pattern; Figure 137.3A-C).[71,75] The growth pattern was infiltrative in 71% of tumors, nodular in 20%, multinodular in 6%, and polypoid in 2% of the 156 tumors examined by Andea and coworkers.[72] Tumor cells vary from round to oval to spindle[75] and are usually basophilic with round nuclei, finely granular chromatin, absent or small inconspicuous nucleoli, and scant amphophilic cytoplasm (Figure 137.3C).[71] Mitotic figures are usually numerous,[71] there are scattered apoptotic tumor cells,[74] and zones of "geographic" coagulative necrosis occur in about half of MCCs.[71] Lymphovascular invasion is considered an early event in MCC,[76] and it was identified by Andea and colleagues in 60% of 156 tumors.[72] The tumor stroma is highly vascularized,[75] and tumor-infiltrating lymphocytes vary from absent to brisk.[72] MCCs may sometimes exhibit areas of squamous, glandular, sarcomatous, follicular, or porocarcinoma differentiation.[77]

MCC tumor cells usually express broad-spectrum keratins such as AE1/AE3 (Figure 137.3D), cytokeratin 20 (CK20; Figure 137.3E), neuroendocrine markers (chromogranin A, synaptophysin [Figure 137.3F], CD56), NFP, special AT-rich sequence-binding protein-2 (SATB2), and often MCPyV.[74] CK20 expression is usually a perinuclear dot pattern "often admixed with circumferential cytoplasmic staining."[74] A dot-like pattern of CD99 expression is strongly associated with MCPyV-positive tumors (sensitivity = 81% and specificity = 90%).[78] MCPyV-negative MCCs are frequently positive for expression of thyroid transcription factor 1 (TTF1) and CK7 and negative for expression of NFP, and they more frequently have larger tumor cells with more abundant cytoplasm.[78] Identification of blood vessel and lymphatic invasion is facilitated using antibodies to blood vessel endothelium (eg, CD31 or factor VIII-related antigen) or podoplanin for lymphatics (Figure 137.4A and B). Locating minute metastases or single-tumor cells in lymph nodes is aided by using antibodies to cytokeratins or neuroendocrine markers (Figure 137.4C and D).

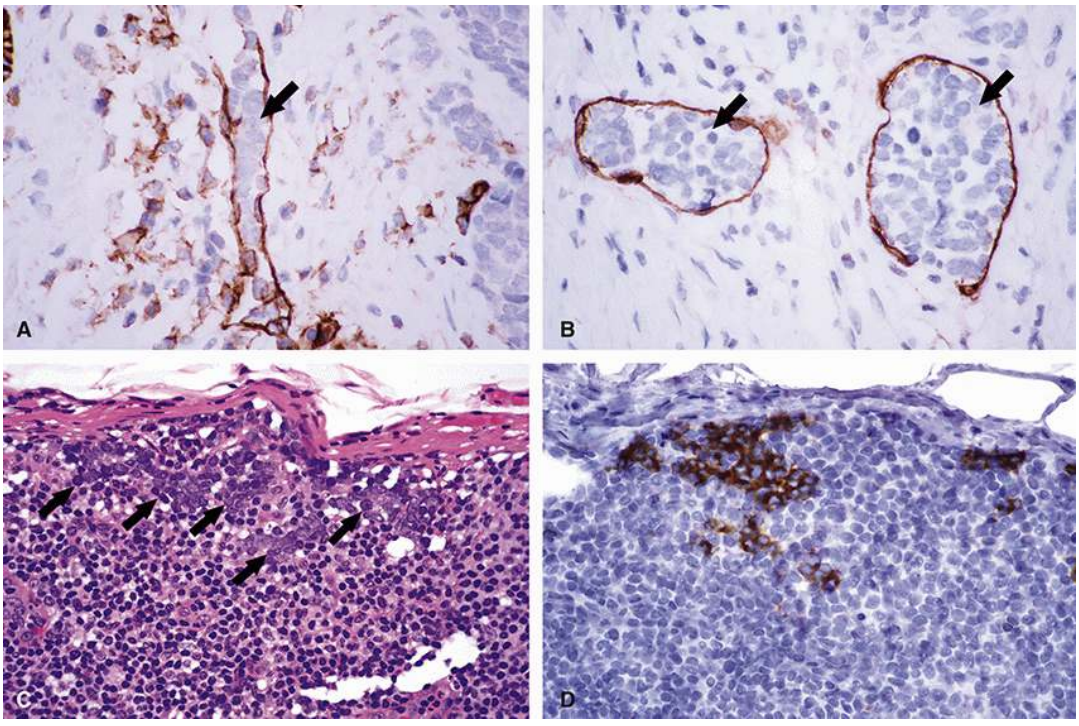

FIGURE 137.4 Merkel cell carcinomas (MCCs) commonly have lymphovascular invasion (LVI). Identifying LVI is aided using immunohistochemical stains for blood vessel (A; anti-CD31 antibodies) and lymphatic endothelium (B; D2-40 anti-podoplanin antibody). Endothelial cells (brown) surround tumor cells in the lumen of a vein (A, arrow) and two lymphatics (B, arrows). C, Small MCC lymph node metastases (arrows) are often difficult to distinguish from large lymphocytes. D, Small subcapsular metastases and individual tumor cells are highlighted brown using antibodies to synaptophysin.

Pathological staging of eyelid MCC is similar to these tumors at other sites and incorporates tumor size, invasion of other structures (fascia, muscle, cartilage, or bone), lymph node status, and distant metastases.[79] Histological features of likely prognostic

significance that are in the College of American Pathologists protocol for MCC include tumor thickness, *(Print pagebreak 919)* lymphovascular invasion (not identified or present), mitotic rate (<1/mm^2 or >1/mm^2 [specify number]), tumor-infiltrating lymphocytes (not identified; present, nonbrisk; present, brisk), and tumor growth pattern (nodular or infiltrative).[80]

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CHAPTER 138

Metastatic Tumors to the Eyelids

Key Points

- Eyelid metastasis is very rare accounting for less than 1% of malignant eyelid lesions
- Breast carcinoma is most frequent, followed by skin melanoma, gastric carcinoma, uveal melanoma, lung carcinoma, and kidney carcinoma
- Clinically, metastatic lesions generally appear as a painless diffuse eyelid swelling, or solitary acutely inflamed tender nodule mimicking acute chalazion, but may show no specific clinical features that distinguish them from primary eyelid malignancies
- They typically occur as a late event in the course of systemic disease, and in the case of breast cancer may appear 2 to 10 years after the initial diagnosis
- The management of metastases is directed at the systemic disease with systemic chemotherapy and immunotherapy
- Local eyelid treatment may include observation, excisional biopsy, and external beam radiotherapy
- The prognosis of patients with eyelid metastatic tumors varies depending on the type of malignancy, primary tumor stage, and extent of systemic metastatic disease

Eyelid metastasis is a very rare condition that accounts for less than 1% of malignant eyelid lesions.[1,2,3,4,5] In a survey of 892 eyelid lesions, of which 214 were malignant, only 3 cases (0.3%) were metastatic tumors.[2] In another review, out of 1502 eyelid lesions evaluated histopathologically, only 1 case (0.07%) of eyelid metastasis was found.[3] Up to 50% of cases are derived from a breast carcinoma, which explains why eyelid metastasis occurs more frequently in women than in men. However, no sex differences have been observed for metastases of other origins.[6] Eyelid metastases predominantly occur in adulthood, although very rare cases related to sarcoma or embryonic tumors of a neural origin can occur in children.[7] The majority of metastatic lesions to the eyelid are carcinomas, with the breast, gastrointestinal tract, and lung as common sites for the primary lesion.[8,9] Most eyelid metastases appear in patients with a known history of systemic cancer, but eyelid metastasis can be the first symptom of systemic cancer in 7% to 45% or the first sign of metastatic recurrence from known cancer.[1,6,8,10] There should be a high level of suspicion for the possibility of metastatic disease when dealing with rapidly growing lesions of the ocular adnexa, especially when there is a known history of malignancy elsewhere in the body.

Three clinical presentations of eyelid metastases have been observed. The most frequent is a painless, subcutaneous, skin-colored nodule, seen in up to 62% of all cases. These lesions are often mistaken clinically for a chalazion. The second type of presentation is a diffuse, infiltrative, inflammatory pattern seen in 30% of cases. Such lesions are characterized by a red to brown induration of the eyelids, with a morpheaform appearance. Finally, the ulcerated type (8%) results from invasion of the epidermis by neoplastic cells and may appear in conjunction with either of the aforementioned types.[3,8] Zimmermann et al[11] described a fourth, edematous variant of eyelid metastasis presentation, but this may just be an earlier stage of the diffuse type. This is seen more commonly with breast metastases.

Three surveys plus several later individual case descriptions totaling 76 cases have reported the distribution of eyelid metastases by primary tumor site.[1,6,8,12,13,14,15,16,17] Taken together, breast carcinoma was the most common primary site (32%), followed by skin melanoma (20%), gastric carcinoma (8%), uveal melanoma (8%), lung carcinoma (5%), and kidney carcinoma (4%). Other rarely reported primary sites for eyelid metastases include salivary duct carcinoma, leiomyosarcoma, osteogenic carcinoma, Kaposi sarcoma, carcinoid tumor, neuroendocrine carcinoma, lymphoma, thyroid carcinoma, rectal carcinoma, bladder urothelial carcinoma, mediastinal teratoma with malignant transformation, hepatocellular carcinoma, prostate cancer, and uterine cervical carcinoma.[18,19,20,21,22,23,24,25,26,27,28,29,30,31]

Etiology and Pathogenesis

Metastasis is a complex, multistage process that requires carefully timed, diverse stages and properties acquired by cancer cells. Metastatic cells must move from the primary tumor site, enter the bloodstream and survive there, and then exit the bloodstream at the arrest organ. They then must colonize the distant tissue and grow into a macroscopic metastatic lesion.[32] Circulating tumor cells represent an intermediate stage between the primary tumor and the metastatic tumor.

Specific tumor-host cell interactions facilitate the initiation of metastatic spread and determine the distribution of metastatic tumor deposits in various organs and tissues.[33,34,35,36,37] Individual tumor types form metastatic tumors in specific organs, unrelated to the route of tumor cell migration.[33] Studies have shown that breast cancer cells obtained from *(Print pagebreak 922)* metastasis-free organs of mice that suffer from lung and lymph node metastases are not only alive but can resume neoplastic growth and metastatic behavior if reinoculated into compatible organs. This supports the idea that metastatic tumor cells are dependent on suitable stromal environments for their growth.[33] As a result, mature metastases are not just aggregations of tumor cells, but consist of a mixed population of neoplastic and non-neoplastic cells.[38] Among the non-neoplastic cells are various cell lineages including fibroblasts, macrophages, and endothelial cells, among others. Over time, the architecture of the lesion becomes organized into a distorted histologic version of the original organ that produced the primary tumor.

Intrinsic properties, such as gene expression patterns in the metastasizing cells, help drive the metastatic event,[33] and individual tumor cells differ in their metastatic potential.[39,40,41,42] The programmed steps initiated in metastatic cells follow an orderly sequence that has been speculated to superficially resemble embryonic cell migration,[33] and the orderly migration of lymphocytes as they move around the body.

Primary tumor cells that invade surrounding tissue lose E-cadherin function resulting in decreased intercellular adhesion. This is a molecule that links cells together through their actin cytoskeleton. This loss of function is caused by mutations or gene downregulation. These epithelial tumor cells can then migrate across the basement membrane to enter the tissue stroma facilitated by enzymes, such as matrix metalloproteinases, which cleave proteins.

Emerging evidence supports the concept that different stromal components in the primary tumor microenvironment also contribute to the regulation of cancer formation and promote the development of metastasis. These include cancer-associated fibroblasts, macrophages, neutrophils, myeloid-derived suppressor cells, regulatory T cells, natural killer cells, and extracellular matrix, among others.[43] Certain tumor cells acquire the ability to induce epithelial-to-mesenchymal transition, which helps them to break loose from the primary tumor.[44]

The metastatic process begins when cells from the primary tumor separate from other cells and invade the surrounding stroma where they are directed toward blood vessels by growth factor gradients. Through the process of intravasation, they penetrate the vessel, aided by increased permeability and fragility of the vessel wall from tumor-associated dysregulation of angiogenic signaling,[45] and inflammatory signaling.[46] Cancer cells can also access the bloodstream indirectly via the lymphatic system.[32]

When the circulating tumor cells reach the bloodstream they are subjected to attack by immune cells, especially by natural killer cells.[47] However, they can employ several mechanisms to avoid immune surveillance, such as coupling to reactive platelets and allowing them to imitate host cells and to be protected from shear forces.[48,49] The platelets also release transforming growth factor-β, which can downregulate a surface receptor that in turn downregulates the antitumor function of CD8+ T lymphocytes and natural killer cells.[50]

These circulating tumor cells are also characterized by an increased ability to survive in the bloodstream,[51] although over time a majority of these cells die. In one study, only 2.5% went on to form micrometastases, and far fewer (0.01%) of these cells induced macrometastases.[52] They are also believed to possess stem-like properties that are capable of self-renewal and tumor formation.[53,54]

Anatomical and molecular factors determine the organs in which circulating cancer cells arrest. The microvasculature of the arrest organ and its relation to the primary tumor influence the development of the metastasis. Organs with rich capillary beds, such as the liver and lungs, become major metastatic sites for many primary tumor types. Structures such as the eyelids have limited vascular access, which partially explains the rarity of eyelid metastasis. It is also proposed that certain organ tissues are predisposed to metastasis because their microenvironment is compatible with specific tumor cells.[55] This stromal interaction between metastatic cells and the arrest organ is essential to the proliferation of metastatic cells.

At the distant organ sites of tumor arrest, extravasation from the blood vessel occurs by several mechanisms. One is thought to proceed in a manner similar to the extravasation of leukocytes, enabling them to transmigrate the endothelial barrier at the metastatic site.[56] This occurs primarily in the small capillaries at branch points between blood vessels.[57,58] The tumor cell interacts with the blood vessel endothelium[59,60] and penetrates the wall of the blood vessel in response to factors produced by the tumor cell.[61,62]

Another mechanism involves blood vessels in organs such as the liver and bone marrow that are normally fenestrated, thus providing less of a barrier to the extravasation of circulating tumor cells. In other organs, extravasation can occur through small gaps in the blood vessels created by the normal turnover in endothelial cells or through vessel wall damage that attracts platelets and tumor cells associated with them.[55] Once extravasated from the circulation, the tumor cells cross the basement membrane and enter the tissue stroma where they can proliferate.

Clinical Presentation

Metastases to the eyelids can manifest with several different characteristics. Morgan et al[21] reported that metastases from breast cancer tend to appear as a painless diffuse eyelid swelling, whereas those from lung cancer tend to be solitary nodular lesions. Others have reported no specific clinical features to distinguish metastatic lesions from different primaries.[1]

Metastasis from breast carcinoma is typically a late event in the course of the disease. In these patients the primary breast cancer is usually already known, preceding the eyelid lesions by 2 to 10 years. Regional lymph node involvement is known in most cases at the time of the mastectomy. When eyelid involvement occurs, patients often already have metastases to the viscera, bones, or skin (Figure 138.1). The orbit, as *(Print pagebreak 923)* well as the eyelid, may also be involved by metastasis, and both may have bilateral involvement. Rarely, the eyelid, orbit, and choroid can all be involved simultaneously.[8] Malignant melanoma constitutes another major primary tumor giving rise to metastatic eyelid tumors (Figure 138.2A). Most cases result from cutaneous lesions, with rare occurrences from a uveal primary. In some instances, the primary melanoma tumor is already known, but occasionally the eyelid metastasis may occur with no indication of a primary site. These may represent cases of spontaneous involution of lentigo maligna.[8,63] Contrary to the relatively late metastatic spread of breast carcinoma and cutaneous melanoma, where the eyelid lesions occur as part of a more generalized carcinomatous process, metastatic eyelid lesions from gastrointestinal sites may be the initial manifestation of the disease.[8]

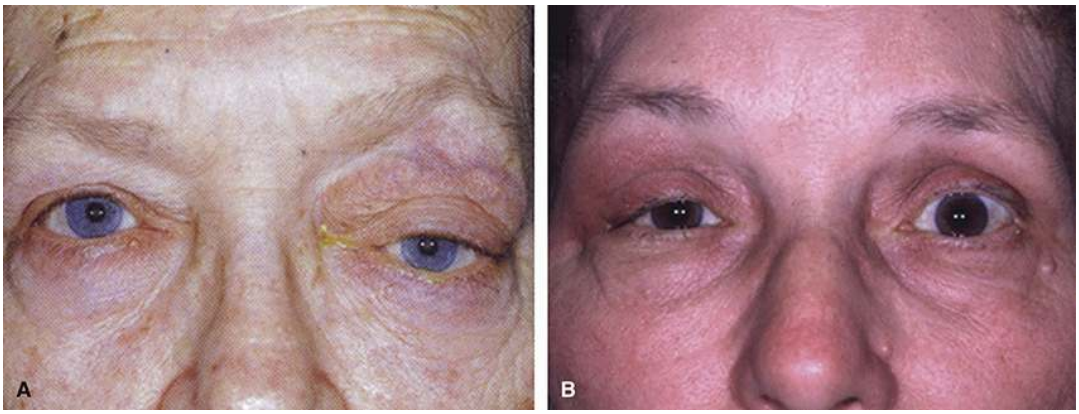

FIGURE 138.1 A and B, Metastatic breast carcinoma to the eyelids in patients with a previous history of breast cancer and systemic metastases.

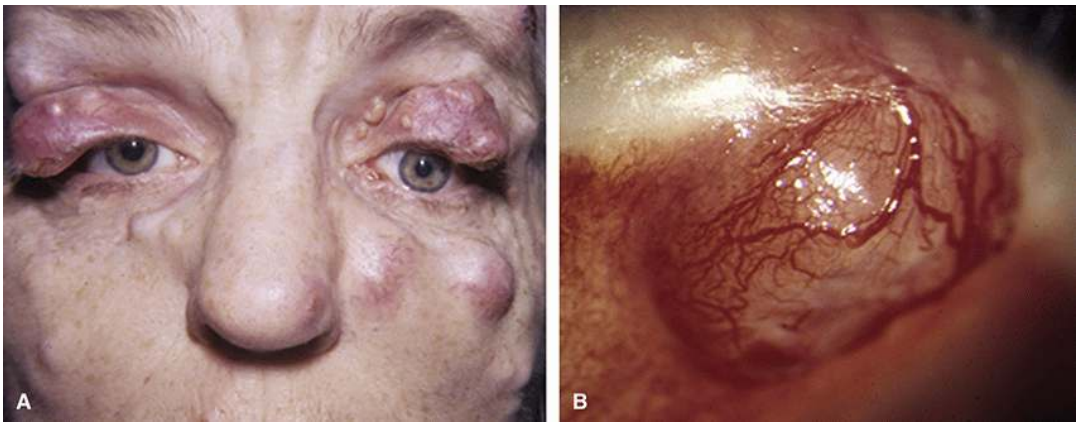

FIGURE 138.2 A, Multiple metastatic cutaneous melanoma nodules to the bilateral eyelids and face. B, Nasopharyngeal metastasis to the eyelid.

Riley[8] described three forms of clinical presentation of metastasis to the eyelid: a nontender and uninflamed solitary subcutaneous nodule (Figure 138.2A), a diffuse nontender indurated lesion causing relative immobility of the eyelids, and an ulcerative lesion. Arnold et al[3] introduced a fourth presentation category as an acutely inflamed tender nodule, mimicking acute chalazion (Figures

138.2B and 138.3). Most commonly, metastases to the eyelid present as a painless nodule, a diffuse swelling, or an ulcerated lesion, and both the lower and upper eyelids are involved equally.[6,64] Most patients are between 50 and 80 years of age, and women are involved more commonly because of the high percentage of breast carcinoma. Clinically, most of these lesions are unilateral or single and less commonly multiple. Bilateral lesions are rare and involvement of all four eyelids is exceptional.[8,9,11,65,66,67,68]

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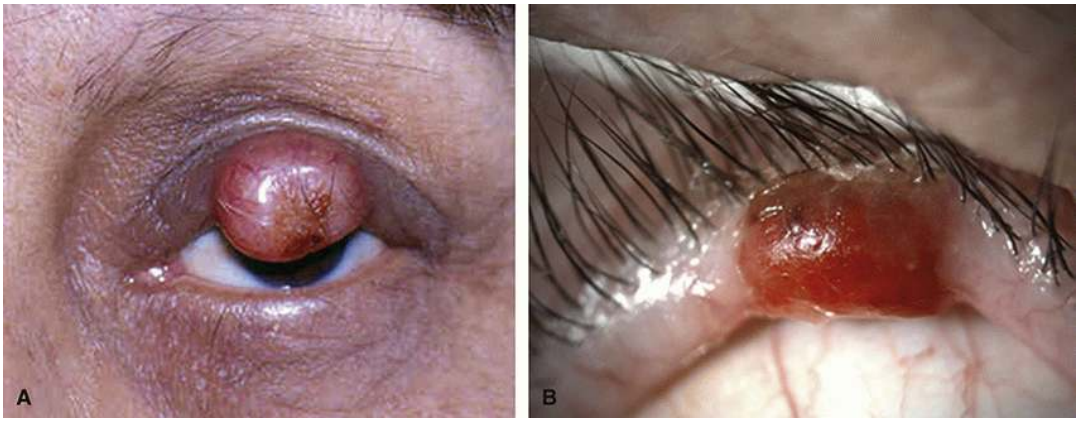

FIGURE 138.3 A, Metastatic leiomyosarcoma to the upper eyelid. B, Small cell carcinoma to the eyelid margin. (A and B, Courtesy of Dr. Bita Esmaeli.)

Differential Diagnosis

Metastatic eyelid tumors often can be mistaken for a chalazion because of their location and possible associated inflammatory signs. The differential diagnosis also includes other benign lesions such as cyst, pyogenic granuloma, and xanthoma.[1,3] Malignant lesions should also be considered, including basal cell carcinoma, squamous cell carcinoma, melanoma, sebaceous carcinoma, primary neuroendocrine tumors of the skin, and Merkel cell carcinoma.[6,64,69] In an analysis of 31 patients with eyelid metastasis, only 10 of 17 cases (59%) with a known primary carcinoma were clinically suspected to be malignancies.[6]

Treatment

The management of eyelid metastases is not directed at a cure since these patients already have systemic involvement. Treatment is usually palliative to preserve eyelid function and protect vision. This can include observation, excisional biopsy, external beam radiotherapy, systemic chemotherapy, and immunotherapy. The choice of treatment depends upon clinical features of the tumor such as size and location, the degree of eyelid dysfunction, and a threat to vision, as well as the systemic status of the patient. Observation may be appropriate for patients undergoing treatment for active systemic disease. Small, solitary nodular eyelid lesions are usually managed with excisional biopsy alone.

Radiotherapy is indicated in patients with multiple or recurrent lesions. It is usually administered to control tumor growth and to preserve visual function, improve patient comfort, and relieve symptoms.[7] The recommended dose is 20 to 40 Gy delivered in fractions over 1 to 2 weeks.[7,70] Systemic chemotherapy may also be helpful in the treatment of ocular adnexal metastases, especially for lesions that are chemosensitive, such as small cell lung cancer and neuroblastoma.[71] Hormonal therapy can sometimes be indicated in the treatment of metastases from hormone-sensitive tumors, such as breast or prostate cancer.

Prognosis

The survival of patients with eyelid metastatic tumors varies greatly and depends on the type of malignancy, primary tumor stage, and extent of systemic metastatic disease. The prognosis varies from good to dismal for different tumors. Patients with multiple metastases carry a worse prognosis, regardless of treatment. A somewhat better prognosis may be seen in patients with single nodules that are surgically excised and do not recur.

Histopathology

The histopathological features of tumors metastatic to the eyelid reflect their site of origin. As noted in the introduction to this chapter, adenocarcinoma of the breast is the primary tumor that most frequently metastasizes to the eyelid. Metastatic breast adenocarcinoma resembles the primary tumor, forming islands and cords of tumor cells within the dermis. Vacuolation of tumor cells reflects their glandular differentiation, and "signet ring" cells may be present (Figure 138.4).[70] Cutaneous melanomas metastatic to the eyelid may be recognizable by the presence of melanin, or they can be identified using immunohistochemistry. Immunohistochemistry[72] and gene expression[72] profiling assist in narrowing the possible primary sites for other tumors metastatic to the eyelid when the primary site is uncertain.

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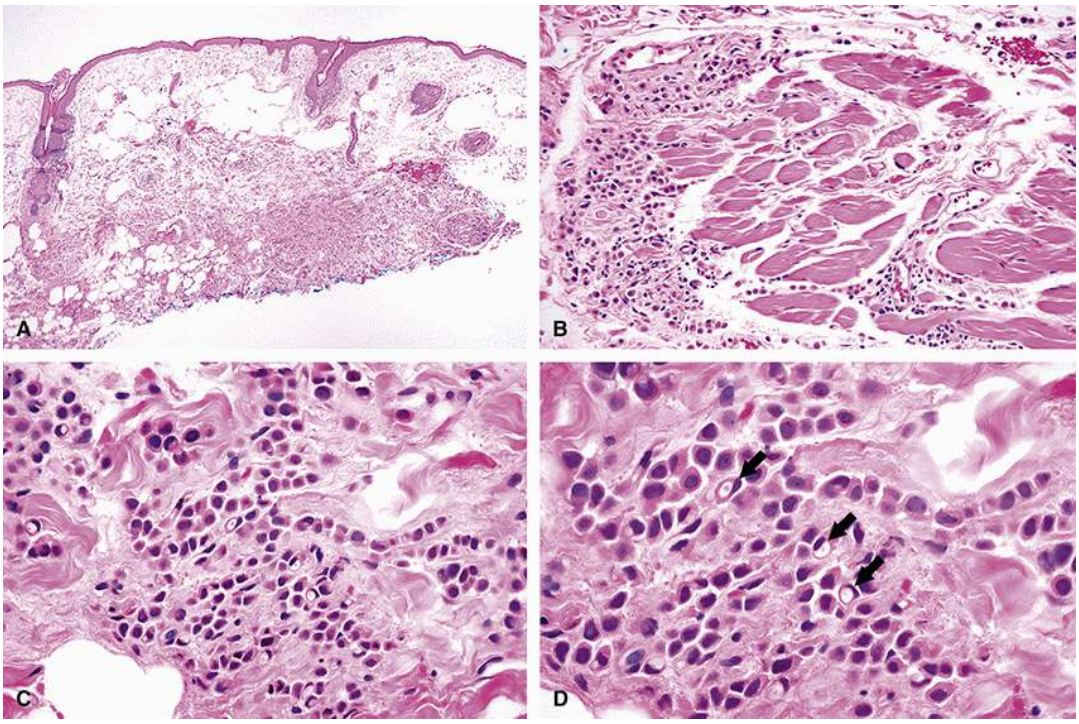

FIGURE 138.4 A woman in her late 50s presented with eyelid swelling and ptosis. Following a biopsy of her right upper eyelid, she was found to have a lobular carcinoma of the breast metastatic to the eyelid and orbit. A, The papillary dermis and superficial reticular dermis are edematous. The metastatic tumor is in the deeper reticular dermis, orbicularis oculi muscle, and the subcutis crating the more cellular appearance evident at low magnification. B, Tumor cells surround and infiltrate between orbicularis oculi muscle fibers. C, Tumor cells are found individually, as small clusters, and in one to two cell-wide columns. D, Many of the tumor cells have a histiocytoid appearance, while others have a signet ring character due to large cytoplasmic vacuoles displacing the nucleus peripherally (arrows).

Primary signet ring cell/histiocytoid carcinoma of the eyelid (Figure 138.5) must be considered before diagnosing breast carcinoma metastatic to the eyelid based on morphology and immunohistochemistry. Primary signet ring cell/histiocytoid carcinoma arises mainly in the eyelid,[73,74,75,76,77,78,79,80,81,82,83] with fewer cases reported in the axilla.[81] These tumors are rare, with fewer than 50 eyelid tumors reported.[80,81,82,83] Primary periocular signet ring cell/histiocytoid carcinomas affect predominantly older men (mean age of approximately 67 years) and present as gradual swelling, thickening, and firmness of the eyelid.[78] The tumor usually starts in one eyelid but may spread to the other, creating a monocle's appearance.[79,84] They are aggressive tumors that recur locally, metastasize, and may cause death.[75,76,78] Clinical and radiological findings must be employed to distinguish primary signet ring cell/histiocytoid carcinoma from a metastatic tumor since there are no immunohistochemical or molecular markers capable of differentiating primary and metastatic lesions.[80] Neoplastic cells may react to antibodies against CAM5.2, CK7, AE1/AE3, high molecular weight cytokeratins (34βE12 antibody), MNF116 cytokeratins, carcinoembryonic antigen, epithelial membrane antigen, gross cystic disease fluid protein-15, p63, mucin-1, epithelial cell adhesion molecule (BerEP4), E-cadherin, α-smooth muscle actin, vimentin, thyroid transcription factor 1, mucin 2, podoplanin, N-cadherin, GATA-3, and sometimes nuclear estrogen and/or progesterone receptors.[76,80] Tumor cells are characteristically negative for expression of CK20, S100 protein, muscle-specific actin (MNF116 antibody), calponin, CD68, CDX-2, mammaglobin, calretinin, HER2-neu, and placental alkaline phosphatase.[76,79,80] Molecular profiling has been reported in only two tumors, but in both cases identified potential targets for chemotherapy.[81,82]

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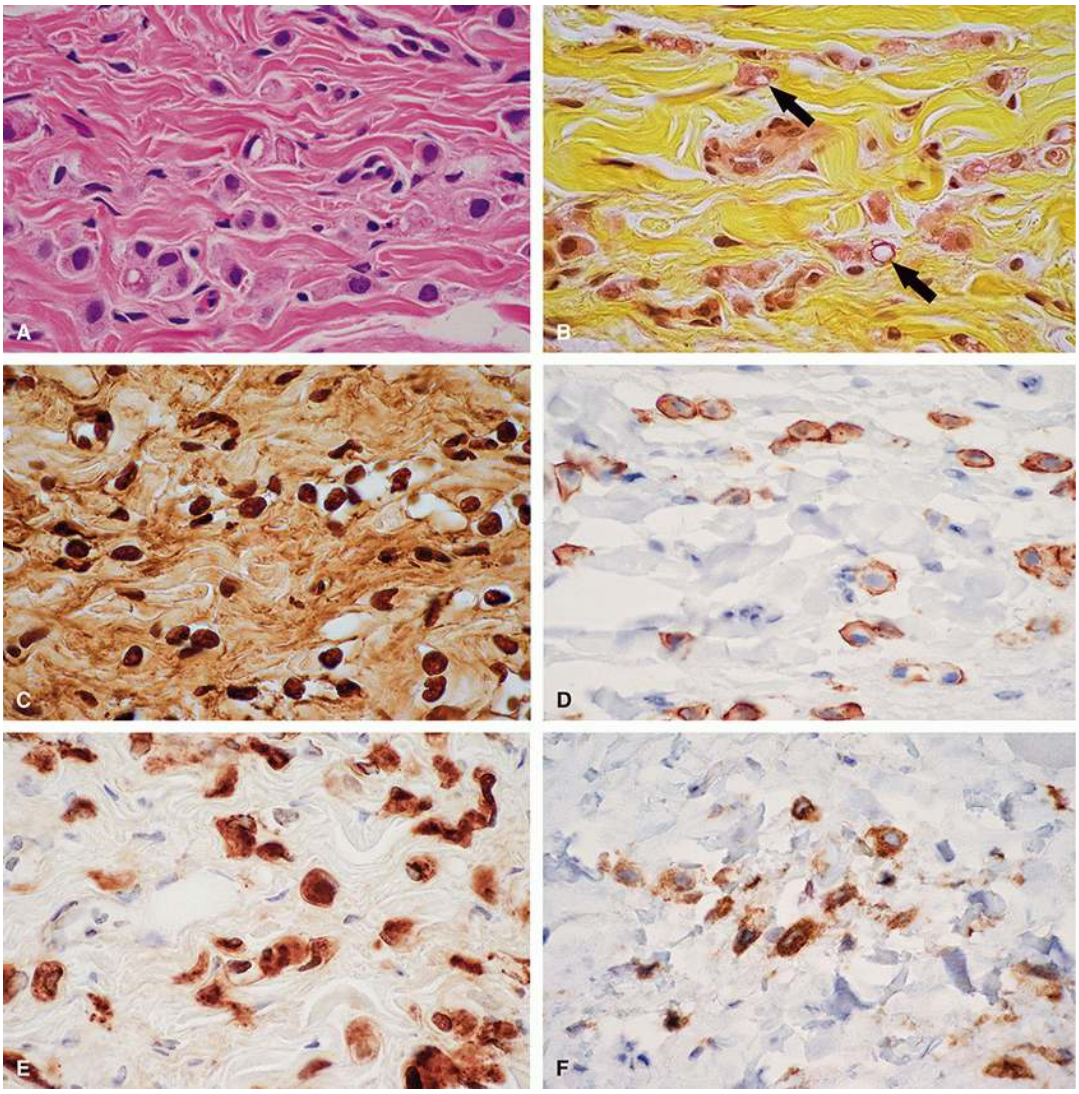

FIGURE 138.5 This primary signet ring cell/histiocytoid arose in the left upper eyelid of a man in his early 60s. The diagnosis was based on the histological and immunohistochemical appearance of the tumor and the lack of a primary tumor detectable elsewhere in the body by clinical and radiological examination. A, Histiocytoid and signet ring tumor cells dissect individually and in small clusters between the dermal collagen fibers. B, The tumor cells have finely vacuolated pink-brown cytoplasm using mucicarmine stain. The rim of large cytoplasmic vacuoles (arrows) stains red. The tumor cells were immunoreactive using a cocktail of antibodies to low-and high molecular weight cytokeratins, CK7 (C), E-cadherin (D), gross cystic disease fluid protein-15 (E), carcinoembryonic antigen (F), epithelial membrane antigen, and p63. The tumor cells were negative using antibodies to CK20, CD68, mammaglobin, epithelial cell adhesion molecule (BerEP4), thyroid transcription factor 1, CDX-2, podoplanin, S100 protein, and prostate-specific antigen.

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CHAPTER 139

Microcystic Adnexal Carcinoma

Key Points

- Microcystic adnexal carcinoma (MAC) is a slow-growing, locally aggressive cutaneous adnexal malignancy derived from eccrine sweat glands
- It occurs predominantly on the head and neck region in about 85% to 90% of cases
- The etiology is unknown, but ultraviolet radiation exposure has been suggested to be a major risk factor
- It generally presents as an asymptomatic, slowly growing, flesh-colored or pale yellow, solitary, indurated subcutaneous nodule, plaque, or cyst-like tumor
- Perineural invasion is usually associated with a more aggressive course and a higher recurrence rate
- MAC tends to be local aggressive with deep infiltration and a high recurrence rate
- Complete tumor excision with histologic control of surgical margins is the treatment of choice
- Recurrence rates range between 17% and 60% but distant metastases occur in less than 1%
- The overall 10-year survival rate is excellent at 97.7%

Microcystic adnexal carcinoma (MAC) is a slow-growing, locally aggressive cutaneous adnexal malignancy derived from eccrine sweat glands. The appellation MAC was first applied by Goldstein, Barr, and Santa Cruz[1] in 1982, based on the review of six tumors, two of which had been reported previously as sweat gland carcinomas. MAC is one of several malignant adnexal tumors, including adenoid cystic carcinoma, apocrine carcinoma, cylindrocarcinoma, digital papillary adenocarcinoma, endocrine mucin-producing sweat gland carcinoma, hidradenocarcinoma, porocarcinoma, and primary cutaneous mucinous carcinoma.[2] As noted by Goldstein and coworkers, MAC "may be synonymous with previously reported cases called malignant syringoma, sweat gland carcinoma with syringomatous features, or aggressive trichofolliculoma."[1] It is a very rare tumor,[3] and occurs at a reported incidence of 1.6 to 6.5 per 1,000,000 population.[4]

MAC occurs predominantly in the head and neck region in about 85% to 90% of cases.[5,6] However, very few cases have involved the eyelids and periorbital region.[7,8,9,10,11,12,13] The tumor can be highly invasive and destructive locally and can invade dermis, muscle, adipose tissue, nerves, periosteum, and bone, causing significant morbidity.[14,15,16] However, regional lymph node involvement and distant metastases are rarely reported.[17,18] The tumor occurs mainly in Caucasians (90%),[4,19] and only seven cases have been described in patients of African descent.[20,21,22,23,24,25,26] Patients usually present in the fourth to seventh decades of life, with a median age of 68 years.[4] The age range is very broad, extending well into old age, but only about a dozen reported cases have been younger than 18 years, the youngest only 2 months of age.[6,19,27,28]

A male predominance is often cited in the literature, and some reports note an equal sex distribution.[29] But, in the largest analysis involving 223 patients from the Surveillance, Epidemiology and End Results (SEER) database the sex ratio was male 43% vs female 57%.[4]

Etiology and Pathophysiology

Fewer than 700 cases of MAC have been reported in the world's literature,[3] and its rarity makes it difficult to determine its etiology. Ultraviolet exposure, ionizing radiation, and immunosuppression have all been proposed.[4,30,31,32] Ultraviolet radiation exposure has been suggested to be a major risk factor for MAC.

Not only are the head and neck the most common sites for MAC, but in a large series of patients in the United States, 52% of tumors

were located on the left side (driver's side). This compared with an Australian series where the driver's side is the right side, and 56% of MAC tumors were on the right.[4] MAC has also been reported following ionizing radiation therapy with an incidence of about 10% to 19%.[19,30,33] The average latency period between radiation exposure and MAC was reported to be 7 to 30 years.[34]

The risk of nonmelanoma skin cancer in immunocompromised patients is well known for other tumors. Several cases of MAC developing in an immunocompromised patient have been reported, but a firm relationship has not been established.[30,31]

Clinical Presentation

Eyelid MAC is frequently misdiagnosed as a benign lesion or another more common skin malignancy such as squamous cell carcinoma.[11] Clinically, MAC can present as eyelid swelling with surface ecchymoses (Figure 139.1A). More *(Print pagebreak 930)* commonly, they appear as an asymptomatic, slowly enlarging eyelid thickening or a flesh-colored or pale yellow, solitary, indurated subcutaneous nodule, plaque, or cyst-like tumor (Figure 139.1B). It is firm with ill-defined margins and has prominent overlying telangiectatic vessels. The surface is smooth, and ulceration is uncommon (Figure 139.1C).[7,35] Pain, burning, anesthesia, and paresthesia can be seen with perineural invasion.[36] The average size at presentation is usually less than 2 cm in 80% of patients; however, the absolute size may be difficult to determine due to its indistinct borders (Figure 139.1D).[37] The tumor spreads by local invasion into deeper tissues early in its course[38] but only rarely metastasizes to regional lymph nodes or distant sites.[30,36,39,40] Orbital invasion by periocular MAC is very rare with only six cases reported.[7,41,42,43,44]

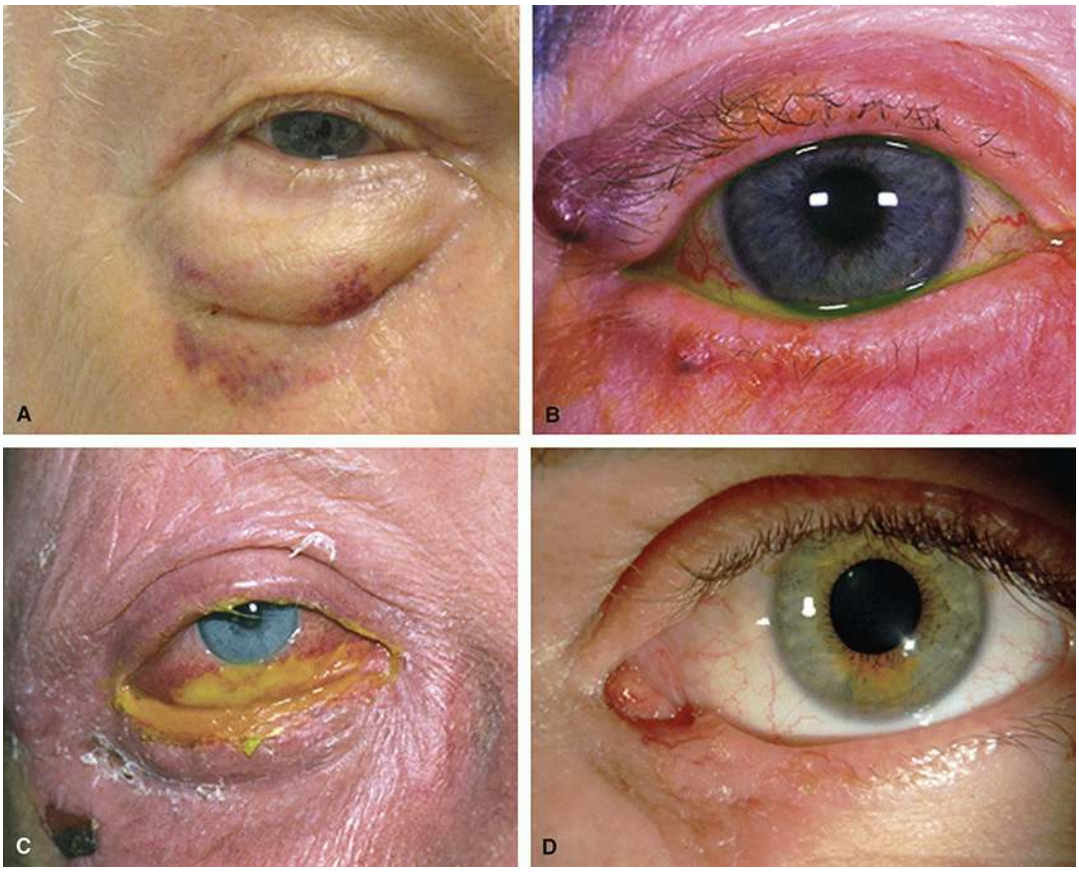

FIGURE 139.1 A, MAC presenting as lower eyelid swelling with ecchymoses. B, Reddish MAC nodule on the medial upper eyelid. C, Eyelid margin ulceration with diffuse eyelid and lateral canthal infiltration of tumor. D, Indistinct tumor margins infiltrating the medial lower eyelid, with madarosis. B, (Courtesy of Dr. David Jordan) D, (Courtesy of Dr. Alan McNab.)

A biopsy is necessary to confirm the diagnosis of MAC. However, a full-thickness biopsy is necessary to recognize infiltration into deeper tissues. Several recent studies have reported optical coherence tomography and reflectance confocal microscopy to be useful in evaluating tumor extent.[45,46]

Perineural invasion is usually associated with a more aggressive course and a higher recurrence rate. For skin malignancies in general, perineural invasion is seen in less than 5% of patients.[47,48] For MAC, the occurrence of perineural invasion was found to be 12% to 32%, possibly related to the infiltrative nature of this tumor.[31,49,50]

Differential Diagnosis

The clinical differential diagnosis includes both benign and neoplastic adnexal tumors and lesions. These include chalazion, trichoepithelioma, trichoadenoma, syringoma, desmoplastic trichoepithelioma, scars, and cysts, as well as other skin malignancies such as morpheaform basal cell carcinoma and squamous cell carcinoma.[10,37,51,52] This can make MAC difficult to diagnose.

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Treatment

Because of the local aggressiveness, deep infiltration, and high recurrence rate of MAC, complete tumor eradication with histologic control of surgical margins is the treatment of choice.[53] However, even with wide local excision, the recurrence rates are high, ranging between 17% and 60%.[5,6,14,16,19,27] Mohs micrographic surgery has shown better results, with recurrence rates ranging from 0% to 22% at 5 years.[4,10,27,37,54,55,56]

Radiation therapy is not considered an effective therapy because MAC is relatively radioresistant, and there is little evidence to support its use as monotherapy. However, in one study on the use of adjuvant radiation therapy in 14 patients following surgery, 11 of whom had positive margins, 93% had good local control at a median follow-up of 5 years.[57] Recurrence rates following radiotherapy are higher than with surgery.[7]

The role of chemotherapy for MAC is unsettled. Two cases of metastatic MAC did respond to chemotherapy.[58,59] Only one case of primary MAC has been reported treated with chemotherapy but with unsuccessful results.[36]

Prognosis

Even with wide-margin surgical resection recurrences of MAC are very common, with 40% to 60% of patients having one or more recurrences between 6 months and 30 years after initial treatment.[7,36] This is despite the fact that about 74% of these tumors initially occur in the skin only, with only 7% invading the subcutaneous tissue and 9% invading underlying muscle or bone.[4] However, the involvement of regional lymph nodes is low at only 1% of cases, and distant metastases occur in less than 1% so that the overall 5- and 10-year survival rates are excellent at 97.7%.[4] Long-term follow-up of the patients with MAC is recommended given the high recurrence rate.

Histopathology

Goldstein, Barr, and Santa Cruz described MACs as composed of islands and strands of basaloid keratinocytes embedded in a desmoplastic stroma with rare tumor communication with the overlying epidermis.[1] Some tumors had abundant horn cyst formation with peripherally palisaded keratinocytes having minimal atypia, and a few cysts had early calcification.[1] Tumor cells also formed epithelial strands and ductal structures often lined by two layers of cuboidal cells.[1] The proportion of horn cysts and ductal structures varied between tumors.[1] All tumors had extensive infiltration of subcutaneous fat, and perineural and intramuscular invasion were common.[1] Mitoses were rare.[1]

Cooper and coworkers noted two histological patterns in their study of 20 sclerosing sweat duct (syringomatous) carcinomas.[14] Twelve tumors (group 1; Figure 139.2) mainly had cords and nests of uniform squamous cells with glassy eosinophilic cytoplasm, and some had blunt or pointed tails. The tumor cells often formed squamous whorls, and a variable number of nests had central cores of laminated keratin. Keratinization was abrupt, and keratohyaline granules were usually absent. Tumor nests were in a hyalinized collagenous stroma, and all tumors infiltrated subcutaneous tissue and associated skeletal muscle. There were sparse mitoses, usually <1 per 10 high power fields. Of the 12 group 1 tumors, 10 had perineural tumor invasion. Eight tumors (group 2) lacked well-developed squamous features but had “innumerable small cellular aggregates that were often sparse in the superficial dermis and were concentrated, instead, in the deep dermis and underlying tissues. The aggregates were in the form of round to oval nests, elongate or branched strands, and parallel cords” with polygonal or cuboidal cells having dense eosinophilic cytoplasm and distinct cell borders. Many of the nests, cords, and strands had lumens, some with eosinophilic material. All group 2 tumors had dense sclerotic stroma that sometimes formed nodules surrounding the subcutaneous tumor. Six of the eight group 2 neoplasms had perineural or intraneural invasion. Mitoses were sparse, similar to group 1 tumors.

More recent publications on MAC have emphasized a stratified pattern to MAC (Figure 139.3), with the upper part of the neoplasm having tumor islands[50] and cornifying cysts.[60] The midzone has basaloid strands rather than islands[50] or solid nests, strands, and

columns of cells.[60] The deep portion of the tumors have "even smaller nests and strands of cells"[50] or "duct-like structures composed of two layers of small cuboidal cells (empty or filled with eosinophilic material)."[60]

Immunohistochemical studies of MAC have given conflicting results,[61] and the immunohistochemical profile is not specific.[50,61] A key tumor to differentiate from MAC is desmoplastic trichoepithelioma (DTE).[1,50,60] Tse and colleagues compared the expression of cytokeratin 19 (CK19) in MAC and DTE biopsies.[50] Of 20 MACs, 14 (70%) expressed CK19: 6 tumors had CK19 expression by 51% to 100% of tumor cells, 3 had CK19 expression in 26% to 50% of cells, and 5 had CK19 expressed by 6% to 25% of tumor cells.[50] In contrast, only 4 of 18 (22%) DTEs expressed CK19: 2 had CK19 expressed by 26% to 50% of cells, and 2 tumors had CK19 expression by 6% to 25% of the cells.[50] Tse et al concluded that "a tumor that exhibits CK19 expression by >51% of tumor cells is "probably a MAC despite the overlapping immunoprofile."[50] Evangelista and North compared CK20 and androgen receptor (AR) expression in 15 DTEs and 6 MACs.[62] All 15 DTEs were positive for CK20 and negative for AR expression, while all 6 MACs were negative for CK20 and 5/6 were negative for AR expression.[62] In cases with an equivocal immunoprofile or when immunostains are not performed, the presence of subcutaneous involvement,[1,50] perineural invasion,[1,50] and ductal differentiation [50] are usually adequate to distinguish MAC from DTE.[63]

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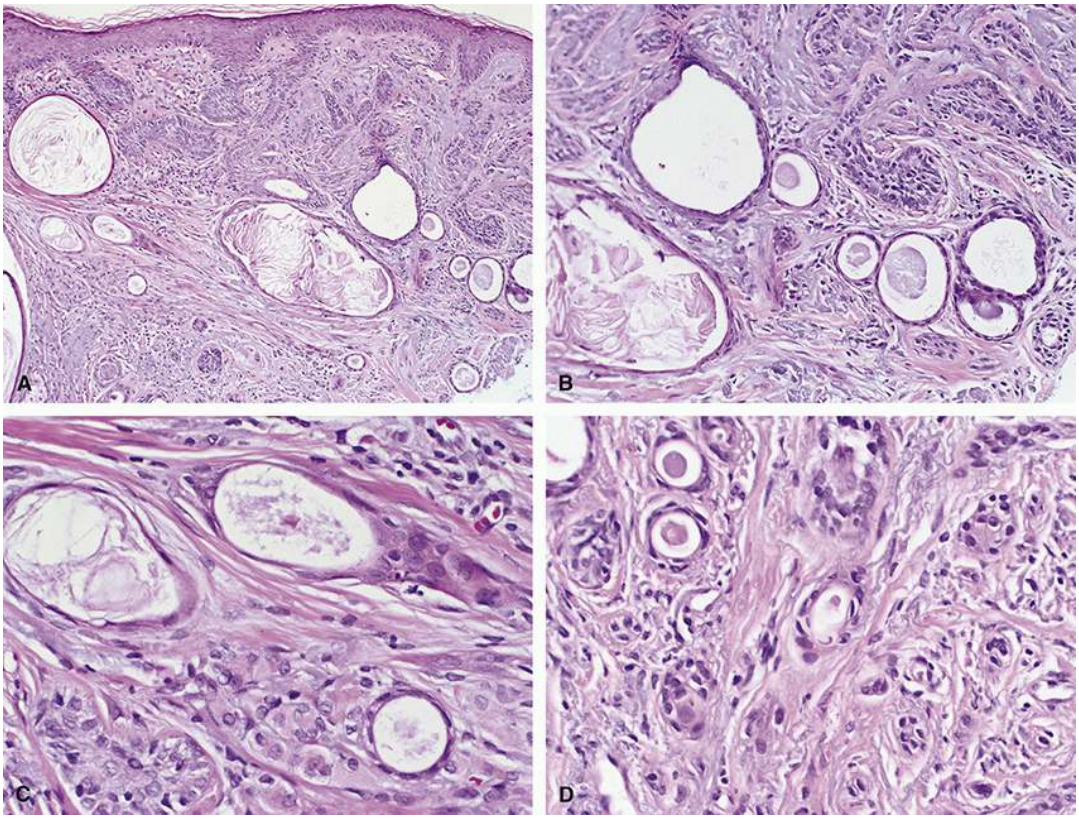

FIGURE 139.2 A man in his early 60s developed a MAC in his left lower eyelid margin. A, Cords and nests of cytologically uniform squamous cells and horn cysts within a desmoplastic stroma form the tumor. The superficial tumor islands have palisaded tumor peripherally. B, A horn cyst filled with keratin is at the bottom left. Other tumor nests are solid or have ductal differentiation with empty lumens or intraluminal amphophilic to lightly eosinophilic amorphous material. C, A small horn cyst is on the left. The tumor nest at the top right has ductal differentiation and a tail of tumor cells. The collagenous tumor stroma is partially hyalinized (top left corner). D, The deep aspect of the tumor is composed of small tumor nests, with lumens indicating ductal differentiation. Two layers of cells line the ducts.

A negative immunostain using Ber-EP4 antibodies to epithelial cell adhesion molecule favors a diagnosis of MAC vs sclerosing/morpheic basal cell carcinoma (BCC).[60,64] Krahl and Sellheyer reported no expression of Ber-EP4 in 13 MACs,[63] while 28/28 infiltrating BCCs expressed Ber-EP4.[63] The infiltrating BCCs had Ber-EP4 expression by >80% of tumor cells in 23/28 (82%) tumors.[63] Hoang et al noted 10/10 infiltrative BCCs had Ber-EP4 expressed by >50% of tumor cells, while 8/13 MACs were negative for Ber-EP4 expression.[65] Three MACs had Ber-EP4 expressed by >50% of tumor cells, and two tumors had Ber-EP4 expression by 10% to 49% of tumor cells.[65]

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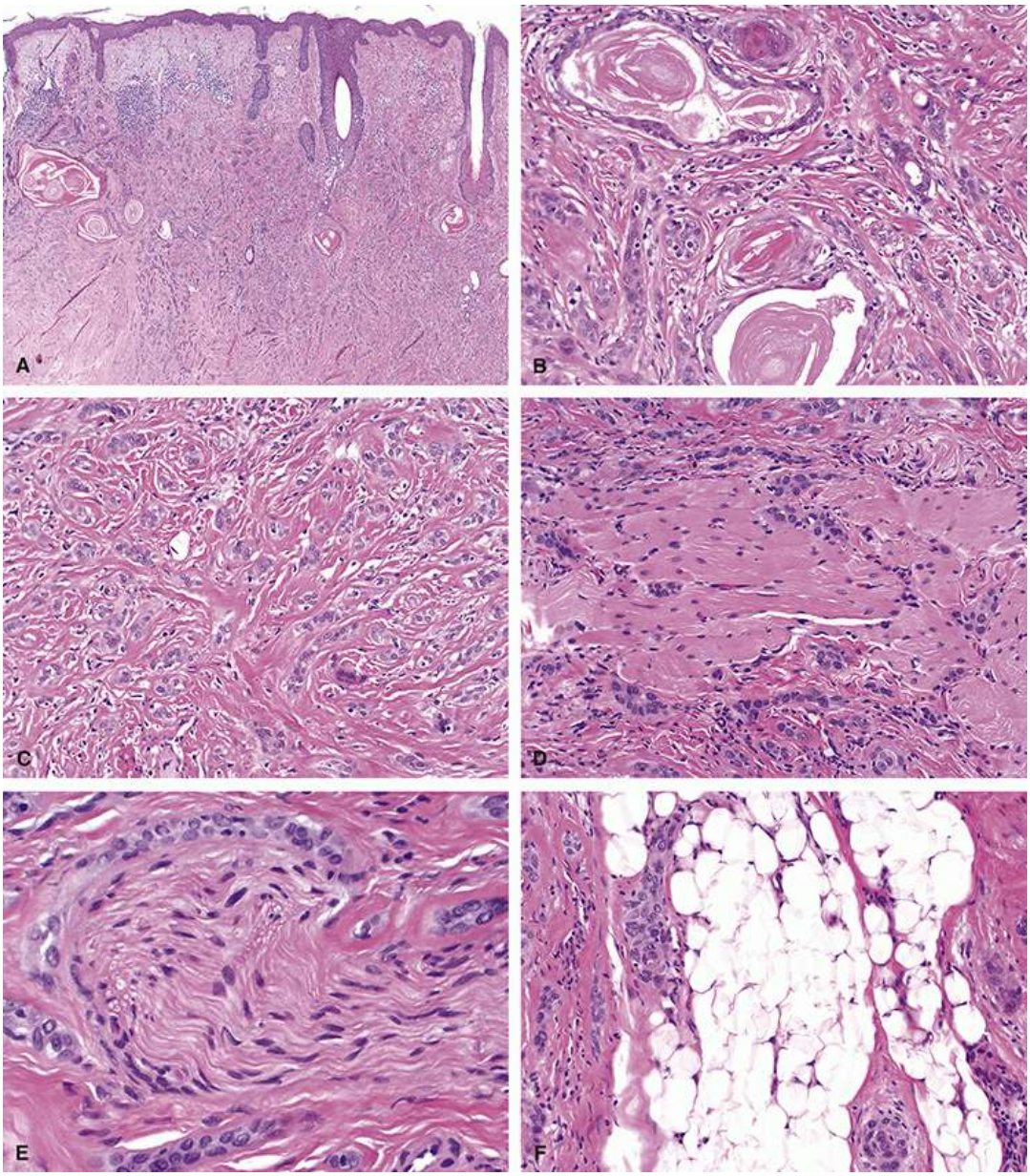

FIGURE 139.3 This MAC arose in the left eyebrow of a man in his early 50s. A, This tumor has a stratified appearance with tumor islands, cornifying cysts, and tumor strands in a sclerotic dermis. The midzone has mostly strands of tumor cells, while the deeper tumor (not seen in this photomicrograph) was smaller nests and strands of cells, often with two layers of small cuboidal cells. B, This tumor area in the superficial dermis shows the characteristic cornifying cysts along with small tumor islands, strands, and a small duct-like structure. C, The middle and deeper dermis had two-cell thick cords of tumor cells embedded in densely sclerotic, hyalinized stroma. D, Tumor widely infiltrates the frontalis muscle. E, Small tumor nests and cords are in sclerotic stroma around a nerve and invade the perineurium. F, Tumor within the subcutaneous adipose tissue forms nodules surrounded by dense sclerotic stroma.

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CHAPTER 140

Mucoepidermoid Carcinoma

Key Points

- Mucoepidermoid carcinoma (MEC) is a highly malignant epithelial neoplasm comprising mucus-secreting, proliferating squamous, and nondescript intermediate epidermoid cells
- Although the pathophysiology is unclear, a novel translocation fusion oncogene, MECT1-MAML2, is present in 34% to 81% of MECs of the salivary glands, but it has not been identified in eyelid or lacrimal sac MECs
- In the ocular adnexa, about 80% of cases involve the conjunctiva, followed by the lacrimal sac (17%), and the eyelid skin (3%)
- It appears as a red, pink, yellow, brownish, or leukoplakic nodular or pedunculated conjunctival mass
- When the lacrimal sac is involved, symptoms may include epiphora, associated with dacryocystitis, or a palpable medial canthal mass
- The recommended treatment is surgical excision with wide margins; with orbital extension, enucleation or even orbital exenteration may be indicated
- MEC tends to be aggressive locally and regionally and recurrence rates after surgical excision range from 70% to 100%

Mucoepidermoid carcinoma (MEC) is a highly malignant epithelial neoplasm comprising mucus-secreting, proliferating squamous, and nondescript intermediate epidermoid cells. The term “mucoepidermoid” tumor was originally introduced by Stewart et al in 1945,[1] for tumors having two principal histologic elements, mucus-secreting cells and epidermoid cells. Mucoepidermoid tumors primarily occur in the major salivary glands.[1,2,3] They have also been reported in the minor salivary glands,[4,5] in the upper respiratory tract (larynx, trachea, or bronchi),[4,5,6,7,8] and in the nasal mucosa,[9] liver,[10] anus,[9] maxilla,[11] mandible,[12] uterine cervices,[9] and penis.[13] These tumors rarely arise from the skin.[14,15,16] In the periocular region, MEC primarily involves the conjunctiva,[17,18,19,20,21,22,23,24] lacrimal sac,[25,26] and lacrimal gland.[27,28] It very rarely arises in the eyelid skin.[20,29,30,31,32,33,34]

Etiology and Pathogenesis

There have been very few studies on the genetic changes associated with MEC. A novel translocation fusion oncogene, MECT1-MAML2, between chromosomes 11 and 19 was described in 2003.[35,36,37] This gene product is present in 34% to 81% of MECs of the salivary glands.[38] It is related to tumorigenesis, and knockdown of the protein product inhibits tumor growth.[39] However, MAML2 rearrangement has not been identified in the eyelid or lacrimal sac MECs.

Several studies examined epidermal growth factor receptor (EGFR) signaling in the etiology of MEC and suggested that this pathway might play a role in its pathogenesis. Also, mutations in p53 have been identified in MEC of the salivary gland.[37,40] There is a correlation between *p53* expression and the proliferation marker Ki-67, suggesting that mutations in *p53* might represent a genetic switch associated with the transformation of a low-grade tumor to a high-grade one.[41]

Clinical Presentation

In the ocular adnexa, about 80% of cases involve the conjunctiva, followed by the lacrimal sac (17%), and the eyelid (3%). Only 11 cases of eyelid MEC have been reported in the literature.[29,30,31,32,34,42,43,44,45,46] Males are affected more commonly than females (76%-80%) for periocular MEC,[47] but for eyelid lesions, there is no gender predilection.[42] About 80% of eyelid lesions involve the lower eyelid.[42] The duration of symptoms before presentation is relatively short, usually 2 to 6 months, but occasionally progression can be indolent over many years.[30,42]

In most cases, the lesion involves the bulbar conjunctiva near the corneal limbus (70%), with rare occurrences in the conjunctival fornix or eyelid skin (Figure 140.1).[24] Aggressive lesions may invade the orbit, seen in about 20% of cases, and rarely the tumor can invade an adjacent paranasal sinus.[29,47,48,49] The most common periocular presentation is a painless, rapidly progressive conjunctival or eyelid cutaneous mass.[42] Lesions may appear as a red, pink, yellow, brownish, or leukoplakic nodular or pedunculated mass that may be irritated or occasionally ulcerated. When the lacrimal sac is involved, symptoms may include epiphora associated with dacryocystitis and a palpable medial canthal mass. Regional lymph node involvement has been described, but distant metastasis is very unusual.[18,43]

Differential Diagnosis

The differential diagnosis of MEC includes conjunctivitis and conjunctival squamous cell carcinoma (SCC), both of which need to be excluded by critical analysis of representative tissue sections.

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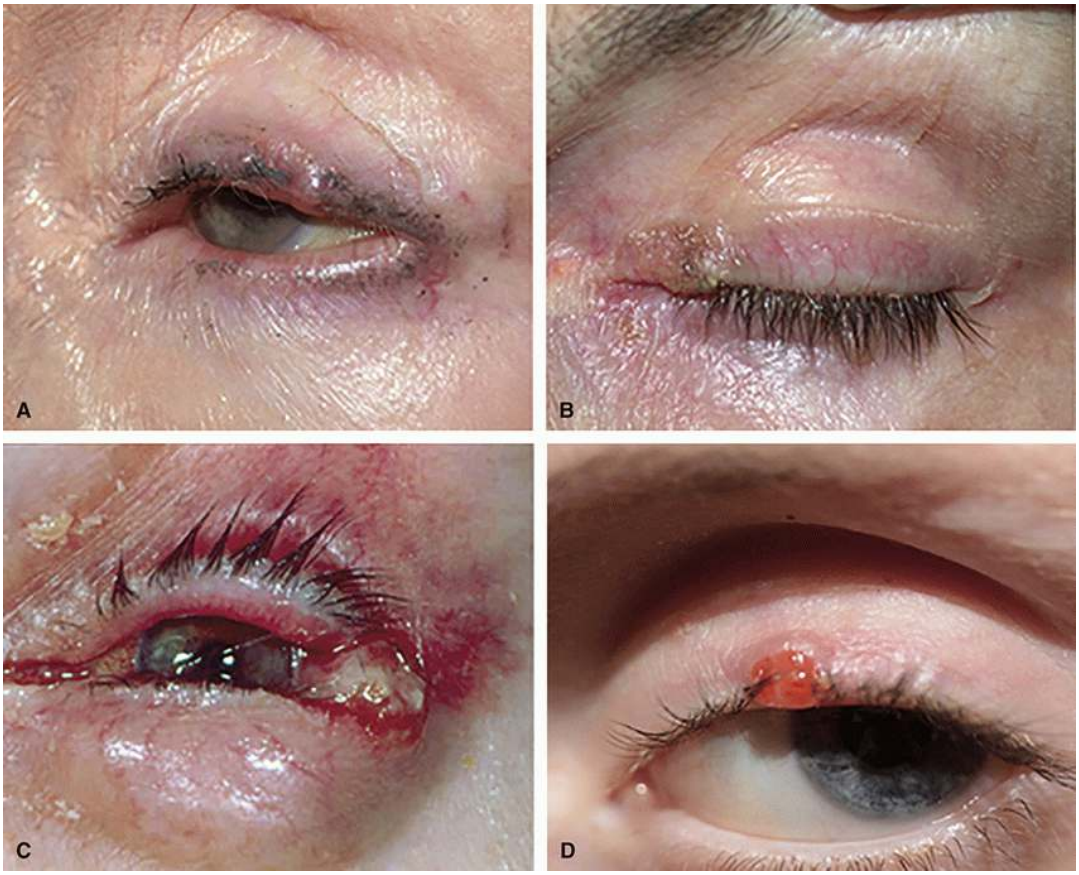

FIGURE 140.1 A, Mucoepidermoid carcinoma (MEC) of the central upper eyelid margin. B, Medial upper eyelid MEC with scaling and madarosis. C, Extensive MEC of the lateral canthal conjunctiva and eyelid margin. D, Nodular MEC on the upper eyelid margin. (A and B, Courtesy of Dr. Charles Soparkar; C, Courtesy of Dr. Seymour Brownstein; D, Courtesy of Dr. Rachel Sobel.)

Treatment

The recommended treatment for conjunctival MEC is surgical excision with wide margins. For cases with only superficial invasion, adjuvant cryotherapy, topical interferon, or mitomycin have been recommended, with follow-up biopsies at regular intervals to confirm the adequacy of treatment.[50] For more invasive lesions, a superficial or deep sclerectomy is performed. In some cases with orbital extension, radical surgery, such as enucleation or even orbital exenteration, may be indicated.[51]

Fractionated epibulbar I^{125} plaque brachytherapy has been used for some MECs with good results.[52,53] However, other studies using laser therapy, brachytherapy, and external beam radiotherapy have not been promising.[18,19,54]

For eyelid lesions, more conservative therapies such as local excision and radiotherapy have not proven sufficient, with high recurrence rates. The longest reported follow-ups without recurrence were 3 and 4 years following Mohs microsurgical excision.[42]

Prognosis

Compared to basal cell carcinoma and SCC, MEC has a higher malignant potential and tends to be more aggressive, both locally and regionally,[47,55] and has even been reported to invade the globe.[22] Recurrence rates after surgical excision range from 40% to 100%, so that prolonged follow-up after surgery is necessary.[29,49,54,55,56] From the very limited eyelid cases reported, Mohs surgery may provide the best long-term results.

Histopathology

The existence of primary MEC of the skin as a distinct entity is controversial.[57,58] Some authors distinguish cutaneous MEC from adenosquamous carcinoma,[57,59,60] while others use the terms synonymously.[16] In salivary glands, "MEC is a malignant epithelial tumor composed of varying proportions of mucous, epidermoid, intermediate, columnar, clear, and occasionally, oncocytic cells."[61] Stewart, *(Print pagebreak 938)* Foote, and Becker defined epidermoid cells as including cells resembling those in basal cell carcinoma and those "resembling squamous cells without intercellular bridges and keratohyaline granules."[1] They noted, "another frequent cellular component of the malignant tumors was the intermediate cell which, it must be admitted, is difficult to distinguish verbally from the basal cells other than by saying that they are slightly larger, have somewhat more vesicular nuclei and more abundant cytoplasm."[1] Intermediate cells predominate in most salivary gland tumors,[61] and tumors featuring "appreciable numbers of every cell type described were rather exceptional even when many blocks of tissue were sectioned."[1] The ambiguity in defining intermediate cells and the wide variability in proportions of intermediate, epidermoid, and mucous cells has undoubtedly been a significant contributor to the difficulty in classifying tumors as MEC in nonsalivary gland sites. Salivary gland adenosquamous carcinoma lacks intermediate cells and is defined as a "malignant neoplasm that simultaneously arises from mucosal surface epithelium and salivary gland ductal epithelium as squamous cell carcinoma and adenocarcinoma, respectively."[61]

Riedlinger and colleagues[57] applied the histological features of the salivary gland neoplasms to differentiate primary cutaneous MEC from adenosquamous carcinoma, as follows:

Histological Feature	Mucoepidermoid Carcinoma	Adenosquamous Carcinoma
Intraepidermal carcinoma	-	+
Well-differentiated adenocarcinoma	-	+
Dermal-based solid/cystic tumor	+	-
Papillary features	+	-
Mucigenic cells	+	-
Peritumoral fibrosis	+	-
High-grade nuclear features	-	±

They used these criteria to conclude that MEC of the skin, while extremely rare, is distinct from adenosquamous carcinoma.[57] Kazakov et al, however, disagree that MEC exists as a primary skin neoplasm.[58] They opine that "many, if not all, of these so-called primary cutaneous MEC, including purported 'bona fide' cases," are hidradenocarcinoma or nodular hidradenoma with mucinous differentiation, SCC with mucinous differentiation, or MEC of a salivary gland with secondary skin involvement.[58] Since the eyelids contain accessory lacrimal glands (glands of Wolfring), they are a potential source from which MEC could arise. Other purported cases of eyelid MEC may represent endocrine mucin-producing sweat gland carcinoma unless endocrine markers, such as synaptophysin,[62,63,64] chromogranin,[62,63,64] CD56,[62,64] or CD57,[63] and negative staining for Wilms tumor 1 (WT1)[65] protein have excluded this possibility. Excluding endocrine mucin-producing sweat gland carcinoma is particularly important since these tumors have a predilection for the eyelids.[66]

The terminology for conjunctival MECs is also contentious.[67] Historically, tumors arising from the conjunctiva that exhibit both epidermoid and mucus-secreting cells have been classified as MEC since the seminal publication of Rao and Font in 1985.[17] Rao and Font reported five conjunctival tumors, three located at the corneoscleral limbus, one in the superior bulbar conjunctiva, and one in the lower cul-de-sac.[17] All tumors originated in the epithelium and were a mixture of epidermoid cells and mucus-secreting cells in different proportions, with four being predominantly epidermoid.[17] Rao and Font did not mention intermediate cells as a component of any of the tumors.[17] Since then, conjunctival tumors with a mixture of epidermoid and mucus-secreting cells have

been classified as MEC,[68,69] until 2018, when the World Health Organization (WHO) reclassified such tumors as adenosquamous carcinoma due to lack of intermediate cells and the presence of in situ neoplasia in some tumors.[70] Most recently, Mudhar et al[67] examined 14 "MECs" of the conjunctiva (9 involved the tarsal and forniceal conjunctiva) and classified the 11 tumors with an invasive component into four morphological groups:

1. Group 1: One tumor (9%) had in situ carcinoma with mucinous differentiation and *invasive SCC*.

2. Group 2: Six tumors (55%) had *invasive SCC with mucinous differentiation* (Figure 140.2). Three tumors had nonkeratinizing SCC, two had nonkeratinizing SCC with acantholysis, and one had keratinizing SCC with acantholysis. Mucinous differentiation was manifest as scattered cells with intracellular mucin with or without extracellular mucin. These tumors lacked true glandular differentiation.

3. Group 3: Three tumors (27%) were *adenosquamous carcinoma* with invasive SCC and invasive adenocarcinoma (Figure 140.3). There was invasive nonkeratinizing SCC in two cases and invasive keratinizing SCC in one case. The adenocarcinomatous component varied from well-formed glands composing at least 50% of the tumor to focal glandular differentiation manifest as confluent groups of goblet cells. The invasive SCC and adenocarcinoma "tended to be side-by-side."[67]

4. Group 4: One tumor (9%) was pure *adenocarcinoma*. This tumor was in the caruncle and was a well-differentiated adenocarcinoma with prominent goblet cells and luminal mucin.

None of the 14 tumors had intermediate cells, and none were diagnosed as MEC using criteria applied to salivary gland tumors. Based on their findings, the authors proposed that the WHO classification of conjunctival tumors be revised to include SCC with mucinous differentiation and adenosquamous carcinoma.[67] We concur with this *(Print pagebreak 939) (Print pagebreak 940)* proposal and recommend that pathology reports include a diagnostic comment noting that these tumors were previously classified as MEC. This diagnostic comment will allow the treating ophthalmologists and oncologists to place the tumor in a historical context for treatment and prognostic guidance.

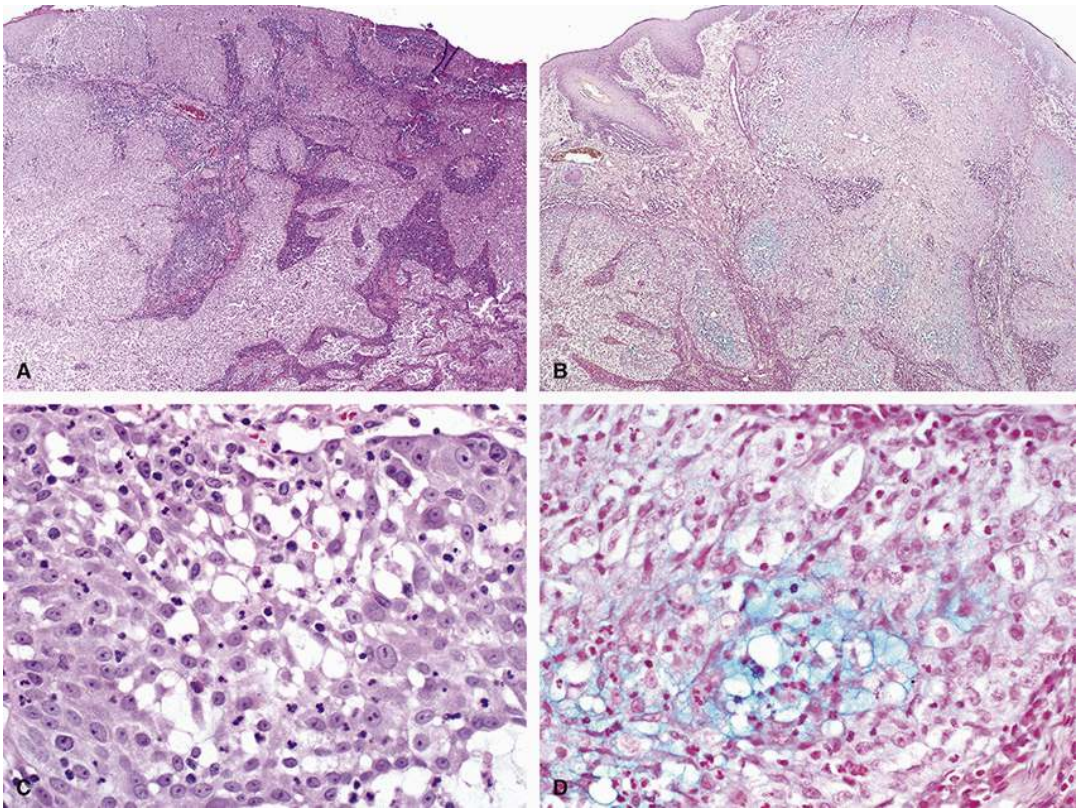

FIGURE 140.2 This tumor arose from the tarsal conjunctiva of the left upper eyelid and invaded the orbit. It was originally classified as mucoepidermoid carcinoma but is better classified as squamous cell carcinoma with mucinous differentiation using the terminology proposed by Mudhar et al.[67] A, The tumor features neoplastic conjunctival epithelium and extensive substantia propria invasion. B, Alcian blue stain highlights areas of mucinous differentiation. C, Most of the tumor is nonkeratinizing squamous cell carcinoma with areas of acantholysis. D, Alcian blue stain shows the intracellular location of the mucin.

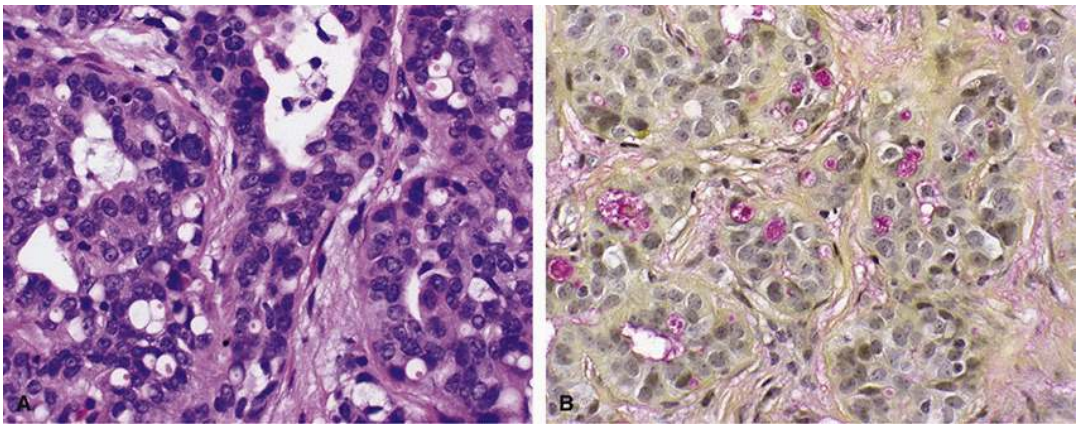

FIGURE 140.3 This "mucoepidermoid carcinoma" arose in the limbal conjunctiva of the left eye. It is better classified as an adenosquamous carcinoma using the terminology proposed by Mudhar et al.[67] A, The tumor has areas of glandular differentiation with intracellular and intraluminal mucin. B, This area stained with mucicarmine shows nests of nonkeratinizing squamous epithelium, cells with intracellular mucin, and glands with intraluminal mucin.

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CHAPTER 141

Plasmacytoma

Key Points

- Plasma cell tumors are derived from a terminally differentiated cell in the B-lymphocyte lineage
- They originate in the bone marrow during the maturation process from B-blasts to plasmablasts
- Clinically, they present as multiple myeloma, as a solitary bone and extramedullary plasmacytoma without multiple myeloma, or as plasma cell leukemia
- Eyelid plasmacytoma is a rare extramedullary form occurring in the conjunctiva, orbit, or in the eye
- It is hypothesized that primary extramedullary plasmacytoma may represent a special type of marginal zone cell lymphoma with extensive plasmacytic differentiation initiated by inflammatory infiltrate
- Eyelid lesions generally appear as a slow-growing, well-circumscribed, painless, firm, mobile, discrete, violaceous, or reddish-blue nodule that may be associated with eyelid swelling and ecchymosis
- Management must begin with systemic evaluation to rule out multiple myeloma or other lymphoproliferative disorders
- Radiation therapy is considered the treatment of choice with a response rate as high as 93%
- Surgical excision is an alternative option and chemotherapy is used for cases that progress to multiple myeloma
- For eyelid lesions the prognosis is very good, but progression to multiple myeloma is reported in about 14% of cases

Plasma cell tumors are neoplasms derived from a terminally differentiated cell in the B-lymphocyte lineage, which is generally believed to only undergo a limited number of cell divisions before it exits the cell cycle.[1] They originate in the bone marrow during the maturation process from B-blasts to plasmablasts that dedifferentiate and transform into malignant plasmablasts.[2,3] These tumors usually develop in the bone marrow and less commonly in extramedullary sites.

Plasma cell neoplasms can present clinically in several different forms including multiple myeloma, solitary bone and extramedullary plasmacytoma without multiple myeloma, and plasma cell leukemia.[4] Multiple myeloma is usually located in the bone marrow,[5] but neoplastic cells can invade or migrate to soft tissues including the skin.[6,7] Plasmacytomas are immunoproliferative, monoclonal plasma cell tumors that are classified as a non-Hodgkin lymphoma.[8] While most are associated with multiple myeloma, others are solitary lesions not associated with any systemic disease. Solitary plasmacytomas are rare and are further subclassified as either solitary plasmacytoma of bone (SPB) or as extramedullary plasmacytoma of soft tissue (EMP).

In a large study of 1354 patients with plasma cell neoplasms, 94% had multiple myeloma, 4% had SPB, and 2% had EMP.[9] In a recent Swedish study,[10] solitary bone plasmacytoma in vertebrae, femurs, pelvis, and ribs represented 70% of all solitary plasmacytomas.

Extramedullary plasmacytomas are lesions that are not associated with a bony focus or any evidence of multiple myeloma.[8,11] They are seen most often in the upper respiratory passages (80%) and less frequently in the gastrointestinal and genitourinary tracts, skin, lung, kidney, bladder, breast, thyroid, lymph nodes, and other locations.[6,8,12,13,14,15,16,17,18,19] Patients with a solitary plasmacytoma are usually aged from 50 to 80 years, but rarely this tumor can be seen in children.[20] Occurrence on the eyelid is uncommon,[2,6,21,22,23,24,25,26] and very rare cases have been described in the conjunctiva,[27,28,29,30] orbit,[20,24,31,32,33] and even in the eye.[6,34]

Solitary plasmacytoma has a predilection to progress to multiple myeloma. This is especially true for SPB with an overall progression rate of 30% to 40%. However, patients with SPB plus evidence of occult clonal bone marrow plasma cell involvement by flow cytometry in areas distant from the plasmacytoma have a greater progression rate of 60% to 70%.[35,36] In contrast, the

progression of EMP to multiple myeloma is less, with most reported rates ranging between 9 and 14%,[8,37,38,39,40] although Liebross et al[9] reported a rate of 32%. Risk factors that increase the likelihood of progression include presence of the lesion in bone, larger tumors greater than 5 cm in diameter, lymph node involvement, and older age of patients.[41]

Etiology and Pathogenesis

In 1976, Wiltshaw[40] proposed that EMP is distinct from SPB and multiple myeloma, based on several distinct differences. These included a predilection for EMP to arise from plasma cells located in mucosal surfaces, particularly the upper pulmonary passages, as opposed to SPB and multiple myeloma which originate from bone marrow plasma cells. Also, while most cases of SPB will eventually progress to multiple myeloma of bone, when EMP progresses, it more often spreads to other soft tissue sites. Also, the overall prognosis of EMP is significantly better with a longer median survival period.[42] The definition and classification adopted in a recent WHO update also support a divergence of EMP from SPB based on their biologic differences.[43]

It has been hypothesized that primary EMP, whether occurring in mucosal sites or lymph nodes, may represent a *(Print pagebreak 943)* special type of marginal zone cell lymphoma with extensive plasmacytic differentiation.[44] Like EMP, marginal zone B cell lymphomas (MZL) are found in nodal (monocytoid B cell lymphoma) and extranodal (mucosa-associated lymphoid tissue lymphoma) sites,[44] and plasma cell differentiation is a common feature seen in MZL.[44,45,46,47,48,49] It is also interesting to note that inflammatory cells can be seen on histopathological examination of EMP,[20,21,23] and it has been postulated that an inflammatory infiltrate could initiate a monoclonal plasma cell proliferation.[50]

Clinical Characteristics

The diagnosis of EMP is based on the morphologic appearance as well as the immunophenotypical finding of monoclonal plasma cells without other systemic plasma cell or lymphocytic collections, including in the bone marrow.[8] Males are affected more often than females in a ratio of about 3:1,[24] and the age at presentation is usually in the sixth and seventh decades of life.

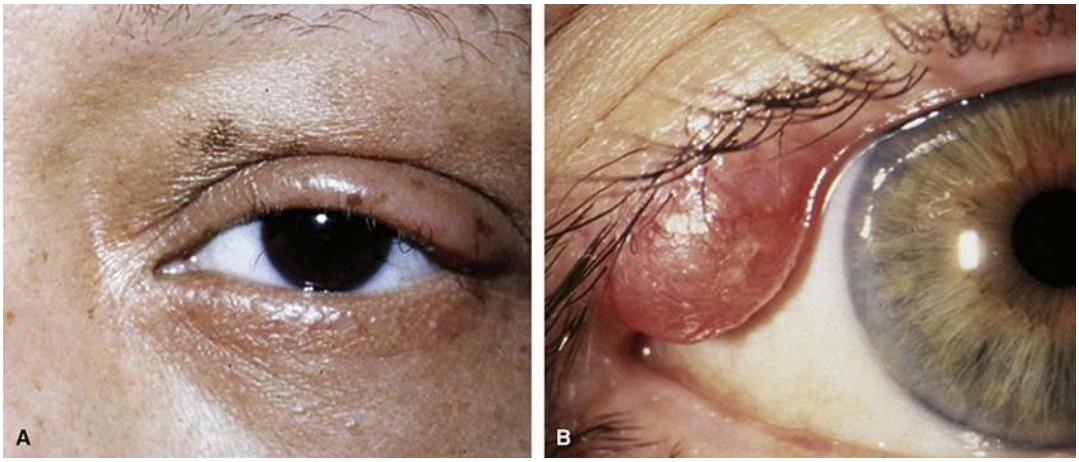

FIGURE 141.1 Plasmacytoma of the eyelids. A, Circumscribed nodular mass on the medial eyelid margin. B, Diffuse eyelid swelling from lateral eyelid plasmacytoma. (A, Courtesy of Dr. Henry D. Perry.)

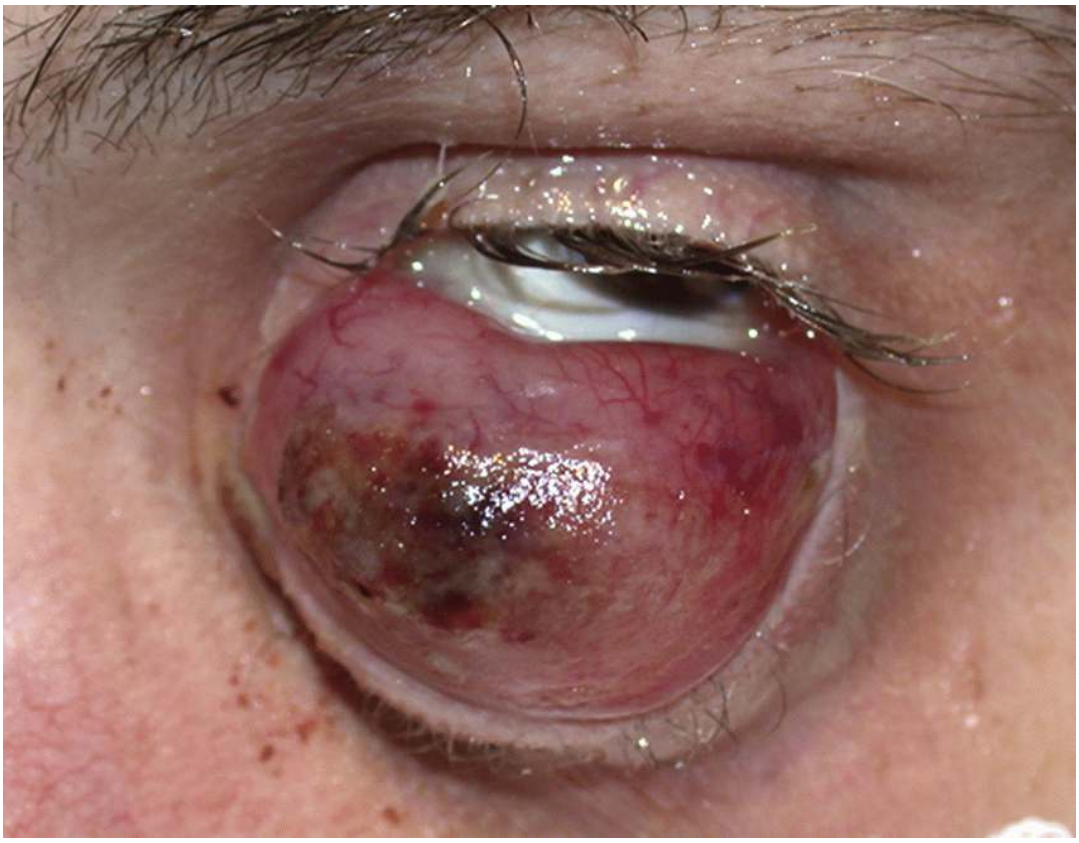

FIGURE 141.2 Large plasmacytoma of the posterior eyelid lamella. (Courtesy of Dr. Jurij Bilyk.)

Eyelid lesions generally appear as a slow-growing, well-circumscribed, painless, firm to hard, mobile, discrete nodule that may be violaceous or reddish-blue in color (Figure 141.1A).[2,6,21,22,23,25,26] Occasionally, more diffuse eyelid swelling may be seen, and ecchymosis can be an initial finding (Figure 141.1B). The lesion may infiltrate into deeper eyelid structures such as the tarsal plate and posterior lamella (Figure 141.2). Rarely ulceration may occur.[22] EMP involving the surface of the eye can occur on the palpebral or bulbar conjunctiva and present as pink to reddish-tan, smooth, mobile vascularized nontender nodules ranging from 2 mm to 2 cm in diameter (Figure 141.3).

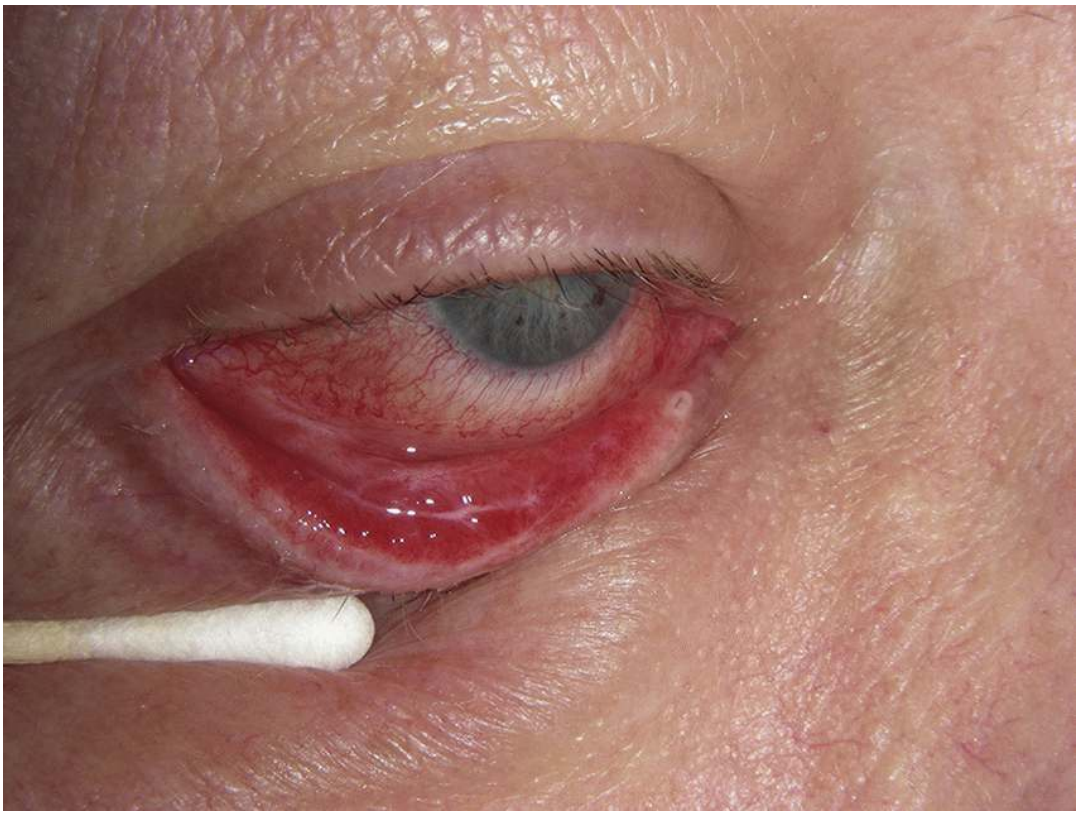

FIGURE 141.3 Recurrent plasmacytoma involving the lower eyelid conjunctiva. (Courtesy of Dr. Philip Custer.)

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Extension into the orbit can be associated with proptosis, diplopia, orbital cellulitis, hemorrhage, decreased vision, and increased intraocular pressure.[6,51] Lesions that involve the paranasal sinuses can present as sinusitis.[52]

Differential Diagnosis

Eyelid EMP is rarely diagnosed clinically and is most often misdiagnosed as a chalazion or a malignant tumor such as sebaceous carcinoma. Conjunctival lesions have been misidentified clinically as vascular or inflammatory lesions or conjunctival amyloid.

Treatment

Management of solitary extramedullary plasmacytoma must begin with a systemic evaluation, including a complete blood cell count with differential, serum and urine protein electrophoresis, bone marrow biopsy, CT skeletal survey, and MRI of the chest and abdomen to rule out multiple myeloma or other lymphoproliferative disorders.

Plasma cell tumors are highly sensitive to radiation,[9,53,54] so that radiation therapy is considered the treatment of choice for both SPB and EMP. The response rate has been reported as high as 93%.[55,56,57] Ozsahin et al. retrospectively assessed the outcome in 266 patients with SPB and EMP treated with radiotherapy, radiotherapy combined with chemotherapy, or surgery alone.[58] The local response rate to radiotherapy was greater than 80%, and the 5-year overall survival, disease-free survival, and local control rates were 74%, 50%, and 86%, respectively. Radiotherapy was associated with a lower relapse rate of 12%, compared to 60% for patients who did not receive radiotherapy. Based on the available clinical data, the recommended treatment for most patients with solitary plasmacytomas is localized, fractionated radiotherapy given at a dose of 40 to 50 Gy over approximately 4 weeks.[59] Despite the widespread use of radiotherapy for solitary plasmacytomas, few cases of eyelid EMP have been treated with this modality.[23,28,60]

Surgery is an alternative option.[55] Alexiou et al.[8] reported a rate of progression to multiple myeloma of 6.3% in patients with EMP treated with surgery compared with 17.5% of those treated with radiation. For patients treated with both surgery and radiotherapy, the rate was 13.5%. For large tumors, surgery can be followed by radiotherapy.[4,20,25] For eyelid and conjunctival EMP, most cases have been treated with surgery alone,[2,21,23,25,26,27] which avoids the risk of ocular exposure to radiotherapy and its potential complications. Of eight reported eyelid cases managed with surgery alone, none experienced recurrence in follow-up intervals of 3 months to 5 years.

Chemotherapy is used for those patients who progress to multiple myeloma and those refractory to other therapies.[59] However, its role after radiation therapy remains controversial. Holland et al[57] reported no benefit from adjuvant chemotherapy with respect to the overall incidence of progression to multiple myeloma (36%), although the transition was delayed from 29 to 59 months. Tokita et al[61] reported a case of extraosseous plasmacytoma with multiple metastases treated with chemotherapy that failed to control the disease.

Autologous stem cell transplantation has been used for patients having multiple myeloma with bone and soft tissue plasmacytomas.[62] Multiple myeloma patients with soft tissue plasmacytoma showed worse survival outcomes compared to those with skeletal plasmacytoma. The median progression-free survival was 12 months for EMP versus 28 months for SPB.[63]

Prognosis

Multiple myeloma with extramedullary spread is usually associated with a poor prognosis. Extramedullary plasmacytoma generally has a better prognosis, but solitary bone plasmacytoma can be associated with a rate of progression to multiple myeloma ranging up to 53%.[57,58] In contrast, the progression of EMP to multiple myeloma is generally reported at 36%.[57]

For eyelid EMP, the prognosis is very good, with most cases managed surgically resulting in a cure with no recurrence. However, the number of reported eyelid cases is very limited so that these data may not be reliable. Treatment of EMP in other regions carries a small but real risk of both recurrence and progression to systemic disease. In a literature review of 155 cases of non-upper aerodigestive EMP, 55.6% were treated with surgery, 19.8% with surgery plus radiotherapy, and 11.1% with radiotherapy alone,

and patients were followed for up to 140 months.[8] The authors reported that 64.7% had no recurrence after treatment, 21.2% had a recurrence, and 14.1% progressed to multiple myeloma.

Histopathology

Plasmacytomas,[43] including those in the skin,[64,65,66] are composed of normal-appearing and/or atypical plasma cells. Normal plasma cells are oval with an eccentrically placed round nucleus and abundant amphophilic or basophilic cytoplasm with a perinuclear pale-staining area corresponding to the Golgi apparatus (Figure 141.4).[67,68] Nuclear chromatin is clumped and often arranged in a distinctive radial ("cartwheel/spoke wheel," "clock face") pattern.[68] Atypical plasma cells have various morphological changes, including reduced cytoplasm (in lymphoplasmacytoid myeloma); altered nuclear appearance with diffuse chromatin, a prominent nucleolus, irregular nuclear membrane contour, and/or an increased nuclear size; or they may resemble plasmablasts with an enlarged nucleus, very prominent centrally located nucleolus, and a moderate rim of basophilic cytoplasm.[68] Atypical plasma cells may be binucleated or multinucleated with nuclei differing in size, having only one nucleolus, and having finely dispersed chromatin.[68] The plasma cells may have inclusions *(Print pagebreak 945)* such as Dutcher bodies (intranuclear vacuolation due to invagination of dilated Golgi cisternae), Russell bodies (globular eosinophilic immunoglobulin inclusions), or rarely rhomboidal crystalline immunoglobulin inclusions.[68] Amyloid may accompany cutaneous plasmacytomas (Figure 141.5A).[69] The neoplastic plasma cells express CD138 (Figures 141.5C and 141.6B)[70] but usually lack or have a weak expression of CD45, an antigen ordinarily present on the cell surface of plasma cells.[43] The neoplastic plasma cells express either kappa or lambda light chain, confirming their clonal origin. The expression of immunoglobulin light chains is evaluated in paraffin tissue sections using immunohistochemistry (Figure 141.5D) or chromogenic in situ hybridization (CISH) with probes against kappa and lambda light chain mRNA (Figure 141.6C). In our experience, CISH is preferred over immunohistochemistry due to less background staining and is beneficial in distinguishing cutaneous plasmacytomas from polytypic plasma cell infiltrates.[43,66]

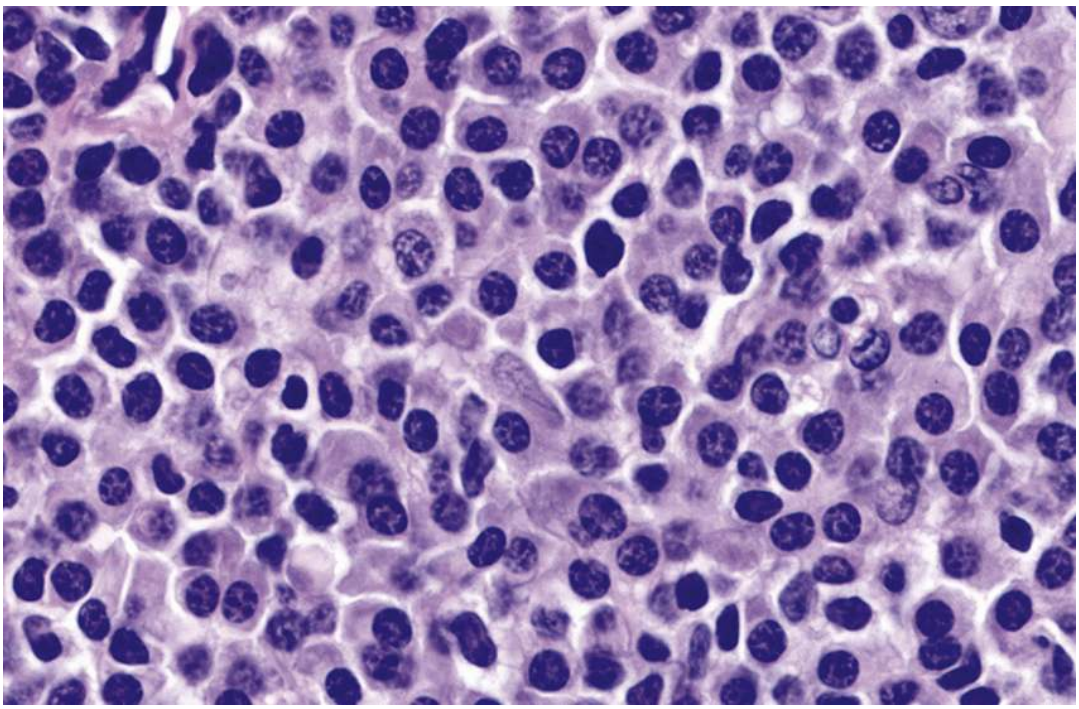

FIGURE 141.4 A sheet of normal-appearing plasma cells forms this plasmacytoma. The cells are oval with an eccentrically placed round to slightly oval nucleus and abundant amphophilic cytoplasm. The nuclear chromatin is clumped, and some cells have chromatin arranged around the periphery of the nucleus in a radial pattern.

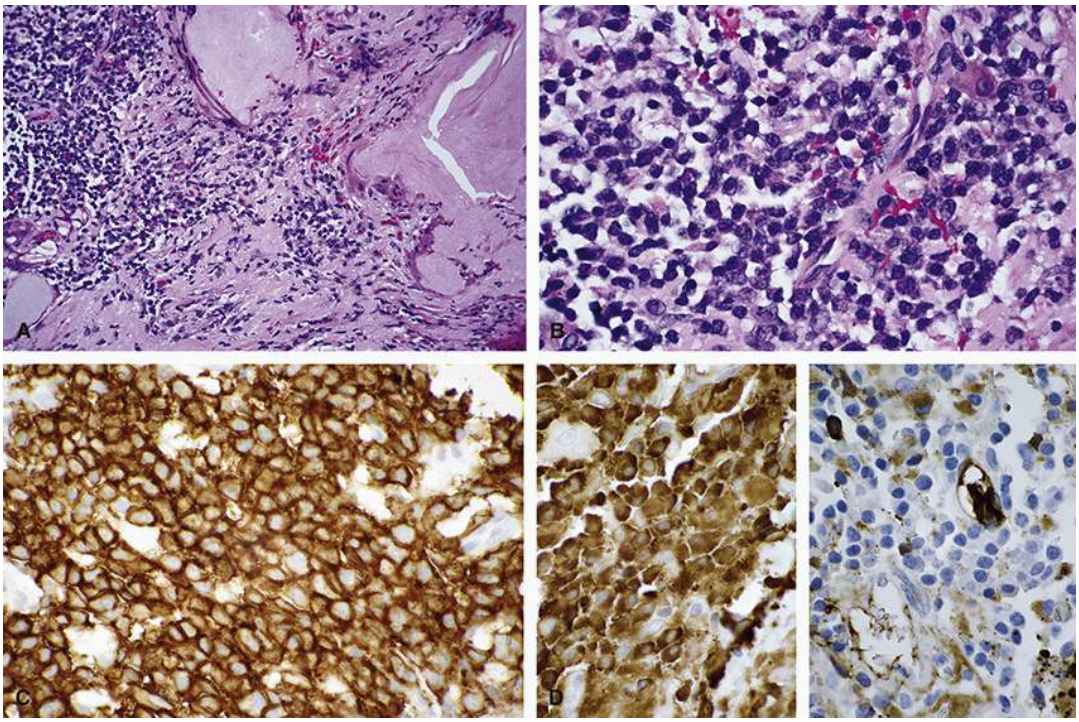

FIGURE 141.5 A woman in her middle 30s developed a nodule in her lateral left upper eyelid. The tumor was located in the eyelid posterior to the orbicularis oculi, extended into the superolateral orbit, and involved the lacrimal gland palpebral lobe. The lesion was resected in its entirety and has not recurred after more than 10 years. A, The plasmacytoma features sheets of lymphoid cells and abundant pink amyloid. B, The plasma cells have a variable appearance. Some resemble normal plasma cells, but many have enlarged nuclei with irregular nuclear borders, diffuse chromatin, and decreased cytoplasm. C, The plasma cells uniformly express CD138 (syndecan-1). D, Immunohistochemical staining showed a vast majority of the plasma cells strongly expressed kappa light chains (left panel) while only rare cells expressed lambda light chains.

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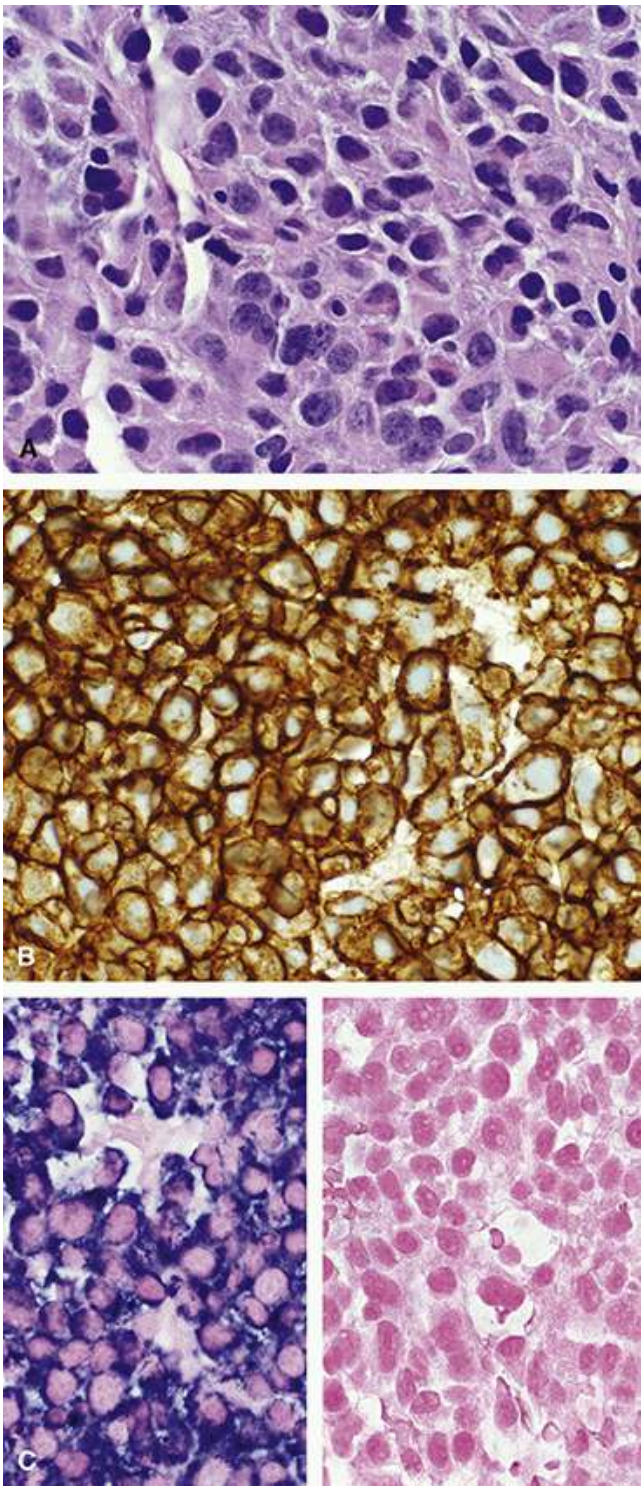

FIGURE 141.6 This octogenarian developed ptosis with a mass in the temporal fossa. A, The plasmacytoma is composed of sheets of cytologically atypical plasma cells with irregular nuclear contours, diffuse chromatin, diminished cytoplasm, and frequent mitoses. B, The tumor cells strongly and uniformly express CD138. C, Chromogenic in situ hybridization shows that 100% of the plasma cells are positive for lambda light chain mRNA (left panel), while none of the cells has kappa light chain mRNA (right panel).

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CHAPTER 142

Primary Cutaneous Mucinous Carcinoma

Key Points

- Sweat gland tumors comprise a large variety of rare lesions that mostly include eccrine carcinomas and less commonly apocrine and mixed eccrine/apocrine tumors
- Primary cutaneous mucinous carcinoma was originally believed to be of eccrine gland origin, but more recent evidence suggests apocrine differentiation
- The role of ultraviolet radiation exposure in the pathogenesis remains unclear, but distribution on the head and neck and the greater occurrence in light-skinned individuals suggest that UV exposure may be a risk factor
- On the eyelids, lesions generally appear as slow-growing, nontender, soft to firm, skin-colored, blue, pink, or red nodular, papular or cystic lesions measuring 5 mm to 2 cm
- The recommended treatment is surgical excision with wide margins
- The roles of radiotherapy and chemotherapy are controversial and inconsistent
- Local recurrence is seen in 30% or more of cases, but lymphatic spread is uncommon and distant metastasis is rare

Sweat gland tumors were first described in 1859 by Lotzbeck (in Hanby et al)[1] and later recognized as a malignancy by Cornil in 1865.[2] They comprise a large variety of rare tumors that mostly include eccrine carcinomas and less commonly apocrine and mixed eccrine/apocrine tumors.[3,4,5,6] The classification of these lesions has been confusing and inconsistent in the literature. However, most schemes subdivide these into eccrine or apocrine subtypes.[7]

Mucinous carcinoma can involve a variety of sites including major and minor salivary glands, lacrimal gland, breast, and the gastrointestinal tract and have been described under a diverse group of names.[8] Primary cutaneous mucinous carcinoma (PCMC) involving the skin is one of the better known terms for these mucinous malignancies. It was first described as a scalp lesion by Lennox et al. in 1952[9] and later more completely defined by Mendoza and Helwig in 1971.[8] Most PCMC lesions present on the head and neck, but they can occur in various other sites, including the axilla, foot, and chest.[10] Males are affected more commonly than females, and most patients tend to be older, in the 7th decade of life.[11] These tumors are biologically indolent, but they are associated with a high local recurrence rate. Regional node involvement is uncommon, and distant metastases are very rare.[11,12,13]

Etiology and Pathogenesis

Primary cutaneous mucinous carcinoma was originally believed to be of eccrine gland origin.[8] However, more recent evidence suggests apocrine differentiation, although this remains somewhat controversial.[14,15,16,17,18] The role of ultraviolet radiation exposure in the pathogenesis of sweat gland carcinomas remains unclear, but the primary distribution on the head and neck and the greater occurrence in light-skinned individuals suggest that this may be a risk factor.[19]

Clinical Presentation

PCMC has a predilection for the head and neck with about 65% to 70% occurring in this region.[20] The most common sites are the scalp, face, eyelids, and neck. The eyelid is one of the more common sites of presentation, but still, only about 60 cases have been described.[11,14,21,22,23,24,25,26,27,28,29,30] On the eyelids, these tumors may present with a variety of clinical presentations but generally are slow-growing, nontender, soft to firm, nodular, papular, or cystic lesions measuring 5 mm to 2 cm (Figures 142.1 and 142.2), but some lesions may be 4 cm or more in size. They are usually single and unilateral but rarely may be multiple or even bilateral.[31,32] Lesions may be skin colored, blue, pink, or red with or without telangiectasias, and rarely may be ulcerated.[27,33] Although growth is usually slow, there have been several reports of rapid enlargement and more aggressive behavior.[8,34]

The upper and lower eyelids are involved equally at about 45% each, and in 10% of cases, the tumor involves the medial canthus. On other parts of the body, PCMC has a high male predominance of about 70% to 80%, but on the eyelids, the sexes seem to be more equivalent with a male predominance of about 56%. They occur primarily in patients from middle to old age with a mean age at presentation of 62 years, but rare cases have been described in children.[22]

Differential Diagnosis

The clinical differential diagnosis includes basal cell carcinoma, squamous cell carcinoma, melanoma, sebaceous carcinoma, cutaneous metastasis, papilloma, chalazion, keratoacanthoma, nevus, apocrine hidrocystoma, and epidermal inclusion cyst.

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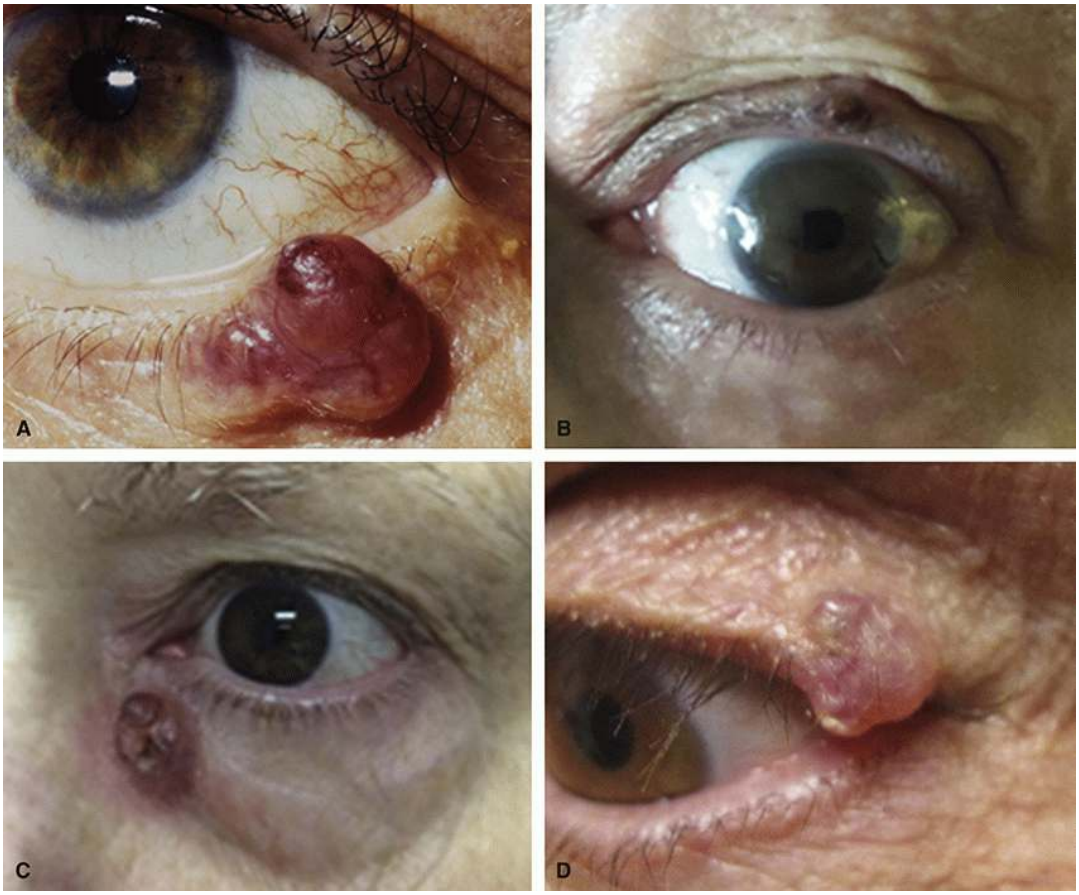

FIGURE 142.1 A, Nodular PCMC on the lateral lower eyelid. B, Small lightly pigmented eccrine carcinoma on the upper eyelid margin. C, Mulitinodular MCMC on the medial lower eyelid. D, Large nodular eccrine tumor on the medial upper eyelid. (B and C, Courtesy of Dr. Roman Shinder.)

Treatment

Although the recommended treatment of PCMC is surgical excision with wide margins of at least 1 to 2 cm,[23,35] such wide margins are usually not possible for eyelid lesions. However, a relatively narrow margin of only 5 mm has been reported with good results.[36] Incomplete excision is associated with a high recurrence rate of 30% to 40% and regional lymph node spread of 10%. Relatively few cases have been treated with Mohs micrographic surgery, but the recurrence rate is reported to be lower at 15% to 25% over 2 years.[37,38,39]

Some early publications of case series noted no benefit from radiotherapy or chemotherapy for PCMC,[40,41,42] and this has been repeated in most subsequent reports.[43,44,45] However, in a paper involving nine patients with a variety of adnexal skin carcinomas of the head and neck including PCMC treated with surgery plus adjuvant radiotherapy, 100% achieved local control with a 5-year progression-free survival of 89%.[46] Several other individual case reports also showed complete response to radiotherapy, either as primary therapy or adjunctive therapy following surgical excision.[47,48,49] Chemotherapy has been

studied in very few cases and has variably been reported to be ineffective[50] or to show some success.[51] There are no accepted guidelines for chemotherapy in this disease.

Prognosis

Following surgical excision, primary cutaneous mucinous carcinomas are associated with a high local recurrence rate of 30% or more.[11,27,34,52,53] However, lymphatic spread to regional *(Print pagebreak 950)* lymph nodes is uncommon with a rate of about 10%, and distant metastasis is rare at about 2%.[11] Tumor recurrence and metastasis are associated with poor outcomes.[38]

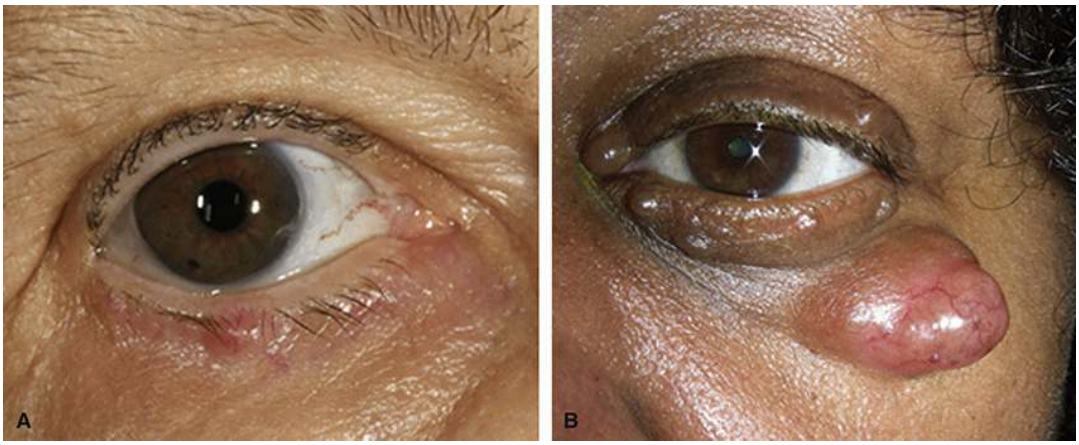

FIGURE 142.2 A, Small nodule of PCMC in the eyelid margin. B, A large protruding PCMC in the lateral lower eyelid. (A, Courtesy of Dr. John Holds; B, Courtesy of Dr. Philip Custer.)

Histopathology

Histopathologic examination reveals an unencapsulated, dermis-based tumor that may show extension into the subcutis and deeper tissues when located outside the eyelid.[8,17] In the eyelid, the tumor often invades the orbicularis oculi muscle.[14] The tumor contains islands of neoplastic basaloid cells having solid to cribriform arrangements within slightly basophilic, PAS-positive mucinous pools, sometimes partitioned by thin fibrous septa (Figure 142.3A-C).[8,18] The mucin is alcian blue positive (pH 2.4-2.5)[8,27,54] and stains with mucicarmine[54,55,56,57] and colloidal iron.[8,54] As a sialomucin, it is hyaluronidase resistant and sialidase labile.[8,54] Cytologically, the tumor cells are characteristically round to cuboidal with moderate amounts of cytoplasm and typically with a low mitotic count and little nuclear atypia.[8,14]

The tumor cells of PCMC may stain positively using antibodies to AE1/AE3 cytokeratins,[15] α-lactalbumin,[25,58] beta-2-microglobulin,[58] carcinoembryonic antigen (CEA),[15,25,58,59] CD56,[57] chromogranin,[15,57,60] CK5/6,[59] CK7/8 (CAM5.2),[57] E-cadherin,[15] epithelial cell adhesion molecule (BerEP4),[59] epithelial membrane antigen (EMA),[15,58,60] gross cystic disease fluid protein-15 (GCDFP-15),[14,15,25,57,59] high-molecular-weight cytokeratin (34βE12),[59] low-molecular-weight cytokeratin,[60] lysozyme,[15] MUC1,[15] MUC2,[15] MUC6,[15] neuron specific enolase,[60] S100 protein,[25,58,59] salivary-type amylase,[58] synaptophysin,[57,61,62] trefoil factor-1 (TFF-1),[63] WT1,[57] and estrogen (ER)[15,57,60,61,62,63] and progesterone (PR)[15,57,60,61,62,63] receptors. PCMC tumor cells are CK7+ and CK20-,[14,15,57,59,61,62,64] similar to breast cancer but different from gastrointestinal adenocarcinoma, which is CK7- and CK20+.[15] Thus, approximately half of cases of mucinous carcinomas (ie, those from the gastrointestinal tract) can be effectively eliminated from consideration using CK7 and CK20 immunostains.[15] The tumor cells are negative for expression of CD10,[15] CDX2,[57] p53 protein,[15,60] prostate-specific antigen (PSA),[15,59] prostate-specific alkaline phosphatase,[15] smooth muscle actin,[15] and thyroid transcription factor 1 (TTF1).[59] Most primary mucinous carcinomas are CK7+, E-cadherin+, EMA+, GCDFP-15+, ER+, PR+, and CK20-.[15]

The expression of p63 by myoepithelial cells in PCMC assists in distinguishing a primary versus metastatic mucinous neoplasm.[15,65,66,67,68,69,70] When p63 immunostaining highlights a peripheral layer of myoepithelial cells (Figure 142.3D), it is considered diagnostic of an in situ tumor component, indicating an origin in the skin.[15,18,69] The significance of p63 expression by invasive tumor cells is uncertain since some cutaneous metastases from breast[68,70] and lung cancer[70] may express this protein. In the absence of an in situ component to the tumor, we recommend complete immunohistochemical, clinical, and radiological examination since lung, gastrointestinal, and breast cancer may rarely present with cutaneous metastasis.[71]

PCMC of the eyelid may coexist with endocrine mucin-producing sweat gland carcinoma (EMPSGC), with EMPSGC likely

representing a precursor.[57,72,73,74,75] EMPSGC is a rare, slow-growing, low-grade neuroendocrine neoplasm with a marked predilection for the eyelids and ocular adn exa.[72,73,74,76] EMPSGCs are typically well circumscribed, multinodular tumors with solid, cribriform, cystic, or papillary architecture (Figure 142.4). Myoepithelial cells, highlighted using antibodies to calponin, smooth muscle actin, or p63 protein,[72,77] are present in areas of in situ *(Print pagebreak 951)* carcinoma. Most large tumor nodules lack myoepithelial cells,[72] but an in situ component was identified in 42 of 63 EMPSGCs (67%) either by immunohistochemistry or light microscopy.[74] EMPSGC tumor cells may react with antibodies to carcinoembryonic antigen,[72,78] chromogranin (Figure 142.4D),[57,72,75,77,78,79] CD56,[57] CD57,[72] CK7,[72,77,78,79] CK7/8 (CAM5.2),[57,72,77] epithelial cell adhesion molecule (BerEP4),[77] epithelial membrane antigen,[72,78,79] estrogen receptor (Figure 142.4E),[72,74,78,79,80] GATA3 (Figure 142.4H),[81] gross cystic disease fluid protein-15,[57] mammaglobin (Figure 142.4I),[82] MYB,[77] neuron-specific enolase,[72,74,77,79] progesterone receptor (Figure 142.4F),[57,72,74,75,80] synaptophysin,[57,72,75,77,78,79] and WT1 (Figure 142.4G).[57,78] Tumor cells are negative for CDX2,[57] CK20,[57,72,77,78,79] and S100 protein.[72] Staining for neuroendocrine markers is often focal,[72,74,78] while CK7, nuclear hormone receptors, and WT1 are typically widespread. When PCMC and EMPSGC coexist in a tumor, the two components have a similar immunohistochemical profile supporting a derivation of PCMC from EMPSGC.[57,73] Owing to a striking resemblance of many hidradenomas to mucin-poor EMPSGC, we recommend using a panel of immunostains including nuclear estrogen receptor, neuroendocrine markers (chromogranin and synaptophysin), and WT1. The tumor should be classified as EMPSGC if it expresses nuclear estrogen receptors, a neuroendocrine marker, and WT1. Complete excision with clear margins is the recommended therapy for EMPSGC.[76] Tumor recurs in about 14% of cases, with recurrence more frequent in tumors with an invasive mucinous component (21%).[74] Metastasis from EMPSGC is not reported.[74]

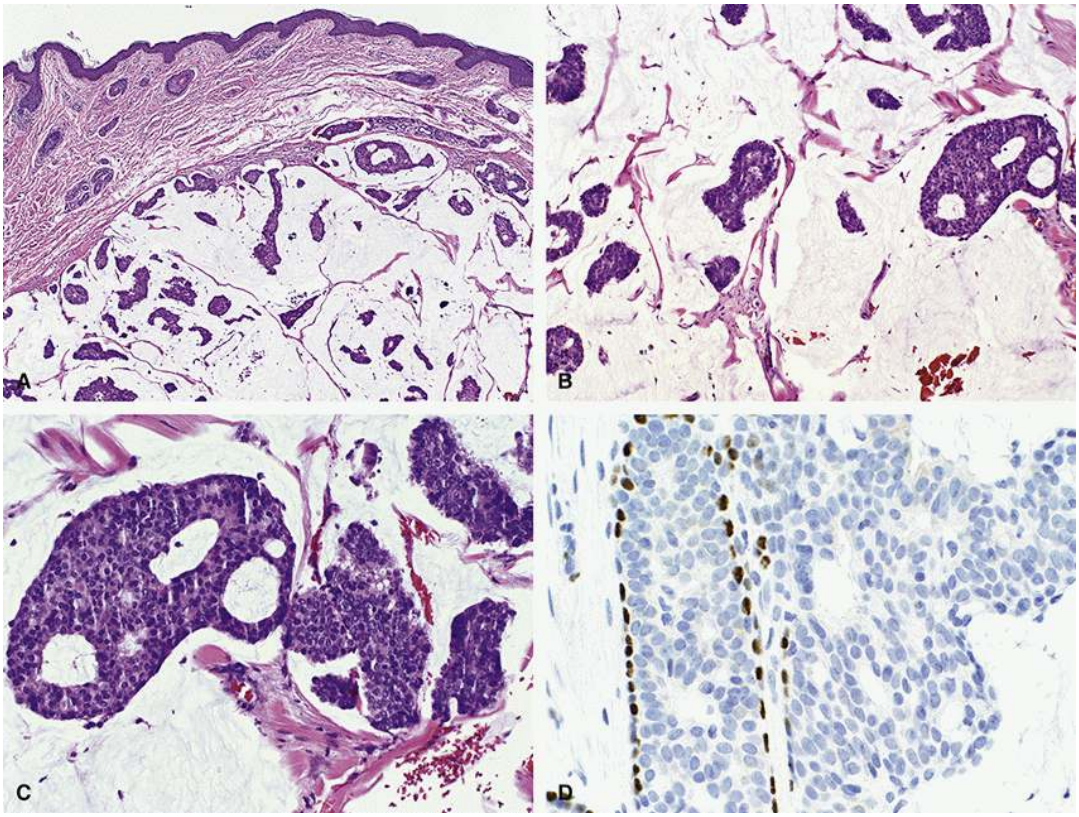

FIGURE 142.3 This PCMC arose in the left lower eyelid of a woman in her late 50s. A, The dermal tumor is well circumscribed with islands of tumor suspended in mucin and separated by delicate fibrovascular septa. B, Some of the tumor islands are solid, and others have a cribriform architecture. The mucin appears clear at this magnification. C, The tumor cells have a basaloid appearance with round to slightly oval nuclei and small amounts of lightly eosinophilic cytoplasm. The mucin is faintly basophilic. D, This tumor has foci of tumor cells surrounded by p63+ myoepithelial cells indicating an in situ tumor component, supporting a PCMC.

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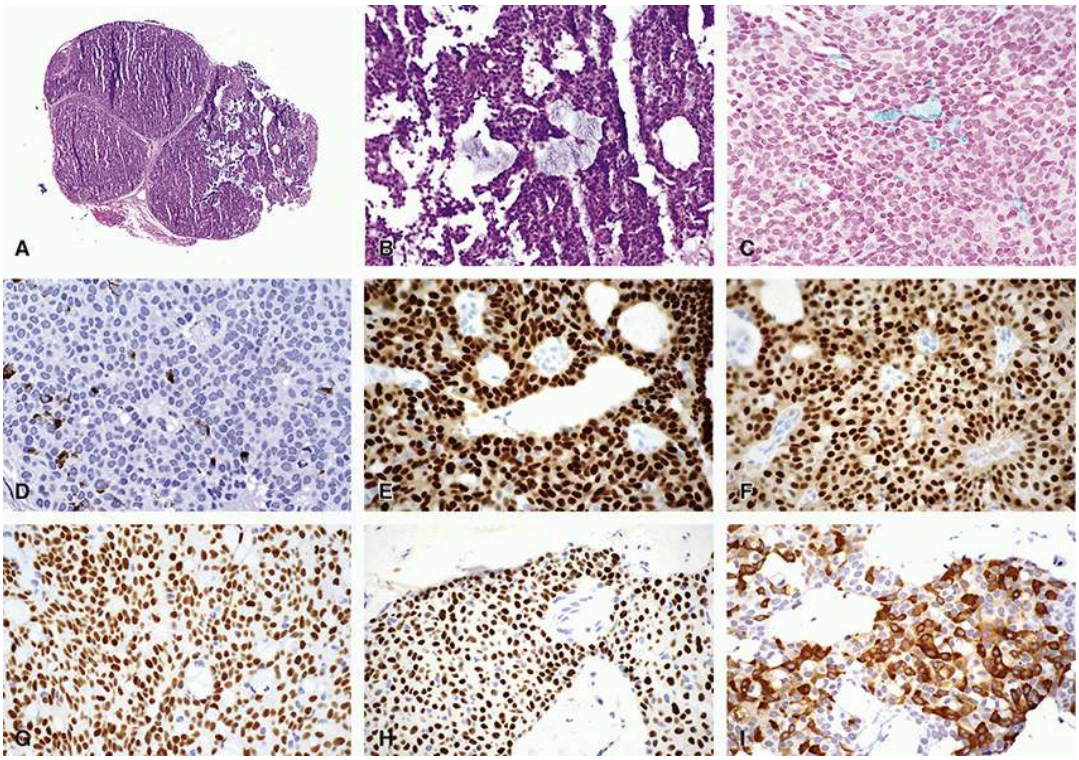

FIGURE 142.4 This endocrine mucin-producing sweat gland carcinoma was in the medial right lower eyelid of a woman in her early 60s. A, The tumor is well circumscribed and multinodular with thin fibrous bands between tumor nodules. Only the nodule on the right has obvious mucin creating the light areas surrounded by tumor cells. B, The small foci of mucin are lightly basophilic. The tumor cells have mostly round nuclei with minimal eosinophilic cytoplasm. C, Colloidal iron stain highlights extracellular and focal intracellular mucin. D, The neuroendocrine marker chromogranin was expressed by scattered tumor cells. E-I, The tumor cells diffusely expressed nuclear estrogen (E) and progesterone (F) receptors, WT1 (G), and GATA3 (H). I, Areas of the tumor had mammaglobin expression by a majority of the tumor cells.

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CHAPTER 143

Rhabdomyosarcoma

Key Points

- Rhabdomyosarcoma (RMS) is an aggressive tumor that develops from mesenchymal cells of uncertain origin
- It can occur in any anatomic location of the body where there is skeletal muscle
- The most common subtype is embryonal, which accounts for about 60% to 70% of cases
- It is believed that the embryonal subtype arises from undifferentiated mesenchymal progenitor cells that have the capacity to differentiate into striated muscle
- Embryonal RMS may show allelic gains in chromosomes 2, 7, 8, 11, 12, 13, 17, 18, and 20, losses in chromosomes 10, 14, 15, and 16, and 35% contain mutant *NRAS* or *KRAS* genes
- For ophthalmic RMS, only 3% occur in the eyelids and most cases represent subcutaneous extensions from anterior orbital tumors
- Clinically, eyelid RMS presents as a firm, immobile, nontender mass with eyelid swelling and occasional ulceration, chemosis, superficial bleeding, and ecchymosis
- Treatment is with radiation therapy and systemic chemotherapy
- Embryonal RMS carries a favorable prognosis if the tumor remains localized, with a 5-year overall survival of about 70%-80%

Rhabdomyosarcoma (RMS) is an aggressive tumor that develops from mesenchymal cells of uncertain origin.[1] While RMS can occur at any age, and case reports occur in patients ranging from 3 weeks to 78 years of age,[2,3] this tumor is far more common in children. It represents 3% to 5% of all childhood cancers and accounts for about 40% to 50% of pediatric soft tissue sarcomas in childhood and adolescence.[1,4,5,6] RMS can occur in any anatomic location of the body where there is skeletal muscle, as well as at sites without skeletal muscle, such as the urinary bladder and common bile duct.[7,8] These tumors occur most commonly in the head and neck (35%), genitourinary tract (24%), extremities (19%), and at other locations (22%).[9]

Ophthalmic RMS accounts for about 10% of all localizations.[10] In a series of 33 ophthalmic RMS cases examined by Shields and coworkers, the tumor had an orbital epicenter in 75%, conjunctival in 12%, intraocular in 9%, and palpebral in 3% of cases.[10] Of the 30 cases of extraocular RMS in the Shields et al study, "all had an orbital component, despite apparent tumor origin in the conjunctiva or eyelid."[10] About 90% of RMS are diagnosed in patients less than 25 years of age, and 60% to 70% less than 10 years old.[11] In the head and neck area, RMS occurs most commonly in the orbit, the nasopharynx, middle ear, paranasal sinuses, and infratemporal and pterygopalatine fossae, and in the larynx, oropharynx, oral cavity, parotid gland, cheek, and scalp.[7,8] Eyelid involvement is uncommon and most cases represent extension from anterior orbital tumors. Primary isolated RMS of the eyelid is exceedingly rare with only 13 cases described. In the early stages, they may be misdiagnosed as a benign lesion, such as chalazion, hordeolum, or an epithelial tumor.[12,13]

RMS has been categorized into several subtypes according to histopathological differences. The most common subtype is embryonal, which accounts for about 60% to 70% of cases in children less than 10 years of age.[5] About 350 new RMS cases are diagnosed per year in the United States,[14] and the estimated incidence is 4.5 cases per million population among individuals aged 0 to 14 years.[5,11] This subtype occurs most commonly in the head and neck region and genitourinary tract.[14] Embryonal RMS has been further subdivided into a botryoid subtype. Botryoid RMS represents 10% of embryonal RMS and characteristically occurs in mucosal-lined organs such as the bladder, vagina, nasopharynx, and respiratory tract and carries a better prognosis than other types.[15]

Alveolar RMS is the second most common subtype and accounts for about 20% to 25% of RMS cases.[4] It is equally distributed among all age groups but is the most common type in teenagers and young adults.[14] This subtype is most common in the extremities and less commonly in the head and neck or on the torso.[14]

The World Health Organization now includes pleomorphic and spindle cell/sclerosing RMS as rare but distinct subtypes of RMS. Pleomorphic RMS is most common in adults in their 50s and often involves the legs.[14] Adult pleomorphic RMS has a poor prognosis with a median overall survival of about 13 months for people with localized disease.[14] Spindle cell/sclerosing RMS accounts for 3% to 10% of RMS, affects all age groups of both sexes, and is most common in the head and neck region followed by the extremities.[16] Congenital and infantile spindle cell/sclerosing RMS have a favorable prognosis when gene fusions are present but a poor prognosis if there is an *MYOD1* mutation.[16]

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Etiology and Pathogenesis

RMSs are generally thought of as skeletal muscle tumors, mainly because they usually arise in or near muscle beds and show features of myogenic differentiation.[17] They exhibit diverse phenotypes that may reflect differences in their genetic mutations and cells of origin.[18] While the specific cell lineage of origin remains uncertain for all subtypes, the pleomorphic subtype is thought to originate from muscle stem cells,[19,20] whereas the alveolar subtype has been proposed to originate from mature differentiating skeletal muscles cells, not satellite cells.[21,22] It is believed that the embryonal subtype arises from undifferentiated mesenchymal progenitor cells that can differentiate into striated muscle,[17] although it has also been suggested that it may develop from a range of muscle lineage cells, including muscle satellite cells and downstream myogenic progenitors such as maturing myoblasts.[23,24]

Environmental risk factors have been associated with RMS. These include paternal smoking, maternal recreational drug use, advanced maternal age, and radiation exposure in utero.[5] Genetic risk factors include several hereditary syndromes including neurofibromatosis type 1 and Li-Fraumeni, Beckwith-Wiedemann, nevoid basal cell carcinoma, Rubinstein-Taybi syndromes, as well as hereditary retinoblastoma.[1,5] Oncogene mutations have been identified in 28% of embryonal and 3.5% of alveolar RMS. Embryonal RMS shows an increased incidence in syndromes with RAS/MAPK pathway and *BRAF* mutations, including cardiofaciocutaneous syndrome, Costello syndrome, and Noonan syndrome.[25,26,27,28]

Eighty percent of alveolar RMS exhibit a translocation between chromosomes 2 and 13 (t(1;13)(q35;q14) (*PAX3-FOX1A*).[1,4,26,29,30,31,32] Embryonal RMS often shows allelic gains in chromosomes 2, 7, 8, 11, 12, 13, 17, 18, and 20, losses in chromosomes 10, 14, 15, and 16,[33,34] and translocations in the 1p11-1q11 region.[33] Moreover, studies have shown that 35% (5 of 14) of embryonal RMS samples contain mutant *NRAS* or *KRAS* genes.[35] P53, RAS, Hedgehog, and PI3K pathways are potentially necessary for the pathogenesis of embryonal RMS and could thus be important for targeted therapy.[35]

FIGURE 143.1 A, Child with a rhabdomyosarcoma of the left upper eyelid presenting as eyelid swelling and ecchymoses. B, Rhabdomyosarcoma of the medial canthus and upper eyelid. (A, Courtesy of Dr. Ilya Leingold. B, Courtesy of Dr. Antonio Augusto Cruz.)

Clinical Presentation

For ophthalmic RMS, 76% occur in the orbit, 12% in the conjunctiva, and 3% in the eyelids.[10] Localized eyelid involvement is quite rare and most cases represent subcutaneous extensions from anterior orbital tumors.[10] Conjunctival and subconjunctival lesions appear as a fleshy, pink lesion often in the fornix. Early stages of eyelid RMS in children may be misdiagnosed as a benign

lesion. For periorbital lesions, the size can vary considerably, from pimple size to 6 cm or more.[36]

Eyelid RMS occurs at all ages with a mean of 11.3 years, a median of 8.0 years, and a range of 1 day to 54 years. Males and females are equally affected, and there is a slight predilection for the right side (70%). All subtypes are represented, with 58% embryonal, 25% anaplastic, and 17% alveolar. The specific localizations are upper eyelid (64%), lower eyelid (18%), caruncle (9%), and medial canthus (9%). Eyelid RMS usually present as a firm, immobile, nontender mass with eyelid swelling and occasional ulceration, chemosis, superficial bleeding, and ecchymosis (Figure 143.1).

Differential Diagnosis

Eyelid RMS usually grows rapidly so that suspicion for a neoplastic process is common. But initially, these tumors can be small, associated with ptosis, dilated vessels, and sometimes *(Print pagebreak 957)* inflammation. They can initially be confused with a variety of benign lesions such as chalazion, hordeolum, epithelial cyst, an epithelial tumor, vascular lesions such as hemangioma, or a subcutaneous hematoma. As they enlarge, they are confused with other primary cutaneous malignancies, lymphoma, or metastases particularly in a patient with a history of prior systemic malignancy. Histologically, RMS can be mistaken for round cell and spindle cell tumors such as leukemia, lymphoma, metastatic neuroblastoma, extraocular spread of retinoblastoma, Ewing sarcoma, peripheral ectodermal tumors, fibrosarcoma, and rhabdoid tumor. Immunohistochemistry and electron microscopy are required for definitive diagnosis.[37]

Treatment

Treatment for RMS of the head and neck has evolved significantly since 1965. Previously, the gold standard was a primary, often radical, surgical excision in all cases, followed by radiation therapy when complete excision could not be achieved. The survival rate was only 5% to 9%. Since 1965, radiation therapy and systemic chemotherapy have become the standard primary treatment, based on the guidelines set forth by intergroup RMS studies. Metastasis from orbital RMS is uncommon because lymphatics are very sparse in the orbit. However, conjunctiva and eyelid RMS are exposed to lymphatic vessels so that metastasis to preauricular or cervical lymph nodes can occur more easily.

Chemotherapy consists of combinations of vincristine, dactinomycin, and cyclophosphamide.[38] Success has been reported with low- and intermediate-risk RMS patients, but the 5-year failure-free survival for high-risk groups has not changed very much over the past 25 years.[4,39] For patients with disseminated tumor having the worst prognosis, chemotherapy with subsequent autologous myogenic stem cell transplantation has been proposed.[40,41]

Radiation therapy at doses of 35 to 50 Gy is used for local tumor control, combined either with surgery or chemotherapy. For eyelid and facial tumors, there is a risk of neuroendocrine dysfunction, intellectual delay, decreased vision, hearing and dental problems, facial asymmetry, thyroid dysfunction, and secondary malignancies.[42] Conformal radiotherapy, intensity-modulated radiation therapy, and proton therapy are mostly recommended.[43,44] Brachytherapy applied directly to the tumor surgical bed has been associated with fewer complications in some sites, but its use in the treatment of head and neck RMS has been limited.[45,46]

Targeted therapies may show some promise. Huang et al[47] showed the sensitivity of RMS cell lines to an IGF-1 receptor small-molecule inhibitor. Other studies showed that dual blockade of the PI3K/AKT/mTOR and RAS/MEK/ERK (AZD6244) pathways, or a combined targeted inhibition of the bromodomain 4 (BRD4) and the Akt/mTOR signaling pathways are highly effective in combating RMS.[48,49] Adjuvant immunotherapy with infusions of the patient's lymphocytes with dendritic cells pulsed with the fusion peptide plus IL2 showed an improvement in overall survival.[50]

Prognosis

Favorable prognostic factors include age less than 9 years, botryoid variant, location such as the orbit, and absence of metastasis at the time of initial treatment. Embryonal RMS is considered more favorable if the tumor remains localized with a 5-year overall survival of about 70%-80%. Alveolar RMS has a higher incidence of metastasis and generally has a worse prognosis.[1,28] Regional lymph node involvement and distant metastases from orbital RMS are relatively rare, but tumors located in the conjunctiva show a higher incidence of regional lymph node involvement.[10] Nevertheless, in general, RMS involving the orbit, conjunctiva, or eyelid has a better prognosis than tumors at other head and neck locations.[10]

RMS in adults at all sites has a poorer prognosis than pediatric tumors, possibly related to a higher incidence of the pleomorphic

histological subtype and more advanced disease at presentation.[51] The 5-year survival is reported to be only about 53%.[52]

About 70% of newly diagnosed cases of RMS that do not involve metastases can be managed with combined chemotherapy, radiation therapy, and more limited surgery.[15,53] However, patients with distant metastases at the time of diagnosis have a significantly worse prognosis, with a 5-year survival rate of only 20% to 30%.[6,54,55,56]

Histopathology

Primary cutaneous RMSs are rare[57,58,59,60,61,62,63,64,65,66,67,68] and include embryonal,[59,60] alveolar,[60,61,62,63,64] pleomorphic,[60,65,66] and epithelioid[67,68,69,70] subtypes. Reports of primary RMS in the eyelid[70,71,72,73] and conjunctiva[74,75,76,77,78,79,80] are even rarer. Reports of primary eyelid RMS include embryonal,[71,72] alveolar,[73] and epithelioid[70] variants, while reported conjunctival RMS includes embryonal[76,77] and botryoid embryonal[74,75,78,79,80] subtypes.

Embryonal RMS has a variable histological appearance (Figures 143.2 and 143.3) depending on the stages of myogenesis exhibited by the tumor cells.[81,82] Tumor cells range from poorly differentiated, recognizable as having muscle differentiation only using immunohistochemical stains, to well-differentiated tumor cells resembling fetal muscle.[81,82] Poorly differentiated tumor cells are small, round or spindle-shaped, with hyperchromatic nuclei and scant cytoplasm.[82] Better differentiated tumor cells have an appearance of rhabdomyoblasts with larger, round or oval cells, with eosinophilic cytoplasm.[82] As the rhabdomyoblasts differentiate, they have increasing amounts of eosinophilic cytoplasm and become elongated with an appearance denoted as "tadpole" or "strap" (Figure 143.2B) cells.[81] Around 50% to 60% of embryonal RMSs have identifiable cross-striations, though they are usually more irregularly distributed than in normal muscle cells.[82] Glycogen is present in tumor cells of most cases of embryonal RMS. Glycogen dissolution during processing may result in multivacuolated cells or cells with thin strands of cytoplasm traversing the cell, causing the appearance of "spider cells."[82] Embryonal RMS has variable cellularity from *(Print pagebreak 958)* one area of the tumor to another, and tumor cells are within a matrix having little collagen and varying amounts of myxoid substance.[82] Embryonal RMS may have a prominent spindle cell morphology (Figure 143.3C and D), though areas of more typical embryonal RMS are usually present.[81] Embryonal RMS, botryoid type, has less cellularity than typical embryonal RMS, abundant mucoid stroma, and a cambium layer "characterized by a subepithelial condensation of tumor cells separated from an intact surface epithelium by a zone of loose stroma."[82] Virtually all embryonal RMS are immunoreactive using antibodies to desmin, myogenin, and MyoD1, though there is variable extent of immunoreactivity.[81] There is frequent expression of muscle-specific actin (Figure 143.2C) and smooth muscle actin.[81]

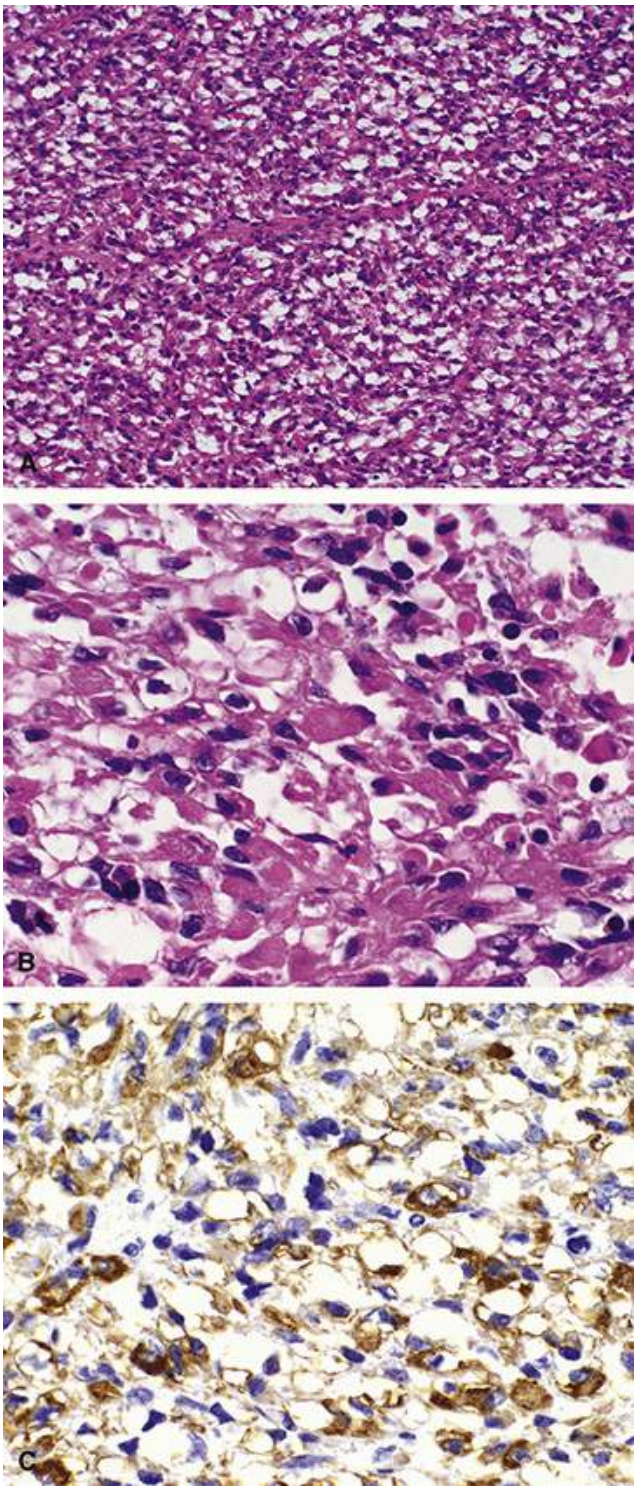

FIGURE 143.2 This embryonal rhabdomyosarcoma was from the right orbit of a 9-year-old girl. A, The tumor is a patternless sheet of small tumor cells. B, Most tumor cells have variable amounts of eosinophilic cytoplasm, while a minority have clear cytoplasm. Some cells, often termed "strap cells," have elongated eosinophilic cytoplasm and their nucleus displaced to one end of the cell. C, All of the tumor cells are immunoreactive using antibodies to muscle-specific actin.

Alveolar RMS is a highly cellular tumor "composed of primitive round cells with scant cytoplasm and hyperchromatic nuclei. Tumor cells are arranged in nests separated by fibrovascular septa, which frequently exhibit loss of cellular cohesion in the center, conferring a pattern of irregular alveolar spaces and a varying degree of cystic change. The solid subtype of ARMS is composed of sheets of neoplastic cells that have cytomorphological features of ARMS but lack septa or discohesion."[83] There is strong and diffuse nuclear expression of myogenin in alveolar RMS, in contrast to embryonal and other subtypes of RMS that have focal staining.[83] Alveolar RMS also express desmin and MyoD1,[83,84] and about one-fifth of tumors express neuroendocrine markers (synaptophysin, chromogranin, neuron-specific enolase, CD56).[84] About 85% of alveolar RMSs have fusion genes, the most common being *PAX3-FOX01* and *PAX7-FOX01* fusions, accounting for 70%-90% and 10%-30% of the fusions, respectively.[83]

Pleomorphic RMS features "sheets of large, atypical, and frequently multinucleated polygonal, spindled, or rhabdoid cells with eosinophilic cytoplasm."[85] There is usually strong expression of desmin and often limited expression of MyoD1 and myogenin.[85] There are no diagnostic molecular abnormalities.[85]

Spindle cell/sclerosing RMS has a variable histological appearance.[16] There may be intersecting fascicles of spindle cells creating a herringbone pattern, undifferentiated areas of round cells, and prominent hyalinization/sclerosis, sometimes with a pseudovascular growth pattern.[16] Spindle cell RMS may have bland cytological features in very young children.[82] There is diffuse expression of desmin in all cases, focal expression of myogenin in most cases, focal or diffuse staining for MyoD1 in spindle cell RMS, and usually diffuse MyoD1 expression in sclerosing RMS.[16] Molecular analyses of spindle cell/sclerosing RMS is important since congenital and infantile tumors with gene fusions have a favorable clinical course, while *MYOD1*-mutant spindle cell/sclerosing RMSs are aggressive tumors with a poor clinical prognosis.[16]

Epithelioid RMS, not yet classified as a distinct RMS subtype by the World Health Organization, has sheets of "uniformly sized epithelioid cells with abundant amphophilic-to-eosinophilic cytoplasm, large vesicular nuclei, and frequently prominent nucleoli."[69] The tumors *(Print pagebreak 959)* have high mitotic counts (median of 23 mitoses per 10 high-power fields), frequent atypical mitoses, necrosis, and infiltration of adjacent structures such as muscle or adipose tissue.[69] Epithelioid RMSs have diffuse desmin expression, focal myogenin expression, and coexpression of cytokeratins occurring in about 40% of tumors.[68] We are aware of only one epithelioid RMS arising in the eyelids that presented as left upper eyelid swelling with metastasis to the preauricular region in an 84-year-old woman.[70]

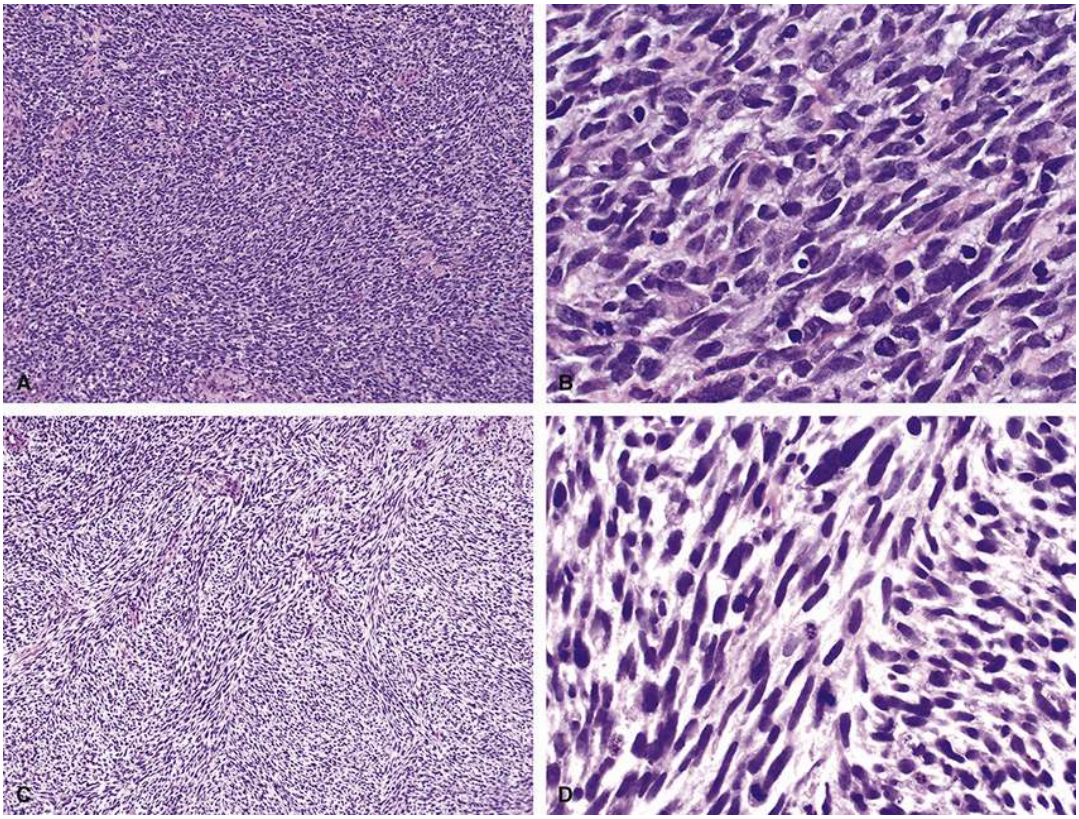

FIGURE 143.3 This embryonal rhabdomyosarcoma arose in the left lower eyelid conjunctiva of a 4-year-old girl. Computed tomography showed 1 cm of preseptal thickening without postseptal involvement. The tumor had two distinct histological features. There were sheets of small basophilic cells with oval nuclei (A and B) and interlacing fascicles of pleomorphic spindle cells (C and D). The tumor cells were immunoreactive using antibodies to desmin, myogenin, and muscle-specific actin. (Photomicrographs are from a microscopic slide distributed by Dr. Norman C. Charles at the 2012 meeting of the Eastern Ophthalmic Pathology Society.)

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CHAPTER 144

Sebaceous Carcinoma

Key Points

- Sebaceous carcinoma (SbC) is a rare malignant and potentially lethal tumor derived from the adnexal epithelium of sebaceous glands
- It represents 0.05% of all cutaneous malignancies and about 5% of all malignant neoplasms in the periocular region
- The pathogenesis is unclear but cases have been associated with the Muir-Torre syndrome, with previous radiation, and with UV exposure
- Eyelid and periocular SbC typically present in the sixth to eight decades of life
- The clinical appearance is very diverse, mimicking benign eyelid inflammations and lesions such as chalazion, blepharitis, sarcoidosis, cutaneous horn, and ocular pemphigoid
- SbC lesions may appear as a unilateral, firm, indurated, yellow, flesh-colored, or pink mass
- Treatment is with wide local surgical resection followed by eyelid reconstruction. Radiotherapy is not generally recommended as a primary treatment
- The mortality rate is generally 5% to 10%, and local recurrence rates of 11% to 36% are often seen within 5 years

Sebaceous carcinoma (SbC), or meibomian gland carcinoma, is a rare malignant and potentially lethal tumor derived from the adnexal epithelium of sebaceous glands.[1] It makes up an estimated 0.05% of all cutaneous malignancies[2] and represents about 5% of all malignant neoplasms arising in the periocular region.[3,4,5] In the periocular region, SbC has a tendency for pagetoid spread, a high recurrence rate following treatment, and a significant rate of metastases.[6,7] It may arise in ocular or extraocular sites; however, presumably because the eyelid and periocular tissues contain a high density of sebaceous glands, up to 40% of SbCs arise in eyelid and periocular locations. These tumors typically exhibit a variety of histologic growth patterns and clinical presentations. The diagnosis is frequently delayed with the mean duration from onset to diagnosis ranging from 1 to 2.9 years.[8,9]

Etiology and Pathogenesis

The occurrence of this tumor varies significantly among different ethnic groups. Among populations from China, Japan, Hong Kong, and Singapore, SbC represents as much as 30% to 40% of all periocular malignancies.[10,11,12,13,14] Among Caucasians, SbC accounts for less than 5% of eyelid malignancies.[7,15] No specific causes for these ethnic differences have yet been determined.

While the pathogenesis is unclear, cases of SbC have been associated with the Muir-Torre syndrome (MTS),[16,17] previous radiation in the area of the tumor,[18] or diuretic use.[19] MTS is an autosomal dominant disorder associated with multiple internal malignancies including head and neck, small bowel, and hematologic cancers. As many as 25% to 30% of MTS patients may develop sebaceous tumors, mostly in the periorbital region.[20,21,22,23,24]

Radiation-associated periocular SbC has been described following radiation treatment for retinoblastoma and cavernous hemangioma.[25,26,27] This can be very long term following radiotherapy and in one case was reported 17 years after treatment for retinoblastoma[28] and after more than 40 years affecting all four eyelids following radiotherapy for juvenile facial eczema.[29]

Sung et al[30] described a case of early-onset SbC in a 32-year-old patient who used a UV tanning bed for 9 years, suggesting that UV exposure could be an additional risk factor, but there is little published evidence to support this conclusion. Several recent studies have identified mutations in tumor suppressor genes, including *TP53, RB1,* and the *p16* gene in SbC patients.[31] The *p53* gene has been well studied in several malignancies. This gene promotes either cell cycle arrest, therefore allowing time for DNA repair, or apoptosis.[31] Harris et al[32] found that 67% of SbCs of the eyelid from Asian patients had *p53* mutations. These were point

mutations, rather than tandem mutations, suggesting that they may not be related to UV exposure. The *p53* mutations in eyelid SbC may be caused by UV-independent processes, in contrast to other skin cancers that are associated with UV exposure.[33]

SbC is well known in the literature as a "great masquerader," clinically mimicking other benign and malignant eyelid lesions, such as chalazion and blepharitis, which are frequently the initial misdiagnoses. This raises an interesting question as to the relationship between these lesions and the development of SbC. The relationship between cancer and inflammation has been recognized since the 17th century.[34] There is a small but intriguing literature regarding the relationship between chronic inflammation and the subsequent development of cutaneous malignancies.[35,36,37] There is much evidence that the inflammatory microenvironment can contribute to the development and progression of epithelial skin cancers by contributing to the physical processes of wound *(Print pagebreak 963)* healing and infection,[35] and it has been estimated that as many as 20% of cancers may be initiated by chronic inflammation or persistent infection.[38] Inflammatory-mediated release of various growth factors as well as cytokines and chemokines help to orchestrate tissue repair, but may also serve as promotors of oncogenesis acting on initiators such as accumulated somatic mutations.[36,37,39] Many of the so-called masqueraders of SbC, such as chalazion and blepharitis, are chronic inflammatory lesions. Although there are no reports documenting the evolution of a chalazion or blepharitis to SbC or other malignancies, the relationship between inflammation and cutaneous tumors should be kept in mind.

Clinical Presentation

Eyelid and periocular SbC typically presents in the sixth to eight decades of life, with a mean age of about 65 to 70 years[3,40]; however, studies from Asia have repeatedly shown that SbC occurs a decade earlier in Asians than in Caucasian populations.[10] A recent study has shown that the median age at diagnosis in Asian Indians was 57 years.[10] Rarely, cases in younger age groups have also been described in Caucasians.[30,41] The tumor involves extraocular sites in about 25% of cases, predominantly on the head, trunk, and genitalia. Ocular SbC arises from the meibomian glands of the upper eyelid in 40% to 60% of cases. It can also arise from accessory glands of Zeis along the eyelid margin, in the caruncle, or on the eyebrow. In a series of 60 cases of eyelid SbC, females were involved in 73%, and Caucasians in 95%.[3] In another large series of 1333 cases, Desiato et al reported a female predominance of 60%, with 62% involving the upper eyelid, 32% the lower eyelid, and 5% both.[42]

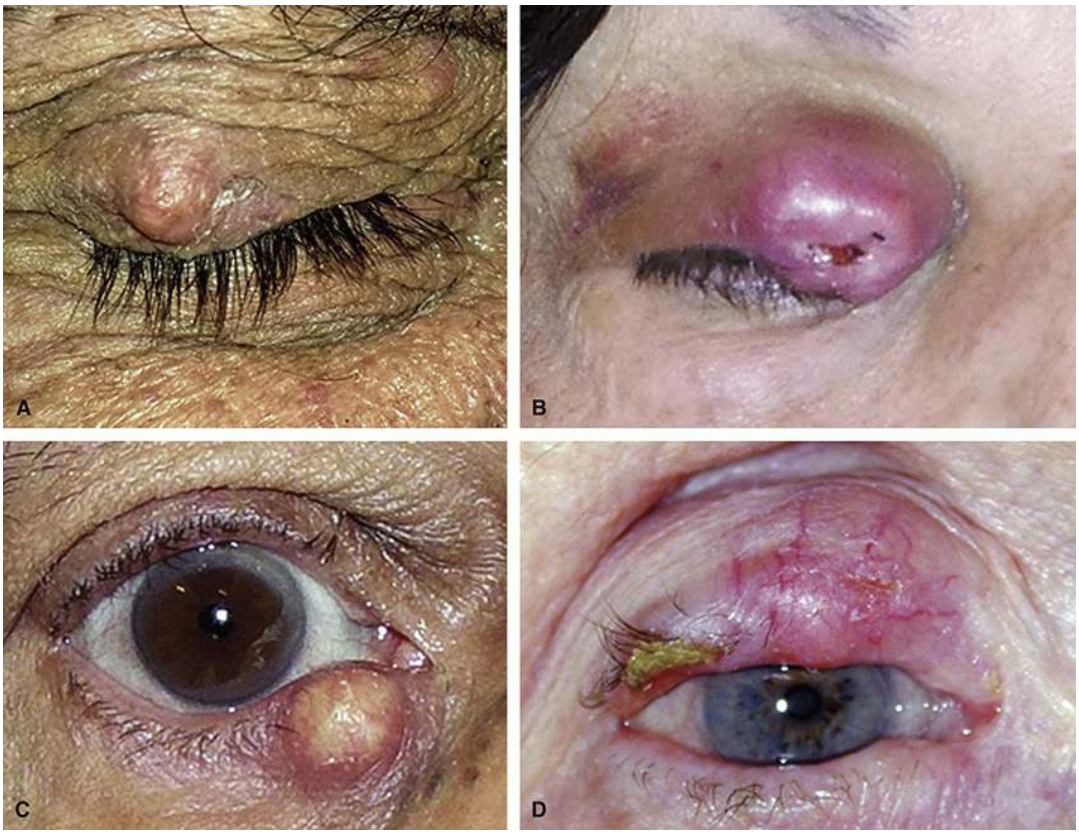

FIGURE 144.1 A-D, Sebaceous carcinoma mimicking benign lesions such as chalazion.

The clinical appearance is very diverse, mimicking a variety of benign eyelid inflammations and lesions such as chalazion, blepharitis, sarcoidosis, and ocular pemphigoid (Figures 144.1 and 144.2).[43,44] Two-thirds of cases are initially misdiagnosed as benign lesions.[3] In cases of unilateral blepharitis or conjunctivitis unresponsive to appropriate treatment, it is essential to rule out SbC. This tumor can also be confused with other malignancies including squamous cell carcinoma (SCC), basal cell carcinoma

(BCC), lymphoma, or Merkel cell carcinoma (Figure 144.3). When SbC arises in the glands of Zeis, it can present as an ulcerated nodule or even a cutaneous horn.[45]

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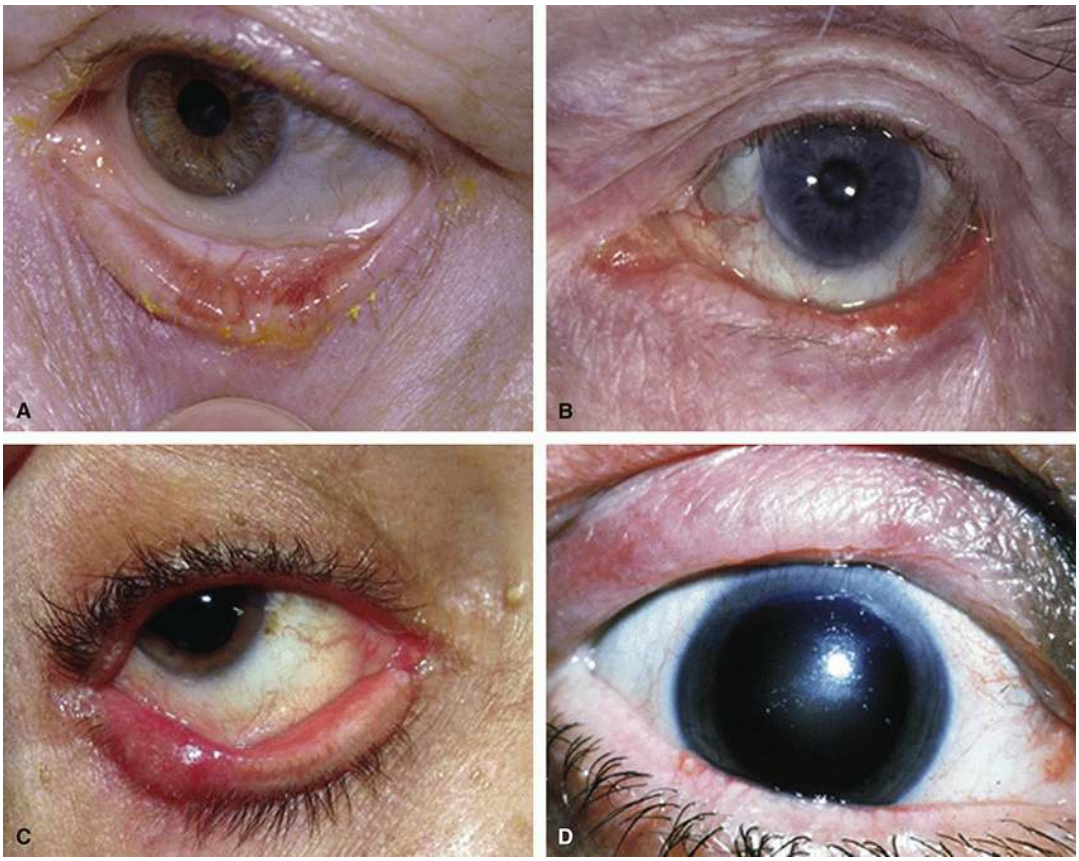

FIGURE 144.2 A-D, Sebaceous carcinoma mimicking inflammatory lesions and blepharitis.

Clinically, SbC appears as a unilateral, firm, indurated, yellow, flesh-colored, or pink mass on the tarsal conjunctiva, caruncle, or eyelid margin, often associated with madarosis and ulceration. The upper eyelid is involved in 75% of eyelid cases. Pagetoid spread is seen in 30% to 80% of cases resulting in diffuse eyelid thickening that can mimic blepharoconjunctivitis.[46] When the conjunctiva is involved, forniceal contraction is often seen, along with invasion of the cornea. SbC can spread to the lacrimal drainage system, and rare orbital invasion has been reported in more advanced cases.[47]

As with other eyelid malignancies, tumor staging is assessed using the TNM definitions in the 8th edition of the American Joint Committee on Cancer (AJCC) recommendations where T1 = ≤10 mm, T2 = >10 mm, T3 = >20 mm but not greater than 30 mm, and T4 is any stage with invasion of adjacent ocular, orbital, or facial structures.[48] Metastasis to regional lymph nodes is common and seen in 10% to 30% of cases.[3,49]

Differential Diagnosis

The differential diagnosis is extensive and includes other malignant tumors such as BCC, SCC, and a variety of benign lesions and inflammations including papilloma, chalazion, blepharitis, ocular cicatricial pemphigoid, cutaneous horns, discoid lupus, and pyogenic granuloma.

A definitive diagnosis requires a high level of suspicion and is best made with a full-thickness eyelid biopsy. Because of the common occurrence of skip lesions and the multicentric nature of this tumor, an adequate wide biopsy is necessary.[3] Pagetoid spread has been reported in 8% to 51% of cases,[50,51] but may not be apparent clinically. Shields et al reported an accurate clinical judgment of conjunctival involvement in only 57.5% of nodular tumor cases.[3] Map biopsies have been advocated to evaluate the conjunctiva for suspected cases of pagetoid spread.[52] However, the accuracy of routine map biopsies has been questioned, and Koreen et al found that 15% of specimens from 144 conjunctival map *(Print pagebreak 965)* biopsies were nondiagnostic due to artifactual epithelial loss, and nondiagnostic specimens were more frequent in patients with extensive pagetoid spread.[53] Immunohistochemical evaluation is important in distinguishing sebaceous carcinoma from other neoplasms.

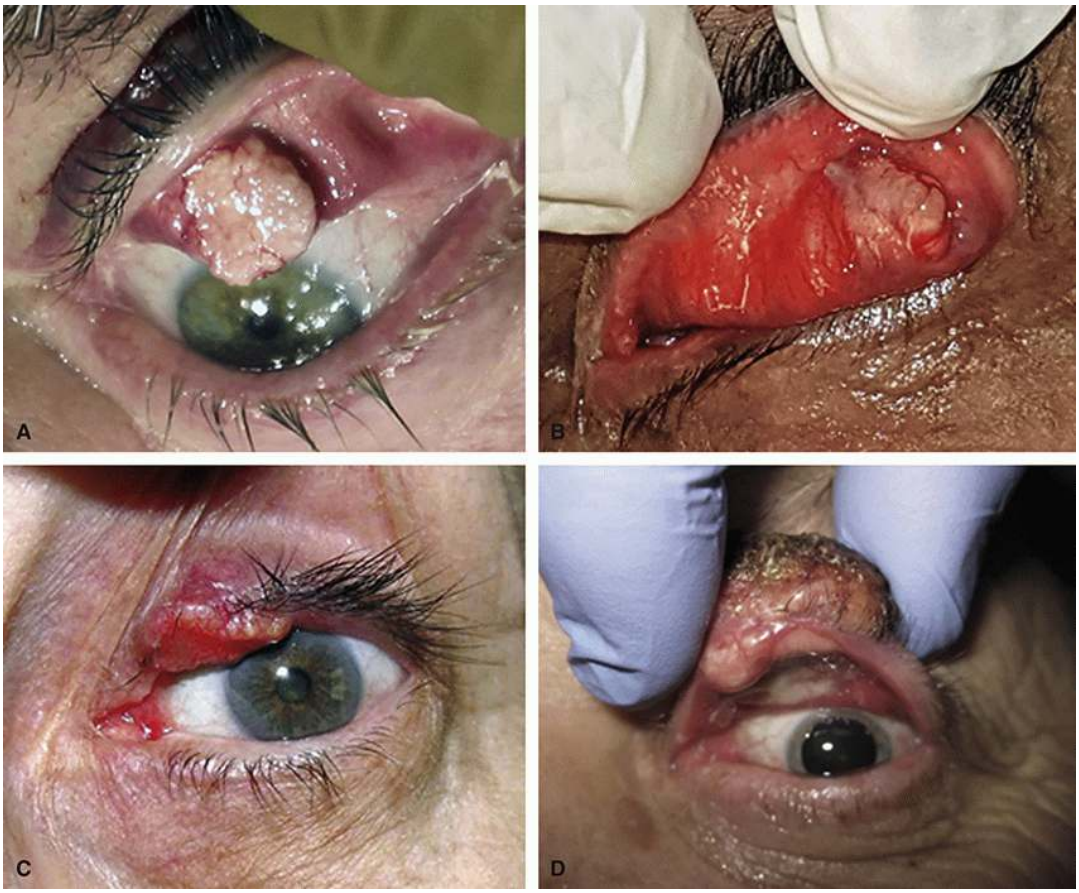

FIGURE 144.3 A-D, Sebaceous carcinoma with features similar to other eyelid malignancies. (D, Courtesy of Dr. Bita Esmaeli.)

Treatment

After a firm diagnosis is achieved, a systemic workup is undertaken with a multidisciplinary team. Systemic evaluation may include liver function tests, chest X-ray, CT, or PET/CT scanning. AJCC tumor, lymph node, and metastasis staging (TNM) should be performed to help determine the most appropriate management options.[48]

Sentinel lymph node biopsy can be used to assess the draining lymph nodes from the eyelid tumor. It is a well-tolerated procedure and has been recommended for larger tumors greater than 10 mm in size.[54,55] However, false negatives have been reported, and patients with identified lymph node disease have not been shown to have improved survival.[56]

The most important and widely recommended treatment of SbC is wide local surgical resection followed by eyelid reconstruction. Confirmation of clear surgical margins is necessary with intraoperative frozen sections or Mohs micrographic surgery. A surgical margin of 5 to 6 mm is recommended. Where frozen section or Mohs surgery is not available, 5-mm surgical margins are obtained, and reconstruction is delayed until the final paraffin sections are returned.[57,58,59] If pagetoid disease is confirmed, cryotherapy is used if the process is localized. Alternatively mitomycin C can be used for diffuse pagetoid spread. Orbital exenteration may be required if deep orbital involvement is found on imaging[60] but in recent years adjuvant therapies and globe-sparing surgery techniques have reduced the need for exenteration.[3]

Radiotherapy is not generally recommended as a primary treatment for SbC but is effective in achieving tumor control in some patients, or as an adjuvant treatment for locally *(Print pagebreak 966)* advanced tumors, or following orbital exenteration.[61,62] The major adverse effects of radiation therapy are ocular surface disease, dry eyes, keratitis, conjunctivitis, and dermatitis.

Cryotherapy using a double freeze-thaw technique can be used as adjuvant therapy for SbC. It is used after resection for tumors involving locations that are difficult for surgery alone or for tumors with conjunctival pagetoid spread. More importantly, cryotherapy is often applied to the resection edges of the palpebral and bulbar conjunctiva.[60] Adverse effects

include edema, erythema, skin blistering, depigmentation, and madarosis.

Prognosis

Periocular Sbcs are generally more aggressive than Sbcs in extraocular sites, and this is generally attributed to pagetoid spread.[31] Local recurrence rates of 0% to 43% have been reported,[51] often seen within 5 years. The most common risk factors for local recurrence are higher AJCC T stage category, tumor size, tumor location, pagetoid spread, diffuse growth pattern, multicentric origin, and delayed diagnosis. Recently, it has been demonstrated in Asian Indians that age may play a key prognostic factor in SbC.[10] In the older age group, the incidence of tumor recurrence is higher possibly due to immune senescence, while death due to disease, locoregional metastasis, and systemic metastasis is more common in the younger age group, possibly because younger patients have a longer number of years to live which hypothetically causes some micrometastasis to become apparent over the years.[10]

Based on the AJCC 8th Edition classification,[48] nodal metastases are significantly more frequent with advanced T3/T4 stages and associated more with poor tumor differentiation.[63,64] The most common sites for systemic metastases include the lungs, regional lymph nodes, liver, brain, and bone. Important risk factors for recurrence and metastasis include medial canthal involvement, occurrence on both upper and lower eyelids, orbital invasion, longer duration of symptoms >6 months, and tumor size >10 mm.[63] Pagetoid spread, lymphatic invasion, and poor histologic differentiation are also associated with a worse prognosis.[3,61] Tumors originating from the glands of Zeis and those associated with MTS are reported to have a better prognosis.[65,66]

The reported mortality rate for SbC is 4% to 16%,[3,42,51,65] with higher rates associated with wide local excision alone, and rates as low as 4% following Mohs surgery.[66] Risk factors for mortality include medial canthal involvement, tumor diameter >10 mm,[67] and poor histologic differentiation.[68]

Histopathology

SbC may arise from the meibomian glands, glands of Zeiss (the sebaceous glands lubricating the cilia at the lid margin), or sebaceous glands of the caruncle.[69] In the eyelid, SbC arises in the meibomian glands much more often than the glands of Zeiss. Of 97 eyelid tumors in the study by Rao and colleagues, 51 (53%) were of meibomian origin, 10 (10%) were from the glands of Zeiss, 12 (12%) were multicentric arising from both the meibomian glands and glands of Zeiss, and 24 (25%) tumors were of undetermined origin.[70] Ni et al reported the location of 80 eyelid SbCs: 57 (71%) were from the meibomian glands, 20 (25%) involved the meibomian and Zeiss glands, and 3 (4%) arose in glands of Zeiss.[71] In both studies, there were no fatalities in patients with tumors arising from the glands of Zeiss.

Eyelid SbC may have a lobular, comedocarcinoma, papillary, or combined histopathological growth pattern.[72,73] The lobular pattern features well-delimited lobules of varying size that usually have "a peripheral row of basophilic cells with scanty cytoplasm and elongated nuclei."[72] Cleavage artifact between the tumor lobules and the surrounding stroma is common.[72] In our experience, the lobular pattern is by far the most common in eyelid SbCs. Eyelid SbC varies from well- to poorly differentiated tumors (Figures 144.4, 144.5, 144.6), depending on the number of neoplastic cells with sebaceous differentiation. The cells with sebaceous differentiation have abundant, finely vacuolated cytoplasm creating a foamy or frothy appearance.[72] The other neoplastic cells have hyperchromatic nuclei, prominent nucleoli, and abundant basophilic cytoplasm.[72] Sebaceous differentiation is most common in the center of tumor lobules.[72] Moderately differentiated tumors exhibit only "a few foci of highly differentiated sebaceous cells," and poorly differentiated neoplasms show anaplastic cells with only a few cells having foamy cytoplasm.[72] Oil red O stain for lipid within the tumor cells was used in the past to identify sebaceous differentiation,[73] but it has now been supplanted by immunohistochemical staining for adipophilin (Figure 144.6D). Infiltrative features range from minimal to moderate to high, with minimally invasive tumors having well-delineated lobules.[72] Moderately infiltrative tumors have "somewhat smaller lobules than those seen in the minimally invasive infiltrative group, and characteristically they showed extension of infiltrating cords of tumor cells into the stroma."[72] Highly infiltrative eyelid SbCs have only focal lobules with most tumor cells forming infiltrative cords.[72] Both the tumor's degree of differentiation and infiltration correlate with mortality, with poorly differentiated and highly infiltrative tumors having the worst prognosis.[70,72] Spread of carcinoma to the epithelium of the conjunctiva (Figure 144.6), cornea, or eyelid (Figure 144.5) occurs in about 40% of eyelid SbCs.[70,72] Intraepithelial spread of carcinoma may be as single cells or small clusters (pagetoid spread; Figure 144.5E), or there may be diffuse, full-thickness replacement of the epithelium by neoplastic cells (in situ carcinomatous change; Figure 144.6B).[72] Both pagetoid and full-thickness areas of intraepithelial spread are present in about 35% of tumors with intraepithelial involvement.[72] Rarely, intraepithelial SbC may arise in the eyelid conjunctiva without an invasive tumor of the meibomian or Zeiss glands.[74]

The differential diagnosis for periocular SbC includes benign sebaceous tumors such as sebaceoma and sebaceous adenoma, very

rare tumors of the eyelids[75,76,77] that are less *(Print pagebreak 967)* common than SbC.[76] Sebaceomas are well-circumscribed dermal tumors composed mainly of basaloid germinative cells (Figure 113.6).[78,79,80] Greater than 50% basaloid cells is the value usually considered as the cutoff for differentiating sebaceoma from sebaceous adenoma.[79,80] The number of histological sections that should be examined to determine the percentage of basaloid cells is not defined,[80] and there is only moderate interobserver agreement among pathologists for diagnosing sebaceous adenoma and sebaceoma.[81] Well-differentiated (grade 1) SbC may be difficult,[78,80] if not impossible,[81] to discriminate from sebaceous adenoma. An increased mitotic rate,[82] increased nuclear survivin expression,[83] cytological atypia,[40,80] or abnormal mitotic figures[84] favor a diagnosis of carcinoma. We concur that, "If in doubt, any sebaceous tumor should be excised completely."[80]

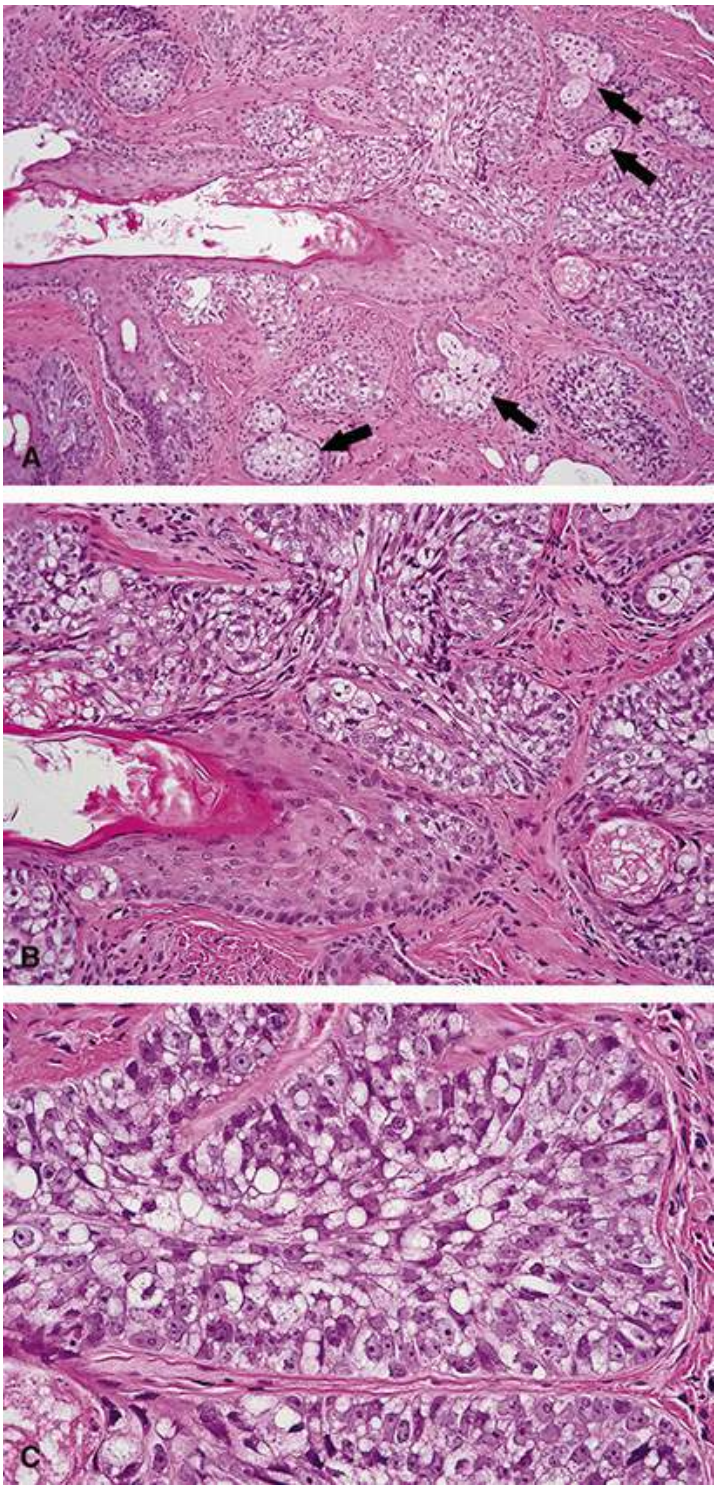

FIGURE 144.4 This well-differentiated (histologic grade 1) sebaceous carcinoma arose in the right lower eyelid meibomian glands of a man in his late 60s. A, Lobules of neoplastic cells are adjacent to a meibomian duct. The neoplastic lobules infiltrate among benign meibomian glands (arrows). B, The tumor lobules have sharp borders, with most cells having sebaceous differentiation. C, Cytoplasmic lipid vacuoles reflect the sebaceous differentiation of the neoplastic cells.

The differential diagnosis of more poorly differentiated SbC includes BCC and SCC, and there have been many attempts to define an immunohistochemical profile to differentiate these neoplasms with conflicting results (Table 144.1, sorted by publication date).[85,86,87,88,89,90,91,92,93,94,95,96,97] Based on our review of the literature and personal experience, we support the use of adipophilin, a protein associated with the surface of lipid droplets,[98] as the best discriminator of SbC from BCC and SCC.[87,92] In the elegant and thorough study by Milman and coworkers, they found "the expression of greater than 5% vacuoles and less than 95% granules to be 100% sensitive and 100% specific in distinguishing sebaceous carcinoma from other periocular and ocular carcinomas."[92]

Pathological staging of eyelid SbC is similar to that of other eyelid carcinomas except for Merkel cell carcinoma.[48] Pathology reports should ideally include factors of prognostic significance, including tumor size; vascular, lymphatic, or orbital invasion; histological grade (differentiation); presence or absence of multicentric origin (if discernible); presence or absence of a highly infiltrative pattern; and the presence or absence of intraepithelial spread.[70]

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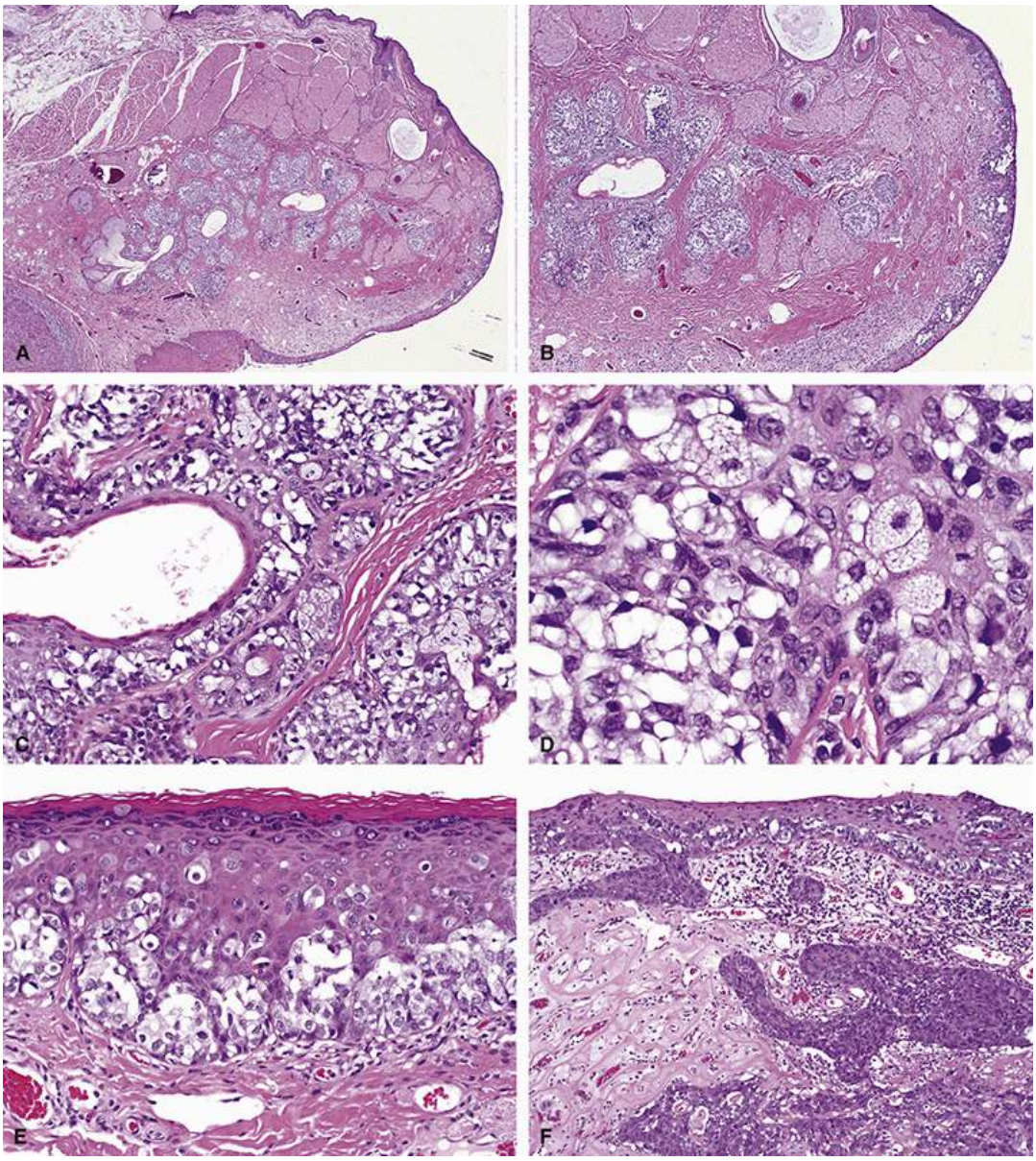

FIGURE 144.5 This well-to moderately differentiated sebaceous carcinoma developed from the right lower eyelid meibomian glands of a man in his early 50s. A, At low magnification, the tumor is in the tarsus around residual meibomian ducts. B, Intraepithelial sebaceous carcinoma extensively involves the eyelid margin. C and D, Tumor in the tarsus is a mixture of cells with sebaceous differentiation and others with minimal or no vacuolation. E, Intraepithelial carcinoma is a mixture of small nests and more superficial individual tumor cells (pagetoid spread). F, This area of the tumor has prominent conjunctival intraepithelial spread over poorly differentiated, moderately infiltrative sebaceous carcinoma that extended into the anterior orbit.

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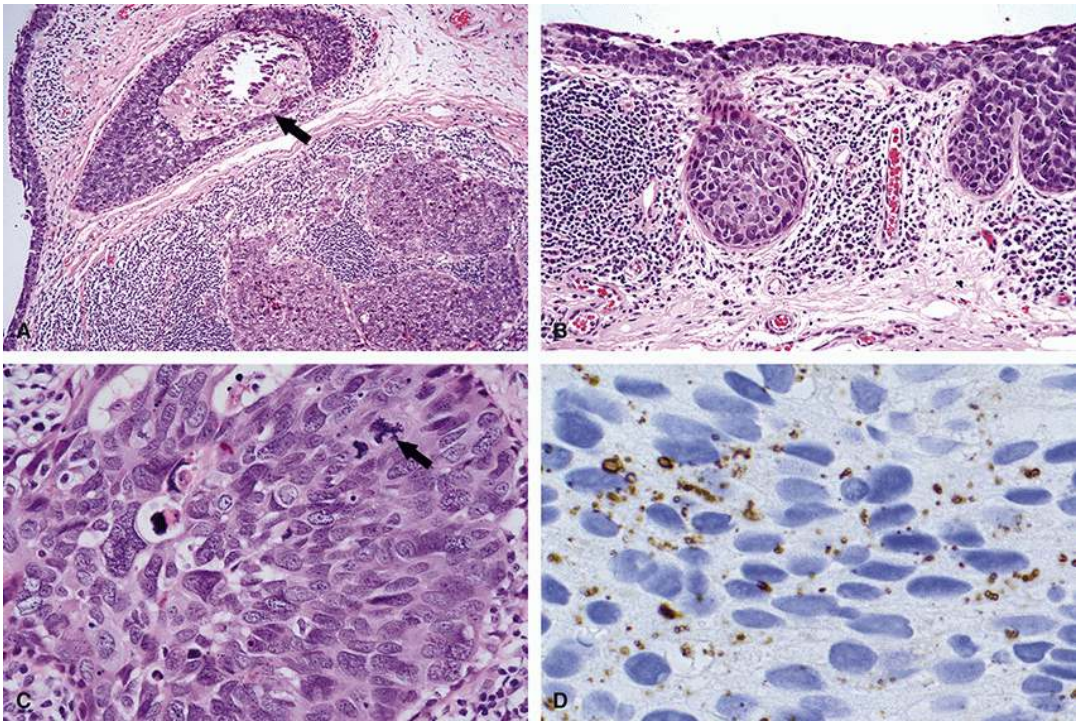

FIGURE 144.6 A man in his late 60s had poorly differentiated sebaceous carcinoma involving the left upper and lower eyelid epidermis and conjunctiva and the bulbar conjunctiva multifocally, with invasive tumor in both eyelids. A, Neoplastic cells replace the conjunctival epithelium and form lobules in the substantia propria. The lobule of invasive tumor at the top left (arrow) has central necrosis with calcification (comedocarcinoma). B, Poorly differentiated neoplastic cells replace the full thickness of the eyelid conjunctival epithelium and push into the substantia propria in several areas. The epithelial basement membrane is intact, indicating that the tumor is not invasive in this area. C, This lobule of invasive tumor has scant sebaceous differentiation and an abnormal mitotic figure (arrow). D, The tumor cells have small vacuoles and granules of staining using antibodies to adipophilin.

TABLE 144.1 Immunohistochemical Analysis of Sebaceous Carcinomas Showing Percentages of Tumors Positive for Various Antibodies

Sinard[85]			
Antibody	**Ocular SCC (*n* = 14)**	**Ocular BCC (*n* = 16)**	**Ocular sebaceous carcinoma (*n* = 11)**
AE1/AE3	100%	100%	100%
BRST-1	36%	0%	64%
CAM5.2	0%	44%	73%
EMA	79%	6%	91%
Sramek et al[86]			
Antibody	**Eyelid SCC (*n* = 6)**	**Eyelid BCC (*n* = 9)**	**Sebaceous carcinoma (*n* = 6)**
Androgen receptor	17%	78%	20%
CAM5.2	83%	100%	100%
EMA	100%	0%	80%
Ber-EP4	0%	100%	80%
CK7	50%	78%	100%
Ostler et al[87]			
Antibody	**SCC (*n* = 17)**	**BCC (*n* = 11)**	**Sebaceous carcinoma (*n* = 25)**
Adipophilin	0%	0%	92% (44% with 26%-75% of cells +, 48% > 75% cells +)
Ansai et al[88]			

Antibody	Ocular SCC (*n* = 5)	Ocular BCC (*n* = 5)	Ocular sebaceous carcinoma (*n* = 16)
CEA	20%	20%	44%
EMA	100%	0%	100%
CA15-3	60%	20%	81%
CA19-9	0%	40%	56%
Androgen receptor	20%	60%	88%
Ber-EP4	0%	80%	0%
Adipophilin	20%	0%	100%

Boussahmain et al[89]

Antibody	SCC (*n* = 28)	BCC	Sebaceous carcinoma (*n* = 26)
Adipophilin	83%	Not tested	100%
Perilipin	0%	Not tested	50%

Jakobiec and Mendoza[90]

Antibody	Eyelid SCC	Eyelid BCC	Sebaceous carcinoma (*n* = 12 pts, 18 surgeries)
EMA	Not tested	Not tested	100% (60% focal and 40% diffuse)
p53 protein	Not tested	Not tested	100% (34%-90% of cells)
Adipophilin	Not tested	Not tested	78% with vacuolar staining

Jakobiec and Werdich[91]

Antibody	Eyelid SCC (*n* = 10)	Eyelid BCC (*n* = 5)	Sebaceous carcinoma (*n* = 11)
Androgen receptor (>20% of nuclei +)	0%	0%	91%
Adipophilin	0%	0%	100%

Milman et al[92]

Antibody	Eyelid SCC (*n* = 9)	Eyelid BCC (*n* = 21)	Sebaceous carcinoma (*n* = 25)
Adipophilin	100%	95%	100% *(>5% vacuoles and <95% granules were 100% sensitive and 100% specific for sebaceous carcinoma)*
	Conjunctival SCC (*N* = 22) 73%		

Mulay et al[93]

Antibody	SCC (*n* = 25)	BCC (*n* = 18)	Sebaceous carcinoma (*n* = 56)
Pan-CK	100%	100%	100%
EMA	100%	0%	96% (32% focal and 64% diffuse)
Adipophilin	28%	0%	100%
Androgen receptor	0%	33%	100%
Ber-EP4	0%	100%	0%
p53	100% (24% of cells)	100% (4% of cells)	100% (average of 29% of cells)

Plaza et al[94]

Antibody	SCC (*n* = 22)	BCC (*n* = 21)	Sebaceous carcinoma (*n* = 27)
EMA	73%	0	100%
CK7	9%	29%	100%
Ber-EP4	0	100%	26% (<25% of cells +)
Factor XIIIa	0	0	0
Androgen receptor	0	10%	33%

p53	14%	19%	44%
Adipophilin	0	0	100%
Progesterone receptor membrane component 1	0	0	81% (mostly <25% of cells +)
Squalene synthase	0	0	52% (<25% of cells +)
Alpha/beta hydrolase domain containing protein 5	0	0	70% (<25% of cells +)

Mittal et al[95]

Antibody	**Eyelid SCC (*n* = 10)**	**Eyelid BCC (*n* = 8)**	**Sebaceous carcinoma (*n* = 9)**
Perforin	0%	0%	100%
Adipophilin	0%	13%	100%
Ber-EP4	0%	100%	100%
EMA	50%	0%	100%

Schmitz et al[96]

Antibody	**Eyelid SCC (*n* = 4)**	**Eyelid BCC (*n* = 4)**	**Sebaceous carcinoma (*n* = 5)**
Pan-CK	100%	100%	100%
CAM5.2	100%	100%	100%
EMA	100%	0%	100%
Androgen receptor	0%	50%	60%
Perforin 1	100%	50%	100%
Adipophilin	0%	0%	100%

Tjarks, et al[97]

Antibody	**SCC (*n* = 20)**	**BCC (*n* = 21)**	**Sebaceous carcinoma (*n* = 30)**
Factor XIIIa (clone AC-1A1, nuclear staining)	5%	0%	73%
GATA3	85%	90%	90%

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CHAPTER 145

Squamous Cell Carcinoma

Key Points

- Squamous cell carcinoma (SCC) is a malignant tumor of the squamous layer of cells of the epidermis, showing keratinocyte differentiation
- It is the second most common malignancy affecting the eyelid skin, accounting for 5% to 10% of such lesions
- The majority of SCCs arise from preexisting lesions such as actinic keratosis, Bowen disease, radiation dermatoses, burn scars, and chronic inflammatory lesions
- 60% to 90% of all SCCs contain mutations in the *p53* cell cycle regulator gene located on chromosome 17p13
- Clinically, SCC appears as a flesh-colored or erythematous, nodule or hyperkeratotic lesion with an indurated border and a central ulcer bed often covered with a thick crust or scale, which may bleed easily
- Mohs micrographic surgery and excisional biopsy with frozen section control are the most important surgical techniques
- Sentinel lymph node biopsy (SLNB) can be a valuable adjunct for the diagnosis of microscopic nodal metastases in some patients
- SCC is associated with local recurrence rates of 5% to 36%, lymph node metastasis in 3% to 24%, perineural invasion in 8% to 24%, and distant metastasis leading to patient death in 2% to 15% of cases

Squamous cell carcinoma (SCC) is a malignant tumor of the squamous layer of cells of the epidermis, showing keratinocyte differentiation. It is the second most common malignancy affecting the eyelid skin, accounting for 5% to 10% of such lesions.[1,2,3,4,5] SCC is much less common than basal cell carcinoma on the eyelids, but it is more aggressive and carries a greater potential for tissue destruction, local invasion, and distant metastatic spread. It may arise de novo where there is no histologic evidence of a preexisting benign lesion or from several premalignant lesions, such as actinic or solar keratosis, intraepidermal carcinoma (Bowen disease), radiation blepharopathy, or xeroderma pigmentosum. This tumor usually affects older individuals and has a predilection for fair-skinned individuals. De novo tumors tend to occur more commonly in younger individuals.[6]

Etiologic factors are similar to other epithelial tumors, such as basal cell carcinoma. Environmental factors that may contribute to its development include ultraviolet radiation (sun exposure), ionizing radiation, arsenic ingestion, hydrocarbons, psoralen plus ultraviolet A (PUVA) therapy for psoriasis, and the human papillomavirus. Intrinsic factors include xeroderma pigmentosum, oculocutaneous albinism, and immunodeficiency.[1,7] Chronic skin dermatoses, ulceration, and scarring also are associated with the development of this tumor.[7] Scarring of the skin is the most common intrinsic factor leading to SCC. In more extensive lesions, lymphatic spread and perineural orbital invasion are possible.

Etiology and Pathogenesis

The majority of SCCs arise from preexisting lesions such as actinic keratosis, Bowen disease, radiation dermatoses, burn scars, and chronic inflammatory lesions.[7] Tumors with no clinical or histologic evidence of a precursor lesion or cutaneous insult are referred to as arising de novo.[8]
This is considered a distinct variant of SCC, primarily occurring in Caucasians in both sun-exposed and sun-protected skin areas.

More than 60% to 90% of all SCCs contain mutations in the *p53* cell cycle regulator gene located on chromosome 17p13 that supports repair of DNA injury and induces apoptosis if the damage is lethal.[1] With *p53* loss by UVB damage, cell proliferation can lead to carcinogenic progression. Other abnormalities of genes regulating tumor suppression and keratinocyte proliferation and differentiation on chromosomes 3, 9, 13, and 17 have been reported.[1]

Clinical Presentation

SCC can present with diverse clinical manifestations ranging from small erythematous scaly patches to very large, ulcerated lesions. It is more common in males where it represents 65% to 75% of cases.[1,9] The age at presentation can be from 30 to 90+ years, with a median of about 65 years. The most common site of eyelid involvement is the lower eyelid, followed by the medial canthus, which together accounts for about 80% of all SCC eyelid tumors.[9] Compared with basal cell carcinoma, squamous cell tumors have a higher tendency toward ulceration and tend to affect the eyelid margin. They often begin as a premalignant lesion, such as actinic keratosis.[6] Early in the course of SCC, lesions can appear erythematous, thickened, and may be associated with loss of lashes (Figure 145.1). As the lesion advances, it can appear as an infiltrative, ulcerated lesion that bleeds easily and may be covered with scales or a thick crust (Figure 145.2). Occasionally, SCC can *(Print pagebreak 975) (Print pagebreak 976)* appear nodular with a central ulceration simulating a basal cell carcinoma, or papillomatous, cystic, pigmented, or even hyperkeratotic (Figure 145.3), and may be masked by an overlying cutaneous horn. Advanced tumors can become more aggressive and can invade the orbit by perineural spread or direct soft tissue extension (Figures 145.3 and 145.4).[10,11,12]

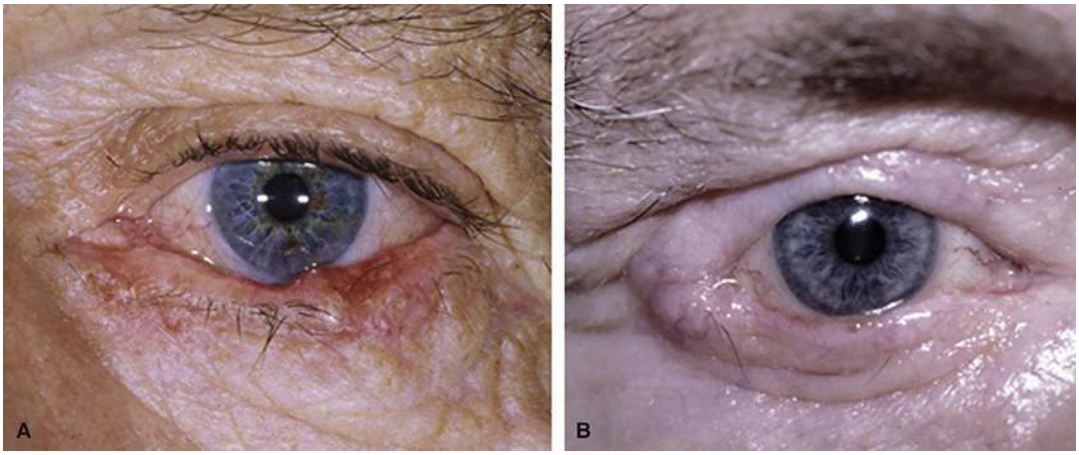

FIGURE 145.1 Early squamous cell carcinoma of the eyelid. A, Localized area of inflammation on the lateral lower eyelid margin. B, Thickening of upper and lower eyelids with complete madarosis.

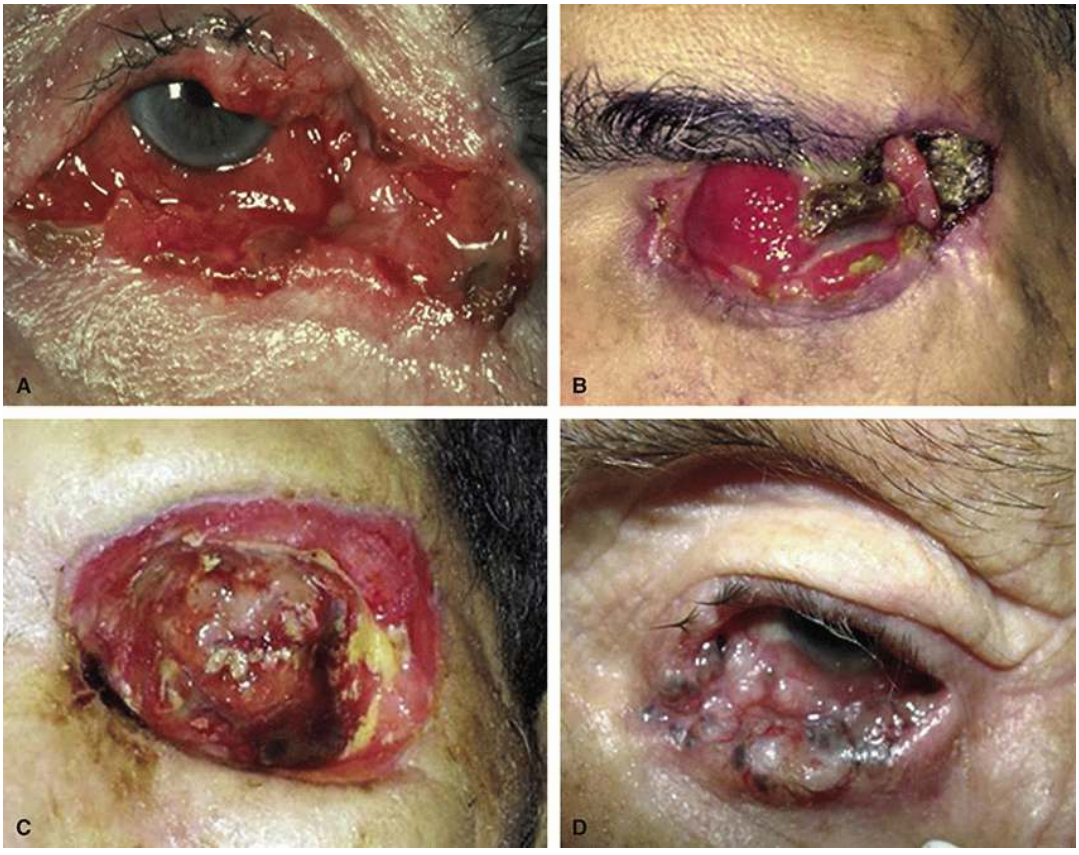

FIGURE 145.2 Advanced squamous cell carcinoma (SCC). A, Deeply invasive, ulcerated lesion involving the upper and lower eyelids and lateral canthus. B, Ulcerated SCC of the conjunctiva and eyelids. C, SCC completely replacing the conjunctiva and eyelids. D, Multinodular SCC of the lower eyelid extending to the palpebral and bulbar conjunctiva.

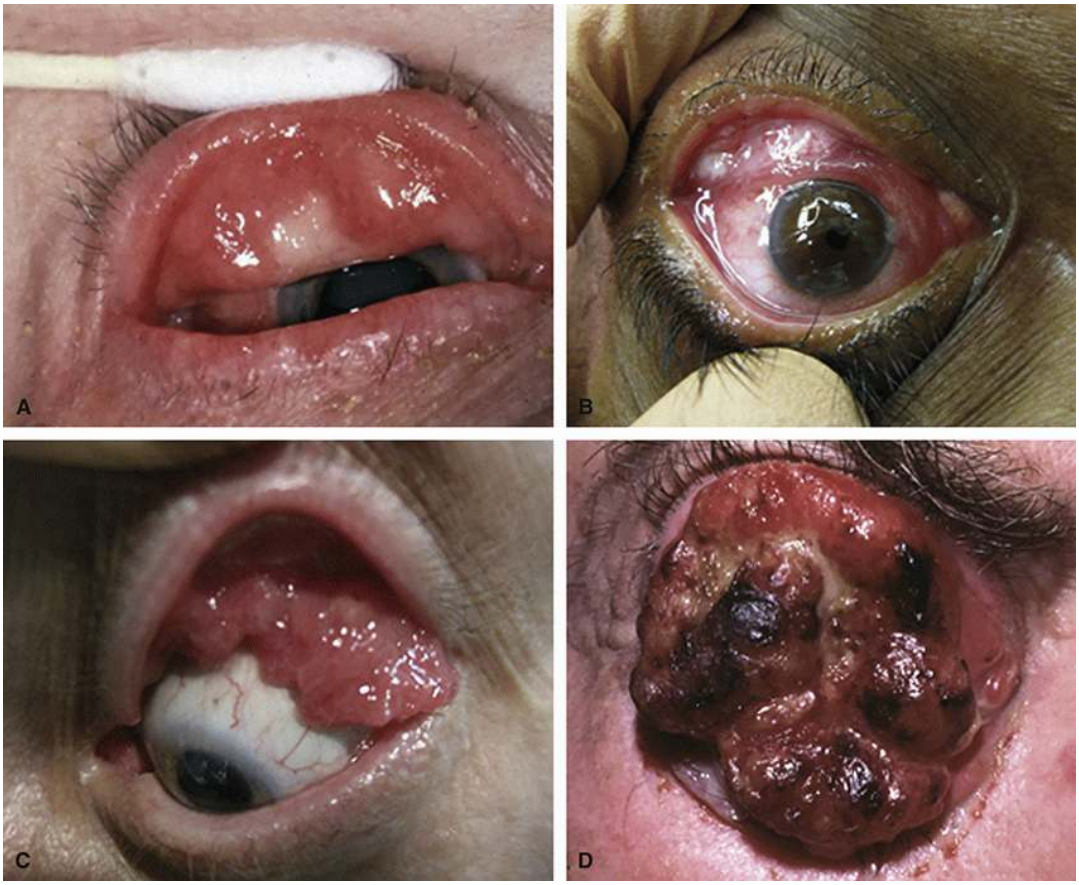

FIGURE 145.3 Conjunctival squamous cell carcinoma (SCC). A, Conjunctival intraepithelial squamous neoplasia (Bowen disease) of the upper eyelid tarsal surface. B, Sessile, minimally elevated SCC arising in the superior bulbar conjunctiva. C, Papillomatous SCC of the superior conjunctiva. D, Extensive conjunctival SCC replacing the globe and invading deeply into the orbit.

Intraepithelial squamous neoplasia, also known as Bowen disease, is a form of SCC that often arises in areas of chronic infection, inflammation, or burns.[6,13] It is confined to the epithelium, but with time it may break through the basement membrane to become invasive SCC. These lesions typically present as slowly enlarging, well-demarcated, vascularized, erythematous plaques with surface crusting or scaling, and they may occur anywhere on a skin surface or on mucosal surfaces. It may become ulcerated with a heaped-up rim. It often spares the basal epidermal layer and typically involves the follicular epithelium. Bowen disease commonly develops on sun-exposed areas of the body and may occur at any age in adults, mostly in patients over 60 years, and rarely before age 30. Although the literature frequently states that females are affected more commonly than males, among 94 cases, Foo et al[14] recorded a slight predominance for males in a ratio of about 1.5:1. When it involves the conjunctiva, it is referred to as conjunctival intraepithelial neoplasia and may present as flat to minimally elevated fleshy, sessile, gelatinous, or papillomatous masses that mostly involve the interpalpebral conjunctiva but may also involve the palpebral conjunctiva (Figure 145.4).[15] Suggested etiologies are similar to SCC and include irradiation, ultraviolet irradiation, radiotherapy, carcinogens such as arsenic, immunosuppression, chronic injury, or dermatoses such as chronic lupus erythematosus. Bowen disease may become invasive in 5% to 19% of cases, and 13% to 20% of those patients may develop distant metastases.[13]

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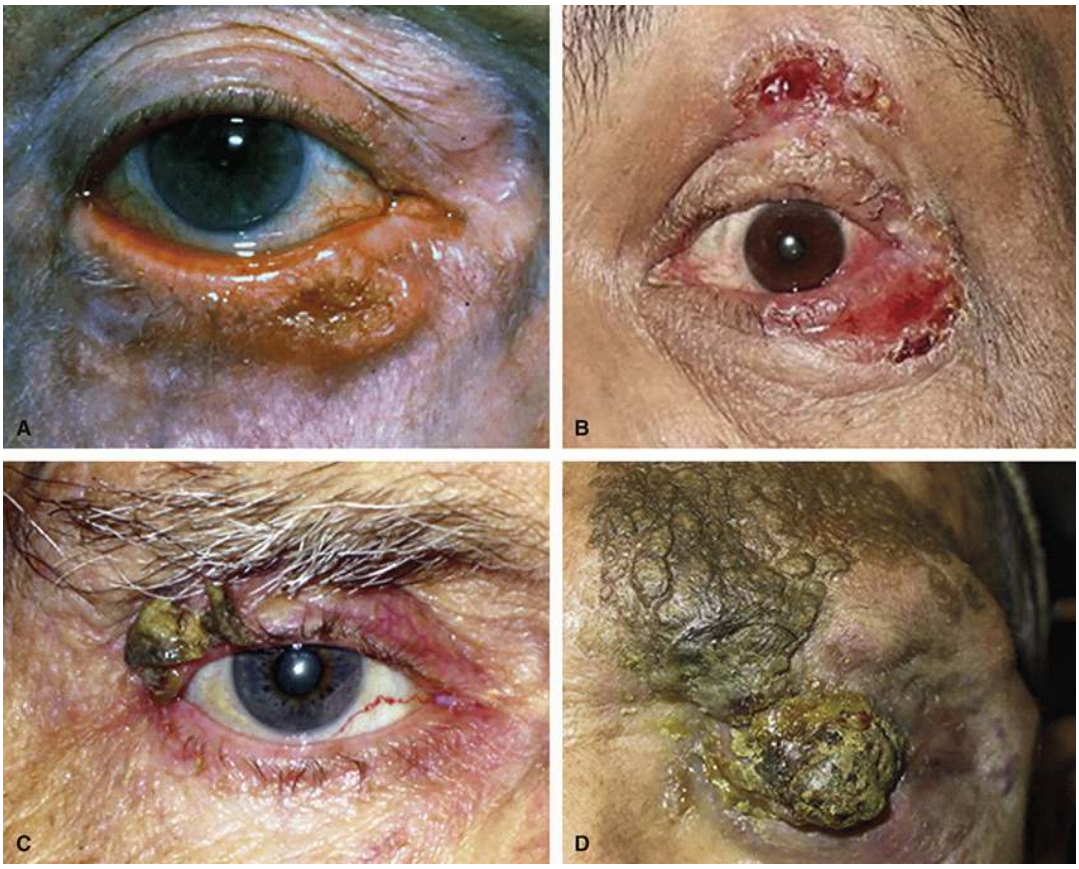

FIGURE 145.4 Unusual presentations of squamous cell carcinoma (SCC) on the eyelids. A, A nodular lesion with a central ulcer crater simulating a basal cell carcinoma. B, Flat erosive plaques of the upper and lower eyelids with crusting and scales. C, SCC with eyelid thickening, madarosis, and crusted exudate. D, Extensive SCC presenting with massive hyperkeratosis and orbital invasion.

Treatment options for Bowen disease include photodynamic therapy, cryotherapy, topical 5-fluorouracil or imiquimod, and surgical excision.[16,17,18,19]

Differential Diagnosis

The differential diagnosis of SCC includes basal cell carcinoma, sebaceous cell carcinoma, Merkel cell carcinoma, Bowen disease, actinic keratosis, keratoacanthoma, inverted follicular keratosis, papilloma, pseudoepitheliomatous hyperplasia, seborrheic keratosis, trichilemmoma, fungal infection, and verruca vulgaris.

Treatment

Diagnosis requires a biopsy for histologic confirmation. Small lesions can be managed by primary excisional biopsy. Larger lesions should be managed with an initial incisional biopsy to establish the diagnosis, followed by more definitive management. A wide variety of treatment options have been employed including surgical and nonsurgical procedures.

Tumor clearance is the ultimate goal of surgery, and Mohs micrographic surgery or excisional biopsy with frozen section control are the most important surgical techniques intended to ensure tumor eradication. Mohs micrographic surgery is the surgical approach of choice and provides the highest cure rate with the most effective preservation of normal tissue.[20,21,22] In a comprehensive evaluation of the literature and analysis of outcomes, Landsbruy et al[23] found a recurrence rate following Mohs excision of 3.0%, marginally lower than any other treatment modality. Excisional biopsy with frozen section control is also an effective way to remove cutaneous tumors and can be performed, in conjunction with reconstruction, in a single surgical setting. The literature pooled recurrence rate using this surgical approach is 5.4%.

Adjuvant therapy is defined as additional lines of treatment, either radiation therapy or systemic treatment options (immunotherapy, epidermal growth factor receptor (EGFR) *(Print pagebreak 978)* inhibitors, chemotherapy and

electrochemotherapy), that are usually given with a curative intent, preferably after complete resection of the primary lesion, and with the aim to reduce the risk of recurrence or metastasis.[3] External beam radiotherapy has not generally been recommended as an initial treatment. However, several reports have shown good results in selected patients, with local control rates of 72% to 90% and 5-year tumor-specific survival rates of 80% to 90%.[24,25,26] It may be more useful in the management of advanced or recurrent lesions in the medial canthal region. Doses are in the range of 4000 to 7000 cGy. Recurrence rates of 3% to 12% with radiation have been reported.

Brachytherapy with iridium-192 interstitial wires has been reported, delivered at total doses of 40 to 70 Gy. Results show that this can achieve good local control rates of 90% to 97%, with excellent cosmetic and functional results comparable to surgery.[27,28]

Cryotherapy has been reported to be safe and effective in treating nonmelanotic skin cancers with 30-year cure rates as high as 99%.[29] Fraunfelder et al[30] reported a recurrence rate of 2% for lesions <10 mm in diameter, which rose to 9.5% for lesions >10 mm. Cryotherapy is more often used to treat nonperiorbital lesions, but when used on the eyelid, notching of the eyelid margin, malpositions of the eyelid such as ectropion, symblepharon formation with fornix foreshortening, and pigmentary changes of the eyelid skin are possible complications.[31]

Recently, a better understanding of SCC mutational burden, and novel discoveries of tumor molecular targets have promoted the use of promising systemic immunotherapeutic agents like the PD-1 inhibiting antibody; cemiplimab.[3,25] However, when compared to radiotherapy, the results of these agents are still suboptimal in metastatic, recurrent, or extensive lesions not amenable to surgery.[25] Imiquimod is a synthetic imidazoquinoline amide derivative that acts as an immune response modifier that activates immune cells via toll-like receptor 7. It biases a T-helper cell-mediated immune response to initiate a cascade leading to the induction of cytokines directed against some cancer cells. Most published reports of this agent in eyelid tumors involve basal cell carcinoma, but some preliminary studies on nonperiorbital SCC have shown it to be less effective than surgery, but more effective than other nonsurgical procedures.[32,33,34]

Sentinel lymph node biopsy (SLNB) can be a valuable adjunct for the diagnosis of microscopic nodal metastases in some patients. Lhote et al[35] reported a rate of positive SLNB of 14%, primarily associated with poorly differentiated tumors, but relapse-free survival and overall survival were not affected by sentinel lymph node status. They suggested that SLNB is not mandatory in the management of SCC and should be used only in patients with higher risk factors, such as poorly differentiated tumors.

Prognosis

SCC is potentially a very aggressive skin tumor.[36] When neglected, it can follow a fulminant course destroying the eye and invading deep into the orbit.[37] It is associated with local recurrence rates of 5% to 36%, lymph node metastasis in 3% to 24%, perineural invasion in 8% to 24%, and distant metastasis leading to patient death in 2% to 15% of cases.[35,38,39,40]

In a study of 594 SCCs, Breuninger et al[41] showed that no tumors smaller than 2 mm in thickness metastasized; lesions between 2 and 6 mm in thickness had a metastatic rate of 4.5%, and tumors >6 mm in depth metastasized at a rate of 15%. Rowe et al[42] showed that poorly differentiated SCC has a much higher rate of metastasis of 32.8% compared with well and moderately differentiated tumors that had a rate of 9.2%. Perineural invasion carries a poor prognosis with higher rates of recurrence up to 47% and of metastasis up to 35% to 80%.[41,42,43,44,45]

Other risk factors for poor prognosis and metastasis include larger tumor size, greater thickness, invasion beyond the subcutaneous fat, poor histologic differentiation, head and neck location, and immunosuppression.[40,42] The rates of lymph node metastasis range from 0% to 24%.[6,39] SCC also has a greater tendency for perineural invasion with extension to the orbit and brain along branches of the trigeminal nerve, reported in 2% to 43% of cases.[8,9,10,39,46,47]

Tumors arising from actinic keratosis appear to have a more favorable prognosis, with a reported metastatic rate of less than 2%.[5,6] De novo SCC tends to be more aggressive in behavior with a rate of regional and distant metastasis of 8% to 14%.[48]

Predisposing Genetic Syndromes

Xeroderma Pigmentosum

As with basal cell carcinoma, xeroderma pigmentosum is associated with a significantly higher risk of cutaneous SCC.[49] This is an autosomal recessive disorder characterized by extreme sensitivity to UV radiation exposure and induced carcinogenesis, leading to a

several thousand-fold increased risk of skin cancer (see Chapter 125). Patients present with photosensitivity, severe sunburns, and chronic skin changes such as actinic damage, poikiloderma, and nonmelanoma skin cancers. The disease can also be associated with mental disability, deafness, and hyporeflexia. Ocular findings include keratitis, iritis, and choroid malignant melanoma. Xeroderma pigmentosum is caused by mutations in nucleotide excision repair (NER) genes that function in identifying and removing UV-induced cutaneous DNA damage.

Dyskeratosis Congenita

Dyskeratosis congenita is a very rare X-linked genetic disorder associated with a significant risk of SCC. Although in most cases the causative mutation is unknown, it has been associated with numerous genetic conditions that are responsible for the maintenance of telomeres, essential for genetic stability, and suppression of cancer development.[49] Patients typically present in childhood and may have mucosal and conjunctival leukoplakia, nail dystrophy, bone marrow dysfunction, cytogenetic instability, reticulate hyperpigmentation, and a predisposition to malignancy. Patients may also have alopecia, premature gray hair, and palmoplantar hyperkeratosis. SCCs often arise from leukoplakic plaques.

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Epidermolysis Bullosa

Epidermolysis bullosa is a rare disorder that presents in childhood and results in skin fragility, blistering, and nonhealing wounds. Affected patients are at increased risk of skin cancer. It is associated with several genetic mutations, including those affecting collagen VII and various keratin and integrin genes.[49] There are 4 major types of the disease based on the level of skin cleavage and 30 distinct phenotypic subtypes. SCC often occurs in patients with recessive dystrophic epidermolysis bullosa, in areas with chronic skin blisters, nonhealing wounds, and scars. These are aggressive tumors associated with significant morbidity and mortality.

Histopathology

SCC of the eyelid skin[50,51] resembles that involving other body sites.[52,53] There were 82 cases of SCC (15 in situ SCC and 67 invasive SCC) in Deprez and Uffer's study of 5504 eyelid skin tumors, accounting for 9.3% of the malignant neoplasms.[54] In situ SCC has thickened epidermis with disorganized cytologically atypical keratinocytes involving the entire thickness of the epidermis (Figure 145.5).[13,53,55,56,57] Parakeratosis may be minimal or exuberant with cutaneous horn formation.[57] In situ SCC of the eyelids usually arises in a background of actinic keratosis. The histological appearance of invasive SCC depends on its degree of differentiation, with most tumors classified as well to moderately differentiated.[53] Well-differentiated SCC (Figure 145.6) has enlarged polygonal tumor cells with abundant eosinophilic cytoplasm, dyskeratotic cells with keratin pearl formation, and readily apparent intercellular bridges.[51,55,56,57] Moderately differentiated SCC has less prominent keratinization and more cellular pleomorphism than well-differentiated SCC.[55] Poorly differentiated SCC has tumor cells with markedly enlarged pleomorphic nuclei, frequent mitoses, atypical mitotic figures, and little or no keratinization.[55,56,57] Pathological staging *(Print pagebreak 980)* of eyelid SCC incorporates tumor size, tarsal plate invasion, and invasion of adjacent ocular or orbital structures.[58] SCC variants reported in the eyelid include spindle cell SCC,[50,51] acantholytic (adenoid) SCC,[50,51,59] and basal cell-signet ring SCC.[60] The lesions most frequently misdiagnosed as eyelid cutaneous SCC are sebaceous carcinoma, basal cell carcinoma, seborrheic keratosis, inverted follicular keratosis, pseudoepitheliomatous hyperplasia, adnexal carcinoma, and keratoacanthoma.[4,61]

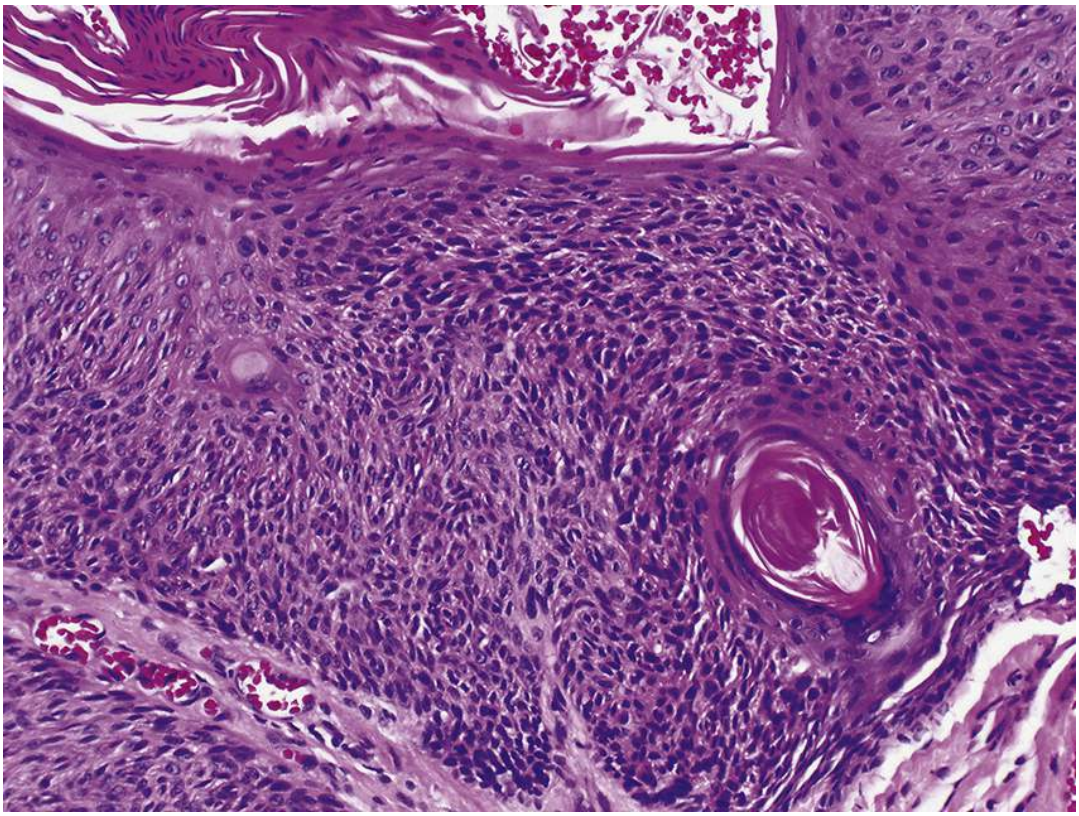

FIGURE 145.5 In situ squamous cell carcinoma arose in a background of actinic keratosis in the right upper eyelid of a man in his early 70s. Cytologically atypical keratinocytes extend through the entire thickened epidermis. The neoplastic cells lack their normal polarity. The surface of the tumor has a layer of parakeratosis.

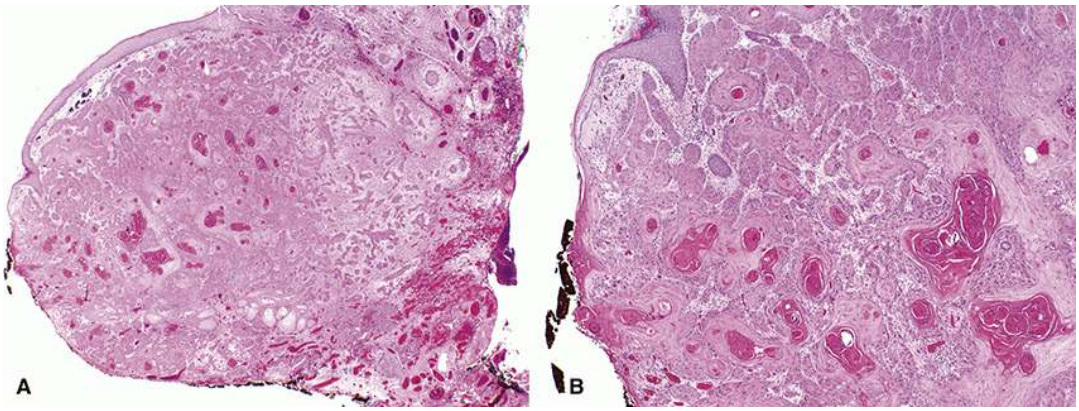

FIGURE 145.6 A, This well-differentiated squamous cell carcinoma (SCC) involved the full thickness of the right lower eyelid in a man who was immunosuppressed following solid organ transplantation. B, The tumor arose along the eyelid margin in an area of in situ SCC. Numerous keratin pearls are evident. C, Squamous cell carcinoma invaded the tarsus with tumor nests adjacent to meibomian glands. D, The tumor cells are pleomorphic with brightly eosinophilic cytoplasm and form keratin pearls, solid nests, and irregular islands. The tumor stroma has an infiltrate of macrophages, lymphocytes, and eosinophils. E, Intercellular bridges are prominent in this tumor island. F, Tumor invades the perineurium and parenchyma of a nerve.

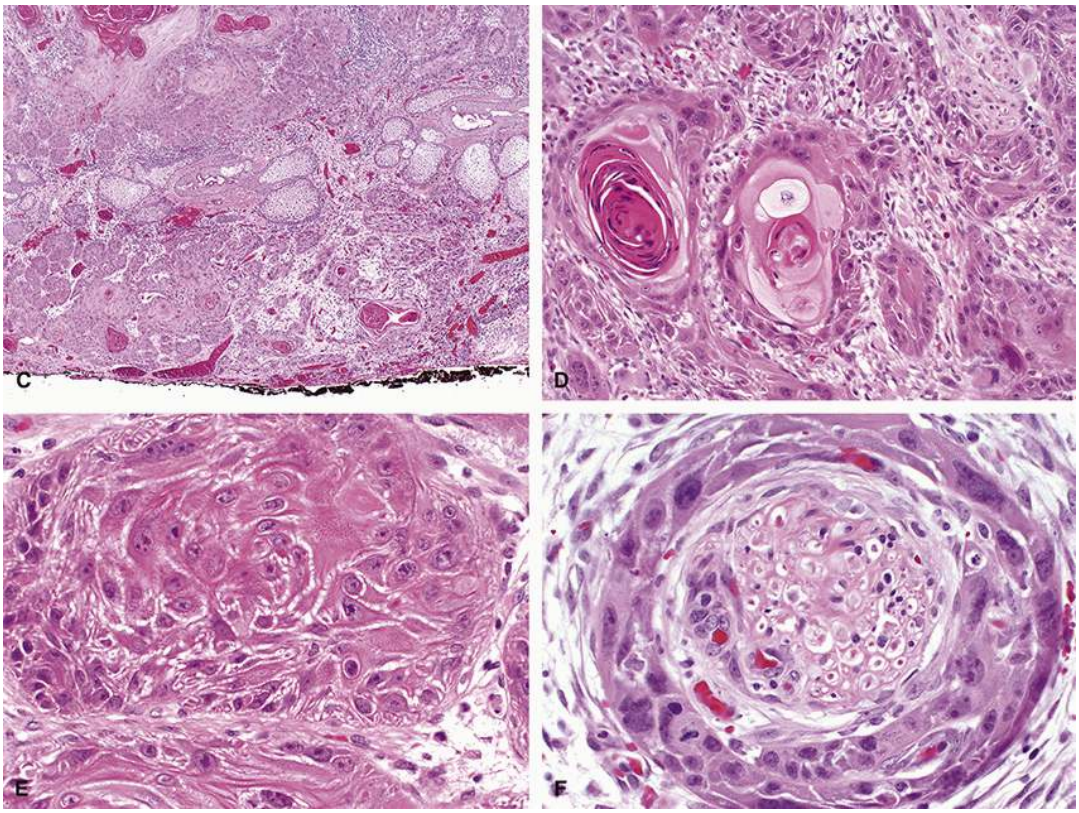

FIGURE 145.6 Continued

There are only rare reports of SCC arising from the palpebral conjunctiva (Figures 145.7 and 145.8),[62,63] including one example of a clear cell SCC.[64] The paucity of reports of palpebral conjunctival SCC prohibit generalizing their histopathological findings, but these tumors will presumably exhibit varying degrees of differentiation similar to bulbar conjunctival SCC.[65]

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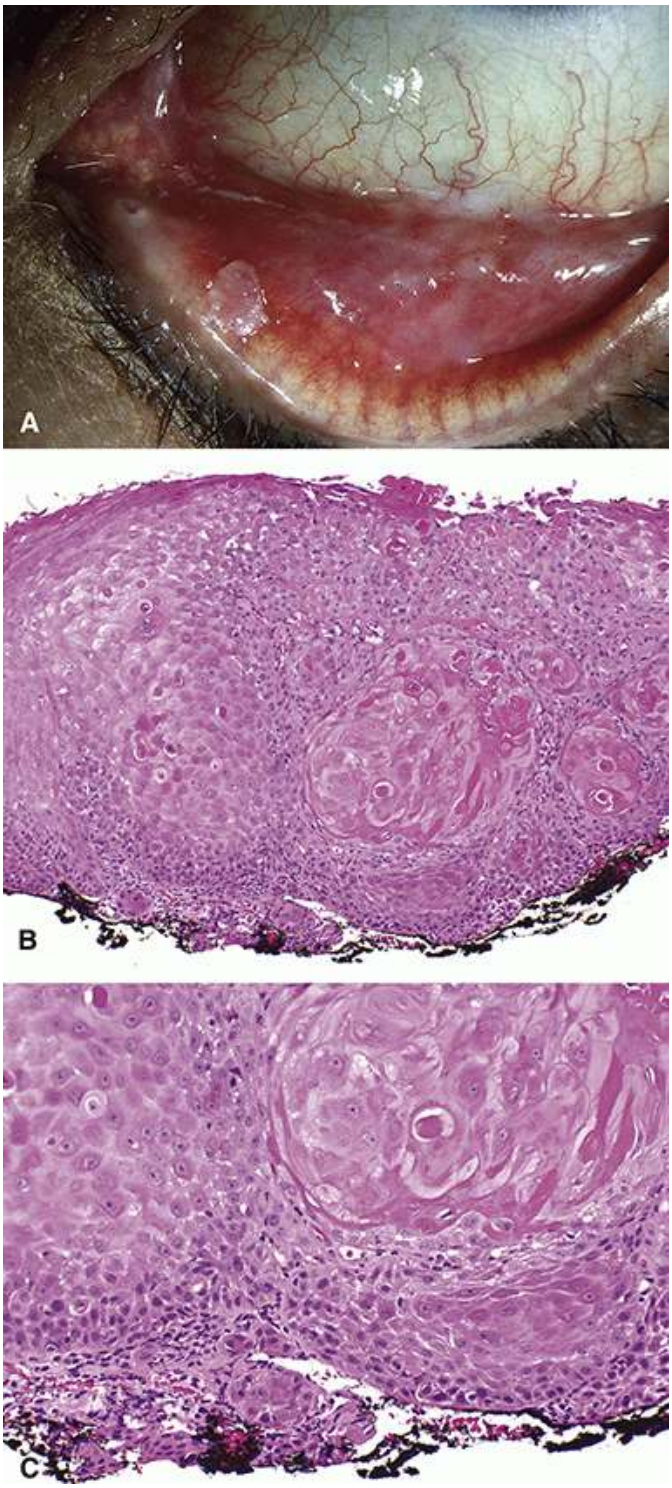

FIGURE 145.7 A, Well-differentiated squamous cell carcinoma developed in a woman's medial left lower eyelid palpebral conjunctiva. B, Tumor cells occupy the entire thickness of the epithelium. The black ink at the base of the tissue was for orienting the specimen. C, At the base of the lesion, a few small tumor nests are in the superficial substantia propria (superficially microinvasive squamous cell carcinoma).

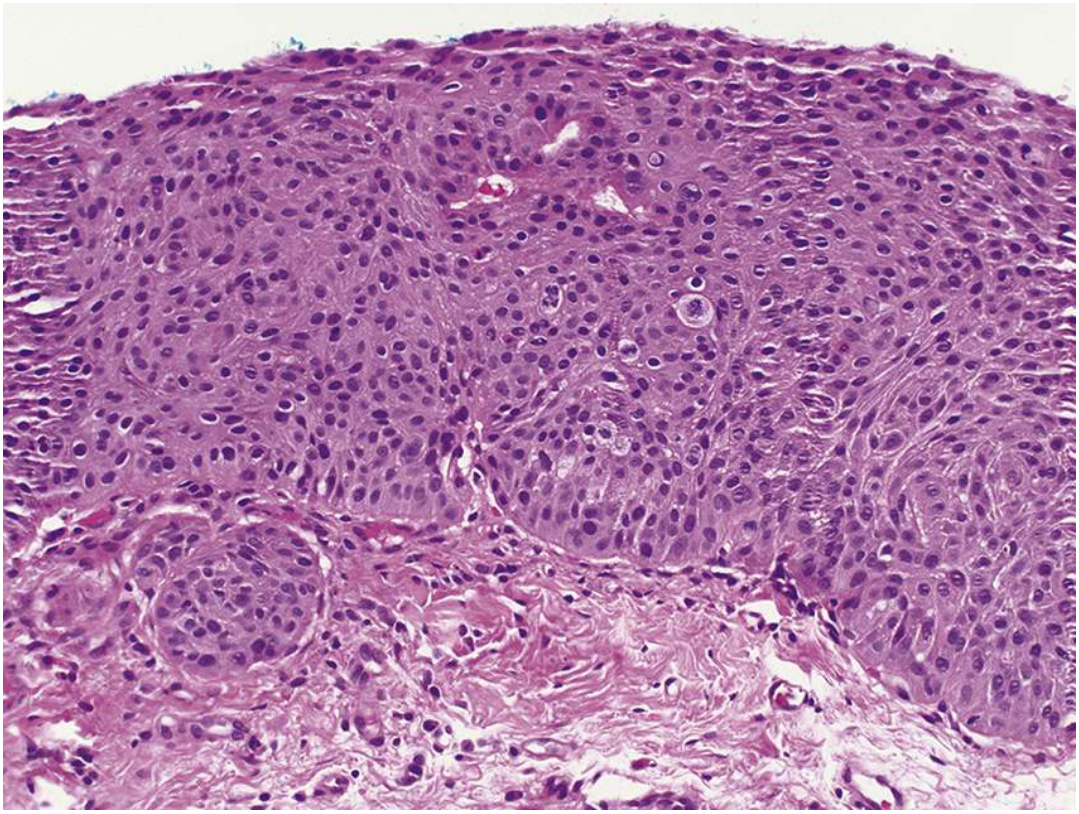

FIGURE 145.8 Superficially microinvasive, moderately differentiated squamous cell carcinoma of the right inferior forniceal conjunctiva from a man in his 80s.

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CHAPTER 146

Trichilemmal Carcinoma

Key Points

- Trichilemmal carcinoma (TC) derives from the outer hair root sheath
- The pathogenesis of TC is not completely understood, but risk factors include UV and ionizing radiation, previous trauma, scars, genetic disorders, and immunosuppression
- Lesions generally present as an asymptomatic tan or flesh-colored solitary, nodular, polypoid, or exophytic lesion, occasionally with ulceration, telangiectasias, and scales
- The recommended treatment of TC is complete surgical excision with wide margins
- Neoadjuvant radiotherapy has been proposed to shrink the tumor before definitive surgical resection, and chemotherapy has been used for distant metastases with limited success
- TC does not usually recur and has a low metastatic potential, but patients with metastasis currently have a poor prognosis

Cutaneous adnexal carcinomas are very rare and represent only 0.005% of all skin tumors.[1] These neoplasms have a heterogeneous origin from different adnexal hair follicle structures and originate from a variety of undifferentiated stem cells.[2] Hair follicle malignancies comprise only 1% of all skin adnexal carcinomas.[3]

Anatomically, the mature hair follicle is divided into several segments distinguished by their vertical position and by their cellular organization and morphology.[4] The deepest portion of the follicle is the bulb, consisting of a central dermal papilla of mesenchymal tissue. This is surrounded by the hair matrix cells of rapidly proliferating keratinocytes that produce the hair shaft. The stem and isthmus are the lowermost and lower portions of the follicle between the bulb and the upper portion called the infundibulum. An inner root sheath is continuous along the bulb and the stem, disappearing at the isthmus, and forms a channel for the growing hair shaft. The outer root sheath is an extension of the epidermal basal layer and envelopes the entire hair follicle. Its lower segment serves as a reservoir of stem cells.

Hair follicle adnexal tumors constitute a large variety of rare benign and malignant neoplasms that arise from the various segments and cellular components of the hair follicle. Trichoblastoma and trichoblastic carcinoma arise from hair germ cells. The hair matrix gives rise to pilomatrixoma (calcifying epithelioma of Malherbe) and pilomatrix carcinoma. Trichilemmoma, proliferating trichilemmal tumors (PTTs), and trichilemmal carcinoma (TC) derive from the outer hair root sheath. Trichofolliculomas are considered to be hamartomas with follicular differentiation, although some authors consider them to represent an abortive differentiation of pluripotent skin cells toward hair follicles.[5]

Currently, there is no generally accepted classification of hair follicle tumors. In 1976, Headington first proposed a classification based on histogenetic features.[6] Mehregan[7] later simplified this into three subgroups: hyperplasias, adenomas, and epitheliomas. More recently, Sia et al[8] published a basic classification of benign and malignant hair follicle tumors according to their cellular origin, as hair germ tumors, hair matrix tumors, and external hair root sheath tumors. In that same report, the authors reviewed 19 previously published case reports of malignant hair follicle tumors occurring in the periorbital region, and among these, there were nine cases of pilomatrix carcinoma, six cases of TC, three cases of malignant proliferating trichilemmal tumor (MPTT), and one case of trichoblastic carcinoma.[8]

The pathogenesis of hair follicle malignant tumors is largely unknown, and it is unclear whether they arise de novo or from preexisting benign lesions. One of the lesions derived from the outer hair root sheath is the trichilemmal (pilar) cyst,[9] which is believed to give rise to PTT with solid/cystic trichilemmal differentiation. Ninety percent of PTTs occur on the scalp, but they have also been found on the forehead, nose, back, chest, abdomen, buttocks, elbow, wrist, mons pubis, and vulva.[10,11] Most patients are female (84%), with a mean age of 65 and a range of 28 to 88 years, and most cases occur in the sixth and seventh decades of life.[9]

Malignant transformation of PTT to MPTT occasionally occurs, heralded by sudden rapid growth,[12,13] an aggressive biologic behavior, and a high rate of recurrence and metastasis. MPTTs are closely related to TCs and occur more commonly in areas with excess hair growth, such as lanugo hair follicles of the bald scalp, and less commonly in areas devoid of nonterminal hair.[14] The gross appearance can range from a smooth mobile nodule to a large lobular or multiple cystic lesion and tends to have more extensive hyperkeratosis and a greater number of cysts compared to TC.

The trichilemmoma is another benign lesion of the outer hair root sheath that is believed to be a precursor of TC.[15] Trichilemmoma is more commonly found on sun-exposed areas of the skin, particularly the face, forehead, and scalp. This distribution is likely related to the higher concentration of skin appendages in these areas.[16] Malignant degeneration may result in TC, first described by Headington in 1976[6] as *(Print pagebreak 985)* "a histologically invasive, cytologically atypical clear cell neoplasm of adnexal keratinocytes that is in continuity with the epidermis and/or follicular epithelium." The existence of TC has been a subject of debate because of its resemblance to clear cell squamous cell carcinoma, but more recent investigations have confirmed its existence as a distinct entity.[17]

Although TC is characterized histologically with features characteristic of malignancy, more benign-appearing lesions can behave aggressively, and malignant-appearing ones can show a relatively benign course.[18] In general, these tumors run an indolent course with a low rate of recurrence following surgical excision and a low metastatic potential. However, despite being commonly regarded as having an indolent clinical course, metastases and multiple recurrences have been reported.[15,19,20,21,22,23,24]

Etiology and Pathogenesis

The pathogenesis of TC and the malignant proliferative trichilemmal tumor is not completely understood. Many risk factors have been identified including UV and ionizing radiation, previous trauma, scars, genetic disorders, and immunosuppression. TCs are usually found on sun-exposed surfaces of elderly patients, suggesting that UV radiation plays a role in their pathogenesis. Chan et al[25] suggested a role for ionizing radiation in a case of TC arising in the supraclavicular region of a patient who had received many chest X-rays and CT scans to this area. Hamman et al[26] summarized 103 reported cases associated with a wide variety of pre-existing conditions. Ko et al[27] reported two cases arising in a burn scar. Reis et al[28] and Mane et al[29] reported cases of TC in young patients with xeroderma pigmentosum. Molecular studies of TC have been very limited, but Ha et al[30] evaluated four patients and found 3 (75%) with *TP53* and *P53* mutations or deletions, 2 (50%) with *TACC3-FGFR3* and *ROS1-GOPC* gene fusions, and isolated cases of *NRAS* and *PTEN* mutations or deletions.

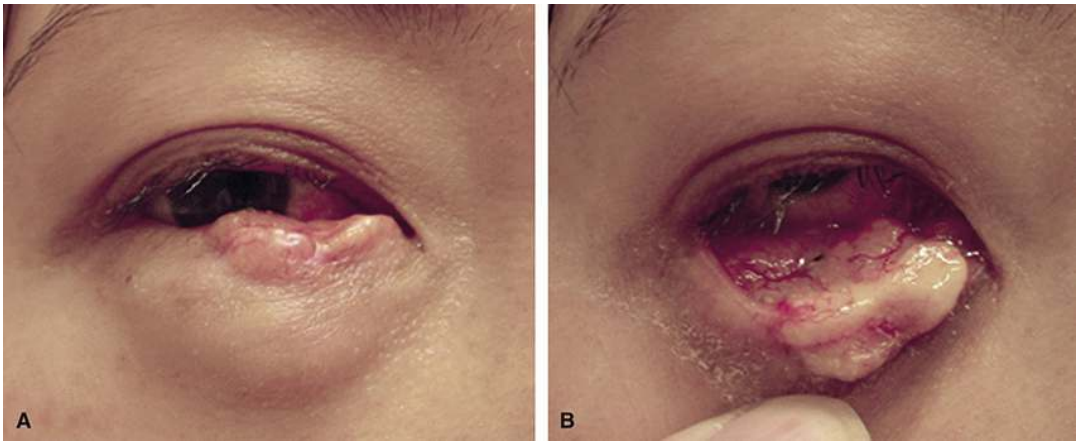

FIGURE 146.1 A, Trichilemmal carcinoma on the lower eyelid margin. B, Same patient as in A, showing the conjunctival surface. (A and B, Courtesy of Dr. Yoon Duck Kim.)

Clinical Presentation

Lesions of TC generally present as a painless tan or flesh-colored solitary, nodular, polypoid, or exophytic lesion, occasionally with ulceration on the face, scalp, and neck[26] (Figure 146.1). It may be associated with madarosis and can have telangiectasias, scales, or rolled borders that resemble basal cell carcinoma, squamous cell carcinoma, keratoacanthoma, or a proliferating pilar cyst.[28,31] Occasionally areas of ulceration and bloody discharge are seen. On presentation, lesions are generally about 2 cm in size but can range from 5 mm to 7.5 cm.[26]

Very few cases of TC have been reported on the eyelid.[26,31,32] Hamman and Jiang[26] reviewed 103 cases of TC from the literature and found 50% on the face. Among these, 18% were on the cheeks, 10% on the forehead, 9% on the nose, 6% on the temple, and 4% on the eyelids. The remaining cases were on the scalp, ears, neck, or elsewhere on the body. The mean age at presentation was

70 years (range 9-93), with less than 5% occurring in patients younger than 40 years.[26] The male to female ratio was about 3:2. Lesions of TC are usually present for less than 1 year before diagnosis, although some lesions have had a reported duration as little as 2 months or as much as 50 years.[33,34]

Differential Diagnosis

The overall clinical appearance is similar to other cutaneous lesions, especially malignancies so that the differential diagnoses of TC includes squamous cell carcinoma, basal cell carcinoma, keratoacanthoma, pilomatrixoma, dermatofibrosarcoma protuberans, cylindroma, angiosarcoma, seborrheic keratosis, chalazion, and epidermoid cyst.[26,35,36,37] The correct diagnosis is usually not suspected until the biopsy and the tumor is differentiated on histopathology.

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Treatment

The recommended treatment of TC is complete surgical excision with wide margins.[26,33,34] Recurrences are uncommon but may be seen following incomplete resections. In a review of 103 TC cases from the literature, 35 cases were treated with surgical excision with a mean follow-up of 33 months.[26] A local recurrence was reported in three cases, and two cases experienced three recurrences despite histologically free margins.[26] Although rare, metastatic disease has been reported even after wide local excision.[22] Mohs micrographic surgery may offer better margin control, especially in cosmetically and functionally important areas such as the eyelids. Mohs micrographic surgery also limits excessive excision of healthy tissue.[15,37,38,39,40,41]

Neoadjuvant radiotherapy for hair follicle malignancies has been proposed to shrink the tumor before definitive surgical resection.[39,42] Chemotherapy has been used when distant metastases were found but has been reported to have limited success.[39] Although chemotherapy similar to regimens used for squamous cell carcinoma has been used, there is no established protocol for metastatic TC.

Prognosis

Only a limited number of studies investigating TC are available, so that prognosis is difficult to estimate.[43] Although TC has a low metastatic potential and does not usually recur, local recurrence and deep invasion are possible.[32] Local cervical lymph node and distant metastases have rarely been reported.[21,33,34] But since there is no optimal treatment for TC metastasis, and there is no established chemotherapy regimen for metastatic disease, patients with metastases currently have a poor prognosis.[22] Although supported by limited data, the risk of recurrence and lymph node metastasis appears to be similar to that of squamous cell carcinoma.[43]

Histopathology

The histopathological features of TC[44] are best described in three studies examining 7-10 tumors (Figure 146.2).[19,28,31] Swanson and coworkers studied 10 tumors and noted 7 diagnostic features: (1) TCs are centered on and often expand pilosebaceous units; (2) TCs exhibit varying degrees of cytological atypia but always have nuclear enlargement with hyperchromasia, prominent nucleoli, and mitoses ranging from 4 to 39 per 10 high-power (400×) microscopic fields; (3) tumor cells with palely eosinophilic or clear cytoplasm due to glycogen accumulation usually predominate; (4) there is trichilemmal keratinization with an abrupt transition from neoplastic cells to keratin without a granular layer; (5) tumors have an abrupt interface with the adjacent normal epidermis, i.e., there is not a transitional zone of dysplastic epidermis; (6) neoplasia involved the interfollicular epidermis near the center of the tumors in seven *(Print pagebreak 987)* cases, and seven tumors were ulcerated; and (7) all cases have "conspicuous" dermal actinic elastosis.[19] Boscaino and colleagues studied seven TCs and noted sharply circumscribed lobular neoplasms in continuity with the epidermis, neoplastic cells with clear glycogen-rich cytoplasm, trichilemmal keratinization, and high mitotic rates.[31] The basal layer of neoplastic lobules "showed a tendency toward palisading and was associated with a prominent basement membrane."[31] Four of the tumors were intraepithelial, and three were invasive.[31] Reis and collaborators examined eight invasive tumors, and all TCs had invasive lobules and strands composed mainly of polygonal cells with glycogen-rich clear cytoplasm, trichilemmal keratinization, many mitoses, and nuclear atypia varying from mild to severe.[28] The tumors all displayed multiple connections with the overlying epidermis with replacement by neoplastic cells.[28] TCs lack immunoreactivity for carcinoembryonic antigen[28,31] and S100 protein.[28] Expressions of cytokeratins 1, 10, 14, and 17 suggest differentiation toward follicular infundibulum.[45]

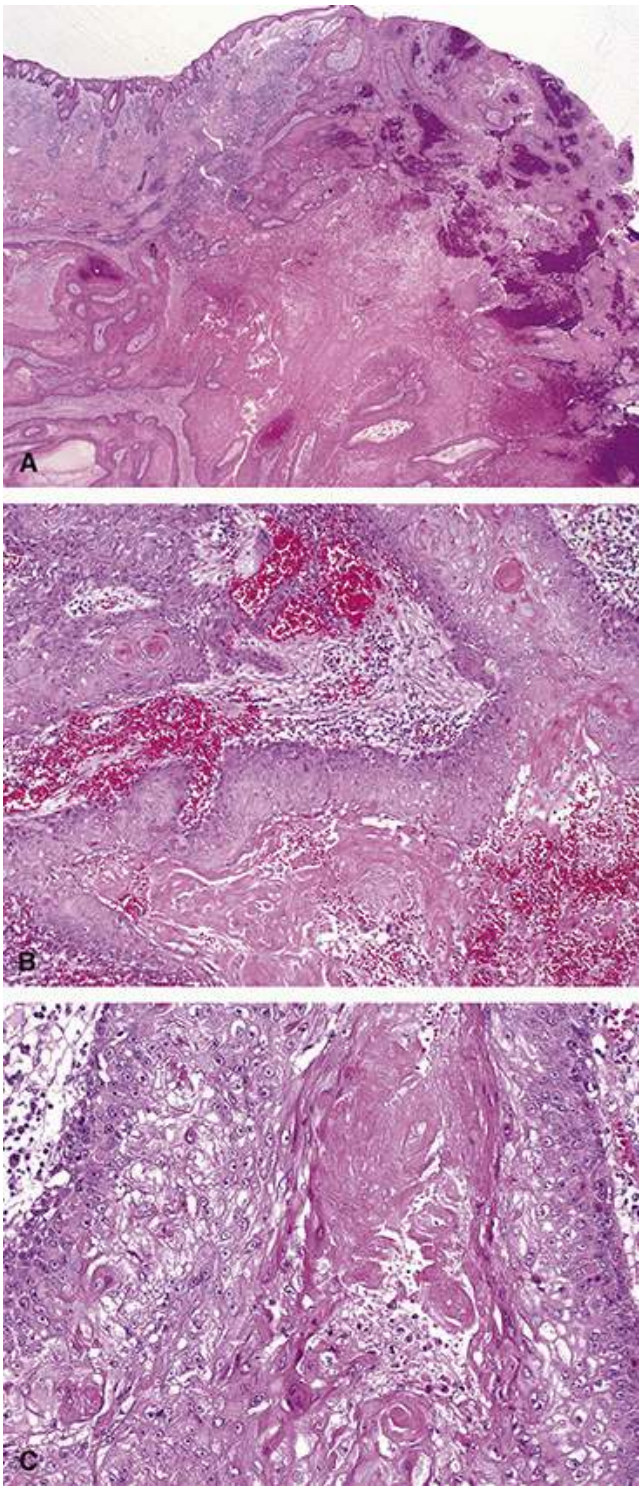

FIGURE 146.2 A, Trichilemmal carcinoma of the scalp showing an abrupt transition from the normal epidermis to an ulcerated, hemorrhagic, invasive tumor composed of lobules and interconnecting cords. B, The interdigitating tumor cords are in a desmoplastic and hemorrhagic stroma. Tumor cells with pale eosinophilic or clear cytoplasm due to abundant cytoplasmic glycogen predominate. The tumor cords have areas of keratinization. C, Tumor cells with clear cytoplasm are evident at higher magnification. Trichilemmal keratinization features an abrupt transition from neoplastic cells to keratin without a granular layer.

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CHAPTER 147

Undifferentiated Pleomorphic Sarcoma (Malignant Fibrous Histiocytoma)

Key Points

- Undifferentiated pleomorphic sarcoma (UPS) describes a soft tissue tumor of primitive mesenchymal origin that involves deep skeletal muscle, fascia, and adipose tissue
- The pathogenesis is unclear, but translocations and gene fusions common in the pathogenesis of other sarcomas have not been found to play a role in the pathogenesis of UPS
- Ionizing radiation appears to be an etiologic factor, and has been reported following radiotherapy for breast carcinoma, malignant lymphoma, cervical carcinoma, and brain tumors
- Clinically, UPS presents as a rapidly enlarging, painless soft tissue swelling and a palpable brownish indurated mass that may be ulcerated with deep invasion of muscles, nerves, periosteum, and bone
- The primary treatment is radical surgical excision with wide margins along with dissection of regional lymph nodes
- Radiotherapy and chemotherapy are of limited benefit
- The recurrence rate is high and 28% may develop distant metastasis with an overall 5-year survival between 35% and 70%

Undifferentiated pleomorphic sarcoma (UPS) was established as a distinct entity by Kauffman and Stout in 1961.[1] It has most often been referred to in the literature as malignant fibrous histiocytoma (MFH) and less frequently as a malignant solitary fibrous tumor. In recent years it has been considered to represent a heterogeneous group of undifferentiated neoplasms. In 2002, the World Health Organization (WHO) declassified MFH as a diagnostic entity and renamed it "undifferentiated pleomorphic sarcoma."[2] This terminology has been supported by evidence suggesting that these tumors represent a final common pathway in tumors progressing toward undifferentiation.[3,4,5,6] However, the term "malignant fibrous histiocytoma" is still commonly used in the literature.

UPS describes a group of soft tissue tumors of primitive mesenchymal origin that involve deep skeletal muscle, fascia, and adipose tissue.[7] However, it can also rarely involve many other tissues such as the heart, pancreas, stomach, and maxillary sinuses. It is the most common soft tissue sarcoma of adulthood but also can be seen in young adults and children, although it is rare in patients younger than 20 years old.[8,9,10,11] Ten percent of these tumors occur on the head and neck, and although it is well known in the orbit,[12,13,14] it only rarely affects the eyelids. When it is seen in the eyelid, it is usually either secondarily extended from an orbital lesion or occurs as a simultaneous independent occurrence. Less than a dozen cases of primary UPS of the eyelid have been described to date,[15,16,17,18,19,20,21,22] and one case of a locally aggressive fibrous histiocytoma was reported in the medial canthus.[23] UPS is also occasionally reported in the conjunctiva.[24]

Etiology and Pathogenesis

Soft tissue sarcomas comprise a large heterogeneous group of tumors that often exhibit aggressive behavior with high morbidity and mortality. Many sarcomas arise due to chromosomal aberrations or mutations in mesenchymal progenitor cells. However, the exact cellular origin of most of these tumors remains uncertain.[25] Genetic abnormalities in sarcomas are common and are divided into two types. The first includes tumors that are characterized by specific genetic mutations, simple karyotypes, and translocations that can result in the formation of fusion genes that can alter the regulatory proteins or transcription factors in tumor cells and contribute to tumorigenesis.[26] The second type includes sarcomas with no specific mutations or chromosomal aberrations, but instead involves complex karyotypes with copy number genetic losses of tumor suppressor genes and amplification of proto-oncogenes that favor oncogenesis.[27] Interestingly, a variety of translocations and gene fusions common in the pathogenesis of other sarcomas have not

been found to play a role in the pathogenesis of UPS.[26,28]

A well-known etiologic factor for UPS is ionizing radiation, and this has been reported following radiotherapy for breast carcinoma, malignant lymphoma, cervical carcinoma, and brain tumors.[29] The most common radiation-induced sarcomas (RIS) are osteogenic sarcoma (36.4%) and UPS (33.3%).[29] The mechanisms resulting in the oncogenesis of RIS involve damage to DNA that results in genomic instability.[30] Radiotherapy has been used in the treatment of head and neck neoplasms, but radiation-induced secondary sarcomas in this region are uncommon, and the annual incidence has been estimated to be only 0.06% to 0.17%,[31,32] compared to an incidence of 1.6% reported for the entire body.[33] Nevertheless, UPS of the head and neck has been described after irradiation for nasopharyngeal tumors and retinoblastoma.[34,35,36,37,38,39,40]

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Clinical Presentation

The age at presentation for UPS can range from childhood to the ninth decade (range, 6-87 years), with a mean of about 67 years.[41] For eyelid lesions, the few reported cases range in age from 70 to 90 years. The duration of symptoms is variable from 1 month to 20 years (mean = 31 months) for benign fibrous histiocytoma to 1 month to 5 months (mean = 3.4 months) for malignant UPS.[7] Overall, UPS shows a high histologic grade, and 90% have deep invasion at the time of presentation.[42] Eyelid and periorbital involvement are rare with less than a dozen cases reported.[16,17,18,19,20,21,22,23,24,34] Females are involved more frequently than males with a F:M ratio of 4:2.

Presentation is typically with a rapidly enlarging, painless soft tissue swelling and a palpable brownish indurated mass on the eyelid or conjunctiva (Figures 147.1 and 147.2), and that may rarely be ulcerated. There may be deep invasion of muscles, nerves, periosteum, and bone, or even extension into the orbit.

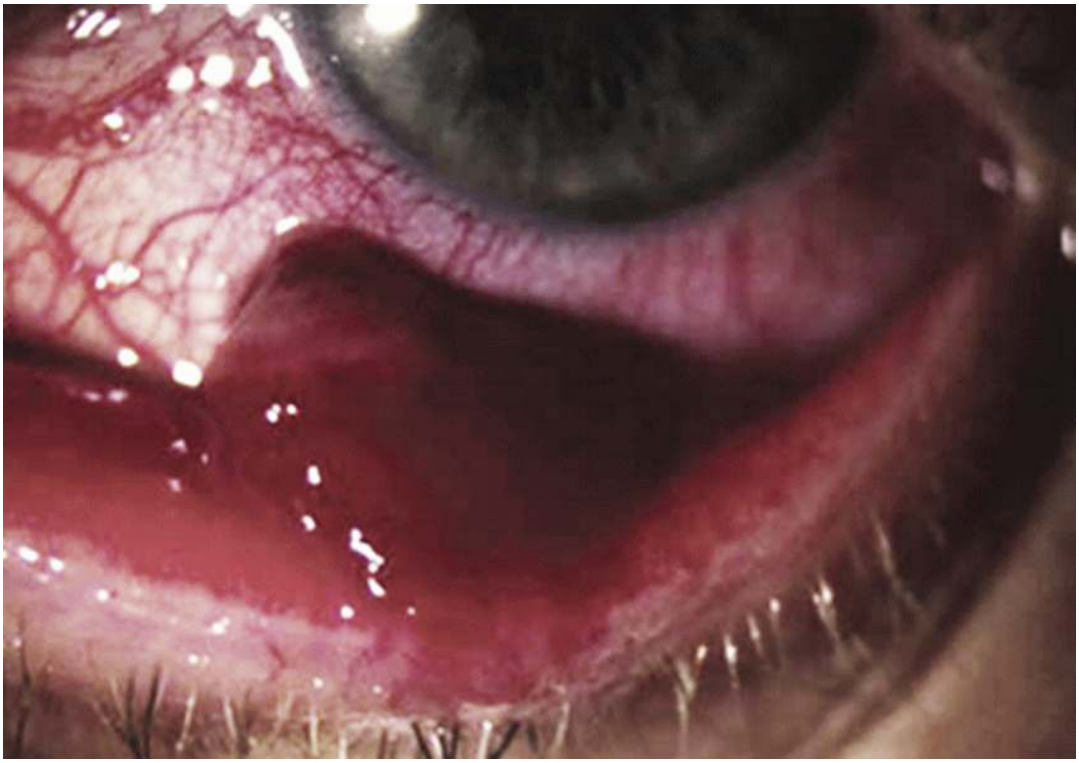

FIGURE 147.1 Large nodular undifferentiated pleomorphic sarcoma on the lower eyelid mucocutaneous border. (Courtesy of Dr. Timothy Sullivan.)

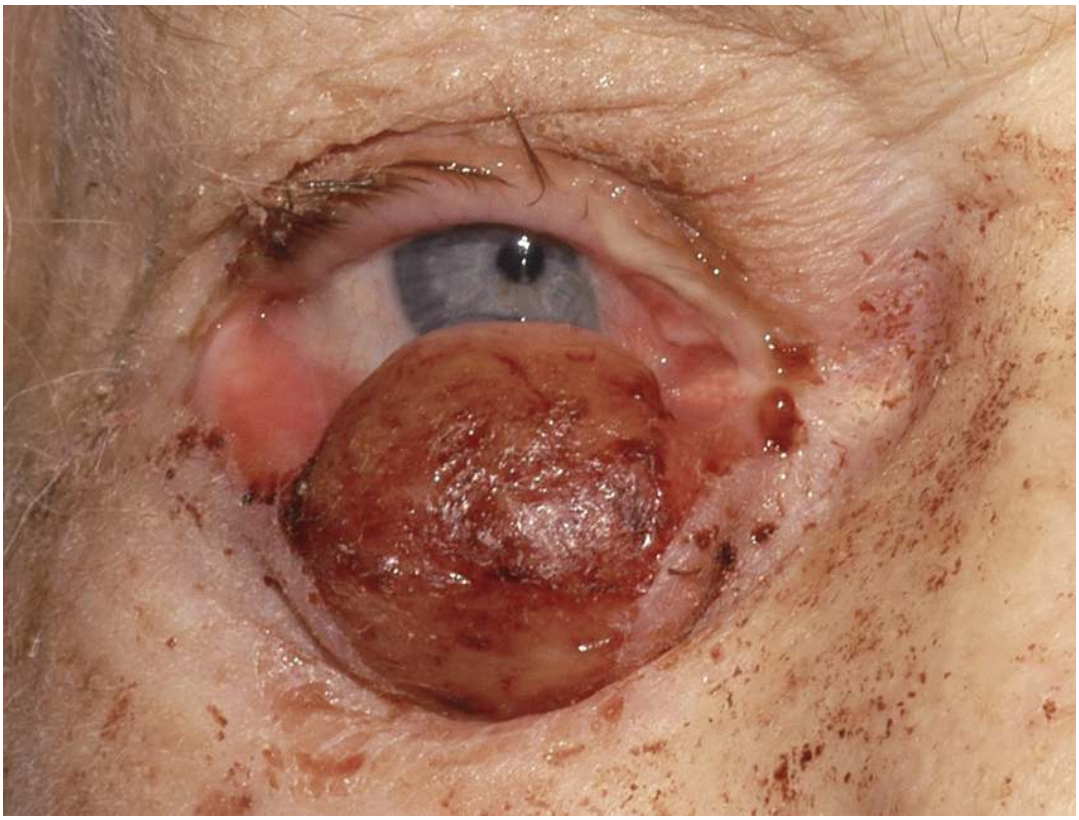

FIGURE 147.2 Undifferentiated pleomorphic sarcoma arising in the palpebral conjunctiva. (Reprinted with permission from Gounder P, Lamb M, Vinciullo C, de Sousad JL. Malignant fibrous histiocytoma masquerading as pyogenic granuloma. *Orbit*. 2017;36:122-123.)

Differential Diagnosis

Clinically, UPS has been confused with inflamed pterygium, juvenile xanthogranuloma, nodular fasciitis, foreign body granuloma, solitary fibrous tumor, leiomyoma, keratoacanthoma, amelanotic melanoma, and squamous cell carcinoma.[15,16,17,18,19,20,21,22,23,24] Pterygia are typically slowly enlarging vascular pink, triangular, or wing-shaped conjunctival lesions, more frequently on the nasal side that can extend onto the cornea. Juvenile xanthogranulomas are often multiple dome-shaped, pink to red papules or nodules that usually progress to a brown or yellowish color and may have telangiectasias or a scaly surface. Nodular fasciitis presents as rapidly growing, firm subcutaneous or submucosal lesions along fascia and occurs in younger patients in the 20 to- 40-year range.

The main histologic differential diagnoses of UPS extending in the superficial subcutis and dermis include spindle cell carcinoma, spindle cell malignant melanoma, leiomyosarcoma, fibrosarcoma, and malignant schwannoma. Other entities such as Kaposi sarcoma, dermal nodular fasciitis, and metastases may also be confused with this tumor.

Treatment

As with most sarcomas, the histologic grade of UPS is important in predicting the biologic behavior of the tumor and for planning the most appropriate management.[43,44,45,46] Kamat et al[42] reported 100% of 55 UPS to be high grade. The primary treatment for such lesions is radical surgical excision with wide margins along with dissection of regional lymph nodes.[41] Clear margins of resection are the most important factor in preventing a recurrence. In a series of 2084 microscopic resection margins of localized soft tissue tumors, positive margins nearly doubled the risk of local recurrence, metastasis, and disease-related death.[47] Wide surgical margins are associated with a better prognosis and reduced recurrence rates.[44,48,49] However, in the head and neck region, an adequate surgical margin is often limited because of the need to preserve tissue for a functional reconstruction, particularly in the periocular area. For this reason, histologically controlled surgical excision can be important. Although Mohs surgery has been advocated for UPS, and some investigators have reported lower recurrence rates than seen with wide surgical resection,[50,51,52,53] other studies showed no added benefit with Mohs surgery compared with wide margin resection.

Adjuvant radiotherapy UPS has been reported to reduce the rate of local recurrence.[43,54,55,56] However, several reports failed to show any added benefit for overall survival from the addition of radiotherapy.[41,42] Chemotherapy has limited use in the treatment of periocular UPS and has not been associated with improved recurrence or survival rates.[42,57,58]

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Prognosis

In a series of 36 cases of UPS, regardless of treatment, the recurrence rate was 47% over 3 years, and 28% developed distant metastasis.[41] There was no benefit from Mohs microsurgery or adjunctive radiotherapy compared with wide surgical resection alone. The overall 5-year survival for UPS has been reported to be between 35% and 70%, depending upon several prognostic factors.[7,43,44,46,59,60] Metastasis is seen in about 40% of cases, with the lung as the most common site.[43,45,61,62,63]

The most important prognostic factors that correlate with survival include tumor grade, depth of invasion, tumor size, metastatic status, patient age, and histologic subtype.[64,65,66] Favorable prognostic factors include age less than 60 years, tumor size less than 5 cm, superficial location, low histologic grade, and the absence of metastatic disease.

Histopathology

Undifferentiated soft tissue sarcoma (USTS) is the current World Health Organization term encompassing undifferentiated spindle cell sarcoma, UPS, and undifferentiated round cell sarcoma.[67] Diagnosis of USTS requires “the absence of any morphological or immunohistochemical feature of specific differentiation; demonstrated absence of distinctive molecular aberration.”[67] Diagnosis of UPS, a subtype of USTS, thus requires the exclusion of pleomorphic leiomyosarcoma, pleomorphic rhabdomyosarcoma, dedifferentiated liposarcoma, extraskeletal osteosarcoma, and metastatic carcinoma and melanoma.[68,69] In the dermatopathology literature, UPS includes the entities termed “atypical fibroxanthoma,” “superficial UPS,” and “pleomorphic dermal sarcoma” when the tumor is superficial, while neoplasms arising deep to the dermal fascia are classified as UPS or deep UPS.[70,71]

UPS has variable architectural patterns ranging from patternless to storiform to fascicular (Figures 147.3 and 147.4), with frequent transitions between storiform and pleomorphic areas.[72] Tumor cells may be pleomorphic spindle cells (Figure 147.3), plump fibroblast-like cells, or multinucleated giant cells with hyperchromatic irregular nuclei and brightly eosinophilic cytoplasm (Figure 147.4).[72] There may be numerous typical and atypical mitotic figures.[72] UPS may have focal myxoid change, a hemangiopericytoma-like vascular pattern, and there may rarely be metaplastic osteoid or chondroid.[72] The stroma may feature xanthoma cells and chronic inflammatory cells.[72] UPS may have focal immunoreactivity for smooth muscle actin or cytokeratins, but the staining should not be diffuse.[72] Tumor cells typically lack immunoreactivity for the smooth muscle markers desmin and h-caldesmon; the skeletal muscle markers myogenin and MyoD1; the liposarcoma markers MDM2 and CDK4; the extraskeletal marker SATB2; the melanoma markers S100 protein and SOX10; and cytokeratins.[68] UPS is negative for CD34 expression characteristic of solitary fibrous tumor and dermatofibrosarcoma protuberans. UPS's histological *(Print pagebreak 992)* grading incorporates tumor differentiation (score 3 for undifferentiated sarcomas), mitotic count, and the amount of tumor necrosis.[73,74] Pleomorphic dermal sarcoma, the superficial analog of UPS, shares histological and immunohistochemical features with UPS (Figure 147.5).[70,71,75,76] Deeper depth of invasion,[70,76] the presence of lymphatic or vascular invasion,[70] and positive resection margins[76] are predictors of a poorer prognosis in atypical fibroxanthoma/pleomorphic dermal sarcoma.

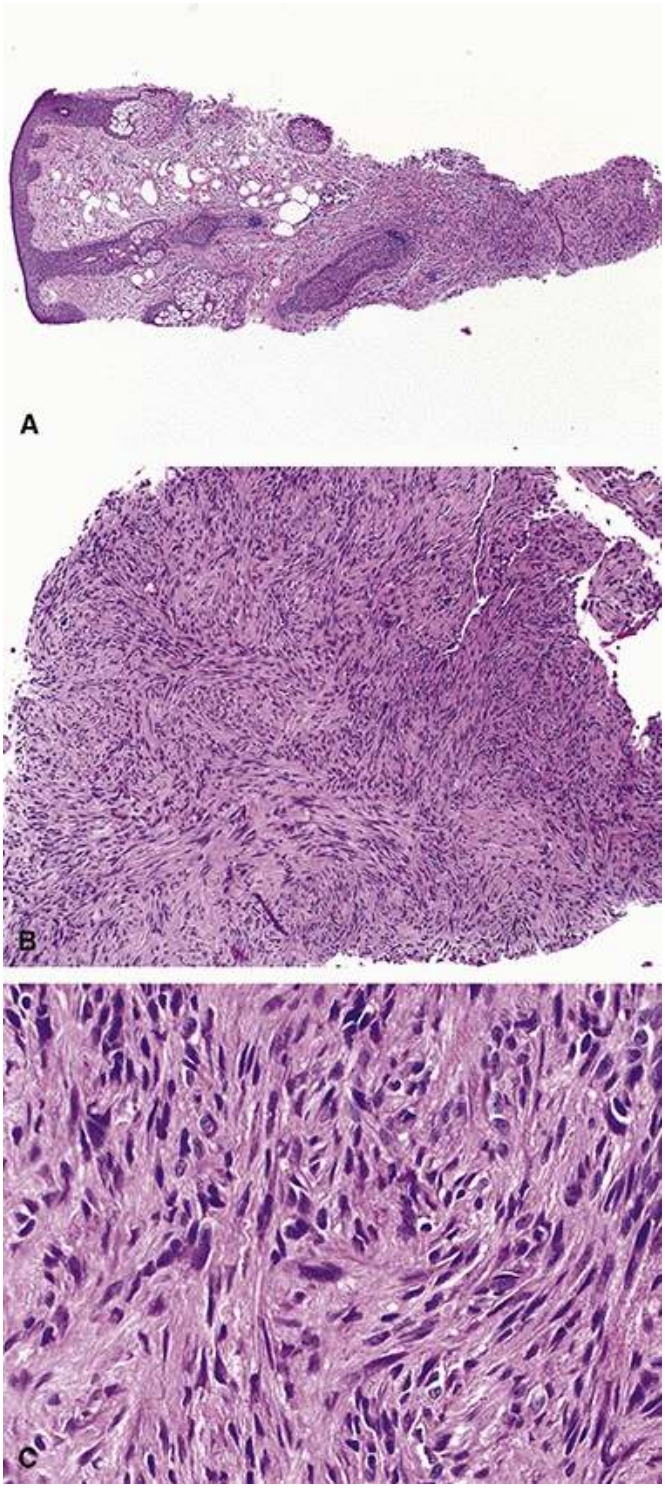

FIGURE 147.3 This undifferentiated pleomorphic sarcoma (UPS) formed a 1-cm diameter, mobile, subcutaneous nodule in the lateral right upper eyelid beneath the eyebrow of a woman in her middle 50s. Following the biopsy, the nodule was completely excised by Mohs micrographic surgery; there has been no recurrence after 10 years. A, The UPS is centered in the subcutaneous tissue on the right side of the photomicrograph. B, The tumor cells form fascicles with a storiform pattern. C, Pleomorphic plump fibroblasts form the fascicles. The tumor cells lacked any immunohistochemical markers for differentiation leading to the diagnosis of UPS.

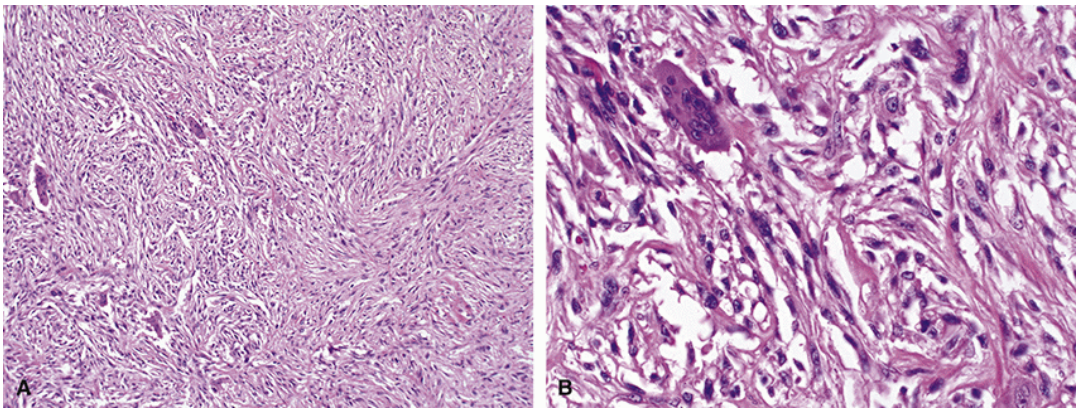

FIGURE 147.4 This undifferentiated pleomorphic sarcoma arose in the right superomedial orbit and recurred following biopsy and Mohs micrographic surgery. Orbitotomy with attempted resection had positive surgical margins, and orbital exenteration was subsequently performed. The tumor recurred following orbital exenteration, and the patient died with metastatic disease. A, The orbital tumor has a storiform pattern with numerous multinucleated giant tumor cells. B, Plump spindle cells with multinucleated giant cells having brightly eosinophilic cytoplasm compose the tumor. The tumor cells lacked immunophenotypic evidence of differentiation.

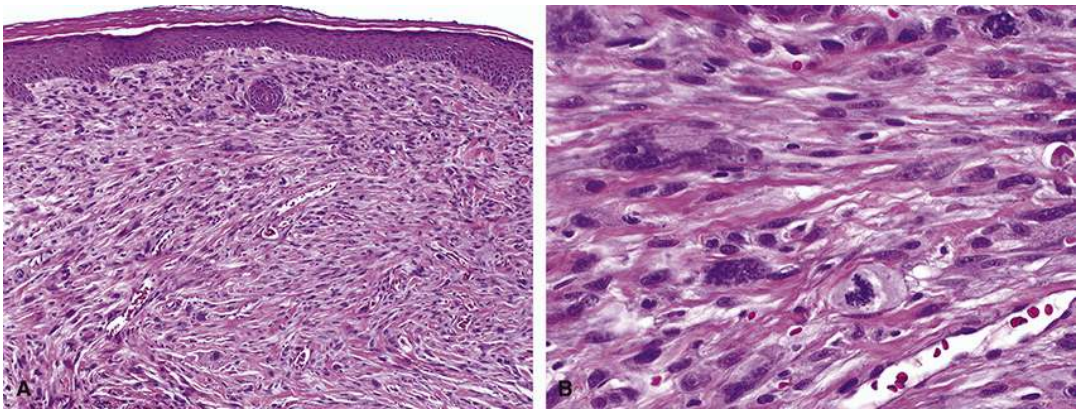

FIGURE 147.5 This atypical fibroxanthoma/dermal pleomorphic sarcoma (superficial undifferentiated pleomorphic sarcoma) arose on the frontal scalp of an octogenarian man. A, Plump spindle tumor cells are in the superficial reticular dermis, replace the papillary dermis, and abut the epidermis. B, The tumor has many multinucleated giant tumor cells. An atypical mitotic figure is at the right of a multinucleated giant cell.

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