

All Dimensions of Pathology

Volume 2: Clinical Aspects

Gulden Diniz
Editor

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Izmir Democracy University Medical School

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*This book is dedicated
to İsmet, Eylül, and Nazım Ünlü, who enriched my life,
to Nazım Kemal, Günsel, and Ahmet Rıza Diniz, who taught me
to fly with my wings and always encouraged me to continue,
to my dear friends, who warm my heart with their presence or
memories,
to my eminent colleagues who inspired me,
to my lovely students who challenged me with their curiosity...*

Gulden Diniz

Preface

I am sure that the new pathology book project did not seem very exciting to any of you. You could not make sense of adding another book to the abundance of pathology books on the market. There are indeed many pathology books in print. There are multivolume, multi-paged, and quite comprehensive pathology books, as well as books that contain summarized information explaining the basic mechanisms of pathology... In fact, due to the gradual expansion of our knowledge base, the old multivolume pathology books have now been divided into many comprehensive books examining each organ or each technique. However, since the stages of writing, editing, and printing take at least 8–10 months depending on the capacity of the book, no matter how up-to-date the books are, they always become outdated. That is why a pathologist can diagnose ordinary lesions without having to look at the book; in lesions where differential diagnosis is difficult, they use current articles rather than books. On the other hand, when a short professional update is needed in every field of pathology from time to time, these books can be overly detailed and confusing. Short student books, on the other hand, are not enough because they do not reveal all dimensions of pathology. This book is designed as a unique resource that adequately teaches all dimensions of pathology, which is sought by a medical student, a pathology resident, or a pathologist aiming to update their professional knowledge or to prepare for a professional exam.

One of the greatest revolutionaries in education is undoubtedly Feynman. The famous physicist who won the Nobel Prize in 1965 was also an extraordinary educator and developed the learning technique named after him. Feynman wrote many educational physics books, arguing that a person learns best while teaching. His most important goal while writing these books was to explain physics in the simplest and most understandable way possible. In fact, he claimed that someone who could not explain a subject in a simple way that even a child could understand did not actually understand that subject himself.

By applying the Feynman technique to pathology, this book aims to provide simple and concise information from all areas of pathology that even a new medical student can understand. Furthermore, our primary goal in future editions is to be the first pathology book ever published that will allow readers to examine and learn about basic lesions using virtual microscopy.

I hope that the book will enlighten everyone who wants to understand pathology in all dimensions...

İzmir, Türkiye

Gulden Diniz

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A Glance at Lesions of the Head and Neck: Oral Cavity, Nasopharynx, and Larynx

1

Ömer Günhan

1.1 Oral Cavity

The oral cavity, except for the hard palate and the attached part of the gums, is covered with the non-keratinized stratified squamous epithelium. The same stratified squamous epithelium extends to the oropharynx and hypopharynx. Above, it continues with the pseudostratified ciliated respiratory epithelium of the nasal and nasopharynx. The nasal vestibulum is lined with keratinized stratified squamous epithelium, while the nasal mucosa is lined with ciliated pseudostratified columnar epithelium. Mucus-secreting glands are located under the epithelium. The olfactory epithelium is a special epithelium located in the upper posterior part of the nasal cavity and lateral to the nasal septum, which serves to detect odors, and contains modified neurons that function as chemoreceptors. The nasal epithelium continues with the ciliated pseudostratified nasopharynx epithelium. The oropharynx is lined with the nonkeratinized stratified squamous epithelium. The sinuses are covered with the ciliated, columnar, pseudostratified Schneiderian epithelium. The primitive oral ectoderm invaginates into the jaw bones and differentiates into ameloblastic cells that form the dental lamina and later the tooth enamel. The mesenchymal tissues of the maxillofacial region differentiate from the neural crest; therefore it is also defined

as ectomesenchyme, and unlike somatic mesenchyme, it provides the development of teeth and jaw bones. At the back of the primitive oral cavity, the primitive oral ectoderm forms the Ratke's pouch recess in the roof of the nasopharynx and from there the anterior lobe of the hypophysis. Therefore, cysts and tumors similar to odontogenic lesions can be seen in the sella turcica region. In all these areas, there are no skin appendages under the epithelium in the mucosa, but there are serous and mucous minor salivary glands. Sometimes, ectopic sebaceous glands that form yellow, millimetric swellings on the cheeks can be found and are called Fordyce granules. In addition, teratomas, ectopic gastric or intestinal tissues, and lingual thyroid can be seen in these regions. White spongiform nevus, which is autosomal dominant, frequently involves bilateral buccal mucosa, and begins to present symptoms at a young age as a widespread white lesion, can be seen in the oral mucosa. Dyskeratosis is present in the mucosal epithelium in the form of irregular acanthosis, pronounced parakeratosis, suprabasal intraepithelial edema, vacuolization, and increased perinuclear eosinophilic condensation.

1.2 Inflammation of Teeth and Supporting Tissues

Tooth decay is the focal destruction of the teeth, first in the tooth enamel and then in the dentin, due to the mineral destruction caused by acids

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released as a result of the fermentation of sugars by the effect of oral bacteria. Caries is the most common cause of tooth loss in young people. Tooth decay progresses and can cause serous inflammation and pain and then infection of the dental pulp (pulpitis), and then the infection spreads to the tip of the tooth root, causing swelling in the surrounding tissues, osteomyelitis, and cellulitis in the soft tissues. Gingivitis is the inflammation of the soft tissues around the teeth caused by inadequate oral care leading to the accumulation of dental plaque and tartar. Treatment is by performing oral care that will ensure the healing of the gums and reducing the inflammation. Periodontitis is the inflammation that affects the supporting tissues of the tooth, namely, the periodontal fibers, alveolar bone, and cementum, and causes destruction. Periodontitis progresses and can result in the loss of the supporting tissues of the tooth and tooth loss. Periodontitis can contribute to the formation of systemic diseases such as rheumatoid arthritis with its high inflammation and tissue destruction effect.

1.3 Inflammatory Mucosal Lesions of the Mouth

Although the oral mucosa is open to trauma and is exposed to many infectious agents, it is a region resistant to inflammation due to saliva flow, effective mucosal immunity, and high blood flow. Most mucosal inflammations are due to immune deficiency states and dental infections. Special oral findings can be seen in some systemic diseases. In scarlet fever, a strawberry tongue appearance characterized by swelling, redness, and prominence of papillae on the tongue is a typical finding. In measles, before skin rashes are seen, mucosal ulcerations known as Koplik spots are seen as the first finding on the cheeks and in areas close to the Stensen duct. In infectious mononucleosis and diphtheria, fibrinous, exudative, gray-white pseudomembranous inflammation can be seen in the tonsils and pharyngeal region.

Traumatic Ulcerative Granuloma with Stromal Eosinophilia (TUGSE: Riga-Fede Disease) It is an ulcerative mucosal lesion that frequently develops after trauma and does not regress easily, therefore raising suspicion of carcinoma [1]. There is a polymorphic inflammatory infiltration and vascularized granulation tissue including eosinophil leukocytes at the ulcer base (Fig. 1.1). It is a benign lesion and regresses with excision. Similar persistent mucosal ulceration is seen in association with Epstein-Barr virus (EBV), which is frequently seen in immunosuppressed or elderly individuals (*EBV-positive mucocutaneous ulcer*). In these lesions, there is a B lymphocyte-dominant lymphoplasmacytic infiltration with polymorphic, some atypical, immunoblastic cells at the ulcer base. This appearance may suggest the possibility of a lymphoproliferative lesion such as diffuse large B cell lymphoma. Clinically, there is a localized ulcerated lesion. There is no lymphadenopathies, systemic involvement, or progressive development. Polymorphic infiltration contains CD20, CD30, and EBV-positive cells. Chemotherapy is applied to persistent lesions.

Hyaline Ring Granuloma It is a foreign body-type reaction that occurs when starchy foods pass into the tissues in open wounds and fistulized cystic lesions in the mouth. Phagocytosis of starchy foods causes hyalinized fibrotic nodules to form and a granulomatous reaction with foreign body-type giant cells around them. For this reason, it is also called pulse granuloma.

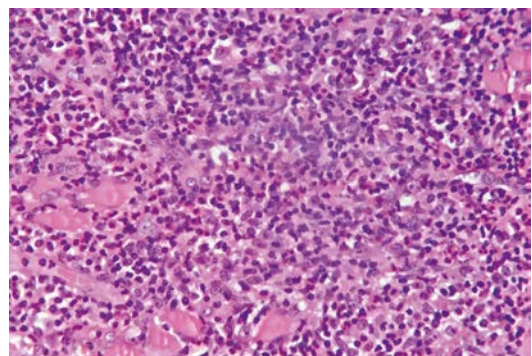


Fig. 1.1 Riga-Fede disease (TUGSE)

Herpes simplex virus (HSV) Infection The type 1 form of the HSV frequently causes infection in the mouth and upper respiratory tract. In children, usually between the ages of 2 and 4, when they first encounter the virus, painful swelling and redness occur in the mouth, gums, pharynx, and mucosa. The swelling sometimes becomes so pronounced that it covers the gums. Systemic findings include fever, fatigue, and regional lymphadenopathy. Later, the lesions ulcerate, and the child may have difficulty eating. The disease spontaneously regresses within 10–15 days. Histopathologically, as seen in most herpes lesions, vesicles and bullae characterized by intraepithelial separation, intranuclear inclusions, and multinucleation can be seen. After the acute herpetic gingivostomatitis improves, the virus becomes latent in the nerve ganglia. In adults, reactivation of the latent virus may be observed. Vesicles form on the lip edges, nasal openings, and buccal mucosa. Its symptoms are milder than primary lesions and heal within 1 week–10 days.

Lesions Caused by Human Papillomavirus (HPV) As in the skin and genital organs, it is possible to see many lesions related to HPV in the mouth and surrounding tissues. The squamous papilloma surface shows papillomatous swellings like cauliflower, the verruca vulgaris surface has thorny protrusions and stalks, and oral condyloma is a broad-based and usually large-sized oral lesion caused by HPV. In children, Heck disease (focal epithelial hyperplasia), which is seen as numerous papillomatous or plaque-shaped mucosal lesions, is caused by types 13 and 32 HPV. Koilocytosis, a viral cytopathic change in the mucosal epithelium, can be seen in lesions related to HPV (Fig. 1.2). Types 2, 4, 6, and 11 often play a role in benign HPV lesions. In oral and laryngeal carcinomas that are HPV-related, HPV 16 and HPV 18 are primarily effective.

Fungal Infections In the oral cavity, *Candida* species can cause infection in children in the form of superficial white lesions called thrush on the palate, tongue, and alveoli during the new-

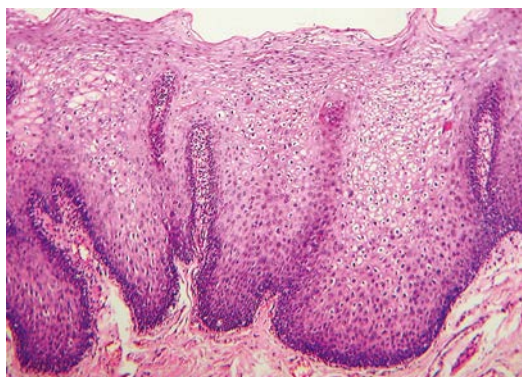


Fig. 1.2 Heck disease associated with HPV

born period. White membranous lesions caused by *Candida* infection can be easily removed by scraping and have a red erythematous base underneath. In adults, *Candida* is seen in diabetics, anemics, those receiving cancer or immunosuppressive treatment, and those with immunodeficiency. In traumatic, dermatological, and leukoplakic lesions that cause increased keratinization in the mucosa, *Candida* can be detected in the keratin layer. In *Candida* infections, inflammatory cell infiltration under the epithelium as well as abundant polymorphous leukocytes is seen inside the epithelium and in the upper layers. *Candida* infections, especially after antibiotic use, are in the form of erosive red lesions and are painful.

Aphthous Ulceration These are frequently seen, recurring, millimetric, multiple, painful superficial ulcerations in the oral mucosa. They occur more frequently in areas that do not show keratinization, are mobile, and are more exposed to trauma, such as the inner surfaces of the lips, fornicies, tongue edges, and floor of the mouth. They are not expected to occur on the hard palate and tongue. Since smoking stimulates keratinization, aphthae are less common in smokers. Those that appear as multiple, small vesicular lesions are called herpetiform aphthae and are less painful. Aphthous ulcerations larger than 1 centimeter in diameter and merging with each other are called major aphthae and, unlike classic aphthae, are seen with syphilis, malignancies, anemias, immune deficiencies, and avitaminosis (Fig. 1.3).



Fig. 1.3 Aphthous ulceration

The lesions have an erythematous appearance in the form of yellow bands and red edges. Histopathologically, there is a nonspecific ulceration. In the stage before ulceration, there is exocytosis and subepithelial infiltration of lymphocytes in the epithelium. Vasculitis is not observed. Regional lymphadenopathy may occur in patients with aphthous ulcers. They heal without scarring within a week to 10 days. Mucosal barrier failure plays an important role in their etiology [2]. It is reported to be more common in those with stress, fatigue, chronic bowel diseases, avitaminosis, and lactose intolerance and in some families. They are lesions that are very painful but not serious because they are open. Aphthous ulcerations can be seen in the oral mucosa in Behçet's disease. However, genital and conjunctival recurrent ulcerations can also be observed in these patients. Behçet's disease is also thought to be associated with mucosal barrier failure and aberrant acquired inflammation. In the first stage of syphilis, numerous ulcers (chancres) that resemble aphthous ulcers but are painless and larger in size can be seen.

Glossitis Inflammation in the tongue is rare and is usually due to ingestion of corrosive and hot substances or galvanic current formation related to poor prosthetic appliance applications and traumas caused by sharp-edged teeth. Most of the inflammations seen are secondary findings of another systemic disease. In scarlet fever and measles, swelling of the tongue, flattening, and redness of the papillae are seen. In pernicious anemia (vitamin B12: cobalamin deficiency), riboflavin (vitamin B2), niacin (vitamin B3), and



Fig. 1.4 Geographic tongue

pyridoxine (vitamin B6) deficiencies, atrophy of the papillae in the tongue and redness, burning, and swelling occur. In iron deficiency anemia, microcytic hypochromic anemia with atrophy of the tongue, glossitis and folds (webs) in the esophagus, and difficulty in swallowing is known as Plummer-Vinson syndrome. As an opportunistic infection, *Candida* infection can be seen in the tongue as in other mucosal areas. Glossitis can cause changes in sensation such as taste change and burning. Glossitis can also be seen due to drug use and psychological factors.

Geographic Tongue (Migratory Glossitis) Lesions that are mostly seen on the back and side of the tongue regress spontaneously or occur in another area after a while and are sometimes multiple. It is often asymptomatic; sometimes it can cause a burning sensation. Characteristically, the middle part is red, there is a white line on the edges, and there is filiform papilla loss. Therefore, it has a map-like appearance (Fig. 1.4). Its etiology is not fully understood. However, since it is more common in individuals with psoriasis and histologically psoriasiform mucositis is observed, it can also be defined as oral psoriasis.

Granulomatous Mucositis Granulomatous inflammation is observed in the mouth due to tuberculosis, sarcoidosis, syphilis, fungal infections, foreign bodies, Crohn's disease, Wegener's

granulomatosis, and Melkersson-Rosenthal syndrome. Each of these lesions has its own clinical findings as well as histological granulomas.

Dry Mouth The washing effect of saliva, containing protective immunoglobulins and antimicrobial peptides, is very important for oral mucosa and dental health. A decrease in the amount of saliva leads to a deterioration in mucosal immunity and mucosal atrophy and erosive lesions. Bad breath and an increase in the probability of tooth decay are also associated with decreased saliva. Chronic sialadenitis and Sjögren syndrome, which cause a decrease in the salivary gland parenchyma, are diseases that can cause dry mouth. In addition, surgical procedures, anticholinergics, antibiotics, chemotherapy drugs, and radiotherapy applied to the head and neck region can cause dry mouth.

1.4 Pigmented Lesions of the Oral Mucosa.

Racial pigmentations and exogenous pigments due to substances used in the mouth and endogenous melanocytic lesions can be seen in the oral mucosa. Melanotic macule is pigment increase without melanocyte increase; it can be racial and can accompany diseases such as neurofibromatosis and Peutz-Jeghers syndrome. Macule-shaped melanosis can also be found in smokers. Some drug use can cause melanin incontinence and macular pigment increase. Drugs used in malaria treatment, hormones, contraceptives, antibiotics, chemotherapeutics, and steroids can cause pigmentation. Pigment increase is also seen in melanoacanthoma, a rare benign lesion seen in black race, clinically resembling melanoma, characterized by increased dendritic melanocytes and pigment incontinence in the acanthotic mucosal epithelium. In lesions with color change such as black hairy tongue, an appearance occurs due to poor oral hygiene, smoking, and other chemicals that cause increased keratinization in the mucosa. Metals such as amalgam and prosthetic chromium-cobalt used for dental fillings can dissolve over time and cause mucosal pigmentation.

Pigmentation can also be found in the majority of mucosal nevi and melanomas that contain increased melanocytes.

1.5 Frequent Dermatological Lesions of the Oral Mucosa

Lichen Planus It is a chronic, probably autoimmune disease that is quite common in the oral mucosa. It is mostly seen in women. It occurs together with skin lesions or only as oral lesions [3, 4]. It is in the form of multiple lesions, especially in the buccal mucosa, tongue edges, gums, and other mucosa. Most of them have the appearance of reticular white lesions (Fig. 1.5). However, bullous, erosive, and hyperkeratotic plaque forms can also be found. Some of the lesions may be asymptomatic, while the erosive ones are painful. The form that involves the gums is clinically called desquamative gingivitis. Histopathologically, it involves the epithelium-submucosa interface in the mucosa (Fig. 1.6). Due to the destruction of the basal layer, it forms an epithelium with a sawtooth appearance. Lymphocytic infiltration rich in CD8 T cells is seen in the form of a subepithelial band. The probability of tumor development from the lichen planus base is increased. Biopsy is necessary during the diagnostic process and



Fig. 1.5 White reticular lines on the buccal mucosa

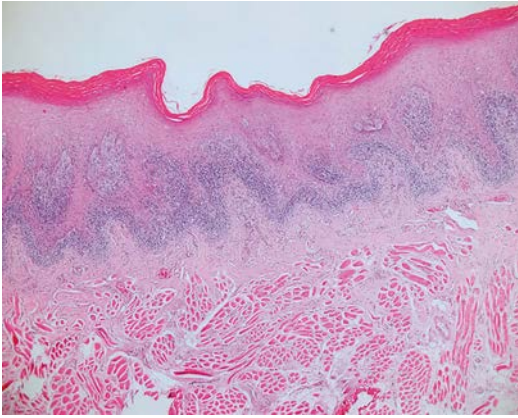


Fig. 1.6 Lichen planus

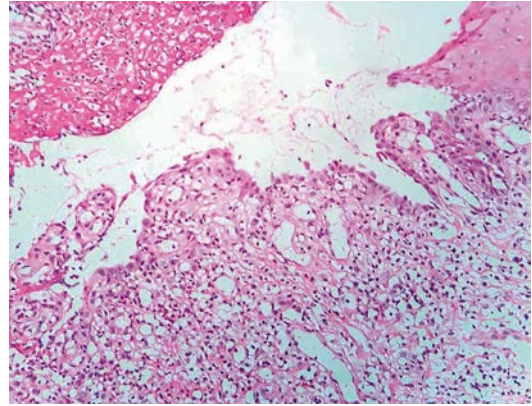


Fig. 1.8 Pemphigus vulgaris



Fig. 1.7 Vesiculobullous lesions in the gums

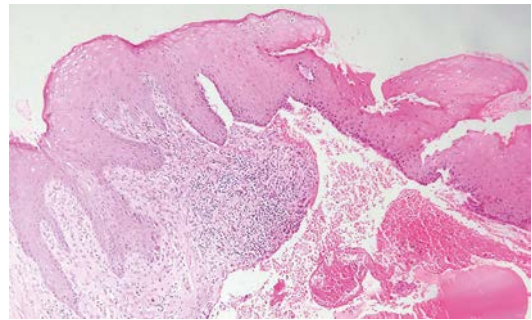


Fig. 1.9 Mucous membrane pemphigoid

for dysplasia evaluation. Drug reactions can also cause lichen-like changes. Unlike lichen planus, these lesions regress with the discontinuation of the drugs [4, 5].

Pemphigus Group Lesions This is a group of autoimmune chronic diseases that first form vesiculobullous and then ulcerated lesions in the oral mucosa [6–9]. Some of these lesions are seen with skin findings. Pemphigus vulgaris, bullous pemphigus, and oral mucous membrane pemphigoid are common in the mouth (Fig. 1.7). These diseases are caused by autoantibodies that develop against adhesion molecules that form the connections between cells. Intraepithelial separation is observed in the pemphigus vulgaris (Fig. 1.8), and subepithelial separation is observed in the bullous pemphigoid and mucous

membrane pemphigoid due to loss of adhesions. There is edema and inflammatory cell infiltration including eosinophil leukocytes in the papillary dermis (Fig. 1.9). Immunocomplex deposits containing immunoglobulin G and C3 are found in the separation area and can be demonstrated by the use of fluorescently labeled antibodies. Vesiculobullous lesions ulcerate easily and are painful. Lesions can be seen anywhere in the mouth and on the soft palate, gums, cheeks, and lips. For histopathological diagnosis, it is important to take samples from the area that is not completely ulcerated and to show the accumulation of immune complexes. Scars can be seen in conjunctival mucosa involvement in bullous pemphigoid.

Erythema Multiforme It is a disease in which acute vesicular or maculopapular skin and mucosal lesions are observed, sometimes with

unknown cause, together with viral infections, drug use, neoplasias, and autoimmune diseases [6]. Lips and cheeks are the most affected areas. The presence of a red, hemorrhagic, crusted, erythematous, circular structure around the lesions is a typical finding and is called a target lesion. It may have a clinical presentation similar to vesiculobullous autoimmune diseases and herpetic lesions. Histologically, widespread single-cell necrosis, hemorrhagic exudate, intraepithelial edema, and submucosal perivascular lymphocytic infiltration are observed in the mucosal epithelium. Mild lesions heal spontaneously. Oral, conjunctival, and genital ulcers are seen together in Steven-Johnson syndrome. Toxic epidermal necrosis is a much more common and serious form. It regresses in a short time with topical or systemic steroid use.

1.6 Reactive Proliferative Mucosal Lesions of the Mouth.

The oral cavity is an area open to chronic irritation due to foods, various chemicals, dental caries and sharp-edged teeth, poor hygiene, and inappropriate dentures. These events can cause inflammation in the mucosa and hyperplasia in the epithelial and subepithelial connective tissue. Due to hyperplasia, pseudotumoral, epithelial, and fibrous tissue developments that can reach large sizes can be observed [10]. Clinically, the term “epulis” is generally used for lesions that are raised on the surface and form a mass in the mouth. The majority of these lesions consist of pathological hyperplasias called fibrous hyperplasias or irritation fibromas. Peripheral giant cell granuloma, pyogenic granuloma, and peripheral ossifying fibromas are other non-tumorous reactive proliferative lesions that create the clinical appearance of epulis. They can develop in the palate due to the use of dentures.

Fibrous Hyperplasia (Irritation Fibroma) It is seen as a nodular lesion due to biting, in the biting line of the buccal mucosa, and on the anterior-lateral edge of the tongue. It has normal mucosa

on it. It is composed of increased collagenized fibrous connective tissue. In addition, in elderly individuals, large fibrous hyperplasias in the form of raised folds or leaves can be seen on the edges of dentures and are clinically called epulis fissuratum. Fibrous hyperplasia can also be seen in the gums. Phenytoin group drugs used in the treatment of diseases such as epilepsy, calcium channel blockers, and cyclosporine have an effect of increasing fibrous connective tissue proliferation. In addition, lesions defined as gingival fibromatosis, which have idiopathic or genetic etiology, are not in the form of a mass but in the form of fibrous hyperplasia limited to the gums.

Peripheral Giant Cell Granuloma It is usually in the form of nodular swellings located in the gums due to chronic inflammations and frequently ulcerated and bleeding. Since the lesion was thought to be due to an abnormal repair event, it was formerly called giant cell reparative granuloma. Histopathologically, it consists of fibrohistiocytic oval-round stromal cells and osteoclast-type multinucleated giant cells (Fig. 1.10). In some of these nodular lesions that develop on the periosteal surface, fibrous connective tissue increase becomes apparent over time, and ectopic ossification may develop inside. Such reactive hyperplasias are defined as peripheral ossifying fibroma.

Pyogenic Granuloma They are pathological hyperplasias of the connective tissue that are frequently localized in the gums in the mouth but can be seen in all mucosal areas, exophytic,

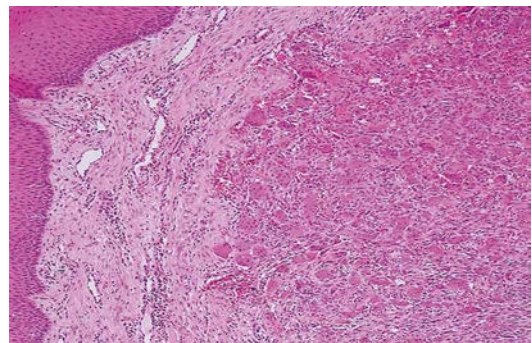


Fig. 1.10 Peripheral giant cell granuloma

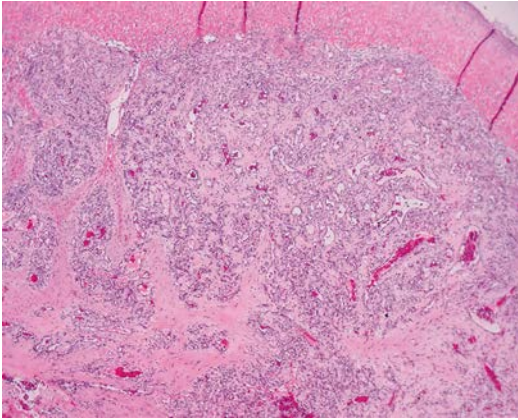


Fig. 1.11 Pyogenic granuloma

ulcerated on the surface, bleeding, and rich in vascular structures and have an increase in granulation tissue (Fig. 1.11). Chronic irritation, trauma, and hormonal factors are effective in its etiology and develop rapidly. Since it is seen more often in women and especially in pregnant women, it is also known as pregnancy tumor. It consists of proliferated capillary vascular structures and inflammatory cells that show lobular arrangement within an edematous connective tissue. Chronic irritations and increased estrogenic effect are important in etiology.

Odontogenic Cysts Cystic lesions can be seen quite frequently in the jaw bones, and it is known that the majority of them develop from odontogenic epithelial residues [10]. Some of these cysts are considered to have inflammatory origin and some to have developmental etiology. In distinguishing most of these cysts, clinical and radiological findings are more important than histological appearance.

Radicular Cyst It is the most common odontogenic cyst. It develops in the form of a radiolucent lesion at the root end of a tooth that has undergone prosthetic application, root canal treatment, and chronic pulp inflammation and is also known as inflammatory odontogenic cyst. It is lined with multi-layered squamous epithelium that does not show keratinization, and there is intense chronic inflammation on its wall. Rushton bodies are observed in the cyst epithelium and cholesterol crystals in its lumen (Fig. 1.12).

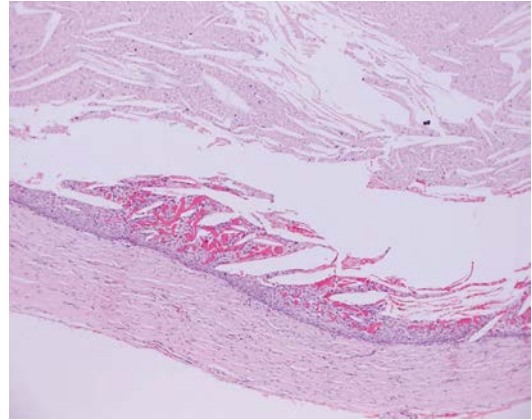


Fig. 1.12 Radicular cyst

Dentigerous Cyst It is an odontogenic cyst that forms around the crown of a tooth that has been impacted in the jaws. It develops from the cells of the enamel epithelium and is common in the lower wisdom tooth region where impaction is common. It is lined with stratified squamous epithelium that does not show keratinization.

Odontogenic Keratocyst It radiologically appears as a multilocular radiolucent lesion that does not cause expansion in the jaw bones, and this appearance is similar to some odontogenic tumors. The cyst is lined with parakeratinized, flat-rite, stratified squamous epithelium without increased stratification and has the potential for recurrence (Figs. 1.13 and 1.14). In *Gorlin syndrome (nevroid basal cell nevus syndrome)*, keratocysts are multiple in the jaws and can be seen together with skin tumors and many other anomalies. There is loss of function of the PTCH gene in all odontogenic keratocysts.

Calcified Odontogenic Cyst (Gorlin Cyst) It is a cyst with ameloblast-like cell line in the basal layer, ghost cells, keratinization, and calcification in the upper layers of the epithelium (Fig. 1.15). Epithelial islands and dentinoid matrix production may be present within the cyst wall and therefore may show recurrence if not completely removed. It is considered a non-neoplastic cystic form of dentinogenic ghost cell tumor.



Fig. 1.13 A multilocular radiolucent cystic lesion

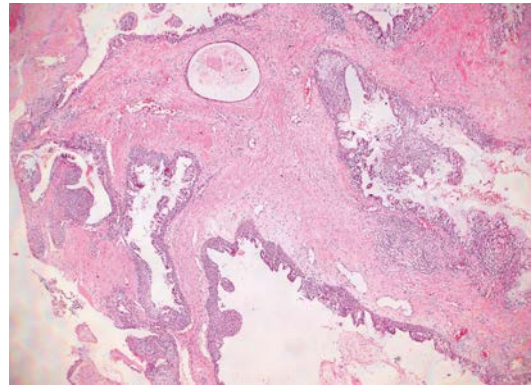


Fig. 1.16 Glandular odontogenic cyst

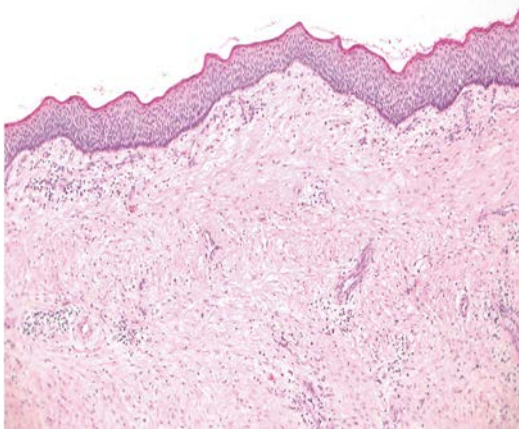


Fig. 1.14 Odontogenic keratocyst

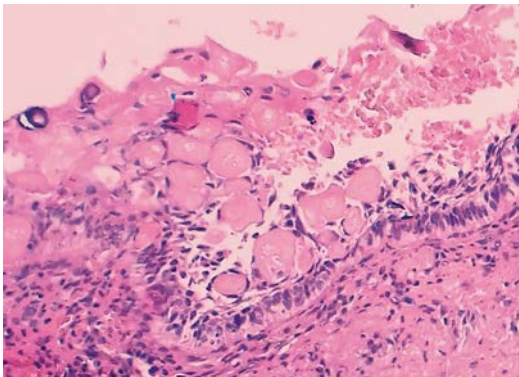


Fig. 1.15 Calcified odontogenic cyst

Glandular Odontogenic Cyst It is lined with nonkeratinized stratified squamous epithelium containing ciliated, lumen-bulging plaques, goblet cells, and gland-like structures (Fig. 1.16). It is mostly seen in the lower jaw and is multilocular. It has the potential for recurrence. It has some

similarities with the intraosseous mucoepidermoid cyst.

Developmental Jaw Cysts They develop in the midline (nasopalatine duct cyst), lateral nasal (nasolabial cyst), and between the maxillary prominences (median palatal cyst), which are the junction areas of bone structures during maxillary development. These cysts may be lined with nonkeratinized stratified squamous epithelium or ciliated columnar epithelium containing mucinous cells similar to the respiratory epithelium.

1.7 Odontogenic Tumors

These tumors, which are mostly benign and develop slowly, contain ectodermal epithelium and ectomesenchymal connective tissue, dentin, cementum, and bone-like structures similar to those seen in the development of odontogenic tissues. Odontogenic tumors are classified into three groups: epithelial, epithelial-ectomesenchymal mixed, and ectomesenchymal [10]. Epithelial tumors include ameloblastoma, adenomatoid odontogenic tumor, calcified epithelial odontogenic tumor (Pindborg tumor), and squamous odontogenic tumor. Tumors with mixed epithelial and ectomesenchymal components include odontoma, ameloblastic fibroma, primordial odontogenic tumor, and dentinogenic ghost cell tumor. Ectomesenchymal tumors

include odontogenic fibroma, odontogenic myxoma, cementoma, and cementing fibroma.

Ameloblastoma It is the most common odontogenic tumor, originating from ameloblast-like odontogenic epithelium. It is frequently seen in the middle ages, in the mandible, and in the wisdom tooth region where impaction and eruption problems are common (Fig. 1.17). However, it can also occur in other regions as a peripheral lesion. Radiologically, it is a multilocular or unilocular lytic lesion. It does not contain odontogenic hard tissue production. Its classic form has irregular borders and may contain solid follicle-like, plexiform, or cystic areas (Fig. 1.18). Since it develops locally invasively, wide excisions and resections with safety mar-

gins are required. The potential for recurrence after simple excisions is high.

Unicystic Ameloblastoma It is a better-behaved form, seen in young people, in the wisdom tooth region of the mandible. There is no tumor infiltration in the wall of the cystic tumor (Fig. 1.19). Therefore, more limited excisions are sufficient. Unicystic or solid ameloblastoma has BRAFV600E mutation in its pathogenesis and can be used in the diagnostic process. Unicystic form with tumor infiltration in the wall (unicystic mural ameloblastoma) should be evaluated and treated like classical ameloblastoma. Ameloblastoma is an analogue of craniopharyngioma, which is a pituitary tumor and develops from Rathke's pouch remnants. Ameloblastoma rarely has metastatic and malignant forms.



Fig. 1.17 Expansive multilobulated radiolucent ameloblastoma with resorption in the roots of the teeth

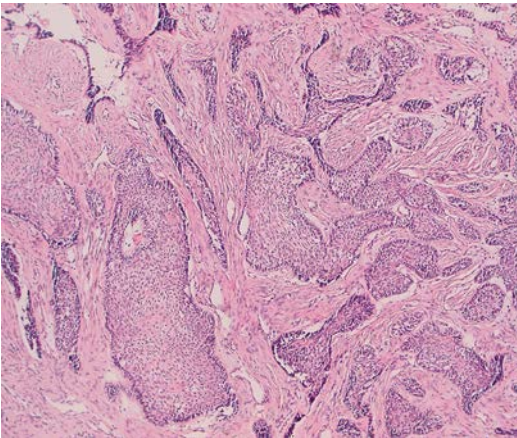


Fig. 1.18 Ameloblastoma

Adenomatoid Odontogenic Tumor It is a limited, benign odontogenic tumor that is seen mostly in the upper jaw and in young people, sometimes associated with impacted teeth, and can displace teeth. It contains solid groups formed by ameloblast-like cells, glandular structures, and eosinophilic dentinoid matrix (Fig. 1.20). Recurrence is not expected after excision.

Squamous Odontogenic Tumor It is a rare epithelial odontogenic tumor. It often occurs as an asymptomatic swelling in the tooth-bearing areas of the jaws. Radiologically, it is seen as a

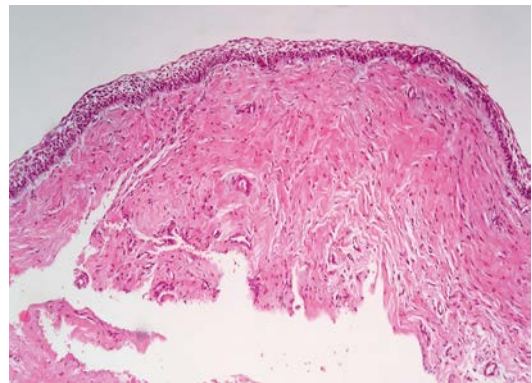


Fig. 1.19 Unicystic variant of ameloblastoma

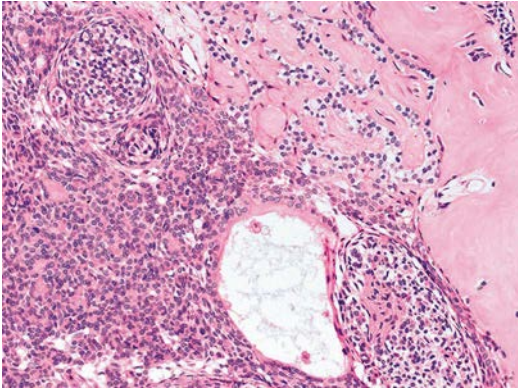


Fig. 1.20 Adenomatoid odontogenic tumor

triangular-shaped, well-circumscribed radiolucent lesion that displaces the teeth. The squamoid cells forming the tumor form islands like an hourglass and do not show a palisade arrangement in their peripheries. It is important to distinguish the tumor without atypia from intraosseous squamous cell carcinoma (SCC) histologically. The tendency to recur after excision is low.

Calcified Epithelial Odontogenic Tumor (Pindborg Tumor) It is a rare tumor seen mostly in the corpus region of the mandible. It has an expansive, partially cystic, radiological appearance with calcified foci like small, calcified snowflakes. It is sometimes associated with impacted teeth. It consists of squamoid cell islands with extensive eosinophilic cytoplasm, and the tumor stroma contains homogeneous eosinophilic, sometimes mineralized amyloid matrix production (Fig. 1.21). Nuclear pleomorphism may be present in tumor cells. Their borders are irregular and develop locally invasively. They should be excised widely. They consist of squamoid cell islands with eosinophilic cytoplasm.

Odontoma It is a common odontogenic tumor containing mixed epithelial and ectomesenchymal components and contains components very similar to dental tissues (Fig. 1.22). It is a slowly developing, well-circumscribed, benign lesion. It is also suggested that it is a hamartomatous lesion, not a neoplastic one. Odontogenic tissue

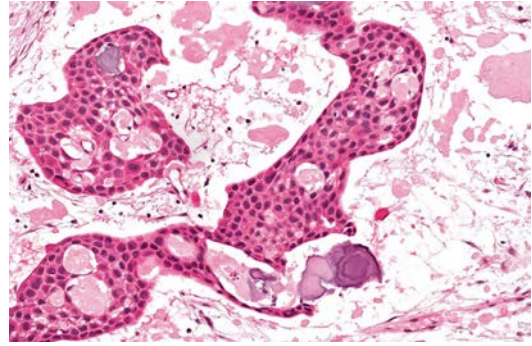


Fig. 1.21 Calcified epithelial odontogenic tumor

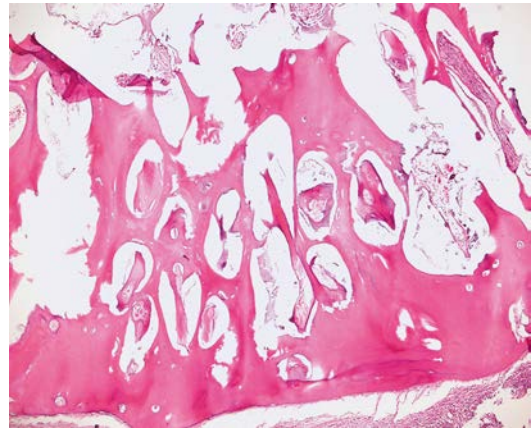


Fig. 1.22 Complex odontoma

production such as enamel, dentin, cementum, and pulp is evident in the tumor. It may contain radiolucency in the early stages, but it usually forms an opaque mass. Compound odontoma is composed of many small tooth-like structures and is often seen in the anterior region of the jaws. Complex odontoma is a large, single mass and is more common in the mandibular molar teeth region. The tumor, which was previously defined as ameloblastic fibroodontoma, is thought to be a developing odontoma. There is maturation and an increase in opacity in the tumor over time. Therefore, it has been removed from the odontogenic tumor classification.

Primordial Odontogenic Tumor It is a newly defined tumor and rare and is seen as a radiolucent, large lesion in children, often in the molar teeth region of the mandible, associated with

unerupted teeth. There is a single ameloblast-like cell line on the ectomesenchymal connective tissue similar to the odontogenic follicle. It is a well-circumscribed benign lesion, and recurrence is not expected after excision.

Adenomatoid Odontogenic Tumor It is a limited, benign odontogenic tumor that is mostly seen in the upper jaw and in young people, sometimes associated with impacted teeth, and can displace teeth. It contains solid groups formed by ameloblast-like cells, glandular structures, and eosinophilic dentinoid matrix (Fig. 1.20). Recurrence is not expected after excision.

Squamous Odontogenic Tumor It is a rare epithelial odontogenic tumor. It often occurs as an asymptomatic swelling in the tooth-bearing areas of the jaws. Radiologically, it is seen as a triangular-shaped, well-defined radiolucent lesion that displaces teeth. The squamoid cells that form the tumor form islands like an hourglass and do not show a palisade arrangement in their peripheries. It is important to distinguish the tumor without atypia from intraosseous squamous cell carcinoma histologically. The tendency to recur after excision is low.

Calcified Epithelial Odontogenic Tumor (Pindborg Tumor) It is a rare tumor, mostly seen in the mandible corpus region. It has an expansive, partially cystic, radiological appearance with calcified foci like small, calcified snowflakes. It is sometimes associated with impacted teeth. It consists of squamoid cell islands with extensive eosinophilic cytoplasm, and the tumor stroma contains homogeneous eosinophilic structure, sometimes mineralized amyloid matrix production (Fig. 1.21). Nuclear pleomorphism may be present in tumor cells. Their borders are irregular and develop locally invasively. They should be excised widely. It consists of squamoid cell islands with eosinophilic cytoplasm.

Odontoma It is a common odontogenic tumor containing mixed epithelial and ectomesenchymal components and contains components very

similar to dental tissues (Fig. 1.22). It is a slowly developing, well-circumscribed, benign lesion. It is also suggested that it is a hamartomatous lesion rather than a neoplastic one. The production of odontogenic tissue such as enamel, dentin, cementum, and pulp is evident in the tumor. It may contain radiolucency in the early stages but mostly forms an opaque mass. Compound odontoma is composed of many small tooth-like structures and is often seen in the anterior region of the jaws. Complex odontoma is a large, single mass and is more commonly seen in the mandibular molar teeth region. The tumor, which was previously defined as ameloblastic fibroodontoma, is thought to be a developing odontoma. Over time, the tumor shows maturation and opacity increase. Therefore, it has been removed from the odontogenic tumor classification.

Primordial Odontogenic Tumor It is a newly defined tumor and rare and is often seen in children as a radiolucent, large lesion associated with unerupted teeth in the molar teeth region of the mandible. There is a single ameloblast-like cell line on the ectomesenchymal connective tissue similar to an odontogenic follicle. It is a well-circumscribed benign lesion, and recurrence is not expected after excision.

Ameloblastic Fibroma It is a rare odontogenic tumor with ameloblastic epithelium and ectomesenchymal fibromatous stroma. In young adults, it often forms a well-circumscribed, expandable, radiolucent lesion in the lateral-posterior region of the mandible. It may be associated with an impacted tooth. It does not contain odontogenic hard tissue matrix production. It is a benign tumor and is treated by excision.

Dentinogenic Ghost Cell Tumor It is a solid and neoplastic form of calcified odontogenic cyst (Gorlin cyst). It is a tumor with ghost-type keratinization of ameloblast-like epithelial cells and dentinoid matrix production. It may contain cystic and solid components. It may be peripherally located under the mucosa or frequently centrally located in the bone and has a mixed radiological appearance with radiolucent and radiopaque

areas. It is a benign tumor, and the probability of recurrence after excision is low. Rarely, malignant forms have been described.

Odontogenic Fibroma It is a benign odontogenic tumor composed of ectomesenchymal fibroblasts, well-circumscribed, often completely radiolucent, and expanding. It is seen a little more frequently in the maxilla. It contains varying amounts of immature odontogenic epithelial islands (Fig. 1.23). It has amyloid-containing, giant cell granuloma-like areas and granular cell shapes. The large diameter of the lesion is important in distinguishing it from hyperplastic dental follicle. Its peripheral shape may cause swelling in the mucosa.

Odontogenic Myxoma It is a hypocellular tumor composed of ectomesenchymal fibroblasts with basophilic myxoid or collagenized fibromyxoid stroma (Fig. 1.24). It is seen more frequently in the mandible and is a unifocal or multifocal multilocular radiolucent lesion. It is expansive, has irregular borders, and extends into the surrounding bone tissues. There is a possibility of recurrence after local excisions. There may be a residual non-neoplastic immature odontogenic epithelium inside.

Cementoblastoma It is a well-circumscribed tumor frequently seen in the tooth-bearing area of the mandible, at the tips of the roots of the

molar teeth. It is a radiopaque mass and may have a mixed radiolucent-opaque appearance in the early stages. It is an analogue of osteoblastoma. It may become very dense and hypocellular in advanced stages. Pagetoid bone formation, cementoblastic activity, and accompanying giant cells are present (Fig. 1.25). Epithelioid cementoblasts have large nuclei and may histologically appear as a malignant tumor. Mitotic activity is rare. Since there is a radiolucent line around it, it is easily excised, and recurrence is not expected.

Cementing Fibroma (Cemento-Ossifying Fibroma) It is a limited, expansive, benign tumor that is also included in ectomesenchymal odontogenic tumors and jaw-face bone tumors. There is a hard tissue production with irregular lamellation in the form of cement bone within the spindle

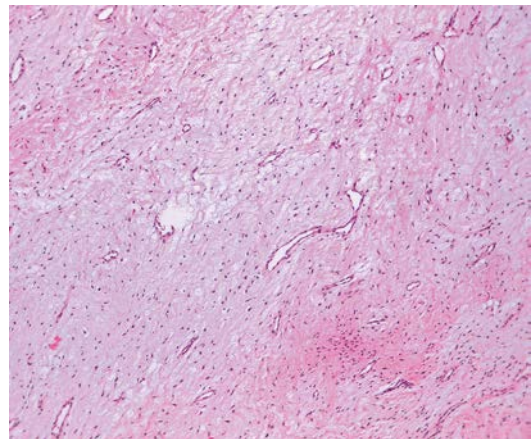


Fig. 1.24 Odontogenic myxoma

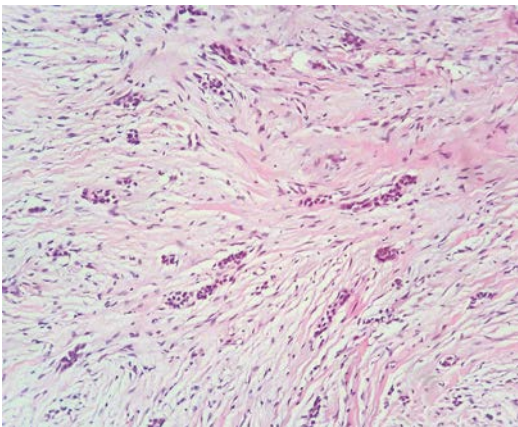


Fig. 1.23 Odontogenic fibroma

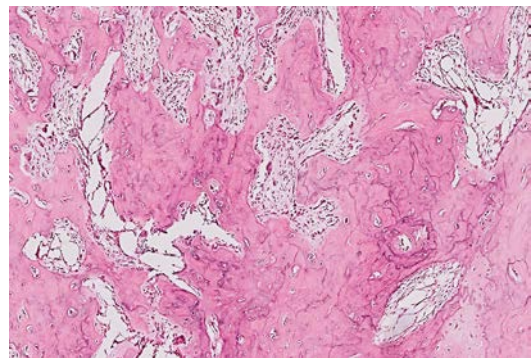


Fig. 1.25 Cementoma

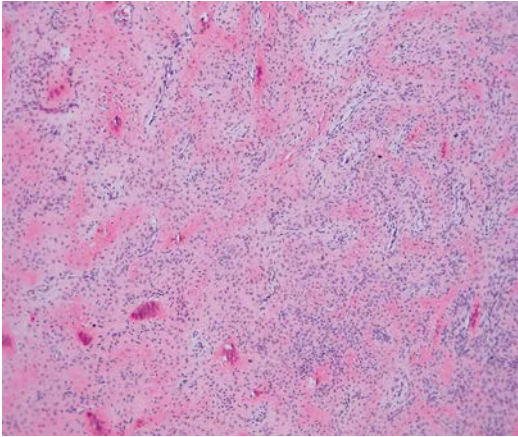


Fig. 1.26 Trabecular type cementing fibroma

fibroblastic, cellular, and hypovascular stroma, sometimes in a psammomatoid structure. It is included in the fibro-osseous lesion group of the jaws, but it is distinguished from fibrous dysplasia and cemento-osseous dysplasia by being neoplastic, progressive, and well-defined. There are trabecular forms seen in infants (Fig. 1.26) and psammomatoid forms seen in adolescents in the bones of the maxilla and facial region. Cemento-ossifying fibromas can sometimes show aggressive behavior with frequent recurrences.

Malignant Odontogenic Tumors Odontogenic malignant tumors can be seen rarely. These are determined by their rapid recurrences and more destructive clinical and radiological appearances. Histologically, they may contain significant atypia, mitosis, and necrosis like malignant tumors in other parts of the body. Ameloblastic carcinoma is the most common malignant tumor and has a short-term recurrence. There are also sclerosing odontogenic carcinoma, clear cell odontogenic carcinoma, ghost cell odontogenic carcinoma, primary intraosseous carcinoma, odontogenic carcinosarcoma, and odontogenic sarcomas.

1.8 Lesions of the Maxillofacial Bones

The maxillofacial bones develop from the neural crest-derived ectomesenchymal connective tissue. Except for the temporomandibular joint

region, other areas become membranous ossified. The effect of this developmental pattern is also reflected in bone lesions. In tooth-bearing regions, proliferative lesions of cementum (hypercementosis, enostosis) around the tooth root are a frequent finding. The cementum is a special bone tissue that is more hypovascular, denser, and less cellular than the bone and has less remodeling. Chewing forces and inflammatory processes can lead to excessive cementum production around the tooth roots. The hereditary lesion of this region is known as cherubism. Cherubism is a rare autosomal dominant disease characterized by bilateral and painless enlargement of the jaw and facial bones, giving the patient the appearance of an angel child (cherub) in Renaissance paintings (Fig. 1.27). The disease also affects tooth eruption, occlusion, and chewing function. Lesions are radiographically observed as bilateral, well-defined, multilocular, radiolucent osteolytic areas. Differential diagnosis includes fibrous dysplasia, central giant cell granuloma, keratocystic odontogenic tumor seen in Gorlin-Goltz syndrome, brown tumor seen in hyperparathyroidism, ameloblastoma, odontogenic myxoma, and aneurysmal bone cyst. If surgical treatment is deemed necessary, surgery can be postponed until after puberty because it is a self-limiting disease and the lesions regress with age. In benign fibro-osseous lesions of the maxillofacial bones, especially in cemento-osseous dysplasia seen as multiple lesions, it is possible to see cementum production in relation to the tooth roots in tooth-bearing areas [11]. Craniofacial dysplasias can involve more than one bone simultaneously, and the proliferated bone tissue may partially contain lamellation in the periphery. Osteomas are dense areas of bone formation seen under the mucosa in the surface areas of the maxillofacial bones. It is also stated that osteomas are not true tumors but reactive proliferations caused by lack of sinonasal ventilation and inflammation. In Gardner syndrome, osteomas can be seen multiple in the maxillofacial bones. Maxillofacial bones are less affected by osteoporotic changes. Since they are bones with rich vascularity, their osteomyelitis covers a more limited area and is treated better than long

bones. Lesions with low pathogenic infectious agents such as Garre osteomyelitis, where sclerosing, periosteal thickening, and new bone formation are evident, may resemble other fibro-osseous lesions of the region. Multiple resorptive bone findings such as brown tumor are more frequently observed in the maxillofacial bones in diseases that resorb bones such as hyperparathyroidism. Similarly, osteonecrosis and osteomyelitis (medication-related osteonecrosis of the jaw) associated with the use of drugs such as bisphosphonates are more commonly seen in the jaw bones. Langerhans cell histiocytosis often has a unifocal form (eosinophilic granuloma) that causes lytic destruction in the jaw and facial bones. Chondromesenchymal hamartoma is a destructive mass lesion that contains spindle-shaped mesenchymal, myxoid, and chondroid components and is more frequently seen in the sinonasal region. Ectomesenchymal chondromyxoid tumor is a tumor of unknown histogenesis, more commonly seen in the tongue and in children, and its analogue has not been described in other parts of the body. Benign cartilage tumors are not expected to be seen except in the joint region. Most bone lesions containing cartilage tissue are

malignant. Osteosarcomas, unlike long bones, show a much wider age distribution, and their radiological appearances do not show any characteristic features. The metastatic potential of osteosarcomas of the maxillofacial bones is lower. Mesenchymal chondrosarcoma, a rare malignant bone tumor, also frequently involves jaw bones.

1.9 Viral Lesions of the Oral Mucosa

Squamous Papilloma It is a common proliferative lesion in the mouth, especially on the tongue, lips, and soft palate [12]. A similar lesion, *verruca vulgaris*, is more commonly seen on the skin. These proliferations associated with HPV types 2, 4, 6, and 11 can be considered as pathological hyperplasia or benign neoplasia. Most of them are small-sized and pedunculated lesions. Koilocytosis, a viral cytological change, can be seen in the stratified flat epithelium forming the lesion (Fig. 1.28). These lesions remain for a long time without changing in size, and malignant transformation is not expected. When they are seen multiple, more attention should be paid to malignant transformation, as it may be associated with immune suppression.

Oral Condyloma They are lesions larger than 1 centimeter in size, shaped like cauliflower or plaque, raised from the mucosa, which can occur with low-risk HPV types such as types 16 and 18



Fig. 1.27 Cherubism

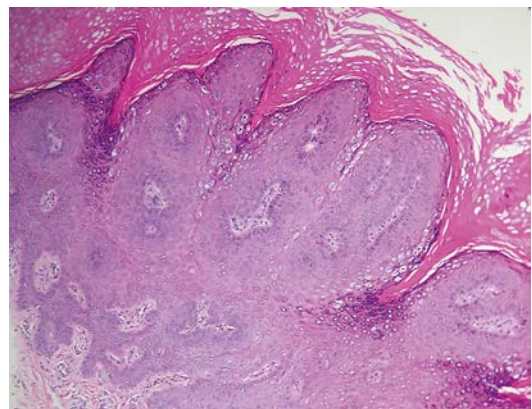


Fig. 1.28 Verruca vulgaris

transmitted through oral-genital sexual contact [12]. Koilocytotic changes are evident in the epithelium. HPV typing should be performed to determine the risk.

Heck's Disease (Focal Epithelial Hyperplasia) They are seen in children and adolescents in the anterior regions of the mouth, lips, cheeks, gums, and tongue, as multiple, raised, papule-plaque or papillomatous, raised lesions in the color of the mucosa. Sometimes they can create a widespread, raised-cobblestone appearance. Proliferative lesions with a significant clinical appearance are frequently reported to be associated with HPV 13 and HPV 32. Cells resembling cells with nuclear fragmentation and called mitosoid cells are observed in the middle layers of the epithelium.

Hairy Leukoplakia It is a white, asymptomatic, mucosal lesion frequently seen on the side of the tongue, associated with EBV (HHV4) identified in human immunodeficiency virus (HIV)-positive, homosexual individuals. It can also be seen in immunocompromised, transplanted, and malignant individuals. It is mostly a single lesion; sometimes it can be observed in multiple areas. Thick hyperkeratosis, parakeratosis, verrucous swelling, and acanthosis are present in the epithelium. Koilocyte-like cytoplasmic ballooning and transparency can be observed in the middle layers of the epithelium. In addition, intranuclear eosinophilic inclusions with perinuclear halo, known as Cowdry A bodies, are seen.

appearance containing red-white areas, widespread and exophytic proliferative verrucous leukoplakia, inverse smoking keratosis and graft-versus-host disease, and autoimmune diseases such as lichen planus and lupus erythematosus [12, 13, 14]. Increased thickness of the epithelium and irregular keratinization cause the lesions to appear as white leukoplakia, and varying thicknesses cause them to appear as erythroplakia or leukoerythroplakia. Oral submucous fibrosis are lesions with a high risk of cancer, mostly seen in Far Eastern countries, with pronounced subepithelial fibrosis and atrophic, hyperplastic, or hyperkeratotic changes in the surface epithelium. They are associated with the habit of using alkaloid-containing substances known as areca-betel (gutka) in the mouth. Due to this lesion, oral cancers are the most common malignant tumors in Far Eastern countries. The risk of cancer of precursor lesions is determined by dysplasia assessment. However, dysplasia grading can be partially subjective, especially in the oral region. Most dysplasias seen in the mouth are differentiated-type dysplasias, where maturation is partially preserved and structural changes are at the forefront (Figs. 1.29 and 1.30). It is possible to evaluate these inadequately. Therefore, clinical data such as the size of the lesion, recurrent lesions, and being in risky areas such as the edge of the tongue should also be included in the risk assessment. *Proliferative verrucous dysplasia* is a precursor lesion in which differentiated structural dysplasia is evident. It is a large and exophytic lesion and indi-

1.10 Lesions with Malignant Potential (Precancerous) of the Oral Mucosa

The most common oral cancer is squamous cell carcinoma. A significant portion of these cancers develop after a precursor stage. It is important to recognize precursor lesions at an early stage in an easily examined area such as the mouth. In this group of lesions, leukoplasias that appear white are the most common precancerous lesions. There are also erythroplakia, which is a red lesion, leukoerythroplakia with a mottled



Fig. 1.29 Clinical appearance of oral leukoplakia involving gingiva and buccal mucosa

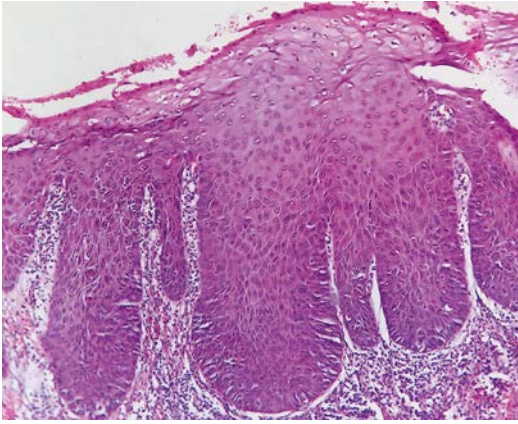


Fig. 1.30 High-grade differentiated dysplasia

icates a tendency for cancer to develop in the mucosal area. Cancer development is more rapid in some precursor lesions. Cancer may occur rapidly in basaloid dysplasias and lesions in the lateral and lower tongue. HPV-related lesions are more common in the oropharyngeal mucosa. Dysplasia near the surgical margin of an excised cancer is important in terms of the possibility of local recurrence and should be noted in pathology reports.

1.11 Malignant Tumors of the Oral Mucosa

Oral cancers are a type of cancer that is increasing in frequency due to the effect of HPV infections. Squamous cell carcinoma is the most common histological type. Smoking, poor oral hygiene, HPV infections, keeping areca-betel nuts in the mouth, immunosuppression, and previous radiotherapy are important in its etiology [12]. Sunlight is effective in lip cancers. Oral cancer frequency also increases in Fanconi anemia and Li-Fraumeni syndrome. Lesions usually start as a non-regressive, white, or red precursor lesion or as ulceration. The lateral and posterior tongue region, the floor of the mouth, and the retromolar region are areas where tumors are common. However, they can be seen in every region of the mouth. Macroscopically, they are often seen as a slowly developing, ulcerated, and some-

times exophytic mass (Fig. 1.31). However, there are also those whose surface is not affected much, with widespread invasion deep down, and therefore presenting as diffuse hardness. Symptoms such as pain, difficulty swallowing, difficulty speaking, and enlargement of neck lymph nodes occur. Histologically, the well-differentiated keratinized form is common (Fig. 1.31). Keratinization does not always indicate a good prognosis for the tumor. Keratinized, differentiated squamous cell carcinomas may exhibit aggressive behavior in relation to their stage. There are papillary, poorly differentiated, and more aggressive basaloid; clear cell; adenosquamous, acantholytic, and spindle cell; sarcomatoid; and metaplastic types that develop by bulging into the lumen and are associated with HPV. There are also less common types of lymphocytes, such as lymphoepithelioma-like and polymorphonuclear leukocyte-rich infiltration. In addition, very well-differentiated forms with very low metastatic potential, such as verrucous carcinoma, keratoacanthoma-like, and carcinoma cuniculatum, may be present. HPV-related oral carcinomas, especially HPV 16 and 18, are seen in the oropharyngeal region. Nuclear protein in testis carcinoma, which tends to be seen in the midline in young people, is a very aggressive squamous cell carcinoma. Neurotrophic, which tends to invade perineurally, those that develop in transplant patients, and those that develop from radiation and burn sites have a worse course. Histological typing and grading are important

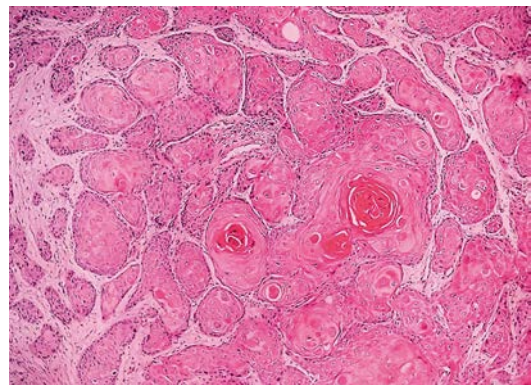


Fig. 1.31 A differentiated SCC sample

because they affect the decision to apply adjuvant radiation therapy (RT) and chemotherapy as well as prognosis. Tumor depth and invasion patterns in the deep section are effective in prognosis. A thickness of 4 millimeters constitutes the optimal risk in terms of the possibility of lymph node metastasis. The most important prognostic factor in oral carcinomas is lymph node involvement. In lymph node dissection, parameters such as lymph node level, number, largest lymph node size and extranodal spread, status of fused lymph nodes and micrometastasis (<2 mm), presence of isolated tumor cells, and presence of tumor focus (skip metastasis) in the surrounding connective tissue are important. In addition to squamous cell carcinoma in the oral region, superficial salivary gland-type adenocarcinomas can also be seen rarely.

1.12 Nose, Paranasal Sinuses, Nasopharynx, and Pharynx

1.12.1 Chronic Rhinitis, Sinusitis, and Nasal Polyps

Viral infections of the upper respiratory tract are common diseases and mostly develop due to adeno, rhino, and echo viruses. In these infections, there is significant edema in the submucosal tissue, and as a result, swelling occurs in the mucosa and the nasal cavity narrows [15]. Bacterial infections may be added secondary to viral infections and cause mucopurulent secretions. Recurrent acute infections, turbinate and septal deviations, and anatomical defects in the development of sinuses and ostia affect upper respiratory tract ventilation and may impair ciliary drainage. Allergic background contributes to the chronicity of lesions. Sinusitis may also be observed after infections of the teeth in the upper jaw. Kartagener syndrome, smoking, and toxic substance inhalation impair cilia movements, so recurrent chronic rhinitis and sinusitis are common findings. Chronic sinusitis develops most frequently in the maxillary sinus. Chronic inflammations, hyperplastic rhinitis, and mucosal thickening seen in sinusitis lead to inflammatory

polyps (Fig. 1.32). Sinonasal inflammatory polyps develop from the sinus mucosa and can reach large sizes in the nose (antrochoanal polyp), obstruct the nasal cavity and choana, cause mucoid secretion, and disrupt drainage. Polyps are smooth and shiny-surfaced, pedunculated, ovoid masses and can be numerous (Fig. 1.33). Nasal and paranasal polyps are found in 10% of cystic fibrosis (mucoviscidosis) cases. Especially when nasal polyposis is detected in children (<20 years of age), this disease should definitely be investigated genetically. They are distinguished from ordinary polyps by the presence of large cystic glands and condensed mucus in the lumen and the small number of eosinophils. Nasal polyposis may also occur in mucopolysaccharidosis. Recurrence is frequent after surgical curettage due to the continuation of the factors

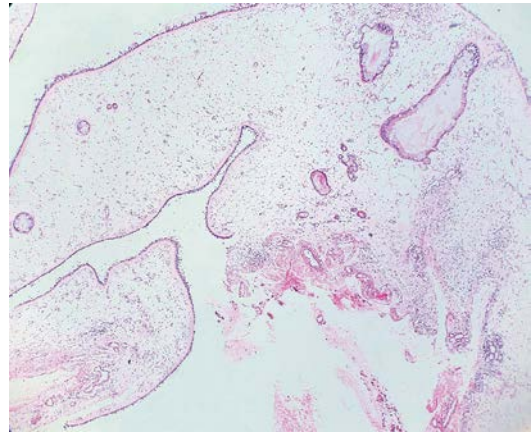


Fig. 1.32 Inflammatory nasal polyp



Fig. 1.33 Antrochoanal nasal polyp

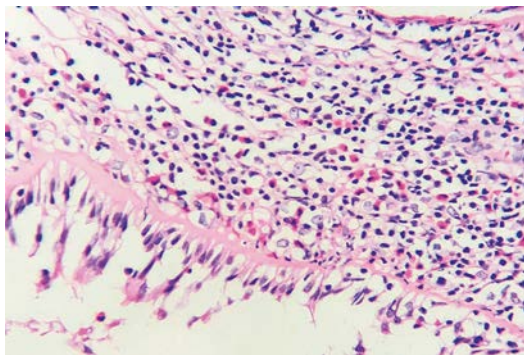


Fig. 1.34 Allergic sinusitis

effective in pathogenesis. Allergic rhinitis is known as hay fever and is a type 1 hypersensitivity reaction to allergens, especially pollens. There is marked edema with serous and mucous exudation, and the nose is blocked. There are abundant eosinophil leukocytes in the submucosal area and exudation fluids. Allergic inflammatory polyps develop in allergic sinusitis and rhinitis (Fig. 1.34). In maxillary sinusitis, mucosa that bulges into the lumen due to submucosal edema forms sinus pseudomucocele. Sinus empyemas may also develop following sinusitis. Opportunistic mucormycosis and aspergillosis infections can be seen in the sinuses in diabetics, elderly patients, and those with immunodeficiency. Mucormycosis has branching, wide, non-septate hyphae and can invade the vascular wall, leading to thrombus and embolism. Septate hyphae and conidial spores are found in aspergillosis and can accumulate in the sinus lumen to form a fungal ball and play a role in the etiology of allergic sinusitis. Rhinosporidiosis is a mycosis caused by *Rhinosporidium*. Intense lymphocytic inflammation surrounding 200-nm-diameter sporangia containing spores is observed in the nasal region (Fig. 1.35). Myospherulosis is an iatrogenic lesion. It develops after nasal packing with petroleum-based ointment and gauze to stop bleeding. It is a lipogranuloma. Brown spherules are seen in large tissue areas within sac-like structures. It can be mistaken for a fungal infection. In fact, these are differentiated erythrocytes.

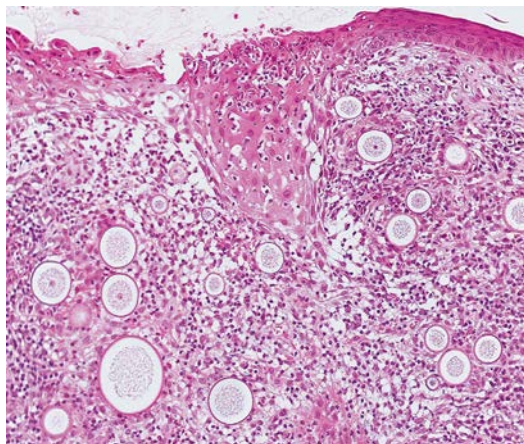


Fig. 1.35 Rhinosporidiosis

Pharyngitis and Tonsillitis They are often seen due to viral upper respiratory tract infections. There is redness and edema in the mucosa. Secondly, bacterial infections, especially *Streptococcus* and *Staphylococcus*, may be added. It is common in children because their immunity is not fully developed and pseudo-membranous inflammations may be seen. In chronic tonsillitis, the lymphoid tissue shows hyperplasia, and the crypts may deepen. Deepening crypts and shed epithelial cells increase the susceptibility to infections and chronicity. Complications such as acute rheumatic fever and exudative proliferative glomerulonephritis may develop after group A *Streptococcus* infections.

Sinonasal Hamartomas Osteochondromatous, respiratory epithelial adenomatoid, and seromucinous hamartomas that form polypoid masses can be seen in the sinonasal region [15]. Chronic inflammatory processes are effective in the formation of such proliferative lesions. Respiratory epithelial adenomatoid hamartoma (REAH) can form tumor-like masses in the middle turbinate of the sinonasal region. The mass lesion may contain hyperplastic epithelial, mesenchymal, and chondro-osseous components. In REAH, glandular-cystic structures are often lined with the ciliated respiratory epithelium containing

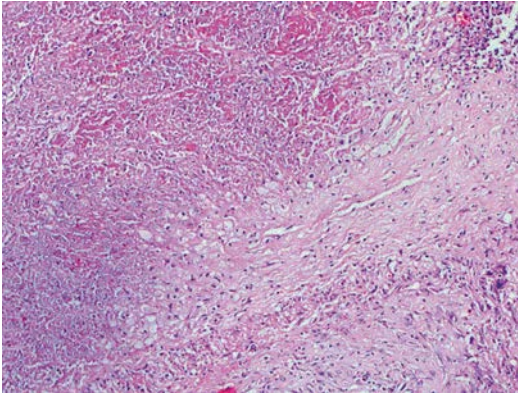


Fig. 1.36 Wegener's granulomatosis

goblet cells. Glandular proliferation sometimes consists of small-diameter serous glands. Cribriform serous and mucinous glandular proliferation may coexist in sinonasal seromucinous hamartoma.

Granulomatosis with Polyangiitis (Wegener's Granulomatosis) It is characterized by necrotizing, ulcerative granulomatous inflammation and vasculitis observed in the elderly, which can involve the midline nasal region, oropharynx, and mouth region (Fig. 1.36) [15]. Nasal discharge, perforation, bleeding, pain, persistent otitis, cough, and sore throat may be observed. Lung and kidney involvement is also present. Most patients have proteinase 3-antineutrophil cytoplasmic antibody (PR3ANCA:C-ANCA) positivity. In this disease, which can be fatal without treatment, good results can be obtained with immunosuppressive treatments. Wegener's granulomatosis, ischemic necrosis associated with cocaine use, vascular thrombosis due to fungal infections, and angiotropic natural killer (NK)/T cell lymphoma are among the factors that cause tissue necrosis, destruction, and perforation in the nasal region.

1.12.2 Sinonasal Tumors

Squamous Papilloma Nasal and paranasal papillomas are benign tumors and are caused by

benign HPV types such as types 6 and 11. Nasal papilloma is an exophytic lesion that causes obstruction and bleeding and has a cauliflower-like surface. According to its cellular components, there are squamous, oncocytic, transitional, and Schneiderian types. There is also inverted papilloma, which shows subepithelial invasive development and has a higher risk of malignant transformation (Fig. 1.37). Papillomas are common in the nasal septum. There are also sinonasal carcinomas that appear clinically like papillomas.

Vascular Tumors They are quite common raised, bleeding benign lesions localized in the nasal cavity, often in the septum. They are called pyogenic granuloma, granulation-type hemangioma, or capillary lobular hemangioma.

Angiofibroma It is a biphasic tumor with a prominent vascular component containing thin-walled vessels within the neoplastic fibrous connective tissue, seen more frequently in young men in the nasopharynx and nasal cavity in the posterior, lateral, and roof regions. It can reach large sizes and create significant clinical problems due to destruction of surrounding tissues and risk of bleeding. It can be common in patients with familial colonic polyposis. The tumor cells are androgen receptor positive. They have a beta-catenin mutation. Excisions are excessively bleeding. Therefore, it is recommended that they

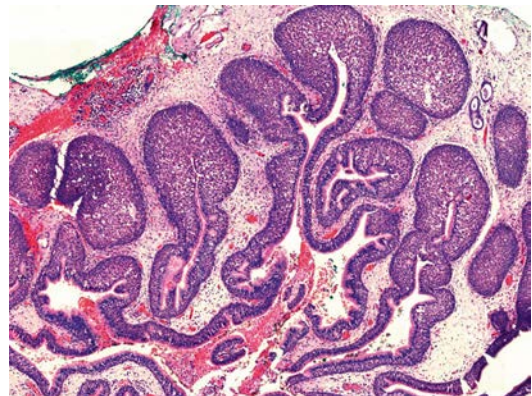


Fig. 1.37 Sinonasal inverted papilloma

be embolized first and then removed. Radiotherapy can also be used in inoperable tumors.

Extranodal NK/T Cell Lymphoma It is an NK/T cell, high-grade, extranodal non-Hodgkin lymphoma with a tendency to invade the vascular wall, destroying midline tissues, especially the nasal septum and hard palate. EBV is important in its etiology. It starts with pain, discharge, bleeding, and ulceration and can cause major tissue destruction. The cells are positive for CD2, CD3, CD16, CD56, and EBV latent membrane protein (LMP). Treatment is primarily chemotherapy and radiotherapy.

Olfactory Neuroblastoma Olfactory neuroblastoma is a malignant tumor that occurs in the upper and lateral parts of the nasal cavity, where the olfactory epithelium is located. It is also called esthesioneuroblastoma and is more common in adults. It is a polypoid, vascular, soft-consistent mucosal mass. It consists of small round atypical neuronal cells on a neurofibrillary base. With this histopathological appearance, it should be distinguished from other small round cell malignant tumors such as undifferentiated carcinoma, lymphoma, Ewing sarcoma, melanoma, and rhabdomyosarcoma. It spreads locally to surrounding tissues and can metastasize to lymph nodes, lungs, and bones.

Sinonasal Carcinomas The most common SCC of the head and neck region is localized in the lip, and SCC of the sinonasal region is rare (3%). More than half of paranasal squamous cell carcinomas are localized in the maxillary antrum, 30% in the nasal cavity, and 10% in the ethmoid sinus. Sinonasal carcinomas are poor prognosis tumors that can be diagnosed in advanced stages and show local invasive development by spreading to the eye, skull base, cheek region, and other surrounding tissues. *Sinonasal carcinomas* are more common in those chronically exposed to minerals such as nickel and chromium, in carpenters who work with wood shavings and use chemical adhesives. In addition, carcinomas may

develop from the base of papillomas. They are more common in the vestibule and lateral wall of the nasal cavity. Histopathologically, most tumors are squamous cell carcinomas and are high-grade. Sometimes, transitional cell carcinoma, adenocarcinoma, or undifferentiated carcinoma and carcinomas resembling salivary gland carcinomas may occur. Sinonasal undifferentiated carcinomas are an aggressive tumor type that forms solid layers that show keratin positivity but no squamoid differentiation (P40 negative) (Fig. 1.38). The majority of tumors in the sinuses have malignant behavior, especially adenoid cystic carcinoma, or undifferentiated adenocarcinomas are seen. Tumors are more common in the ethmoid and maxillary sinuses. Since most sinonasal carcinomas exhibit locally aggressive behavior, a combination of surgery and radiotherapy is used in treatment. Especially low-grade and small ones can cause problems in differentiating from hamartomas. A glandular tumor located in the sinus is more likely to be malignant than a benign tumor. Those that differentiate in the direction of the minor salivary gland in the sinonasal region are often adenoid cystic carcinoma. Demonstration of epithelial and myoepithelial biphasic differentiation and invasive development is important for the diagnosis of salivary gland-type carcinoma. The majority of adenocarcinomas originating from the surface epithelium are low-grade and can be similar to hamartomas in terms of diagnosis (Fig. 1.39).

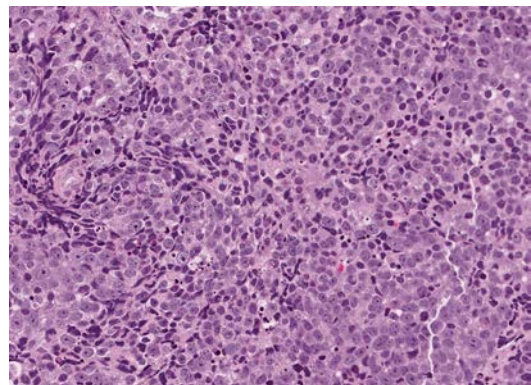


Fig. 1.38 Sinonasal undifferentiated carcinoma

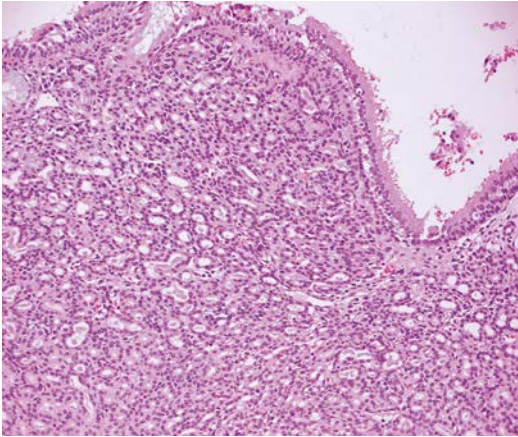


Fig. 1.39 Low-grade adenocarcinoma

Myoepithelial differentiation can be found in some cases at the base, and they may contain papillary structures. Back-to-back acinar structures without leaving any stroma in between are very important for the diagnosis. Sinonasal intestinal-type adenocarcinomas are the least common types; they have colonic, signet ring cell and mucinous shapes. The possibility of a metastatic tumor should be excluded for the diagnosis.

Nasopharyngeal Carcinomas Nasopharyngeal carcinomas which often present with neck lymph node metastasis, occur in two age groups in the young and the elderly. Nasal discharge and bleeding, headache due to skull base invasions, and otitis due to eustachian tube invasions may also occur [15]. All histological types are variants of squamous cell carcinoma. There are nonkeratinizing, keratinizing, and basaloid subtypes. Nonkeratinizing carcinomas are the more common form and are more common in young people (Fig. 1.40). Most of them have normal mucosa and develop endophytically. Rarely, they may cause exophytic papillary protrusions toward the surface. Especially undifferentiated (lymphoepithelioma), nonkeratinizing carcinoma may have histological similarities with lymphoma. In lymphoid hyperplasia and chronic nasopharyngitis, surface epithelial invaginations can be perceived as suspicious invasive

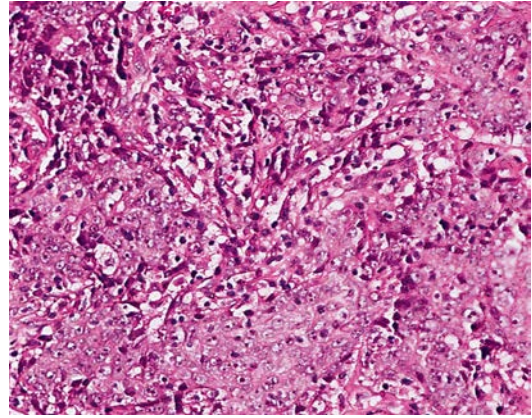


Fig. 1.40 Nasopharyngeal nonkeratinizing carcinoma

epithelial islands in the subepithelial area. In differential diagnosis, evaluation of tangentially cut crypts as benign invaginations is made by the absence of cytologic atypia, small nucleoli, and detection of a relationship with the surface epithelium in serial sections. In most nasopharyngeal carcinomas, no relationship with the surface epithelium and no in situ carcinoma is seen on the surface. Granulomatous inflammation in the nasopharynx is rare; therefore, if there is no history of radiotherapy, the possibility of carcinoma should be carefully investigated with serial sections and cytokeratins in cases with granulomatous reactions. Fibrosis, hyalinization, amyloid globules, granulomatous reaction, and reactive atypia in stromal fibroblasts and endothelial cells that may develop after radiotherapy may sometimes cause problems in terms of diagnosis. These reactions may also prevent the residual tumor from being easily recognized. Most nasopharyngeal carcinomas are EBV positive. EBV etiology can be demonstrated using EBV-encoding RNA 1 and LMP-1. This feature also helps distinguish it from rare secondary and metastatic tumors. If a secondary carcinoma develops due to radiotherapy, it usually occurs in the late period and is often a keratinizing squamous cell carcinoma. In addition, although rare, HPV-related carcinomas may develop in the nasopharynx and in areas close to the oropharynx. Keratinizing carcinomas, which are more commonly seen in the elderly, are unre-

lated to EBV and are more resistant to treatment. Basaloid squamous cell carcinomas may also be seen.

Ear The outer ear consists of the auricle and the external auditory canal. The external auditory canal has a cartilage on the outside and bone on the inside. The auricle and the ear canal are covered with the epidermis, as in the skin, and the epidermis thins in the inner parts of the outer ear and the retes flatten. There are skin appendages and apocrine secretion ceruminous glands under the epithelium. The outer ear is separated from the middle ear by the tympanic membrane. The tympanic membrane has a fibrous connective tissue in its middle part and is lined with thinned squamous epithelium on the outer ear side and with single-layer cuboidal epithelium on the middle ear side. The tympanic cavity in the middle ear contains the ear bones consisting of the malleus, incus, and stapes. The middle ear is connected to the nasopharynx through the Eustachian canal and is associated with the mastoid cavity and pneumatic cavities. The middle ear and mastoid are lined with single-layer squamous epithelium, and the Eustachian canal is lined with the ciliated epithelium. The inner ear is located in the middle part of the temporal bone and contains the cochlea and the vestibular labyrinth. These structures are continuous with the eighth cranial nerve (nervus vestibulocochlearis) that carries the elements of hearing and balance. The vestibular labyrinth contains the endolymphatic sac, and this structure is connected to the membranous structures of the vestibule known as the utricle and saccule.

Inflammatory Lesions *Chondrodermatitis nodularis chronica helices*, which is seen in different parts of the auricle, more commonly in older individuals, ulcerates, and inflammation reaches the perichondrium of the cartilage, probably due to traumas and ischemic nature. This lesion often forms a crusted lesion in the helix clinically; therefore it gives a tumor-like appearance and is painful. Recurrent perichondritis, an episodic painful inflammation of the cartilage, can also

occur in the auricle, as in other cartilaginous tissues of the body such as the nose and in joints. Recurrent perichondritis is an autoinflammatory disease with genetic predisposition. Ear inflammations are mostly in the form of middle ear inflammation. External ear canal inflammations are rare and may be due to fungal infection and allergic causes due to *Aspergillus*. Middle ear inflammations are common in children and start as serous inflammation following obstruction of the Eustachian tube due to the hyperplastic submucosal lymphoid tissue in the nasopharynx after viral upper respiratory tract infections. Later, suppurative bacterial inflammations, especially due to streptococci, are added. Recurrent and persistent infections may cause chronic middle ear disease. In this case, acute inflammation attacks leading to perforation in the tympanic membrane are observed. There is a risk of inflammation in the middle ear spreading to the mastoid bone and skull base. Inflammation may be more aggressive and destructive in diabetics.

Cholesteatoma In cases of chronic otitis media, perforation of the eardrum and proliferation of the squamous epithelium of the external ear canal toward the middle ear or formation of squamous metaplasia in the middle ear epithelium (Fig. 1.41). Keratin is present in the lumen of this cystic lesion in the middle ear; foreign body reaction against keratin, cholesterol crystal accumu-

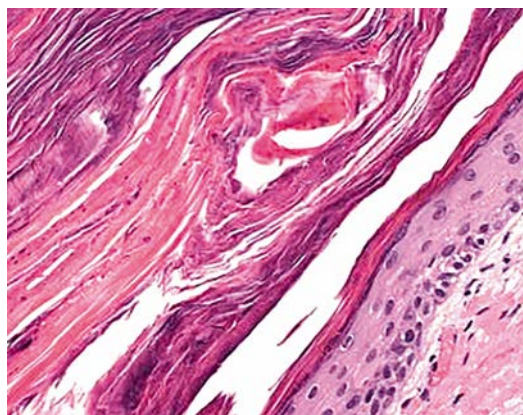


Fig. 1.41 Cholesteatoma

lation, and chronic inflammation are present in its wall. Although the lesion is not neoplastic, it can spread and erode the ear bones and progress toward the inner ear. Sometimes it can extend to the neck region and intracranial areas.

Otosclerosis It is a disease of unknown etiology, rarely seen in young people, slowly progressing, and characterized by bilateral sclerotic excessive bone formation in the ear bones. There is a sclerotic proliferation in the bone similar to Paget's disease, where resorption and new bone formation are seen together. The middle ear bones show fibrous ankylosis. Loss of mobility of the bones leads to hearing loss. The disease may be familial.

Ear Tumors In individuals who work outdoors and are exposed to sunlight, solar keratosis and basal cell carcinoma and, to a lesser extent, squamous cell carcinomas may develop in the auricle [16]. Most carcinomas developing in the external auditory canal are squamous cell carcinomas and may present otitis findings. The prognosis of tumors in the auricle is better than those developing in the external auditory canal. Malignant melanomas, often of the superficial spreading type, may also be seen in the external ear. In children, the external and middle ear region is an area where botryoid-type embryonal rhabdomyosarcoma is seen. When detected, it often invades the ear bones and deep tissues. Ceruminous adenoma in the external ear, neuroendocrine tumor (carcinoid) in the middle ear, and jugulotympanic body paragangliomas (glomus tympanicum) may also be seen. In addition, in the middle ear region, an endolymphatic sac tumor with low malignant potential, containing papillary and follicle-like secretory structures and cystic areas, more commonly associated with von Hippel-Lindau syndrome, can be seen. In the inner ear, there is an acoustic schwannoma (vestibular schwannoma).

Larynx The *larynx* is continuous with the oropharynx and hypopharynx in the upper part and with the trachea below. It is composed of three parts: supraglottic, glottic, and subglottic. The larynx is lined with ciliated pseudostratified epi-

thelium, as in other main respiratory tract regions. The nonkeratinized stratified squamous epithelium is present in the anterior region of the epiglottis and on the vocal cords. Serous and mucinous glands are present in the subepithelial area.

Laryngitis Larynx inflammations are often seen together with upper respiratory tract infections and are usually seen in smokers. It can also occur in isolation due to viral, bacterial, allergic, and chemical causes. Larynx inflammations can be dangerous in infants and children because the respiratory tract and muscles are not fully developed and the edema that may occur can cause obstruction. This risk is particularly high in acute laryngoepiglottitis caused by *Haemophilus influenzae* and beta-hemolytic streptococci. Chronic laryngitis is common in smokers and those chronically exposed to toxic vapors in industry, and the risk of developing carcinoma in these patients is also high.

Laryngeal Nodule/Polyp They are frequently seen in teachers and singers who use their voices a lot and in smokers and do not have a polypoid, neoplastic, or inflammatory etiology. They occur in the anterior one-third of the vocal cords. Changes and hoarseness are observed in the voice. Histopathologically, they are covered with multi-layered squamous epithelium showing hyperkeratosis, and there is an edematous, hyalinized connective tissue with fibrin exit in the subepithelial area (Fig. 1.42). Bilateral and small-sized (<3 mm) nodules are called laryngeal nodules and may regress with voice use treatment. Unilateral large-sized (>3 mm) nodules are called polyps. Polyps are excised.

Laryngeal Contact Ulcer (Contact Granuloma) It is an ulcerated polypoid lesion in the area behind the vocal cords, associated with incorrect use of the voice, trauma, intubation, or reflux. It is detected by voice change and pain findings. It is treated by eliminating the causes.

Laryngeal Papilloma Squamous papilloma and verruca vulgaris can be seen as a solitary lesion in

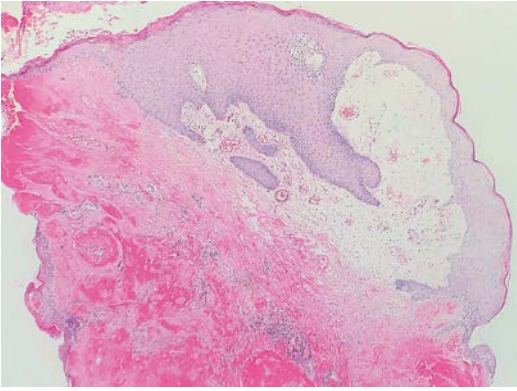


Fig. 1.42 Laryngeal polyp

the vocal cords in adults. In children and adolescents, there is a possibility of multiple papillomas. These lesions, called juvenile laryngeal papillomatosis, are thought to be associated with HPV subtypes 6 and 11, and the virus is acquired from the mother during birth. Multiple papillomas can obstruct the respiratory tract and cause difficulty breathing. Similar lesions can also be seen simultaneously in other parts of the respiratory tract, such as the nose, oropharynx, trachea, and bronchi. Papillomas seen in children are usually treated with surgical excision or are expected to regress with puberty. Papillomas can sometimes resemble verrucous carcinomas clinically. Papillomatosis can sometimes exhibit persistent recurrences and aggressive behavior. Invasive carcinomas may develop in lesions that frequently recur.

Larynx Carcinomas They are more common in smokers, older adults, and men. There is also an increased risk in those who consume alcohol, who have asbestosis, who are exposed to radiation and in those with chronic laryngitis. It is accepted that the majority of larynx cancers develop from precursor lesions that show keratosis and varying degrees of dysplasia. Precursor lesions cause symptoms such as hoarseness, voice distortion, and muffled voice in the early stages. The degree of dysplasia in precursor

lesions is closely related to the risk of developing carcinoma. Clinically and surgically, tumors are divided into glottic, subglottic, and supraglottic. Most tumors (two-thirds) are glottic and localized in the mobile anterior part of the vocal cord. They cause hoarseness, dysphagia, and hemoptysis in the early stages. Since they remain localized for a long time, give early symptoms, and are limited to the thyroid cartilage, the prognosis is good. Cure can be achieved with RT or surgery. Supraglottic tumors (30–35%) are localized in the band, ventricle, and epiglottis. They are common in the anterior one-third of the epiglottis, and 1% invade the glottis. Lymph node metastasis is 40%. Transglottic tumors are less than 5%. They are carcinomas that cross the laryngeal ventricle. They are the type that most frequently metastasizes to the lymph nodes. Glottic tumors can be detected with voice changes at an early stage. Transglottic and subglottic tumors present symptoms later, so the prognosis is worse. Macroscopically, the majority of carcinomas appear as a mass that ulcerates and bulges toward the surface. Histopathologically, the majority are keratinized squamous cell carcinomas [17]. Since the laryngeal cartilages are resistant to tumor invasion, they form a barrier that slows down tumor invasion for a certain period of time. Carcinomas primarily metastasize to regional lymph nodes. Supraglottic tumors metastasize earlier than glottic tumors due to the presence of more lymphatics in this region. Verrucous carcinoma, a special and rare variant of squamous cell carcinoma, shows local aggressive development and has a low metastatic potential. Atypia is not evident in the cells forming the tumor. Differentiation of this tumor from papillomas and verrucous keratoses may be difficult. Rarely, tumors of different histological types such as adenocarcinoma, small cell carcinoma, and salivary gland carcinomas can be seen in the larynx. In larynx carcinomas, very good curative results can be obtained with combinations of surgical treatment and radiotherapy in the early stages. Prognosis is poor in cases with metastasis.

1.13 Neck Region Lesions

Branchial Cysts They are usually unilocular cystic lesions that occur in the anterior-lateral region of the neck, in front of the sternocleidomastoid muscle. Since they develop from branchial cleft remnants, they can be seen in any region from the parotid gland region to the thymus. They often develop in the anterior region of the sternocleidomastoid muscle in the middle part of the neck. Since they are cysts lined with keratinized epithelium, they become infected hematogenously and therefore present as a suddenly developing, painful cystic swelling. Due to their localization, they are clinically similar to lymphoid and metastatic tumors. Histopathologically, they usually appear as a cystic lesion lined with stratified squamous epithelium, containing a lymphoid tissue with reactive follicles on the wall (Fig. 1.43). Lymphoepithelial lesions may be found in the lymphoid tissue on the wall of cystic lesions in the salivary glands and are defined as cystic lymphoepithelial sialadenitis. Cystic lymphoepithelial sialadenitis can sometimes be multilocular and is more common in individuals with Sjögren syndrome and HIV positive.

Thyroglossal Duct Cyst Thyroid development begins in the region behind the tongue and then descends to its place in the anterior neck region. Remnants of thyroid tissue may remain on this line. Lingual thyroid is the thyroid ectopia seen behind the tongue. In the anterior neck region, a

cystic lesion lined with the stratified squamous epithelium may develop from the midline remnants. The wall of the cystic lesion contains remnant thyroid tissue follicles (Fig. 1.44). Hyperplasia and thyroid tumors may develop in the thyroid tissue in the wall of the remnant cyst. Sometimes papillary carcinoma in the thyroid gland metastasizes to the lymph node in the neck region and the metastatic tumor may be completely cystic. In this case, the question of whether the tumor developed from the wall of the thyroglossal duct cyst may arise. Clinical evaluation of the thyroid tissue, thyroidectomy for treatment, and removal of the metastasis in the neck are required.

Fibromatosis and Torticollis Fibromatosis is a neoplastic proliferation formed by cells known as fibroblasts and myofibroblasts. It is mostly seen at a young age. Since it does not have a specific border and is infiltrative, it can be difficult to remove, frequent recurrences can be seen, and therefore terms such as aggressive fibromatosis are also used. The head and neck regions are the areas where fibromatosis is frequently seen. They are deeply located and can cause functional and visual impairments in the surrounding tissues due to infiltration. Surgical scars, radiotherapy history, and burns increase the possibility of fibromatosis. It is important to differentiate them from fibrosarcomas histopathologically, and it is important to evaluate increased cellularity and

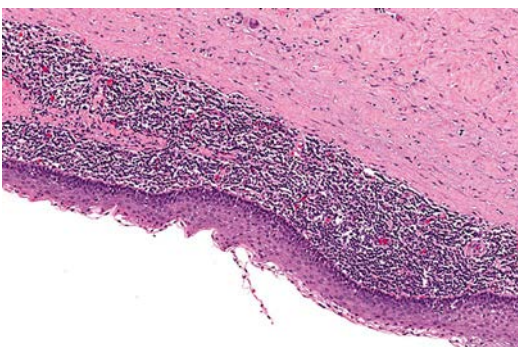


Fig. 1.43 Branchial cleft cyst

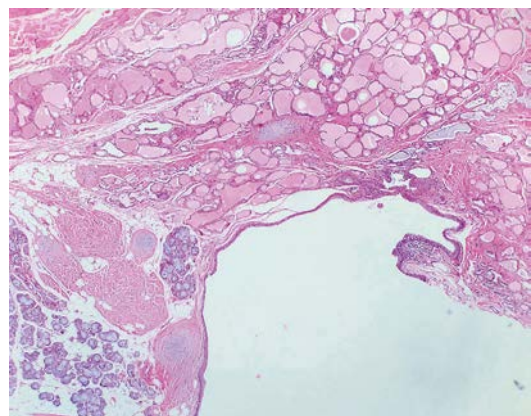


Fig. 1.44 Thyroglossal duct cyst

mitotic activity. It can occur as a component of genetic diseases, especially Gardner syndrome. Torticollis is a painful, localized reactive fibrous proliferation seen congenitally in infants, in the lower part of the sternocleidomastoid muscle, causing the head to lean toward the diseased side. It can develop traumatically or idiopathically. In most cases of torticollis, recovery can be achieved with physical therapy in which appropriate symmetric movements are performed in the early stages. Permanent asymmetry can be seen in the face at an advanced age in untreated cases.

Paragangliomas: Neuroendocrine cells that form the paraganglion system are found in various regions throughout the body, primarily in the adrenal medulla, in association with the sympathetic and parasympathetic systems. Some of these are associated with the sympathetic and some with the parasympathetic system. Neuroendocrine tumors that develop from these organs are also called glomus tumors. In the head and neck region, the carotid, jugular, aortic, jugulotympanic, vagal, and glossopharyngeal bodies are the organs of the paraganglion system in the head and neck region [18]. Paragangliomas are tumors that develop from these system cells and can be seen in the neck, ear, oropharynx, nasopharynx, and larynx and nasopharynx. Carotid body paraganglioma is the most common. Some of these tumors are functional and can secrete metanephrine and adrenaline. They are more common in adults, women, and those living at high altitudes. Tumors can be familial and bilateral in those with mutations in the succinate dehydrogenase gene subunits, von Hippel-Lindau syndrome, and neurofibromatosis. They are slow growing and painless, and the vast majority show benign behavior. Ear lesions are lesions that protrude from the middle ear. Histopathologically, they consist of cell islands known as cell balls within a vascularized stroma. Since they are highly vascularized and associated with large vessels, excessive bleeding may occur during their removal. Therefore, it is recommended that they be removed by embolization.

Metastatic Tumors The neck region is a region where metastases of tumors in the lymph nodes, head-face skin, and mucosa are frequently seen. Tongue, nasopharynx, salivary gland, larynx, and thyroid carcinomas may show metastases, especially in the submandibular and jugular region lymph nodes. Primary salivary gland tumors and lymphoma involvement in this region may also have clinical similarities with metastatic carcinomas. Non-neoplastic, tuberculous lymphadenitis, branchial, thyroglossal, and bronchogenic cysts may also give a suspicious mass appearance. In the lymph nodes close to the supraclavicular region, metastases of visceral cancers, especially lung, breast and stomach cancers on the left side, can be seen.

References

1. Nguyen CG, Wikner EE, Gallagher TG, et al. Diagnosis and management of Riga-Fede disease: a case series. *Laryngoscope*. 2024;134:4803–5.
2. Günhan Ö, Günel A, Avcı A, et al. Oral epithelial barrier function and the role of nuclear factor kappa- β pathway in the pathogenesis of aphthous ulceration. *Turk J Gastroenterol*. 2013;24(6):508–14.
3. Alrashdan MS, Crillo N, McCullough M. Oral lichen planus: a literature review and update. *Arch Dermatol Res*. 2016;308:539–51. <https://doi.org/10.1007/s00403-016-1667-2>.
4. Khammissa RAG, Chandran R, Masilana A, et al. Adverse immunologically mediated oral mucosa reactions to systemic medication; lichenoid tissue reaction/ interface dermatitis-stomatitis, autoimmune vesiculobullous disease and IgE-dependent and immune complex reactions. *J Immunol Res*. 2018;2018:7645465. <https://doi.org/10.1155/2018/7645465>.
5. Wang D, Woo S. Histopathologic spectrum of intra-oral irritant contact hypersensitivity reactions: a series of 12 cases. *Head Neck Pathol*. 2021;15:1172–84.
6. Reinhart JP, Stoopler ET, Crawford GH. Oral hypersensitivity reactions. *Dermatol Clin*. 2020;38:467–76.
7. Saccucci M, DiCarlo G, Bassu M, et al. Autoimmune diseases and their manifestations on oral cavity: diagnosis and clinical management. *J Immunol Res*. 2018;2018:6061825. <https://doi.org/10.1155/2018/6061825>.
8. Rashid H, Lamberts A, Diercks GFH, et al. Oral lesions in autoimmune bullous diseases: an overview of clinical characteristics and diagnostic algorithm. *J Clin Dermatol*. 2019;20(6):847–61. <https://doi.org/10.1007/s40257-019-00461-7>.

9. Du G, Patzelt S, Beek N, Schmidt E. Mucous membrane pemphigoid. *J Autoimmun Rev.* 2022;21(4):103036. <https://doi.org/10.1016/J.autrev.2022.103036>.
10. Günhan Ö. Oral ve Maksillofasal Patoloji. İstanbul: Quintessence yayıncılık; 2015. p. 47–60. 68–100, 118–121
11. Günhan Ö, Kahraman D, Yalçın ÜK. The possible pathogenesis of cemento-osseous dysplasia: a case series and discussion. *Adv Oral Maxillofac Surg.* 2021;3:100105. <https://doi.org/10.1016/j.adoms.2021.100105>.
12. Neville BW, Damm DD, Allen CM, Chi AC. Oral and maxillofacial pathology. Chapter 15. 5th ed. St. Louis: Elsevier; 2016. p. 355–420.
13. Müller S. Oral epithelial dysplasia, atypical verrucous lesions and oral potentially malignant disorders: focus on histopathology. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2018;125(6):591–602. <https://doi.org/10.1016/j.oooo.2018.02.012>.
14. Odel E, Kujan O, Warnakulasuriya S, Sloan P. Oral epithelial dysplasia: recognition, grading and clinical significance. *Oral Dis.* 2021;27:1947–76.
15. Günhan Ö, Kahraman D. Sinonazal ve nazofarengeal bölge lezyonlarında patolojik tuzaklar. *Patolojide Tuzaklar kitabı*. Editör Sergülen Dervişoğlu, 1. basım. Kongre kitapevi, 2022. p. 589–593.
16. Sandison A. Update from the fifth edition of the World Health Organisation classification of head and neck tumors: tumors of the ear. *Head Neck Pathol.* 2022;16:76–86. <https://doi.org/10.1007/s12105-022-01450-9>.
17. Zidar S, Gale N. Update from the fifth Edition of the World Health Organization classification of head and neck tumors: hypopharynx, larynx, trachea and parapharyngeal space. *Head Neck Pathol.* 2022;16:31–9. <https://doi.org/10.1007/s12105-021-01405-6>.
18. Mete Ö, Asa SL, Gill AL, et al. Overview of the 2022 WHO classification of paragangliomas and pheochromocytomas. *Endocr Pathol.* 2022;33:90–114.

Pathology of Salivary Glands

2

Fulya Çakalağaoğlu

2.1 Anatomy Histology

Glands consist of three major glands, namely, parotid, submandibular, and sublingual, as well as many small salivary glands, primarily localized around the mouth. All salivary glands are made up of acini and duct structures. Acini are lined with serous, mucinous, or mixed type cells. There are three types of salivary gland ducts: interlobar and interlobular ducts surrounding the lobes and lobules, intercalated ducts, and striated ducts. Myoepithelial cells are contractile cells that facilitate salivary secretion surrounding the functional units of large and small salivary glands. A large number of myoepithelial cells can be found around the salivary gland acini and intercalated ducts. The number of myoepithelial cells is low in large ducts. Microscopic examination reveals myoepithelial cells as thin, spindle-shaped cells located between the basal membrane and the basal lamina. They can be demonstrated in microscopic immunohistochemical (IHC) staining with smooth muscle actin (SMA), calponin, h-caldesmon, S100, p63, and CD10.

Parotid: It is the largest salivary gland. Depending on the course of the facial nerve, it is divided into two lobes: superficial and deep. In adults, the average weight of the parotid gland is

14–28 g, and it drains its secretion into the oral cavity via Stenson’s main duct. In adults, the parotid acini are completely serous, and there is an adipose tissue and lymph nodes within the parotid parenchyma.

Submandibular: The second largest salivary gland is located in the digastric triangle. It weighs on average 10–15 g. It drains its secretion into the sides of the lingual frenulum via Wharton’s duct. Histologically, the submandibular gland predominantly consists of serous acini with fewer mucinous acini (Fig. 2.1). In the submandibular gland, serous cells are arranged in a crescent shape around mucinous cells. This is called Gianuzzi’s crescent.

Sublingual: It is the smallest salivary gland, predominantly composed of mucinous acini.

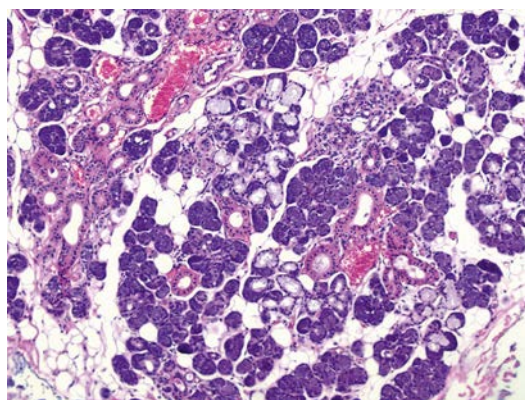


Fig. 2.1 Normal submandibular gland

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Macroscopically, it weighs 2 g and is 2.5 cm long, located over the mylohyoid muscle. It drains its secretion into the oral cavity through numerous ducts. Minor salivary glands: oral cavity, palate, paranasal sinuses, and pharynx.

2.2 Developmental Disorders

Salivary gland agenesis. It can be unilateral or bilateral due to a disruption in the development of the first and second branchial clefts during embryological development. Patients exhibit facial asymmetry, dental caries due to decreased saliva secretion, and dry mouth [1].

Heterotopia: The presence of a mature salivary gland tissue in a location where it should not be histologically present. Salivary gland heterotopia/choristoma has been reported in the extranodal thyroglossal duct, breast, pituitary, ear, and rectum [2].

Nodular oncocytic hyperplasia: It is typically a cluster of oncocytic cells within the parotid gland. As age increases, oncocytic changes within the salivary gland increase. These can be multifocal/nodular or diffuse. Microscopic examination reveals large polygonal-shaped cells with small pyknotic central nuclei and abundant eosinophilic cytoplasm. Differential diagnosis should be performed with oncocytic neoplasms [2, 3].

2.2.1 Inflammatory

Acute sialadenitis: It is primarily the bacterial or viral suppurative inflammation of the parotid gland. The most common bacterial agent is *Staphylococcus aureus*. Other bacterial agents include streptococci, peptostreptococci, and, rarely, mycobacteria. Generally, it occurs due to retrograde contamination as a result of salivary stasis (advanced age, radiation, sialolithiasis). The most common viral agents are paramyxovirus, influenza, coxsackie, human immunodeficiency virus, and cytomegalovirus (CMV). Macroscopically, the structure of the salivary

gland is preserved; in viral sialadenitis, there is lymphocyte-rich inflammation, with viral inclusions in the ducts and acini in CMV, and in bacterial sialadenitis, there is neutrophil-rich inflammation, and ductal destruction occurs.

Obstructive sialadenitis (sialolithiasis): It is the most common form of chronic sialadenitis. Obstruction is usually due to stones and rarely due to tumors, resulting in obstruction of the salivary gland ducts; diagnosis is based on clinical evaluation and radiology. Microscopically, periductal inflammation accompanying ductal obstruction, fibrosis, and dilation in the ducts is observed [3].

Chronic sialadenitis: It occurs due to sialolithiasis or salivary stasis. The submandibular gland is most commonly affected unilaterally. Although the etiology is definitively unclear, an increase in calcium content in saliva and changes in enzyme functions may play a role. Clinically, unilateral pain and swelling are observed. Diagnosis is made through radiological and clinical assessments. Microscopic examination shows an increase in lymphocytes in the salivary gland parenchyma, atrophy of acini, increased fibrosis in between, and squamous and mucous metaplasia in the ducts. In cases associated with tuberculosis, granulomatous inflammation and caseating necrosis are seen.

IgG4-related sialadenitis (chronic sclerosing sialadenitis): It was first described by Küttner in 1896. It is characterized by swelling of the main salivary glands and lacrimal glands. The submandibular gland is most commonly involved. It is most frequently seen in the third to seventh decades of life. In these patients, serum IgG4 levels are elevated. Other IgG4-related sclerosing diseases may accompany the condition, such as pancreatitis, sclerosing cholangitis, retroperitoneal fibrosis, etc. Macroscopically, swelling is observed in the affected gland [4].

Lymphoepithelial sialadenitis: It is morphologically characterized by significant interstitial lymphocytic infiltration, lesions, and

atrophy of the salivary gland parenchyma. Isolated form or associated with Sjögren may be observed. It is usually seen in women, most commonly in the parotid gland. The etiology is multifactorial, with environmental and genetic factors playing a role. An abnormal immune response is observed. In patients with Sjögren, serum anti-Sjögren's syndrome A, anti-Sjögren's syndrome B, or rheumatoid factor and antinuclear antibody may be positive. Differential diagnosis should consider malignant lymphoma, lymphoepithelial carcinoma, and chronic sialadenitis.

Sjögren's syndrome: It was first described by ophthalmologist Henrik Sjögren and is characterized by dry eyes, dry mouth, and polyarthritis. Sjögren's syndrome is evaluated as two separate entities: primary and secondary. For the diagnosis of primary Sjögren's syndrome, it is essential that there is no secondary rheumatological disease apart from the inclusion and exclusion criteria. Minor salivary gland biopsy plays a significant role in the diagnosis of the disease. In these biopsy samples, focal lymphocytic sialadenitis and a focus score greater than 1 are diagnostic (Fig. 2.2). The focus in salivary gland biopsies refers to the presence of more than 50 mononuclear cell aggregates (mostly lymphocytes) in a single localization. The focus score is the number of foci per 4 square millimeters of salivary gland parenchyma [5].

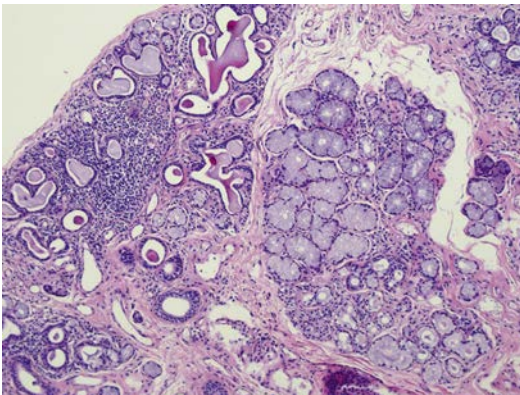


Fig. 2.2 Focus score in Sjögren syndrome

Necrotizing sialometaplasia: It is described as a self-healing benign salivary gland lesion that can mimic malignancy. It is most commonly seen in men in their fourth decade of life. It most frequently occurs in the minor salivary glands in the hard palate.

2.2.2 Non-neoplastic Tumor-Like Lesion

Salivary duct cyst: It is typically a single or multiple cysts with a diameter of 1–3 cm in the parotid gland. Microscopically, the cysts are lined with a single layer of the cuboidal or squamous epithelium, and there may be proliferation or oncocytic metaplasia in the epithelium. Developments of cystadenoma and mucoepidermoid carcinoma have been reported in these cysts.

Intercalated duct lesion: It is the benign proliferation of salivary gland ducts. It is a ductal proliferation lined with a double layer of epithelial and myoepithelial cells. It is a precursor lesion of tumors [6].

2.2.3 Primary Salivary Gland Neoplasm

Benign salivary gland tumors constitute 2–6.5% of all head and neck neoplasms [7, 8]. Most of these are of epithelial origin. Non-epithelial tumors such as hemangioma, lymphangioma, schwannoma, neurofibroma, and lipoma are very rare and will not be discussed here. Fifty-five to seventy-five percent of all salivary gland tumors are benign. The most common benign tumor is pleomorphic adenoma (PA) [7]. While benign salivary gland tumors are most commonly seen in major salivary glands, canalicular adenoma, ductal papilloma, and cystadenoma are more often observed in minor salivary glands [8].

Pleomorphic adenoma: It is a benign tumor that contains ductal, epithelial, and myoepithelial cells within a mesenchymal stroma. PA is the

most common tumor of the salivary gland, most often localized in the superficial lobe or tail of the parotid gland. It is most frequently observed in the palate among the minor salivary glands. PA appears as a well-circumscribed mass, measuring 2–5 cm in size, homogeneous in the salivary gland, usually encapsulated in major salivary glands, and non-encapsulated in minor salivary glands. Its color and consistency vary depending on the amount of epithelial and stromal components. Areas of the cartilage appear bright and translucent. Recurrent tumors are generally multinodular. Histologically, PA under light microscopy shows ductal epithelial cells forming solid, cystic, trabecular, and tubular patterns, along with myoepithelial cells and chondroid-myxoid mesenchymal stroma. Ductal structures are lined with cubic or columnar epithelium, and the myoepithelial cells may exhibit spindled, clear, plasmacytoid, basaloid, squamoid, or sebaceous morphology (Fig. 2.3). Immunohistochemically (IHC), in PA, ductal epithelial and myoepithelial cells are positively stained with cytokeratin (CK), while myoepithelial cells are stained with vimentin, S100, glial fibrillary acidic protein (GFAP), SMA, calponin, CD10, and PLAG1 (pleomorphic adenoma gene 1) [9, 10]. Cytogenetically, the most commonly identified translocation in PA is 8q12 (39%). In this translocation, the target gene PLAG1 can also be demonstrated immunohistochemically. Additionally, cytogenetic findings in PAs show a translocation on 12q13–12q15 (8%) involving the “high mobility group protein gene” HMGA2, along with sporadic gene rearrangements [11, 12, 13]. In the differential diagnosis of PA, morphologically benign tumors of the salivary gland, especially myoepithelioma, basal cell adenoma, and among malignant tumors, polymorphous low-grade adenocarcinoma and adenoid cystic carcinoma (AdCC), should be considered.

Metastatic pleomorphic adenoma: In PAs, tumors that are histologically indistinguishable from PAs have been detected in areas distant from the salivary glands. These very rare tumors are cases that show multiple recurrences occurring 3–52 years after the initial diagnosis of

PA. The most common sites for metastasis are the bone, head-neck, and lung. The prognosis is quite good.

Myoepithelioma: It is a benign salivary gland tumor consisting entirely of myoepithelial cells. It is most commonly found in the parotid gland and secondarily in the soft and hard palates. Myoepithelial adenoma is a synonym for monomorphic adenoma. Macroscopically, it is usually observed as a well-circumscribed, soft, rubbery consistency, white or cream-colored mass in salivary glands, typically smaller than 3 cm. Microscopically, a well-circumscribed tumor is seen under light microscopy, with variable capsular conditions, forming solid-myxoid-reticular-nest-like patterns, composed of spindle-shaped, plasmacytoid, epithelioid, and clear cytoplasmic cells. Varying amounts of collagenization and acellular mucoid stroma may be observed in the stroma. Differential diagnosis of myoepithelioma should include PA, myoepithelial carcinoma, basal cell adenoma, and plasmacytoma, as well as spindle soft tissue tumors [11]. Myoepitheliomas show less recurrence compared to PA, and malignant transformation occurs, especially in highly recurrent, older tumors into malignant myoepithelial carcinoma [11].

Basal cell adenoma: It is a benign salivary gland tumor composed of small basaloid cells. It constitutes 2% of salivary gland neoplasms, most commonly found in the parotid gland (75%),

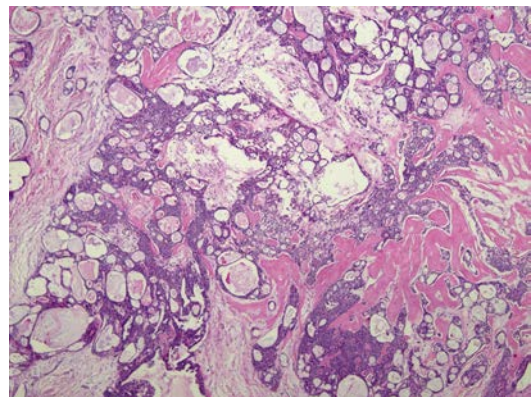


Fig. 2.3 Pleomorphic adenoma

with the remainder seen in the submandibular and minor salivary glands. Macroscopically, it appears as a well-defined pink-brown mass, typically less than 3 cm in size, resembling a lymph node. Under the light microscope, the tumor may exhibit solid, trabecular, tubular, or membranous patterns. The tumor cells are small, basaloid in appearance, poorly cytoplasmic, with indistinct cytoplasmic borders and have oval-round dense nuclei arranged in a fence-like pattern at the periphery. In the center of these basaloid clusters, larger polygonal or angular cells with wider cytoplasm, pale coloring, and round nuclei may be found. Immunohistochemically, all tumor cells are positively stained with pan-CK. The cells causing palisade are also stained with myoepithelial cell markers. Nuclear beta-catenin positivity has been reported in 75% of cases. Genetically, mutations have been shown on chromosomes 8p22, 19q13, and 16q12–16q13. The prognosis for basal cell adenoma is quite good. In differential diagnosis, basal cell adenocarcinoma (BCA), adenoid cystic carcinoma, canalicular adenoma, PA, and myoepithelioma should be considered.

Warthin tumor: Adenolymphoma and papillary cyst adenolymphoma are synonymous terms. It is the second most common salivary gland tumor after PA. It is most commonly localized in the parotid, is seen more in males in the sixth to seventh decades, is a slowly growing tumor measuring 1–4 cm, and is definitively associated with smoking. Although there is no conclusive evidence that Epstein-Barr virus, human papillomavirus (HPV), and human herpesvirus-8 play a role in the development of Wilms tumor (WT), it is thought they may contribute. Bilaterality, synchronous-metachronous tumors can be seen in Warthin tumor. WT is believed to develop from the neoplastic transformation of trapped salivary gland ducts within or adjacent to lymph nodes.

WT is seen as a well-defined oval round mass, cystic, solid in appearance within the salivary gland macroscopically. Upon closer inspection, small papillary projections may draw attention to the cystic areas, while the solid areas resemble the cut surface of a lymph node. Cystic areas can contain cream-colored or brownish fluid. A micro-

scopic examination shows that the tumor consists of papillary-cystic structures lined with oncocytic epithelial cells and lymphoid stroma centered around a germinal center. The epithelium is arranged in two layers, with columnar cells inside and cubic cells outside. The epithelium may contain squamous, mucous, ciliated, or sebaceous cells. In the lumen of the cystic structures, thick homogeneous secretions and materials similar to corpora amylacea can be observed. The lymphoid stroma appears polymorphic (Fig. 2.4). Langerhans-type giant cell granulomatous reaction may contain areas of necrosis related to infarction. Immunohistochemically, all oncocytic epithelial cells in WT are positively stained with pan-Keratin, epithelial membrane antigen (EMA), SK8/18. Myoepithelial markers (GFAP, P63, SMA, calponin, s100) are generally negative; lymphoid stroma is positively stained with CD3 and CD20. The complete removal of the tumor mass is the treatment for WT. Recurrence is rare. Malignant transformation is extremely rare, occurring most commonly as squamous cell carcinoma (SCC) in the epithelial component and as malignant lymphoma non-Hodgkin transformation in the lymphoid component. In differential diagnosis, sebaceous lymphadenoma and salivary gland tumors containing oncocytic cells (oncocytoma, mucoepidermoid carcinoma (MEC), etc.) should be considered.

Oncocytoma: Synonyms—Oncocytic adenoma and oxyphilic adenoma. It is a rare benign tumor

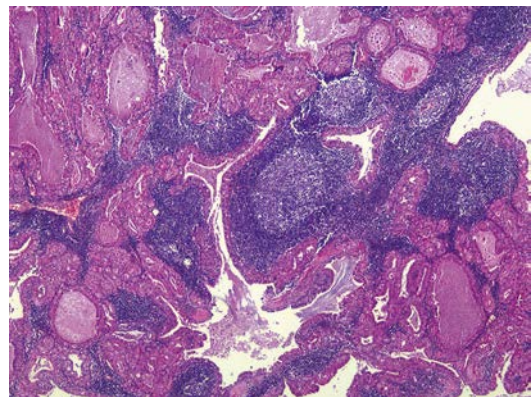


Fig. 2.4 Warthin tumor

composed of large eosinophilic, granular cytoplasm, polygonal uniform cells known as oncocytes. It is most commonly seen in older age, particularly in the parotid gland. It can be bilateral in 7% of cases. Exposure to ionizing radiation for more than 5 years plays a role in its etiology. Grossly, these tumors appear as well-circumscribed, thick-capsulated, reddish, or brownish masses ranging from 1 to 7 cm in diameter in the salivary gland. Microscopically, the tumor consists of cells that are twice the size of normal acinar cells with broad polygonal cytoplasm forming acinar and tubular patterns. The cells stain positively with phosphotungstic acid hematoxylin stain. There is a fine fibrovascular stroma between the cells, and lymphocytes are not frequently observed in this stroma. Immunohistochemically, oncocytomas stain positive for EMA, SK5/6, SK8/18, SK7, SK19, α -1-antitrypsin, and anti-mitochondrial antibody. Pax-8, S100 protein, calponin, GFAP, and SMA do not stain. Mitochondrial gene mutations may be observed genetically in these cases.

In the differential diagnosis, oncocytic metaplasia, oncocytic hyperplasias, Warthin tumor, and acinic cell carcinoma, as well as metastatic renal cell carcinoma observed in salivary gland acini, should be considered along with age [14].

Lymphoepithelioma: It is a well-defined, rare benign salivary gland tumor. It is most frequently seen in the parotid gland. There are sebaceous and non-sebaceous forms. Macroscopically, it appears as a capsulated, solid, or multicystic mass with a gray-yellow cut surface in the salivary gland. Differential diagnoses should include lymphoepithelial carcinoma and metastatic carcinoma [15].

Cyst adenoma: It is a benign tumor that is more commonly seen in women, characterized by a multicystic growth pattern, often lined with papillary epithelium, and is equally frequent in both large and small salivary glands. The epithelium lining the cysts may sometimes have oncocytic characteristics, can rarely be mucinous, and may infrequently show apocrine differentiation. Eosinophilic material, inflammatory cells, and

foam cells are present in the cyst lumens along with the shed epithelium. The treatment is conservative excision of the local mass. Recurrence is rare.

Sialadenoma papilliferum: It is a rare salivary gland tumor mainly seen in the hard palate and buccal mucosa. In its etiology, inflammation and salivary stones play a role. It appears as long-lasting exophytic papillary mucosal lesions. Macroscopically, it is usually a polypoid, pedunculated, verrucous-surfaced, well-circumscribed cystic lesion. Microscopically there are papillary projections on the surface epithelium and submucosal cyst-like spaces. The treatment is the surgical removal of the mass. Recurrence is extremely rare [16].

Ductal papillomas: They are synonymous with epidermoid papillary adenomas. They can be inverted or intraductal. Trauma and HPV are reported in their etiology. The small salivary glands located in the mouth are the most common localization. They appear as painless submucosal lesions. An intraductal papilloma is a nodular well-defined lesion measuring 0.5–2 cm in diameter that develops at the very end of the salivary gland drainage duct opening to the surface. Mucoepidermoid carcinoma should be considered in the differential diagnosis [17].

Sebaceous adenoma: It is very rare, mostly occurring in the parotid gland, and is a benign salivary gland tumor consisting of well-defined sebaceous cell islands ranging in size from 0.4 to 6 cm. In this tumor, pleomorphism and atypia are minimally observed. Squamous metaplasia and oncocytic changes may be seen. Sebaceous adenomas are immunohistochemically positively stained for P63, s100, EMA, adipophilin, and perilipin. It is distinguished from sebaceous lymphadenoma by the absence of a lymphoid stroma [18].

Canalicular adenoma: It is a benign salivary gland tumor that is primarily seen in minor salivary glands, especially in the upper lip. It appears as a non-encapsulated, well-circumscribed lesion,

generally 1–2 cm in diameter, with a pink-brown solid-cystic cut surface in minor salivary glands. Microscopically, the tumor consists of long single-layered columnar-cubic cell strands and tubular structures, interspersed with loosely arranged slightly collagenized stroma. The tumor may be multifocal. In the differential diagnosis, PA, basal cell adenoma, adenoid cystic carcinoma, and polymorphous low-grade adenocarcinoma should be kept in mind. Canalicular adenoma (CA) has a very good prognosis. Recurrence may be observed in multifocal lesions [19].

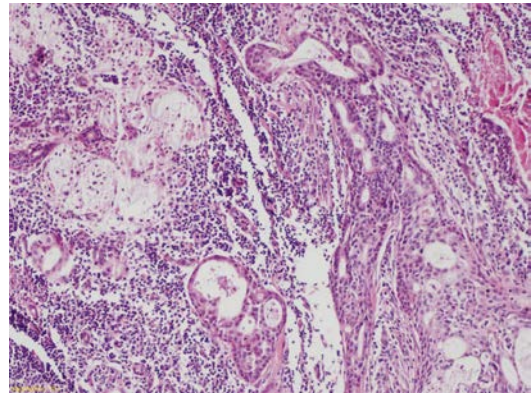


Fig. 2.5 Mucoepidermoid carcinoma

2.3 Malignant Tumors of Salivary Glands

Mucoepidermoid carcinoma: It is the most common malignant tumor of the salivary glands, composed of mucinous, intermediate (clear), and squamoid cells in a cystic or solid pattern. It is seen in children and adults of all ages. It can develop secondary to radiochemotherapy. It is most commonly located in the parotid gland. It also frequently involves the minor glands of the hard palate. Clinical findings vary depending on the tumor's location, size, and grade. Macroscopically, the lesions appear as solid masses with variable consistency, well-defined or infiltrative, and often contain a cystic component. Microscopically, cystic/solid tumoral islands composed of squamoid, mucin-producing, and clear cells are observed. There is no obvious keratinization. Intracytoplasmic mucus is observed with mucicarmine and alcian blue staining. Low-grade MEC is cystic, rich in mucinous cells, and well-defined; intermediate-grade MEC is relatively more solid, with slightly irregular borders. High-grade MEC demonstrates nuclear anaplasia, necrosis, active mitoses, perineural, lymphovascular, and bone invasion. Mucus, even focal, must be evident for the diagnosis of high-grade MEC (Fig. 2.5). Necrotizing sialometaplasia, squamous cell carcinoma, and cystic adenocarcinoma should also be considered in the differential diagnosis. Immunohistochemically, MEC p63 and p40 positivity and the absence of

sox 10 and s100 are helpful in the differential diagnosis. Molecular MEC has a t(11;19) (q21;p13) translocation followed by CRTC1-MAML2 gene translocations. Prognosis depends on stage, location, grade, and surgical excision. While the 10-year survival rate for low- and moderate-grade MEC reaches 90% with surgical treatment, this rate drops to around 25% in high-grade cases [7, 20, 21].

Adenoid cystic carcinoma: It is a slow-growing tumor composed primarily of tubular, cribriform, and solid patterns formed by epithelial and myoepithelial cells. Its incidence increases in the sixth decade, accounting for approximately 10% of all salivary gland neoplasms. While major gland involvement is more common, minor glands are also affected. The primary complaint of these cases includes neurological findings such as paresthesia, pain, and other symptoms due to the neurotrophic properties of the mass and tumor. Macroscopically, the tumor appears as a hard, off-white, irregularly margined mass of variable size. The presence of necrosis and hemorrhage indicates a high grade. Microscopic examination reveals tubular, cribriform, and solid patterns, often presenting as highly variable patterns. The most common pattern, a bilayered population of cribriform epithelial and myoepithelial cells, is surrounded by a basaloid matrix (Fig. 2.6). Both myoepithelial and epithelial cells are observed, forming a true lumen in the tubular pattern. The cytoplasm of the cells is generally

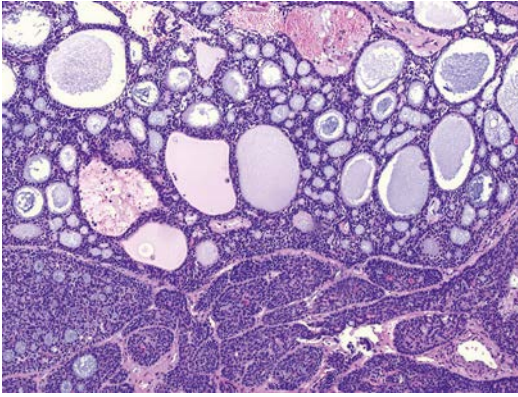


Fig. 2.6 Adenoid cystic carcinoma

narrow, and the nuclei are small and angular. Perineural invasion is seen in almost all cases. High-grade transformation or dedifferentiation may occasionally occur. In the differential diagnosis, polymorphous adenocarcinoma, epithelial myoepithelial carcinoma, and basal cell adenocarcinoma, in addition to benign entities like PA, should be considered. Immunohistochemically, AdCC expresses CD117 (c-kit) in the epithelial component. Myoepithelial cells react positively with myoepithelial markers such as S100, P63, calponin, and smooth muscle actin. Myeloblastosis Viral Oncogene Homolog (MYB) and MYB-Nuclear Factor I/B (NFIB) fusion antibodies also react with the tumor. The primary genetic alteration in these tumors is the t(6;9) and, to a lesser extent, the t(8;9) translocations. As a result, fusion develops in the MYB or MYBL1 oncogenes and the NFIB transcription factor gene. This has created an avenue for targeted therapies and is helpful in diagnosis. The prognosis for solid tumors with 1p and 6q loss is poor [7, 8, 21]. Ten-year survival has been reported between 50% and 90% in series.

Acinic cell carcinoma: It can be defined as a carcinoma of the salivary gland that exhibits serous acinar features. The mean age of onset is 50, the second most common salivary gland carcinoma in the pediatric age group, and is very rare in minor glands. It is most commonly seen in the parotid gland. The mass is usually slow-growing, mobile, and sometimes multinodular. Macroscopically, it

is usually described as a well-defined mass of variable diameter with an off-white cross-sectional surface. Microscopically, vacuolated, clear, oncocytic, and hobnail-like cells form solid, microcystic, follicular, and papillary patterns. The cytoplasm is usually large, vacuolar, granular, round, and eccentric. The cytoplasm is positive with periodic acid-Schiff (PAS) staining. A lymphocytic response to the tumor is observed. The presence of neural invasion, undifferentiated solid, cribriform, and glandular components, and necrosis are signs of a poor prognosis. Immunohistochemically, DOG1 and SOX10 are positive, and p63/p40 are negative. NR4A3 or NR4A2 nuclear staining is seen in 98% and 2% of cases, respectively. In intermediate cases, molecular demonstration of NR4A3 rearrangement is diagnostic [7, 8, 21]. These tumors generally have a good prognosis. While recurrence is possible, distant or local metastases are rare.

Secretory carcinoma (SC): It is a low-grade carcinoma resembling SC of the breast and exhibits an ETV6-NTRK3 gene fusion. It is most commonly seen in the fifth decade and is most commonly located in the parotid gland. Microscopic examination of the mass, which contains cystic areas with irregular borders, reveals secretions within microcystic, tubular, follicular, and papillary-cystic structures with fibrous septa in a lobulated pattern. The cells have small, uniform nuclei with eosinophilic, granular, and vacuolar cytoplasm. The cells are PAS positive and zymogen granules negative. Characteristically, they are S100 and mammaglobin positive and DOG1 negative. High-grade transformation is uncommon. Genetically, the t(12;15)(p13;q25) translocation causes the fusion of the ETV6 gene on chromosome 12 with the NTRK3 gene on chromosome 15 [22].

Polymorphous adenocarcinoma (PAC): The fundamental characteristic of this tumor, as its name suggests, is a cytologically uniform cell population exhibiting a morphologically diverse infiltrative growth pattern. It has classical, conventional, and cribriform subtypes. It most commonly affects the minor salivary glands. The female-to-male

ratio is 2:1, and the average age is around 60. It is rare in the pediatric age group. While most commonly affecting the hard palate, it is also observed in the buccal mucosa, retromolar trigone, and upper lip and tongue base regions. It is rare in the major glands. A painless mass of variable duration may present with bleeding and ulceration, along with the typical presenting complaint.

Macroscopically, the main characteristics are a firm, well-circumscribed, unencapsulated, off-white, nodular mass with variable diameters (average 2 cm). Microscopically, an unencapsulated lesion is observed in the submucosa. Histologically, tumor cells exhibit very uniform but highly variable patterns and invade surrounding tissues. Pattern variations are common within the same tumor as well as between tumors. Basic patterns include lobular, trabecular, microcystic, cribriform, solid, and papillary-cystic. A swirling appearance may be present at the tumor periphery. The cells are small- to medium-sized, with occasional nucleoli and oval nuclei with minimal hyperchromasia. Stromal mucinous or hyalinization findings may be observed, as well as oncocytic, squamoid, and mucous cells. Mitosis and necrosis may occur in high-grade transformation. Perineural invasion is common. Bone infiltration occurs in mucosal areas close to the bone. Immunohistochemical stains show CK 7 and S100 positive in almost all cases, p40 negative, and p63 positive in 70–80%. PRKD1, PRKD2, or PRKD3 mutations may be diagnostic. PAC has a good prognosis. Lymph node metastasis, high-grade transformation and the cribriform subtype, PRKD gene fusion, necrosis, extrapalatal localization, angiolymphatic spread, and perineural spread around major nerves are indicators of a poor prognosis [7, 8, 21].

Hyalizing clear cell carcinoma: It is a rare tumor composed of eosinophilic clear cells in a hyalinized stroma, primarily affecting the minor salivary glands. It usually presents as an ulcerated submucosal swelling. Macroscopically, it appears as a well-circumscribed, solid, white-red mass measuring 4–50 mm in diameter. Microscopically, it shows small cysts within the

hyalinized stroma, forming nests of cells with clear eosinophilic cytoplasm. Clear cells are PAS-positive and diastase-sensitive. Immunohistochemically, staining with epithelial and myoepithelial markers is seen. Molecular identification of the EWSR1 fusion gene aids in diagnosis. It is a slow-growing tumor with a good prognosis [7, 8].

Basal cell adenocarcinoma: It is an infiltrative salivary gland carcinoma composed of basaloid and ductal cells in varying proportions. Patients present with complaints of a slowly growing mass, often affecting the parotid gland. In some cases, multiple skin appendage tumors are noted. Macroscopically, an unencapsulated, white tumor measuring 2–4 cm is observed. Microscopically, an invasive tumor with solid, tubular, trabecular, or membranous patterns is observed. Peripheral palisading of the basal cells and deposits of basement membrane-like material in the underlying light-colored epithelial cells are typical. Perineural and vascular invasion may be observed. The differential diagnosis between AdCC and basal cell adenoma is important. Genetic alterations in CYLD are observed in some cases. Recurrence is not expected in cases of completely surgically resected BCA. Regional and distant metastases are extremely rare [22].

Intraductal carcinoma (IDC): It is an intracystic/ductal proliferation of neoplastic epithelial cells. It is very rare. It is most commonly located in the parotid gland. An asymptomatic mass is the primary presenting finding, and macroscopically, it is described as a small, unencapsulated cystic mass. Microscopically, IDC is observed with low, intermediate, or high nuclear grades. Most low-grade tumors exhibit cribriform and papillary patterns. The cells have a monotonous appearance. Cuboidal, mucinous, and apocrine features are observed. Intermediate- and high-grade tumors may contain necrosis and have a high mitotic index. These cases can present a challenge in the differential diagnosis with adenocarcinoma Not Otherwise Specified (NOS). The prognosis is excellent with complete excision [7, 8, 21].

Salivary duct carcinoma: It is a high-grade carcinoma originating from the exocrine ducts of the salivary glands and histologically resembling ductal carcinoma of the breast. It accounts for approximately 10% of all salivary gland malignancies. It is more common in men, typically between the sixth and eighth decades. It most commonly arises from the Stensen duct of the parotid. Cases have been reported in the submandibular gland, minor palatal glands, and, less frequently, the sublingual gland, paranasal sinuses, and minor palatal glands. A mass that can involve the facial nerve, with or without pain, is the primary complaint. It can occur *de novo* or present as a carcinoma *ex pleomorphic adenoma*. In these cases, history suggests that a long-standing mass has typically grown rapidly in recent years. Macroscopically, a tumorous mass of variable diameters with an ill-defined, off-white cross-sectional area is observed. Microscopic examination reveals tumoral islands with central comedo necrosis, which exhibit intraductal or infiltrative nodular-cystic, lobular, solid, papillary, or cribriform growth patterns. Comedonecrosis is characteristic but not pathognomonic. Stromal fibrosis and lymphoplasmacytic infiltration, sometimes dense, are present, and the neoplastic cells are cuboidal, polygonal, and generally centrally located and show moderate to prominent nuclear pleomorphism. Neural or angioinvasion, as well as invasion of surrounding parenchyma and soft tissue layers, is common. Metastatic breast carcinoma should be excluded in the differential diagnosis. In this regard, history is crucial. Genetically, loss of heterozygosity in regions 9p21, 6q, 16q, 17p, and 17q; ERBB (HER-2) gene amplification; p53 mutation; CASP10 and MMP11 overexpression; CDKN2a/p16 inactivation; and PI3CA, HRAS, and BRAF mutations have been reported [22].

Myoepithelial carcinoma: It is an infiltrative carcinoma composed entirely of myoepithelial cells and is rare, with no age or gender predominance. A painless mass is the most common complaint. Macroscopically, it is slightly firm, gray-white, cystic, hemorrhagic, and sometimes necrotic. Microscopic examination reveals a

solid, trabecular, and reticular tumor with a pushing infiltration pattern. The cells are spindle-shaped, epithelioid, and eccentrically nucleated and stain faintly positive for myoepithelial markers (S100, smooth muscle actin, calponin, etc.) and keratins. Genetic EWSR1 rearrangements have been reported. In some cases, complete surgery has been performed, and approximately 30% of cases have reported uneventful survival, with local or distant metastases [7, 8, 21].

Epithelial myoepithelial carcinoma: It is a biphasic carcinoma composed of luminal ductal epithelial and myoepithelial cells. It is rare (less than 5% of all salivary gland malignancies). It is more common in older women. It predominates in the parotid and submandibular glands. A slowly growing, painless mass is the most common complaint. Macroscopically, a firm, multinodular, partially encapsulated mass with a pushing infiltrative pattern is typically observed. The cut surface is cystic, and mucosal areas are ulcerative. Microscopically, a biphasic, bilayered cellular population infiltrates the surrounding area with nodular pushing borders. The inner ductal luminal cells contain small eosinophilic cytoplasm, while the outer myoepithelial cells contain larger, polygonal, clear cytoplasm and eccentric nuclei. Perineural invasion is common. High-degree transformation consisting of anaplastic myoepithelial cells has been reported. Although the prognosis is generally good, local recurrences may occur [7, 8, 21].

Carcinoma ex pleomorphic adenoma: It is an infiltrative tumor arising from primary or recurrent PA, the component of which may be epithelial and/or myoepithelial. It accounts for more than 10% of all salivary gland malignancies, with some series exceeding 40%. It is slightly more common in women in the sixth and seventh decades, with a higher incidence. The majority of cases are localized to the parotid gland. A painful, rapidly growing mass is typical. While the macroscopic appearance is variable, it is largely infiltrative and may contain focal findings of underlying PA, such as a bright appearance of

chondromyxoid stroma or a nodular growth pattern. A malignant component accompanying PA is observed microscopically. This component is usually a high-grade adenocarcinoma, most of which have a tubuloductal phenotype. MyEC is observed in approximately one-third of the cases. Cases confined to the capsule are high-grade and ductal. Immunohistochemically, epithelial and/or myoepithelial markers stain positive depending on the accompanying component. In addition to fusion genes (PLAG1 and HMGA2) in PA, P53 mutations, MDM2 and HMGA2 (12q13–12q15), and HER2 amplifications have been reported in these tumors [1, 9]. It is an aggressive tumor. Local or distant metastases develop in 70% of cases, and the 5-year survival is 65% in the best series. Although the prognosis is reported to be relatively good in intracapsular and minimally invasive cases (not exceeding 4–6 mm from the PA margin), further studies are needed in this regard [8, 20, 21].

Sialoblastoma: It is a rare, basaloid tumor observed in infancy, involving primitive (anlage) structures of the salivary glands, with uncertain malignant potential. It most often presents at birth or shortly thereafter and is located in the parotid gland. Skin ulceration and facial swelling are present.

Squamous cell carcinoma: Primary salivary gland SCC is very rare, and this diagnosis should not be made without completely excluding SCC of other sites, especially the skin, or squamous metaplasia/differentiation of another salivary gland neoplasm. In general, patients presenting with advanced-stage, painful parotid masses have macroscopic and microscopic findings similar to conventional SCC. Observing dysplastic findings or areas of in situ carcinoma in the ducts is supportive of primary salivary gland SCC [7].

Salivary gland carcinoma: It represents a group of epithelial-type carcinomas of salivary gland origin, forming ductal and/or glandular structures with or without cystic structure. The mean age of onset is the sixth decade, accounting for approximately 10–15% of all salivary gland

carcinomas. It is common in the parotid gland. In the oral cavity, it most commonly arises from the minor glands of the hard palate. An asymptomatic mass is the most common presenting complaint. Macroscopically, the mass may be well-defined, irregularly hard, infiltrating areas of necrosis or hemorrhage of variable diameter, with a solid, off-white cross-sectional area. Microscopically, glandular or ductal structures sometimes form cystic areas. Cells may exhibit a variety of morphologies: columnar, mucous, oncocytic, plasmacytoid, etc. The stroma is usually dense and fibrotic. The diagnosis of adenocarcinoma or NOS requires the exclusion of other carcinomas, such as salivary gland duct carcinoma, mucoepidermoid carcinoma, and metastatic carcinoma [7, 8, 20, 21]. The prognosis is poor in high-grade tumors and advanced stages but very good in those with predominant cystic formation and complete resection.

References

1. Uğuz HA. Salivary glands. In: Sarioğlu S, editor. Head and neck pathology. 1st ed. İzmir: O'Tıp; 2014. p. 261–72.
2. Carney JA. Salivary heterotopia, cysts, and the parathyroid gland: brachial pouch derivatives and remnants. *Am J Surg Pathol*. 2000;24(6):837–45.
3. Harrison JD. Causes, natural history, and incidence of salivary stones and obstructions. *Otolaryngol Clin N Am*. 2009;42(6):927–47.
4. Deshpande V, Zen Y, Chan JK, et al. Consensus statement on the pathology of IgG4-related disease. *Mod Pathol*. 2012;25(9):1181–92.
5. Baldini C, Fulvio G, Ferra F. Update on the pathophysiology and treatment of primary Sjögren syndrome. *Nat Rev Rheumatol*. 2024;20:473–91.
6. Weinreb I, Seethala RR, Hunt JL, Chetty R, Dardick I, Perez-Ordoñez B. Intercalated duct lesions of salivary gland: a morphologic spectrum from hyperplasia to adenoma. *Am J Surg Pathol*. 2009;33(9):1322–9.
7. Everson JW, Auclair P, Gnepp DR, Ei-Nagggar AK. Tumors of the salivary glands. In: Barnes L, Eveson JW, Reichart P, Sidransky D, editors. Pathology and genetics of head and neck tumors. World Health Organization classification of tumors. Lyon: IARC Press; 2021. p. 209.
8. Pinkston JA, Cole P. Incidence rates of salivary gland tumors: results from a population-based study. *Otolaryngol Head Neck Surg*. 1999;120(6):834–40.
9. Triantafyllou A, Thompson LD, Devaney KO, Bell D, Hunt JL, Rinaldo A, et al. Functional histology of sali-

- vary gland pleomorphic adenoma: an appraisal. *Head Neck Pathol.* 2015;9(3):387–404.
10. Rotellini M, Palomba A, Baroni G, Franchi A. Diagnostic utility of PLAG1 immunohistochemical determination in salivary gland tumors. *Appl Immunohistochem Mol Morphol.* 2014;22(5):390–4.
 11. Jo VY, Fletcher CD. Myoepithelial neoplasms of soft tissue: an updated review of the clinicopathologic, immunophenotypic, and genetic features. *Head Neck Pathol.* 2015;9(1):32–8.
 12. Li BB, Zhou CX, Jia SN. Basal cell adenoma of salivary glands with a focal cribriform pattern: clinicopathologic and immunohistochemical study of 19 cases of a potential pitfall for diagnosis. *Ann Diagn Pathol.* 2014;18(1):5–19.
 13. Skálová A, Vanecek T, Simpson RH, Vazmitsel MA, Majewska H. CRTC1-MAML2 and CRTC3-MAML2 fusions were not detected in metaplastic Warthin tumor and metaplastic pleomorphic adenoma of salivary glands. *Am J Surg Pathol.* 2013;37(11):1743–50.
 14. Wakely PE Jr. Oncocytic and oncocyte-like lesions of the head and neck. *Ann Diagn Pathol.* 2008;12(3):222–30.
 15. Seethala RR, Thompson LD, Gnepp DR, Barnes EL, Skalova A, Montone K. Lymphadenoma of the salivary gland: clinicopathological and immunohistochemical analysis of 33 tumors. *Mod Pathol.* 2012;25(1):26–35.
 16. Kubota Y, Kubo C, Mori Y. Sialadenoma papilliferum of the hard palate: a case report. *J Oral Maxillofac Surg.* 2012;70(7):1609–12.
 17. Brannon RB, Sciubba JJ, Giuliani M. Ductal papillomas of salivary gland origin: a report of 19 cases and a review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2001;92(1):68–77.
 18. Pattnaik N, Parmar D, Rao BR, Rao ES. Sebaceous lymphadenoma of submandibular gland. *J Indian Med Assoc.* 2013;111(1):62–3.
 19. Huebner TA, Almubarak H, Drachenberg CB, et al. Canalicular adenoma—search for the cell of origin: ultrastructural and immunohistochemical analysis of 7 cases and review of the literature. *Ultrastruct Pathol.* 2014;38(2):74–82.
 20. Skálová A, Hyrcza MD, Leivo I. Update from the 5th edition of the World Health Organization classification of head and neck tumors: salivary glands. *Head Neck Pathol.* 2022;16(1):40–53.
 21. Toper MH, Sarioglu S. Molecular pathology of salivary gland neoplasms: diagnostic, prognostic, and predictive perspective. *Adv Anat Pathol.* 2021;28(2):81–93.
 22. Skálová A, Vanecek T, Sima R, et al. Mammary analogue secretory carcinoma of salivary glands, containing the ETV6-NTRK3 fusion gene: a hitherto undescribed salivary gland tumor entity. *Am J Surg Pathol.* 2010;34(5):599–608.

Pathology of the Esophagus and Stomach

3

Semin Ayhan

3.1 Pathology of the Esophagus

The esophagus, a tubular structure with the lumen extending from the epiglottis to the gastroesophageal junction (GEJ), is covered with the multilayered squamous epithelium. Its main function is to convey food from the pharynx to the stomach and to prevent gastric contents from escaping backward. It achieves this function through coordinated peristaltic muscle movements and the upper and lower esophageal sphincters, which are not anatomical but physiological mechanisms. Unlike other organs of the gastrointestinal (GI) tract, the esophagus has no role in digestive, endocrine, or metabolic functions. Therefore, when pathologies in the esophagus impair its function, they cause only symptoms such as dysphagia, retrosternal pain, burning sensation, weight loss, and hematemesis [1–3].

3.1.1 Congenital Anomalies of the Esophagus

Congenital anomalies such as atresia, fistula, agenesis, duplication, and stenosis can cause mechanical obstruction of the esophagus. Atresia is a malformation characterized by the replacement of a segment of the esophagus into a thin, lumenless,

cord-like fibrous tissue. It most commonly occurs at the level of the tracheal bifurcation and is associated with fistulas. The cause of this anomaly is the failure of the foregut to completely divide into the esophagus and trachea during the fourth week of gestation. This leads to the formation of tracheoesophageal fistulas. The most common form of tracheoesophageal fistulas is the blind termination of the upper segment of the esophagus and fistulation of the lower esophageal segment into the trachea along with the gastric pouch (Fig. 3.1). In this form of tracheoesophageal fistula, which occurs in 85% of cases, stomach contents regurgitate into the trachea, causing aspiration, respiratory distress, pneu-

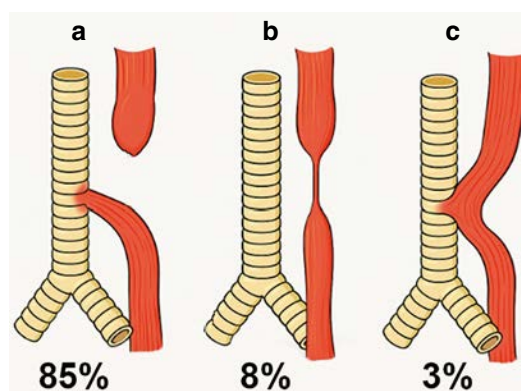


Fig. 3.1. The three most common types of esophageal atresia and tracheoesophageal fistula are numbered 1–3 in order of frequency: (a) Blind upper segment and fistula between the lower segment and the trachea (b). Blind upper and lower esophagus connected by a thin strand of the connective tissue (c). Fistula without atresia between the esophagus and the trachea

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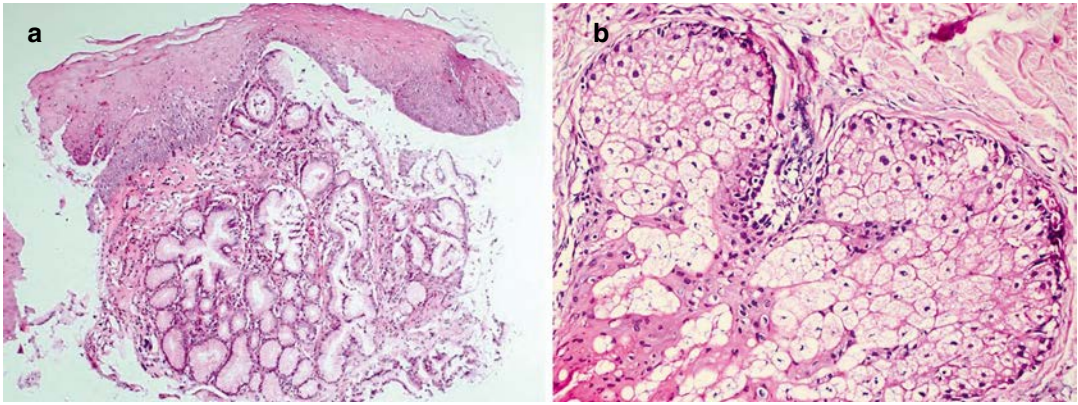


Fig. 3.2. (a) Gastric heterotopia inlet patch. Cardiac-type mucosa is seen under the squamous esophageal mucosa. (b) Mature sebaceous glands are present surrounded by esophageal squamous mucosa

monia, asphyxia, and fluid-electrolyte imbalance in the infant after feeding. If appropriate surgical treatment is not administrated early, this situation results in 90% mortality. Esophageal agenesis, or the complete absence of the esophagus, is a very rare congenital anomaly. Duplications appear as cystic structures, are more commonly found in the lower third of the esophagus, and create a mass lesion effect. These anomalies arise due to developmental deficiencies of the esophagus around the fifth to eighth weeks of gestation. They are typically intramural cystic structures within the esophageal wall, unrelated to the lumen. The muscularis propria appears intact, and the inner surface of the duplications is covered by squamous, cuboidal, or ciliated columnar epithelium. Stenoses, which manifest as fibrous thickening of the esophageal wall and narrowing of the lumen, are either congenital or, more commonly, acquired abnormalities. The acquired forms result from severe esophageal damage caused by gastroesophageal reflux disease (GERD), radiation, scleroderma, or ingestion of caustic substances. In stenoses, atrophy and ulceration of the esophageal epithelium, as well as fibrous thickening of the submucosa and atrophy of the muscle layer, may be observed. Ectopic tissues are also the most common congenital anomalies in the entire gastrointestinal tract. The most common ectopic tissue in the esophagus is gastric mucosa, which is observed in the proximal third. The gastric mucosa may exhibit cardiac, antral, or oxyntic characteristics. This condition is clinically referred to as an inlet patch. In addition to

gastric mucosa, pancreatic and adipose tissue ectopias may also be observed in the esophagus (Fig. 3.2). Gastric and pancreatic tissues can secrete enzymes, causing an inflammatory reaction in the esophageal epithelium and associated dysphagia. In rare cases, they may also lead to the development of adenocarcinomas [1–3].

3.1.2 Acquired Anomalies of the Esophagus

Mucosal webs and Schatzki rings, which cause esophageal stenosis, are acquired lesions rather than congenital ones. Webs, which are concentric narrowings in the esophageal lumen in the shape of a half ring, are more common in women aged >40 years. The Schatzki ring, located in the distal esophagus just above the squamo-columnar junction, is a mucosal fold extending toward the lumen in a circular manner. Histopathologically, submucosal edema, increased fibrovascular connective tissue, and sometimes hypertrophy of the muscularis propria are observed beneath the normal-appearing esophageal epithelium in both acquired lesions. Diverticula are outpouchings of the wall of the esophagus, either proximal or distal, involving all layers of the wall. The proximal diverticulum, known as Zenker's (pharyngeal) diverticulum, is located in the distal pharynx, where the cricopharyngeal muscles are weak. This mucosal protrusion, which also includes the submucosa and surrounding fibrous tissue, can reach several centi-

meters in diameter and may serve as a site for food accumulation as a result of regurgitation during sleep. Diverticula in the middle part of the esophagus are located at the level of the tracheal bifurcation. They often develop as a result of fibrotic mediastinal lymphadenitis and are known as traction diverticula. Diverticula located immediately above the lower esophageal sphincter are epiphrenic diverticula. These diverticula usually occur in conjunction with hiatal hernia, and in most cases, abnormal movements in the form of impaired peristalsis are observed [1–3].

3.1.3 Functional Obstructions of the Esophagus

Functional obstructions of the esophagus are the result of esophageal dysmotility. This condition arises from the disruption of coordinated peristaltic muscle movements in the esophageal wall or due to muscle spasms. Esophageal dysmotility is relatively rare and can manifest in different clinical forms, depending on the disorder of peristalsis in the esophageal muscles. The most well-known of these disorders is achalasia. Achalasia, which occurs between the ages of 25 and 60 years and causes symptoms such as dysphagia, belching, and chest pain, is associated with an increased risk of developing squamous cell carcinoma (SCC) of the esophagus. Achalasia is characterized by a triad of inadequate relaxation of the lower esophageal sphincter, increased lower esophageal sphincter tone, and aperistalsis. Primary achalasia is an idiopathic disease resulting from the degeneration of inhibitory neurons in the distal esophagus. These degenerative changes occur in the extraesophageal vagus nerve or the dorsal motor nucleus of the vagus nerve. The secondary form of achalasia develops in Chagas disease, which is caused by *Trypanosoma cruzi* infection leading to destruction of the myenteric nerve plexus, in diabetic autonomic neuropathy affecting the same nerve regions, in infiltrative diseases associated with malignancy, amyloidosis, and sarcoidosis and in systemic sclerosis. Endoscopically, in achalasia, the esophageal lumen is dilated, and vascularity is prominent. Residual food material and debris adhering to the

mucosal surface, and sometimes strictures, may be present. The mucosal biopsy appears normal or may be inflamed and ulcerated due to stasis [2, 3].

3.1.4 Esophageal Varices

All products absorbed from the intestines are first directed to the liver via the portal vein for processing. However, portal hypertension develops if portal blood flow is blocked or disrupted for any reason. Portal hypertension leads to the development of collateral vessels that allow portal blood to shunt into the caval system. Thus, instead of going to the liver, blood in the portal system is directed through the coronary veins of the stomach to the subepithelial and submucosal venous plexus of the distal esophagus and from there to the vena azygos and superior vena cava. During this process, increased pressure in the esophageal vascular plexus causes tortuously dilated veins called varices in the distal esophageal veins. Esophageal varices occur in 50% of patients with cirrhosis and are most commonly associated with alcoholic liver disease. Endoscopically, they appear as submucosal, bluish, irregularly bulging veins in the distal esophagus and proximal stomach lumen. If they do not rupture, the overlying mucosa may appear normal, but erosion and inflammation of the mucosa often occur due to the proximity of the veins to the mucosa and the weakness of the tissue supporting the dilated veins. Rupture of varices may cause extensive intramural hemorrhage associated with massive hematemesis. Varices do not cause any clinical symptoms until they rupture. Fifteen to twenty percent of patients die during the first bleeding episode. The cause of death is either direct hemorrhage or hepatic coma caused by hypovolemic shock and metabolic disorders. Once variceal bleeding begins, it rarely stops spontaneously; sclerotherapy, balloon tamponade, or band ligation is usually required [3].

3.1.5 Esophageal Lacerations

The most common esophageal lacerations are Mallory-Weiss tears, which occur after severe

retching and vomiting. Normally, the antiperistaltic contraction wave that occurs during vomiting is followed by reflex relaxation of the gastroesophageal muscles. However, in prolonged vomiting, this relaxation of the muscles does not occur completely, and as a result, tears develop in the stretched esophageal wall. These tears, which extend along the longitudinal axis of the GEJ, are linear and superficial. Mallory--Weiss tears, which account for approximately 10% of upper gastrointestinal bleeding, cause hematemesis but usually heal rapidly without any interventional procedures. Boerhaave tears, which are transmural esophageal tears, are more serious condition. They can cause distal esophageal rupture and require emergency surgical intervention [1–3].

3.1.6 Esophagitis

3.1.6.1 Reflux Esophagitis

The most common cause of esophagitis worldwide is reflux esophagitis, which occurs when stomach contents reflux into the distal esophagus. This condition, which occurs when the stomach acid-sensitive esophageal epithelium is damaged, is clinically defined as GERD. Under normal conditions, the multilayered squamous epithelium of the esophagus is resistant to friction damage during the passage of food, but it is

sensitive to stomach acid. Mucin and bicarbonate secreted by the submucosal glands in the distal esophagus protect the esophageal epithelium from the stomach acid. However, the most important protective mechanism of the esophagus is the high tone of the lower esophageal sphincter, which prevents the reflux of stomach contents into the esophagus. Therefore, the pathophysiological event that leads to the development of GERD is lower esophageal sphincter dysfunction. GERD occurs in conditions that cause a decrease in lower esophageal sphincter tone, such as alcohol and tobacco use, pregnancy, obesity, hiatal hernia, use of central nervous system depressants, delayed gastric emptying, and increased gastric volume, as well as in events that increase intra-abdominal pressure. In severe cases, duodenal bile reflux can also damage the esophageal epithelium. In cases of reflux esophagitis, clinically, there may be retrosternal burning sensation, regurgitation, sometimes dysphagia, and even angina-like severe chest pain attacks; however, endoscopic and histopathological findings are generally not correlated. Therefore, the condition is often classified clinically as erosive and non-erosive GERD. Endoscopically, erythema may be the only change observed in the esophagus. However, in some cases, damage ranging from erosion to deep ulcers is detected. Histopathological examination reveals proliferative changes rather than inflammatory infiltration

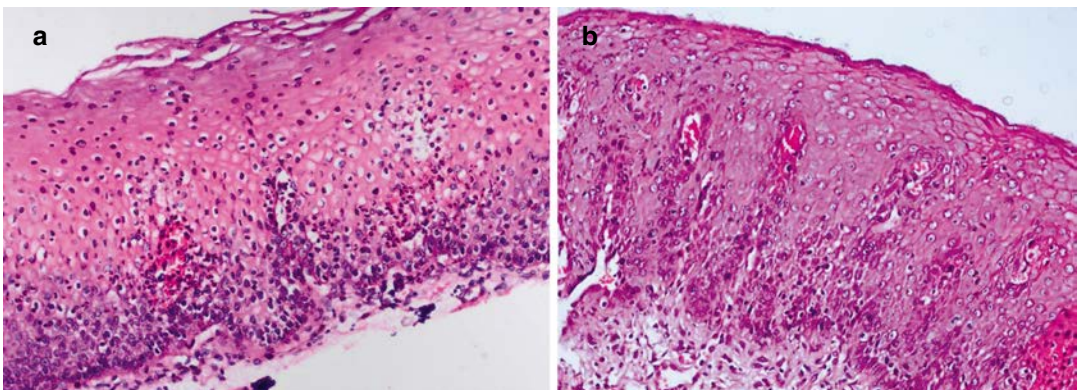


Fig. 3.3 Reflux esophagitis: (a) Basal cell hyperplasia, lack of surface maturation with the presence of nucleated squamous cells at the surface of the epithelium, and

marked neutrophil and lymphocyte infiltration. (b) Increased epithelial thickness and elongated submucosal papillae with dilated capillary

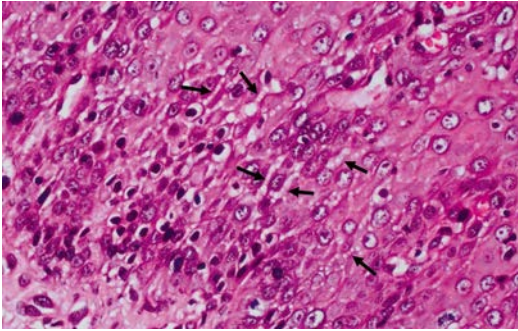


Fig. 3.4 In reflux esophagitis, increased intraepithelial lymphocytes and enlarged intercellular spaces/spongiosis (arrows) are observed

in the distal esophageal epithelium (Fig. 3.3). These changes include hyperplasia exceeding 15–20% of the total epithelial thickness in the basal cell layer, submucosal papillae extending to the superficial third of the epithelium, spongiosis (dilated intercellular spaces), and ballooning of squamous cells (Fig. 3.4). Lymphocytes and eosinophils are at the forefront of the inflammatory cell infiltration that occurs in reflux esophagitis, and as the damage becomes more severe, neutrophils also participate in this infiltration. However, eosinophil infiltration is never as intense as in eosinophilic esophagitis. Treatment may include a diet that prevents reflux, reduced tobacco and alcohol consumption, and the use of proton pump inhibitors (PPIs) to reduce stomach acid, which may alleviate clinical symptoms. In severe, long-standing cases, complications such as esophageal ulceration, hematemesis, melena, strictures, and Barrett's esophagus may develop [4–7].

3.1.6.2 Chemical and Iatrogenic Esophagitis

Corrosive acids and alkalis ingested accidentally, as well as irritants such as excessively hot beverages and alcohol, can damage the esophageal mucosa as they pass through the esophagus. Similarly, medications used for medical purposes can adhere to the esophageal mucosa and dissolve there, causing drug-induced esophagitis. Cytotoxic chemotherapy and radiotherapy can also cause iatrogenic esophageal damage.

All of these types of chemical damage typically cause localized pain in the esophagus and may cause difficulty in swallowing. When the damage is severe, hemorrhage, ulcers, and strictures may occur. Ingestion of caustic substances can cause more severe damage, leading to esophageal and gastric perforation, mediastinitis, and peritonitis. The damage caused by alkaline caustic substances is more severe than that caused by acidic substances. Morphological changes observed in chemical damage exhibit nonspecific findings, ranging from acute inflammation to necrosis and ulceration. In drug-induced esophagitis, damage usually occurs in the area where residual drug fragments adhere to the esophageal wall. Therefore, they usually form multiple, isolated ulcers. In cases receiving chemotherapy and radiotherapy, significant atypia such as nuclear hyperchromasia, multinucleation, and vacuolization in the cytoplasm in epithelial and stromal cells, as well as fibrosis and hyalinized vessels in submucosal areas, may occur (Fig. 3.5). In cases where damage due to chemical agents is suspected, a careful and thorough medical history, as well as endoscopic features, aids in differential diagnosis. Discontinuation of the medication, taking medications with plenty of water, and anti-reflux therapy alleviate symptoms, and antibiotics and steroids may be used in necessary cases. Esophageal dilation may be performed in cases where strictures develop [1–3, 7].

3.1.6.3 Infectious Esophagitis

Infectious agents can cause esophagitis, especially in immunocompromised individuals but also in healthy people. The most common agents are herpes simplex virus (HSV), *Cytomegalovirus* (CMV), and *Candida*. Endoscopically, HSV presents with deep ulcers resembling puncture wounds, whereas CMV presents with shallower ulcers. In candidiasis, pseudomembranes resembling those seen in the oral mucosa are observed, consisting of dense fungal hyphae and inflammatory cells, which are adherent to the mucosa and grayish-white in color. Biopsies taken from these areas should reveal *Candida* hyphae and spores not only on the epithelial surface but also within

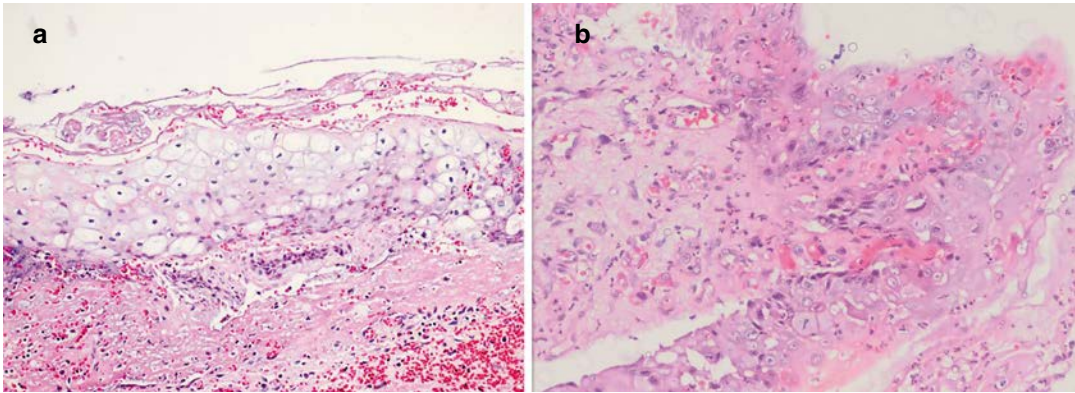


Fig. 3.5 (a) In caustic alkali-induced damage, balloon cells are present along the squamous mucosa of the esophagus, subepithelial separation, and hemorrhage. (b) In case with receiving radiotherapy, atypia such as cytomeg-

aly with pale nuclei, abundant cytoplasm, vacuolization in the cytoplasm, and multinucleation in the epithelial cells as well as edema and hyalinized vessels in submucosal areas

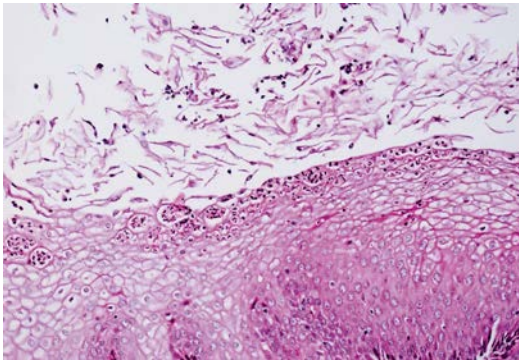


Fig. 3.6 The presence of parakeratosis and epithelial desquamation with cellular debris top of the squamous mucosa are diagnostic for *Candida* esophagitis. This esophageal biopsy shows dense acute inflammatory infiltrate admixed with intraepithelial neutrophilic abscesses most prominent in the superficial epithelial layers

the squamous epithelium (Fig. 3.6). Periodic acid-Schiff (PAS) and Gomori silver staining aid in the detection fungal hyphae and spores (Fig. 3.7). Histopathologically, viral inclusions are detected in the nuclei of degenerated epithelial cells in biopsies taken from the edge of the ulcer in cases of HSV. In CMV, nuclear and cytoplasmic inclusions are characteristic not only in epithelial cells but also in endothelial and stromal cells (Fig. 3.8). Immunohistochemical staining is helpful in detecting HSV and CMV inclusions. Care should be taken to obtain biopsies from the edge of the ulcer. Additionally, it should be noted

that non-pathogenic oral bacteria and fungi may also accompany pathological lesions [8].

3.1.6.4 Eosinophilic Esophagitis

Eosinophilic esophagitis, characterized histologically by dense eosinophilic infiltration, is a chronic immunological disorder. It presents with GERD-like symptoms, accompanied by food intolerance and dysphagia. Individuals with eosinophilic esophagitis are often atopic. They have findings such as allergic rhinitis, atopic dermatitis, asthma, and peripheral eosinophilia. Unlike reflux esophagitis, the entire esophagus is affected, and endoscopically, circumferential rings (trachealization), lines, and strictures are observed in the upper and middle esophagus. The main histological finding is dense eosinophils infiltrating the squamous epithelium in areas distant from the GEJ and eosinophilic microabscesses in the superficial areas of the epithelium. Dense eosinophilic infiltration, seen at a rate of ≥ 15 / high-power field (HPF), distinguishes eosinophilic esophagitis from other causes of esophagitis (Fig. 3.9). The rate of eosinophilia in the epithelium is higher in biopsies taken from the proximal segments of the esophagus. Other histological findings associated with reflux esophagitis also accompany eosinophilia. As eosinophilic esophagitis is resistant to proton pump inhibitor therapy, dietary restrictions and elimination of

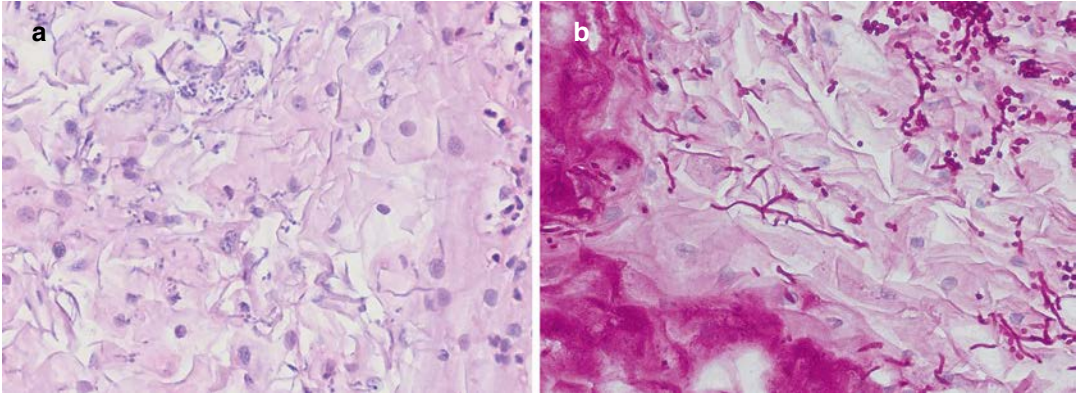


Fig. 3.7 (a) *Candida* esophagitis showing abundant pseudohyphae and budding yeast forms in the squamous epithelium, readily seen on routine hematoxylin and eosin

(H&E). (b) PAS stain highlights pseudohyphae and budding yeast forms of *Candida*

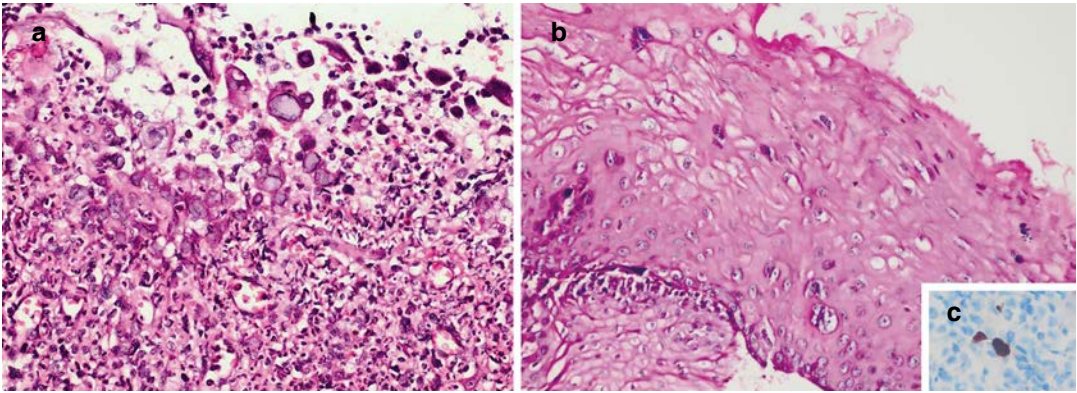


Fig. 3.8 (a) Herpes esophagitis showing diagnostic herpes virus nuclear inclusions and multinucleated cells with nuclear molding. These cells are most prominent in the superficial portions of the epithelium and particularly

adjacent to areas of ulceration. (b) *Cytomegalovirus* esophagitis shows characteristic nuclear enlargement. (c) Immunohistochemical staining is helpful in detecting CMV

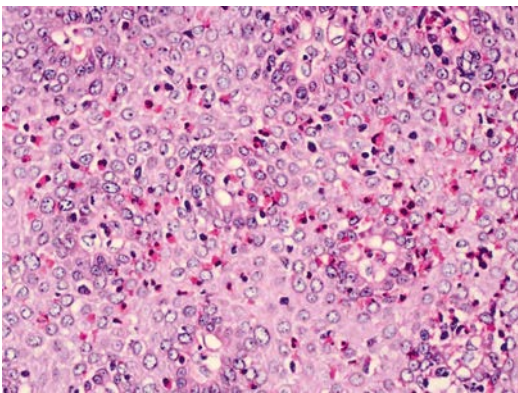


Fig. 3.9 Intense eosinophilic infiltrate in eosinophilic esophagitis

allergenic foods may be beneficial, and in necessary conditions, corticosteroids should be used [9].

3.1.6.5 Lymphocytic Esophagitis

Another form of esophagitis with poorly defined criteria is lymphocytic esophagitis. Lymphocytes normally present in small numbers in the esophageal mucosa are CD8+ T lymphocytes. Some studies have shown that increased intraepithelial lymphocytes in dysmotility-associated lymphocytic esophagitis are CD4+ T lymphocytes. In these cases, which present with classic esophagi-

tis symptoms, endoscopic findings vary from normal appearance to erythema, mucosal rings, plaques, and strictures. Histopathological examination reveals a marked increase in lymphocytes, spongiosis, and basal cell hyperplasia, particularly in the peripapillary squamous epithelium. Neutrophils and eosinophils are not observed in these patchy areas of lymphocytosis. Since a wide range of 20–50/HPF is defined for the number of intraepithelial lymphocytes in the diagnosis of lymphocytic esophagitis, a descriptive definition such as “damage in the lymphocytic esophagitis pattern” is recommended. It should also be noted that intraepithelial lymphocytosis may also be observed in Crohn’s disease affecting the esophagus, inflammatory skin diseases such as lichen planus, and achalasia [10].

3.1.7 Barrett’s Esophagus

Barrett’s esophagus, a complication of long-standing gastroesophageal reflux, occurs in more than 10% of cases with symptomatic reflux. Patients who develop Barrett’s esophagus are typically Caucasian males between the ages of 40 and 60. Barrett’s esophagus is simply defined as the metaplasia of a normal squamous epithelium in the distal esophagus to the intestinal epithelium. The most significant aspect of this condition is the increased risk of developing adenocarcinomas. In individuals with Barrett’s esophagus, the risk of developing epithelial dysplasia, which is

considered a precancerous lesion, is approximately 1% per year, and this rate increases with the patient’s age and the duration of symptoms. In addition, the length of the segment with Barrett’s esophagus is also a factor that increases the risk of adenocarcinoma. Furthermore, molecular studies have shown that the acquired driver mutations detected in Barrett’s esophagus epithelium are the same as those detected in esophageal adenocarcinomas. Although these findings suggest that Barrett’s esophagus is a precursor lesion, cancer does not develop in all individuals suffering this condition. GERD symptoms are commonly observed in individuals with Barrett’s esophagus. Endoscopically, Barrett’s esophagus is characterized by red, velvety mucosa extending from the gastroesophageal junction to the distal esophagus in the form of patches, spots, and islands. Thus, this metaplastic mucosa is observed to transition into pale pink-gray, smooth, even-surfaced esophageal mucosa and the light brown, velvety gastric mucosa. Microscopic examination reveals metaplasia of the squamous epithelium of the esophagus into the columnar intestinal epithelium, containing goblet cells (Fig. 3.10). This specialized epithelium contains gastric foveolar-type columnar cells, absorptive-type columnar cells, goblet cells, and Paneth cells. The epithelium, referred to as “multilayered epithelium,” is a hybrid epithelium in which a layer of columnar cells containing mucin is present on the surface of the squamous cells at the base. It is thought that the multilayered epithelium, in which columnar

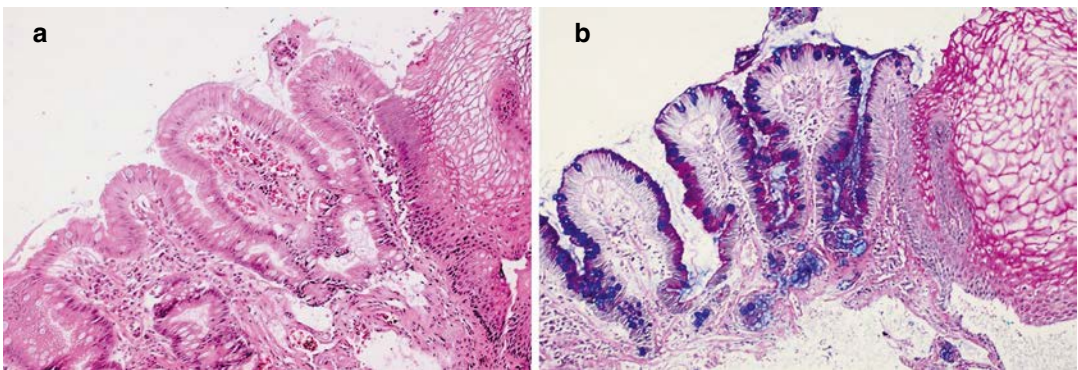


Fig. 3.10 (a) Barrett’s esophagus. This biopsy specimen is taken from the tubular esophagus and shows intestinal metaplasia. (b) PAS and Alcian blue (AB) stains can be used to highlight goblet cells

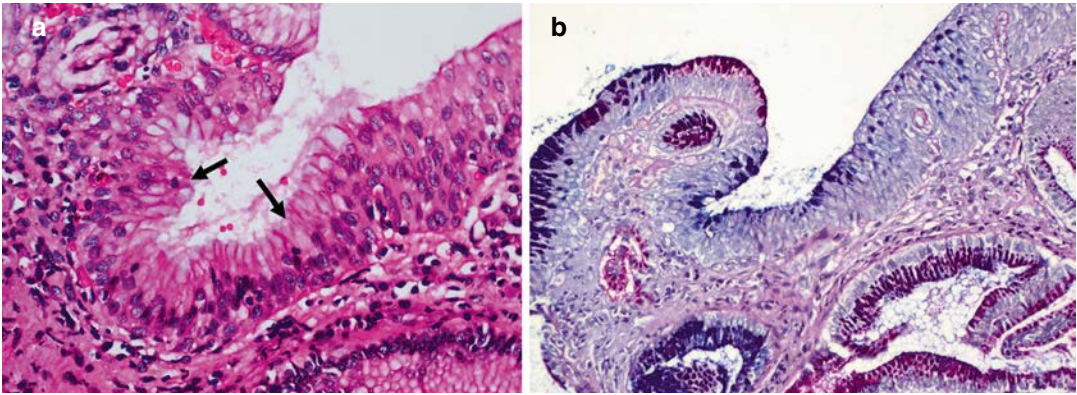


Fig. 3.11 (a) Multilayered epithelium (arrows) is a hybrid epithelium demonstrating features of both squamous and columnar differentiation and may be a precursor

of Barrett's esophagus (H&E). (b) Multilayered epithelium is positive for PAS and AB

and squamous differentiation are seen together, may be a precursor to Barrett's esophagus (Fig. 3.11). Since Barrett's mucosa may be present in a focal area, problems may arise in establishing a diagnosis through biopsy. Therefore, repeated and multiple endoscopic biopsies from the distal esophagus are necessary. Currently, there is consensus that the diagnosis of Barrett's esophagus requires the detection of columnar mucosa extending up to 1 cm above the GEJ by endoscopic examination and histopathological confirmation of columnar metaplasia in this mucosa. However, there is disagreement among gastrointestinal pathologists regarding the presence or absence of goblet cells in metaplastic columnar mucosa. While the presence of columnar cells is sufficient for diagnosis in the British and Japanese communities, the presence of goblet cells in the biopsy is mandatory in the USA and parts of Europe. The important point in the pathological evaluation of patients with Barrett's esophagus is the investigation of dysplastic mucosal changes that may be precursor to cancer. Dysplasia in columnar cells is cytologically characterized by enlargement of nuclei, hyperchromasia, coarse chromatin pattern, irregular nuclear contours, prominent nucleoli, and atypical mitoses. These cytologic changes are accompanied by structural neoplastic changes such as cell crowding, pseudostratification, loss of superficial maturation, villiform appearance of the epithelium,

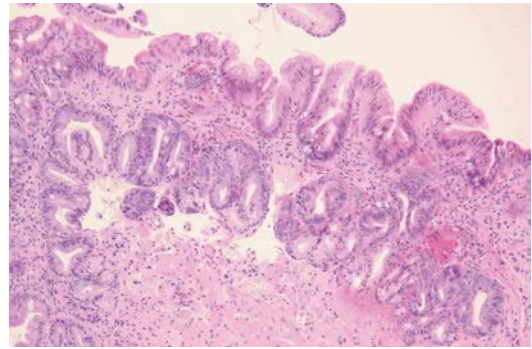


Fig. 3.12. A biopsy specimen from a patient with Barrett's esophagus (BE) showing low-grade dysplasia limited to the crypt bases but with evidence of surface maturation

glandular crowding, and loss of stroma between glands (Fig. 3.12). One of the important features in the differential diagnosis of dysplasia is that these morphological changes show an abrupt transition from normal-appearing mucosa. Dysplasia should be classified and reported as low-grade or high-grade. Non-dysplastic Barrett's epithelium shows p53 expression in a wild-type pattern with rare and weak nuclear positivity, while dysplastic epithelium shows expression in a mutant pattern with diffuse strong staining or complete loss of staining, which may be helpful in differential diagnosis. However, in Barrett-related dysplasia, histopathological findings remain the gold standard for diagnosing dysplasia and determining its

grade, as wild-type and mutant-type p53 expressions may coexist in the same biopsy and detection of mutant-type expression may be inadequate in biopsies. Periodic endoscopic follow-up for dysplasia is required in individuals with Barrett's esophagus who are undergoing anti-reflux treatment with proton pump inhibitors. If high-grade dysplasia or more advanced neoplastic lesions are detected in follow-up biopsies, treatments such as radiofrequency ablation, endoscopic mucosal or submucosal resection, or esophagectomy are performed [11–14].

3.1.8 Esophageal Tumors

Esophageal tumors mainly occur in two types: squamous cell carcinomas, which are the most common worldwide, and adenocarcinomas, which are becoming increasingly common. Rarely, neuroendocrine tumors (NETs), submucosal gland-derived carcinomas, leiomyomas, gastrointestinal stromal tumors (GISTs), and metastases may also be observed in the esophagus [15–19].

3.1.8.1 Esophageal Adenocarcinomas

Esophageal adenocarcinomas develop in the setting of long-standing GERD or Barrett's esophagus. Due to the significant increase in the incidence of these two clinical conditions over the past 50 years, esophageal adenocarcinoma now accounts for approximately half of all esophageal tumors, particularly in Western countries and the USA. Incidence also varies by country. The incidence of adenocarcinoma is high in Western countries such as the USA, Canada, the UK, Australia, and the Netherlands but low in Eastern Asia. The risk of developing adenocarcinoma is higher in smokers, obese people, and patients who received radiotherapy, especially those with epithelial dysplasia. Adenocarcinomas are seven times more common in men than in women and are more prevalent in Caucasians. Esophageal carcinoma has a very insidious onset. Symptoms include dysphagia, difficulty swallowing, weight loss, chest pain, and vomiting. Diagnosis can be made using imaging techniques

and endoscopic biopsy. Molecular studies indicate specific genetic and epigenetic changes in the progression from Barrett's esophagus to adenocarcinoma. Mutations accumulated in non-dysplastic Barrett's mucosa show a progression to dysplasia and invasive carcinoma. The most common chromosomal abnormality in the early stages is p53 gene (TP53) mutations. Progression is accompanied by deletions in the Rb, p16, and adenomatous polyposis coli (APC) genes and overexpression of epidermal growth factor receptor (EGFR) and transforming growth factor- α (TGF- α). Esophageal adenocarcinomas occur in the distal third of the esophagus and may invade the cardia of the stomach. Macroscopically, in the early stages, they appear as flat or thickened patches on the mucosa, while in advanced stages, they may take the form of large exophytic masses, deep ulcers, or diffuse infiltration. Microscopically, the tumor consists of mucosecreting glands with intestinal-type features (Fig. 3.13). Adenocarcinoma areas may exhibit tubular, papillary, mucinous, and signet ring cell patterns. Tumor cells exhibit an immunoprofile that is CK7 positive, CDX2 variably positive, and CK20 generally negative. Barrett's esophagus is frequently found in areas adjacent to the tumor. In segments with Barrett's esophagus, the muscularis mucosa is thickened and duplicated, so it should be noted that this muscle layer may cause a false impression of submucosal invasion or deep invasion by misinterpreting as muscularis propria. It is also essential to distinguish whether an adenocarcinoma in GEJ region originates from the distal esophagus or stomach, as prognostic characteristics, stage, and treatment protocols of these two tumors are different. In tumors of this region, the decision is made based on the location of the tumor epicenter according to the Siewert classification. If the tumor epicenter is located within the first 2 cm of the proximal stomach, i.e., if the tumor epicenter is 2 cm or closer to the GEJ, it should be classified as esophageal cancer. If the tumor epicenter is more than 2 cm distal to the GEJ, it should be classified as gastric cancer. Since these cancers invade the rich esophageal lymphatics and adjacent structures, surgical treatments such as endoscopic mucosal

or submucosal resection and esophagectomy are rarely beneficial. Neoadjuvant chemotherapy prior to surgical excision or radiotherapy after esophagectomy may be considered in cases of deeply invasive tumors. In a small group of tumors, human epidermal growth factor receptor 2 (HER2) amplification or programmed cell death ligand 1 (PDL1) positivity may be detected, and these cases may benefit from HER2-targeted therapy or anti-PDL1 immunotherapy cell death protein 1 immunotherapy. In adenocarcinomas, 5-year survival is 80% in the early stage but less than 25% in the advanced stage [15–18].

3.1.8.2 Squamous Cell Carcinomas of the Esophagus

Unlike adenocarcinomas, SCCs of the esophagus are more common in rural and low socioeconomic areas. Iran, China, Hong Kong, South Africa, Argentina, and Brazil are the countries with the highest incidence rates. SCCs typically occur in individuals over the age of 45 and are four times more common in men than in women. Similar to adenocarcinomas, alcohol and tobacco use, radiation therapy, consumption of very hot beverages, chronic irritation, chemical damage to the esophagus, achalasia, and Plummer-Vinson syndrome are important risk factors. Exposure to polycyclic aromatic hydrocarbons, nitrosamines, mutagenic products, mold-contaminated foods, and human papillomavirus infection are also notable risk factors in high-

risk regions. In SCCs of the esophagus, mutations are frequently detected in genes that regulate squamous differentiation, such as TP63 and NOTCH, and in genes that regulate proliferation, such as cyclin D1, cyclin-dependent kinases, TP53, Rb, and p16. Half of esophageal SCCs occur in the middle third, while adenocarcinomas almost always occur in the distal esophagus. Squamous dysplasia is a precursor lesion of SCCs and is seen in more than 90% of SCCs in the adjacent mucosa. Squamous dysplasia, which begins in the early stages as small, gray-white plaques and mucosal thickening, appears endoscopically as pale areas that do not stain with Lugol's iodine because of glycogen lost in epithelial cells. More advanced techniques such as narrow band imaging also facilitate the detection of squamous dysplasia. Microscopically, at this stage, changes ranging from low-grade dysplasia limited to atypical basaloid cells in the lower third of the mucosa to high-grade dysplasia characterized by atypical cells involving more layers of the epithelium are observed. Over time, tumors may form a polypoid mass that obstructs the esophageal lumen or cause ulceration, or they may thicken and harden the esophageal wall as a diffuse-infiltrative tumor, narrowing the lumen. Most are well- or moderately differentiated keratinizing tumors, but they may also be poorly differentiated or undifferentiated (Fig. 3.13). p40/p63 and CK5/6-positive immunophenotype of tumor cells confirms their

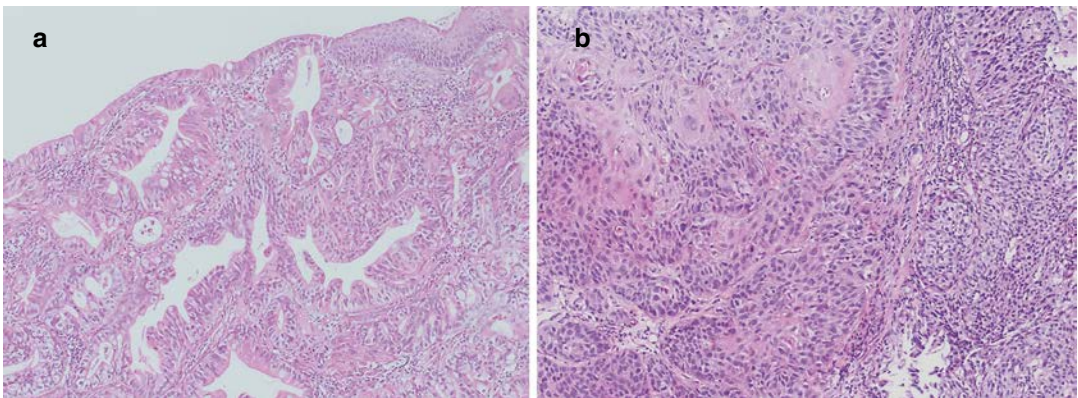


Fig. 3.13 (a) Esophageal adenocarcinoma growing as back-to-back glands containing mucin. (b) Squamous cell carcinoma composed of nests of malignant cells that have squamous differentiation

squamous cell origin [17]. These tumors can rapidly infiltrate the surrounding soft tissues, respiratory tree, aorta, mediastinum, and pericardium. Esophageal SCCs have an insidious onset, and most symptomatic cases are often at an advanced stage at the time of diagnosis. The rich submucosal lymphatic network facilitates easy spread of tumor along the circumferential and longitudinal axes. Metastatic lymph nodes vary depending on the location of the tumor in the esophagus. Tumors located in the upper third of the esophagus metastasize to cervical lymph nodes; those in the middle third to mediastinal, paratracheal, and tracheobronchial lymph nodes; and those in the lower third to gastric and celiac lymph nodes. Esophagectomy is generally performed for palliative purposes, with chemotherapy or radiotherapy being the primary treatment options. In SCC, the 5-year survival rate is 75% in early stages and approximately 5–10% in advanced stages [17, 19].

3.2 Pathology of the Stomach

3.2.1 Structure of the Stomach

The stomach, which has both digestive and endocrine functions, begins just below the GEJ with the proximal stomach, which has mucosal folds known as rugae. Distally, it ends with the pyloric sphincter, which is formed by the thickening of the muscularis propria. The stomach, a pouch-shaped organ with a capacity of 1.5–3 L, has a concave edge on the right side known as the lesser curvature and a convex edge on the left side called the greater curvature. The sharp corner bend located on the lesser curvature, where the stomach lumen begins to narrow, is called the incisura angularis. Anatomically, the stomach consists of four main sections: the cardia, fundus, corpus, and antrum. The surface of all these areas is covered by a mucin-secreting foveolar epithelial component. Mucin-secreting foveolar cells are long and columnar, with nuclei located at the base and pale pink cytoplasm due to the mucin granules they contain. This epithelial component of the stomach is

completely renewed every 2–6 days through the proliferation of epithelial cells in the neck region of the foveolae. The thickness and composition of the deep epithelial component of the mucosa varies according to anatomical regions. The cardia, located immediately below the gastroesophageal junction, is the proximal part of the stomach, 0.1–0.4 cm long, cone-shaped, with shallow foveolae and a small number of mucous glands. Sometimes, oxyntic glands are mixed with mucous glands. The fundus, the dome-shaped proximal part of the stomach located just below the diaphragm, has an oxyntic mucosa covered with mucus-secreting foveolar epithelium. The corpus, the main body of the stomach, extends to the incisura angularis and is also covered with oxyntic mucosa. The thick glandular mass forming the oxyntic mucosa consists of parietal cells that secrete acid and have bright, eosinophilic cytoplasm near the luminal surface and chief cells that are located toward the base of the mucosa. Chief cells have basophilic cytoplasm and secrete digestive enzymes, such as pepsinogen. The antrum, part of the stomach distal to the angular incisura, contains cells that secrete mucus and endocrine cells. At the corpus-antrum junction, the oxyntic mucosa gradually diminishes, giving way to a thinner glandular layer called the mucous pyloric glands. Endocrine cells, which are triangular cells with bright eosinophilic granules at the base of their cytoplasm, are scattered between the oxyntic and mucous glands. The most densely found endocrine cells in the antral mucosa are G cells, which secrete the hormone gastrin. Those located in the corpus are enterochromaffin-like cells, which secrete histamine. Another type of endocrine cell in the oxyntic mucosa is D cells, which secrete somatostatin [1, 3, 20].

3.2.2 Congenital Anomalies of the Stomach

Stomach agenesis and atresia are extremely rare. As in the entire gastrointestinal tract, ectopic tissues may be observed in the stomach. The most

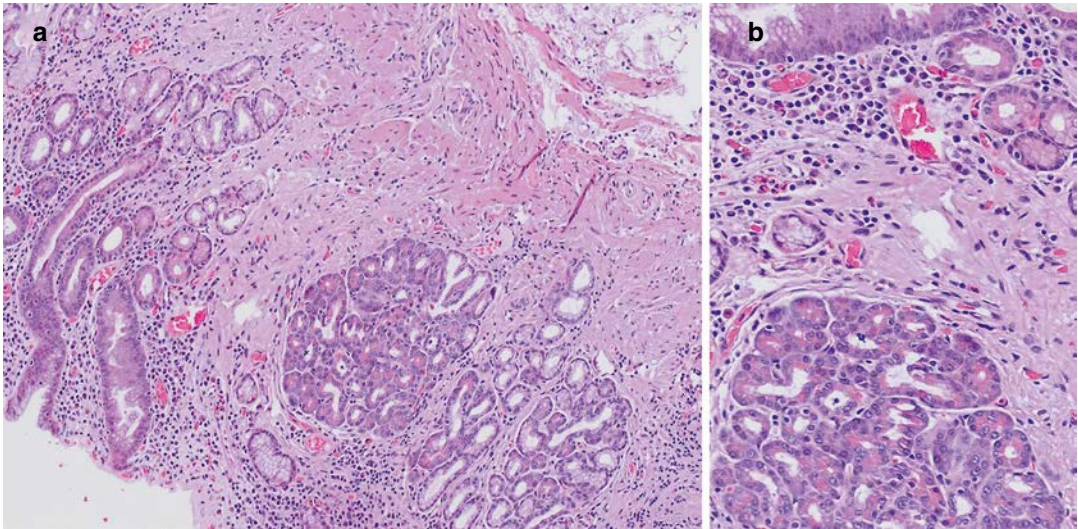


Fig. 3.14 (a) Pancreatic heterotopia is the most common ectopic tissue in the stomach. (b) Note the brightly eosinophilic granules in the acinar cells

common ectopic tissue in the stomach is the pancreas. In pancreatic heterotopia, pancreatic tissue can be seen in the submucosa, muscle layer, or subserosal area of the stomach, rarely as a nodule >1 cm (Fig. 3.14). It generally does not contain an endocrine component. When located in the pylorus, it can cause obstruction. If the pancreatic tissue is functional, its secretions can cause mucosal damage and inflammatory reactions.

Pyloric stenosis in the stomach may be congenital or acquired. The incidence of the congenital form is 1/300–900 live births. It is three to five times more common in males than in females. It usually manifests in the third to sixth week of life with projectile, bile-free vomiting and regurgitation. Narrowing occurs due to hyperplasia of the muscularis propria in the pyloric canal. Edema and inflammatory changes in the mucosa and submucosa further increase the narrowing. In the acquired type seen in adults, there is a history of ulcers near the pylorus or long-term antral gastritis. Gastric carcinoma, lymphoma, or adjacent pancreatic carcinoma are among other causes. In these cases, the cause of pyloric stenosis is not muscle hyperplasia, but inflammatory fibrosis or malignant infiltration [3].

3.2.3 Acute Gastritis

3.2.3.1 Acute Erosive/Hemorrhagic Gastritis

Acute erosive hemorrhagic gastritis is the most common form of acute gastritis and often results from severe and acute mucosal damage in the stomach. The most common causes of this damage are iatrogenic causes such as alcohol, bile reflux, steroids, and nonsteroidal anti-inflammatory drugs (NSAIDs) or stress. The pathogenesis of acute hemorrhagic gastritis involves a balance between factors that damage the gastric mucosa, such as acid, pepsin, bile salts, NSAIDs, and other chemicals, and factors that protect the gastric mucosa, such as mucin, bicarbonates, prostaglandins, growth factors, mucosal blood flow, and the proliferative capacity of the gastric mucosa. Normally, gastric pH is around 1–2, making it one million times more acidic than blood. While these values are necessary for the stomach to perform its digestive functions, they also have a high capacity to damage tissues. To protect against this damage, various protective barriers exist in the gastric mucosa. The mucus secreted by the foveolar epithelial cells on the surface covers the entire surface of the mucosa, protecting it from the effects of acid, and the

bicarbonate ion secreted by these cells into the mucus creates a buffering neutral pH on the epithelial surface. The rich blood flow in the gastric mucosa also rapidly buffers the protons reabsorbed into the lamina propria. Acute or chronic gastritis and gastropathies develop when these protective mechanisms are lost. Inhibition of the cyclooxygenase enzyme by NSAIDs results in decreased synthesis of prostaglandin E₂ and I₂, leading to direct damage to the foveolar epithelium and disruption of the secretion of mucus and bicarbonate by these cells, which protect the mucosa. Similarly, mucosal blood flow and epithelial repair processes are also disrupted. Increased ammonium ions in uremic patients and in *Helicobacter pylori* (*H. pylori*) infections that secrete the urease enzyme may inhibit gastric bicarbonate transport. Mucin and bicarbonate secretion decrease with aging. The incidence of acute gastritis increases due to hypoxemia and decreased oxygen transport at high altitudes. Corrosive acids and alkalis ingested accidentally or intentionally cause direct damage to epithelial and stromal cells. Excessive alcohol consumption, NSAID use, radiotherapy, and chemotherapy also cause direct mucosal damage. The clinical picture resulting from any of these causes is usually a sudden onset, presenting with burning epigastric pain, nausea, vomiting, and gastrointestinal bleeding. Gastrointestinal bleeding can be minimal or life-threatening. In acute gastritis, the appearance varies from localized involvement to diffuse inflammation, from superficial involvement to inflammation affecting the entire mucosa, with petechiae and erosions. However, all changes are limited to the mucosa. Erosions and hemorrhages are easily visible with endoscopy and are termed acute erosive hemorrhagic gastritis. Erosions are mucosal defects formed by damage to the surface epithelium, leading to necrosis and sloughing. They are 2–5 mm in diameter, round, and limited to the lamina propria. Their surface is covered by hemorrhage and fibrin exudation. Inflammatory infiltration, including chronic inflammatory cells along with mucosal edema and neutrophils, is observed in both acute and chronic forms of gastritis. However, in acute gastritis, neutrophils are the predominant cellular

component, and lymphoplasmacytic infiltration is minimal. Edema in the lamina propria, interstitial hemorrhage, and vascular congestion are prominent. During the healing phase of the mucosa, regenerative changes, such as prominent nucleoli, large and hyperchromatic nuclei, amphophilic cytoplasm, and increased mitosis in the surface epithelial cells, are noticeable. These changes should not be confused with dysplasia or adenocarcinoma. In more severe damage, multiple subepithelial petechiae, hemorrhages, and larger erosions may be seen. Most patients recover within a short period. The most important factor determining the prognosis is the nature of the cause of the damage. Removing the causative agent; using PPIs, prostaglandin analogs, and histamine receptor blockers; and increasing fluid intake form the basis of treatment [20, 21].

3.2.3.2 Stress-Related Gastritis

Stress-related gastric damage occurs in cases of severe trauma, severe burns, major surgery, sepsis, shock, hypothermia, intracranial diseases, and other severe physiological stress conditions. In more than 75% of patients, lesions visible by endoscopy develop within the first 3 days of the disease. Some lesions are given specific names based on their location and the disease pattern with which they are associated. These are stress ulcers (develop with shock, sepsis, and severe trauma), Curling ulcers (develop in the proximal duodenum of patients with severe burns and trauma), and Cushing ulcers (develop in the stomach, duodenum, or esophagus in cases with central nervous system damage). Stress-related gastric mucosal damage is most often due to ischemia caused by systemic hypotension or decreased gastric blood flow. Decreased blood flow reduces bicarbonate secretion and the buffering capacity of the blood. Systemic acidosis and hypotension developing in severe illnesses contribute to a decrease in the pH of mucosal cells, which are already hypoxic due to impaired blood flow. Intracranial lesions increase gastric acid secretion by directly stimulating the vagal nuclei as a result of increased intracranial pressure. Stress-related gastric mucosal injury presents with a range of appearances, from super-

ficial epithelial damage and erosion to deep lesions that penetrate the mucosa. Acute ulcers are typically round lesions less than 1 cm in diameter. The base of the ulcer is dark brown in color due to the digestion of blood. Unlike chronic peptic ulcers, acute stress ulcers can occur anywhere in the stomach. They are usually multiple along the stomach and duodenum but may also occur as a single lesion. Microscopically, they are sharply bordered lesions surrounded by intact mucosa. Although the depth of lesions varies from superficial erosions to deep ulcers involving the entire mucosal thickness, even the deepest lesions do not penetrate the muscularis propria. The thickening and scarring of blood vessels seen in chronic peptic ulcers are never observed. The majority of patients are those receiving treatment in intensive care units due to sepsis, severe burns, or trauma. In these patients, despite the use of prophylactic antacids and blood transfusions, the most important factor determining the clinical course is the resolution of the underlying causes. If the patient can overcome the primary disease, the gastric mucosa returns completely to normal [3].

3.2.3.3 Reactive (Chemical) Gastropathy

Reactive gastropathy refers to changes that occur as a result of damage to the mucosal surface due to bile, chemical agents, various medications, and medical procedures. The terms chemical gastritis, bile reflux gastritis, and alkaline reflux gastritis are synonymous names used to describe this condition. Bile reflux developing after gastroenterostomy, vagotomy, and pyloroplasty surgeries, chronic aspirin and NSAID use, medications used for medical purposes, gastric dysmotility, alcohol, and cigarette use are among the most common causes of reactive gastropathy. Patients are usually asymptomatic, rarely developing abdominal pain, nausea, and vomiting. Endoscopy may be normal or show erythema and localized erosions. Damage to the mucosal surface leads to mucin loss and regenerative epithelial changes, causing marked hyperplasia, corkscrew-like folds, and elongation in the foveolae (Fig. 3.15). This is accompanied by edema, congestion, and

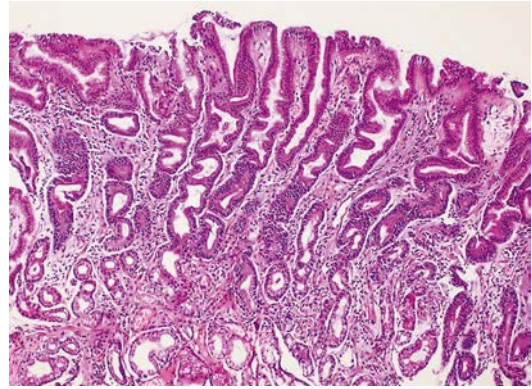


Fig. 3.15 Reactive (chemical) gastropathy showing sparse chronic inflammation and marked foveolar hyperplasia, corkscrew appearance of gastric pits, mucin depletion, edema, and smooth muscle hyperplasia

smooth muscle proliferation in the lamina propria. Significant foveolar hyperplasia may require differential diagnosis with hyperplastic polyps; therefore, it is important that no lesions such as polyps or nodules are present. The absence of lymphoplasmacytic infiltration in the lamina propria is a typical feature. For this reason, the term gastropathy is preferred over gastritis. These changes are generally limited to the antrum; changes in the oxyntic mucosa are rare and limited only to the superficial foveolar epithelium. Drug-induced gastric mucosal damage most commonly presents as reactive gastropathy. Among these, the most frequently observed changes are typical reactive gastropathy, such as that seen with chronic NSAID use. Additionally, changes such as ferrous pigment accumulation in the lamina propria caused by iron tablets or unique changes like polygonal, plaque-like, purple crystals formed by kayexalate may also be observed. Another frequently seen drug reaction is changes associated with long-term PPI use. PPIs cause dilatation of oxyntic glands, clear cell changes, pseudohypertrophy in parietal cells, and apocrine-appearing protrusions. Chemotherapy and radiotherapy can also cause edema, congestion, and vascular dilation in the gastric mucosa, as well as atypia in endothelial and stromal cells, and may even exhibit significant epithelial atypia findings that can be confused with dysplasia and adenocarcinoma. In particular, chronic damage

associated with radiotherapy can cause fibrosis and abnormal vascular changes that destroy normal mucosal structure. In reactive gastropathies, identifying and removing the causative agent lead to mucosal healing [3, 21].

3.2.4 Chronic Gastritis

3.2.4.1 *Helicobacter pylori* Gastritis

Following the discovery of the relationship between *H. pylori* and peptic ulcer disease (PUD), there has been a major breakthrough in the pathogenesis of chronic gastritis, and it has been understood worldwide that *H. pylori* is the primary cause of chronic gastritis. *H. pylori* gastritis is the most common form of chronic gastritis worldwide. *H. pylori* is a 3.5- μ m-long, S-shaped, seagull wing-shaped, comma-shaped or spiral-shaped, gram-negative rod. It shows tropism to the gastric epithelium and is not found in the intestinal epithelium. It is a common infectious agent worldwide. It is particularly prevalent in countries with low socioeconomic status and poor sanitation. Most people infected with *H. pylori* are asymptomatic carriers of the microorganism. Others develop moderate-to-severe symptoms such as abdominal pain, nausea, vomiting, dyspepsia, and weight loss. Furthermore, *H. pylori* has been classified as a group I carcinogen by the World Health Organization (WHO) due to its association with peptic ulcer disease, MALT (mucosa-associated lymphoid tissue) lymphoma, and gastric adenocarcinoma etiology. The most important factor enabling *H. pylori* to adapt to the gastric environment is gastric mucus. The microorganism concentrates in the mucus covering the surface of foveolar cells. *H. pylori* can invade the gastric mucosa, but colonization of the microorganism appears to be sufficient to cause disease. Four factors can be mentioned in relation to the virulence of *H. pylori*. These factors are flagella, which enable the bacterium to move within the mucus; urease that produces ammonia from endogenous urea, thereby creating a local alkaline microenvironment that protects the bacterium from stomach acid; adhesins such as BabA and SabA, which enable the bacterium to adhere to surface foveolar cells; and tox-

ins encoded by the CagA (cytotoxin-associated gene A) and CagE genes. These toxins stimulate the release of cytokines such as interleukin 8, which has a chemotactic effect on neutrophils. *H. pylori* infection primarily begins in the antrum. The microorganism and the inflammatory reaction it triggers stimulate G cells, leading to gastrin secretion. This results in hyperacidity and peptic ulcer disease. Over time, the infection spreads to the corpus, which can result in parietal cell loss, gastric atrophy, and intestinal metaplasia. Endoscopic findings may vary from mucosal erythema and erosion to nodularity and ulcers in severe cases. Rarely, the mucosa may appear completely normal. Therefore, it is recommended that at least two biopsies be taken from both the antrum and corpus for optimal evaluation. *H. pylori* gastritis is typically a chronic active gastritis of varying severity. Histologically, inflammatory changes are more pronounced in the superficial mucosa and involve infiltration of lymphocytes and plasma cells in the lamina propria. This inflammatory reaction also contains a variable number of neutrophils in the lamina propria. In more severe cases, neutrophils infiltrate the epithelium, accumulate in gastric pits, and form pit abscesses. Intraepithelial neutrophils and subepithelial plasma cells are characteristic of *H. pylori* gastritis. Since neutrophils can be seen in both acute and chronic inflammatory conditions in the gastrointestinal system, the term active inflammation is preferred over acute inflammation on a chronic background. Inflammation can cause varying degrees of destruction of glands, mucosal atrophy, regenerative foveolar hyperplasia, intestinal metaplasia, and dysplasia. Prominent submucosal lymphoid follicles with germinal centers are frequently observed, and this activated MALT has the potential to transform into gastric lymphoma. This florid lymphoid hyperplasia can be distinguished from lymphoma by the lack of monotony in lymphoid cells. Furthermore, the intraepithelial lymphocytes in *H. pylori* gastritis are CD3-positive T lymphocytes. This may also support differentiation from B-cell neoplasms. *H. pylori* is found colonizing the mucus layer covering the surface of the mucosal epithelium, particularly in the antrum and corpus. When present in large num-

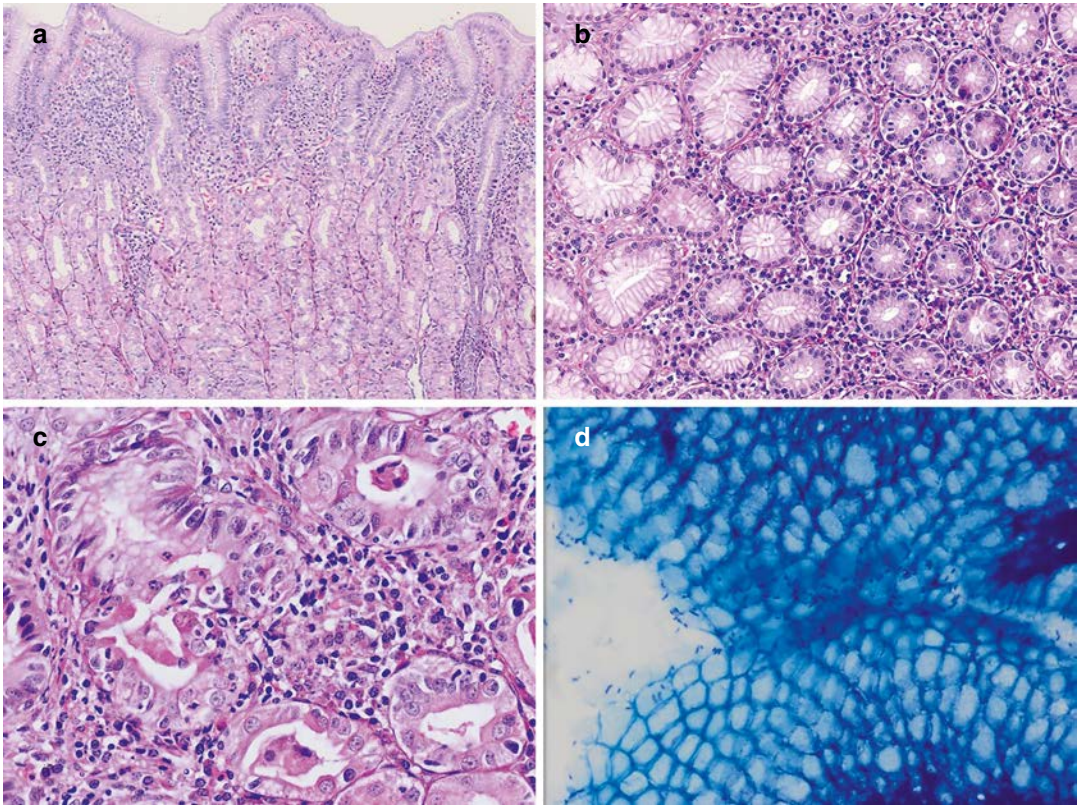


Fig. 3.16 (a) In corpus, lymphoplasmacytic infiltration forms a band that fills the lamina propria of the mucous cell neck region, a common feature in *Helicobacter pylori* gastritis. (b) In chronic gastritis lymphocytes and plasma cells infiltrate also the antral mucosa. (c) Neutrophils typi-

cally infiltrate the lamina propria and the surface, foveolar and glandular epithelium in *Helicobacter pylori* infection. (d) Innumerable *Helicobacter pylori* organisms (toluidine blue stain) are seen within the lumen of a pit and in the intercellular spaces of the foveolar cells

bers, it can be seen in H&E sections and can also be demonstrated using special stains such as Giemsa, Diff-Quik, Warthin-Starry, toluidine blue, and immunochemical stains (Fig. 3.16). It should be remembered that microorganisms may disappear or transform into a coccoid form in biopsy samples taken after antibiotic therapy. Furthermore, the gastritis pattern in these post-treatment samples may also be in the form of chronic inactive gastritis, where only residual mononuclear cells are observed in the lamina propria. The most commonly used treatment for *H. pylori* gastritis is a 14-day course of dual antibiotic therapy combined with PPI or bismuth therapy. This treatment achieves a cure rate of 95% in cases. However, relapses due to inadequate eradication and recurrent colonization of the organism are observed [22, 23].

3.2.4.2 Autoimmune Gastritis

Approximately <10% of chronic gastritis cases are caused by autoimmune gastritis, which develops due to the formation of autoantibodies against parietal cells and intrinsic factors in the gastric mucosa. This form of gastritis is most commonly seen in northern European countries and Scandinavia. It is associated with other autoimmune diseases such as Hashimoto's thyroiditis, type I diabetes, Graves' disease, and Addison's disease. It is most commonly seen around the age of 60 and is slightly more prevalent in women. Patients may be asymptomatic or present with symptoms such as abdominal pain, weight loss, diarrhea, neurological complaints, pernicious anemia due to vitamin B12 deficiency, and iron deficiency anemia. Antiparietal antibodies, which cause immune-mediated damage, destroy the

parietal cells of the oxyntic mucosa and lead to mucosal atrophy limited to the corpus. These antibodies can be detected in serum and gastric secretions. Hypochlorhydria or achlorhydria, which develops due to mucosal atrophy, leads to hypergastrinemia and hyperplasia of gastrin-producing antral endocrine G cells. A decrease in serum pepsinogen I levels is detected. Intrinsic factor deficiency also causes vitamin B12 deficiency by impairing its absorption. As a result, pernicious anemia and neurological changes develop. In autoimmune gastritis, the corpus and fundus mucosa are thinned due to diffuse atrophy, and the mucosal folds are flattened. The antrum and cardia are usually preserved. Inflammatory infiltration in the lamina propria contains lymphocytes and plasma cells and is found more in the deeper parts of the mucosa

(Fig. 3.17). As a physiological response to reduced acid production due to atrophy, hypergastrinemia develops, and hyperplasia occurs in the corpus enterochromaffin-like neuroendocrine cells stimulated by gastrin. When this neuroendocrine cell proliferation in autoimmune gastritis develops into a nodule larger than 0.5 mm, it is diagnosed as a well-differentiated neuroendocrine tumor. In some cases, pyloric, pancreatic, or intestinal metaplasia may be observed. Intestinal metaplasia is a significant finding because intestinal-type gastric carcinomas may develop from dysplasia in the metaplastic epithelium. In advanced stages of the disease, the corpus mucosa becomes atrophic and indistinguishable from the antral mucosa. At this stage, gastrin and chromogranin immunostaining can be used to distinguish between corpus and antral mucosa. While gastrin

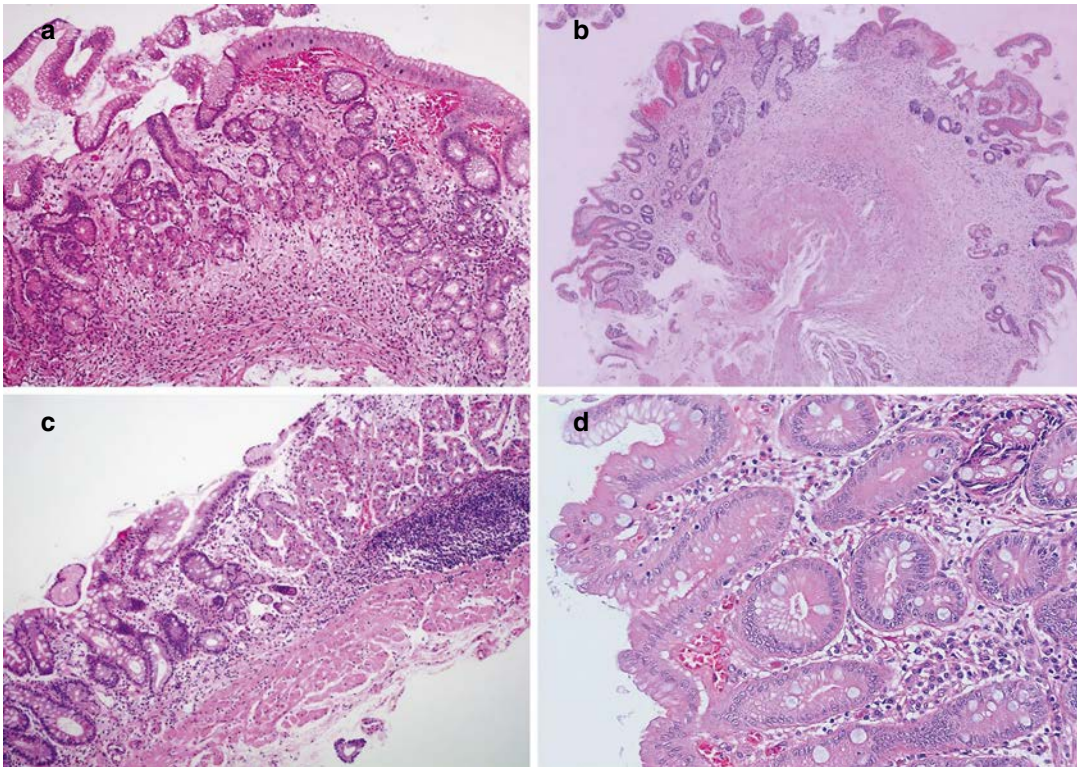


Fig. 3.17 (a) Gastric body biopsy sample showing loss of oxyntic glands, chronic lymphoplasmacytic infiltrate more in the deeper aspect, and pyloric gland metaplasia in autoimmune gastritis. (b) The corpus mucosa are thinned due to completely loss of oxyntic glands, prominent intestinal metaplasia, and diffuse atrophy. (c) The corpus

shows diffuse moderate chronic inflammation with more extensive loss of the oxyntic mucosa, intestinal metaplasia, and a prominent lymphoid aggregate. (d) Biopsy shows marked intestinal metaplasia with goblet cells in the corpus mucosa

immunostaining shows G cells in the antral mucosa, chromogranin-positive/gastrin-negative neuroendocrine cells should be considered enterochromaffin-like neuroendocrine cells in the corpus. Thus, it is proven that the detected changes belong to the corpus mucosa. Consequently, autoimmune gastritis should always be investigated in cases of *H. pylori*-negative, corpus mucosa-limited, patchy, and deep mucosal chronic atrophic gastritis and intestinal metaplasia. Medical treatment is administered for pernicious anemia and iron deficiency anemia in patients with autoimmune gastritis. Cases must be followed up for the development of neuroendocrine tumors and gastric adenocarcinoma. In necessary cases, endoscopic polypectomy, mucosal resection, antrectomy, or rarely gastrectomy may be performed [24].

3.2.4.3 Other Specific Gastritis

3.2.4.3.1 Granulomatous gastritis

Granulomatous gastritis is among the rarer forms of chronic gastritis. Granulomas located in the mucosa or submucosa can be seen in bacterial and fungal infections, primarily *Mycobacterium*, parasitic infections, systemic diseases such as sarcoidosis and Crohn's disease, and foreign body reactions. *Mycobacterium tuberculosis* infection is the most common cause of gastrointestinal granulomatous disease worldwide. It causes granulomas containing caseating necrosis in the stomach, particularly in the prepyloric and antral regions of the lesser curvature. Neutrophilic infiltration in granulomas should primarily suggest fungi, while eosinophilic infiltration should primarily suggest parasites. When granulomas

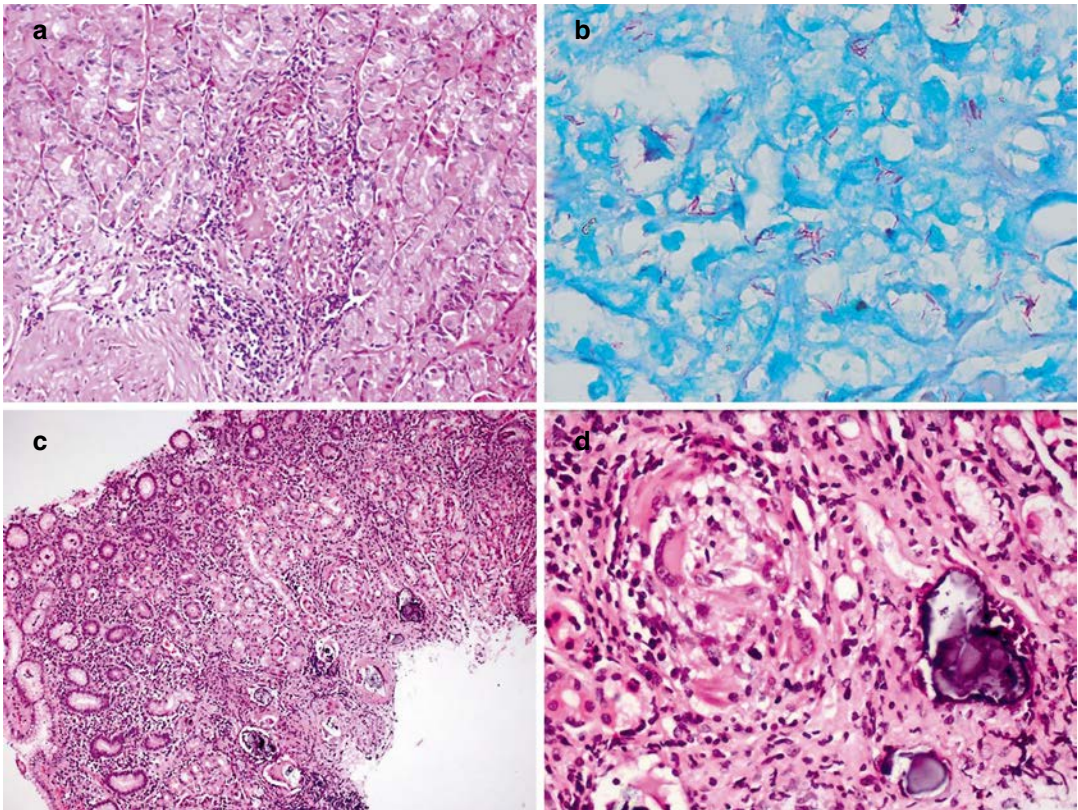


Fig. 3.18 (a) Corpus mucosa showing noncaseating granulomas in the lamina propria. This case of granulomatous gastritis resulted from gastric Crohn's disease. (b) In patients with tuberculosis acid-fast bacillus (EZN stain) will be diagnostic. (c) Biopsy shows some granulomas

deep in the gastric mucosa in a patient with sarcoidosis. (d) This biopsy exhibits characteristic non-caseating granuloma with the presence of Schaumann bodies in the cytoplasm of multinucleated giant cells

are detected in H&E sections, special stains such as acid-fast staining, Gomori methenamine silver, and PAS must be performed for differential diagnosis (Fig. 3.18). One of the most common forms of granulomatous gastritis is gastric Crohn's disease. These cases occur in young adults and even in the pediatric age group. Crohn's granulomas are small clusters of epithelioid histiocytes and are mostly found in normal mucosa. A patchy gastritis pattern involving several foveolae in the surrounding normal mucosa and forming gastric pit abscesses may be present. This picture is called focally enhanced gastritis. Sometimes, severe chronic active gastritis may also be present. The granulomas seen in gastric involvement of sarcoidosis, a systemic disease, are noncaseating granulomas, and calcified Schaumann bodies can be observed within giant cells [25].

3.2.4.3.2 Lymphocytic Gastritis

Lymphocytic gastritis is a rare form of gastritis characterized by marked intraepithelial lymphocytosis in the surface and pit epithelium of the stomach. The majority of cases of lymphocytic gastritis are patients with celiac disease or *H. pylori* gastritis. It can be seen in all age groups, predominantly in females. Endoscopically, it may appear normal, or erosions, nodules, and large gastric folds reminiscent of Ménétrier's disease may be observed. Due to this appearance, it is also referred to as variciform gastritis. Cases associated with celiac disease predominantly affect the antrum, while those associated with *H. pylori* infection predominantly affect the corpus. Drug-induced reactions result in a pangastritis picture. Histologically, there is marked intraepithelial lymphocytosis in the surface foveolar epithelium and pit epithelium. The deep gland component is preserved. Intraepithelial lym-

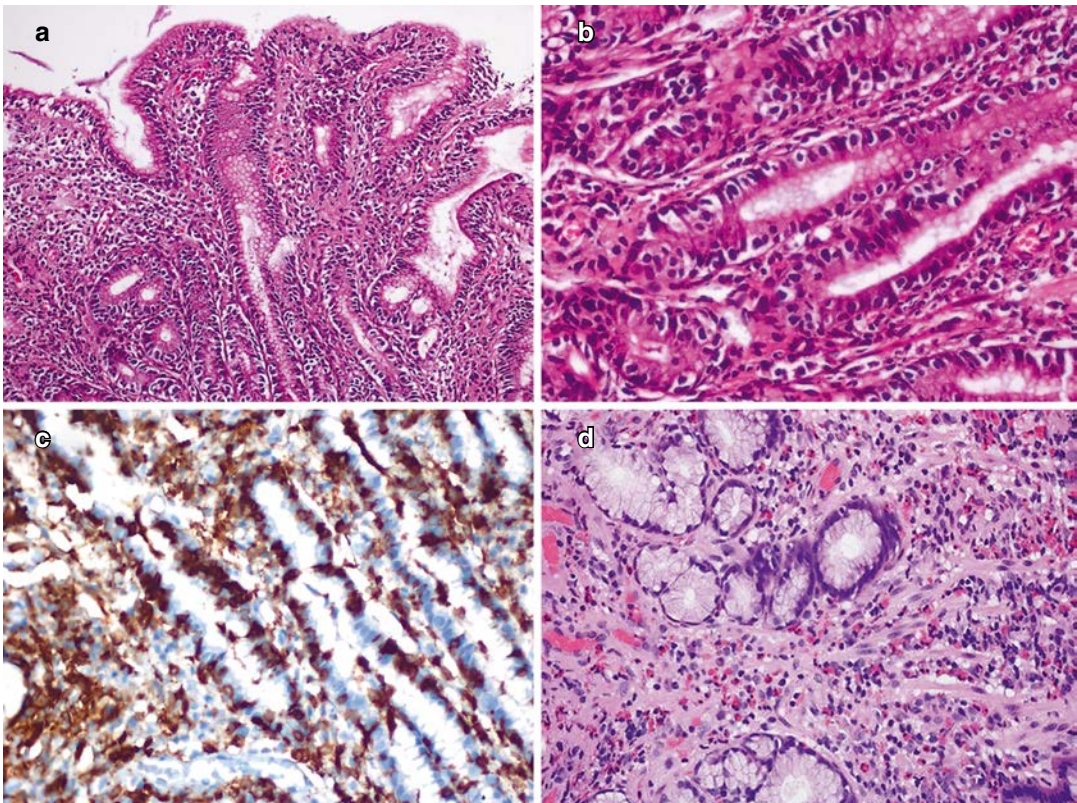


Fig. 3.19 (a) Lymphocytic gastritis with marked intraepithelial lymphocytosis and a marked lymphoplasmacytic infiltrate in the lamina propria. (b) High-power view showing condensed dark nuclei of the intraepithelial lym-

phocytes surrounded by a clear halo. (c) CD3 immunohistochemistry highlights the intraepithelial T cells. (d) There are innumerable eosinophils in the lamina propria in this example of eosinophilic gastritis

phocytes showing CD3 and CD8 positivity are condensed, hyperchromatic nuclei with a clear halo surrounding the nucleus (Fig. 3.19a–c). The diagnostic threshold for lymphocytic gastritis is considered to be >25 lymphocytes/100 epithelial cells. The foveolar pits are long and convoluted. Lymphoplasmacytic infiltration is present in the lamina propria. Treatment consists of treating the underlying disease such as celiac disease, *H. pylori* gastritis, drug-induced gastritis, and so on [26].

3.2.4.3.3 Eosinophilic Gastritis

It is a specific gastritis pattern characterized by dense eosinophil infiltration in the lamina propria and focal epithelial destruction by eosinophils. The underlying etiological factors may include primary eosinophilic gastroenteritis, allergic reactions, drug-induced hypersensitivity reactions, and parasitic infections. To diagnose eosinophilic gastroenteritis, gastrointestinal symptoms and eosinophil infiltration in the gastrointestinal tract must be present, along with the absence of eosinophil infiltration in any other organ and the absence of other causes of eosinophilia in the patient, such as parasitic infection, drug reaction, hypereosinophilic syndrome, or Langerhans cell histiocytosis [8]. Eosinophilic gastroenteritis occurs in adults and does not show gender differences. Although it can affect the entire gastrointestinal tract, the gastric antrum is the most commonly affected area. Histologically, eosinophil infiltration can be seen in all layers of the gastric wall, and the infiltration may be diffuse or patchy (Fig. 3.19d). The diagnostic criterion is the presence of at least 5 HPF with >30 eosinophils/HPF. This infiltration is accompanied by eosinophilic crypt abscesses, epithelial damage, regenerative changes, and edema. Patients with eosinophilic gastroenteritis respond very well to steroid treatment, but discontinuation of the drug may cause relapses [26, 27].

3.2.4.3.4 Collagenous Gastritis

Collagenous gastritis is a very rare form of gastritis characterized by subepithelial collagen deposition and inflammatory infiltration in the lamina propria. It can occur in all age groups regardless of gender. It is recommended that subepithelial collagen deposition should be >10 μm as a histological marker for

diagnosis. However, this assessment must be performed in well-oriented sections. It should also be noted that collagen deposition may be focal and patchy. Inflammatory infiltration in the lamina propria is lymphoplasmacytic in nature [26, 27].

3.2.4.4 Complications of Chronic Gastritis

3.2.4.4.1 Peptic Ulcer Disease

Peptic ulcer disease (PUD), one of the most common diseases worldwide, most frequently occurs with *H. pylori* and NSAIDs. It is characterized by solitary ulcers in the stomach and duodenum. It is a severe clinical condition that most commonly occurs in the 20–40 age group, presenting with symptoms such as severe epigastric pain, nausea, vomiting, weight loss, hematemesis, and melena and leading to complications such as gastric outlet obstruction, pyloric stenosis, peritonitis, and perforation. Although it can occur anywhere in the gastrointestinal tract exposed to acidic gastric fluid, it is most commonly seen in the gastric antrum and the first part of the duodenum. More than 70% of PUD cases involve *H. pylori* infection, and ulcers usually develop on the basis of chronic gastritis. The fact that PUD does not develop in all patients infected with *H. pylori* is due to host factors and the variation of the infecting *H. pylori* strains. Hyperacidity, the most important event in PUD pathogenesis develops due to causes such as *H. pylori* infection, Zollinger-Ellison syndrome, parietal cell hyperplasia, and inability to inhibit acid secretion. In Zollinger-Ellison syndrome, because gastrin-secreting tumors are involved, multiple ulcers appear in the stomach, duodenum, and even the jejunum. NSAID use suppresses mucosal prostaglandin synthesis, smoking impairs mucosal blood flow and the healing process, high-dose corticosteroids act as cofactors, and hypercalcemia stimulates gastrin production, thereby increasing acid secretion. Therefore, PUD development is facilitated in patients with alcoholic cirrhosis, chronic obstructive pulmonary disease, chronic renal failure, and hyperparathyroidism. Peptic ulcers are four times more common in the proximal duodenum than in the stomach.

Duodenal ulcers occur on the anterior wall and near the pyloric valve and are smaller in diameter than gastric ulcers. In the stomach, they are found at the corpus-antrum junction and more commonly on the lesser curvature side. Peptic ulcers are classically round, oval, and sharply defined and appear as if punctured by a punch. The base of the ulcer crater is smooth and appears clean due to the digestion of inflammatory exudate and necrotic tissue. These areas histologically appear as vascularized granulation tissue. PUD patients benefit more from medical treatment than surgery. Antibiotics for *H. pylori* eradication and PPI therapy to neutralize stomach acid are very useful [27, 28].

3.2.4.4.2 Mucosal Atrophy and Intestinal Metaplasia

Long-term chronic gastritis causes mucosal atrophy and intestinal metaplasia, defined as the transformation of the gastric epithelium into intestinal epithelium containing columnar and goblet cells. Gastric mucosal atrophy associated with intestinal metaplasia leads to achlorhydria, which in turn causes excessive growth of bacteria capable of producing carcinogenic nitrosamines. Ultimately, gastric adenocarcinomas may develop from these carcinogenic products. If chronic *H. pylori* gastritis is treated and eradication of the microorganism is achieved, intestinal metaplasia may also regress.

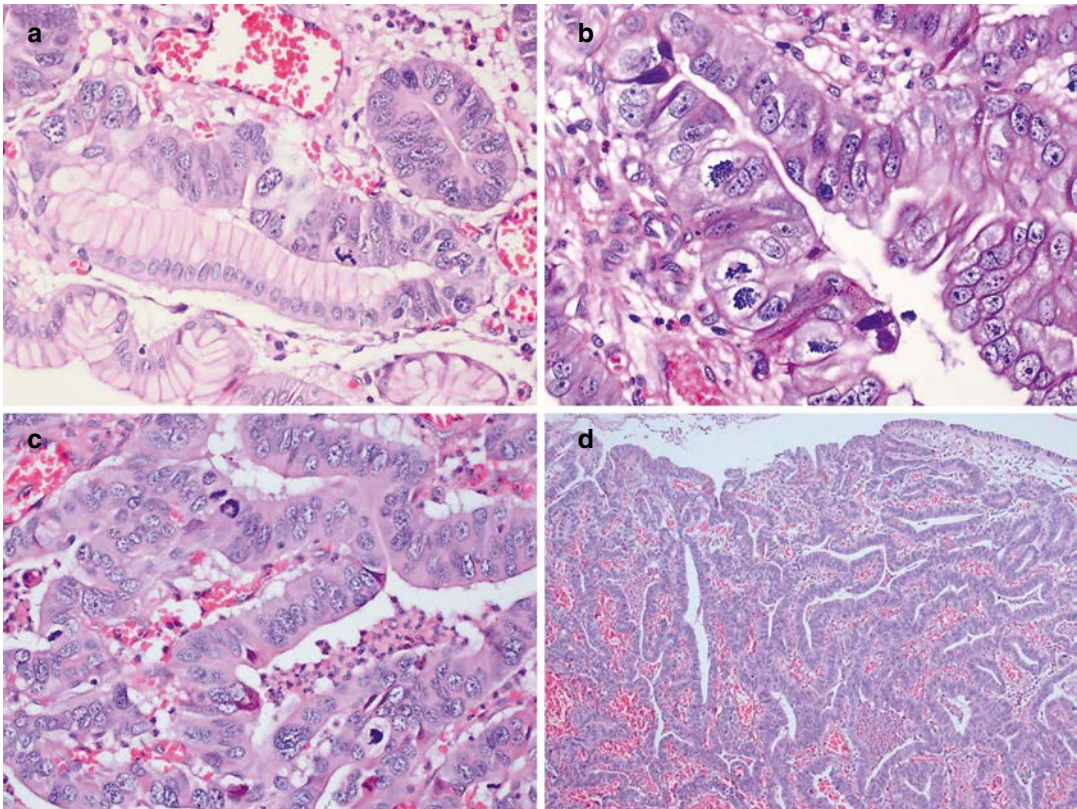


Fig. 3.20 (a) Biopsy shows the abrupt transition between non-neoplastic epithelium and dysplastic epithelium on the bottom that show nuclear pleomorphism with loss of polarity and coarse chromatin distribution. (b) High-grade gastric dysplasia exhibits increased cellularity with severe cytological pleomorphism, including enlarged, irregularly

shaped, overlapping, and stratified nuclei along with increased mitoses. (c) High-grade gastric dysplasia may consist of fusing neoplastic glands and high-grade nuclear features. (d) Intramucosal carcinoma is characterized by syncytial growth pattern with fused glands and single neoplastic cells in lamina propria

3.2.4.4.3 Dysplasia

During the chronic gastritis process, free radicals that arise due to inflammatory reactions damage epithelial cells. This triggers the repair process, leading to epithelial cell proliferation. Increased proliferative processes can create a basis for genetic changes. Regenerative changes in epithelial cells may progress to dysplasia, including abnormalities in shape, size, and arrangement, nuclear enlargement, hyperchromasia, and coarse chromatin distribution (Fig. 3.20).

3.2.5 Hypertrophic Gastropathies

Hypertrophic gastropathies are characterized by the folds of the gastric mucosa taking on a cerebriform appearance, similar to brain gyri, due to hyperplasia of the mucosal cells. Two diseases with this appearance have been identified. These are Ménétrier's disease and Zollinger-Ellison syndrome.

3.2.5.1 Ménétrier's Disease

Ménétrier's disease is characterized by diffuse hyperplasia of foveolar epithelial cells resulting from hyperactivation of EGFR in the foveolar epithelial cells of the stomach and excessive secretion of TGF- α , which is the ligand of this receptor. It is three times more common in men, and the majority of cases involve CMV or *H. pylori* infection. It may be asymptomatic, but nausea, vomiting, diarrhea, weight loss, and severe stomach pain may also be present. Patients have hypoproteinemia due to albumin loss, excessive increase in gastric mucus secretion, and hypochlorhydria due to glandular atrophy. The gastric folds are very large and irregular. This appearance, reminiscent of brain gyri, is prominent in the corpus and fundus, while the antrum is preserved. Histologically, the most striking finding is the hyperplasia of foveolar mucous cells. The elongate and tortuous foveolae have a corkscrew-like appearance.

Cystic dilatations are seen in some glands. The parietal and chief cells, on the other hand, are atrophied. Inflammatory reaction is either very little or absent. However, in order to distinguish these changes in the mucosa identified in the biopsy, the samples taken must include the entire mucosal layer. It is a chronic and progressive disease. Antibiotics, H₂ receptor blockers, anticholinergic drugs, and somatostatin analogues are used to relieve symptoms. Partial or total gastrectomy may be necessary in severe cases with findings such as massive bleeding or refractory protein loss. The risk of gastric adenocarcinoma is also increased in adult cases [28].

3.2.5.2 Zollinger-Ellison Syndrome

Zollinger-Ellison syndrome is characterized by hyperplasia of the parietal and chief cells of the stomach due to a neuroendocrine tumor (gastrinoma) that secretes excessive gastrin. Gastrinomas are almost always located in the small intestine or pancreas. Hyperacidity due to gastrin secretion leads to ulcers in the duodenum and stomach and diarrhea. The gastric folds in the corpus and fundus of the stomach are markedly hypertrophic. The most prominent histological finding is thickening of the oxyntic mucosa and parietal cell hyperplasia. Gastrin also causes hyperplasia of foveolar mucous cells and neuroendocrine cells. Hyperacidity may resolve when the gastrinoma is surgically removed. However, it should be noted that while 80% of gastrinomas are sporadic and solitary tumors, the remaining 20% may be multiple and associated with multiple endocrine neoplasia type 1 (MEN1) syndrome. The use of PPIs for acid blockage and somatostatin analogs in metastatic disease is recommended. These diseases are clinically important in two ways: Radiologically, they can mimic carcinomas or lymphomas of the stomach. Additionally, Zollinger-Ellison syndrome creates a favorable environment for the development of PUD [28].

3.2.6 Gastric Polyps

Gastric polyps are usually detected incidentally as a result of ever-increasing endoscopic examinations. Most gastric polyps are epithelial in origin and are seen in 4–6% of patients undergoing endoscopy. Almost all gastric polyps are asymptomatic; rarely, they may cause bleeding due to erosion on their surface, and when pedunculated, they may cause obstruction [29–32].

3.2.6.1 Fundic Gland Polyps

With the increasing use of PPIs and the decline in *H. pylori* prevalence, fundic gland polyps (FGPs) have become the most common type of gastric polyp. Although most fundic gland polyps are

sporadic, they are seen in multiple numbers in association with gastrointestinal polyposis syndromes. They have been reported in 20–100% of FAP (familial adenomatous polyposis) cases and in 11% of MUTYH-associated polyposis cases. Sporadic cases likely arise from the development of glandular hyperplasia in the oxyntic mucosa due to decreased acidity associated with PPIs and a corresponding increase in gastrin secretion. Sporadic cases occur in middle-aged women, while in FAP, polyps occur at an earlier age and are equally common in women and men. FGPs are typically <1 cm, sessile, hemispheric, smooth polyps, preferring gastric corpus and fundus. Histologically, they consist of irregularly shaped, dilated oxyntic glands, some of which show a

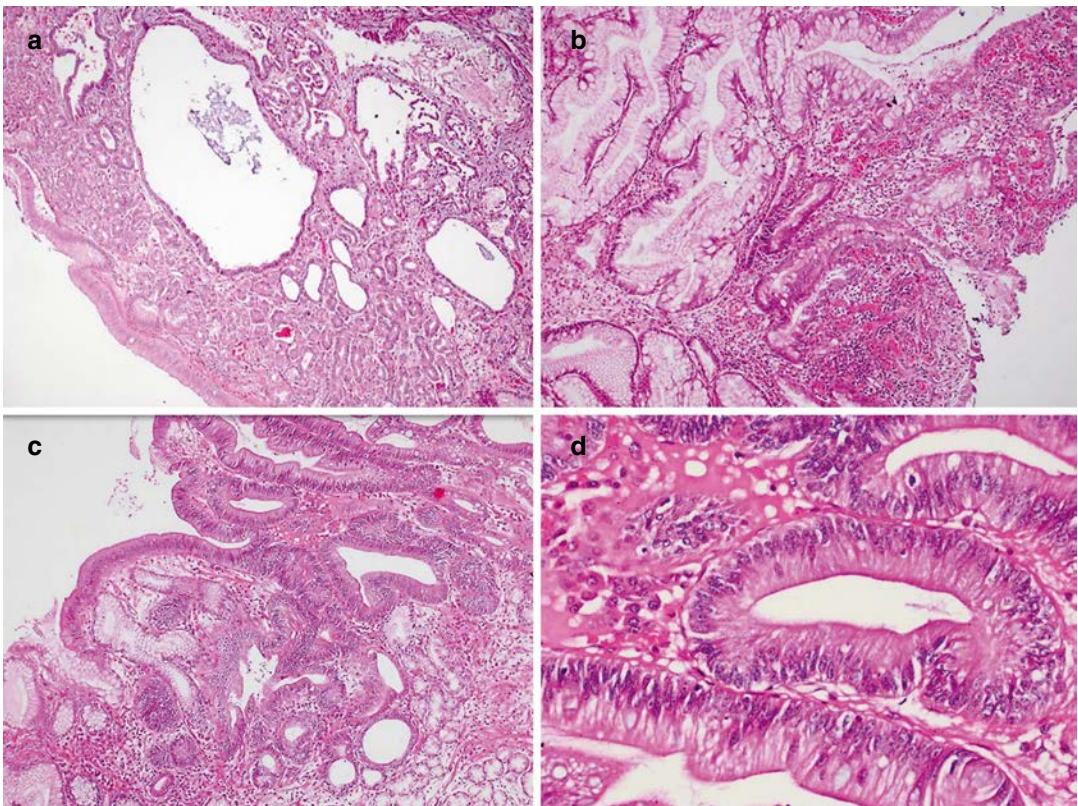


Fig. 3.21 (a) Fundic gland polyp with cystically dilated fundic glands lined by parietal and chief cells. (b) Elongated, dilated, tortuous gastric foveolar epithelium in a gastric hyperplastic polyp with edematous and inflamed stroma. (c) Neoplastic epithelial cells with intestinal phenotype exhibit a tubular growth pattern in gastric adenoma. The abrupt transition between non-neoplastic epithelium and atypical epithelium is noteworthy. (d) Low-grade intestinal-type dysplasia with nuclear enlargement, hyperchromasia, coarse chromatin distribution, and nuclear crowding are observed in moderately distorted, crowding, and irregular glands in gastric adenoma

nomia. The abrupt transition between non-neoplastic epithelium and atypical epithelium is noteworthy. (d) Low-grade intestinal-type dysplasia with nuclear enlargement, hyperchromasia, coarse chromatin distribution, and nuclear crowding are observed in moderately distorted, crowding, and irregular glands in gastric adenoma

microcystic configuration. Among them are convoluted or stellate glands, showing parietal cell hypertrophy. The lamina propria is edematous, and inflammatory reaction is minimal (Fig. 3.21a). Malignant transformation occurs in approximately 1% of sporadic FGP cases. Discontinuing PPI use in these cases may lead to regression of the polyps. In FAP cases, low-grade dysplasia is observed in 25–45% of FGP cases. Detection of somatic APC gene mutations in 50% of syndromic FGP cases and presence of activated β -catenin mutations in 90% of sporadic cases emphasize the neoplastic nature of these polyps. Therefore, endoscopic mucosal resection should be performed for FGPs that are large in diameter, ulcerated, or located in the antrum. FAP should be considered in patients with multiple polyps, FGP in the antrum, FGP showing dysplasia, or patients younger than 40 years of age, and a colonoscopy should be recommended for these patients. Upper endoscopic follow-up should also be recommended for these cases [29, 31].

3.2.6.2 Hyperplastic Polyp

Hyperplastic polyp, which constitutes 75% of all gastric polyps in regions where *H. pylori* is prevalent, has become the second most common type after fundic gland polyps, especially in North America, due to the decline in *H. pylori* prevalence and the increase in PPI use over the past 20 years. These polyps, which develop from the epithelium showing reactive hyperplasia in response to chronic inflammatory stimulation, are seen in individuals aged 50–60 years. These are generally solitary lesions mostly located in the antrum, which vary in diameter between 0.5 and 1 cm, have a smooth surface, and are ovoid in shape. Approximately 20% of cases are multiple and can be seen in all regions of the stomach. Microscopically, they consist of elongated, convoluted, dilated, cystic structures formed by hyperplastic foveolar epithelium and the edematous, inflammatory lamina propria between them (Fig. 3.21b). Hyperplastic foveolar cells may take on a globoid appearance similar to goblet cells due to increased mucin in their apical cytoplasm. Regenerative epithelial changes, intestinal and pyloric metaplasia, erosion, and ulceration

may be present on the surface of the polyp. In well-developed hyperplastic polyps, smooth muscle fibers extending from the muscularis mucosa to the surface of the polyp may also be seen. Dysplastic foci have been reported in 1–20% of hyperplastic polyps. The risk of malignancy increases in polyps larger than 1.5 cm and those with a stalk. Therefore, hyperplastic polyps larger than 0.5 cm should be completely excised, and normal-appearing mucosa should also be sampled for cancer, dysplasia, and *H. pylori*. If present, *H. pylori* eradication therapy should be performed. This treatment also promotes regression of hyperplastic polyps. Cases of hyperplastic polyps associated with dysplasia and carcinoma risk, such as chronic atrophic gastritis with intestinal metaplasia, or those with a family history of gastric cancer, should be monitored at regular intervals [29–32].

3.2.6.3 Gastric Adenomas

Gastric adenomas, which are precursors to gastric adenocarcinomas, account for approximately 10% of all gastric polyps. They are most commonly seen between the ages of 50 and 60 and are three times more frequent in men than in women. They almost always develop on a background of chronic atrophic gastritis with intestinal metaplasia. They most commonly occur in the antrum, usually solitary and < 2 cm in diameter, forming a flat or polypoid mass. The noninvasive neoplastic epithelial proliferation forming the lesion may exhibit an intestinal or foveolar-gastric phenotype. These cells typically exhibit a tubular growth pattern, while less frequently a villous or tubulovillous pattern is seen. Both intestinal and foveolar types of dysplasia show cytological changes in the columnar epithelium, such as nuclear enlargement, hyperchromasia, coarse chromatin distribution, irregular nuclear contours, prominent nucleoli, atypical mitoses, and structural changes in the glands, such as crowding; irregular, cribriform appearance of the glands; and loss of stroma between glands. The abrupt transition between the non-neoplastic epithelium and the atypical epithelium is indicative of neoplasia (Fig. 3.21c, d). Molecular changes in TP53, APC, and Kirsten rat sarcoma virus

genes and inactivation of Mismatch Repair (MMR) genes may be observed in gastric dysplasias. The risk of invasive cancer developing in gastric adenomas is higher than in colon adenomas. This risk correlates with the size of the polyp and the degree of dysplasia, as in colon polyps. It is higher for adenomas in the stomach that are >2 cm in diameter and show elevation. Since gastric adenomas are precursor lesions for gastric cancer, all gastric adenomas should be completely excised, regardless of their size and degree of dysplasia. The option of endoscopic mucosal or submucosal resection or partial gastrectomy should be evaluated based on the size, location, and macroscopic appearance of the adenoma. The remaining gastric mucosa should also be examined due to the possibility of concomitant cancer and sampled to uncover atrophic gastritis/dysplasia. Annual follow-up should be recommended for patients after adenoma resection because of recurrence or new polyp development risks [33, 34].

3.2.7 Gastric Cancer

Stomach cancer ranks fifth among cancers worldwide. The incidence of gastric carcinoma varies greatly between countries. While low rates are observed in Northern Europe, North America, and Africa, the incidence rate is very high in Eastern Asia countries such as Japan, Korea, and Chile, Colombia, Costa Rica, and Eastern Europe. Endoscopic screening programs implemented in countries with high stomach cancer incidence have significantly reduced the frequency of occurrence. It is most common in the seventh decade of life and occurs twice as often in men as in women. Stomach cancer is more common in low socioeconomic groups and in individuals with multifocal mucosal atrophy and intestinal metaplasia. *H. pylori* infection is the best-known cause of stomach cancer worldwide. Chronic gastritis, Epstein-Barr virus (EBV) infection, partial gastrectomy, bile reflux, and hypochlorhydria are also factors that increase the risk of stomach cancer. Environmental factors

that also increase cancer risk include foods rich in nitrites, nitrates, salt, and complex carbohydrates, smoked foods, smoking, reduced consumption of fresh fruits and vegetables, and obesity. In the context of chronic gastritis, increased epithelial proliferation in response to chronic damage, epigenetic changes associated with intestinal metaplasia, and suppression of local adaptive immunity trigger oncogenic changes in the inflamed gastric mucosa. Gastric cancer is a genetically heterogeneous tumor, but certain molecular alterations are frequently found. The most well-known of these is the germline mutation in the CDH1 gene, which is commonly seen in familial gastric cancers. Mutations in the CDH1 gene, which encodes the epithelial intercellular adhesion protein E-cadherin, are frequently seen in familial diffuse gastric cancer. Somatic mutations in the CDH1 gene are also found in 50% of sporadic diffuse gastric cancers, and in these cases, E-cadherin expression is significantly reduced or completely lost. Loss of E-cadherin function is a critical step in the development of diffuse gastric cancer. The APC gene, which undergoes germline mutation in FAP cases, is a negative regulator of the Wnt signaling pathway and is associated with intestinal gastric cancer. Beta-catenin mutations are frequently observed in sporadic intestinal gastric cancers. In addition, TP53 mutations are common in both types of sporadic gastric cancer, and amplifications in genes encoding HER2 tyrosine kinase are found in 10–20% of cases [3, 35].

Approximately 50–60% of gastric cancers occur in the pylorus and antrum, 25% in the cardia, and the remainder in the fundus and corpus. The lesser curvature of the antral region is the most common site of occurrence. Advanced intestinal-type cancers typically form ulcerated, polypoid, or fungating masses on the surface. Diffuse-type cancers, on the other hand, form infiltrative or depressive-type tumors that are not visible to the naked eye in the mucosa. Linitis plastica is the name given to a stomach that has become hard, thick-walled, and “leather bottle” due to diffuse cancer infiltrating a large portion of the stomach wall. An invasive adenocarcinoma

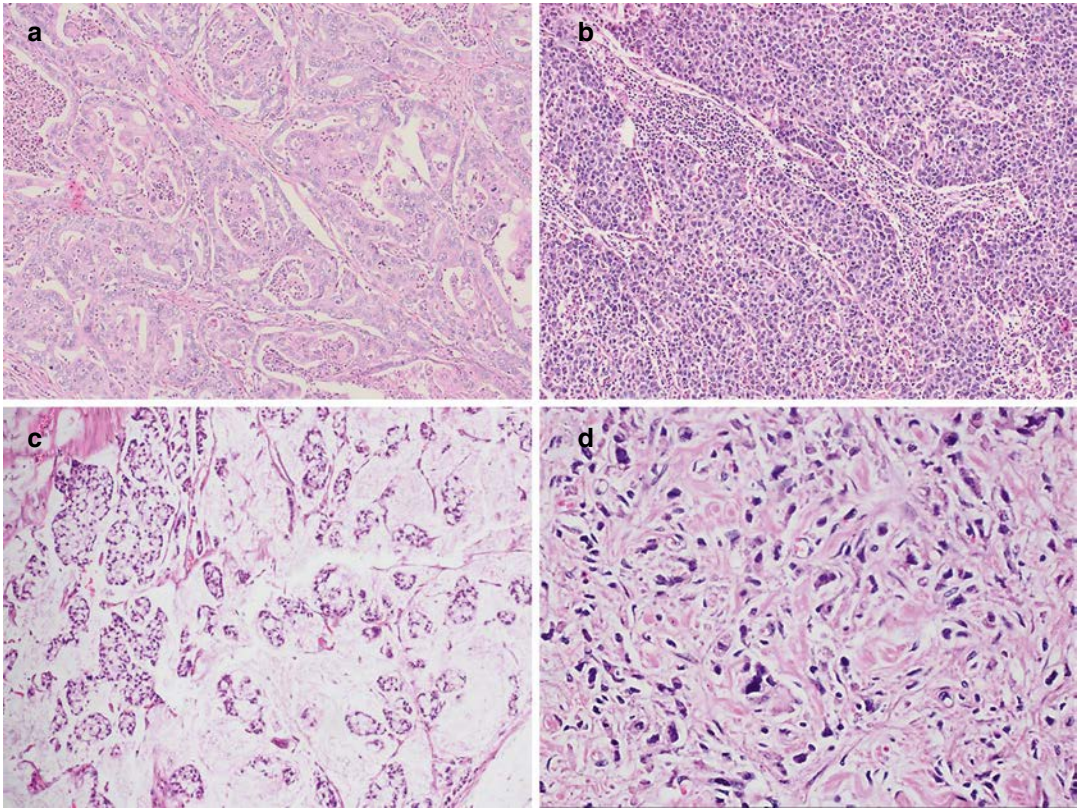


Fig. 3.22 (a) Tubular adenocarcinomas characteristically compose of neoplastic tubules with an infiltrative growth pattern and show a variable grade of differentiation. (b) This biopsy shows a gastric carcinoma with lymphoid stroma characterized by irregular sheets of epithelial cells embedded within a dense lymphocytic infiltrate. (c)

Mucinous carcinoma is characterized by pools of extracellular mucin that compose at least 50% of the tumor volume. (d) Poorly cohesive carcinomas (diffuse-type carcinoma) compose of single cells and cells forming small aggregates, some with various cytologic features

confined to the mucosa or submucosa, regardless of the presence of lymph node metastasis, is defined as early gastric carcinoma. Early gastric carcinoma is usually asymptomatic and can only be detected in high-risk individuals through repeated endoscopic examinations. Its prognosis is very good. Approximately 95% of gastric carcinomas are adenocarcinomas. The 2019 WHO classification subdivides adenocarcinomas into the following subtypes: tubular, papillary, mucinous, poorly cohesive, signet ring cell, micropapillary, hepatoid, medullary with lymphoid stroma, fundic gland type, and undifferentiated (Fig. 3.22). The older and more widely used Lauren classification divides gastric carcinomas

into two types: diffuse and intestinal. The intestinal type corresponds to tubular, papillary, and mucinous carcinomas with well-developed glandular structures, while the diffuse type corresponds to poorly cohesive carcinoma. In diffuse gastric carcinoma, tumor cells showing an infiltrative pattern individually or in small groups sometimes contain abundant intracytoplasmic mucin. This mucin pushes the tumor cell's nucleus toward the periphery, causing it to have a signet ring appearance (Fig. 3.23). These cells are the characteristic cells of signet ring cell carcinoma or poorly cohesive carcinoma and are very difficult to detect in the early invasive stage. Gastric adenocarcinomas are immunohistochem-

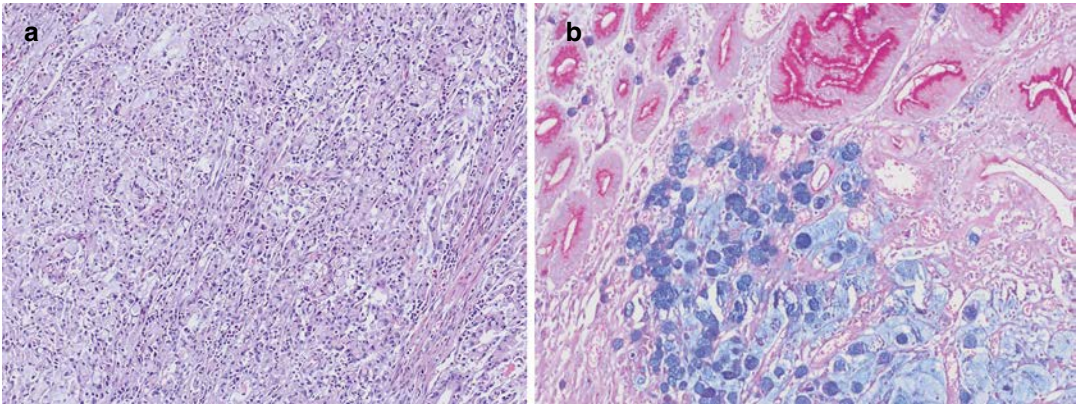


Fig. 3.23 (a) Signet ring cell carcinoma cells exhibit diffuse infiltrative pattern with the presence of a central, optically clear, or eosinophilic globoid droplet of cytoplasmic

mucin with eccentrically placed nuclei creating crescents. (b) PAS and AB stains may be helpful for identification of the neoplastic cells

ically positive for cytokeratin, epithelial membrane antigen, and monoclonal carcinoembryonic antigen and show CK7-positive/CK20-negative expression. HER2 test is performed to determine the suitability of anti-HER2 therapy in metastatic or unresectable tumors. Cases that are considered suspicious on immunohistochemical examination should always be examined by in situ hybridization. Additionally, Epstein-Barr virus-encoded small RNA in situ hybridization for EBV-associated tumors and PDL1 and MMR tests for treatment planning can also be performed. Regardless of histological type, all gastric carcinomas penetrate the gastric wall, involving the serosa, spread to regional and distant lymph nodes, and cause widespread metastasis. Invasion depth, lymph node metastasis, and distant metastasis are strongest prognostic factors. Histological tumor type is not an independent prognostic factor. Invasion of the duodenum, pancreas, and retroperitoneum is frequently observed. Gastric cancers are mostly diagnosed at an advanced and metastatic stage. If possible, the most appropriate treatment method for today is total surgical resection. The 5-year survival rate is 90–95% in early gastric carcinoma, while it is below 30% in advanced gastric carcinoma. Personalized treatment methods can be applied for suitable patients. For example, cases with HER2 overexpression benefit from anti-HER2 therapy, and immuno-

therapy can be administered to cases with PDL1 positivity [35–37].

3.2.8 Neuroendocrine Tumor

Gastric NETs, formerly known as “carcinoids,” are tumors originating from the neuroendocrine cells of the stomach. Gastric NETs, which mostly develop with hormonal stimulation, are classified by WHO according to their underlying pathogenesis. Type I NETs are tumors that develop with chronic atrophic gastritis and secondary hypergastrinemia with hypochlorhydria, occurring with autoimmune gastritis in the corpus. They account for 80–90% of all gastric NETs. Type II NETs are tumors that develop due to hypergastrinemia caused by Zollinger-Ellison syndrome and are almost always associated with MEN1. Type III NETs are sporadic tumors that arise independently of hypergastrinemia and neuroendocrine cell hyperplasia. Type I and Type II NETs are multifocal, small, well-defined, slow-growing, and asymptomatic tumors located in the corpus and fundus. These tumors, which are confined to the mucosa and submucosa and are less than 1 cm in diameter, do not show angioinvasion and rarely metastasize. Type III NETs are solitary masses, often located in the prepyloric region, >2 cm in size.

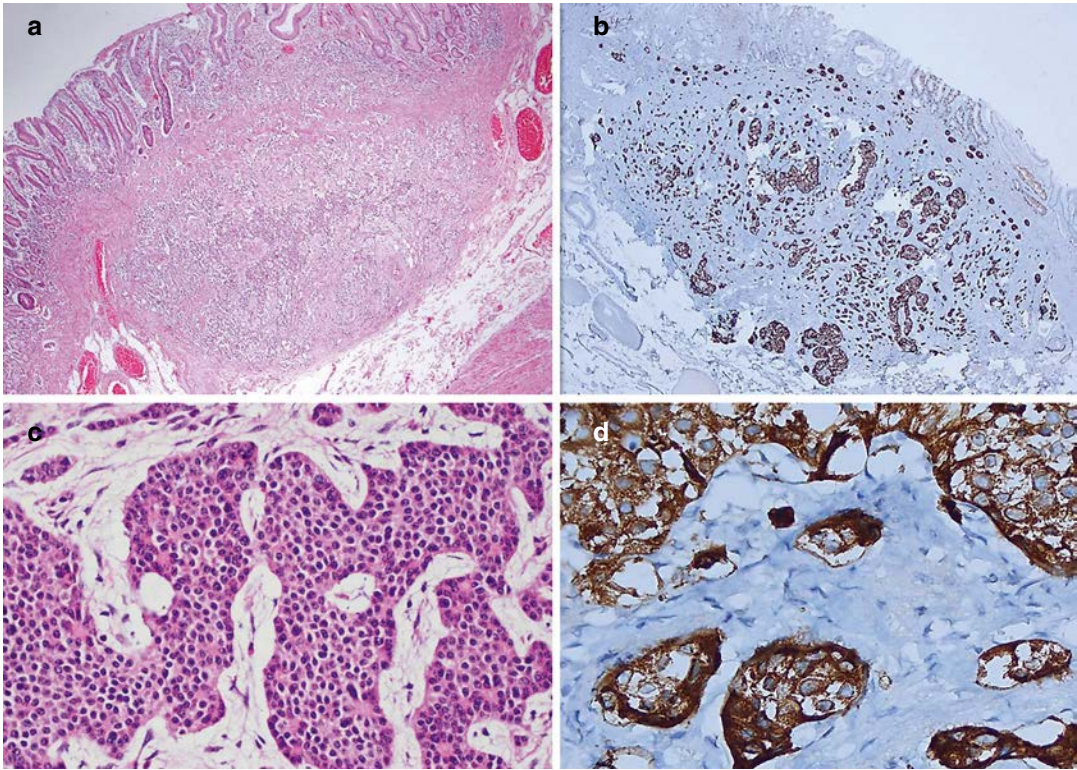


Fig. 3.24 (a) Type I neuroendocrine tumor is seen involving the submucosa and the muscularis mucosae. (b) This tumor is highlighted by synaptophysin immunohistochemistry. (c) Tumor cells characterized by enlarging

nests of small, uniform, cuboidal cells with lightly eosinophilic cytoplasm and regular, round nuclei showing minimal nuclear pleomorphism. (d) Tumor cells are also positive for chromogranin A immunostain

The overlying mucosa may be ulcerated, while the surrounding mucosa appears normal. They can cause hemorrhage, obstruction, and metastasis to regional lymph nodes and the liver. Neuroendocrine carcinomas, on the other hand, are large, high-grade, aggressive tumors that form polypoid masses growing into the lumen and cannot be distinguished from adenocarcinomas. Microscopically, the tumor consists of uniform cells with oval-round nuclei, pink granular cytoplasm, and a chromatin pattern referred to as a “salt-and-pepper appearance,” forming nests, layers, glands, or trabeculae. Tumor cells express neuroendocrine markers such as chromogranin A, synaptophysin, and insulinoma-associated protein 1, which determine the tumor origin (Fig. 3.24). The most important prognostic factors for gastrointestinal neuroendocrine

tumors are histological differentiation grade, mitotic rate, Ki-67 proliferation index, and localization. NETs located in the stomach, esophagus, and proximal duodenum rarely metastasize and are easily resectable surgically. Five-year survival is close to 100% in type I NETs in particular. Type III NETs, as expected, have a poor prognosis, with a 5-year survival rate of around 50%. Low-grade NETs can be regressed with somatostatin analogs or treated with endoscopic excision. In type I NETs with multiple polyps, antrectomy may be effective by removing the stimulation of antral G cells. Tumors that are large, have multiple polyps, and are of high-grade should be referred for surgery. In neuroendocrine carcinomas, intensive chemotherapy is required regardless of whether surgery is performed or not [35, 38].

3.2.9 Gastric Lymphoma

Although extranodal lymphomas can be found in various organs, they are most commonly seen in the gastrointestinal system and, within this system, most frequently in the stomach. Lymphomas account for approximately 5% of all stomach tumors and are mostly low-grade extranodal marginal zone B-cell lymphomas. These tumors are also called MALT lymphomas. The second most common type of lymphoma in the stomach is diffuse large B-cell lymphoma. Lymphomas are characterized by neoplastic lymphoid infiltrates infiltrating the gastric mucosa, and atypical lymphoid cells infiltrate the glandular epithelium,

forming diagnostic lymphoepithelial lesions. Nearly all GI lymphomas are B-cell phenotype and therefore show positivity for the B lymphocyte markers CD20 and CD19. They have a better prognosis than carcinomas [3, 35].

3.2.10 Gastrointestinal Stromal Tumor

These are mesenchymal tumors originating from interstitial Cajal cells, which are pacemaker cells that enable peristalsis in the gastrointestinal tract. They are most commonly found in the stomach within the entire GI tract. They occur between the

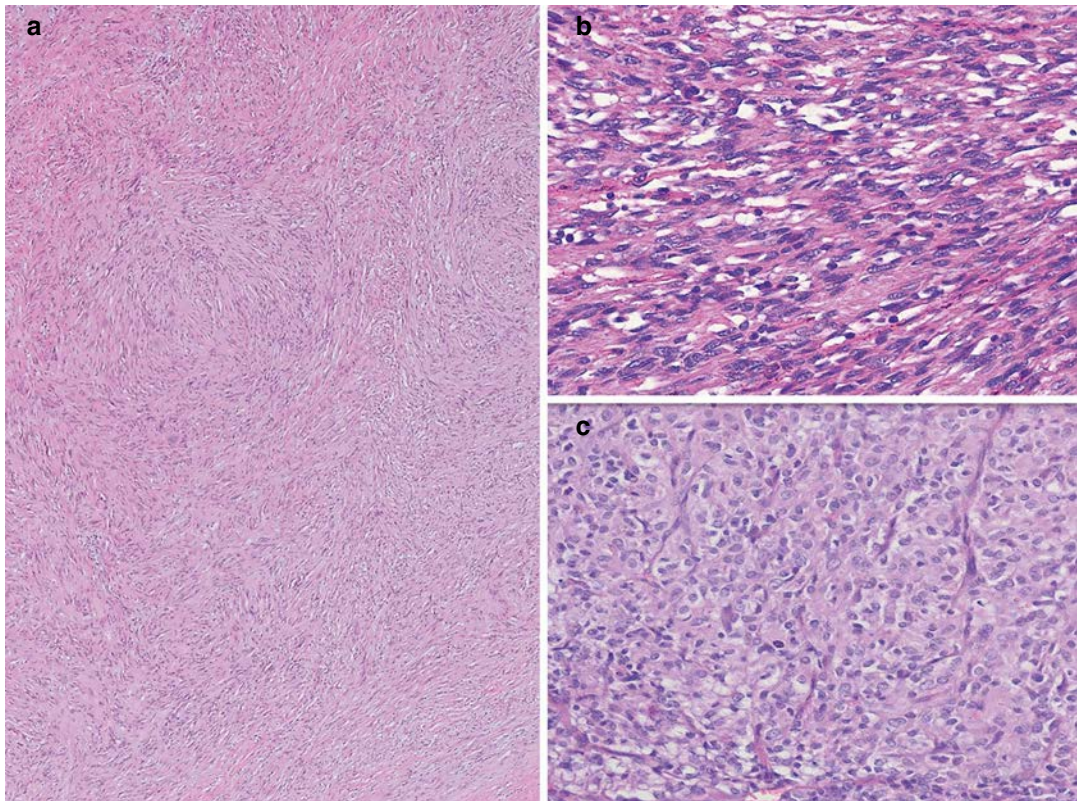


Fig. 3.25 (a) Gastric GISTs consist of thin, elongated spindle cells with eosinophilic cytoplasm, arranged in loose interweaving fascicles. (b) Most of the GISTs exhibit spindle cell morphology, with short fascicles of bland cells with indistinct cell borders, pale eosinophilic cytoplasm, and uniform nuclei with evenly dispersed

chromatin. (c) Tumor cells in some of the GISTs has epithelioid appearance in which individual tumor cells have more abundant cytoplasm and a rounded (rather than spindle) morphology. Epithelioid cells may demonstrate prominent cytoplasmic borders

ages of 40 and 60 and are slightly more common in men. Mutations are found in the gene encoding the tyrosine kinase receptor KIT in 75% of cases and in the PDGFRA gene in 8% of cases. Gastric GISTs are solitary, well-defined, submucosal tumors with a fleshy cut surface that can reach 30 cm in diameter. Microscopically, they consist of thin, elongated spindle cells or plump epithelioid cells forming short fascicles and bundles (Fig. 3.25). Immunohistochemical positivity for c-kit (CD117) and DOG1 is detected in 95% of cases. The most important factors determining prognosis are tumor size, mitotic rate, and tumor location. Gastric GISTs are less aggressive than GISTs in other parts of the gastrointestinal tract. The most common sites of metastasis are the peritoneal cavity and the liver. While the primary treatment is surgical excision, the tyrosine kinase inhibitor imatinib is an important treatment option for cases with KIT mutation, unresectable tumors, recurrent tumors, and metastatic tumors [35].

References

1. Russo P. Congenital and developmental disorders of the gastrointestinal tract. In: Odze RD, Goldblum JR, editors. *Surgical pathology of the GI tract, liver, biliary tract, and pancreas*. 4th ed. Philadelphia: Elsevier; 2023. p. 200–23.
2. Gordon IO. Non-neoplastic disorders of the esophagus. In: Srivastava A, Allende DS, Goldblum JR, editors. *Gastrointestinal and liver pathology*. 3rd ed. Philadelphia: Elsevier; 2024. p. 1–28.
3. Turner JR. The Gastrointestinal Tract. In: Aster JC, Kumar V, Abbas A, Debnath J, Das A, editors. *Robbins&Kumar Pathology Basis of Disease*. 11th ed. Philadelphia: Elsevier; 2026. p. 684–747.
4. Savarino E, Bredenoord AJ, Fox M, et al. Advances in the physiological assessment and diagnosis of GERD. *Nat Rev Gastroenterol Hepatol*. 2017;14:665–76.
5. Orlando LA, Orlando RC. Dilated intercellular spaces as a marker of GERD. *Curr Gastroenterol Rep*. 2009;11:190–4.
6. Vieth M, Mastracci L, Vakil N, et al. Epithelial thickness is a marker of gastroesophageal reflux disease. *Clin Gastroenterol Hepatol*. 2016;14(11):1544–51.
7. Katzka DA, Kahrilas PJ. Advances in the diagnosis and management of gastroesophageal reflux disease. *BMJ*. 2020;371:m3786.
8. Hoversten P, Kamboj AK, Katzka DA. Infections of the esophagus: an update on risk factors, diagnosis, and management. *Dis Esophagus*. 2018;31(12):1–9.
9. Collins MH, Martin LJ, Alexander ES, et al. Newly developed and validated eosinophilic esophagitis histology scoring system and evidence that it outperforms peak eosinophil count for disease diagnosis and monitoring. *Dis Esophagus*. 2017;30:1–8.
10. Pittman EM. Lymphocytic esophagitis: current understanding and controversy. *Am J Surg Pathol*. 2022;46(1):e55–63.
11. Goldblum JR. Current issues in Barrett's esophagus and Barrett's-related dysplasia. *Mod Pathol*. 2015;28(Suppl 1):S1–6.
12. Shaheen NJ, Falk GW, Iyer PG, et al. Guideline to practice: diagnosis and management of Barrett's esophagus: an updated ACG guideline. *Am J Gastroenterol*. 2022;117:559–87.
13. Odze R. Histology of Barrett's metaplasia: do goblet cells matter? *Dig Dis Sci*. 2018;63(8):2042–51.
14. Choi WT, Lauwers GY, Montgomery EA. Utility of ancillary studies in the diagnosis and risk assessment of Barrett's esophagus and dysplasia. *Mod Pathol*. 2022;35(8):1000–12.
15. Odze R, Frei N, Khoshiwal AM, et al. Degree of crypt atypia correlates with progression to high-grade dysplasia/adenocarcinoma in non-dysplastic Barrett's oesophagus. *Histopathology*. 2023;83:406–13.
16. Chen X, Lingjia Liu B, Harpaz N, et al. Aberrant p53 expression is associated with neoplastic progression in Barrett oesophagus diagnosed as indefinite for dysplasia. *Histopathology*. 2023;82:454–65.
17. Odze RD, Lam AK, Ochiai A, Washington MK. Tumors of oesophagus. In: WHO classification of tumours editorial board, International Agency for Research on Cancer, editor. *WHO classification of tumours: digestive system tumours, Classification of tumours series*. 5th ed. Lyon: WHO; 2019. p. 23–58.
18. Ajan JA, In H, Sano T, et al. Stomach. In: Amin MB, editor. *AJCC cancer staging manual*. 8th ed. New York: Springer; 2017. p. 205–26.
19. Lam AK, Bourke MJ, Chen R, et al. Dataset for the reporting of carcinoma of the esophagus in resection specimens: recommendations from the international collaboration on cancer reporting. *Hum Pathol*. 2021;114:54–65.
20. Kövari B, Odze RD, Lauwers GY. Inflammatory disorders of the stomach. In: Odze RD, Goldblum JR, editors. *Surgical pathology of the GI tract, liver, biliary tract, and pancreas*. 4th ed. Philadelphia: Elsevier; 2023. p. 396–453.
21. Bindu S, Mazumder S, Bandyopadhyay U. Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: a current perspective. *Biochem Pharmacol*. 2020;180:114147.
22. Zamani M, Ebrahimitabar F, Zamani V, et al. Systematic review with meta-analysis: the worldwide prevalence of helicobacter pylori infection. *Aliment Pharmacol Ther*. 2018;47(7):868–76.

23. Batts KP, Ketover S, Kakar S, et al. Appropriate use of special stains for identifying helicobacter pylori: recommendations from the Rodger C. Haggitt gastrointestinal pathology society. *Am J Surg Pathol*. 2013;37(11):e12–22.
24. Rugge M, Bricca L, Guzzinati S, et al. Autoimmune gastritis: long-term natural history in naïve helicobacter pylori-negative patients. *Gut*. 2023;72(1):30–8.
25. Liang Y, Cui S, Polydorides AD. Clinicopathological characteristics and aetiological factors of granulomatous gastritis. *Histopathology*. 2021;79(6):1040–50.
26. Zimaity H, Choi WT, Lauwers GY, Riddell R. The differential diagnosis of helicobacter pylori negative gastritis. *Virchows Arch*. 2018;473:533–50.
27. Umetsu SE, Lauwers GY. Non-neoplastic disorders of the stomach. In: Srivastava A, Allende DS, Goldblum JR, editors. *Gastrointestinal and liver pathology*. 3rd ed. Philadelphia: Elsevier; 2024. p. 1–28.
28. Bancila I, Popescu I, Herlea V, et al. Ménétrier's disease: a rare entity which mimicks gastric cancer. *J Gastrointestin Liver Dis*. 2016;25(2):137.
29. Assarzagdegan N, Montgomery E. Gastric polyps. Mini-symposium: gastrointestinal and hepatic pathology. *Diagn Histopathol*. 2017;23(12):521–9.
30. Imura J, Hayashi S, Ichikawa K, et al. Malignant transformation of hyperplastic gastric polyps: an immunohistochemical and pathological study of the changes of neoplastic phenotype. *Oncol Lett*. 2014;7:1459–63.
31. Brosens LAA, Wood LD, Offerhaus GJ, et al. Pathology and genetics of syndromic gastric polyps. *Int J Surg Pathol*. 2016;24(3):185–99.
32. Kövari B, Baek HK, Lauwers GY. The pathology of gastric and duodenal polyps: current concepts. *Histopathology*. 2021;78:106–24.
33. Rokutan H, Abe H, Nakamura H, et al. Initial and crucial genetic events in intestinal-type gastric intramucosal neoplasia. *J Pathol*. 2019;247:494–504.
34. Gullo I, van der Post RS, Carneiro F. Recent advances in the pathology of heritable gastric cancer syndromes. *Histopathology*. 2021 Jan;78(1):125–47.
35. Fukuyama M, Rugge M, Washington MK. Tumors of stomach. In: WHO Classification of Tumours Editorial Board, International Agency for Research on Cancer, editor. *WHO classification of tumours: digestive system tumours, WHO classification of tumours series*. 5th ed. Lyon; 2019. p. 59–109.
36. Carneiro F, Lauwers GY. Epithelial neoplasms of the stomach. In: Odze RD, Goldblum JR, editors. *Surgical pathology of the GI tract, liver, biliary tract, and pancreas*. 4th ed. Philadelphia: Elsevier; 2023. p. 811–44.
37. Joshi SS, Badgwell BD. Current treatment and recent Progress in gastric cancer. *CA Cancer J Clin*. 2021;71:264–79.
38. Ogata Y, Hatta W, Kanno T, et al. Type 2 and type 3 gastric neuroendocrine tumors have high risk of lymph node metastasis: systematic review and meta-analysis. *Dig Endosc*. 2025;37(8):834–43.

Pathology of Small and Large Bowels

4

Gülen Doğusoy Bülbül

4.1 Developmental Anomalies

Some rare anomalies like intussusceptions, atresia (imperforate mucosal diaphragm or string-like segment of the bowel), or stenosis (narrowing of the lumen) may occur because of developmental failure or intrauterine vascular accidents. Their common complications are perforation and meconium peritonitis.

Enterogenous Cysts They are found in the wall of the small bowel, mesentery, posterior mediastinum, or rectorectal space and may be associated with vertebral body abnormalities. The cyst is lined by either respiratory or small intestinal or gastric epithelium, and there is an irregularly oriented smooth muscle in the bowel wall under this epithelium [1, 2].

Meckel Diverticulum It is a congenital disorder caused by incomplete obliteration of the omphalomesenteric duct (also called the vitelline duct), which results in a true diverticulum. It is typically located in the ileum within 2 feet from the ileocecal valve. This lesion is the most common congenital malformation of the gastrointestinal (GI) tract (GIT), affecting 2–4% of the population. As it consists of all layers of the

intestinal wall, it is a true diverticulum. The ectopic tissue, most commonly gastric mucosa, may be seen in 50% [3].

Hirschsprung Disease It is the absence of enteric ganglion cells in the submucosal and myenteric plexuses of the distal rectum (called the short segment) or along a variable length of large bowels (long segment). This absence causes functional obstruction and colonic dilation proximal to the affected segment.

Volvulus It is the torsion of the colon leading to colonic necrosis and then intestinal obstruction that has a high mortality rate. This lesion usually involves the cecum or sigmoid.

Omphalocele It is the congenital defect of the periumbilical abdominal wall through the umbilical cord. It occurs due to failure of the abdominal musculature that leaves behind a membranous sac and intestines herniate into this sac [1, 2].

4.2 Enterocolitis

Acute Self-Limited Enterocolitis It usually resolves completely within 2–4 weeks so it is defined as a transient disorder of the bowels [2]. This type of enterocolitis is mostly due to infections, nonsteroidal anti-inflammatory drugs or other drugs, bowel preparation, or procedure-associated injury (e.g., glutaraldehyde disinfection).

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tion of the endoscope) [3]. There is a wide variety of infectious pathogens, and the most common bacterial organisms are *Campylobacter jejuni*, *Salmonella*, *Shigella* species, *E. coli*, and *Yersinia enterocolitica* [3–5]. In gross description, there are mucosal erythema, erosion, friability, ulceration, erosion, pseudopolyps, and hyperemia, and, in some, exudates may be present on the surface (pseudomembranes). A microscopic (histologic) feature is the inflammation of the lamina propria. If there are neutrophils, it is called active, and if only lymphoplasmacytic cells are present, it is called chronic colitis. In some we can only see edema and hemorrhage in the bowel that usually lacks features of chronicity. Neutrophil-induced epithelial injury (cryptitis or crypt abscess) may be seen. In active colitis, neutrophils disappear within the second or third weeks, with persistent monocytic lymphocytic infiltration [4, 5]. Cytotoxins of some bacteria cause direct epithelial cell necrosis (e.g., Shiga toxin); some bacteria have the capacity to invade epithelial cells, and this phase is followed by intracellular proliferation, cell lysis, and cell-to-cell spread (e.g., *Shigella*).

Shigella It affects the distal colon and causes acute hemorrhagic mucosal inflammation, erosions, or shallow ulcers and pseudomembranes.

Yersinia enterocolitica* and *Y. pseudotuberculosis They affect the ileum, appendix, and colon and cause mucosal hemorrhage and ulceration.

Salmonella It has two major subtypes, namely, *S. typhi* causing typhoid fever and nontyphoid species causing others, especially food poisoning. In typhoid fever, ulceration of Peyer's patches in the ileum (longer dimension parallel to the long axis of the intestine) is seen; later, intestinal bleeding, perforation, and shock occur. Peyer's patch invasion by *S. typhi* leads to mesenteric lymph node enlargement with suppurative granulomas. *S. typhi* and *Y. enterocolitica* pass through the mucosal epithelial cells en route to lymphatics and bloodstream, so systemic spread is seen.

Nontyphoid Salmonella species (S. paratyphi, S. typhimurium, and Others) They cause food-borne disease, as a major cause of common-source outbreaks of enterocolitis, localized mucosal disease in the ileum and colon. Fecal-oral transmission is the primary cause of the disease, and contact with infected animals is another source. Salmonellosis is also the common cause of traveler diarrhea.

Mycobacterium (M. bovis in Milk or M. tuberculosis in Food or Swallowed Sputum) It causes chronic inflammation and caseous necrotizing granuloma formation in bowels and regional lymph nodes (Fig. 4.1). Circular or oval ulcers of varying size are seen in the transverse plane of the bowel. The bowel is indurated, and serosa is filled with grayish white nodules which are microscopically composed of caseous granulomas.

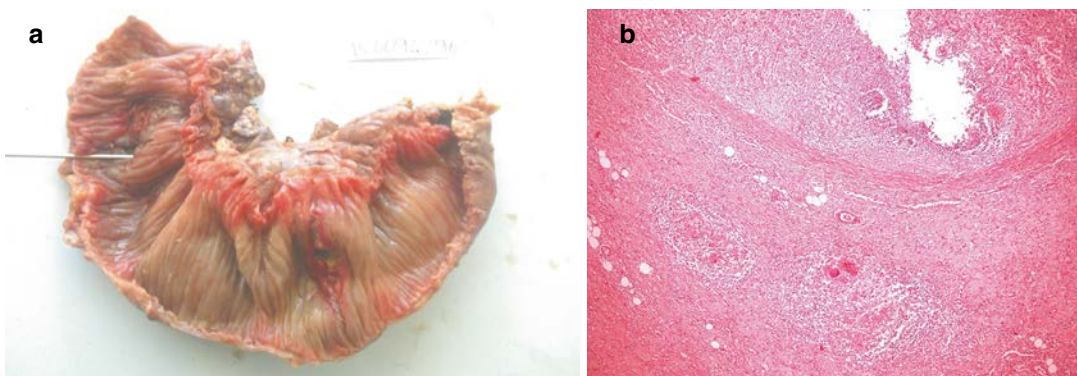


Fig. 4.1 Microscopic features of tuberculosis: ulceration in the mucosa and caseous granulomas in the bowel wall

***Escherichia coli* (A Versatile Organism)** It is a major foodborne pathogen and has different strains. Some of them affect the small intestines or colon, similar to *V. cholera* or *Shigella*. Some species cause hemorrhage and ulceration.

Clostridium difficile It is a normal gut organism, but cytotoxin-producing strains may emerge after systemic antibiotic use. A characteristic feature is the plaque-like adhesion of fibrinopurulent debris and mucus on the damaged superficial mucosa. This disease is called antibiotic-associated or pseudomembranous colitis as membranes on the surface are not true membranes (Fig. 4.2) [4, 5].

Necrotizing Enterocolitis It is an acute, necrotizing inflammation of the small bowel and colon in patients with myelosuppression (neutropenic enterocolitis) and the most common acquired GI emergency of neonates. It is common in premature or low-birth-weight infants, particularly when they start on oral foods at 2–4 days. This enterocolitis is seen also in adults with various myeloproliferative disorders, solid malignancies, and immunosuppression after transplantations. It affects the terminal ileum and ascending colon. Intestinal bacteria invade the immature intestinal epithelium, causing subsequent inflammation and tissue necrosis. Bacteria in food produce more cytokines and injure the mucosa. It may also be due to deranged intestinal blood flow. Initially damage is mucosal, but in severe cases, the entire wall is hemorrhagic, gangrenous, necessitating surgical resection [2, 6].

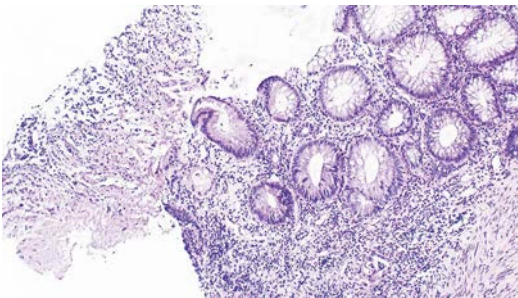


Fig. 4.2 Microscopic appearance of pseudomembranous colitis

Amebic Colitis or Amebiasis It is caused by a protozoan called *Entamoeba histolytica*. This protozoan is transmitted through the fecal-oral route and causes a type of dysentery. Amebae invade the colonic crypts and burrow down into the submucosa and then fan out laterally to create a flask-shaped ulcer with a narrow neck and broad base. There is little inflammatory infiltrate within the ulcer [4, 5].

Giardiasis It is another protozoan disease caused by *Giardia lamblia*/*Giardia intestinalis*, a common parasite that can be detected in small bowel biopsies and also in stool. Clinical presentation ranges from asymptomatic shedding of giardial cysts to symptomatic giardiasis (i.e., malabsorption, chronic diarrhea). It is found throughout the world but less common in developed countries, common in areas with poor sanitation and limited water treatment facilities. Infection is seen in children more than adults. *Giardia* organisms are found in the small intestine, classically the duodenum (Fig. 4.3). The other possible sites are the jejunum, ileum, and stomach. *Giardia intestinalis* infection causes enterocyte damage and loss of brush border of the epithelial cells of the small intestine, which leads to shortening of microvilli and altered epithelial barrier function [5, 7].

Whipple Disease It is an extremely rare, multi-system infection due to *Tropheryma whippeli*

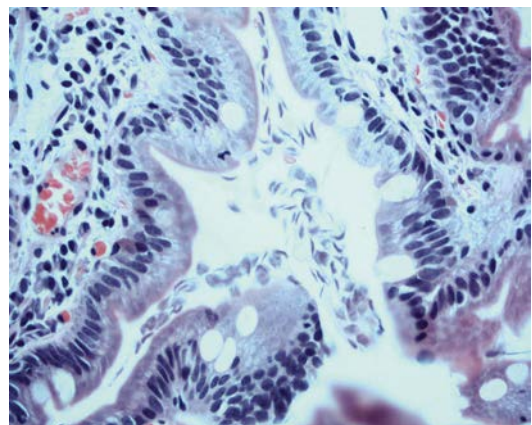


Fig. 4.3 *Giardia* organisms on the duodenal surface

that most commonly affects the small bowel but may involve any part of the gastrointestinal tract (esophagus, stomach, appendix, colorectum). Histologically, small intestinal biopsies show infiltration of the lamina propria by foamy macrophages containing periodic acid-Schiff-positive, acid-fast bacilli-negative bacteria. It is a multisystem infection, which most often involves the gastrointestinal tract. It may involve the mesenteric lymph nodes, joints,

heart, lungs, eyes, and central nervous system. The lamina propria is expanded by foamy macrophage infiltrate, and this infiltrate may be diffuse or patchy and may cause blunt or distended villi (Fig. 4.4) [8].

Viral infections cause shortening and blunting of villi in the small intestine, epithelial vacuolization, nuclear disarray, lymphocytosis, and intranuclear inclusions (Fig. 4.5) [4, 5].

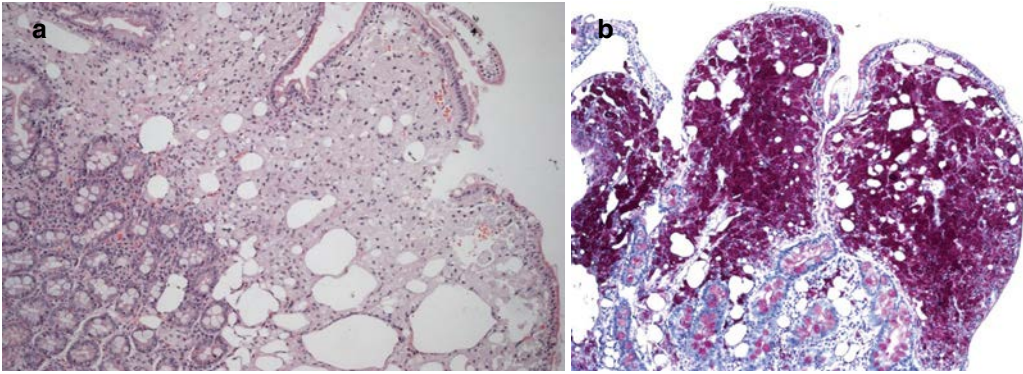


Fig. 4.4 Whipple disease: Lamina propria is expanded by foamy macrophage infiltrate, which causes blunt or distended villi (a, HE; b, PAS)

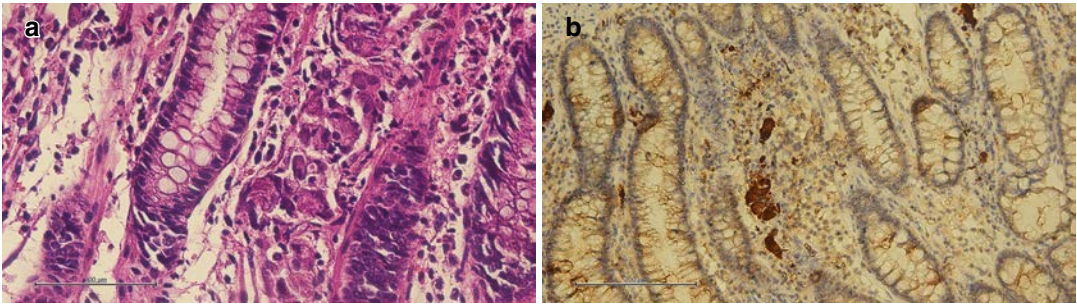


Fig. 4.5 Cytomegalovirus colitis with intranuclear inclusions (a, HE; b, immunohistochemistry)

4.3 Malabsorption Disorders

The small bowel is important for absorption of fats, fat-soluble vitamins, proteins, carbohydrates, electrolytes, minerals, and water. Most common malabsorption disorders are celiac sprue, pancreatic insufficiency, and Crohn's disease (CD). Steatorrhea means bulky, greasy stools associated with weight loss, anorexia, and muscle wasting [2, 3].

Celiac Sprue/Celiac Disease (Gluten-Sensitive Enteropathy) It is a kind of malabsorption and immune-mediated inflammatory disease of the small intestine. Absorption is defective due to reduction in small intestinal absorptive surface area. It is seen in genetically predisposed individuals and is caused by sensitivity to water-insoluble protein gliadin (prolamins), found in wheat (gliadin), barley (hordein), rye (secalin), and oats (avenin). Adaptive immune response to prolamins leads to characteristic infiltration of the lamina propria and the epithelium with chronic inflammatory cells (T cells) and partial or total villous atrophy, leading to malabsorption (Fig. 4.6). The disease is characterized by intraepithelial lymphocytosis in the small bowel, also in the stomach and colon [9].

Abetalipoproteinemia It is a rare, genetic, autosomal recessive deficiency of apolipoprotein B. Because of this deficiency, free fatty acids and monoglycerides cannot be assembled into chylo-

microns and triglycerides. They start to be stored within surface epithelial cells of the small bowel, causing lipid vacuolization. So, marked fat vacuoles are seen in the apical villous cytoplasm (Fig. 4.7). Fat stains highlight these lipid vacuoles [10, 11].

Tropical Sprue It affects the people living in or visiting the tropics, particularly Caribbean (not Jamaica), Africa, India, Southeast Asia, and Central/South America. This sprue shows endemic and epidemic features, with variable villous atrophy (none, partial, total), injury to the entire small bowel (not in the proximal part as in celiac sprue), inflammatory infiltrate, and crypt hyperplasia [12].

Microvillus Inclusion Disease It is a disorder of the intestinal brush border with severe villous abnormality with crypt hypoplasia, resembling celiac sprue but without lymphocytosis. Increased enterocyte apoptosis and proliferation, bubbly vacuolated apical cytoplasm with extensive or patchy absence of brush border, and absence of inflammation are characteristic features [6, 10].

Tufting Enteropathy Villus abnormality, epithelial crowding, disorganization, and focal tufting are seen in the epithelium. There is no epithelial lymphocytosis [6, 10].

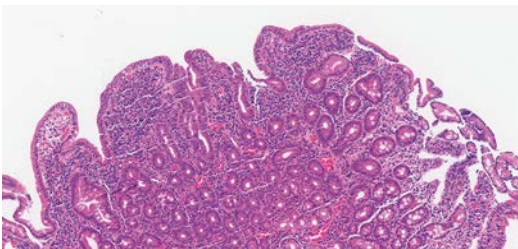


Fig. 4.6 Microscopic features of gluten enteropathy: villous atrophy and intraepithelial lymphocytosis

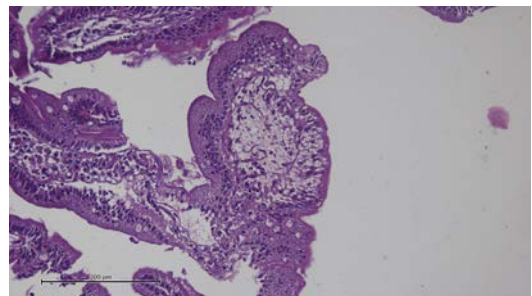


Fig. 4.7 Abetalipoproteinemia: In microscopic examination, marked fat vacuoles are seen in the apical villous cytoplasm

4.4 Inflammatory Bowel Disease

Crohn's disease and ulcerative colitis (UC) are two main chronic relapsing disorders of unknown origin which not only share many common features but also have some differences to justify them as two separate diseases. CD is a granulomatous disease that affects any portion of the GI tract from the esophagus to the anus but most often the small bowel and colon, but UC is a non-granulomatous disease limited to the colon. Both diseases remain unexplained (idiopathic); there is unregulated and exaggerated immune response to gut microbes in genetically susceptible persons. The role of the intestinal flora and abnormal T-cell response is also a known factor. Inflammation is the final common pathway, and clinical and morphologic changes are a result of activation of the inflammatory cells. The products of these inflammatory cells cause nonspecific tissue injury: mucosal destruction, loss of mucosal barrier, and absorption. Therapy is the downregulation of the immune system [2, 3].

Crohn's Disease It is a chronic, relapsing, idiopathic inflammatory gastrointestinal disease, with involvement of the upper and lower gastrointestinal tract in a discontinuous and transmural manner. Segmental, patchy involvement is most often seen in the ileum, sometimes in the colon and in the upper GI tract (5–30%, 50% in children and adolescents). Histologically it is charac-

terized by chronic active enterocolitis with aphthous ulcers associated with transmural lymphoid aggregates; in a progressive disease, these ulcers coalesce into long, serpentine linear ulcers and occur in the along axis of the bowel, and also fissuring ulcers occur. Noncaseating granulomas are characteristic but not seen in all cases and neither sensitive nor specific (Fig. 4.8). The main differential diagnosis is with ulcerative colitis, indeterminate colitis, and infectious colitis.

Segmental involvement of the bowel and creeping fat (mesenteric fat wraps around the bowel surface) due to transmural inflammation are other characteristic findings. Thickened and fibrotic bowel walls with stricture formation, mucosal aphthous ulcers surrounded by hyperemia with eventual formation of a cobblestone appearing mucosa, inflammatory pseudopolyps, fissures, sinus and fistulous tracts, and abscesses are seen in the setting of complicated disease (Fig. 4.8) [2, 3, 13–15].

C reactive protein is a nonspecific marker for acute inflammation and correlates with disease activity; anti-*Saccharomyces cerevisiae* antibody is positive in 60–70% of patients with Crohn's disease, 10–15% of patients with ulcerative colitis, and <5% of patients without inflammatory bowel disease. Perinuclear anti-neutrophil cytoplasmic antibody is positive in 10–15% of patients with Crohn's disease and positive in 60–70% of patients with ulcerative colitis [15].

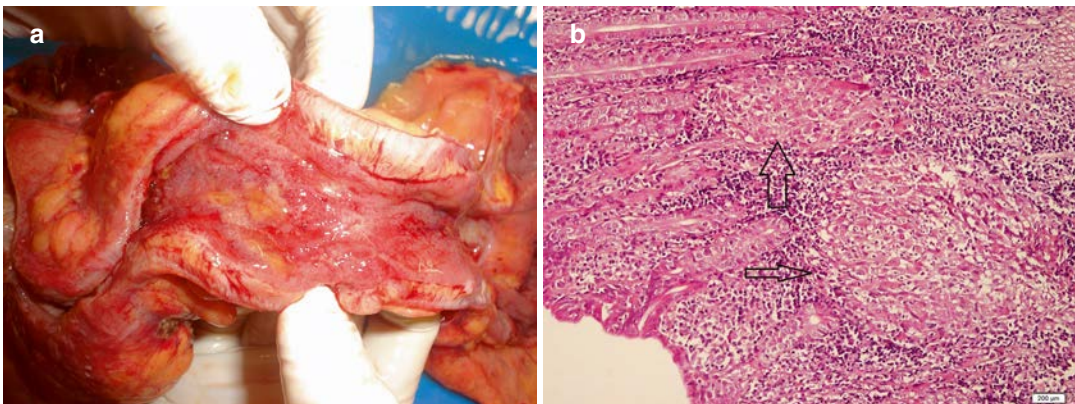


Fig. 4.8 Gross appearance (a): segmental ulceration and fibrosis. Microscopic appearance (b): noncaseous granulomas of Crohn's disease

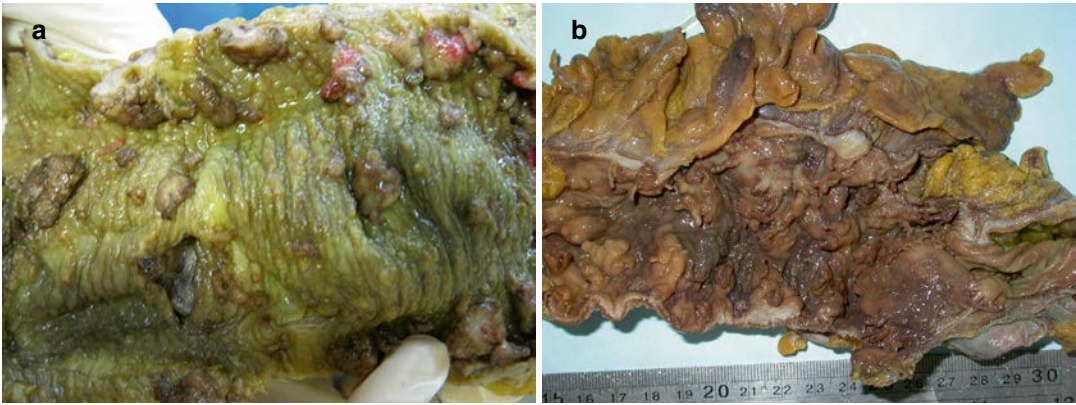


Fig. 4.9 Gross appearance of ulcers and pseudopolyps (a) and filiform polyps (b) of ulcerative colitis

Ulcerative Colitis It is the other chronic disorder of IBD that involves the colon mucosa, generally starts in the rectum, and extends proximally in a continuous pattern. The disease begins in the rectum and continues proximally in a continuous pattern to include up to the entire colon (pancolitis). Patch of inflammation in the cecum, often involving the periappendiceal mucosa (cecal patch), can be present. Approximately 20% of patients will have inflammation in the terminal ileum (backwash ileitis). Histologically characterized by active chronic colitis, with inflammation and superficial ulceration limited to the mucosa/submucosa, absence of granulomas and fissuring ulcers, strictures, fistulas, and creeping fat. Pseudopolyp formation is characteristic due to ulceration with intervening areas of the preserved mucosa. Filiform polyposis is an exaggerated form of pseudopolyp formation and shows elongated, finger-like mucosal projection (Fig. 4.9). Toxic megacolon may occur as a complication and shows marked dilation and thinning of the colonic wall.

UC is caused by a complex multifactorial process involving an overwhelming T helper type 2-like immune response, leading to mucosal injury in response to gut microbial dysbiosis in genetically predisposed patients. The risk of colorectal carcinoma, compared with the general population, is increased with duration of disease and severity of inflammation. Extraintestinal manifestations in the locomotor system, skin, and

liver (primary sclerosing cholangitis) can be seen [15–17].

Inflammatory Bowel Disease (Indeterminate Type) It is a provisional term used to describe cases of IBD in which a definitive diagnosis of ulcerative colitis or Crohn's disease cannot be established on the basis of histopathological and clinical (including radiologic and endoscopic) data. It comprises 5–15% of IBD cases, but most will eventually be declared as one of the two subtypes (only up to 15% thought to be Crohn's disease) [15–17].

4.5 Vascular Disorders

Ischemic Bowel Disease It is caused by decreased blood flow to the intestines, restricted to the small or large bowel, or both, depending on the vessel/vessels involved. Acute occlusion of one of three major supply trunks: celiac, superior, and inferior mesenteric arteries cause infarction of extensive segments. Insidious loss of one vessel may be without any effect or produce small focal ischemic lesions, owing to rich anastomotic interconnections and lesions of end arteries. Transient, reversible vascular obstruction often leads to mild superficial changes, whereas sudden, complete obstruction results in complete infarction of the affected segment. Infarct is briefly the necrosis of the bowel due to loss of

blood supply. The severity of injury varies by the duration and extent of ischemia, and the result is either transmural, mural, and mucosal infarction. Gross lesions are ulcers, pseudopolyps, frank blood or dark mucus in the lumen, segmental thinning in areas of full-thickness infarction or gangrene, tan-brown dusky areas of the bowel mucosa, and pseudomembranous appearance in exudative cases (Fig. 4.10). In severe cases, perforation and, in late cases, fibrosis and stricture formation can be seen. Rarely, ischemic colitis can produce mass-forming lesions. Histologically, early transient ischemia may result in mild changes, such as mucosal edema, denudation, hemorrhage, and congestion. With more advanced ischemia, superficial mucosal necrosis ensues. A reduced number and size of crypts and fibrosis in the lamina propria suggests a more severe injury. Necrosis, ulceration, and granulation tissue extend into the submucosa and surrounding smooth muscle fibers of muscularis mucosae in more severe cases. Acute cases may exhibit acute inflammatory exudate (pseudomembranes) on the mucosa, even when noninfectious. Atypical reactive or degenerative changes may be seen, mimicking dysplasia or malignancy. In patients with chronic ischemia, histologic findings may represent a mixture of ischemic features described above, with foci of chronic mucosal injury, such as crypt architectural distortion, Paneth cell metaplasia, basal lymphoplasmacyto-

sis, and active inflammation, mimicking inflammatory bowel disease. Vessels may show necrotizing phlebitis, hyaline thrombi or capillary microthrombi, cholesterol crystals (athero-embolism), or myointimal hyperplasia [2, 18].

Hemorrhoids Variceal dilations of anal and perianal submucosal venous plexuses are rarely due to constipation and prolonged straining; pregnancy; dietary factors including low-fiber diet, spicy foods, and alcohol intake; and portal hypertension, usually due to cirrhosis of the liver. They may be *internal* (above the anorectal line, covered by rectal mucosa) or *external hemorrhoids* (below the anorectal line, covered by anal mucosa). They are thin-walled, dilated vessels that commonly bleed and may become thrombosed, particularly due to trauma from passage of stool, and the thrombi may be recanalized. Other complications are ulceration, fissure formation, and infarction with strangulation [2].

Diverticular Disease (Diverticulosis) Diverticula are anatomic changes in the colon characterized by small, flask-like/spherical outpouchings of the mucosa and submucosa through the muscularis propria. They are 0.5–1 cm in diameter, from a few to several hundreds in number. The sigmoid colon and left colon are most common sites (90%). The mucosa is normal to markedly abnormal. Most colonic diverticula are false diverticula; only the mucosa and the submucosa herniate through the defect or weakness in the muscularis layer, and it is covered by serosa. True diverticula are uncommon and involves the outpouching of all layers of the intestinal wall (e.g., Meckel diverticulum). They occurs in weaker portions of the colonic wall where vasa recta infiltrate the circular muscle layer. A greater amount of injury exposition may cause diverticulitis and can lead to bleeding [18].

Volvulus It is a complete twisting of a bowel loop around its mesenteric base of attachment, and it causes obstruction and infarction. Clinical torsion of the colon leads to colonic necrosis as seen in ischemia. It usually involves the cecum or sigmoid [18].



Fig. 4.10 Ischemic bowel disease: full-thickness infarction or gangrene, tan-brown dusky areas of the bowel mucosa

Intussusception It is telescoping of a proximal segment of the bowel immediately into the distal segment. In children, it sometimes occurs without apparent anatomic basis, and sometimes the cause may be rotavirus infection. In adults, often an intraluminal mass (e.g., tumor) is trapped by a peristaltic wave and pulls its point of attachment along with it into the distal segment. This pulling then causes intestinal obstruction and infarction of the trapped segment [2].

4.6 Appendix Disorders

Acute Appendicitis Acute inflammation of the vermiform appendix is not attributable to distinct inflammatory disorders, such as idiopathic inflammatory bowel disease. Chronic appendicitis is not seen; if seen, it may represent recurrent acute appendicitis. Pathogenesis includes obstruction of appendiceal orifice and subsequent bacterial infection. Obstruction of appendiceal orifice leads to an increase in intraluminal and intramural pressure, resulting in small vessel occlusion and lymphatic stasis. The wall of the appendix becomes ischemic and necrotic. Bacterial infection then occurs in the obstructed appendix. Aerobic organisms are predominant in early appendicitis, and mixed aerobes and anaerobes later in the course. If left untreated, acute appendicitis can progress to mural necrosis and perforation, local abscess formation, and peritonitis. Gross and microscopic extent of inflammation may not correlate. Inflammation may involve the entire appendix or only a segment. The appendix may appear grossly normal when inflammation is limited to the mucosa and submucosa or appears swollen and erythematous when inflammation extends into the muscularis propria. When the serosa is affected, a purulent exudate appears. The appendiceal wall may be completely necrotic in gangrenous appendicitis, and perforation occurs in severe cases. Microscopic findings include variable acute inflammation with predominance of neutrophils, involving some or all layers of the appendiceal wall [19].

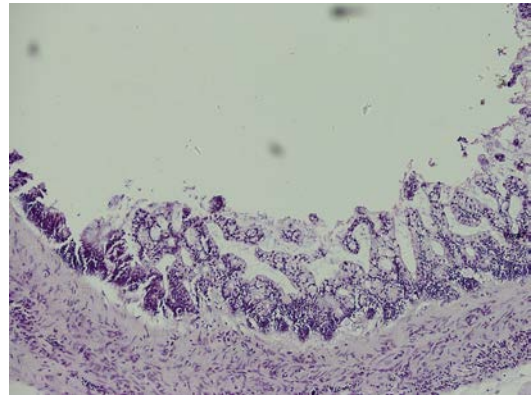


Fig. 4.11 LAMN: noninvasive epithelial proliferation in the absence of infiltrative growth

Appendix Tumors Adenocarcinoma (malignant gland-forming neoplasm) may be a mucinous or nonmucinous type. Low-grade appendiceal mucinous neoplasm (LAMN) is a low-grade noninvasive epithelial proliferation in the absence of infiltrative growth (Fig. 4.11). Similarly, rare lesions with high-grade nuclear dysplasia are termed high-grade appendiceal mucinous neoplasm. Both of them can cause [pseudomyxoma peritonei](#) if the appendix ruptures and disseminated disease may present with abdominal or ovarian masses. Prognosis depends on the tumor subtype, grade and stage [20, 21].

Pseudomyxoma peritonei is strictly a clinical term for apparent mucinous ascites or peritoneal mucin deposition.

Mucocele is strictly a clinical term for dilated, mucin-filled appendix [2, 3].

Neuroendocrine tumors (NETs) and mixed adenocarcinoma and endocrine cell tumors as goblet cell carcinoma are seen rarely in appendix [20].

4.7 Small and Large Bowel Tumors and Tumor Like Lesions

The small bowel represents 75% length of GIT, but its tumors make only 3–6% of GI tumors and have a slight preponderance of benign ones [2].

Polyps A polyp is an exophytic or sessile lesion distinct from the mucosal surface and may be neoplastic or non-neoplastic. All polyps may be stalked or pedunculated (due to traction) or sessile (without stalk). Non-neoplastic polyps may be the result of abnormal mucosal maturation, inflammation, or architecture, having no or minimal malignant potential. True neoplastic ones are because of epithelial proliferation and dysplasia, and they are called adenomatous polyps or adenomas (“new growth”) and are precursors of carcinoma.

Hyperplastic Polyps They are the common lesions and the most common type of serrated colorectal polyp (80%) [20]. They are detected most often in adulthood (more than 60 years old) and males. They have little or no associated risk of colorectal cancer development. This type of polyps can occur throughout the large bowels but is most common in the sigmoid colon and rectum, usually multiple in the rectum. They may occur as part of a spectrum of serrated polyposis syndrome that also includes sessile serrated lesions [22]. They share lifestyle risk factors with colorectal adenoma and colorectal cancer; for example, low dietary fiber content, increased body mass index, and increased alcohol consumption and cigarette smoking are all associated with an increased risk of hyperplastic polyp development. Most are small (<5 mm), nipple-like, hemispheric, smooth protrusions of the mucosa and may be single but more often multiple. In microscopic examination, serrated architecture with a sawtooth appearance, with these

serrations generally limited to the upper half of the crypts, is characteristic (Fig. 4.12).

Juvenile polyps (usually sporadic in the rectosigmoid colon of children and rarely part of juvenile polyposis syndrome) and hamartomatous polyps, as part of rare autosomal dominant Peutz-Jeghers or other less common syndromes, are accepted as non-neoplastic polyps; however in syndromic cases, there is an increased risk of both intestinal and also extraintestinal malignancies [2, 20].

Adenomas They are benign, premalignant neoplasms composed of dysplastic colorectal epithelium. Most (perhaps all) invasive colorectal adenocarcinomas arise in pre-existing adenomatous lesions. There is a “adenoma-carcinoma sequence” in which genetic changes occur before morphologically identifiable tumor formation, including a small set of driver genes (Adenomatous Polyposis Coli: APC, Catenin Beta 1: CTNNB1, Kirsten Rat Sarcoma Viral Oncogene Homolog: KRAS, SMAD4, and TP53) (Fig. 4.13). However, most adenomas do not progress through the adenoma carcinoma sequence. The progression risk is associated with a higher number of lesions, larger size, higher proportion of villous architecture, and extent of high-grade dysplasia. There are subtypes on the basis of epithelial architecture: *Tubular adenomas* are composed of mostly tubular glands, and it is the most common histologic type, usually small and pedunculated. There is at least low-grade dysplasia in the tubular glands. *Villous adenomas* have >75% villous projections and make 1% of all adenomas. Tubulovillous adenoma is a mixture of the above, with 25–75% of villous component, usually large and sessile; it makes 5–10% of adenomas. In villous component, the architecture resembles small intestinal villi (Fig. 4.14). In histologic grading, a two-tiered system, low grade versus high grade, is used. Architecture has a marked complex glandular crowding with glandular irregularity in high grade. For progression through the adenoma carcinoma sequence, the risk is associated with a higher number of lesions, larger size, higher proportion of villous architecture, and extent of high-grade dysplasia.

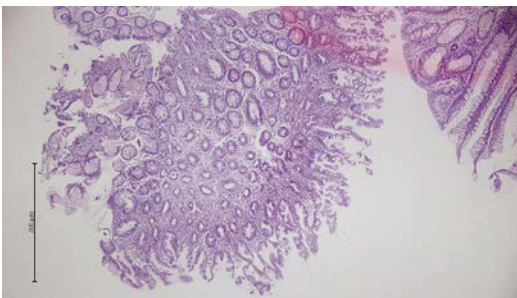


Fig. 4.12 Microscopic examination of hyperplastic polyp: Serrated architecture with a sawtooth appearance, with serrations generally limited to the upper half of the crypts, is the characteristic

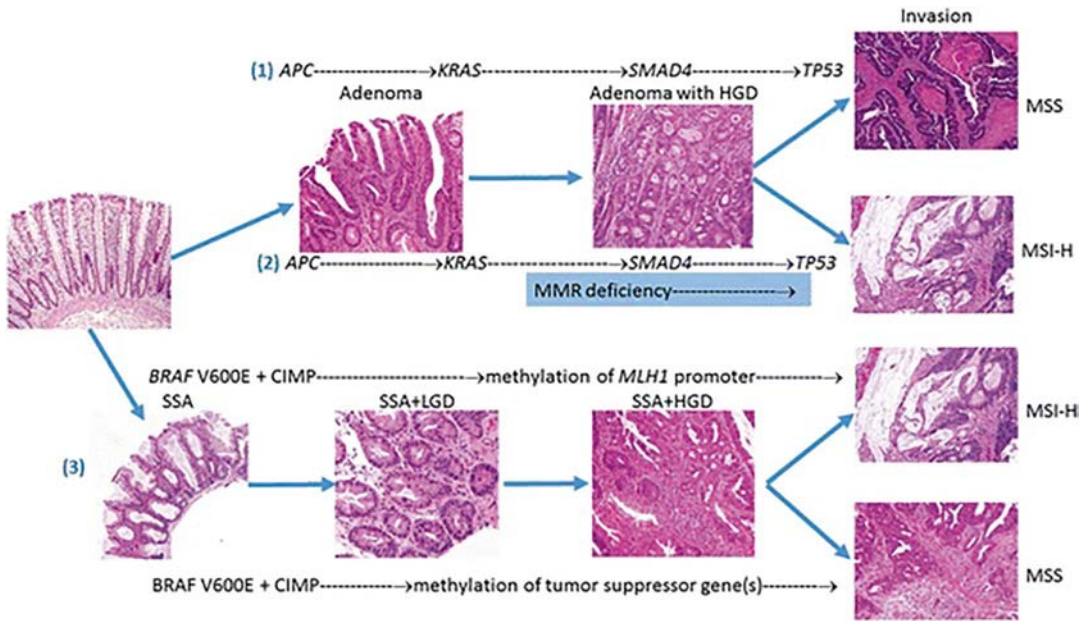


Fig. 4.13 Scheme of adenoma-carcinoma sequence

Familial Polyposis Syndromes The most frequent one, familial adenomatous polyposis (FAP) syndrome which is an uncommon autosomal dominant disorders, due to a germline mutation in the *APC* gene (5q21), shows malignant transformation and has provided a molecular basis of colorectal cancer. There are 500–2500 colonic adenomas on the mucosal surface; minimum number is 100. Essentially 100% of patients develop colonic adenocarcinoma, by midlife, unless a prophylactic colectomy is performed (Fig. 4.15). Lynch syndrome and variants (*MLH1*, *MSH2*, *MSH6*, and *PMS2* genes) are less common [2, 20].

Colon Carcinoma It is the second or third most common cancer and cause of cancer deaths in men and in women and is the most common gastrointestinal tumor. Major risk factors are older age, obesity, physical inactivity, alcohol consumption, inflammatory bowel disease, schistosomiasis, and family history of colorectal neoplasia. Polyposis syndromes including FAP and variants; juvenile polyposis; Peutz-Jeghers syndrome; dietary risk factors like low vegetable fiber (prolongs transit time leaving toxic oxida-

tive byproducts in longer contact with colonic mucosa); high refined carbohydrates; increased beef consumption (enhances synthesis of bile acids by the liver, which may be converted into carcinogens by bile acids and alters bacterial flora); and decreased vitamins A/C/E are all predisposing factors.

Poor prognostic factors of colon carcinoma are high-stage, positive margins (particularly radial margin in rectal carcinoma), poor differentiation, signet ring cells in histologic appearance, flat or ulcerative gross configuration, tumor budding, tumor perforation, free tumor cells in peritoneal space, lymphovascular invasion, and perineurial invasion [20]

Adenocarcinoma It is the glandular neoplasm of the bowels as other sites in the body, representing 98% of colonic cancers, 30–40% of small intestinal cancers (large majority seen in the duodenum, including ampulla of Vater). Most (perhaps all) invasive colorectal adenocarcinomas arise in pre-existing adenomatous lesions. There is an increased carcinoma risk in patients with polyposis syndromes, Lynch syndrome, and

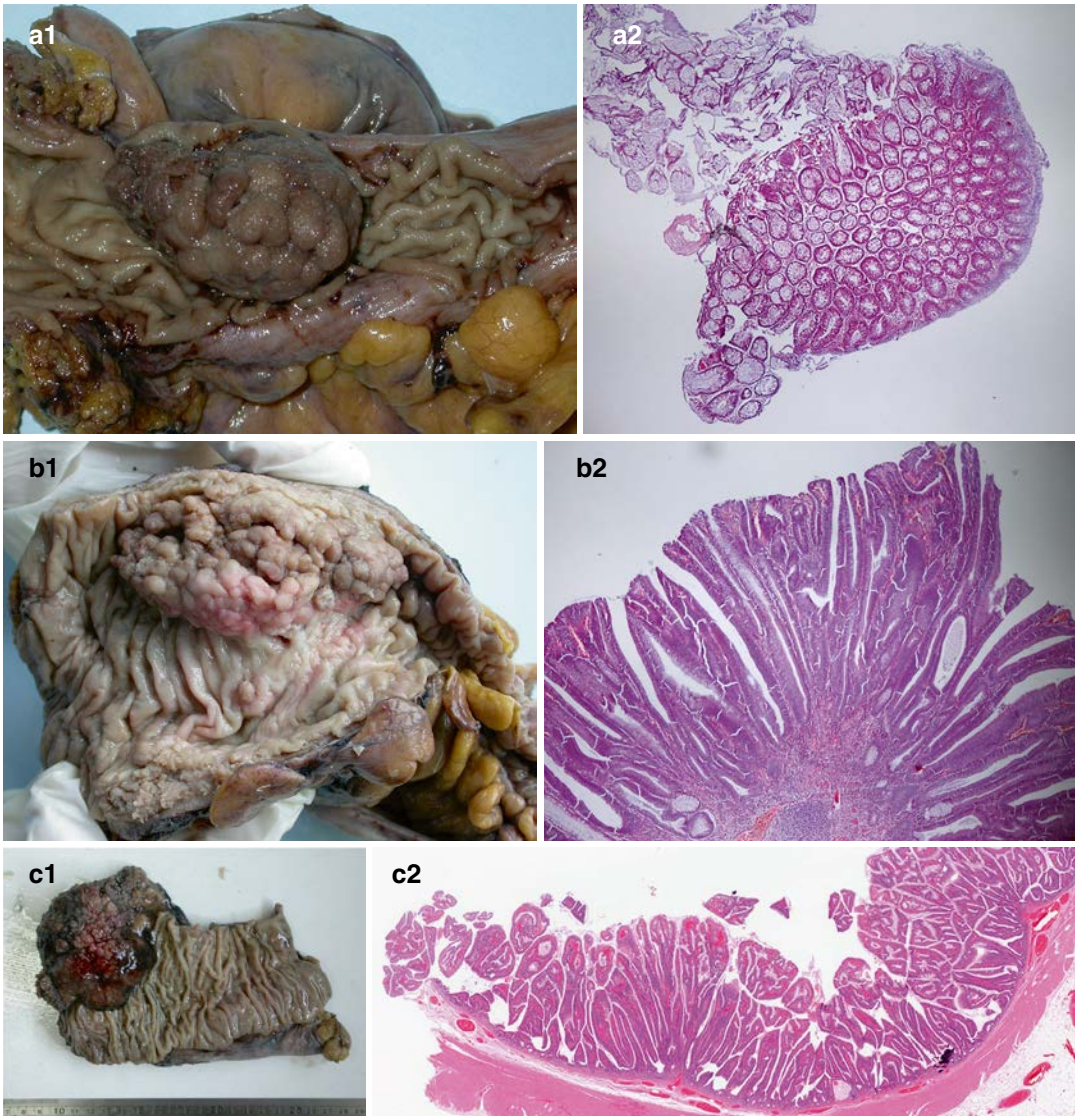


Fig. 4.14 Tubular (a), tubulovillous (b), and villous adenomas (c): gross [1] and microscopic [2] appearance

inflammatory bowel disease. Superficial tumors only rarely cause lymph node metastases due to distribution of lymphatics in the colon. Usually single, right colon tumors tend to be polypoid and exophytic, while left colon tumors tend to be annular, encircling lesions (Fig. 4.16).

Other histologic types like signet ring cell carcinomas and mucinous carcinomas are rare [20].

Neuroendocrine Tumors More than 95% of duodenal NETs are located in part 1 or 2 (those in part 2 are predominantly in the ampullary region), and majority of jejunoileal NETs are located in the distal ileum, with only 11% of the jejunal origin. Colorectal neuroendocrine tumors have been continuously increasing over the past few decades and comprise roughly 30% in the digestive system. In the large intestine (excluding the appen-

dix), the most frequent location is the rectum (34% of all GIT NETs). Intestinal NETs arise from Kulchitsky cells or enterochromaffin cells located within the crypts of Lieberkuhn in the mucosa. NETs are graded as World Health



Fig. 4.15 Familial adenomatous polyposis and carcinoma development at the left side, gross appearance

Organization (WHO) grade 1, 2, and rare 3 lesions depending on the proliferative rate (mitoses and Ki67 proliferation index). Well-differentiated tumors are previously termed as carcinoid tumor. WHO grade is an independent predictive factor of lymph node metastasis, and the number of positive locoregional lymph nodes is an independent prognostic factor of survival.

Majority of NETs are nonfunctioning; functional (hormone secreting) neuroendocrine tumors are rare: gastrin-expressing NETs are seen in the duodenum, and somatostatin-expressing NETs in the ampulla. Functioning NETs can cause symptoms related to hormone secretion. For example, gastrinomas cause Zollinger-Ellison syndrome (hypergastrinemia, gastric hypersecretion, refractory peptic ulcer disease, diarrhea), and patients with Zollinger-Ellison syndrome have worse prognosis and higher rate of metastasis. Somatostatinomas

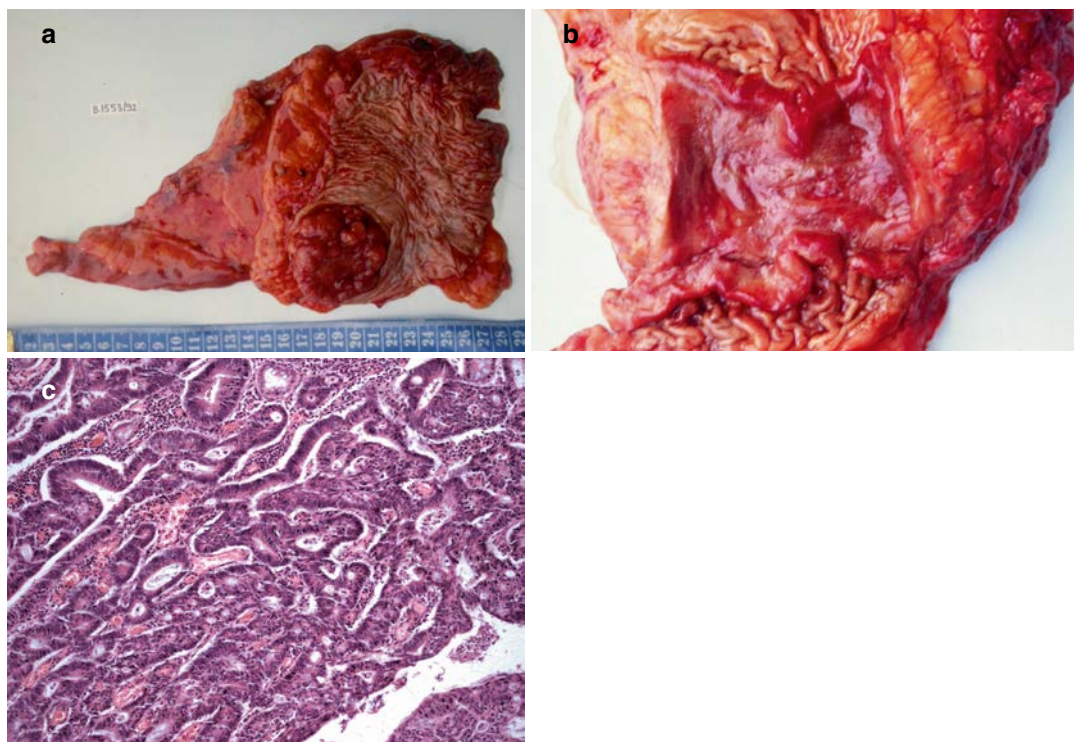


Fig. 4.16 Gross types of colon adenocarcinoma: fungative (a), ulcerous (b), and microscopic features (c)

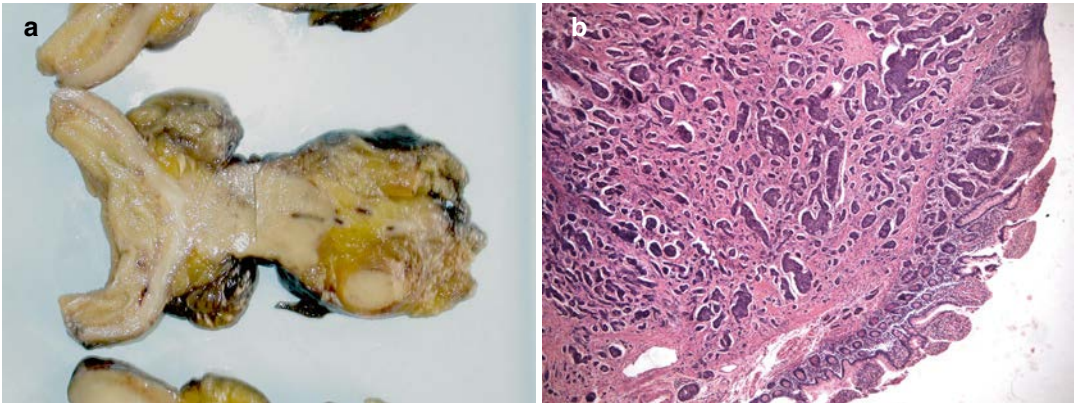


Fig. 4.17 Gross (a) and microscopic appearance (b) of neuroendocrine tumors

rarely cause somatostatinoma syndrome (diabetes mellitus, diarrhea, steatorrhea, hypochlorhydria or achlorhydria, anemia, gallstones). Carcinoid syndrome (diarrhea, bronchospasms, flushing, tricuspid valve fibrosis) occurs in <10% of cases and only if liver metastasis is present. Small intestine NETs often present with metastatic disease (locoregional lymph nodes and liver most common), and most have prolonged survival due to low proliferative rate. Long-term recurrence rates are ~50%. Rectal neuroendocrine tumors are commonly small and generally low-to-intermediate grade (G1 or G2), whereas colonic tumors are often aggressive, poorly differentiated, and higher grade (G3). They may be indolent and incidental or present with widespread metastases and have aggressive clinical courses. Colorectal tumors <10 mm have a low rate (1.95%) of lymph node metastasis.

Most low-grade neuroendocrine tumors appear as yellow or pale, polypoid or flat, doughnut-shaped lesions or submucosal nodules. In well-differentiated neuroendocrine pattern, there are monotonous regular cells with round or oval nuclei, salt and pepper chromatin, and moderate eosinophilic granular cytoplasm and organoid architecture: tumor cells arranged in nests and trabecular or insular pattern (Fig. 4.17). Poorly differentiated neuroendocrine malignancy includes large cell and small cell neuroendocrine carcinoma. It is rare and aggressive (distant metastases common, with poor survival rate).

Histology is similar to neuroendocrine carcinomas elsewhere. It usually occurs in the cecum or right colon but can arise anywhere. Small cell type resembles pulmonary small cell carcinoma, with aggressive behavior [20, 21, 23, 24].

MiNEN (Mixed Neuroendocrine-Exocrine Neoplasm) According to the 2017 WHO classification, the term MiNEN comprises mixed neuroendocrine and non-neuroendocrine proliferations. The non-neuroendocrine component may be adenocarcinoma, squamous cell carcinoma, or others. Each component must be ≥30% to fall into the category of MiNEN [20].

4.8 Mesenchymal Tumors

Gastrointestinal Stromal Tumor (GIST) These are tumors that differentiate along lines of interstitial cells of Cajal in the muscularis layer; they are called the gut's pacemaker cells. The small bowel is the second most common site after the stomach. The mesenchymal spindle cell GISTs of the colon are caused by *KIT* or *PDGFR*A mutations. However, *NF1* and *BRAF*-mutated GISTs are more common in the small bowel versus other sites. Prognosis depends on size, mitotic rate, and location. Small bowel GISTs are more likely to be malignant (35–40%) compared with gastric GISTs (25%). GISTs are very rare in the colon; rectal GISTs account for

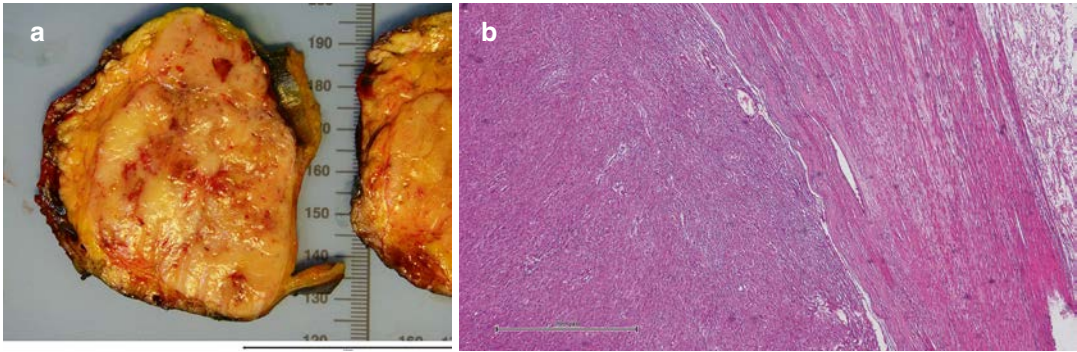


Fig. 4.18 Gastrointestinal stroma tumor of the small bowel, gross appearance



Fig. 4.19 Multiple liposarcoma occurring in the small bowel, gross appearance

roughly 5% of all GISTs. The risk of disease progression for rectal GISTs depends on tumor size and mitotic rate. Often they are large, bulky, intramural masses, with fish flesh or tannish brown parenchyma, some with hemorrhage, necrosis, and cystic softening and usually centered in the muscularis propria (Fig. 4.18). Spindle cell GISTs are composed of intersecting fascicles of plump spindle cells with eosinophilic cytoplasm within variably hyalinized or edematous stroma. Epithelioid GISTs are less common and have rounded epithelioid cells with pseudocompartmental organization [25].

Other mesenchymal tumors in the colon are extremely rare (Fig. 4.19) [20].

4.9 Lymphomas

Immunoproliferative Small Intestinal Disease (ISID) It is also called Mediterranean lymphoma or Middle Eastern lymphoma, because it is more common among non-European Jews, Middle Eastern Arabs, and South African blacks. This type is a B-cell lymphoma that arises in the background of chronic diffuse mucosal plasmacytosis, with immunoglobulin A heavy-chain synthesis (no variable chain synthesized). Many patients have pre-existing malabsorption and may initially respond to antibiotics, e.g., often due to *Campylobacter jejuni*, another human pathogen responsible for immunoproliferative states. Grossly, in low-grade lymphomas, there is a nonflattened mucosa, whereas in high-grade lymphomas, diffusely thickened folds with small nodules in the distal duodenum and proximal jejunum. Microscopic (histologic) description includes in low-grade, heavy lymphoplasmacytic infiltrate by mature cells. In high-grade cases, it resembles diffuse large cell lymphoma with plasmacytoid features and may have a starry sky pattern and follicular hyperplasia.

MALT Lymphomas They are extranodal, low-grade B-cell lymphoma that is composed of a heterogeneous population of centrocyte-like, monocytoid, scattered immunoblasts and centroblast-like cells. It may occur in any extranodal site with lymphoid follicles and is under the umbrella of marginal zone lymphoma showing same features like in the stomach.

Burkitt Lymphoma It is a highly aggressive non-Hodgkin B-cell lymphoma, associated with Epstein-Barr virus (EBV), especially in endemic subtype and characteristic t(8;14) between *c-MYC* (8q24) and *IGH* (14q32) genes. Sporadic subtype (Western countries) affects children and young adults, involving the right colon.

High-Grade Large B-Cell Lymphomas They may occur in the colon in some cases as a complication of ulcerative colitis [2, 26].

References

- Ludwig K, De Bartolo D, Salerno A, Ingravallo G, Cazzato G, Giacometti C, Dall'Igna P. Congenital anomalies of the tubular gastrointestinal tract. *Pathologica*. 2022;114(1):40–54. <https://doi.org/10.32074/1591-951X-553>. PMID: 35212315; PMCID: PMC9040549
- Turner JR, Lingen MW. Oral cavity and gastrointestinal tract. In: Kumar V, Abbas AK, Aster JK, editors. *Robbins basic pathology*. 11th ed. Elsevier; 2023. p. 551–602.
- Odze RD, Goldblum JR. *Surgical pathology of the GI tract, liver, biliary tract and pancreas*. 4th ed. Elsevier; 2022. p. 3–732.
- Villanacci V, Reggiani-Bonetti L, Leoncini G, Parente P, Cadei M, Albarello L, Mandelli G, Caputo A. Histopathology of non-IBD colitis. A practical approach from the Italian Group for the study of the gastrointestinal tract (GIPAD). *Pathologica*. 2021;113(1):54–65. <https://doi.org/10.32074/1591-951X-234>. PMID: 33686310; PMCID: PMC8138693
- Westerhoff M. Histologic features of colonic infections. *Pathologie*. 2022;43(1):16–30. <https://doi.org/10.1007/s00292-021-01015-7>. Epub 2021 Nov 12. PMID: 34767063; PMCID: PMC8588779
- Rossi C, Simoncelli G, Arpa G, Stracuzzi A, Parente P, Fassan M, Vanoli A, Villanacci V. Histopathology of intestinal villi in neonatal and paediatric age: main features with clinical correlation – Part I. *Pathologica*. 2022;114(1):12–21. <https://doi.org/10.32074/1591-951X-337>. Epub 2021 Dec 2. PMID: 34856604; PMCID: PMC9040547
- Grillo F, Campora M, Carlin L, Cornara L, Parente P, Vanoli A, Remo A, Migliora P, Roberto F, Fassan M, Mastracci L. “Stranger things” in the gut: uncommon items in gastrointestinal specimens. *Virchows Arch*. 2022;480(2):231–45. <https://doi.org/10.1007/s00428-021-03188-1>. Epub 2021 Oct 1. PMID: 34599376; PMCID: PMC8986674
- Hujoel IA, Johnson DH, Lebowitz B, Leffler D, Kupfer S, Wu TT, Murray JA, Rubio-Tapia A. Tropheryma whipplei infection (Whipple disease) in the USA. *Dig Dis Sci*. 2019;64(1):213–23. <https://doi.org/10.1007/s10620-018-5033-4>. Epub 2018 Mar 23. PMID: 29572616
- Ensari A, Marsh MN. Diagnosing celiac disease: a critical overview. *Turk J Gastroenterol*. 2019;30(5):389–97. <https://doi.org/10.5152/tjg.2018.18635>. PMID: 31060993; PMCID: PMC6505646
- Ensari A, Kelsen J, Russo P. Newcomers in paediatric GI pathology: childhood enteropathies including very early onset monogenic IBD. *Virchows Arch*. 2018;472(1):111–23. <https://doi.org/10.1007/s00428-017-2197-9>. Epub 2017 Jul 17. PMID: 28718031; PMCID: PMC6171108
- Takahashi M, Okazaki H, Ohashi K, Ogura M, Ishibashi S, Okazaki S, Hirayama S, Hori M, Matsuki K, Yokoyama S, Harada-Shiba M. Current diagnosis and management of Abetalipoproteinemia. *J Atheroscler Thromb*. 2021;28(10):1009–19. <https://doi.org/10.5551/jat.RV17056>. Epub 2021 May 16. PMID: 33994405; PMCID: PMC8560840
- Guissoama J, Ben Ali H, Allouche H, Trabelsi I, Hammami O, Yahia Y, Mchirgui I, Mabrouk M, Ghadhoune H. Case report: tropical sprue, diagnostic challenges of an old but unrecognized disease. *F1000Res*. 2024;11:1206. <https://doi.org/10.12688/f1000research.125305.1>. PMID: 39211424; PMCID: PMC11359971
- Gupta A, Yu A, Peyrin-Biroulet L, Ananthakrishnan AN. Treat to target: the role of histologic healing in inflammatory bowel diseases: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2021;19(9):1800–1813.e4. <https://doi.org/10.1016/j.cgh.2020.09.046>. Epub 2020 Sep 30. PMID: 33010406
- Gros B, Kaplan GG. Ulcerative colitis in adults: a review. *JAMA*. 2023;330(10):951–65. <https://doi.org/10.1001/jama.2023.15389>. PMID: 37698559
- Magro F, Langner C, Driessen A, Ensari A, Geboes K, Mantzaris GJ, Villanacci V, Becheanu G, Borralho Nunes P, Cathomas G, Fries W, Jouret-Mourin A, Mescoli C, de Petris G, Rubio CA, Shepherd NA, Vieth M, Eliakim R, European Society of Pathology (ESP); European Crohn's and Colitis Organisation (ECCO). European consensus on the histopathology of inflammatory bowel disease. *J Crohns Colitis*. 2013;7(10):827–51. <https://doi.org/10.1016/j.crohns.2013.06.001>. Epub 2013 Jul 17. PMID: 23870728
- Goldblum JR, Lamps LW, McKenney JK, Myers JL. *Rosai and Ackerman's surgical pathology*. 11th ed. Elsevier; 2018. p. 566–702.
- Greenon JK. Diagnostic pathology. *Gastrointestinal*. 2016:204–519.
- Wong NA. My approach to bowel ischaemia. *J Clin Pathol*. 2023;76(5):293–300. <https://doi.org/10.1136/jcp-2023-208764>. Epub 2023 Feb 22. PMID: 36813561
- Hoffmann JC, Trimbom CP, Hoffmann M, Schröder R, Förster S, Dirks K, Tannapfel A, Anthuber M,

- Hollerweger A. Classification of acute appendicitis (CAA): treatment directed new classification based on imaging (ultrasound, computed tomography) and pathology. *Int J Colorectal Dis.* 2021;36(11):2347–60. <https://doi.org/10.1007/s00384-021-03940-8>. Epub 2021 Jun 18. PMID: 34143276
20. WHO Classification of Tumours online. Digestive system tumours. 5th ed; 2019.
21. Assarzadegan N, Montgomery E. What is new in the 2019 World Health Organization (WHO) classification of tumors of the digestive system: review of selected updates on neuroendocrine neoplasms, appendiceal tumors, and molecular testing. *Arch Pathol Lab Med.* 2021;145(6):664–77. <https://doi.org/10.5858/arpa.2019-0665-RA>. PMID: 32233993; PMCID: PMC9281538
22. Rex DK, Ahnen DJ, Baron JA, Batts KP, Burke CA, Burt RW, Goldblum JR, Guillem JG, Kahi CJ, Kalady MF, O'Brien MJ, Odze RD, Ogino S, Parry S, Snover DC, Torlakovic EE, Wise PE, Young J, Church J. Serrated lesions of the colorectum: review and recommendations from an expert panel. *Am J Gastroenterol.* 2012;107(9):1315–29. <https://doi.org/10.1038/ajg.2012.161>. quiz 1314, 1330. Epub 2012 Jun 19. PMID: 22710576; PMCID: PMC3629844
23. Cavalcanti MS, Gönen M, Klimstra DS. The ENETS/WHO grading system for neuroendocrine neoplasms of the gastroenteropancreatic system: a review of the current state, limitations and proposals for modifications. *Int J Endocr Oncol.* 2016;3(3):203–19. <https://doi.org/10.2217/ije-2016-0006>. Epub 2016 Jul 14. PMID: 30338051; PMCID: PMC6190579
24. Inzani F, Rindi G. Introduction to neuroendocrine neoplasms of the digestive system: definition and classification. *Pathologica.* 2021;113(1):1–4. <https://doi.org/10.32074/1591-951X-227>. PMID: 33686304; PMCID: PMC8138697
25. Miettinen M, Lasota J. Gastrointestinal stromal tumors. *Gastroenterol Clin North Am.* 2013;42(2):399–415. <https://doi.org/10.1016/j.gtc.2013.01.001>. Epub 2013 Mar 13. PMID: 23639648; PMCID: PMC3644178
26. Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, IBO A, Berti E, Bhagat G, Borges AM, Boyer D, Calaminici M, Chadburn A, JKC C, Cheuk W, Chng WJ, Choi JK, Chuang SS, Coupland SE, Czader M, Dave SS, de Jong D, Du MQ E-JKS, Ferry J, Geyer J, Gratzinger D, Guitart J, Gujral S, Harris M, Harrison CJ, Hartmann S, Hochhaus A, Jansen PM, Karube K, Kempf W, Khoury J, Kimura H, Klapper W, Kovach AE, Kumar S, Lazar AJ, Lazzi S, Leoncini L, Leung N, Leventaki V, Li XQ, Lim MS, Liu WP, Louissaint A Jr, Marcogliese A, Medeiros LJ, Michal M, Miranda RN, Mitteldorf C, Montes-Moreno S, Morice W, Nardi V, Naresh KN, Natkunam Y, Ng SB, Oschlies I, Ott G, Parrens M, Pulitzer M, Rajkumar SV, Rawstron AC, Rech K, Rosenwald A, Said J, Sarkozy C, Sayed S, Saygin C, Schuh A, Sewell W, Siebert R, Sohani AR, Tooze R, Traverse-Glehen A, Vega F, Vergier B, Wechalekar AD, Wood B, Xerri L, Xiao W. The 5th edition of the World Health Organization classification of haematolymphoid tumours: lymphoid neoplasms. *Leukemia.* 2022;36(7):1720–48. <https://doi.org/10.1038/s41375-022-01620-2>. Epub 2022 Jun 22. Erratum in: *Leukemia.* 2023;37(9):1944–1951. doi:10.1038/s41375-023-01962-5. PMID: 35732829; PMCID: PMC9214472

Non-neoplastic Diseases of the Liver and Bile Ducts

5

Gulden Diniz  and Hale Kırımlıoğlu

5.1 Introduction

Non-neoplastic liver and biliary tract diseases encompass a wide range of conditions, including inflammation (hepatitis), fibrosis-scarring (cirrhosis), cholangitis, and non-neoplastic nodules. The non-neoplastic liver diseases occur because of infectious, metabolic, vascular, autoimmune, toxic, and congenital disorders. Unlike neoplastic diseases, these entities do not involve abnormal proliferation of malignant cells but can lead to significant morbidity and mortality due to liver dysfunction and portal hypertension. These disorders can affect hepatocytes, bile ducts, vasculature, and interstitial tissue of the liver [1].

5.2 Non-neoplastic Liver Diseases

Non-neoplastic liver diseases can be roughly categorized into five groups as infectious, autoimmune, metabolic, vascular, and toxic/drug-induced diseases based on their etiology.

Hepatitis refers to inflammation of the liver, often caused not only by a viral infection but also by other factors like alcohol abuse, autoimmune conditions, or certain medications. Hepatitis caused by various agents has very similar morphologies. Therefore, a definitive etiological diagnosis of hepatitis cannot be made based solely on morphological findings. The definition of acute and chronic hepatitis in the presence of liver inflammation is also confusing. In other tissues and organs, acute inflammation generally describes a process in which neutrophils and macrophages predominate, while lymphocytes play a leading role in chronic inflammation. However, in hepatitis, lymphocytes always play a leading role in both acute and chronic processes. The affected areas of the liver differ in hepatitis. While all hepatitis is diffused, the damage in acute hepatitis is described as panlobular (Fig. 5.1). However chronic hepa-

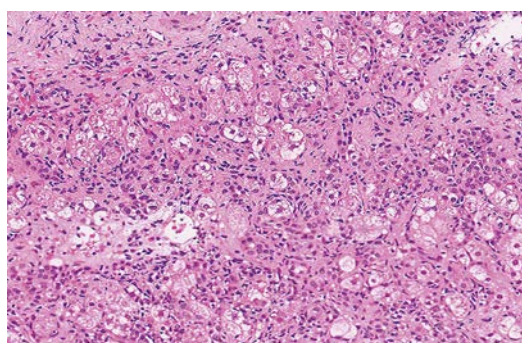


Fig. 5.1 Acute (panlobular) hepatitis

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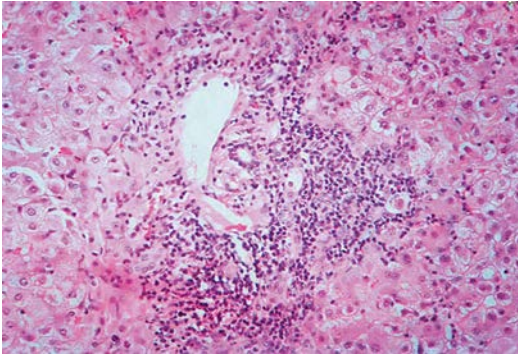


Fig. 5.2 Chronic (interface) hepatitis

titis is described as interface hepatitis. The primary affected areas are the portal/periportal areas (Fig. 5.2).

5.2.1 Infectious Liver Diseases: Infectious Hepatitis

When the term “hepatitis” is used clinically, it most often refers to viral hepatitis caused by hepatotropic viruses. However, hepatitis symptoms can occur under almost any condition where infectious agents enter the bloodstream. These can include bacterial infections, as well as infections with Epstein-Barr virus (EBV), rubella virus, adenovirus, and cytomegalovirus (CMV). However, the term viral hepatitis is almost always used for infections caused by hepatotropic viruses.

The hepatotropic viruses that most commonly cause hepatitis are A, B, C, D, and E. Viral hepatitis can cause symptomatic/asymptomatic acute hepatitis, chronic hepatitis, fulminant hepatitis, and carrier state. Viral hepatitis can lead to the development of cirrhosis and hepatocellular carcinoma (HCC). Hepatitis B virus (HBV) and hepatitis C virus (HCV) are indirectly associated with carcinogenesis due to their capacity to induce chronic inflammation in infected organs [2]. Viral hepatitis and their liver biopsy findings are described in detail in Volume 3, Chapter 14 [2–5].

5.2.2 Autoimmune Hepatitis

Autoimmune hepatitis (AIH) is a chronic immunologic disorder in which the immune system

targets the liver. The epidemiologic heterogeneity seen in serologic tests and clinical presentation across various populations can be explained by the disease’s genetic foundation. The incidence of AIH increases with age into the 70s and seems to be increasing in prevalence. Most patients test positive for some special serological indicators, but nearly in 20% of patients, serological markers are negative. Symptomatic patients may clinically present with acute liver failure, chronic hepatitis, or decompensated cirrhosis. In addition, some patients may be asymptomatic with elevated transaminases. Autoimmune hepatitis presents a histopathological picture virtually indistinguishable from chronic viral hepatitis, except for inflammatory cell infiltration including predominantly plasma cells (Fig. 5.3).

The findings may be like hepatitis C virus. Especially in type 2, high levels of anti-HCV antibodies are found in patient sera. Although HCV primarily occurs as a viral infection affecting the liver, previous studies have demonstrated an astonishing link between HCV and the development of AIH. The immune system’s response to HCV appears to predispose to an aberrant autoimmune response that leads to the onset of autoimmune hepatitis. Studies have also shown a higher prevalence of autoimmune markers in individuals with chronic HCV infection, suggesting a potential relationship between viral and autoimmune liver diseases. Given the complexities of viral replication, immune response dynamics, and genetic predisposition, HCV and AIH can be considered overlapping pathologies. Most cases are female (4/5). It affects predominantly young to middle-aged women. Serum immunoglobulin G (IgG) and gamma globulin levels are 1.5 times higher than normal, and autoantibodies may be present. Antinuclear antibody (ANA), anti-liver/kidney microsomal antibody (ALKM), anti-kidney/pancreas antibody (AKP), anti-liver cytosol antibody (ALC), anti-mitochondrial antibody (AMA), anti-soluble liver antigen, anti-sialo glycoprotein receptor, anti-liver-pancreas (LP), anti-liver-specific protein, and anti-smooth muscle antibody (ASMA) can be detected in autoimmune diseases. Different types are distinguished based on the type of autoantibodies detected in

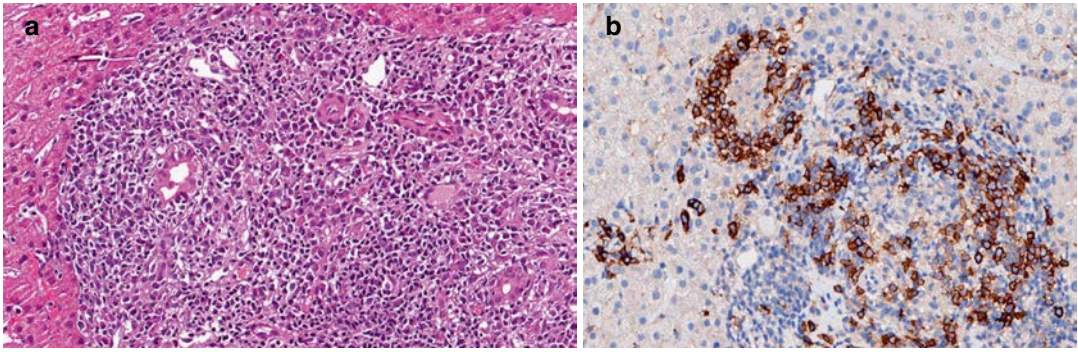


Fig. 5.3 (a) Plasma cell-rich portal and periportal inflammation in AIH (b) Plasma cells are highlighted by CD38

the serum: Type 1 (lupoid hepatitis) is more likely to be ASMA and ANA positive, while type 2 is ALKM-1 and/or ALC-1 positive. Previously, type 3, which is SLA/LP positive, was described but has been abandoned. ANA, ASMA, and LKM-1 are positive in 80% of cases, while AMA is absent. Type 1 is associated with other autoimmune diseases such as rheumatoid arthritis (RA), thyroiditis, and Sjögren's syndrome in 60% of cases. Distinguishing this condition from chronic viral hepatitis is important because it responds well to steroid treatment. Autoimmune hepatitis type 2 is seen in the pediatric age group (2–18 years). The rate of progression to cirrhosis is around 80%. Autoimmune hepatitis can have an atypical course. Cirrhosis may be established at the time of diagnosis up to 30% of patients with adult-onset autoimmune hepatitis. Nearly half of those with a pronounced systemic disease die within 6 months if untreated. At least 40% of survivors develop cirrhosis. A scoring system has been developed for the diagnosis of autoimmune hepatitis. This system takes into account autoantibodies, IgG titer, biopsy findings, and the presence of viral hepatitis. A low ANA or ASMA titer is 1 point. A high titer of these two antibodies, or a positive ALKM or SLA-like antibody, is 2 points. However, a maximum of 2 points can be awarded for each autoantibody. IgG levels around the upper limit of normal are 1 point, and higher levels are 2 points. The presence of hepatitis is 1 point, the presence of more typical findings of autoimmune hepatitis (interface hepatitis) is 2 points, and the absence of viral hepatitis is 2 points. A total score of 6 is considered probable,

and a score of 7 is considered definite autoimmune hepatitis. Findings such as male gender or the presence of bile duct lesions are clinical features that exclude autoimmune hepatitis. Histopathologically, interface hepatitis and dense lymphoplasmacytic portal infiltrate are determined. Bridging necrosis is developed in advanced stages and lobular inflammation can be seen in severe disease. In approximately 90% of patients, immunosuppressive therapy results in remission. End-stage disease is a constitutive indication for liver transplantation. After transplantation, the 10-year survival rate is 75% and recurrence rate is 20% [6–10].

5.2.3 Metabolic and Genetic Liver Diseases

5.2.3.1 Metabolic Dysfunction-Associated Fatty Liver Disease Nonalcoholic Steatohepatitis

Fatty liver diseases (FLD) are strongly associated with alcohol or common metabolic disorders such as obesity, metabolic syndrome (MetS), and type 2 diabetes mellitus (T2DM), and dyslipidemia. Histopathologically, three types of alteration are observed in FLD. These alterations are simple steatosis (fatty changes), steatosis complicated with inflammation (steatohepatitis), and fibrosis. The previous definition of nonalcoholic fatty liver disease-nonalcoholic steatohepatitis (NASH) was modified to the definition of metabolic dysfunction-associated fatty liver disease/metabolic dysfunction-associated steatohepatitis

(MAFLD/MASH) as the disease based on the presence of metabolic dysfunction. Steatosis is an abnormal neutral lipid (triglyceride) accumulation within hepatocytes. Steatosis may be microvesicular or macrovesicular. In the microvesicular steatosis, many small lipid droplets are seen in the cytoplasm of hepatocyte, giving foamy appearance to hepatocyte. It is less common than macrovesicular steatosis, and diffuse microvesicular steatosis can be associated with severe conditions. In the macrovesicular steatosis, large lipid drops fill and expand the hepatocyte. The nucleus of hepatocyte is pushed outwards (Fig. 5.4). Fat accumulation generally begins in the centrilobular hepatocytes, and fatty changes are reversible in many cases. MAFLD has rapidly become the most common liver disease globally and is currently estimated to affect 38% of the global population. Rapid urbanization; the transition toward more processed, calorie-dense diets; and the reduction in physical activity have become ubiquitous risk factors, especially in middle- and low-income countries. As MAFLD progresses to MASH, fibrosis, cirrhosis, and ultimately liver cancer, the demand on healthcare systems grows, often outpacing the capacity of low-resource settings to manage such cases effectively. The mortality rates linked to MASH-related liver cancer, which have already surpassed those due to alcohol-related HCC, are set to rise further, underscoring the need for pre-emptive healthcare interventions. The diagnostic criteria for MAFLD include the presence of hepatic steatosis confirmed by biopsy, imaging, or blood markers, along with the coexistence of

one or more conditions such as overweight/obesity, T2DM, or evidence of metabolic dysregulation in lean individuals. Liver biopsy remains the gold standard for accurately diagnosing liver steatosis [11–15].

The **pathophysiology** underlying MAFLD involves a multitude of interlinked processes, including insulin resistance underlying the MetS, **lipotoxicity** attributable to the accumulation of toxic lipid species, and infiltration of proinflammatory cells causing hepatic injury and ultimately leading to **hepatic stellate cell** (HSC) activation and **fibrogenesis**. Activation of HSCs is the common final pathway for diverse signals from damaged hepatocytes and proinflammatory cells. Activated HSCs then secrete excess **extracellular matrix** which accumulates and impairs structure and function of the liver. TAZ (a transcriptional regulator), hedgehog (HH) ligands, transforming growth factor- β (TGF- β), **bone morphogenetic protein 8B** (BMP8B), and **osteopontin** play important roles in activating these HSCs. Dysfunctional **gut microbiome**, dysregulated **bile acid metabolism**, endogenous alcohol production, and intestinal fructose handling modify individual susceptibility to MASH [16]. The diagnosis of MAFLD requires the presence of steatosis (fat), ballooning degeneration of hepatocytes, and inflammation. The steatosis in steatohepatitis is usually initially in zone 3 and gradually spread to zones 2 and 1. Steatotic hepatocytes contain large lipid vacuoles that displace the nuclei to the periphery of the cells. Ballooning degeneration is characterized by enlarged and swollen hepatocytes with granular material in the cytoplasm, which represents collapsed cytoskeleton (Fig. 5.5). Mallory hyaline (i.e., Mallory-Denk bodies) refers to clumps of rosy eosinophilic material in the cytoplasm. They represent misfolded and aggregated keratin filaments. Inflammatory cell aggregates can be found scattered throughout liver lobules. Portal inflammation can be seen occasionally, but it is usually mild. MAFLD activity and fibrosis score was the combination of semiquantitative scores of macrosteatosis, activity (balloon degeneration and lobular inflammation), and fibrosis that first begin in zone 3 (around the central vein). The scoring

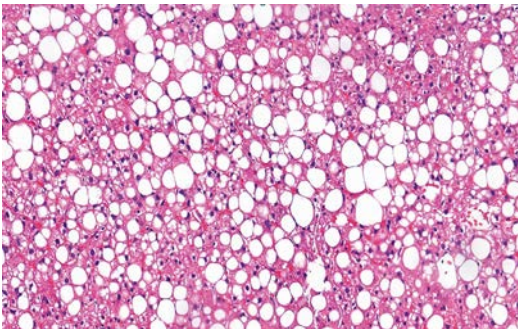


Fig. 5.4 Macrovesicular steatosis

system was initially proposed by Brunt et al. in 1999, modified in 2005 as “Brunt/Kleiner” scoring system, and further refined by the NASH Clinical Research Network. According to this system, *NAFLD activity score* is calculated by summing the scores for steatosis, lobular inflammation, and hepatocellular ballooning, ranging from 0 to 8. It’s used to assess the overall activity of the disease.

Steatosis refers to the amount of fat in liver cells, typically graded on a scale (0–3): 0, <5% of hepatocytes affected; 1, 5–33% of hepatocytes affected; 2, 34–66% of hepatocytes affected; and 3, >66% of hepatocytes affected (Fig. 5.6).

Lobular inflammation assesses the presence and severity of inflammation within the liver lobules, also graded on a scale (0–3): 0, none; 1,

<2 foci per 20× field; 2, 2–4 foci per 20× field; and 3, >4 foci per 20× field.

Hepatocyte ballooning evaluates the presence of ballooning degeneration of liver cells, a sign of cell damage, typically graded 0–2: 0, none; 1, few ballooned cells; and 2, many ballooned cells.

Fibrosis assesses the extent of scarring in the liver, often staged from 0 to 4: 0, no fibrosis; 1, perisinusoidal fibrosis; 2, periportal and perisinusoidal fibrosis; 3, bridging fibrosis; and 4, cirrhosis.

MAFLD fibrosis score uses a combination of clinical and laboratory parameters (age, body mass index, international normalized ratio, aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), platelet count, and history of diabetes) to identify advanced fibrosis in MAFLD patients, according to the National Institutes of Health. These scoring systems are used in conjunction to provide a comprehensive assessment of MAFLD severity and progression, guiding treatment decisions. The main histologic differential diagnosis for MAFLD is alcoholic steatohepatitis (ASH). Features that are more often seen in ASH include prominent ballooning degeneration (often ringed by neutrophils), frequent Mallory-Denk bodies, and centrilobular sclerosing hyaline necrosis. However, MAFLD and alcohol-associated liver disease (ALD) still overlap greatly in histologic appearance; thus, the diagnosis ultimately relies upon the clinical impression [11–16].

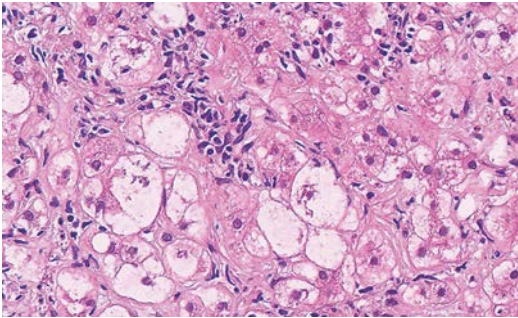


Fig. 5.5 Steatosis, balloon degeneration, and lobular inflammation

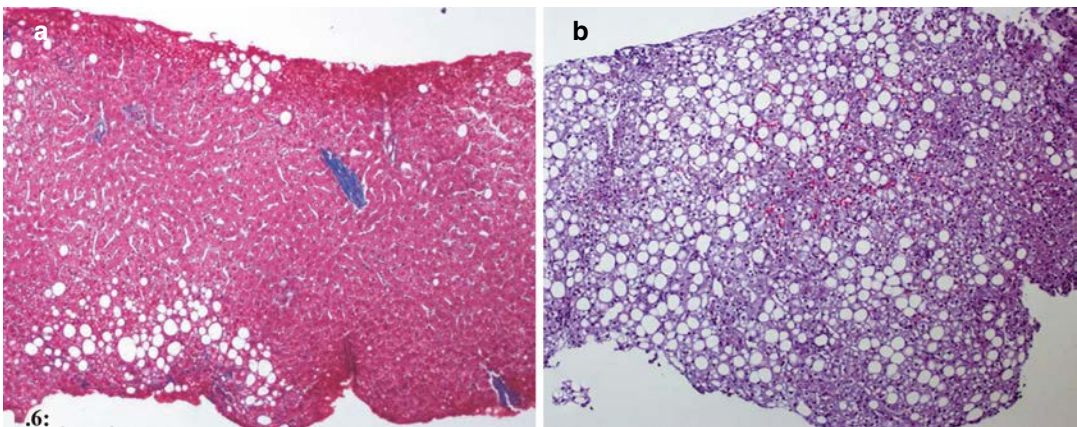


Fig. 5.6 (a) Grade 1 steatosis localized in zone 3 (Masson trichrome × 100). (b) Grade 3 diffuse steatosis in zone 1–3 (HE × 100)

5.2.3.2 Wilson's Disease

Wilson's disease is an autosomal recessive disease caused by a disorder of copper metabolism. The asymptomatic heterozygous carrier rate is 1/90; the disease prevalence is 1/30,000. There is a defect in the ATP7B gene on chromosome 13, which encodes a transmembrane protein, the copper-transporting ATPase. This protein is localized in the canalicular membrane of hepatocytes and facilitates the excretion of copper into the bile. Normally, the required copper is transported to the liver bound to albumin after being absorbed from the stomach and duodenum. Ceruloplasmin, a copper-carrying metallothionein in the alpha-2 globulin structure, is synthesized in the endoplasmic reticulum and released back into the plasma. Used or dysfunctional ceruloplasmin is degraded in hepatocyte lysosomes and excreted in the bile. Ninety to ninety-five percent of plasma copper is in the form of ceruloplasmin. Because ceruloplasmin synthesis is also controlled by chromosome 13, its levels are low, but the primary defect is in the excretion of copper in the bile. By the age of approximately 5 years, free copper begins to leak from hepatocytes and enter the circulation. Hemolytic anemia and accumulation in organs other than the liver then occur. Serum copper levels can be variable. Ceruloplasmin levels are low, and urinary copper levels are high due to increased copper excretion in the urine. Alkaline phosphatase levels may be low. The liver tissue contains 30–40 $\mu\text{g/g}$ of free copper. In patients, this value is $>250 \mu\text{g/g}$.

Copper accumulates primarily in the liver, brain, eyes, and kidneys. Because ceruloplasmin is a protein with ferroxidase activity and plays a role in iron metabolism, iron accumulation, similar to hemochromatosis, may be observed. Accumulated copper can be demonstrated with rhodanine or rubeanic acid stains. Orcein stains copper-bound proteins, not copper itself. Diagnosis is made between the ages of 3 and 40. While liver symptoms predominate in children, neuropsychiatric symptoms become prominent after age 20. Therefore, the possibility of Wilson's disease should be considered when encountering chronic liver disease in children. Non-immune hemolytic anemia, accompanied by very high bilirubin levels ($>20 \text{ mg/dl}$), may develop. Fulminant hepatitis, with progressive jaundice, ascites, and liver and kidney failure, may occur in children and adolescents. Neurological symptoms such as tremor, rigidity, speech impairment, ataxia, chorea, and behavioral changes are caused by neuronal necrosis due to the toxic effects of copper. The accumulation of copper in the renal tubules, leading to excessive urinary excretion of protein, glucose, phosphate, urate, and calcium, can lead to kidney stones, distal tubular acidosis, and renal osteodystrophy. Wilson's cirrhosis resembles chronic hepatitis cirrhosis or alcoholic cirrhosis (Fig. 5.7). Glycogenated nuclei, macrovesicular steatosis, periportal lipofuscin, and Mallory bodies are observed. Copper accumulation in the descemet membrane at the corneal limbus of patients with neurological findings results in the

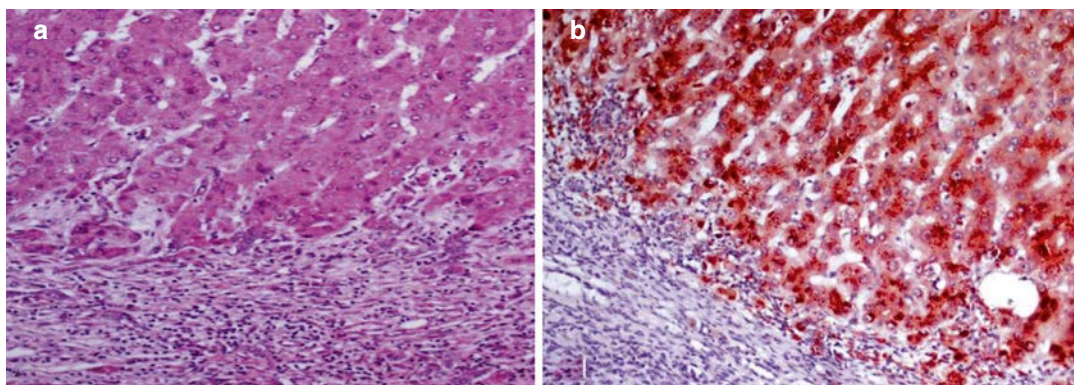


Fig. 5.7 (a) Cirrhotic stage of Wilson's disease. (b) Intense intracellular copper accumulation (rhodanine $\times 200$)

development of a green-brown Kayser-Fleischer ring. Over time, a sunflower-type cataract develops. Because the accumulation in the brain is prominent in the lenticular nuclei, the disease is also called hepatolenticular degeneration. Copper-binding agents such as penicillamine are used to prevent disease progression. Definitive treatment is liver transplantation. Without transplantation, it is fatal [17–19].

5.2.3.3 Hemochromatosis

Hemochromatosis is a disease characterized by excessive iron accumulation in the body, which can be primary (hereditary) or secondary. The body normally contains 2–6 g of iron; approximately 10% of this is in the cytoplasm of liver cells. It's important to remember that hemosiderosis can be observed in all types of cirrhosis except biliary cirrhosis. Normally, iron absorption and excretion are under strict metabolic control; even when the requirement is high, only a small portion of the oral intake is absorbed. In primary hemochromatosis, this mechanism is impaired. The amount of iron in the body gradually increases from birth. The primary defect is transfer. The High Fe (iron) gene (HFE) gene product is the HFE protein, a member of the human leukocyte antigen (HLA) family. It is found primarily in the crypt epithelial cells of the small intestine, where it forms complexes with B2 microglobulin. The presence of the HFE-B2 microglobulin complex is essential for transferrin, the serum iron-carrying protein, to bind to the transferrin receptor (TfR). Primary hemochromatosis is an autosomal recessive disease caused by a defect in the HFE gene, located on the short arm of chromosome 6 (6p21.3), near the HLA gene locus. In the HFE gene mutation, the HFE protein is inactivated by the substitution of a cysteine for a tyrosine at the C282Y site. This change in the beta-2 microglobulin-binding arm of HFE prevents the TfR from connecting. Furthermore, the mutant HFE protein's iron uptake-facilitating effect is lost. Normally, ingested iron is processed and stored in the intracellular iron pool. The vacancy in this pool leads to an increase in the iron regulatory protein (IRP), which stimulates iron absorption mechanisms.

This protein activates four distinct iron absorption mechanisms. Duodenal cytochrome B stimulates ferric reductase, increasing the reduction of trivalent iron to usable divalent iron. Iron reduced by DMT-1 (divalent metal transporter) on the surface of the villus enterocyte is taken into the cell. It binds to ferritin, the cytoplasmic iron-binding protein. It is transported to ferroportin (FP-1) at the cell base, where it binds to transferrin. In patients with hemochromatosis, dysfunction of HFE leads to uncontrolled functioning of IRP and other iron absorption pathways [10]. It is more common in males (1 in 4–7). The homozygosity rate in Caucasians is 0.3%, and the heterozygosity rate is 8–10%. The HLA-A3 histocompatibility antigen is detected in a significant portion of patients. The disease usually becomes symptomatic in men around the age of 35–40; however, it occurs slightly later in women, or in the post-menopausal period, due to greater iron loss due to physiological events such as menstruation and pregnancy. In hereditary hemosiderosis, because the absorption mechanism is impaired compared to the need, approximately 0.5–1 g of excess iron is absorbed each year. Symptoms occur when total body iron exceeds 20 g. In hereditary hemochromatosis, this amount can exceed 50 g. More than one-third of the accumulated iron is in the liver. Patients develop diabetes mellitus due to accumulation in the pancreatic islets, and due to accumulation in the pituitary gland, melanin production in the skin increases under the influence of melanocyte-stimulating hormone. Furthermore, due to hemosiderin accumulation, the skin becomes hyperpigmented. These clinical findings have led to the disease being referred to as bronze diabetes. Hypogonadism due to testicular atrophy, cardiomyopathy due to accumulation in the heart muscle, and arthropathy due to synovial accumulation may also occur. Excessive iron is hepatotoxic, causing hepatocyte necrosis, fibrosis, and micronodular cirrhosis. Accumulation in the liver is initially observed only in the cytoplasm of hepatocytes near the biliary canaliculi; later, in periportal hepatocytes, ductal epithelium, and cirrhotic septa. In secondary hemochromatosis, the accumulation is initially in sinusoidal endo-

thelial cells and Kupffer cells. Over time, it also appears in the cytoplasm of hepatocytes (Fig. 5.8). In cases secondary to circulatory disturbance, the accumulation is more prevalent around the central vein. Increased plasma iron alone is not diagnostic. It should be evaluated together with the serum ferritin level and iron-binding capacity. Definitive diagnosis is achieved by measuring the amount of iron in the liver. Patients have over 10,000 micrograms of iron per gram of liver tissue. Normally, this amount is 1000 micrograms. For necrosis and fibrosis to develop, the accumulation must exceed 20,000. After cirrhosis develops, accumulation ceases. The toxic effects of iron occur through three distinct mechanisms: lipid peroxidation in cell membranes by iron-catalyzed free oxygen radicals, direct stimulation of collagen synthesis, and interaction with DNA, leading to malignant transformation. The rate of HCC development (15–25%) is approximately 200 times higher than in the normal population. This high risk persists even if iron accumulation is prevented. The

metabolic diseases that carry the greatest risk of malignancy are hemochromatosis in adults and tyrosinemia cirrhosis in children [20, 21].

5.2.4 Drug- and Toxin-Induced Liver Injury

also known as hepatotoxicity, refers to liver damage caused by medications, herbs, or other xenobiotics (Table 5.1). Drug- and toxin-induced liver injury (DILI) can mimic any form of acute or chronic liver disease and remains a significant cause of liver failure and drug withdrawal. DILI is generally classified based on pathogenesis, clinical patterns, and histological features. According to its mechanism, DILI may be intrinsic (predictable) or idiosyncratic (unpredictable). Intrinsic DILI is dose-dependent and has short latent periods. It develops via formation of toxic metabolites (e.g., N-acetyl-p-benzoquinone imine from acetaminophen/paracetamol), mitochondrial dysfunction, oxidative stress, and ade-

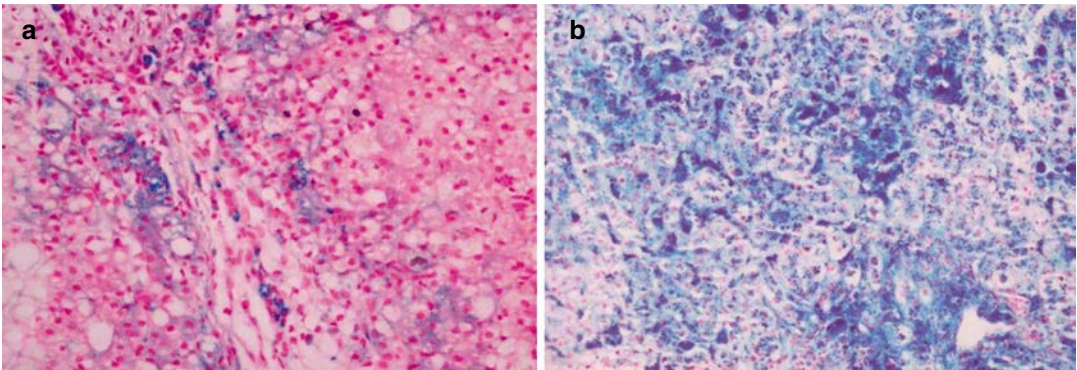


Fig. 5.8 (a) Iron accumulation in periportal hepatocytes. (b) Diffuse iron accumulation (Prussian blue $\times 100$)

Table 5.1 Drugs that are common causative agents of DILI and their characteristics

Drug/class	Type of injury	Pattern
Acetaminophen	Intrinsic	Hepatocellular
Amoxicillin-clavulanate	Idiosyncratic	Cholestatic
Isoniazid	Idiosyncratic	Hepatocellular
Nitrofurantoin, minocycline	Immune-mediated	Autoimmune-like
Methotrexate	Chronic toxicity	Fibrosis/steatosis
Statins	Mild transaminase $\uparrow$	Hepatocellular
Herbal and dietary supplements	Variable	Any

nosine triphosphate (ATP) depletion. However idiosyncratic DILI is dose-independent, has variable latency, and can be immune-mediated. Hypersensitivity reactions (e.g., eosinophilia, rash), genetic polymorphisms (e.g., HLA-B*5701 in flucloxacillin injury), and immune system activation (e.g., checkpoint inhibitor-induced hepatitis) are associated with this type of DILI. For example, isoniazid and amoxicillin-clavulanate cause unpredictable DILI. Clinical pattern can be hepatocellular, cholestatic, or mixed. It is evaluated with R score. The R score is calculated by dividing the alanine aminotransferase (ALT)/upper limit of normal (ULN) by the alkaline phosphatase (ALP)/upper limit of normal. The value below 2 is considered cholestatic, between 2 and 5 is considered mixed, and above 5 is considered hepatic pattern. Hepatocellular injury pattern is characterized by lobular necrosis, apoptosis, and ballooning degeneration of hepatocytes. Canalicular bile plugs, bile duct injury or loss, and ductular reaction are determined in the cholestatic injury pattern. In mixed patterns, granulomas (e.g., allopurinol, sulfonamides), steatosis (e.g., methotrexate, amiodarone), sinusoidal obstruction syndrome (e.g., oxaliplatin, herbal supplements), or autoimmune-like hepatitis (e.g., minocycline, nitrofurantoin) can be observed. Clinical findings are developed after a latent period ranging from hours (e.g., acetaminophen) to months (e.g., isoniazid). The symptoms of DILI are nausea, fatigue, jaundice, pruritus, abdominal pain, and fever. Signs of liver injury are increased ALT, AST (hepatocellular), increased ALP, GGT, bilirubin (cholestatic), or encephalopathy in severe injury. Management of DILI includes immediate discontinuation of suspected agent, supportive care for mild-to-moderate cases, therapy of N-acetylcysteine for acetaminophen overdose, corticosteroids for autoimmune-like reactions, and liver transplantation in fulminant hepatic failure. Most cases resolve after stopping the drug. Poor prognosis indicators are high bilirubin levels ($>3\times$ ULN), elevated ALT, presence of coagulopathy, and encephalopathy. Mortality rate is up to 10% in idiosyncratic DILI with jaundice [22–25].

Alcohol-Associated Liver Disease

Alcohol-associated liver disease (ALD) is the name given to a spectrum of liver damage symptoms that develop in some individuals who consume excessive amounts of ethanol over a long period of time. This process, from the mildest to the most severe, includes steatosis, steatohepatitis, and alcoholic cirrhosis. The most important factor that makes it difficult to quantify concepts such as excessive alcohol consumption and long-term alcohol consumption is the significant variation in the degree of alcohol exposure. Poor nutrition associated with alcoholism increases the likelihood of liver damage; in fact, it is believed that this nutritional deficiency is responsible for the damage. Women who consume the same amount and duration of alcohol are more likely to experience damage than men, and the disease progresses more severely [25].

Once alcohol is absorbed from the GI tract; more than 90% is metabolized in the liver. There are three primary oxidation pathways in the liver. The most is metabolized by cytosolic alcohol dehydrogenase in the smooth endoplasmic reticulum and the microsomal ethanol-oxidizing system (MEOS). MEOS activity increases with chronic alcohol consumption. In alcohol detoxification, the function of the catalase pathway in peroxisomes is limited. Acetaldehyde is formed this way and converted to acetate by the enzyme aldehyde dehydrogenase in the mitochondria. With chronic alcohol consumption, the level of this enzyme decreases, and acetaldehyde levels increase. In summary, alcohol dehydrogenase is the most important cytoplasmic enzyme that metabolizes alcohol. Metabolism is carried out to a lesser extent by MEOS. Under the influence of alcohol dehydrogenase, the hydrogen ion concentration in the environment increases. Some of this hydrogen is used for MEOS's functioning. Overactivity of MEOS due to alcoholism causes the endoplasmic reticulum and mitochondria to enlarge and become larger in alcoholics. Furthermore, the reduction of nicotinamide adenine dinucleotide levels by alcohol dehydrogenase and acetaldehyde dehydrogenase, two important enzymes in alcohol metabolism,

reduces the normal catabolism of lipids. As the normal oxidation of fatty acids decreases and cholesterol production increases, neutral fat begins to accumulate in the cytoplasm of hepatocytes. The hepatic effects of acetaldehyde include increasing lipid peroxidation, binding to the plasma membrane, disrupting the mitochondrial electron transport chain, inhibiting nuclear repair mechanisms, and disrupting microtubule function. These changes induced by alcohol and acetaldehyde can lead to alterations in the immune response by altering hepatocellular proteins and their epitopes. Induction of cytochrome P-450, which is involved in alcohol catabolism in the endoplasmic reticulum, increases the conversion of some drugs, such as acetaminophen, to toxic forms. Its ability to combine with proteins to form toxic products, activate complement, induce superoxide production from neutrophils, and increase collagen synthesis also plays a role in the pathogenesis of alcohol-induced liver injury. Acetaldehyde and malondialdehyde formed during lipid peroxidation together form methacrylic acid (MAA) products. These products modulate the inflammatory response. The release of certain cytokines, particularly TGF- β and tumor necrosis factor (TNF)- α , from leukocytes increases fibrogenic and inflammatory responses. It also has a direct toxic effect on hepatocytes, leading to the formation of more MAA products. Because acetaldehyde and free radicals are most abundant here, the pericentral region is most affected [25, 26].

In alcoholics, the liver weight can increase to two to three times normal due to macrosteatosis. Fatty change alone does not negatively impact liver function. However, in chronic alcoholics, fatty change is often associated with other organic problems, such as vitamin deficiencies. Vitamin deficiency, particularly B12, is related to chronic alcohol-induced gastric and intestinal mucosal damage and subclinical pancreatitis, rather than nutritional deficiency. Alcohol impairs methionine metabolism, increases intrahepatic glutathione levels, and makes the liver susceptible to oxidative damage. Alcoholic hepatitis occurs in approximately one-third of people who consume alcohol excessively, and only

one-third of these develop cirrhosis. In alcoholic hepatitis, which is often superimposed on macrosteatosis, balloon degeneration of hepatocytes and clusters of percutaneous nephrolithotomy (PNL) in the parenchyma are observed. The presence of Mallory bodies (alcoholic hyaline) in the cytoplasm of some hepatocytes is typical (Fig. 5.9). These bright red lumps are composed of degenerated gallbladder-type cytokeratin and ubiquitin molecules. Besides alcoholic hepatitis, Mallory bodies are also observed in nonalcoholic steatohepatitis, extrahepatic biliary obstruction, primary biliary cirrhosis, and Wilson's disease. Interestingly, all these diseases are associated with excess hepatic copper. Furthermore, iron accumulation is detected in the bile canaliculi, hepatocytes, and Kupffer cells of alcohol users. Macromitochondria, detectable in size (1–7 microns), can be observed under light microscopy because ethyl alcohol is toxic to the mitochondria themselves. Most importantly, the appearance of collagen fibers surrounding individual hepatocytes (Fig. 5.10). This condition, called pericellular (subsinusoidal) fibrosis, leads to the loss of hepatocytes and, over time, disrupts the normal microanatomical relationships of the liver and liver microcirculation, paving the way for cirrhosis [25–28].

Alcoholic cirrhosis can develop gradually following episodes of alcoholic hepatitis in approximately 20–30% of people who consume excessive amounts of alcohol for years. However, prior symptomatic or alcoholic hepatitis is not neces-

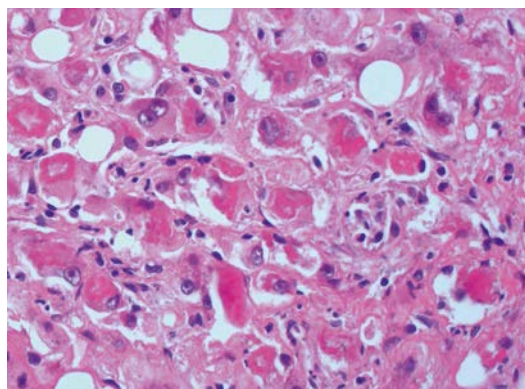


Fig. 5.9 Mallory bodies (HE $\times$ 200)

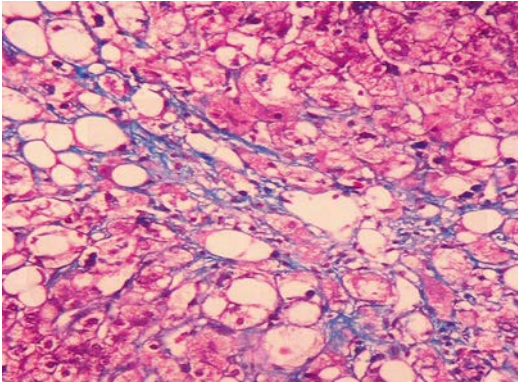


Fig. 5.10 Pericellular (subsinusoidal) fibrosis by trichrome stain

sary for cirrhosis to develop. Alcoholic cirrhosis can also develop without a significant inflammatory infiltrate, following insidiously progressive pericellular/perivenular fibrosis. The development of cirrhosis is associated with many factors, including alcohol sensitivity, alcohol dehydrogenase isoforms, cytokine expression (especially TNF), and collagen transcription. Early detection of the lesion and cessation of alcohol consumption can halt the progression of cirrhosis. Because alcoholic cirrhosis progresses more slowly than other forms of cirrhosis, reducing alcohol consumption may be beneficial even after cirrhosis develops. Alcoholic cirrhosis is often accompanied by steatosis. Therefore, the liver is initially larger than normal and yellow in color. Cirrhosis develops in a micronodular pattern with increased connective tissue. Continued regenerative activity and decreasing steatosis led to mixed macro- and micronodular cirrhosis over time. In the final stage, the liver becomes granular and smaller. Mallory bodies disappear, and bile stasis occurs. In the final stage, it is very difficult to distinguish alcoholic cirrhosis from cirrhosis caused by other factors [25–28].

5.2.5 Vascular Liver Diseases

Vascular liver diseases refer to a diverse group of conditions that affect the liver's blood vessels, including the hepatic artery, portal vein, hepatic

veins, and sinusoids. These disorders can lead to significant hepatic dysfunction and portal hypertension. The liver has a dual blood supply. Therefore, extensive ischemic necrosis of the liver is rare, except in transplanted livers. Portal veins provide nearly 75% of blood flow and bring nutrient-rich blood from the gastrointestinal tract, while hepatic artery provides 25% of blood flow and supplies oxygen-rich arterial blood. Hepatic veins drain into the inferior vena cava (IVC). Disruption of this system can cause ischemia, congestion, portal hypertension, and even liver failure [23–25].

5.2.5.1 Budd-Chiari Syndrome

Budd-Chiari syndrome (BCS) develops as a result of obstruction of hepatic venous outflow at the level of the hepatic veins or the IVC. Etiologies of BCS are myeloproliferative neoplasms, especially polycythemia vera and thrombophilia such as factor V Leiden or antiphospholipid syndrome. Clinical features are hepatomegaly, ascites, abdominal pain, and eventually liver failure. Histopathologically it is characterized with centrilobular congestion and necrosis, sinusoidal dilatation, and fibrosis with “nutmeg liver” appearance (Fig. 5.11). For therapy, anticoagulation, angioplasty/stenting, transjugular intrahepatic portosystemic shunt, and liver transplantation are applied [29].

5.2.5.2 Sinusoidal Obstruction Syndrome (Formerly Veno-occlusive Disease)

Sinusoidal obstruction syndrome (SOS) (formerly veno-occlusive disease) is caused by injury to hepatic sinusoidal endothelium leading to congestion and necrosis. It develops associated with bone marrow transplantation and chemotherapeutics, especially oxaliplatin. Symptoms are weight gain, hepatomegaly, ascites, jaundice, and liver failure. There is centrilobular congestion, fibrosis of small hepatic venules, endothelial swelling, sinusoidal congestion, and obliteration of central veins. Management includes supportive care and defibrotide which is the only Food and Drug Administration-approved drug for severe SOS [29].

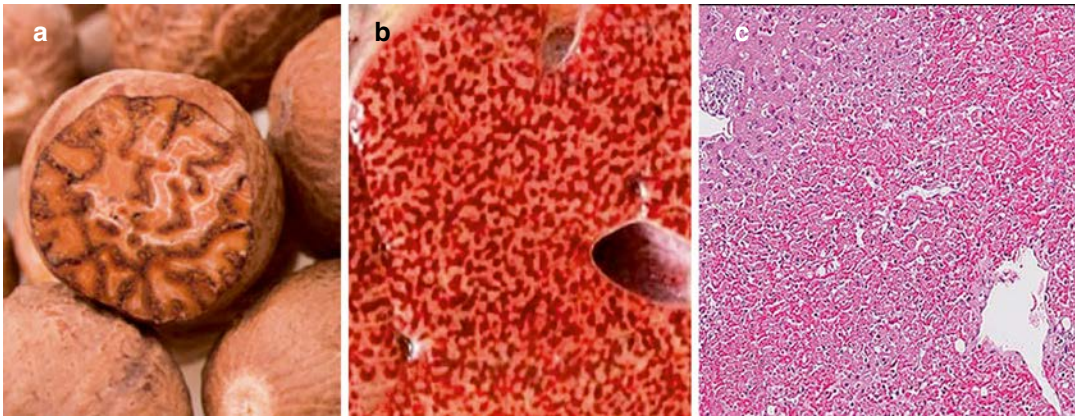


Fig. 5.11 (a) Nutmeg. (b) Nutmeg liver. (c) Centrilobular congestion (HE $\times 100$)

5.2.5.3 Hepatic Artery Thrombosis

Hepatic artery thrombosis is commonly seen after liver transplantation, and it is the most feared early complication of transplantation. Clinical signs are acute graft dysfunction, fever, sepsis, and elevated liver enzymes. Hepatic arterial flow is absent on a Doppler ultrasound. Treatment can be made by urgent revascularization or retransplantation [30].

5.2.5.4 Some Other Conditions

Some other conditions affect the liver's blood vessels. For example, passive congestion from right-sided heart failure or constrictive pericarditis causes congestive hepatopathy, which is characterized by hepatomegaly, elevated liver enzymes, ascites, and nutmeg liver due to centrilobular congestion and necrosis. It may lead to cardiac cirrhosis if it becomes chronic. Underlying cardiac disease must be treated with diuretics and anticoagulation. In addition, some different diseases like hereditary hemorrhagic telangiectasia, or portosinusoidal vascular disease (formerly idiopathic non-cirrhotic intrahepatic portal hypertension) can cause vascular liver disorders [31].

5.2.6 Granulomatous Hepatitis

Granulomatous hepatitis is a histopathological diagnosis characterized by the presence of granu-

lomas, which are organized collections of macrophages, in the liver parenchyma. It is not a specific disease but a manifestation of a wide range of infectious, autoimmune, drug-induced, and neoplastic disorders. Common infectious causes of granulomatous hepatitis include *Mycobacterium tuberculosis*, certain fungi such as *Histoplasma*, *Coccidioides*, and *Cryptococcus*, as well as other contagious diseases, including brucellosis, Q fever (*Coxiella burnetii*), syphilis, toxoplasmosis, and hepatitis C virus, which can sometimes be associated with granulomas. Non-caseating granulomas are common in sarcoidosis and primary biliary cholangitis (PBC). On the other hand, caseating granulomas are suggestive of tuberculosis or fungal infections. Epithelioid histiocytes and multinucleated giant cells are associated with portal or lobular inflammation. In autoimmune conditions, fibrinoid necrosis may be seen [32].

5.3 Non-neoplastic Bile Duct Diseases

5.3.1 Primary Biliary Cholangitis

Primary biliary cholangitis is characterized by autoimmune destruction of intrahepatic bile ducts. This disorder was named primary biliary cirrhosis for long years. Because cirrhosis develops only in the advanced stages of the disease, it

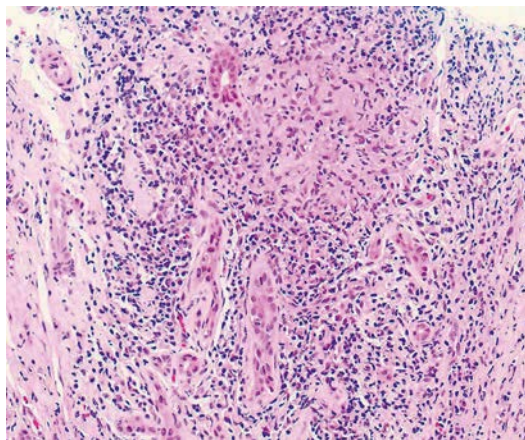


Fig. 5.12 Florid duct lesion

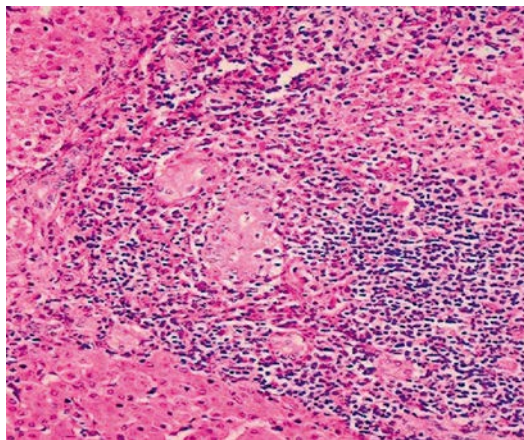


Fig. 5.13 Dense inflammation surrounds bile ducts

is more accurate to describe chronic nonsuppurative destructive cholangitis. PBC develops much more frequently in women than in men (M/F: 1/6–9) and has an insidious onset. It is most commonly seen between the ages of 40 and 60. Ten to fifty percent of cases are asymptomatic. The most common findings are pruritus, jaundice, increased skin pigmentation, and portal hypertension. It is frequently seen in association with other autoimmune diseases such as scleroderma, thyroiditis, and RA. Death is usually due to hepatocellular failure. Gradually increasing jaundice and hepatomegaly are observed in patients. ALP and cholesterol may be very elevated. Xanthelasma may develop due to hypercholesterolemia. ALT and AST levels are relatively mildly elevated. Liver failure and portal hypertension develop over months or even years. One of the most characteristic features of the disease is the presence of autoantibodies in the serum. The positivity rate for AMA (especially M2) is over 90%. IgM levels are also elevated. In PBC, the main bile ducts are intact; the disease affects the small intrahepatic bile ducts. Based on histopathological findings, it is divided into three stages: early (ductal injury), late (scarring), and cirrhotic. Findings may vary from one area of the liver to another. The interlobular and septal bile ducts are damaged focally and segmentally; ductal loss in the portal areas is variable. Initially, florid duct lesions are observed (Fig. 5.12). The involved ducts are surrounded by a dense lymphoplasma-

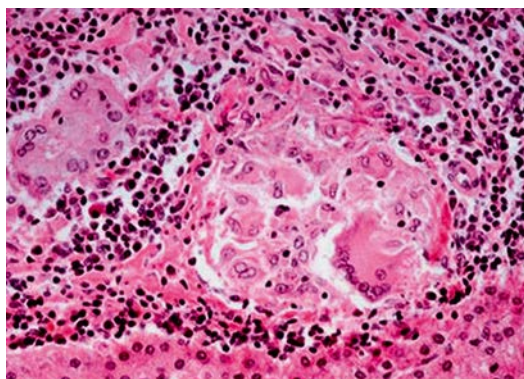


Fig. 5.14 Granuloma and giant cell in a portal area

cytic portal infiltrate, which often invades the epithelium. A small number of eosinophils may be present, and neutrophils are often absent. Periductal lymphocytic infiltration (Fig. 5.13) may become dense enough to form a germinal center. Macrophages may form loose aggregates or well-formed granulomas (Fig. 5.14). In extensive damage, the epithelium ulcerates, leaving behind Periodic acid-Schiff-positive material due to basement membrane fragmentation. Ductopenia is a significant finding. Bile ducts accompanying the hepatic arteries are absent in half to most portal areas. Parenchymal lesions include the presence of inflammatory cells predominantly composed of lymphocytes in the sinusoids and nonspecific changes such as Kupffer cell hypertrophy. Rarely, single-cell

necrosis and focal lesions that can be confused with acute hepatitis may occur. Canalicular cholestasis is uncommon in early PBC. Duct loss, perinodular edema, and lamellar fibrosis are late-stage features of PBC. Over time, cholestasis due to collapsed bile ducts contributes to hepatocyte injury and fibrosis. During this stage, the disease extends beyond the portal area. As bile duct destruction continues, signs of chronic cholestasis appear. During the development of biliary cirrhosis, portal areas expand with periportal fibrosis. Portal-portal bridges occur. Preservation of the normal anatomic relationship between the portal area and the central vein until the advanced stage is a typical feature. The resulting cirrhosis is initially micronodular and difficult to distinguish morphologically from secondary biliary cirrhosis. Nodules are irregularly distributed, and areas with preserved acinar architecture may be present. Microscopic distinction from other cirrhosis is difficult. Ursodeoxycholic acid is used in treatment. It is a hydrophilic bile acid that reduces intrahepatic bile salt concentration and inhibits intestinal absorption. Clinically, cholestatic enzymes return to normal. Corticosteroids may be effective when started in the early stages of ductopenia [25, 33].

5.3.2 Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) is a chronic disease characterized by destruction of the intra- and extrahepatic biliary ducts due to nonsuppurative inflammation, seen more frequently in men (M/F: 2–4/1). Periductal concentric fibrosis, ductal loss, cicatrization, and segmental involvement are characteristic features. Clinically, the 70% rule has been defined. According to this rule, 70% of cases are male, 70% are under 45 years of age, and chronic inflammatory bowel disease coexists in 70% of cases. The incidence of PSC in patients with ulcerative colitis is 2–7%. The etiopathogenesis of this disease, which develops saccular dilatations as a result of irregular inflammation and strictures in any part of the biliary tree, is unclear. Extrahepatic and large intrahe-

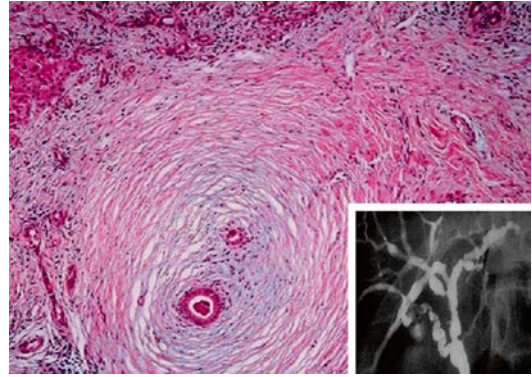


Fig. 5.15 Microscopic onion skin appearance and beading sign on endoscopic retrograde cholangiopancreatography (ERCP) (bottom right)

patic bile ducts are usually affected. Only 5% of cases have widespread small duct involvement. Because they often involve large ducts, lesions are seen in only 10% of liver biopsies. The affected bile ducts may be further away and deeper than areas reached by standard needle biopsy. Therefore, diagnosis is primarily cholangiographic, and the typical beading sign is observed on ERCP. Patients may be asymptomatic. They may also present with complaints such as malaise, fatigue, pruritus, upper abdominal pain, cholangitis attacks, and jaundice. Laboratory tests, unlike peripheral blood smear, show higher ALP, IgM levels are usually normal, and AMA is negative. Antineutrophil cytoplasmic antibodies may be present. There is no satisfactory treatment other than transplantation. The risk of cholangiocellular carcinoma is increased in PSC, which develops biliary cirrhosis over time. The classic lesion is concentric periductal lamellar fibrosis accompanied by atrophy and damage of the ductal epithelium (Fig. 5.15). The affected duct is surrounded by lamellar fibrosis, resembling an onion skin. This fibrosis narrows and obliterates the ductal lumen. A nodular fibrous scar may remain in place of the duct (fibro-obliterative scar). Periductal fibrosis alone is not diagnostic; it is significant if accompanied by ductal atrophy and luminal obliteration. Lymphocyte and plasmacytic infiltration is present in the portal areas. PNL may also be observed. Later, due to bile duct loss, signs of chronic cho-

lestasis, biliary fibrosis, and secondary biliary cirrhosis develop. There is also similar lesions that resemble PSC but with identifiable causes. These lesions are named *secondary sclerosing cholangitis*. Prolonged obstruction, ischemia, infections, and toxins cause secondary sclerosing cholangitis [25, 34].

5.3.3 Congenital and Pediatric Disorders

5.3.3.1 Biliary Atresia

Biliary atresia (BA) is the obliteration of the extrahepatic biliary tree in neonates and the leading cause of pediatric liver transplant. Etiopathogenesis remains multifactorial and incompletely understood, involving genetic susceptibility, environmental triggers, immune dysregulation, and perinatal insults. Developmental abnormalities such as polysplenia, situs inversus, and congenital heart defects (known as laterality defects) represent 10–20% of cases. The majority of cases (80–90%) are proposed to be postnatal bile duct injury with progressive inflammation and fibrosis. In addition, some perinatal infection leads to immune-mediated bile duct destruction. Viruses implicated to be associated with the development of BA are reovirus type 3, CMV, rotavirus, EBV, human papillomavirus, and human herpesvirus 6. In the cases, there is overexpression of pro-inflammatory cytokines like $\text{TNF-}\alpha$, $\text{IFN-}\gamma$, IL-2, and IL-17. $\text{IFN-}\gamma$ induces epithelial apoptosis, $\text{TGF-}\beta 1$ promotes fibrosis, and MMPs and TIMPs mediate extracellular matrix remodeling. There are also autoantibodies and elevated immunoglobulins. Regulatory T cells are downregulated. Predominance of Th1/Th17-type immune response is determined. In histopathological investigation, bile ductuli proliferation, portal fibrosis, and inflammatory infiltrations are determined (Fig. 5.16). Kasai portoenterostomy was applied in early stage. In untreated patients, cirrhosis develops in months. The clinical features of neonatal hepatitis, which can develop in newborns for various reasons and some resolve without treatment, may overlap with those of biliary atresia. While neonatal hep-

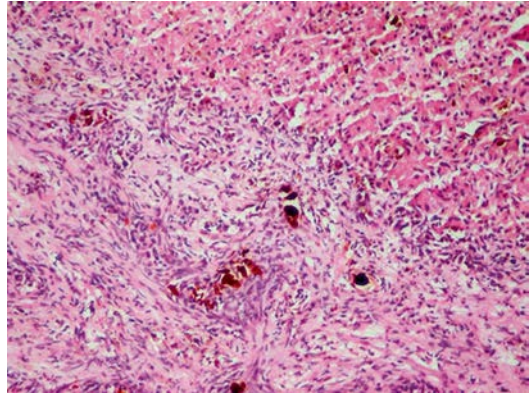


Fig. 5.16 Bile plugs in a biliary atresia

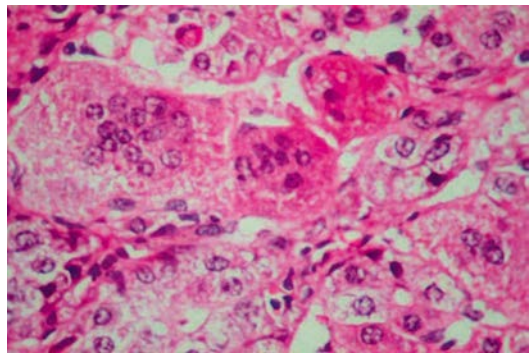


Fig. 5.17 Giant cells in a neonatal hepatitis

atitis is characterized by panlobular hepatitis with giant cells (Fig. 5.17), portal fibrosis, portal inflammation, and ductular proliferation are prominent in biliary atresia [35].

5.3.3.2 Other Diseases of Bile Ducts

Congenital hepatic fibrosis (CHF), Polycystic liver disease, and Caroli's disease (communicating cavernous biliary ectasia) are three diseases that, rather than being distinct entities, encompass different areas of the same spectrum, with a clinical presentation (portal hypertension or cholangitis) that varies depending on the degree of fibrosis and ectasia, sometimes overlapping. In polycystic liver disease, numerous cysts, large and small, are not associated with the biliary tree, most of which are lined by cuboidal epithelium. It is inherited as an autosomal dominant trait and frequently coexists with autosomal dominant polycystic kidney disease. There is congenital

dilation of intrahepatic bile ducts in Caroli's diseases. These two entities usually lead to recurrent cholangitis, while CHF generally presents with portal hypertension. The genes that cause polycystic kidney disease have been identified, and the genes that cause the recessive form are designated polycystic kidney-hepatic disease gene 1 and 2. von Meyenburg complexes are found in 40% of cases of polycystic liver disease. These lesions, which occur sporadically and develop near or within the biliary tree, are microhamartomas composed of dilated bile ducts embedded in a stroma of hyalinized fibrous tissue. Pigmentation is absent. They are believed to develop from embryological bile duct remnants. Like polycystic liver disease, they can be seen in association with autosomal dominant polycystic kidney disease. In Caroli disease, cysts of various sizes are present in association with the biliary tree. The lining epithelium is usually biliary epithelium and resembles ectatic bile ducts. Bile pigment is observed within the lesions. Patients complain of recurrent attacks of cholangitis. CHF is often also present. Both lesions (Caroli disease and CHF) are inherited as autosomal recessive traits. They are associated with both recessive and dominantly inherited polycystic kidney diseases and carry a high risk (1–7%) of developing biliary adenocarcinoma. Microscopically, congenital hepatic fibrosis reveals ductal plate malformation, portal fibrosis, porta-portal septum, proliferating dysmorphic ducts within the septums, and ductal cholestasis without jaundice (Figs. 5.18 and 5.19). Distinguishing features

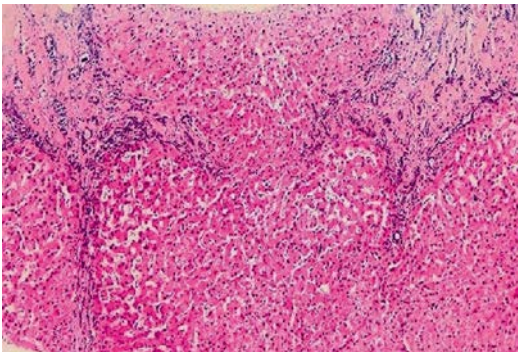


Fig. 5.18 Wide fibrous septa in CHF

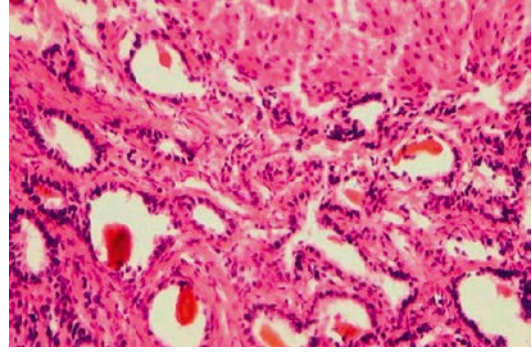


Fig. 5.19 Ectatic malformed bile ducts in CHF

from cirrhosis are the absence of regenerating nodules and intact parenchyma. The clinical manifestation is usually portal hypertension. Therefore, cirrhosis is also taken into consideration in differential diagnosis. Four entities that can be confused with cirrhosis on microscopic examination are congenital hepatic fibrosis, nodular regenerative hyperplasia, hepatoportal sclerosis, and focal nodular hyperplasia [36].

In conclusion, non-neoplastic liver and biliary diseases are diverse in etiology and presentation. Histopathological examination remains a cornerstone in the diagnosis and classification, guiding clinical management. Recognition of specific histological features, combined with serological and imaging studies, allows for accurate diagnosis and monitoring of disease progression.

References

1. Rastogi A. An approach to grossing of hepatectomy specimens. *Indian J Pathol Microbiol.* 2021;64(Supplement):S121–6. https://doi.org/10.4103/IJPM.IJPM_870_20.
2. Usuda D, Kaneoka Y, Ono R, Kato M, Sugawara Y, Shimizu R, Inami T, Nakajima E, Tsuge S, Sakurai R, Kawai K, Matsubara S, Tanaka R, Suzuki M, Shimozawa S, Hotchi Y, Osugi I, Katou R, Ito S, Mishima K, Kondo A, Mizuno K, Takami H, Komatsu T, Nomura T, Sugita M. Current perspectives of viral hepatitis. *World J Gastroenterol.* 2024;30(18):2402–17. <https://doi.org/10.3748/wjg.v30.i18.2402>.
3. Hubscher SG. Histological grading and staging in chronic hepatitis: time for a re-evaluation? *Curr Opin Gastroenterol.* 2019;35(3):144–50.

4. Neuhoﬀ BKS. Viral hepatitis. *Clin Obstet Gynecol*. 2025;68(2):180–7. <https://doi.org/10.1097/GRF.0000000000000938>.
5. Bhatti TK, Singal AK, Kwo PY. Viral hepatitis and acute-on-chronic liver failure. *Clin Liver Dis*. 2023;27(3):617–30. <https://doi.org/10.1016/j.cld.2023.03.006>.
6. Shiffman ML. Autoimmune hepatitis: epidemiology, subtypes, and presentation. *Clin Liver Dis*. 2024;28(1):1–14. <https://doi.org/10.1016/j.cld.2023.06.002>.
7. Mack CL, Adams D, Assis DN, Kerkar N, Manns MP, Mayo MJ, Vierling JM, Alsawas M, Murad MH, Czaja AJ. Diagnosis and Management of Autoimmune Hepatitis in Adults and Children: 2019 practice guidance and guidelines from the American Association for the Study of Liver Diseases. *Hepatology*. 2020;72(2):671–722. <https://doi.org/10.1002/hep.31065>.
8. Reau NS, Lammert CS, Weinberg EM. Autoimmune hepatitis: current and future therapies. *Hepatol Commun*. 2024;8(6):e0458. <https://doi.org/10.1097/HC9.0000000000000458>.
9. Soldera J. Immunological crossroads: the intriguing dance between hepatitis C and autoimmune hepatitis. *World J Hepatol*. 2024;16(6):867–70. <https://doi.org/10.4254/wjh.v16.i6.867>. PMID: 38948443; PMCID: PMC11212656
10. Hennes EM, Zeniya M, Czaja AJ, Parés A, Dalekos GN, Krawitt EL, Bittencourt PL, Porta G, Boberg KM, Hofer H, Bianchi FB, Shibata M, Schramm C, Eisenmann de Torres B, Galle PR, McFarlane I, Dienes HP, Lohse AW, International Autoimmune Hepatitis Group. Simplified criteria for the diagnosis of autoimmune hepatitis. *Hepatology*. 2008;48(1):169–76. <https://doi.org/10.1002/hep.22322>.
11. Wong VW, Ekstedt M, Wong GL, Hagström H. Changing epidemiology, global trends and implications for outcomes of NAFLD. *J Hepatol*. 2023;79:842–52.
12. Guo Z, Wu D, Mao R, Yao Z, Wu Q, Lv W. Global burden of MAFLD, MAFLD related cirrhosis and MASH related liver cancer from 1990 to 2021. *Sci Rep*. 2025;15:7083.
13. Younossi ZM, Golabi P, Paik JM, Henry A, Van Dongen C, Henry L. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH): a systematic review. *Hepatology*. 2023;77(4):1335–47. <https://doi.org/10.1097/HEP.0000000000000004>.
14. Cusi K, Isaacs S, Barb D, Basu R, Caprio S, Garvey WT, et al. American Association of Clinical Endocrinology Clinical Practice Guideline for the diagnosis and Management of Nonalcoholic Fatty Liver Disease in primary care and endocrinology clinical settings: co-sponsored by the American Association for the Study of Liver Diseases (AASLD). *Endocr Pract*. 2022;28:528–62. <https://doi.org/10.1016/j.eprac.2022.03.010>.
15. Habibullah M, Jemmeh K, Ouda A, Haider MZ, Malki MI, Elzouki AN. Metabolic-associated fatty liver disease: a selective review of pathogenesis, diagnostic approaches, and therapeutic strategies. *Front Med (Lausanne)*. 2024;11. <https://doi.org/10.3389/fmed.2024.1291501>.
16. Kuchay MS, Choudhary NS, Mishra SK. Pathophysiological mechanisms underlying MAFLD. *Diabetes Metab Syndr*. 2020;14(6):1875–87. <https://doi.org/10.1016/j.dsx.2020.09.026>.
17. Manivannan A, Husain S, Shukr B. Wilson disease: uncommon but not to be forgotten. *Cureus*. 2023;15(5):e39247. <https://doi.org/10.7759/cureus.39247>.
18. Chanpong A, Dhawan A. Wilson disease in children and young adults – state of the art. *Saudi J Gastroenterol*. 2022;28(1):21–31. https://doi.org/10.4103/sjg.sjg_501_21.
19. Roy D, Mukherjee A, Chakravarty A. Pitfalls in the diagnosis of Wilson disease. *Curr Neurol Neurosci Rep*. 2025;25(1):40. <https://doi.org/10.1007/s11910-025-01424-8>.
20. Bloomer SA, Brown KE. Iron-induced liver injury: a critical reappraisal. *Int J Mol Sci*. 2019;20(9):2132. <https://doi.org/10.3390/ijms20092132>.
21. Barton JC, Barton JC, Patel N, McLaren GD. Abdominal pain and cirrhosis at diagnosis of hemochromatosis: analysis of 219 referred probands with HFE p.C282Y homozygosity and a literature review. *PLoS One*. 2021;16(12):e0261690. <https://doi.org/10.1371/journal.pone.0261690>.
22. Chalasani NP, Hayashi PH, Bonkovsky HL, Navarro VJ, Lee WM, Fontana RJ. ACG clinical guideline: diagnosis and management of idiosyncratic drug-induced liver injury. *Am J Gastroenterol*. 2021;116(5):878–98. <https://doi.org/10.14309/ajg.0000000000001251>.
23. Garcia-Cortes M, Robles-Diaz M, Stephens C, Ortega-Alonso A, Lucena MI, Andrade RJ. Drug induced liver injury: an update. *Arch Toxicol*. 2020;94(10):3381–407. <https://doi.org/10.1007/s00204-020-02885-1>.
24. Björnsson ES. Review article: drug-induced liver injury in clinical practice. *Aliment Pharmacol Ther*. 2020;51(6):652–62. <https://doi.org/10.1111/apt.15642>.
25. Kumar V, Abbas AK, Aster JC, Deyrup AT, Das A, Robbins, Kumar. Basic pathology. 11th ed. Philadelphia: Elsevier; 2023.
26. Chaudhry H, Sohal A, Iqbal H, Roytman M. Alcohol-related hepatitis: a review article. *World J Gastroenterol*. 2023;29(17):2551–70. <https://doi.org/10.3748/wjg.v29.i17.2551>.
27. Kasper P, Lang S, Steffen HM, Demir M. Management of alcoholic hepatitis: a clinical perspective. *Liver Int*. 2023;43(10):2078–95. <https://doi.org/10.1111/liv.15701>.
28. Heinemann F, Gross P, Zeveleva S, Qian HS, Hill J, Höfer A, Jonigk D, Diehl AM, Abdelmalek M, Lenter MC, Pullen SS, Guarnieri P, Stierstorfer

- B. Deep learning-based quantification of NAFLD/NASH progression in human liver biopsies. *Sci Rep.* 2022;12(1):19236. <https://doi.org/10.1038/s41598-022-23905-3>.
29. Quaglia A. Histopathology of Budd–Chiari Syndrome. *Diagnostics.* 2023;13(15):2487. <https://doi.org/10.3390/diagnostics13152487>.
30. Simpson S, Breshears E, Basavalingu D, Khatri G, Chan S, Fite J, Swanson P, Dighe M. Review of imaging findings in hepatic veno-occlusive disease. *Eur J Radiol.* 2024;177:111526. <https://doi.org/10.1016/j.ejrad.2024.111526>.
31. Buros C, Dave AA, Furlan A. Immediate and late complications after liver transplantation. *Radiol Clin North Am.* 2023;61(5):785–95. <https://doi.org/10.1016/j.rcl.2023.04.002>.
32. Mironova M, Gopalakrishna H, Rodriguez Franco G, Holland SM, Koh C, Kleiner DE, Heller T. Granulomatous liver diseases. *Hepatol Commun.* 2024;8(4):e0392. <https://doi.org/10.1097/HJC9.0000000000000392>.
33. Tanaka A, Ma X, Takahashi A, Vierling JM. Primary biliary cholangitis. *Lancet.* 2024;404(10457):1053–66. [https://doi.org/10.1016/S0140-6736\(24\)01303-5](https://doi.org/10.1016/S0140-6736(24)01303-5).
34. Sarcognato S, Sacchi D, Grillo F, Cazzagon N, Fabris L, Cadamuro M, Cataldo I, Covelli C, Mangia A, Guido M. Autoimmune biliary diseases: primary biliary cholangitis and primary sclerosing cholangitis. *Pathologica.* 2021;113(3):170–84. <https://doi.org/10.32074/1591-951X-245>.
35. Antala S, Taylor SA. Biliary atresia in children: update on disease mechanism, therapies, and patient outcomes. *Clin Liver Dis.* 2022;26(3):341–54. <https://doi.org/10.1016/j.cld.2022.03.001>.
36. Mirza H, Besse W, Somlo S, Weinreb J, Kenney B, Jain D. An update on ductal plate malformations and fibropolycystic diseases of the liver. *Hum Pathol.* 2023;132:102–13. <https://doi.org/10.1016/j.humpath.2022.06.022>.

Neoplasms of the Liver and Bile Ducts

6

Arzu Avcı

6.1 Nodules and Tumours

Hepatic mass lesions include non-neoplastic processes such as focal nodular hyperplasia (FNH), regenerative nodules, abscesses, and other infectious processes. Non-neoplastic mass lesions include benign hepatocellular nodules such as hepatocellular adenoma, malignant primary liver epithelial neoplasms such as hepatocellular carcinoma (HCC) or intrahepatic cholangiocarcinoma, and non-epithelial neoplasms such as angiosarcoma and metastatic tumours [1].

6.2 Non-neoplastic Mass Lesions

6.2.1 Focal Nodular Hyperplasia

Focal nodular hyperplasia is a benign, non-neoplastic lesion most commonly seen in adult women.

6.2.1.1 Pathogenesis

FNH is thought to result from altered blood flow leading to hyperplastic changes in hepatocytes. FNH-like nodules may occur adjacent to other tumours and in vascular conditions such as haemangiomas and Budd-Chiari syndrome.

Multifocal FNH may occur in association with hepatic or extrahepatic haemangiomas, vascular malformations, or (interestingly) brain tumours such as meningiomas and astrocytomas.

6.2.1.2 Morphology

FNH is well-defined, typically lacks a capsule, and has a central stellate scar in up to 80% of cases (Fig. 6.1). Most lesions are 5 cm or smaller in diameter. Microscopically, the lesion consists of fibrous septa extending from the central scar and dividing the hepatic parenchyma into nodules [2]. The fibrous septa and central scar contain thick-walled arteries with intimal and



Fig. 6.1 Focal nodular hyperplasia. Resected specimen showing lobular contours and central stellate scar

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fibromuscular hyperplasia and poorly formed elastic laminae (Figs. 6.2 and 6.3). A marked ductular reaction is frequently present, but interlobular bile ducts are absent. Hepatocytes within the nodules are arranged in plates one to two cells thick; cytological and morphological atypia is absent. Immunohistochemistry for glutamine synthetase (GS), an enzyme normally found in centrilobular hepatocytes, is very useful for diagnosis. In FNH, a highly characteristic ‘map-like pattern’ of strong cytoplasmic GS staining is seen within groups of hepatocytes that anastomose.

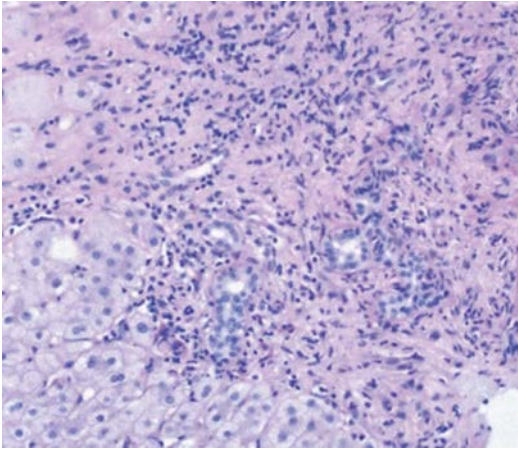


Fig. 6.2 Focal nodular hyperplasia. Appearance of extensive fibrous scarring without interlobular bile ducts, showing thick-walled arteries and ductal reaction

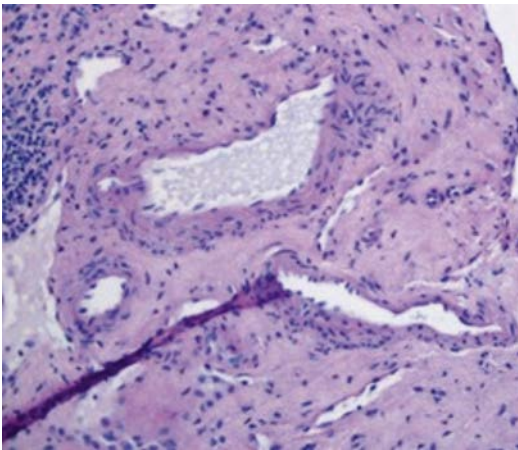


Fig. 6.3 Focal nodular hyperplasia. Fibrous scar appearance

6.2.1.3 Clinical Features

Most cases are asymptomatic and are clinically detected during imaging or surgery. The presence of central scarring is a highly characteristic finding and aids in diagnosis on imaging. FNH is a benign lesion and does not require any treatment. Resection is considered for large and symptomatic lesions.

6.3 Other Non-neoplastic Mass Lesions

Non-neoplastic mass-forming lesions such as abscesses, granulomas, and inflammatory pseudotumours can mimic true neoplasms. Large regenerative nodules may form in vascular lesions such as Budd-Chiari syndrome, haemangioma, and vascular malformations, as well as in non-cirrhotic liver. In some cases, the entire liver becomes nodular without marked fibrosis; this condition is called nodular regenerative hyperplasia (NRH).

NRH can lead to portal hypertension and mimic cirrhosis on imaging. Benign biliary proliferations include bile duct adenoma and biliary hamartoma (von Meyenburg complex). Both are asymptomatic and usually less than 2 cm in size.

These lesions may be mistaken for small nodules or cysts on imaging or for metastatic disease. They are particularly noticeable during abdominal surgery as small subcapsular lesions. In both lesions, random bile ducts are seen within the fibrous stroma, and no atypical cytological findings or morphological features are observed. While the ductal proliferations in bile duct adenoma are round and not dilated, those in biliary hamartoma are dilated and tortuous and often contain bile or secretions in their lumens (Fig. 6.4) [3]. Biliary hamartoma is thought to be a remnant of ductal plate malformation. The recent identification of pathogenic, acquired BRAF mutations in bile duct adenomas has resolved the long-standing debate by demonstrating that it is a benign neoplasm.

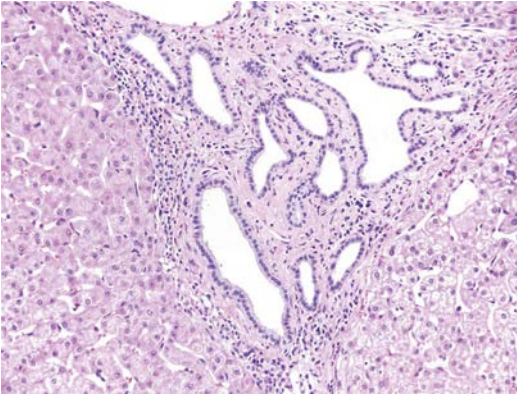


Fig. 6.4 Ductal proliferations in biliary hamartoma

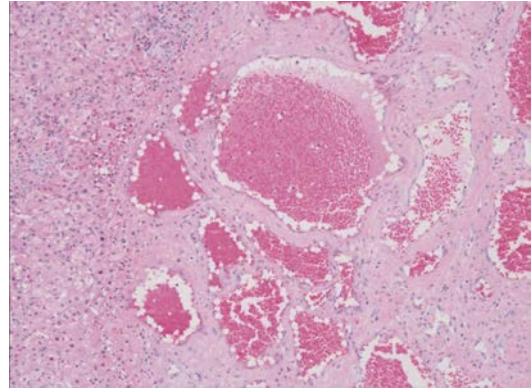


Fig. 6.5 Cavernous haemangioma. Blood-filled vascular channels separated by a dense fibrous stroma

6.3.1 Benign Neoplasms

6.3.1.1 Cavernous Haemangioma

Cavernous haemangioma is the most common benign liver tumour. It is usually subcapsular, less than 2 cm in size, and reddish-blue in colour and appears as a soft nodule. Histologically, the tumour consists of dilated, thin-walled vascular channels (Fig. 6.5). Most are asymptomatic and are detected incidentally on imaging.

6.3.1.2 Hepatocellular Adenoma

Hepatocellular adenoma is a benign neoplasm typically seen in young women and associated with oral contraceptive and anabolic steroid use. Its incidence has increased over the past decade, possibly related to obesity and metabolic syndrome. Multiple hepatocellular adenomas (ten or more) are termed hepatic adenomatosis and can occur both in familial and sporadic forms.

6.3.1.3 Pathogenesis

Three molecular subtypes have been identified in adenomas, each associated with distinct clinico-pathological features and risk of progression to hepatocellular carcinoma.

- *Hepatocyte nuclear factor 1-alpha (HNF1α)-inactivated hepatocellular adenoma*: By definition, all of these tumours have loss-of-function mutations in the HNF1-α gene, which encodes a transcription factor that regulates many genes in hepatocytes and pancreatic

islets. Heterozygous germline mutations are responsible for young-onset diabetes of autosomal dominant maturity, type 3, and are also associated with 10% of HNF1α-inactivated hepatocellular adenomas. This subtype accounts for 40–50% of cases, has a strong female predilection, and carries a minimal risk of transformation to hepatocellular carcinoma.

- *Inflammatory hepatocellular adenoma*: This subtype arises from acquired activating mutations in gp130, an accessory receptor for interleukin-6, leading to structural activation of the Janus kinase/signal transducers and activators of transcription (JAK-STAT) signalling pathway. This subtype accounts for 40–50% of cases, is more common in women, and is associated with obesity and metabolic syndrome. β-Catenin-activating mutations are present in 10% of inflammatory hepatocellular adenomas, and these tumours have a higher risk of malignant transformation.
- *β-Catenin-activated hepatocellular adenoma*: Defined by activating mutations in the β-catenin gene (CTNNB1) or other components of the Wnt pathway (such as adenomatous polyposis coli [APC]). These tumours are at high risk of malignant transformation into hepatocellular carcinoma and are associated with oral contraceptive and anabolic steroid use. Approximately 40% occur in males.

6.3.1.4 Morphology

Hepatocellular adenomas appear as discrete masses composed of hepatocytes arranged in plates one to two cells thick, sometimes containing associated haemorrhage (Figs. 6.6 and 6.7). Large arteries are present within a small amount of fibrous stroma, while interlobular bile ducts and normal portal channels are absent. Tumours with HNF1 α mutations typically contain marked fat in the lesion hepatocytes and lack liver fatty acid-binding protein (LFABP), a protein regulated by HNF1 α , as demonstrated by immunohistochemistry (Fig. 6.8). Tumours with β -catenin mutations generally exhibit atypical cytological

or morphological features, and areas showing hepatocellular carcinoma transformation may be present. Due to β -catenin mutations or other mutations activating Wnt signalling, strong nuclear expression of β -catenin is seen in at least some tumour cells. Inflammatory tumours typically show sinusoidal dilation and may have features mimicking focal nodular hyperplasia, such as fibrous septa and ductal reaction [4]. Due to hyperactive JAK-STAT signalling, these tumours overexpress acute-phase reactants such as C-reactive protein and serum amyloid A.

6.3.1.5 Clinical Features

Hepatocellular adenomas may be incidentally detected by imaging or may be noted due to symptoms related to abdominal pain or haemorrhagic necrosis. Rupture of hepatocellular adenomas can cause massive abdominal haemorrhage and may require surgery. Resection is recommended for tumours activated by β -catenin, as well as tumours 5 cm or larger, due to the risk of haemorrhage and malignant transformation. Close follow-up and discontinuation of exposure to oral contraceptives or anabolic steroids may be sufficient for smaller tumours without β -catenin activation.

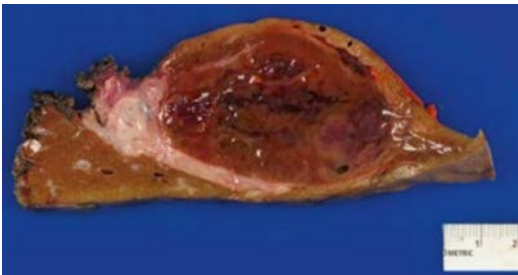


Fig. 6.6 Hepatocellular adenomas, sometimes containing haemorrhage, as separate masses

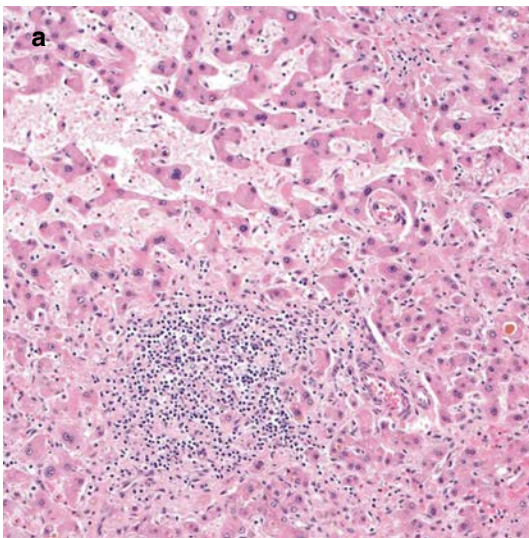
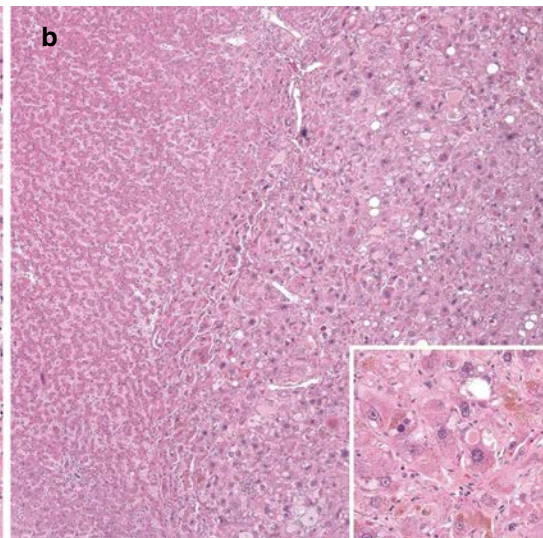


Fig. 6.7 (a) Hepatocyte cords with marked sinusoidal dilatation alongside a focus of minimal atypia, intracytoplasmic bile accumulation, and predominantly mononu-



clear inflammatory cells characteristic of hepatocellular adenoma. **(b)** Features of hepatocellular adenoma

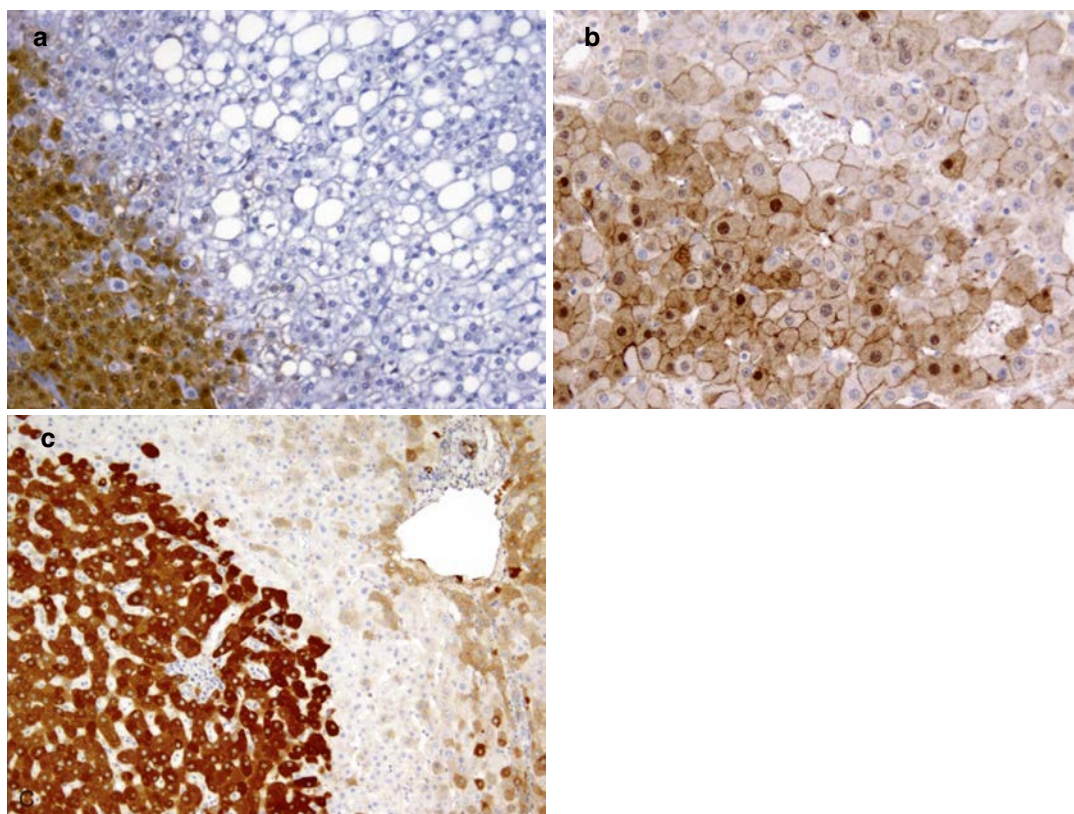


Fig. 6.8 Molecular subtypes of hepatocyte adenoma. (a) HNF1 α -inactive hepatocellular adenoma. LFABP, whose expression is dependent on HNF1 α , is absent in the tumour by immunostains but present in adjacent normal hepatocytes (bottom left). (b) β -Catenin-activated hepatocellular adenoma. Some neoplastic hepatocytes lack

nuclear immunostaining (compared to other tumour hepatocytes that retain normal membranous staining). (c) Inflammatory hepatocyte adenoma. Neoplastic hepatocytes show a marked increase in C-reactive protein compared to the adjacent hepatic parenchyma, where expression is highly variable and low

6.3.2 Primary Malignant Neoplasms

Malignant tumours in the liver may be primary or metastatic. The most common primary epithelial tumours are hepatocellular carcinoma and intrahepatic cholangiocarcinoma. Hepatoblastoma is a rare hepatocellular tumour seen in the paediatric age group. Non-epithelial tumours such as angiosarcoma are extremely rare [5].

6.3.2.1 Hepatoblastoma

Hepatoblastoma is the most common liver tumour in early childhood. It is rarely seen in children over the age of 3, and its overall incidence is increasing. Activation of the Wnt signaling pathway is a characteristic feature of

hepatoblastoma and leads to increased expression of Wnt target genes, such as nuclear β -catenin and GS, in almost all cases. These tumours are associated with familial adenomatous polyposis (caused by germline loss-of-function mutations in APC) and various syndromes, including Beckwith-Wiedemann syndrome. The latter is caused by abnormal epigenetic repression of a region of chromosome 11, excessive expression of insulin-like growth factor-2, and loss of expression of CDKN1C, a tumour suppressor gene encoding the cyclin-dependent kinase inhibitor p57.

6.3.2.2 Morphology

Hepatoblastoma has various histological subtypes, which can be broadly grouped into two

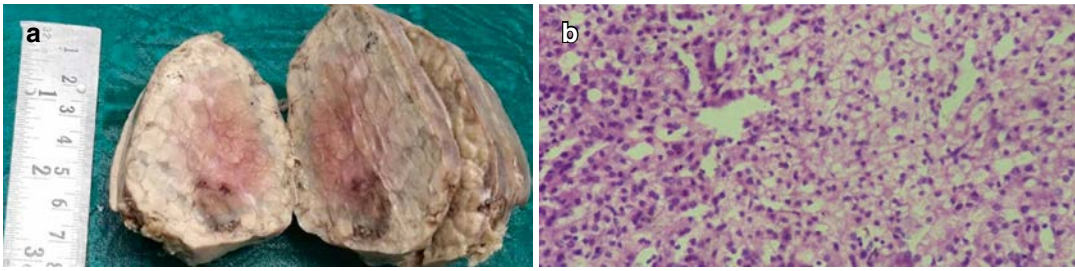


Fig. 6.9 Hepatoblastoma: (a) Macroscopically nodular tumour mass. (b) Type composed of small polygonal foetal cells

categories: (1) the epithelial type, consisting of small polygonal foetal cells or smaller embryonic cells forming trabecular, acinar, tubular, or papillary structures, vaguely resembling the developing liver (Fig. 6.9), and a mixed epithelial and mesenchymal type (Fig. 6.10) that may contain foci of additional mesenchymal differentiation consisting of primitive mesenchyme, osteoid, cartilage, or striated muscle.

6.3.2.3 Clinical Features

Hepatoblastoma usually draws clinical attention due to abdominal distension in an asymptomatic infant or child. Symptoms related to liver dysfunction (jaundice, pruritus) are seen in a subset of patients, and approximately 20% of tumours have metastasised to the lungs at the time of diagnosis. The tumour is treated with surgical resection and chemotherapy, which improves outcomes. The overall 5-year survival rate is approximately 80%.

6.3.3 Hepatocellular Carcinoma

HCC accounts for approximately 5.4% of all cancers worldwide and is one of the most common cancers in geographical regions with high rates of hepatitis B infection. Over 85% of cases occur in Asian countries (southeast China, Korea, Taiwan) and sub-Saharan African countries where chronic hepatitis B virus (HBV) infection is prevalent. In these regions, the highest incidence of HCC is seen in young adults aged 20 to 40 who acquired the HBV through maternal-fetal transmission. Due to hepatitis B vaccination, HCC incidence is

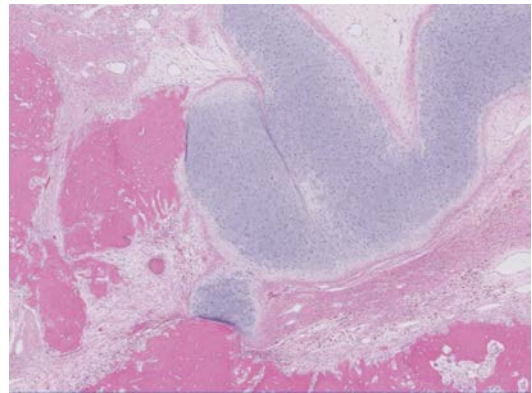


Fig. 6.10 Mixed epithelial and mesenchymal type containing foci of additional mesenchymal differentiation that may consist of osteoid, cartilage, or striated muscle

declining in Asia, but at the same time, incidence is increasing in Western countries due to the rise in hepatitis C infection and metabolic syndrome rates. For reasons that are unclear, there is a marked male predominance at a ratio of 8:1 in high-incidence areas.

6.3.3.1 Pathogenesis

While most HCCs occur in the context of chronic liver disease with cirrhosis, 15 to 20% arise in non-cirrhotic livers (Fig. 6.11a). The most common underlying diseases are chronic viral hepatitis, metabolic diseases such as hereditary haemochromatosis and α 1-antitrypsin deficiency, and alcoholic liver disease. Non-alcoholic fatty liver disease also increases the risk of HCC, even in the absence of cirrhosis. Although the details are not clearly defined, it is believed that the chronic damage, inflammation, and hepatocyte regeneration seen in these diseases contribute to

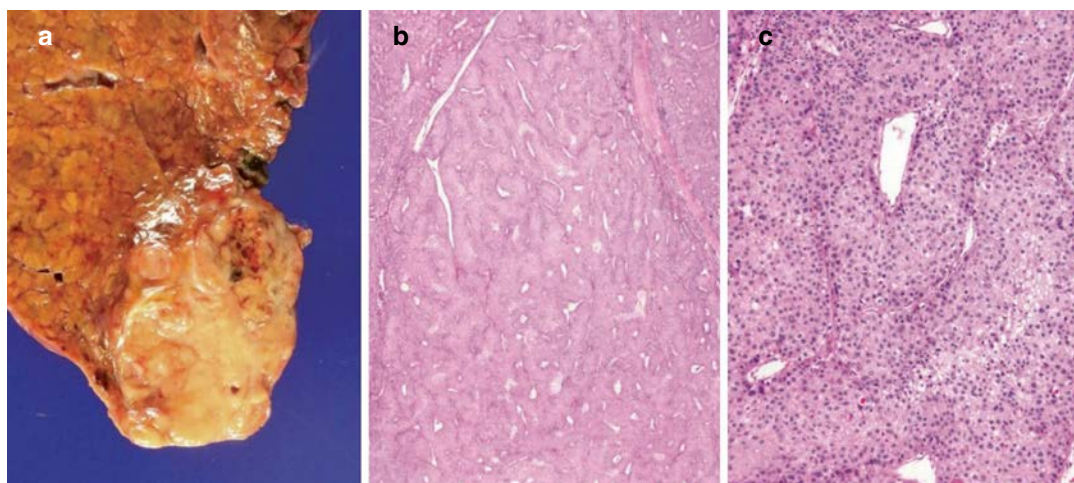


Fig. 6.11 Hepatocellular carcinoma. (a) Unifocal neoplasm. (b) Abnormal morphology, including large pseudoacinar spaces (malformed, dilated bile canaliculi) and thickened hepatocyte trabeculae, composed of malignant hepatocytes

the acquisition of driver mutations that lead to HCC development. Part of the risk in Africa and Asia appears to be related to the contamination of crops with aflatoxin, a mycotoxin produced by *Aspergillus* species that acts synergistically with alcohol and hepatitis B. The risk of HCC is slightly lower in cirrhosis due to other aetiologies, such as Wilson's disease and chronic biliary diseases, but it is still above the population average.

As with other cancers, HCC is associated with complementary driver mutation processes that lead to the acquisition of cancerous characteristics [6]. The most common are activating mutations in the β -catenin gene (40% of tumours), mutations regulating telomerase activity in the telomerase reverse transcriptase gene promoter (50–60% of tumours), and inactivating mutations in TP53 (up to 60% of tumours). Fibrolamellar HCC, an unusual histological subtype frequently seen in adolescents and young adults in the absence of pre-existing liver disease, is strongly associated with a fusion gene that leads to abnormal activity of protein kinase A, an enzyme involved in a cAMP-regulated signalling pathway.

6.3.3.2 Morphology

Various precursor lesions have been identified for HCC. As discussed earlier, HCC in a non-

cirrhotic liver may arise from hepatocellular adenoma, particularly those with β -catenin-activating mutations. In chronic liver disease, the earliest morphological changes, which appear to be associated with the presence of 'at-risk' hepatocytes, are termed 'large cell change' and 'small cell change' (Fig. 6.11b, c). Large cell change refers to hepatocytes that are larger than normal and often have enlarged, multiple, pleomorphic nuclei without an increase in the nuclear-to-cytoplasmic ratio (Fig. 6.12a). In small cell change, hepatocytes have a high nuclear-to-cytoplasmic ratio and mild nuclear hyperchromasia and/or pleomorphism (Fig. 6.12b). Nodular lesions called dysplastic nodules in a cirrhotic liver, which are usually associated with small cell change, are more concerning. Dysplastic nodules differ from neighbouring cirrhotic nodules in terms of size, colour, and vascularisation, show varying degrees of dysplasia, and possess clonal aberrations associated with fully developed HCC. Small areas of HCC may sometimes be seen in high-grade dysplastic nodules ('nodule-within-nodule appearance') (Fig. 6.13a, b).

HCC may form a single mass or multiple separate masses, or it may diffusely infiltrate the liver. They may be pale and yellow due to fatty degeneration or green due to cholestasis. Tumours larger than 2 cm are more likely to be associated with vascular invasion and intrahepatic metastasis.

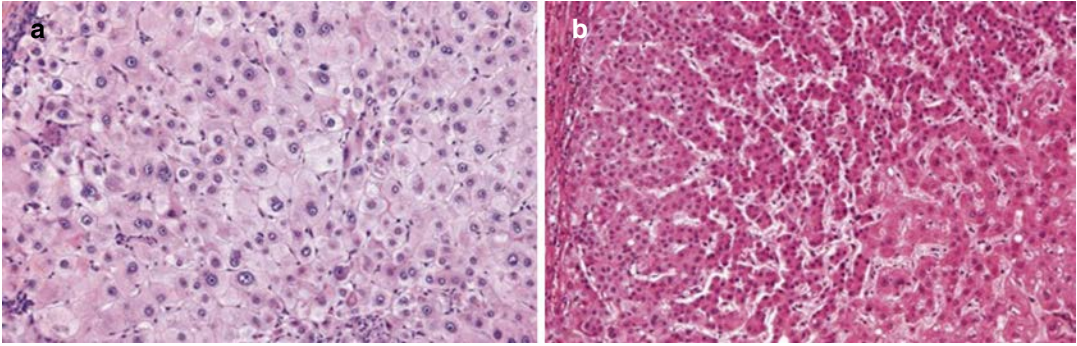


Fig. 6.12 Premalignant changes in hepatocytes. **(a)** Large cell change. Large hepatocytes, often with atypical nuclei, are scattered among normal-sized hepatocytes with round, typical nuclei. **(b)** Small cell change.

Abnormal cells have a high nuclear-cytoplasmic ratio and are separated by thickened plates. Normal-appearing hepatocytes are in the lower right corner

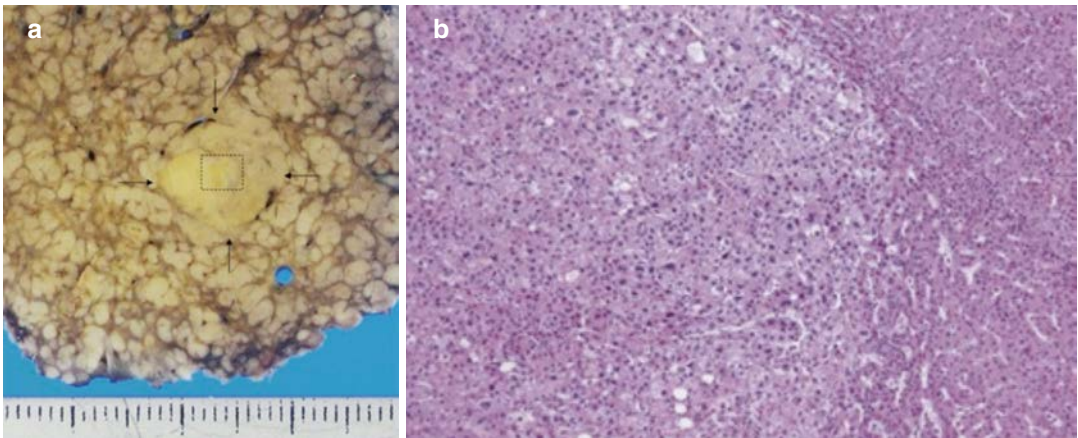


Fig. 6.13 **(a)** Hepatitis C-associated cirrhosis containing a distinctly large nodule (arrows). The nodule suggests a cancer developing within the nodule. **(b)** Histologically,

the area shown in the box in A demonstrates a well-differentiated HCC (right side) and a moderately differentiated HCC subnodule within it (centre, left)

ses. Vascular invasion extending to the portal vein, inferior vena cava, and even the right side of the heart may be observed [7].

Microscopically, well- and moderately differentiated HCC consists of cells resembling normal hepatocytes, while poorly differentiated tumours show marked cytological atypia. Tumour cells grow in thick layers or trabeculae, pseudoglandular structures containing bile plugs, or sheets. The fibrolamellar variant exhibits a characteristic triad: large polygonal cells with granular (oncocytic) cytoplasm rich in

mitochondria, vesicular nuclei with prominent nucleoli, and parallel lamellae of dense collagen bundles (Fig. 6.14a, b).

6.3.3.3 Clinical Features

The clinical manifestations of HCC are nonspecific and include abdominal pain, fatigue, weakness, weight loss, and hepatomegaly. Features of the underlying chronic liver disease may be present. Elevated serum α -fetoprotein levels are a common finding in advanced disease, but are not sensitive as a screening test for early tumours and

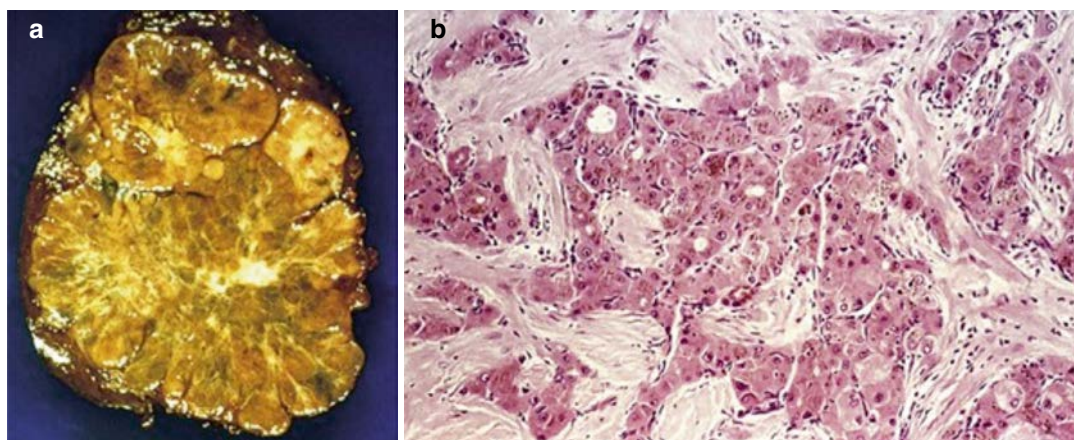


Fig. 6.14 Fibrolamellar carcinoma. (a) Resected specimen showing a well-defined nodule. (b) Microscopic appearance showing clusters and cords of malignant-appearing, oncocytic hepatocytes separated by dense collagen bundles

are not associated with the fibrolamellar variant. Ultrasonography is used to screen high-risk patients, such as those with cirrhosis. Computed tomography and contrast-enhanced magnetic resonance imaging provide highly characteristic findings. Early tumour enhancement in the arterial phase followed by rapid venous washout, due to contrast uptake, is considered diagnostic for HCC [8].

Surgical resection is the preferred treatment for tumours in non-cirrhotic livers and in cirrhotic livers with adequate function, when feasible. Liver transplantation is considered for HCC in advanced cirrhosis. For unresectable tumours or those not meeting the transplantation criteria, tumour ablation using alcohol or radiofrequency waves under image guidance may be performed. Haematogenous metastases, particularly to the lungs, tend to occur in the later stages of the disease. Lymph node metastases are seen in <5% of cases.

Overall outcomes in HCC are poor due to the underlying liver disease and the intrinsic resistance of HCC to conventional chemotherapy. The overall 5-year survival rate is 30% for tumours confined to the liver but only 5% to 10% for cases with extrahepatic spread. Outcomes are better for the fibrolamellar variant, with 40% of patients surviving 10 years or longer. This is largely

because, in the absence of underlying liver disease, extensive surgical resection is possible due to the regenerative capacity of the remaining liver.

6.3.4 Malignant Biliary Tumours

Adenocarcinomas arising from the intrahepatic biliary tree are called ‘intrahepatic cholangiocarcinoma’, while similar tumours arising from the extrahepatic bile ducts are called biliary adenocarcinoma. Intrahepatic cholangiocarcinoma is the second most common primary malignant tumour of the liver after HCC. Its incidence is increasing in the United States. It accounts for 7.6% of cancer deaths worldwide and 3% of cancer deaths in the United States. It is highly prevalent in Southeast Asian countries such as Thailand, Laos, and Cambodia, where liver fluke infestation is endemic.

6.3.4.1 Pathogenesis

Developmental disorders such as fibro-polycystic liver disease and primary sclerosing cholangitis, invasion by liver flukes (particularly *Opisthorchis* and *Clonorchis* species), and chronic inflammatory conditions affecting the bile ducts, such as hepatolithiasis, are risk factors for biliary tract

neoplasms. Chronic liver diseases that predispose to HCC, such as hepatitis B, hepatitis C, and non-alcoholic fatty liver disease, also increase the risk of intrahepatic cholangiocarcinoma.

As in HCC, chronic damage, inflammation, and regeneration of the biliary epithelium in these conditions may predispose to the acquisition of driver mutations leading to cancer. Driver mutations in intrahepatic cholangiocarcinoma and extrahepatic biliary adenocarcinoma overlap only partially.

KRAS mutations are common in both tumours. In addition, there are distinctive driver mutations in IDH1 and IDH2 (isocitrate dehydrogenase), which produce ‘oncometabolites’, and in chromatin-modifying genes such as BAP1 and PBRM1 in subgroups of intrahepatic cholangiocarcinoma. Fusion genes involving fibroblast

growth factor receptor 2 are also common. In contrast, in addition to KRAS mutations, extrahepatic biliary adenocarcinomas are more likely to have TP53 and SMAD4 mutations, genetic features similar to those of pancreatic adenocarcinoma [9].

6.3.4.2 Morphology

Intrahepatic cholangiocarcinoma is usually seen in non-cirrhotic liver (Fig. 6.15a) and typically forms a firm grey-white mass. Extrahepatic biliary adenocarcinomas include perihilar tumours located where the right and left hepatic ducts join, known as Klatskin tumours. These tumours account for 60 to 70% of extrahepatic biliary adenocarcinomas, while the remaining 30 to 40% involve the common bile duct. Extrahepatic biliary adenocarcinomas are usually small at the

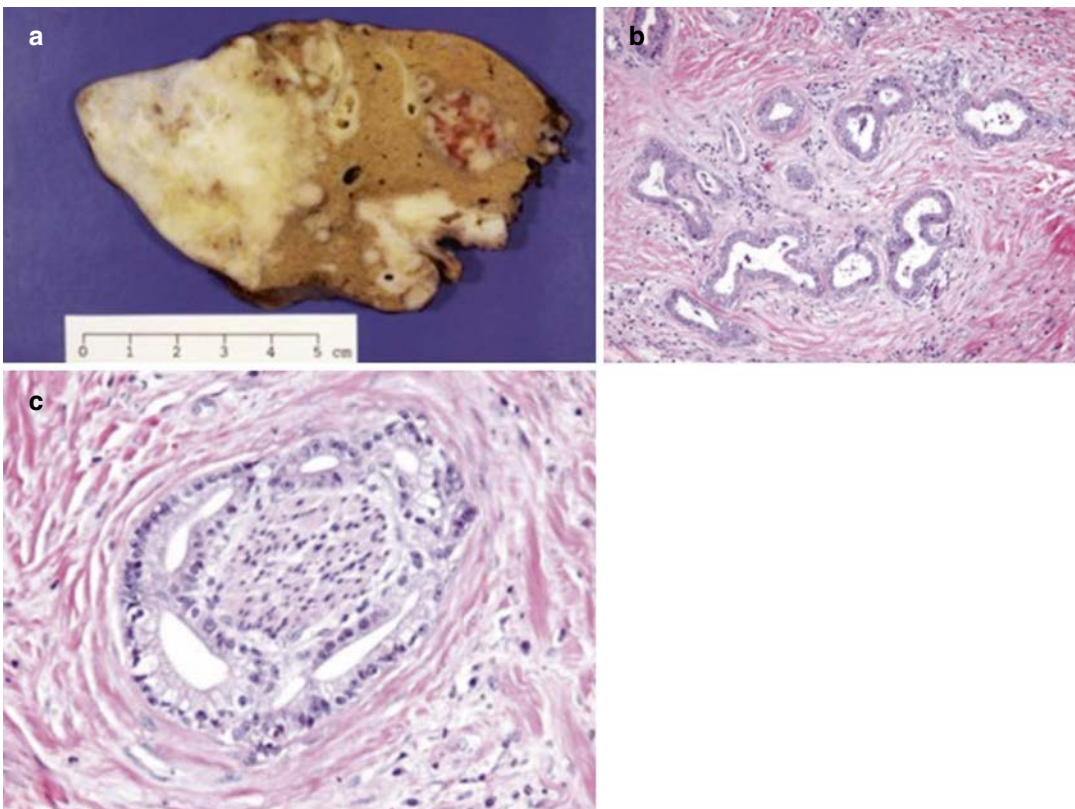


Fig. 6.15 Cholangiocarcinoma. (a) Multifocal cholangiocarcinoma in the liver of a patient infested with the liver fluke *Clonorchis sinensis*. (b) Invasive malignant

foci within reactive, sclerotic stroma. (c) Perineural invasion by malignant foci, forming a wreath-like pattern around a central, compressed nerve

time of diagnosis because they are detected early due to their obstructive nature. These tumours may form a hard nodule in the bile duct wall, be diffusely infiltrative, or form papillary lesions.

Microscopically, both intrahepatic and extrahepatic tumours, exhibit adenocarcinoma features. Most are well to moderately differentiated and are organised into glandular/tubular structures composed of malignant epithelial cells embedded in abundant fibrous stroma (Fig. 6.15b). Lymphovascular and perineural invasion (Fig. 6.15c) is common. These tumours are thought to arise from premalignant lesions, often referred to as biliary intraepithelial neoplasia. Other less common precursor lesions include mucinous cystic neoplasms and intraductal papillary neoplasms.

6.3.4.3 Clinical Features

Intrahepatic cholangiocarcinoma may be incidentally detected on imaging or present with cholestatic features or a symptomatic liver mass, whereas extrahepatic adenocarcinoma typically presents with symptoms related to biliary obstruction. Negative margins at tumour resection and absence of lymph node involvement are favourable factors. Lymph node metastasis is present in 50 to 60% of patients at presentation. Adjuvant chemotherapy is usually given after resection, but tumour responses are often transient. Recurrences are common, and the overall prognosis is poor, with a 5-year survival rate after surgical resection of 20 to 40%.

6.4 Other Primary Hepatic Malignant Tumours

A number of other cancers can arise in the liver. Among the most common or pathologically interesting are the following:

- Combined hepatocellular-cholangiocarcinoma consists of cells resembling both HCC and intrahepatic cholangiocarcinoma. These tumours share the same risk factors as HCC.
- Angiosarcoma is a malignant vascular tumour historically associated with exposure to vinyl

chloride, arsenic, or the imaging agent Thorotrast. This tumour has become rare with the decline in exposure to these agents.

- Epithelioid haemangiopericytoma is another vascular tumour with moderate malignant potential and a slightly better prognosis than angiosarcoma, which is almost invariably fatal.
- Primary hepatic lymphoma is a rare type of liver malignancy. Its most common subtype is diffuse large B-cell lymphoma, a form of non-Hodgkin lymphoma that frequently arises in extranodal sites. Another rare subtype is hepatosplenic T-cell lymphoma; it most commonly occurs in young adult males and tends to grow in the sinusoids of the liver, spleen, and bone marrow.

6.5 Metastasis

Involvement of the liver by metastatic malignancy is much more common than primary hepatic neoplasia. Although the most common primary sources are the colon, breast, lung, and pancreas, almost any tumour can spread to the liver. Typically, there are numerous nodular metastases, often causing marked hepatomegaly and replacing most of the normal liver parenchyma. The liver weight may exceed several kilograms. Metastases may also present as a single nodule, which is then resectable surgically. The extent of metastatic involvement is always surprising when there are no clinical or laboratory findings of liver failure; hepatomegaly is usually the only sign. However, jaundice and other evidence of liver dysfunction inevitably emerge with massive destruction of hepatocytes or direct obstruction of the main bile ducts.

6.6 Liver Tumours

- The liver is the most common site for metastatic cancer originating from primary tumours of the colon, lung, and breast.
- Hepatocellular adenomas are benign tumours of neoplastic hepatocytes and can be subclassified based on different driver mutation sets.

- HCC is the most common primary hepatic malignancy and frequently arises in a cirrhotic environment associated with chronic liver diseases such as chronic hepatitis B and C, autoimmune hepatitis, alcoholic/non-alcoholic fatty liver disease, and haemochromatosis.
- Intrahepatic cholangiocarcinoma and extrahepatic biliary adenocarcinoma exhibit similar histological features and share risk factors such as primary sclerosing cholangitis and infestation by liver flukes such as *Opisthorchis* and *Clonorchis*. The prognosis for these tumours is poor.

References

1. Sempoux C, Chang C, Gouw A, et al. Benign hepatocellular nodules: what have we learned using the patho-molecular classification. *Clin Res Hepatol Gastroenterol*. 2013;37(4):322–7. [From the team largely responsible for the new molecular subclassifications of hepatocellular adenomas]
2. Koyama Y, Brenner DA. Liver inflammation and fibrosis. *J Clin Invest*. 2017;127(1):55–64. <https://doi.org/10.1172/JCI88881>. Epub 2017 Jan 3; PubMed PMID 28045404 PubMed Central PMCID: PMC5199698; Review; [A recent review of the complex interplay between the immune system and hepatic fibrosis]
3. Desmet VJ. Congenital diseases of intrahepatic bile ducts: variations on the theme “ductal plate malformation”. *Hepatology*. 1992;16:1069. [A classic paper in liver pathology]
4. Choi WT, Kakar S. Atypical hepatocellular neoplasms: review of clinical, morphologic, immunohistochemical, molecular, and cytogenetic features. *Adv Anat Pathol*. 2018;25(4):254–62. [Review of pathologic and molecular aspects of adenomas and atypical tumours with borderline HCC features]
5. WHO Classification of Tumours Editorial Board. Digestive system tumours. Lyon: International Agency for Research on Cancer; 2019. [WHO classification of tumours series, ed 5, vol 1]
6. International Consensus Group for Hepatocellular Neoplasia. Pathologic diagnosis of early hepatocellular carcinoma. *Hepatology*. 2009;49:658. [A good example of how change comes to medicine, individual efforts combining, over years, to achieve a new consensus]
7. Massarweh NN, El-Serag HB. Epidemiology of hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *Cancer Control*. 2017;24(3):1073274817729245. [Review of epidemiology and trends in hepatocellular carcinoma and cholangiocarcinoma]
8. Vogel A, Cervantes A, Chau I, et al. ESMO Guidelines Committee: hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;29(Suppl 4):iv238–55. [Review of guidelines for diagnosis and management of HCC]
9. Rizvi S, Khan SA, Hallemeier CL, et al. Cholangiocarcinoma – evolving concepts and therapeutic strategies. *Nat Rev Clin Oncol*. 2018;15(2):95–111. [Review of epidemiology, pathogenesis, and management of cholangiocarcinoma]

Pathology of the Pancreas

7

Anıl Aysal Ağalar and Özgül Sağol

7.1 Genetic and Congenital Structural Malformations of the Pancreas

The pancreas develops from the ventral and dorsal buds of the foregut endoderm. Proper signaling, fusion, and differentiation depend on a tightly regulated network of transcription factors (pancreatic and duodenal homeobox 1 (PDX1), pancreas-associated transcription factor 1A (PTF1A), hepatocyte nuclear factor 1 β (HNF1B), GATA binding protein 6 (GATA6), SRY-box transcription factor 9 (SOX9)) and developmental pathways (Notch, Hedgehog, Wnt). Germline mutations or disruptions in these factors can result in congenital structural malformations of the pancreas. These malformations differ from acquired or neoplastic conditions in that they are developmental in origin, often syndromic, and sometimes incompatible with life [1, 2].

7.1.1 Pancreatic Agenesis and Hypoplasia

- Complete agenesis: This extremely rare anomaly is the absence of the pancreas, which is usually lethal in the neonatal period.
- Partial agenesis/hypoplasia: This anomaly is the deficiency of either dorsal or ventral components, which is variably compatible with life. Dorsal pancreatic agenesis is the absence of body and tail of the pancreas due to regression or failure of dorsal bud development.

Several molecular alterations are related to pancreatic agenesis:

- PDX1 mutations: Biallelic mutations cause complete agenesis [1].
- PTF1A mutations: Exocrine pancreas agenesis and neonatal diabetes [4].
- HNF1B mutations: Pancreatic hypoplasia and maturity-onset diabetes of the young type 5 (MODY5) [2].
- GATA6 mutations: Pancreatic agenesis or hypoplasia, often with congenital heart disease [1].
- HNF1B mutations are the most frequent genetic cause of dorsal pancreatic agenesis [3]. Dorsal pancreatic genesis is also linked with MODY5 and renal anomalies [4].

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7.1.2 Annular Pancreas

The annular pancreas is a congenital defect in which the pancreatic tissue encircles the duodenum, resulting in intestinal obstruction. This malformation is typically caused by improper rotation of the ventral pancreatic bud during embryological development. Reports of familial cases indicate a possible hereditary component. Moreover, overexpression of the **TM4SF3** gene has been implicated in the pathogenesis of this anomaly [5].

7.1.3 Pancreas Divisum

Pancreas divisum, which is the most common developmental anomaly of the pancreas, arises when the dorsal and ventral pancreatic ducts fail to fuse during embryonic development. This condition typically occurs sporadically and may increase the risk for recurrent pancreatitis [6].

7.1.4 Ectopic Pancreas

This anomaly is the presence of the pancreas outside its normal location, without vascular or ductal connection to the native gland. It usually occurs in the stomach, duodenum, and proximal jejunum, although rare sites such as the gallbladder, mesentery, and spleen have also been reported [7]. Most cases are asymptomatic and discovered incidentally [8]. Complications including pancreatitis, pseudocyst formation, and, in rare circumstances, malignant transformation may occur [9].

7.1.5 Syndromic Disorders with Pancreatic Malformations

- Johanson-Blizzard syndrome: Ubiquitin protein ligase E3 component N-recognin 1 (UBR1) mutation, exocrine aplasia, nasal hypoplasia, and deafness [10]

- Renal-hepatic-pancreatic dysplasia (Ivemark II): Nephronophthisis 3 (NPHP3) mutations, pancreatic fibrosis, and renal/hepatic malformations [11]
- Peutz-Jeghers syndrome: serine/threonine kinase 11 (STK11) mutations and predisposition to pancreatic abnormalities [2]
- Cystic fibrosis: Cystic fibrosis transmembrane conductance regulator (CFTR) mutations, ductal maldevelopment, hypoplasia, and fibrosis [4]

7.2 Pancreatitis

Pancreatitis encompasses a heterogeneous group of inflammatory disorders of the pancreas, broadly divided into acute pancreatitis (AP) and chronic pancreatitis (CP). AP is typically a self-limiting inflammatory process, while CP is characterized by irreversible parenchymal fibrosis, exocrine and endocrine insufficiency, and increased risk of malignancy. An important immune-mediated subtype of CP is autoimmune pancreatitis (AIP), particularly type 1 AIP, which is now recognized as the pancreatic manifestation of immunoglobulin G4 (IgG4)-related disease (IgG4-RD).

The pathology of pancreatitis ranges from reversible acute inflammatory injury to progressive fibrosing chronic disease. Autoimmune pancreatitis is a unique form, often mimicking pancreatic cancer clinically and radiologically, but is distinguished by its immunopathology and responsiveness to steroids. Recognizing IgG4-related disease as a systemic fibroinflammatory condition has reshaped our understanding of pancreatic pathology and highlights the importance of clinicopathologic correlation for accurate diagnosis and optimal management.

7.2.1 Acute Pancreatitis

AP is an acute inflammatory process that occurs as a result of self-digestion of the pancreas due to premature activation of digestive enzymes. The central event is inappropriate activation of tryp-

sinogen to trypsin, which then activates other digestive proenzymes, leading to widespread tissue necrosis and systemic inflammation [12, 13].

The disease arises from the interplay of three fundamental mechanisms: duct obstruction, acinar cell injury, and defective intracellular transport.

Gallstones or biliary sludge can obstruct the ampulla of Vater, increasing ductal pressure and causing reflux of the bile into the pancreatic ducts. This in turn injures acinar cells and precipitates premature enzyme activation.

Direct acinar cell injury occurs through alcohol, drugs, ischemia, trauma, or infection, which release proenzymes into the cytoplasm. Colocalization of lysosomal hydrolases and zymogen granules results in cathepsin B-mediated activation of trypsinogen. Mitochondrial dysfunction and adenosine triphosphate depletion then accelerate necrosis. Defective intracellular trafficking further contributes, as proenzymes are inappropriately directed into lysosomal compartments instead of secretory pathways, promoting premature activation. Once trypsin is generated, a cascade follows: proelastase is activated to elastase, causing vascular wall destruction and hemorrhage; phospholipase A2 is activated, producing fat necrosis; and kallikrein activation leads to bradykinin release and coagulation disturbances. The release of damage-associated molecular patterns from necrotic cells recruits neutrophils and macrophages, which amplify the response through proinflammatory cytokines. This cas-

cade produces interstitial edema, fat necrosis, hemorrhage, and in severe cases necrotizing pancreatitis.

If unchecked, systemic inflammatory response syndrome (SIRS), acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), and multiorgan failure may develop [12].

Grossly, in edematous interstitial pancreatitis, the pancreas is swollen, soft, and hyperemic with expansion of interlobular septa by edema fluid. The peripancreatic fat shows small, chalky white deposits due to enzymatic fat necrosis (Fig. 7.1a).

In necrotizing or hemorrhagic pancreatitis, the gland appears mottled red-black because of hemorrhage and yellow-white because of fat necrosis. Areas of necrosis may extend into the mesenteric and retroperitoneal fat, resulting in widespread saponification. Blood vessels frequently show thrombosis or wall necrosis, with large hemorrhagic collections accumulating in the lesser sac [12, 13]. If patients survive long enough, early pseudocyst precursors may form as liquefied necrotic areas lacking epithelial lining [14].

Microscopically, early AP shows interstitial edema, vascular congestion, and neutrophilic infiltrates. Acinar necrosis is evident, with eosinophilic ghost acini lacking nuclei. Necrotic adipocytes surrounded by basophilic calcium deposits (fat saponification) are characteristic. Hemorrhage is frequent in necrotizing cases, reflecting elastase-mediated vascular wall destruction. In advanced necrotizing pancreatitis,



Fig. 7.1 Pancreatitis. **(a)** A case of acute pancreatitis; grossly invisible fat necrosis areas. **(b)** An example of chronic pancreatitis; grossly, pseudocysts and pancreatolithiasis in the background of fibrotic pancreas can be seen

diffuse coagulative necrosis replaces much of the parenchyma. During healing, necrotic zones are replaced by granulation tissue and fibrosis, which may progress to pseudocyst formation [12].

7.2.2 Chronic Pancreatitis

CP is defined as a long-standing, irreversible fibro-inflammatory disorder of the pancreas characterized by progressive loss of acinar tissue, variable involvement of islets, and distortion of the ductal system [12]. The disease often arises as a consequence of recurrent AP, where repeated cycles of necrosis and inflammation heal by fibrosis, ultimately distorting normal architecture. Pancreatic stellate cells (PSCs) play a pivotal role in this process. Normally quiescent, they are activated by cytokines such as transforming growth factor (TGF- β), platelet-derived growth factor, tumor necrosis factor- α , and interleukin-1, as well as by oxidative stress from alcohol and smoking. Once activated, PSCs synthesize collagen, fibronectin, and laminin, leading to progressive fibrosis [15].

Alcohol contributes through multiple mechanisms: it generates toxic metabolites such as acetaldehyde and reactive oxygen species, sensitizes acinar cells to cholecystokinin-mediated stimulation, increases the protein content of pancreatic secretions, and promotes formation of protein plugs that obstruct ducts.

Genetic mutations also predispose to CP. Serine protease 1 (PRSS1) gain-of-function mutations make trypsinogen resistant to degradation, while Serine protease inhibitor kazal-type 1 (SPINK1) loss-of-function mutations remove the inhibitory control on trypsin, allowing uncontrolled enzymatic activity. CFTR mutations impair bicarbonate secretion, favoring ductal obstruction by protein-rich plugs [12]. Autoimmune mechanisms are also implicated, especially in type 1 autoimmune pancreatitis, where IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis contribute to the pathology [14, 16].

The final common pathway of CP is extensive fibrosis, loss of acinar cells, ductal distortion, and occasional pseudocyst formation (Fig. 7.1b). These

changes result in exocrine insufficiency with malabsorption and steatorrhea, endocrine insufficiency with secondary diabetes mellitus, and an increased risk of developing pancreatic carcinoma.

7.2.2.1 Autoimmune Pancreatitis

Autoimmune pancreatitis is a distinct fibroinflammatory form of CP that mimics pancreatic ductal adenocarcinoma but responds to corticosteroid therapy [12, 16]. Two subtypes are recognized. Type 1 AIP is the pancreatic manifestation of IgG4-RD, typically affecting older men, presenting with painless jaundice or a pancreatic mass, and often accompanied by systemic disease such as sclerosing cholangitis, retroperitoneal fibrosis, sialadenitis, and tubulointerstitial nephritis. Serum IgG4 is elevated in most cases [16, 17].

Type 2 AIP, in contrast, is not related to IgG4 and usually affects younger patients without sex predilection. It is often associated with inflammatory bowel disease, particularly ulcerative colitis, and serum IgG4 levels are normal [17].

Grossly, the pancreas is diffusely enlarged, firm, and pale, sometimes surrounded by a capsule-like rim [12].

Microscopically, type 1 AIP shows a lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis, whereas type 2 AIP is characterized by granulocytic epithelial lesions without IgG4 predominance [16].

Diagnostic criteria include the HISORt system (Histology, Imaging, Serology, Other organ involvement, and Response to therapy) and the International Consensus Diagnostic Criteria (ICDC, 2011), which integrate serology, imaging, histology, extrapancreatic involvement, and response to steroids [14].

The differential diagnosis includes pancreatic ductal adenocarcinoma, which is distinguished by the presence of perineural and vascular invasion and the absence of IgG4-positive infiltrates, and alcoholic CP, which shows patchy fibrosis, calculi, and pseudocysts rather than the diffuse fibrosis of AIP [15].

Treatment is based on corticosteroids, which induce dramatic remission. Type 1 AIP has a high

Table 7.1 Key features of pancreatitis

Feature	Acute pancreatitis	Chronic pancreatitis	Type 1 AIP	Type 2 AIP
Gross	Edematous/necrotic, fat necrosis	Fibrotic, shrunken, calculi, pseudocysts	Sausage-like enlargement, capsule-like rim	Similar but often focal
Microscopic	Necrosis, fat saponification	Fibrosis, duct distortion, acinar loss	Storiform fibrosis, IgG4+ plasma cells, obliterative phlebitis	Neutrophils in ducts, duct-centric inflammation
Systemic involvement	Systemic SIRS in severe cases	Malabsorption, diabetes	Part of IgG4-RD, multiple organs	Limited to the pancreas ± inflammatory bowel disease
Treatment	Supportive	Supportive, enzyme replacement	Steroid responsive, high relapse	Steroid responsive, low relapse

relapse rate of up to 40–50% and may require immunosuppressive therapy such as azathioprine or rituximab, whereas type 2 AIP rarely relapses and is usually cured with a single steroid course. With correct diagnosis and treatment, the prognosis is excellent, but misdiagnosis as carcinoma can lead to unnecessary surgical resection [14, 16] (Table 7.1).

[20]. They appear as well-defined masses that can resemble mucinous neoplasms radiologically [21]. Since LECs carry no risk of malignant transformation, integrating imaging findings with cytology and cyst fluid studies is essential to prevent unwarranted surgical intervention [22].

7.3 Non-neoplastic Cystic Lesions

7.3.1 Pseudocyst

Pancreatic pseudocysts represent fluid-filled cavities that lack an epithelial lining and most commonly develop following episodes of AP or CP. Their walls are composed of a fibrous tissue and may contain necrotic material, blood products, and inflammatory infiltrates [18]. Patients can remain asymptomatic, but some experience abdominal discomfort, gastric outlet obstruction, or secondary infection. Pseudocysts have no malignant potential and are often treated conservatively or managed with endoscopic drainage rather than surgical resection [19].

7.3.2 Lymphoepithelial Cyst

Lymphoepithelial cysts (LECs) of the pancreas are uncommon, benign cystic lesions defined by squamous epithelial lining with a rim of lymphoid tissue, usually found in middle-aged men

7.3.3 Retention Cyst

Pancreatic retention cysts are small cystic structures that typically result from obstruction of the pancreatic ducts, often due to chronic inflammation, stones, or mucin plugs. These cysts are lined by simple epithelial cells and may contain mucin, but unlike neoplastic lesions, they lack solid components or mural nodules and do not pose a risk of malignancy [21].

7.4 Pancreatic Neoplasms

The World Health Organization fifth edition classifies pancreatic tumors mainly by cell lineage (ductal, acinar, neuroendocrine, or mesenchymal), with emphasis on precursor lesions (pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasm (IPMN), intraductal tubulopapillary neoplasm (ITPN), mucinous cystic neoplasm (MCN)), ordinary pancreatic ductal adenocarcinoma (PDAC) and its histologic variants, and the major non-ductal malignant tumors (acinar carcinoma, pancreatoblastoma, pancreatic neuroendocrine

neoplasms (PanNENs), solid pseudopapillary neoplasm (SPN)) [23]. PDAC is the most frequent among these tumors and among the deadliest of all human malignancies, and it is the fourth leading cause of cancer-related death worldwide. Its dismal prognosis is attributed to late-stage diagnosis, aggressive biology, and resistance to therapy. One crucial feature of PDAC is that it evolves from non-invasive precursor lesions over many years. Understanding these precursors is central to both early diagnosis and preventive strategies [24, 25].

7.4.1 Precursors of Pancreatic Ductal Adenocarcinoma

Three precursor lesions are well established: PanIN, IPMN, and MCN. Each represents a different spectrum of histopathological and molecular alterations, but they share common driver pathways of carcinogenesis.

7.4.1.1 Pancreatic Intraepithelial Neoplasia

PanINs are microscopic, non-cystic, non-invasive epithelial proliferations involving small-to-medium pancreatic ducts. Despite their small size (<5 mm), they represent the most frequent and well-characterized precursor to PDAC [24].

According to the *World Health Organization (WHO) Classification of Tumours of the Digestive System, Fifth Edition (2019)*, PanIN lesions are graded using a two-tiered system: low-grade PanIN (encompassing the former PanIN-1 and PanIN-2) and high-grade PanIN (corresponding to the former PanIN-3). Low-grade PanINs display minimal-to-moderate atypia, while high-grade PanINs demonstrate severe architectural and cytological atypia, approaching carcinoma in situ [23].

Molecular alterations mirror histologic progression. Early PanINs frequently harbor Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations (>90%), often in codon 12 (Hingorani et al., 2003). Telomere shortening is also an early hallmark. As PanINs advance, CDKN2A/p16

inactivation emerges, followed by tumor protein 53 (TP53) mutations and SMA- and MAD-related protein 4 (SMAD4) loss in PanIN-3 lesions. These changes represent the canonical “PanIN to PDAC” pathway [26].

7.4.1.2 Intraductal Papillary Mucinous Neoplasm

IPMNs are grossly visible (>5 mm), mucin-producing tumors that involve the main pancreatic duct, branch ducts, or both (Furukawa et al., 2010). Their recognition has revolutionized pancreatic pathology, since some can be monitored radiologically and resected before invasion.

Macroscopic features: IPMNs are typically seen as cystically dilated ducts, either involving the main pancreatic duct, branch ducts, or both. The main duct IPMNs manifest as diffuse or segmental dilatation of the main pancreatic duct, sometimes producing a “fish mouth” appearance at the ampulla, with extrusion of mucin. Branch duct IPMNs appear as grape-like clusters of cystic dilatations that may communicate with the main duct. Grossly, they range in size from a few millimeters to several centimeters, and the cysts often contain abundant thick mucin. Papillary excrescences or mural nodules projecting into the lumen may be visible on cut surface (Fig. 7.2). These macroscopic features are important in differentiating the main duct from branch duct IPMNs and in assessing the risk of malignancy.

Histologically, IPMNs are divided into three subtypes according to the type of cells lining the cysts:

- Gastric type: Resembling gastric foveolar epithelium, typically arising in branch ducts, often with low-grade dysplasia.
- Intestinal type: Villous morphology resembling colonic adenomas, often associated with invasive colloid carcinoma; express MUC2 and CDX2 [27].
- Pancreatobiliary type: Complex papillae, high-grade atypia, frequent association with tubular adenocarcinoma.

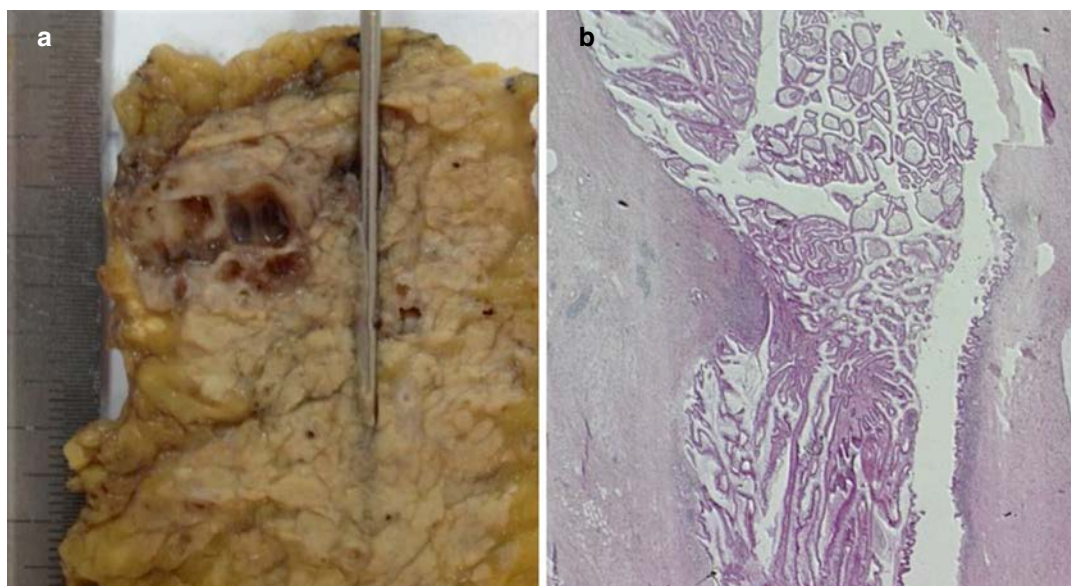


Fig. 7.2 Intraductal papillary mucinous neoplasm. (a) In this example of branch duct IPMN, macroscopically, the lesion larger than 1 cm and consisting of multiple cystic

structures is seen. (b) Microscopically, a lesion within the duct, lined by mucinous epithelium, and forming papillary structures is seen (HE, $\times 2$)

Genetic alterations include KRAS mutations in most IPMNs and guanine nucleotide-binding protein (GNAS) mutations in about 60%, particularly in intestinal types [28]. RNF43 mutations are also common, leading to Wnt pathway dysregulation. These molecular features help distinguish IPMNs from other cystic lesions.

The risk of malignancy correlates with location and type. The main duct IPMNs and those with mural nodules carry a higher risk of progression to invasive carcinoma [29].

7.4.1.3 Intraductal Oncocytic Papillary Neoplasm

Intraductal oncocytic papillary neoplasm (IOPN) is a distinct pancreatic epithelial tumor characterized by oncocytic cytoplasm and complex papillary architecture. Unlike conventional IPMNs, IOPNs rarely harbor KRAS or GNAS mutations and instead exhibit unique genetic alterations, including mutations in genes like *ERBB4* and *EPHA8* [30]. Immunohistochemically, IOPNs frequently express mesothelin and mucin 6 (MUC6), further supporting their classification as a separate neoplastic entity [30, 31].

7.4.1.4 Intraductal Tubulopapillary Neoplasm

ITPN is a rare pancreatic tumor composed of tightly packed tubules or cribriform structures lined by atypical cuboidal cells without mucin production. Immunohistochemically, it shows diffuse positivity for cytokeratin 7 (CK7), CK19, MUC1, and MUC6 but lacks expression of MUC2, MUC5AC, and pancreatic enzymes, distinguishing it from IPMN and acinar cell neoplasms. Molecularly, ITPNs are notable for the absence of common pancreatic mutations such as KRAS and v-Raf murine sarcoma viral oncogene homolog B1 (BRAF), supporting their classification as a distinct entity. Associated ductal adenocarcinoma is detected in the majority of cases [32, 33].

7.4.1.5 Mucinous Cystic Neoplasm

MCNs are unique mucin-producing cystic tumors almost exclusively seen in women, predominantly in the pancreatic body and tail. They are defined by the presence of an ovarian-type stroma beneath the mucinous epithelium [34].

Macroscopic features: MCNs are typically large, multilocular cystic lesions, ranging from several

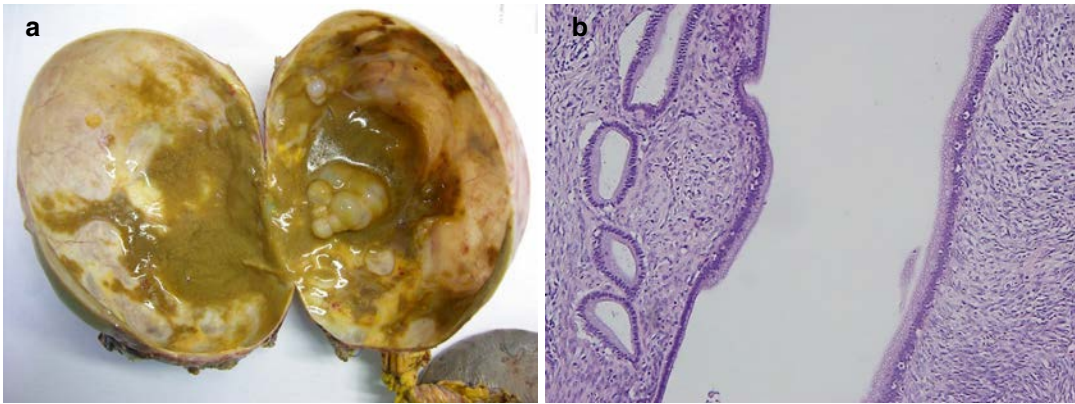


Fig. 7.3 Mucinous cystic neoplasm. (a) Macroscopically, a well-circumscribed, large cystic lesion, which contains smaller cyst structures in its wall. (b) Microscopically, a

cystic lesion lined with a mucinous epithelium, with sub-epithelial ovarian-type stroma (more prominent along the right side) (HE, ×10)

centimeters to over 15 cm in diameter. They are usually located in the pancreatic body or tail and present as well-circumscribed masses with thick fibrous capsules. On the cut surface, they reveal multiloculated cystic spaces filled with thick, viscous, mucoid material. Hemorrhage, calcification, or areas of necrosis may also be observed. The absence of communication with the pancreatic ductal system is a key diagnostic feature distinguishing MCNs from IPMNs.

Histologically, the cyst lining epithelium may range from flat to papillary, with varying degrees of dysplasia. The stroma resembles an ovarian tissue, expressing estrogen and progesterone receptors (Fig. 7.3). Invasive carcinoma may arise within MCNs, particularly when high-grade dysplasia is present.

Like IPMNs, MCNs frequently harbor KRAS and RNF43 mutations, but GNAS mutations are absent. Without surgical removal, MCNs may evolve from low-grade to high-grade dysplasia and ultimately to invasive carcinoma [34].

7.4.2 Pancreatic Ductal Adenocarcinoma and Its Variants

Macroscopic features: PDAC most commonly arises in the pancreatic head (60–70% of cases), followed by the body and tail. Grossly,

it appears as a firm, ill-defined, infiltrative, gray-white mass, typically ranging from 2 to 5 cm. The tumor often induces obstruction of the common bile duct and/or pancreatic duct, resulting in upstream ductal dilatation and secondary CP. Cut sections frequently reveal a gritty, fibrotic tissue with areas of necrosis or hemorrhage in advanced cases [23].

Microscopic features: PDAC consists of infiltrating, angulated, mucin-producing glands with irregular contours and incomplete lumina, embedded within a characteristic desmoplastic stroma (Fig. 7.4). Perineural invasion and lymphovascular invasion are common and serve as diagnostic clues. Tumor grading depends on glandular differentiation: well-differentiated (>95% gland formation), moderately differentiated (50–95%), and poorly differentiated (<50%) tumors.

The stroma of PDAC is desmoplastic, meaning it is composed of abundant fibroblasts, activated pancreatic stellate cells, extracellular matrix proteins (collagen, fibronectin, hyaluronan), and inflammatory cells. This stromal reaction plays an active role in tumor progression, immune evasion, and therapeutic resistance. Dense collagen and hyaluronan contribute to increased interstitial pressure, reduced vascular perfusion, and impaired drug delivery [35]. Variability exists: in some tumors, the stroma is loose and myxoid, while in others, it is densely sclerotic.

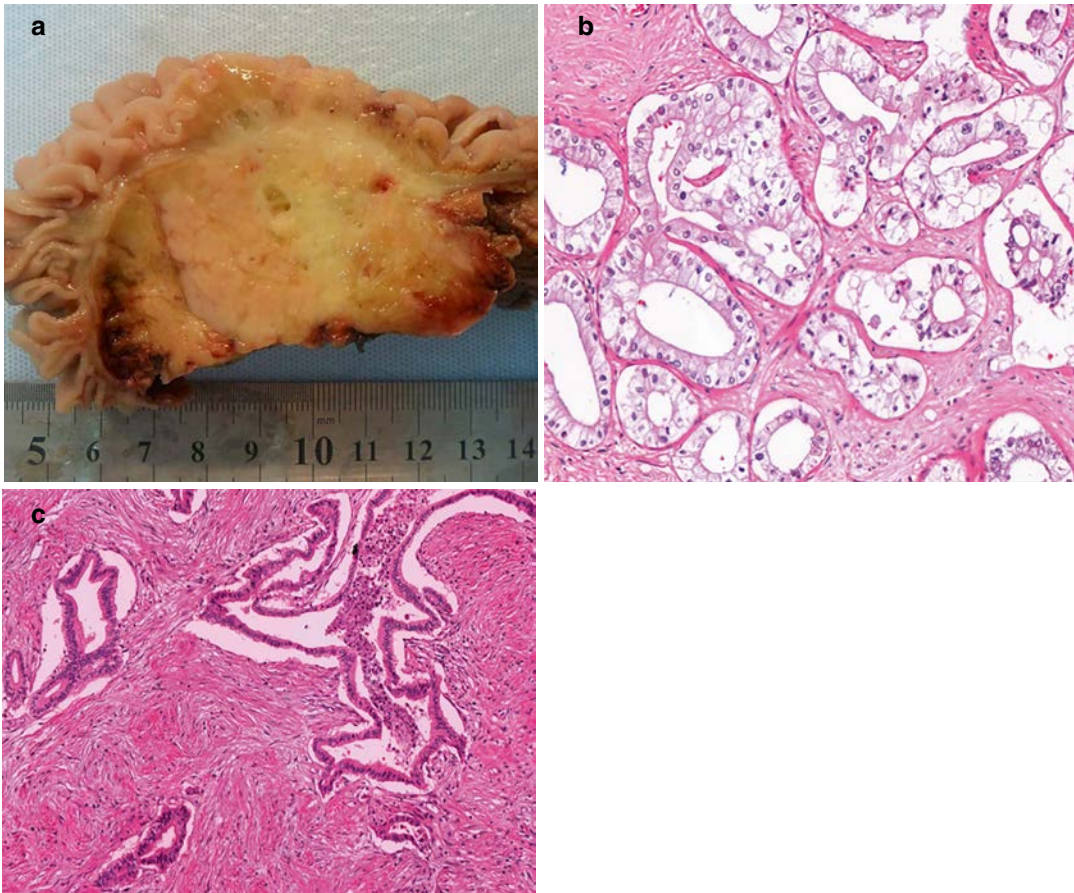


Fig. 7.4 Ductal adenocarcinoma. (a) Macroscopically, an unencapsulated, irregularly bordered, firm tumor. (b and c) Two different microscopic examples: (b) relatively rounded malignant glandular structures composed of a

single layer of epithelial cells with vacuolated cytoplasm (HE, ×10). (c) More irregular and larger malignant glandular structures with luminal necrotic debris (HE, ×4)

Molecular alterations are the mutations in KRAS, TP53, CDKN2A/p16, and SMAD4 genes. Nearly all PDACs harbor activating KRAS mutations. TP53 mutations occur in ~75%, leading to impaired genomic surveillance. CDKN2A/p16 loss disrupts cell cycle regulation, while SMAD4 inactivation impairs TGF- β signaling. The presence of multiple driver mutations correlates with aggressive disease [26, 36].

PDAC shows morphological heterogeneity which is revealed by different microscopic growth patterns including classic gland-forming, foamy gland, large duct, micropapillary, cribriform, papillary, and clear cell types [35]. Stromal heterogeneity adds to this complexity by creating microenvironments that can suppress or promote tumor cell proliferation.

7.5 Variants of PDAC

Adenosquamous carcinoma: It contains at least 30% squamous differentiation and is associated with worse prognosis than conventional PDAC [29].

Colloid carcinoma: It is defined by extracellular mucin comprising >80% of tumor volume, with neoplastic cells floating in mucin lakes (Fig. 7.5), and is frequently derived from intestinal-type IPMN. Prognosis is better than that of conventional PDAC [37].

Signet-ring cell carcinoma: It is extremely rare. Cells contain mucin-pushing nuclei to the periphery. Aggressive with poor prognosis [38].

Medullary carcinoma: It is characterized by syncytial sheets of poorly differentiated cells,

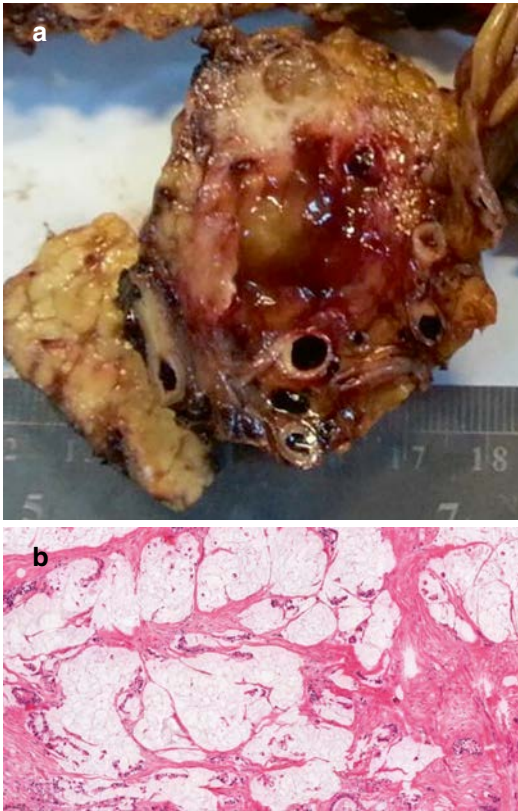


Fig. 7.5 Colloid carcinoma (a variant of PDAC). (a) Macroscopically, an irregularly bordered lesion with mucinous content visible. (b) Microscopically, malignant epithelial cells floating in mucinous pools (HE, $\times 4$)

pushing tumor borders, and prominent lymphoid infiltration. It is often associated with microsatellite instability (MSI)-high status and Lynch syndrome [39].

Hepatoid carcinoma: It mimics hepatocellular carcinoma with trabecular growth and hepatocytic features. It is rare and highly aggressive [23].

Undifferentiated carcinoma with osteoclast-like giant cells: It contains pleomorphic mononuclear tumor cells and abundant non-neoplastic osteoclast-like giant cells. Prognosis varies but can be more favorable when the undifferentiated component is limited [23].

7.5.1 Other Tumors

7.5.1.1 Serous Cystic Neoplasms

According to the *WHO Classification of Tumours of the Digestive System, Fifth Edition (2019)*, serous

cystic neoplasms (SCNs) are benign cyst-forming epithelial tumors of the pancreas. They represent approximately 1–2% of all pancreatic exocrine neoplasms and occur predominantly in women, usually in the sixth to seventh decade of life [23].

Macroscopic features: SCNs are typically well-circumscribed, multicystic lesions, often located in the pancreatic body or tail. The most common form is the serous microcystic adenoma, characterized by a spongy appearance with numerous small cysts imparting a honeycomb-like pattern. A central stellate scar with or without calcification is a frequent hallmark. Less commonly, SCNs may present as oligocystic/macrocystic lesions with larger cysts, which can mimic mucinous cystic neoplasms radiologically.

Microscopic features: The cysts are lined by a single layer of glycogen-rich, cuboidal epithelial cells with clear cytoplasm and round, uniform nuclei. Mitoses are absent, and there is no cytologic atypia. The stroma is fibrous and may radiate from the central scar (Fig. 7.6).

The majority of serous cystic neoplasms harbor somatic mutations in the VHL (von Hippel-Lindau) tumor suppressor gene, leading to dysregulation of hypoxia-inducible pathways. This molecular feature explains their strong association with VHL disease, in which multiple SCNs may occur. Other genetic alterations are uncommon, and SCNs generally lack KRAS, GNAS, and RNF43 mutations that characterize mucinous cystic neoplasms and IPMNs [23, 40].

SCNs are considered benign, and malignant transformation (serous cystadenocarcinoma) is exceedingly rare, with only isolated case reports in the literature. Most lesions are asymptomatic and incidentally discovered; however, large tumors may cause abdominal discomfort or compression of adjacent structures.

Management: Because of their benign nature, surgical resection is not usually required unless symptomatic, very large, or diagnostic uncertainty exists [23].

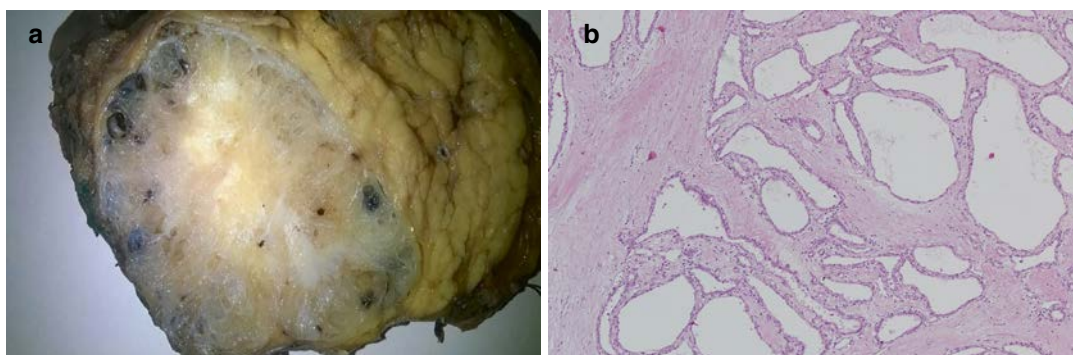


Fig. 7.6 Serosus cystic neoplasm. (a) Grossly multicystic lesion with central scar. (b) Microscopically multiple microcysts lined by cells with glycogen-rich, clear cytoplasm and uniform nucleus (HE, $\times 4$)

7.5.1.2 Neuroendocrine Neoplasms

Pancreatic neuroendocrine neoplasms represent a distinct group of epithelial tumors derived from the endocrine cells of the pancreas. They are biologically and clinically distinct from ductal neoplasms. They comprise approximately 5% of malignant pancreatic tumors [41]. Unlike PDAC, PanNENs display highly variable biological behavior, ranging from indolent lesions to aggressive carcinomas. Advances in histopathology, molecular profiling, and clinical studies have refined their classification and prognostic evaluation [23, 42].

Classification: According to the *WHO Classification of Tumors of the Digestive System, Fifth Edition (2019)*, PanNENs are divided into well-differentiated pancreatic neuroendocrine tumors (PanNETs) and poorly differentiated pancreatic neuroendocrine carcinomas (PanNECs). Well-differentiated PanNETs are graded by mitotic activity and Ki-67 index as follows: NET G1 (<2 mitoses/10 HPF and Ki-67 $\leq 3\%$), NET G2 (2–20 mitoses/10 HPF or Ki-67 3–20%), and NET G3 (>20 mitoses/10 HPF or Ki-67 $>20\%$ but with well-differentiated morphology). Poorly differentiated PanNECs include small cell and large cell types. They are genetically and biologically distinct from PanNET G3, with near-universal TP53 and RB1 alterations [41].

Macroscopic features: Grossly, PanNETs are typically well-circumscribed, solid, tan-to-yellow tumors, often richly vascular, and occasionally cystic. PanNECs, by contrast, are

usually larger and infiltrative and often exhibit extensive necrosis [41].

Microscopic features: PanNETs show nested, trabecular, or organoid growth patterns composed of uniform polygonal cells with eosinophilic to amphophilic cytoplasm and characteristic “salt-and-pepper” chromatin (Fig. 7.7). Necrosis and mitotic activity correlate with increasing grade. PanNECs demonstrate either small-cell morphology, with scant cytoplasm and nuclear molding, or large-cell morphology, with abundant cytoplasm and vesicular nuclei. They are characterized by high mitotic activity and widespread necrosis.

Immunohistochemistry: PanNETs typically express neuroendocrine markers including chromogranin A, synaptophysin, and insulinoma-associated protein 1 and may produce peptide hormones such as insulin, glucagon, gastrin, somatostatin, and vasoactive intestinal peptide. PanNECs also express synaptophysin strongly but often show only patchy chromogranin staining. Abnormal p53 accumulation and loss of Rb protein expression are characteristic of PanNECs [41]. **Functionality:** PanNETs are classified as functional or nonfunctional based on hormone secretion. Functional tumors, which account for 10–30% of cases, secrete bioactive hormones and cause clinical syndromes. These include insulinomas (hypoglycemia), gastrinomas (Zollinger-Ellison syndrome with peptic ulcers and diarrhea), glucagonomas (necrolytic migratory erythema, diabetes),

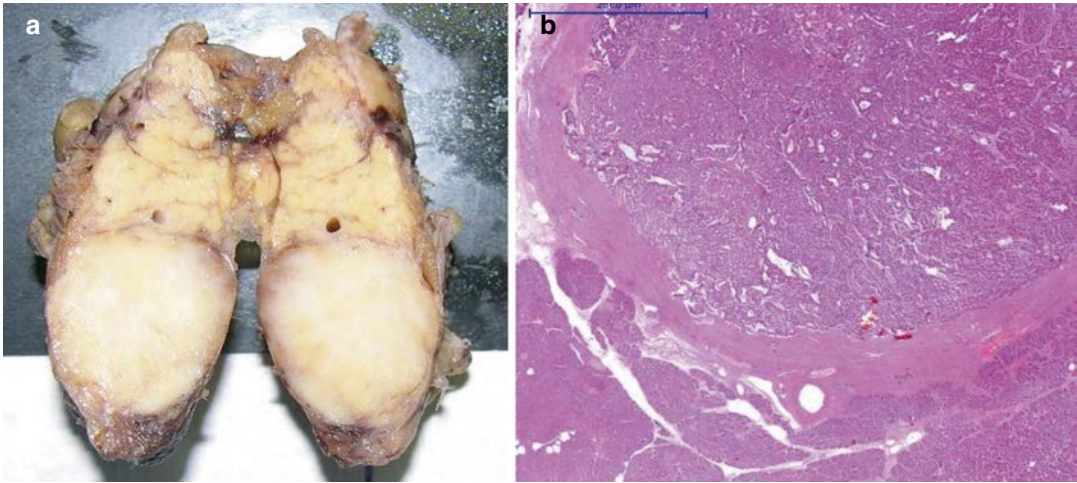


Fig. 7.7 Neuroendocrine tumor. (a) Grossly well-demarcated, nodular lesion. (b) Microscopically, a tumor separated from the surrounding pancreas by a capsule,

composed of uniform cells and exhibiting trabecular, nested, glandular, etc. patterns. (HE, $\times 2$)

VIPomas (watery diarrhea, hypokalemia, achlorhydria), and somatostatinomas (diabetes, gallstones, steatorrhea). Nonfunctional PanNETs, which account for 70–90% of cases, do not cause hormonal syndromes and are often diagnosed incidentally or at advanced stage [23].

Molecular pathogenesis: Accurate classification into PanNETs and PanNECs requires integration of histology, immunoprofile, and molecular features. Well-differentiated PanNETs frequently harbor multiple endocrine neoplasia type 1 (MEN1), alpha thalassemia/mental retardation syndrome X-linked (ATRX), and death-domain-associated protein (DAXX) mutations, which lead to chromatin remodeling defects and activation of the alternative lengthening of telomeres pathway. Alterations in mammalian target of rapamycin pathway genes such as tuberous sclerosis complex 2 (TSC2) and phosphatase and tensin homolog (PTEN) provide a rationale for targeted therapies [41, 42]. By contrast, poorly differentiated PanNECs almost universally harbor TP53 and retinoblastoma 1 (RB1) inactivation, paralleling pulmonary neuroendocrine carcinomas (NECs). They lack MEN1/ATRX/DAXX mutations and are molecularly distinct from PanNET G3 [41]. Epigenetic regu-

lation also differs: PanNETs commonly show Ras association domain family member 1 isoform A (RASSF1A) promoter hypermethylation and distinct miRNA profiles, whereas PanNECs overlap with PDAC in molecular profile [42].

Clinical features and prognosis: The prognosis of PanNETs depends on size, grade, stage, and functionality. Small, low-grade tumors often follow an indolent course. PanNET G3 tumors are aggressive but still have a better prognosis than PanNECs. Poorly differentiated PanNECs are highly aggressive, with median survival often measured in months [41]. Loss of ATRX or DAXX expression and a high Ki-67 index are adverse prognostic indicators. A study by Aysal and Sağol (2021) emphasized that vascular invasion, lymphatic invasion, tumor size >10 cm, and nonfunctionality are strongly correlated with worse survival in PanNETs [43].

Treatment: Surgical resection remains the mainstay of therapy for localized PanNETs. Functional tumors may also require perioperative management of hormone excess. Somatostatin analogs are used for symptom control and to slow tumor growth [42, 44]. Recent molecular updates and clinicopathologic prognostic reassessments highlight the

Table 7.2 Comparison of PanNETs and PanNECs

Feature	PanNET (G1–G3)	PanNEC
Prevalence	≈5% of pancreatic malignancies	Rare
Gross	Well-circumscribed, vascular, sometimes cystic	Large, infiltrative, necrotic
Microscopy	Nested/trabecular, salt-and-pepper chromatin	Small/large cell, high mitoses, necrosis
Immunohistochemistry	Chromogranin A, synaptophysin, hormone markers	Patchy chromogranin, p53+, Rb loss
Genetics	MEN1, ATRX, DAXX, TSC2/PTEN	TP53, RB1
Epigenetics	RASSF1A hypermethylation, miRNA changes	Similar to PDAC
Functionality	Functional or nonfunctional	Nonfunctional
Clinical course	Variable; G1 indolent, G3 more aggressive	Highly aggressive, poor survival
Treatment	Surgery, SSA, targeted therapies	Platinum-based chemotherapy

importance of combining morphologic, molecular, and clinical parameters to refine prognosis and guide personalized therapy (Table 7.2).

7.6 Solid Pseudopapillary Neoplasm

Solid pseudopapillary neoplasm of the pancreas is a rare epithelial tumor, accounting for about 1–2% of all pancreatic neoplasms. SPN predominantly affects young women and is considered a low-grade malignant tumor with overall favorable prognosis [45, 46]. It has distinct clinical, morphologic, and molecular features but occasionally poses diagnostic challenges, particularly in differentiating it from pancreatic neuroendocrine tumors or acinar cell carcinoma (ACC).

Macroscopic features: Grossly, SPNs are usually large (average 5–10 cm) and well-circumscribed and demonstrate mixed solid and cystic components with areas of hemorrhage and necrosis. **Microscopic features:** SPNs are composed of poorly cohesive cells forming solid nests and pseudopapillary structures (Fig. 7.8). Neoplastic cells have uniform, oval nuclei with finely dispersed chromatin, frequent nuclear grooves, and eosinophilic or vacuolated cytoplasm. Foamy macrophages, cholesterol clefts, and hyaline globules are common. Rare histologic variants include oncocytic, clear cell and pigmented types [45]. In the clinicopathological series by Ersen

et al., uncommon examples were also reported, highlighting the heterogeneity of SPNs [47].

Immunohistochemistry: SPNs have a unique immunophenotype:

- Positive: β -Catenin (nuclear/cytoplasmic), CD10, progesterone receptor, vimentin, cyclin D1, CD99 (paranuclear dot-like), SOX11, TFE3, and LEF1
- Negative: Chromogranin A (distinguishing from PanNET) and acinar markers (trypsin, BCL10)
- Variable: Synaptophysin and CD56 (positive in some cases, contributing to overlap with PanNETs)

This profile is helpful in distinguishing SPN from other pancreatic neoplasms [45, 46].

Molecular pathogenesis: The molecular hallmark of SPN is activating mutations in exon 3 of the CTNNB1 gene, leading to abnormal stabilization and nuclear localization of β -catenin and subsequent activation of the Wnt/ β -catenin signaling pathway [45, 48]. This results in overexpression of downstream targets such as cyclin D1, glutamine synthetase, and androgen receptor. Recent studies have also identified alterations in epigenetic regulators (KDM6A, BAP1) in metastatic SPNs [49].

Prognosis and clinical outcome: SPN is considered a low-grade malignant tumor. Complete surgical excision offers cure in the majority of cases. Local invasion and distant metastasis occur in about 10–15% of cases, most fre-

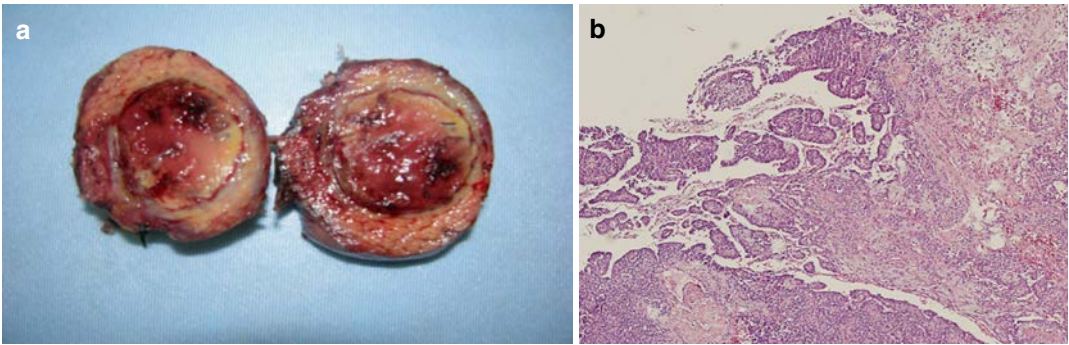


Fig. 7.8 Solid pseudopapillary neoplasm. (a) Macroscopically, a solid nodular lesion with relatively well-defined borders and containing central degenerative changes (cystic degeneration, hemorrhage). (b) Microscopically, a tumor composed of uniform, poorly cohesive cells, with solid, cystic, and pseudopapillary structures is seen (HE, ×4)

Table 7.3 Key features of SPN

Feature	SPN
Epidemiology	1–2% of pancreatic tumors, young women (mean age ~28 years)
Gross	Large, well-circumscribed, solid + cystic, hemorrhagic, necrotic
Microscopy	Poorly cohesive cells, solid/pseudopapillary structures, nuclear grooves, hyaline globules
Immunohistochemistry	β-Catenin nuclear+, CD10+, PR+, CD99 dot+, variable synaptophysin/CD56, chromogranin A–
Molecular hallmark	CTNNB1 exon 3 mutations (Wnt/β-catenin pathway activation)
Prognosis	Low-grade malignant, 10–15% metastasis, >95% 10-year survival
Treatment	Surgical resection (curative in majority)

quently to the liver or peritoneum. Prognostic factors include tumor size, Ki-67 index (>4–5% associated with recurrence), presence of vascular/perineural invasion, and undifferentiated/sarcomatoid transformation [45, 47]. Despite its malignant potential, the 10-year disease-specific survival exceeds 95%.
Treatment: Surgery is the standard of care, including resection of metastases when feasible. Prognosis remains excellent after R0 or even R1 resection. Limited resections can be adequate for small tumors. There is no established role for chemotherapy or radiotherapy in localized disease [46] (Table 7.3).

7.7 Acinar Cell Carcinoma

Acinar cell carcinoma is a rare malignant epithelial neoplasm of the pancreas, accounting for approximately 1–2% of pancreatic exocrine tumors. Unlike PDAC, ACC is characterized by acinar differentiation, defined by the production of digestive enzymes such as trypsin and chymotrypsin. ACC may occur across a wide age spectrum but is most commonly diagnosed in adults with a slight male predominance. Despite being aggressive, ACC generally carries a better prognosis than PDAC, though its clinical course is variable [50, 51].

Macroscopic features: Grossly, ACCs are typically large, well-circumscribed tumors, often exceeding 10 cm in diameter at presentation. They may show areas of hemorrhage and necrosis. **Microscopic features:** The hallmark is acinar differentiation, with tumor cells forming acinar, solid, or trabecular patterns. The cells are pyramidal with granular eosinophilic cytoplasm, prominent nucleoli, and basally oriented nuclei. Mitotic activity is usually high, and necrosis is frequently present. Variants include mixed acinar-neuroendocrine carcinomas and acinar cell cystadenocarcinomas [52].

Immunohistochemistry: Immunohistochemistry is critical for diagnosis:

- Positive markers: trypsin, chymotrypsin, lipase, BCL10 (cytoplasmic granular pattern)
- Variable: cytokeratins, synaptophysin (in mixed tumors)
- Negative: chromogranin A (helps distinguish from PanNET)

The sensitivity and specificity of BCL10 make it a valuable diagnostic marker [52].

Molecular pathogenesis: Molecular studies have revealed that ACC is distinct from PDAC and PanNET. Unlike PDAC, KRAS mutations are rare. Instead, ACC demonstrates frequent alterations in the APC/ β -catenin pathway, similar to colorectal carcinoma. Other reported alterations include DNA damage repair gene

mutations (e.g., BReast CAncer genes 1 and 2 (BRCA1/2), ATM), mismatch repair deficiency, and rare actionable fusions in genes such as rearranged during transfection (RET) and neurotrophic tyrosine kinase, receptor, type 1 (NTRK1) [53, 54]. These findings provide opportunities for targeted and precision therapies. Recent reviews emphasize that the molecular heterogeneity of ACC requires integrated genomic and clinicopathologic evaluation [51].

Prognosis and clinical outcome: ACC is aggressive but has a prognosis intermediate between PDAC and PanNET. Median survival ranges between 18 and 47 months. Complete surgical resection offers the best outcome, though recurrence is common. Advanced disease is frequent at diagnosis due to large tumor size. Prognostic factors include stage, resection margin status, and molecular features such as DNA repair deficiency, which may also predict response to platinum chemotherapy or Poly(ADP-ribose) polymerase (PARP) inhibitors [50, 54].

Treatment: Surgical resection is the cornerstone of therapy for localized ACC. Even in metastatic disease, surgical debulking may improve survival. Chemotherapy regimens incorporating platinum agents and fluoropyrimidines are commonly used. In the setting of BRCA-mutated or other homologous recombination deficient tumors, PARP inhibitors have shown promise. Targeted therapies against RET or NTRK fusions are emerging options [53, 54] (Table 7.4).

Table 7.4 Key features of ACC

Feature	Acinar cell carcinoma
Epidemiology	1–2% of pancreatic tumors, male predominance, adults
Gross	Large (>10 cm), circumscribed, necrosis and hemorrhage common
Microscopy	Acinar, trabecular, or solid growth; pyramidal cells with granular cytoplasm; high mitoses
Immunohistochemistry	Trypsin+, chymotrypsin+, lipase+, BCL10+; chromogranin–
Molecular alterations	APC/ β -catenin pathway, DNA repair genes (BRCA, ATM), rare RET/NTRK fusions
Prognosis	Intermediate, median survival 18–47 months; resection improves survival

7.8 Pancreatoblastoma

Pancreatoblastoma (PB) is a rare malignant neoplasm, most often occurring in children, and defined histologically by squamoid nests in a background of acinar differentiation. It is molecularly linked to APC/ β -catenin signaling alterations and syndromic conditions such as Familial adenomatous polyposis (FAP) and Beckwith-Wiedemann syndrome. Although aggressive, PB in children often responds to surgery and multimodal therapy, whereas adult PB is typically associated with a worse prognosis. Recent advances in molecular characterization may guide future targeted therapies [55, 56].

References

- Jennings RE, Berry AA, Strutt JP, Gerrard DT, Hanley NA. Human pancreas development. *Development*. 2015;142(18):3126–37.
- Brosens LAA, Hackeng WM, Offerhaus J, Hruban RH, Wood LD. Pancreatic adenocarcinoma pathology: changing “landscape”. *J Gastrointest Oncol*. 2015;6(4):358–74.
- Mehta V, Hopson PE, Smadi Y, Patel SB, Horvath K, Mehta DI. Development of the human pancreas and its exocrine function. *Front Pediatr*. 2022;10:909648. <https://doi.org/10.3389/fped.2022.909648>.
- Hackeng WM, Hruban RH, Offerhaus GJA, Brosens LAA. Surgical and molecular pathology of pancreatic neoplasms. *Diagn Pathol* [Internet]. 2016;11(1):1–17. <https://doi.org/10.1186/s13000-016-0497-z>.
- Aleem ASH. Annular pancreas. [Updated 2023 May 29]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025.
- Cano DA, Hebrok M, Zenker M. Pancreatic development and disease. *Gastroenterology*. 2007;132(2):745–62.
- Farah A, Mansour S, Khuri S. Gastrointestinal tract heterotopic pancreas: asymptomatic pathology? *Gastroenterol Res*. 2021;14(1):45–7.
- Zhang Y, Sun X, Gold JS, Sun Q, Lv Y, Li Q, et al. Heterotopic pancreas: a clinicopathological study of 184 cases from a single high-volume medical center in China. *Hum Pathol*. 2016;55:135–42.
- Menias C, Olpin JD, Elsayes KM, Shaaban AM. Heterotopic pancreas: histopathologic features, imaging findings. *Radiographics*. 2017;37:484–99.
- Al-Dosari MS, Al-Muhsen S, Al-Jazaeri A, Mayerle J, Zenker M, Alkuraya FS. Johanson-Blizzard syndrome: report of a novel mutation and severe liver involvement. *Am J Med Genet Part A*. 2008;146(14):1875–9.
- Cagan Appak Y, Baran M, Ozturk Hismi B, Ozyilmaz B, Vardi K, Ozer Kaya O, et al. Renal-hepatic-pancreatic dysplasia: an ultra-rare ciliopathy with a novel NPHP3 genotype. *J Pediatr Genet*. 2020;09(02):101–3.
- Kumar V, Abbas AKAJ. Robbins basic pathology. 10th ed. Philadelphia: Elsevier.
- Hruban RH, Klimstra DS. Adenocarcinoma of the pancreas. *Semin Diagn Pathol*. 2014;31(6):443–51.
- Lanzillotta M, Vujasinovic M, Löhr JM, Della Torre E. Update on autoimmune pancreatitis and IgG4-related disease. *United Eur Gastroenterol J*. 2025;13(1):107–15.
- Klöppel C, Adsay NV. Chronic pancreatitis and the differential diagnosis versus pancreatic cancer. *Arch Pathol Lab Med*. 2009;133(3):382–7.
- Zen Y. Autoimmune pancreatitis: biopsy interpretation and differential diagnosis. *Semin Diagn Pathol* [Internet]. 2024;41(2):79–87. <https://doi.org/10.1053/j.semdp.2024.01.001>.
- Okazaki K, Kawa S, Kamisawa T, Ikeura T, Itoi T, Ito T, et al. Amendment of the Japanese consensus guidelines for autoimmune pancreatitis, 2020. *J Gastroenterol* [Internet]. 2022;57(4):225–45. <https://doi.org/10.1007/s00535-022-01857-9>.
- Luchini C, Fassan M, Doglioni C, Capelli P, Ingravalle G, Renzulli G, et al. Inflammatory and tumor-like lesions of the pancreas. *Pathologica*. 2020;112(3):197–209.
- Elta GH, Enestvedt BK, Sauer BG, Lennon AM. ACG clinical guideline: diagnosis and management of pancreatic cysts. *Am J Gastroenterol* [Internet]. 2018;113(4):464–79. <https://doi.org/10.1038/ajg.2018.14>.
- Adsay NV, Hasteh F, Cheng JD, Bejarano PA, Lauwers GY, Batts KP, et al. Lymphoepithelial cysts of the pancreas: areport of 12 cases and a review of the literature. *Mod Pathol*. 2002;15(5):492–501.
- Abdelkader A, Hunt B, Hartley CP, Panarelli NC, Giorgadze T. Cystic lesions of the pancreas differential diagnosis and cytologic-histologic correlation. *Arch Pathol Lab Med*. 2020;144(1):47–61.
- Chen W, Ahmed N, Krishna SG. Pancreatic cystic lesions: a focused review on cyst clinicopathological features and advanced diagnostics. *Diagnostics*. 2023;13(1)
- Gill A, Klimstra D, Lam A, et al. Tumors of the pancreas. In: WHO classification of tumors: digestive system tumours. 5th ed. Lyon: International Agency for Research on Cancer; 2019. p. 295–376.
- Hruban RH, Adsay NV, Albores-Saavedra J, Compton C, Garrett ES, Goodman SN, et al. Pancreatic intraepithelial neoplasia: a new nomenclature and classification system for pancreatic duct lesions. *Am J Surg Pathol*. 2001;25(5):579–86.
- Basturk O, Hong SM, Wood LD, et al. A revised classification system and recommendations from the Baltimore consensus meeting for neoplastic precursor lesions in the pancreas. *Am J Surg Pathol*. 2015;39(12):1730–41.

26. Jones S, Zhang X, Parsons DW, Lin JCH, Leary RJ, Angenendt P, et al. Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. *Science* (80–). 2008;321(5897):1801–6.
27. Wu J, Jiao Y, Dal Molin M, Maitra A, De Wilde RF, Wood LD, et al. Whole-exome sequencing of neoplastic cysts of the pancreas reveals recurrent mutations in components of ubiquitin-dependent pathways. *Proc Natl Acad Sci U S A*. 2011;108(52):21188–93.
28. Moskaluk CA, Hruban RHKS. p16 and K-ras gene mutations in the intraductal precursors of human pancreatic adenocarcinoma. *Am J Pathol*. 1997;160(1):23–9.
29. Furukawa T, Klöppel G, Volkan Adsay N, Albores-Saavedra J, Fukushima N, Horii A, et al. Classification of types of intraductal papillary-mucinous neoplasm of the pancreas: a consensus study. *Virchows Arch*. 2005;447(5):794–9.
30. Basturk O, Chung SM, Hruban RH, Adsay NV, Askan G, Iacobuzio-Donahue C, et al. Distinct pathways of pathogenesis of intraductal oncocytic papillary neoplasms and intraductal papillary mucinous neoplasms of the pancreas. *Virchows Arch*. 2016;469(5):523–32.
31. Basturk O, Tan M, Bhanot U, Allen P, Adsay V, Scott SN, et al. The oncocytic subtype is genetically distinct from other pancreatic intraductal papillary mucinous neoplasm subtypes. *Mod Pathol*. 2016;29(9):1058–69.
32. Basturk O, Adsay V, Askan G, Dhall D, Zamboni G, Shimizu M, Cymes K, Carneiro F, Balci S, Sigel C, Reid MD, Esposito I, Baldaia H, Allen P, Günter Klöppel DSK. Intraductal tubulopapillary neoplasm of the pancreas: a clinicopathologic and immunohistochemical analysis of 33 cases. *Am J Surg Pathol*. 2017;41(3):313–25.
33. Kölby D, Thilén J, Andersson R, Sasor A, Ansari D. Multifocal intraductal tubulopapillary neoplasm of the pancreas with total pancreatectomy: report of a case and review of literature. *Int J Clin Exp Pathol*. 2015;8(8):9672–80.
34. Adsay NV, Klimstra DSCC. Cystic lesions of the pancreas: introduction. *Am J Surg Pathol*. 2004;28(9):1192–3.
35. Esposito I, Konukiewitz B, Schlitter AM, Klöppel G. Pathology of pancreatic ductal adenocarcinoma: facts, challenges and future developments. *World J Gastroenterol*. 2014;20(38):13833–41.
36. Biankin AV, Waddell N, Kassahn KS, Gingras MCMLB, Johns AL, Miller DK, Wilson PJ, Patch AM, Wu JCD, Cowley MJ, Gardiner BB, Song S, Harliwong I, Idrisoglu SNC, Nourbakhsh E, Manning S, Wani S, Gongora M, Pajic MSCJ, Gill AJ, Pinho AV, Rooman I, Anderson M, Holmes OLC, Taylor D, Wood S, Xu Q, Nones K, Fink JL, Christ ABT, et al. Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes. *Nature* [Internet]. 2012;491(7424):399–405. Available from: <http://www.ebi.ac.uk/ega>
37. Adsay NV, Merati K, Basturk O, Iacobuzio-Donahue C, Levi E, Cheng JD, et al. Pathologically and biologically distinct types of epithelium in intraductal papillary mucinous neoplasms: delineation of an “intestinal” pathway of carcinogenesis in the pancreas. *Am J Surg Pathol*. 2004;28(7):839–48.
38. Lüttges J, Zamboni G, Longnecker D, Klöppel G. The immunohistochemical mucin expression pattern distinguishes different types of intraductal papillary mucinous neoplasms of the pancreas and determines their relationship to mucinous noncystic carcinoma and ductal adenocarcinoma. *Am J Surg Pathol*. 2001;25(7):942–8.
39. Wilentz RE, Goggins M, Redston M, Marcus VA, Adsay NV, Sohn TA, et al. Genetic, immunohistochemical, and clinical features of medullary carcinoma of the pancreas: a newly described and characterized entity. *Am J Pathol*. 2000;156(5):1641–51.
40. Reid MD, Choi HJ, Memis B, Krasinskas AM, Jang KT, Akkas G, et al. Serous neoplasms of the pancreas. *Am J Surg Pathol*. 2015;39(12):1597–610.
41. Shi C, Klimstra DS. Pancreatic neuroendocrine tumors: pathologic and molecular characteristics. *Semin Diagn Pathol*. 2014;31(6):498–511.
42. Klöppel G, La Rosa S. Ki67 labeling index: assessment and prognostic role in gastroenteropancreatic neuroendocrine neoplasms. *Virchows Arch*. 2018;472(3):341–9.
43. Aysal A, Agalar C, Egeli T, Unek T, Oztup I, Obuz F, et al. Reconsideration of clinicopathologic prognostic factors in pancreatic neuroendocrine tumors for better determination of adverse prognosis. *Endocr Pathol* [Internet]. 2021;32(4):461–72. <https://doi.org/10.1007/s12022-021-09687-w>.
44. Mpilla GB, Philip PA, El-Rayes B, Azmi AS. Pancreatic neuroendocrine tumors: therapeutic challenges and research limitations. *World J Gastroenterol*. 2020;26(28):4036–54.
45. la Rosa S, Bongiovanni M. Pancreatic solid pseudopapillary neoplasm: key pathologic and genetic features. *Arch Pathol Lab Med*. 2020;144(7):829–37.
46. Uguz A, Ünalp ÖV, Akpinar G, Karaca CA, Oruc N, Nart D, et al. Solid pseudopapillary neoplasms of the pancreas: case series with a review of the literature. *Turkish J Gastroenterol*. 2020;31(12):930–5.
47. Ersen A, Agalar AA, Ozer E, Agalar C, Unek T, Egeli T, et al. Solid-pseudopapillary neoplasm of the pancreas: a clinicopathological review of 20 cases including rare examples. *Pathol Res Pract* [Internet]. 2016;212(11):1052–8. <https://doi.org/10.1016/j.prp.2016.09.006>.
48. Tanaka Y, Kato K, Notohara K, et al. Frequent beta-catenin mutation and cytoplasmic/nuclear accumulation in pancreatic solid-pseudopapillary neoplasm. *Cancer Res*. 2001;61:8401–4.
49. Amato E, Mafficini A, Hirabayashi K, Lawlor RT, Fassan M, Vicentini C, et al. Molecular alterations associated with metastases of solid pseudopapillary neoplasms of the pancreas. *J Pathol*. 2019;247(1):123–34.
50. Calimano-Ramirez LF, Daoud T, Gopireddy DR, Morani AC, Waters R, Gumus K, et al. Pancreatic aci-

- nar cell carcinoma: a comprehensive review. *World J Gastroenterol.* 2022;28(40):5827–44.
51. Ikezawa K, Urabe M, Kai Y, Takada R, Akita H, Nagata S, et al. Comprehensive review of pancreatic acinar cell carcinoma: epidemiology, diagnosis, molecular features and treatment. *Jpn J Clin Oncol.* 2024;54(3):271–81.
52. Sigel CS, Klimstra DS. Cytomorphologic and immunophenotypical features of acinar cell neoplasms of the pancreas. *Cancer Cytopathol.* 2013;121(8):459–70.
53. Balachandran Pillai A, Yousef M, Yousef A, Alfaro-Munoz KD, Smaglo BG, Willis J, et al. Molecular and clinical features of pancreatic acinar cell carcinoma: a single-institution case series. *Cancers (Basel).* 2024;16(19)
54. Eslinger C, Patel S, Johnson C, et al. Clinical outcomes and molecular profiling of pancreatic acinar cell carcinoma: insights for precision oncology. *JCO Precis Oncol.* 2025;9:e2400375.
55. Reid MD, Bhattarai S, Graham RP, Pehlivanoglu B, et al. Pancreatoblastoma: cytologic and histologic analysis of 12 adult cases reveals helpful criteria in their diagnosis and distinction from common mimics. *Cancer Cytopathol.* 2019;127:708–19.
56. Omiyale AO. Adult pancreatoblastoma: current concepts in pathology. *World J Gastroenterol.* 2021;27(26):4172–81.

Pathology of Endocrine System: Hypophysis, Thyroid, Parathyroid, and Adrenal Glands

8

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8.1 Hypophysis: Pituitary Gland

The pituitary gland is an endocrine organ located within the sphenoid bone sella turcica that is surrounded by dura mater. It is composed of two distinct components both morphologically and functionally: the adenohypophysis and the neurohypophysis. Adenohypophysis, also called the anterior lobe, constitutes nearly 80% of the pituitary gland. This lobe develops from the Rathke cleft in the oral cavity. Neurohypophysis (the posterior lobe), on the other hand, is connected to the hypothalamus via the pituitary stalk. This lobe develops downward from the brain [1].

Secretion of pituitary hormones depends on hypothalamic hormones, which are transported to the anterior lobe via portal vascular channels. Pituitary hormones, including thyroid-stimulating hormone (TSH), adrenocorticotrophic hormone (ACTH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH), are secreted via positive stimulatory effects of the hypothalamic hormones, namely, thyrotropin-releasing hormone, corticotropin-releasing hormone, and gonadotropin-releasing hormone. Secretion of growth hormone (GH) occurs by both stimulatory and inhibitory effects of the hypothalamic hormones, growth hormone-releasing hormone

and growth hormone-inhibiting hormone (somatostatin), respectively, whereas prolactin is the only pituitary hormone that is secreted via inhibitory effects of the hypothalamic hormone, prolactin-inhibiting factor (dopamine). Two peptide hormones secreted from neurohypophysis are oxytocin and antidiuretic hormone (ADH). These hormones, unlike the ones in the anterior lobe, are synthesized in the hypothalamus and stored in the axonal processes of the posterior lobe. They are secreted directly to the systemic circulation in response to appropriate stimuli [1, 2].

The main clinical symptoms of pituitary diseases are hyperpituitarism, which is due to hypersecretion of trophic hormones; hypopituitarism, due to deficiency of the trophic hormones; and local mass effects. The most common cause of hyperpituitarism is pituitary adenoma. The term pituitary adenoma has evolved into pituitary neuroendocrine tumor (PitNET) in the most recent World Health Organization (WHO) classification of endocrine tumors [3]. Nevertheless, both terms have been used interchangeably in the literature [4]. Hypopituitarism may arise as a result of ischemic injury, surgery, radiation exposure, or inflammatory reactions. The most common local mass effect of pituitary diseases is an ocular defect, called bitemporal hemianopsia.

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8.1.1 Hyperpituitarism

Pituitary neuroendocrine tumors, the most common cause of hyperpituitarism, can be primary or metastatic, formerly known as pituitary adenoma and carcinoma. PitNETs that used to be classified according to hormones secreted from the neoplastic cells are currently classified according to cell lineage, based on transcription factors. Tumors derived from somatotrophs, lactotrophs, mammosomatotrophs, and thyrotrophs display pituitary-specific positive transcription factor 1 (PIT1) lineage, tumors derived from corticotrophs display T-box transcription factor (TPIT) lineage, and tumors derived from gonadotrophs display steroidogenic factor 1 (SF1) lineage (Table 8.1). Functional adenomas are associated with excess hormone secretion, and their clinical symptoms occur correspondingly. Nonfunctional adenomas, on the other hand, do not display clinical symptoms due to excess hormone secretion. However, both immunohistochemically and ultrastructurally, hormone secretion can be demonstrated within neoplastic tissues. Adenomas that are less than 1 cm in size are called microadenomas, whereas those ≥ 1 cm in size are macroadenomas [1, 5–7].

Most pituitary adenomas (nearly 95%) are sporadic, and the only somatic mutation identified in most sporadic cases is G-protein mutation. G-proteins have a significant function in transporting genetic information; they transfer information from specific cell surface receptors to intracellular effectors. Nearly 40% of somatotroph cell adenomas display guanine nucleotide-binding protein, alpha stimulating (*GNAS*) mutations, which remove guanosine triphospha-

tase activity of G_{α} . *GNAS* mutations have been identified in rare corticotroph cell adenomas, as well. In addition, 30% to 60% of corticotroph cell adenomas have activating mutations in *USP8* (ubiquitin-specific protease 8) gene [1, 8].

Only 5% of pituitary adenomas are part of hereditary syndromes, such as multiple endocrine neoplasia type 1 (MEN1), Carney complex, familial isolated pituitary adenoma, and MEN4. Mutations that cause loss of germline function in *MEN1*, *PRKARIA*, *AIP*, and *CDKN1B* genes, respectively, have been shown in these syndromes [8, 9].

Morphologically, pituitary adenomas are typically soft, well-circumscribed lesions located within sella turcica. Larger lesions, on the other hand, usually extend along the suprasellar region causing pressure to optic chiasma and certain cranial nerves. In nearly 30% of cases, tumors are not encapsulated, and they may invade cavernous and sphenoid sinuses, dura, and rarely even the brain tissue. These are called aggressive adenomas. Aggressive adenomas usually grow faster and show resistance to conventional therapies [6]. Microscopically, pituitary adenomas consist of uniform, polygonal cells arranged in sheets and/or cords (Fig. 8.1). The neoplastic cells may have eosinophilic, basophilic, or chromophobic cytoplasm. A stromal component is usually scant, which is confirmed by the absence of reticulin network by histochemical stains.

The most common functional pituitary adenomas are prolactinomas (lactotroph cell adenoma). They can arise as microadenomas or as large, expansile tumors that cause local mass effects. Microscopically, most tumors consist of weak acidophilic or chromophobic cells.

Table 8.1 Pituitary adenoma (pituitary neuroendocrine tumor) classification

Cell of origin	Hormone secreted	Cell lineage/transcription factor	Clinical manifestation
Lactotroph	PRL	PIT1	Galactorrhea, amenorrhea, infertility, loss of libido
Somatotroph	GH	PIT1	Acromegaly (adults), gigantism (children)
Thyrotroph	TSH	PIT1	Secondary hyperthyroidism
Gonadotroph	FSH/LH	SF1	Hypogonadism, mass effect
Corticotroph	ACTH	TPIT	Cushing disease, Nelson syndrome
Null	Nonfunctioning		Mass effect

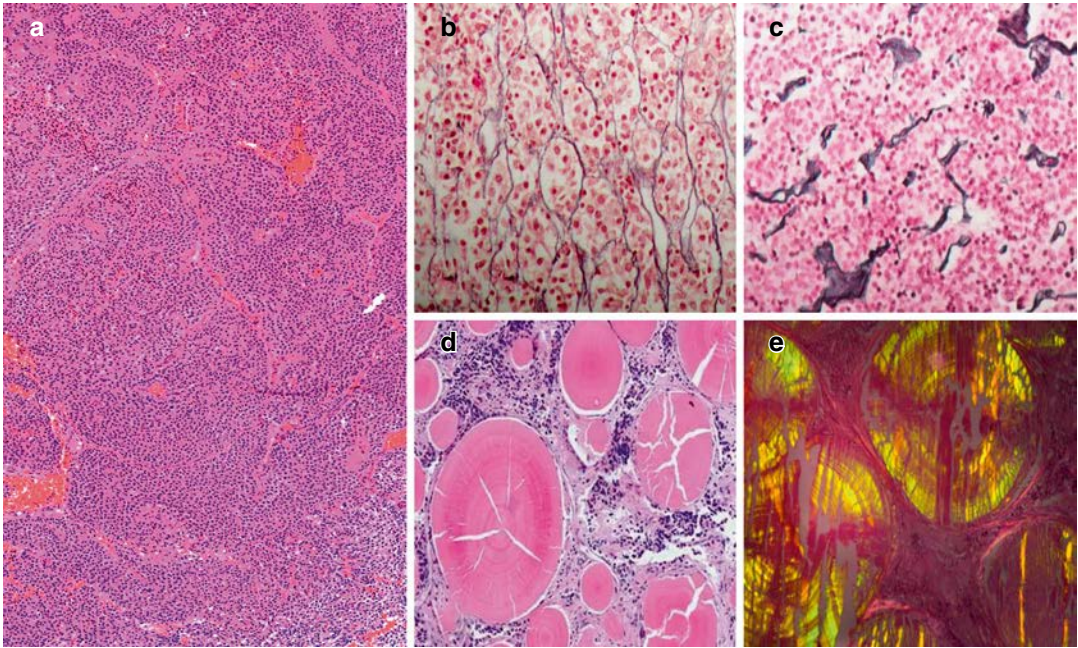


Fig. 8.1 (a) Pituitary adenoma. Solid sheets of uniform epithelioid neoplastic cells within a fibrovascular stroma. (b) Reticulin network in normal hypophysis and (c) in

pituitary adenoma. (d) Amyloid deposition in prolactinoma, (e) as seen under polarized light

Immunohistochemically, prolactin within secretory granules in the cytoplasm can be displayed. Dystrophic calcification, also known as “pituitary stone,” is one of its distinguished features. The most common symptoms of these patients are amenorrhea, galactorrhea, loss of libido, and infertility, due to prolactinoma. Medical treatment with dopamine receptor agonists (bromocriptine) is the first-line treatment; however, surgery is applied to patients who do not respond to medical therapy [1, 5].

Somatotroph cell adenomas that secrete GH are the second most common functional pituitary adenomas. Microscopically, they consist of monomorphic acidophilic cells and pleomorphic chromophobe cells. Immunohistochemically, strong cytoplasmic GH and perinuclear cytokeratin staining is seen in acidophilic cells, whereas chromophobe cells show focal, weak cytoplasmic GH staining. In these tumors, due to high levels of GH, secretion of insulin-like growth factor 1 from the liver is stimulated. The clinical manifestation of this tumor differs in children

and adults, due to epiphyseal closure period [1]. In children clinical symptoms are called gigantism, and since the growth plates are open, the patients have very tall stature. On the other hand, acromegaly, the clinical manifestation in adults, cause enlargement in the skin and soft tissues, followed by visceral organs and bones of the face, hand, and feet. Corticotroph adenomas are usually diagnosed as microadenomas. Excess ACTH secretion causes hypercortisolism (Cushing syndrome) in these patients. If the adrenal glands are excised surgically for treatment, large destructive pituitary adenomas may occur in these patients, causing Nelson syndrome.

8.1.2 Hypopituitarism

Hypopituitarism is defined as deficiency of the secretion of pituitary hormones. Hypofunction of the anterior lobe does not occur until approximately 75% of the parenchyma is destroyed. Hypopituitarism can be due to both hypothalamic

and pituitary diseases, such as pituitary adenoma (due to compression), traumatic brain injury, radiation exposure, and ischemic necrosis of the pituitary gland.

Two main syndromes are associated with the posterior lobe: diabetes insipidus and syndrome of inappropriate ADH secretion (SIADH). Deficiency of ADH in the posterior lobe causes central diabetes insipidus. However, unresponsiveness of ADH in the renal tubules causes nephrogenic diabetes insipidus. In SIADH, due to excess ADH secretion, water resorption increases that causes hyponatremia [1].

8.1.3 Craniopharyngioma

Craniopharyngioma is a benign epithelial tumor that usually occurs in the suprasellar region. This slow-growing tumor is derived from remnants of the Rathke pouch. The histological features of this tumor differ in children and adults. The adamantinomatous type, in children, is composed of nests or cords of stratified squamous epithelium; compact, lamellar keratin (wet keratin); dystrophic calcification; cysts; fibrosis; and chronic inflammatory infiltration. Papillary craniopharyngioma, on the other hand, is seen in adults and typically forms papillary architecture lined by squamous epithelium. Genetic alterations differ in these two types as well: the adamantinomatous type harbors beta-catenin mutations, whereas the papillary type shows BRAF V600E mutations [9].

8.2 Thyroid

The thyroid gland, composed of two lobes joined by an isthmus, originates from a pharyngeal endodermal outgrowth that migrates to the anterior neck; this embryologic pathway explains an occasional ectopic thyroid tissue (ETT) such as lingual thyroid. Structurally, it consists of follicles lined by epithelial cells that store thyroglobulin, the precursor of thyroid hormones. Under pituitary TSH stimulation, follicular cells produce thyroxine (T4) and triiodothyronine (T3),

which circulate largely protein-bound. In peripheral tissues, most T4 is converted to T3, the more active form, which binds nuclear receptors to regulate gene transcription. These actions increase metabolic activity across tissues. Clinically, thyroid disorders are significant because they may lead to hyperthyroidism, hypothyroidism, or mass lesions, many of which are treatable by medical or surgical means [1].

8.2.1 Congenital Disorders

8.2.1.1 Thyroglossal Duct Cyst

Thyroglossal duct cyst (TGDC) is the most common congenital anomaly of the thyroid tract, arising from incomplete involution of the embryonic thyroglossal duct. Histologically, TGDCs are lined by squamous or pseudostratified ciliated columnar epithelium, and about one-third contain ectopic thyroid follicles within the cyst wall. Although usually benign, rare cases show malignant transformation, most often to papillary thyroid carcinoma (PTC), which can mimic primary thyroid or nodal disease [10].

8.2.1.2 Ectopic Thyroid Tissue

ETT arises from aberrant migration of the thyroid primordium during embryogenesis and represents a form of thyroid dysgenesis. The most frequent sites are along the thyroglossal duct tract, particularly the tongue base and anterior midline of the neck, although lateral neck and mediastinal locations may also occur. Histologically, ectopic thyroid shows normal thyroid follicular architecture with colloid-containing follicles but can undergo adenomatous hyperplasia or rarely malignant transformation, most often into papillary carcinoma [11]. Genetic studies implicate transcription factors such as NKX2-1, PAX8, FOXE1, and HHEX in thyroid precursor cell specification and migration, and their dysfunction contributes to ectopy and other dysgenetic conditions [12].

8.2.1.3 Solid Cell Nests

Solid cell nests (SCNs) are embryologic remnants of the ultimobranchial body, incidentally

found in thyroidectomy specimens. Histologically, they appear as small clusters of the main cells (p63–/p40-positive, TTF-1-negative) intermixed with calcitonin-positive C-cells, arranged in solid or cystic patterns. Although SCNs may mimic papillary thyroid carcinoma due to overlapping nuclear features, they are benign, show a very low proliferative index, and lack BRAF mutations, which helps in their distinction [13].

8.2.2 Hyperthyroidism

Hyperthyroidism is defined as a pathological state in which the thyroid gland synthesizes and secretes excess thyroxine (T4) and triiodothyronine (T3), leading to increased metabolic activity at the tissue level [14]. Histologically, the underlying causes show distinct patterns: in Graves' disease, diffuse follicular hyperplasia is present with scalloped colloid and lymphoid infiltrates; in toxic multinodular goiter or toxic adenoma, nodules show variable follicle sizes with hyperplastic epithelium, sometimes with papillary infoldings, independent of TSH regulation [14]. Other etiologies include thyroiditis, where follicular disruption and release of preformed hormone dominate, and iatrogenic or exogenous hyperthyroidism, resulting from excessive L-thyroxine administration [15, 16]. Subclinical hyperthyroidism—characterized by suppressed TSH but normal circulating T4/T3—is commonly seen in patients receiving TSH-suppressive therapy for nodular disease or thyroid carcinoma [15, 16]. Across these conditions, the unifying pathological feature is inappropriate thyroid hormone excess, with histological correlates ranging from diffuse hyperplasia to nodular autonomy or follicular cell injury.

8.2.3 Hypothyroidism

Hypothyroidism is defined as an endocrine disorder in which insufficient thyroid hormone production leads to systemic metabolic slowing [17]. Its etiologies are diverse, with histopathological

features varying according to the underlying cause. Autoimmune thyroiditis (most commonly Hashimoto's disease) shows diffuse lymphoplasmacytic infiltration, germinal centers, and Hürthle cell metaplasia, often accompanied by fibrosis [18]. Iodine-induced hypothyroidism demonstrates enlarged follicles with papillary infoldings, epithelial cells with clear cytoplasm, reduced or absent colloid, and frequent capillary dilatation; these changes are reversible with iodine restriction [19]. Musculoskeletal involvement is another pathological expression, with hypothyroid myopathy characterized by type II fiber atrophy, glycogen accumulation, mitochondrial dysfunction, and core-like structural changes in muscle fibers [20]. Additional causes include congenital defects, prior thyroid surgery or radioiodine therapy, and drug-induced hypothyroidism [17].

8.2.4 Thyroiditis

8.2.4.1 Hashimoto's Thyroiditis

Hashimoto's thyroiditis (HT) is the most common autoimmune thyroid disease and a leading cause of hypothyroidism worldwide. Histopathologically, HT is characterized by a diffuse lymphocytic infiltration of the thyroid parenchyma, often forming germinal centers within the gland. Follicular epithelial cells undergo atrophy, while many transform into oncocytic cells, which display abundant granular eosinophilic cytoplasm due to mitochondrial hyperplasia [21]. The interstitium frequently shows progressive fibrosis, sometimes mimicking nodular lesions, with more prominent stromal changes in the fibrous variant [22]. In IgG4-related HT, an intense lymphoplasmacytic infiltrate enriched in IgG4-positive plasma cells can be observed, often associated with obliterative phlebitis and storiform fibrosis [21]. Over time, the gland may shrink to a small, atrophic, fibrotic remnant. Importantly, this chronic inflammatory microenvironment has been associated with an elevated risk of papillary thyroid carcinoma and thyroid lymphoma, highlighting the oncogenic potential of long-standing autoimmune injury [23].

8.2.4.2 Riedel's Thyroiditis

Riedel's thyroiditis is a rare fibroinflammatory disorder of the thyroid characterized by extensive replacement of the gland by dense, keloid-like collagen and fibroblasts, with infiltration extending beyond the capsule into adjacent neck structures. Histologically, the thyroid parenchyma is nearly obliterated, leaving only occasional entrapped follicles, while a mixed inflammatory infiltrate of lymphocytes, plasma cells, neutrophils, and eosinophils permeates the fibrous stroma [24].

8.2.4.3 Subacute (Granulomatous) Thyroiditis

Subacute thyroiditis is a self-limiting inflammatory thyroid disorder, often triggered by viral infections in genetically predisposed individuals, with HLA-B*35 and other alleles linked to susceptibility [25]. Histopathologically, the thyroid shows disrupted follicles with granulomatous inflammation, including clusters of epithelioid histiocytes, multinucleated giant cells ingesting colloid, and a mixed inflammatory infiltrate of lymphocytes, macrophages, and occasional neutrophils [26]. Clinically, patients often experience painful neck swelling, fever, and transient thyrotoxicosis, though painless variants have been increasingly recognized, particularly during COVID-19-associated cases [25]. Long-term outcomes are usually favorable, but a minority of patients may develop persistent hypothyroidism after resolution [27].

8.2.5 Graves' Disease

Graves' disease is an autoimmune thyroid disorder in which thyroid-stimulating hormone receptor (TSH-R) autoantibodies drive uncontrolled follicular cell proliferation and hormone release, leading to hyperthyroidism [28]. Histopathologically, the thyroid typically shows diffuse follicular epithelial hyperplasia, with tall columnar cells and scalloped colloid, often accompanied by lymphocytic infiltrates. In contrast to nodular hyperplasia, the process is uniform across the gland, giving rise to diffuse

goiter. In extrathyroidal tissues, particularly the orbit and dermis, fibroblasts and preadipocytes respond to TSH-R stimulation, resulting in glycosaminoglycan deposition, edema, and tissue remodeling, which underpin Graves' ophthalmopathy and dermopathy. Recent immunopathological studies emphasize the role of dendritic cells, B-cell activating factor, CD40/CD40L signaling, and chemokines such as CXCL9–CXCL11 in amplifying inflammation and autoantibody production [29].

8.2.6 Follicular Nodular Disease

Follicular nodular disease (FND), introduced in the 2022 WHO classification, refers to a spectrum of multifocal follicular lesions that frequently present clinically as multinodular goiter. Histologically, FND demonstrates nodules with highly variable morphology, ranging from large colloid-rich macrofollicular structures to small cellular microfollicular proliferations, sometimes with incomplete or absent capsules [30] (Fig. 8.2). Some nodules mimic adenomas, while others show hyperplastic features, reflecting a mixture of polyclonal hyperplasia and clonal neoplasia; this duality explains why malignant transformation may arise within multinodular goiter [31]. At the molecular level, FND is often associated with activating mutations in the TSH-R and GNAS genes, as well as alterations in EZH1, ZNF148, and SPOP, which drive activation of the cAMP-PKA pathway and contribute to nodular growth and, occasionally, functional autonomy [32].

8.2.7 Tumors of the Thyroid

8.2.7.1 Papillary Carcinoma

Papillary thyroid carcinoma represents the most frequent thyroid malignancy of follicular epithelial origin and is primarily diagnosed based on its nuclear features including optically clear chromatin (ground-glass appearance), irregular nuclear contours, pseudoinclusions, and grooves [33]. The ground-glass nuclei are enlarged, optically clear, and overlapping, with a distinct

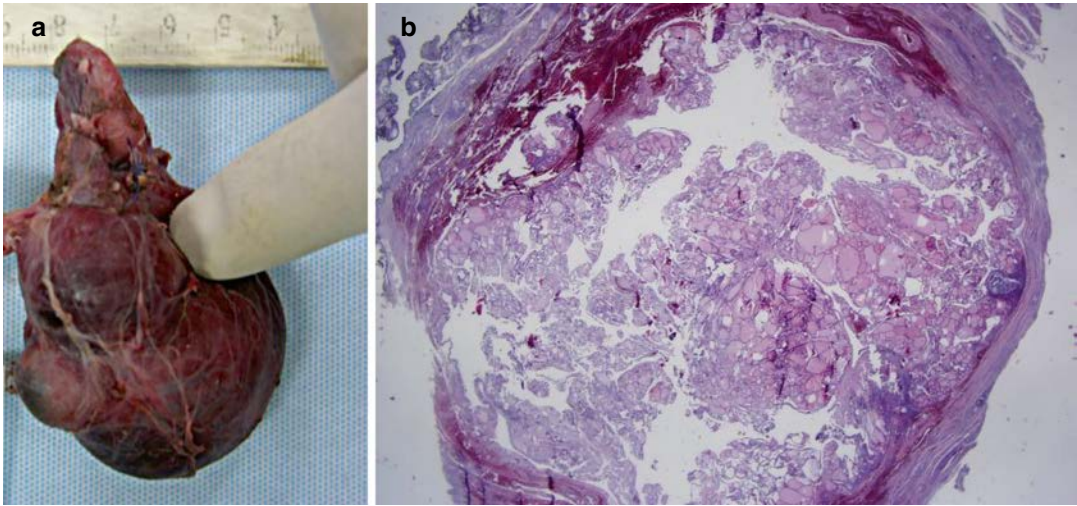


Fig. 8.2 Follicular nodular disease. (a) Macroscopically, large and small, multiple nodular lesions. (b) Microscopically, relatively well-defined nodule composed

of large colloid-rich macrofollicular and microfollicular proliferations, with degenerative changes (hemorrhage, cystic degeneration) (HE, ×20)

nuclear membrane that gives the impression of an empty nucleus. This artifact, observed only in paraffin sections, is considered a defining diagnostic feature. Nuclear pseudoinclusions, formed by invagination of cytoplasm into the nucleus, are also characteristic. These inclusions are referred to as “Little Orphan Annie eyes,” a term derived from the comic strip character created by Harold Gray in 1924. Unlike ground-glass nuclei, they may be seen not only in paraffin sections but also in frozen sections and fine-needle aspiration cytology specimens. Nuclear longitudinal grooves formed by infolding of the nuclear membrane are likewise considered a key diagnostic feature. Psammoma bodies are found in about half of papillary carcinoma cases, and the presence of psammoma bodies alone in a cervical lymph node is regarded as strong evidence of metastatic papillary carcinoma. Similarly, the demonstration of psammoma bodies in frozen sections or cytology preparations is highly suggestive of papillary carcinoma. Mitoses are rare or absent. Histologically, the classic variant shows well-developed papillae with fibrovascular cores, often accompanied by psammoma bodies and stromal fibrosis (Fig. 8.3). Recent WHO 2022 classification updates emphasize the need for detailed subtyping of PTCs, even when they

are ≤ 1 cm in size, to better capture the biological variability of papillary microcarcinomas [30].

Morphological variants provide critical prognostic information. The classic type often harbors *BRAF V600E* mutations and is associated with lymph node metastasis. The follicular variant includes encapsulated (RAS-like, indolent) and infiltrative (BRAF-like, aggressive) forms, highlighting the importance of growth pattern and nuclear morphology in classification [33]. High-risk subtypes such as the tall cell, columnar cell, and hobnail variants are characterized by prominent nuclear atypia, mitotic activity, and frequent vascular invasion; these subtypes correlate with poorer outcomes. The diffuse sclerosing variant, enriched in younger patients, shows widespread stromal fibrosis, dense lymphocytic infiltrates, and abundant psammoma bodies.

On the molecular level, PTCs can be divided into two broad groups: BRAF-like tumors, driven by *BRAF V600E* or fusions involving *RET*, *NTRK*, and *ALK*, which usually display infiltrative growth, classic nuclear features, and higher metastatic potential, and RAS-like tumors, which include encapsulated follicular variants and often carry *NRAS*, *HRAS*, or *KRAS* mutations, corresponding to indolent clinical behavior [30, 34]. In addition, telomerase reverse transcriptase (TERT)

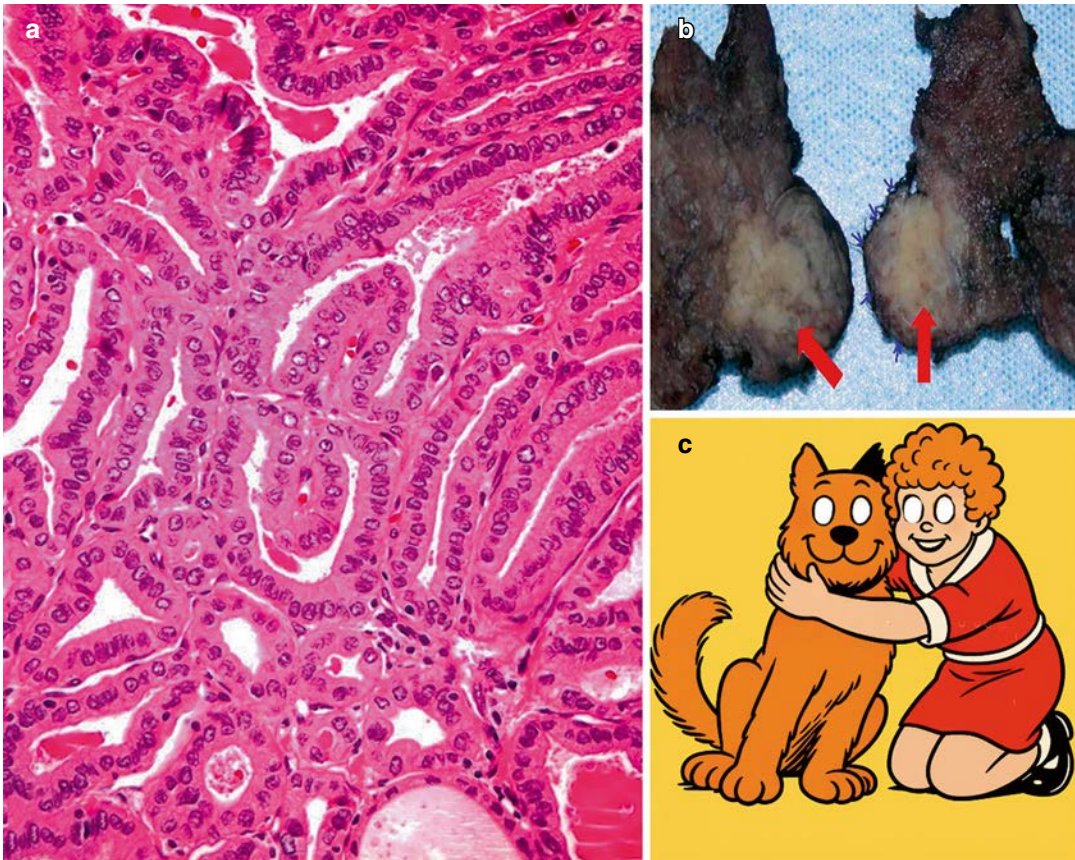


Fig. 8.3 Thyroid papillary carcinoma. (a) Microscopically, tumor presents papillary structures, and nuclei are characterized with irregular nuclear contours, grooves, and clear chromatin. (b) Macroscopically, white-

colored, firm, solid lesion with irregular borders (arrows). (c) Little Orphan Annie, the famous comic strip character who gave her name to the special transparent nuclei of tumor cells

promoter mutations and *TP53* alterations mark progression to more aggressive phenotypes and overlap with poorly differentiated thyroid carcinoma (PDTC).

A significant new development is the recognition of differentiated high-grade thyroid carcinoma, a category that includes tumors with classical PTC morphology but with ≥ 5 mitoses per 2 mm² and/or tumor necrosis. These lesions bridge the gap between well-differentiated and poorly differentiated carcinoma, underscoring the continuum of thyroid tumor progression [34].

Collectively, these advances highlight the integration of histopathology with molecular diagnostics in modern thyroid pathology. Morphological subtyping, combined with mutational profiling, refines risk stratification, guides

management, and prevents overtreatment of indolent forms such as noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) while ensuring appropriate recognition of aggressive PTC variants.

8.2.7.1.1 Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features

NIFTP was established to reclassify noninvasive encapsulated follicular variant of papillary thyroid carcinoma as a borderline tumor, reflecting its indolent biological behavior and avoiding overtreatment associated with the term “carcinoma” [35]. Histopathologically, NIFTP presents as a well-circumscribed, often encapsulated follicular-patterned neoplasm

lacking vascular or capsular invasion. The nuclei display papillary carcinoma-type alterations such as clearing, grooves, and irregular membranes, but true papillae, psammoma bodies, necrosis, or high mitotic activity are absent [36]. To ensure accurate diagnosis, extensive sampling of the capsule is critical, since even focal invasion would exclude the diagnosis of NIFTP. From a molecular standpoint, NIFTP is strongly associated with RAS mutations, while BRAF V600E and RET/NTRK fusions are characteristically absent [30]. Clinically, lobectomy alone is curative, and long-term follow-up studies confirm an extremely low risk of recurrence or metastasis, supporting conservative management.

8.2.7.2 Follicular Neoplasms

Follicular thyroid neoplasms encompass benign follicular adenoma (FA) and malignant follicular thyroid carcinoma (FTC), both originating from follicular epithelial cells. Histopathologically, FAs are well-circumscribed, frequently encapsulated nodules composed of follicular structures without evidence of capsular or vascular invasion. Variants include oncocytic adenomas, defined by >75% oncocytic cells, and adenomas with papillary architecture, often associated with functional activity [30]. By contrast, FTC is diagnosed when capsular and/or vascular invasion is demonstrated, while papillary-type nuclear features are absent. According to the 2022 WHO classification, FTC is subdivided into minimally invasive, encapsulated angioinvasive, and widely invasive types, with prognosis worsening as the extent of invasion increases [34]. Both FA and FTC are part of the RAS-like molecular pathway. FAs frequently show RAS mutations, TSH-R and GNAS alterations, and occasionally EZH1 mutations in functional adenomas. FTCs also harbor NRAS, HRAS, KRAS, PAX8-PPARG, and THADA fusions, supporting their clonal neoplastic nature. Oncocytic tumors often demonstrate mitochondrial DNA mutations and widespread chromosomal copy number alterations. Importantly, BRAF V600E mutations—common in papillary thyroid carcinoma—are absent in both FA and FTC [30]. FTC prognosis depends

on invasion pattern. Minimally invasive FTC has an excellent outcome, often cured surgically. In contrast, angioinvasive and widely invasive FTCs carry a higher risk of hematogenous spread, especially to the bone and lungs, and therefore a worse prognosis [30, 34]. Oncocytic carcinomas tend to behave more aggressively than conventional FTCs.

8.2.7.3 Medullary Carcinoma

Medullary thyroid carcinoma (MTC) is a C-cell-derived neuroendocrine neoplasm characterized by calcitonin production and distinct morphologic and molecular features. Histologically, MTC often presents as solid, trabecular, or nested growth patterns with polygonal, plasmacytoid, or spindle-shaped tumor cells (Fig. 8.4). Tumor stroma commonly contains amyloid deposits derived from altered calcitonin peptides, and immunohistochemistry confirms expression of calcitonin, CEA, chromogranin A, and synaptophysin, distinguishing it from follicular-derived thyroid carcinomas [30]. The 2022 WHO classification recognizes MTC within the thyroid C-cell neoplasm category, with grading based on mitotic activity, necrosis, and Ki-67 index. The International Medullary Thyroid Carcinoma Grading System defines high-grade tumors by ≥ 5 mitoses/2 mm², necrosis, or Ki-67 $\geq 5\%$ and has proven prognostic relevance [34, 37]. Molecular genetics play a central role in MTC pathogenesis. About 20–25% of cases are hereditary, associated with germline RET mutations in MEN2A, MEN2B, or familial MTC. Sporadic MTCs often harbor somatic RET alterations, or less commonly HRAS/NRAS mutations, which are mutually exclusive with RET [38]. RET copy number alterations and rare MET variants have also been described. Prognosis is influenced by stage, grade, and molecular profile. Low-grade MTCs, particularly those without angioinvasion, often have a relatively favorable course, whereas high-grade tumors and those with RET p.M918T mutations carry higher risks of recurrence and metastasis to lymph nodes, lung, and liver. Hereditary MTC patients benefit from early detection and prophylactic thyroidectomy based on RET mutation type, while advanced disease

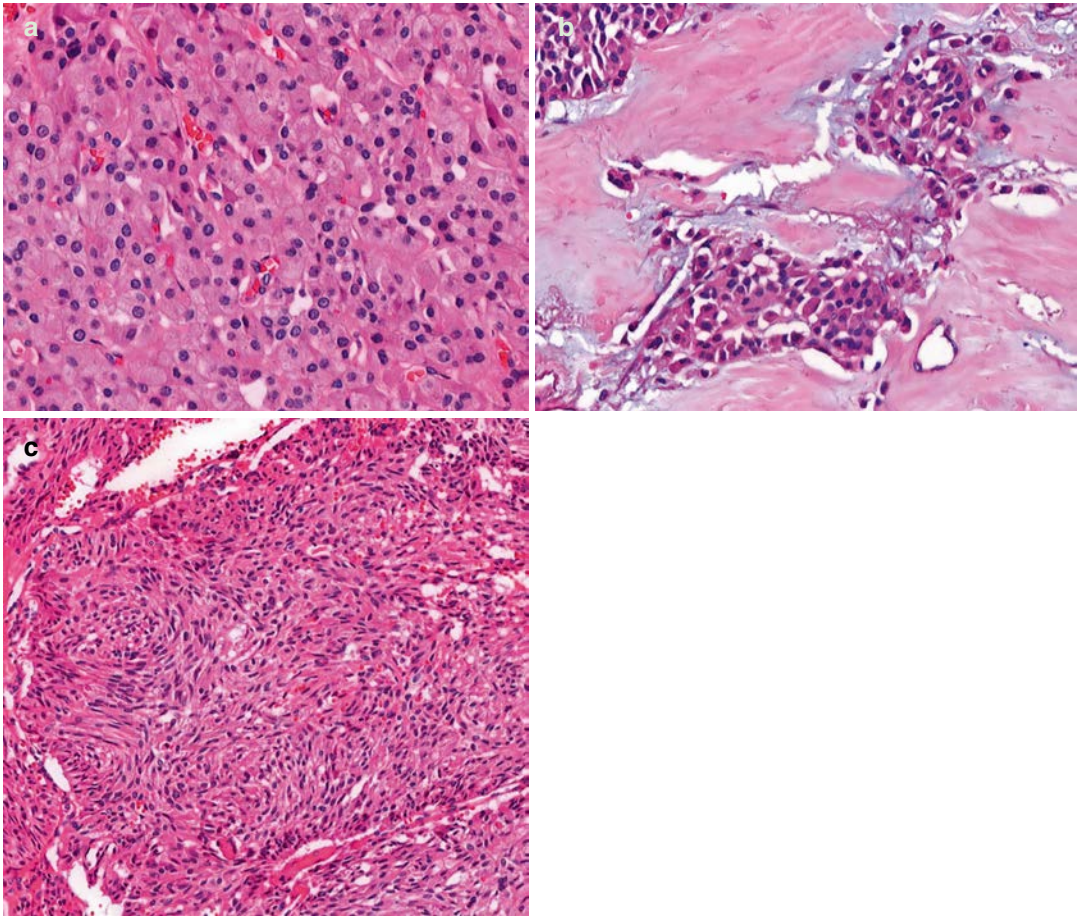


Fig. 8.4 Multiple faces of thyroid medullary carcinoma. Microscopically, solid, trabecular, or nested growth patterns with polygonal (a), plasmacytoid (b), and spindle-shaped tumor cells (c) (HE, $\times 200$, $\times 100$)

may respond to selective RET inhibitors or peptide receptor radionuclide therapy in selected cases [30, 38].

8.2.7.4 Poorly Differentiated Thyroid Carcinoma

PDTC represents an intermediate entity between well-differentiated (papillary and follicular) carcinomas and undifferentiated (anaplastic) carcinomas. The Turin proposal established uniform diagnostic criteria, requiring a solid, trabecular, or insular growth pattern, the absence of classic papillary carcinoma nuclear features, and the presence of such as convoluted nuclei, ≥ 3 mitoses per 10 HPF, or tumor necrosis [39]. PDTC often displays insular or trabecular nests of small, hyperchromatic tumor cells, sometimes with convoluted or raisin-like nuclei. Mitotic figures and

necrotic foci are frequent, and vascular invasion may be prominent. Immunohistochemically, tumors retain expression of thyroglobulin and TTF-1, though often with weaker or dot-like cytoplasmic staining compared to well-differentiated counterparts [39]. PDTCs harbor RAS mutations, TERT promoter mutations, or less frequently BRAF V600E, particularly in tumors arising from papillary carcinoma. Mutations in TP53 and alterations in the PI3K/AKT/mTOR pathway are more frequent in widely invasive or dedifferentiated forms, contributing to their aggressive course [30, 34]. Clinically, PDTC is more aggressive than differentiated thyroid carcinomas but less lethal than anaplastic carcinoma. The extent of necrosis, mitotic activity, and extrathyroidal extension correlate strongly with outcome. Five-year survival

rates range from 50% to 70%, with mortality largely due to distant metastasis, commonly to the lungs and bones [39].

8.2.7.5 Anaplastic Thyroid Carcinoma

Anaplastic thyroid carcinoma (ATC) is the most aggressive form of thyroid malignancy, representing the endpoint of follicular cell dedifferentiation. Histologically, it demonstrates diverse morphologies, including spindle cell, epithelioid, giant cell, rhabdoid, and squamoid patterns, frequently with marked nuclear pleomorphism, high mitotic activity, and extensive tumor necrosis [40]. Immunohistochemically, ATC often retains cytokeratin and PAX8 expression but lacks thyroglobulin and TTF-1, aiding distinction from well-differentiated thyroid carcinomas [30]. The 2022 WHO classification designates ATC as the most undifferentiated follicular cell-derived tumor, and squamous cell carcinoma of the thyroid is now included as an ATC subtype [30, 34]. Molecular alterations in ATC include frequent mutations in TERT promoter ($\approx 75\%$), TP53 ($\approx 60\%$), BRAF V600E ($\approx 45\%$), RAS ($\approx 25\%$), and PIK3CA/PTEN/EIF1AX. Many tumors harbor co-mutations (e.g., BRAF or RAS with TERT), which correlate with more aggressive behavior [40]. Prognosis remains extremely poor, with median survival of only 3–5 months and $<20\%$ 1-year survival. While conventional therapy offers limited benefit, targeted agents such as BRAF/MEK inhibitors (dabrafenib + trametinib) and RET/ALK inhibitors have shown responses in molecularly selected patients [41].

8.3 Parathyroid

Parathyroid pathology encompasses a continuum from benign proliferations to aggressive malignancies. The 2022 WHO classification introduced key updates, discouraging the generic term “primary hyperplasia” and redefining it as multiglandular parathyroid disease (multiglandular neoplasia), particularly in the context of hereditary syndromes such as MEN1, MEN4, and CDC73-related disorders [42]. Multiglandular parathyroid disease usually affects all four glands, though enlargement may be asymmetric.

Histologically, it is most often chief cell hyperplasia, but oxyphil and water-clear cell variants occur. Growth can be diffuse, with uniform replacement of adipose tissue, or nodular, sometimes mimicking adenomas [43]. Molecular studies support a neoplastic origin in at least a subset, with alterations in MEN1, CDKN1B (p27), and CASR in hereditary forms. Prognostically, hyperplasia is benign, though persistence or recurrence of hyperparathyroidism is frequent due to multigland involvement, particularly in MEN1 patients [44].

Primary hyperparathyroidism most often arises from a solitary parathyroid adenoma, less commonly from diffuse hyperplasia, and rarely from carcinoma. Microscopically, adenomas are composed mainly of chief cells with little intervening adipose tissue and a rim of compressed normal parathyroid at the periphery. Genetic drivers include cyclin D1 rearrangements and MEN1 mutations. Clinically, bone resorption leads to osteitis fibrosa cystica and brown tumors, while renal changes include nephrolithiasis and nephrocalcinosis [1].

Secondary hyperparathyroidism typically develops in chronic renal failure, where phosphate retention and reduced vitamin D activation cause persistent hypocalcemia. Histologically, the parathyroid glands are hyperplastic, often showing nodular or diffuse chief cell proliferation, sometimes with “water-clear” cytoplasm. The glands lack adipose tissue, and skeletal lesions may resemble those of primary disease, although generally less severe. In advanced cases, calciphylaxis due to vascular calcification may occur. Hypoparathyroidism, by contrast, is rare and usually results from surgical removal of parathyroids, autoimmune destruction, or congenital absence (e.g., DiGeorge syndrome). Histologically, there is absence or atrophy of parathyroid tissue. Clinically, hypocalcemia manifests with neuromuscular irritability (tetany, muscle spasms, seizures) and in chronic settings may cause calcification of basal ganglia, cataracts, and dental abnormalities [1].

Parathyroid adenomas are typically solitary, well-circumscribed proliferations of chief cells with reduced stromal fat (Fig. 8.5). Variants include oncocytic adenomas and those with pap-

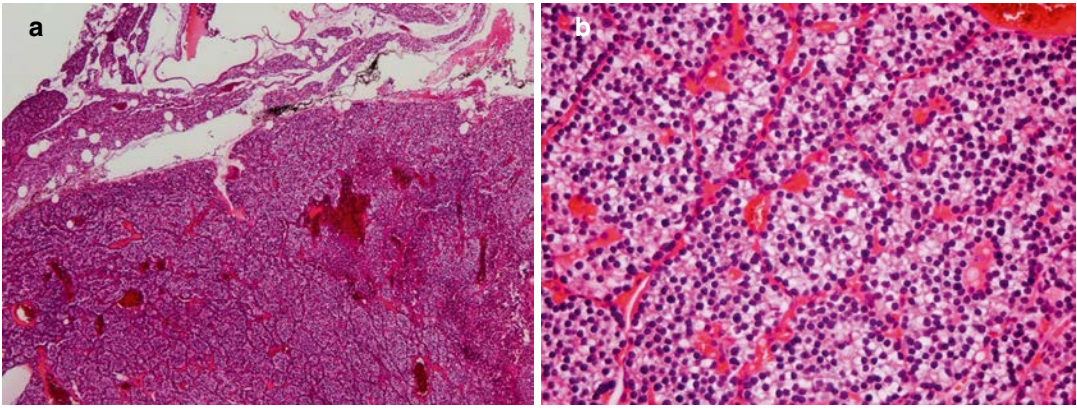


Fig. 8.5 Parathyroid adenoma. (a) Well-circumscribed, solid, nodular lesion with adjacent normal parathyroid tissue (HE, $\times 40$). (b) Proliferation of uniform cells, with reduced stromal fat (HE, $\times 200$)

illary architecture. They are benign and curable with excision.

Atypical parathyroid tumors, formerly “atypical adenomas,” demonstrate fibrous bands, mitotic activity, or focal necrosis but lack unequivocal invasive features. Their malignant potential is uncertain, and long-term surveillance is recommended [42].

Parathyroid carcinoma is rare (<1% of primary hyperparathyroidism) and defined by vascular, lymphatic, or perineural invasion, direct extension, or metastasis. Morphologically, PCs are bulky and fibrotic, with high mitotic activity and atypical nuclei [45]. Molecularly, CDC73/HRPT2 mutations with parafibromin loss are characteristic, and germline CDC73 alterations occur in up to 30% of apparently sporadic cases. Additional markers such as Rb, galectin-3, and Ki-67 may aid distinction [43]. Recurrence and metastasis, particularly to the lungs and bones, are common, and only complete en bloc resection offers durable remission [44].

8.4 Adrenal Glands

The adrenal gland is an endocrine organ composed of two parts: cortex and medulla. Adrenal cortex, which constitutes 90% of the gland, has three zones called zona glomerulosa (the outermost layer), zona fasciculata (the middle,

thickest layer), and zona reticularis (the innermost layer). Each layer synthesizes different steroids: glucocorticoids (mainly cortisol) are synthesized primarily in zona fasciculata, mineralocorticoids (mainly aldosterone) is synthesized in zona glomerulosa, and sex steroids (androgens) are synthesized in zona reticularis. The adrenal medulla, on the other hand, is composed of chromaffin cells (specialized neural crest cells) which synthesize catecholamines (mainly epinephrine) and sustentacular cells [1, 46].

Adrenal cortical diseases occur either as hyperfunction or hypofunction of the gland. Adrenocortical hyperfunction, also known as hyperadrenalism, appears as hypercortisolism, hyperaldosteronism, or adrenogenital (virilizing) syndromes, according to overproduction of hormones from the adrenal cortex. Adrenal cortical proliferations, formerly known as nodular hyperplasia or primary bilateral macronodular hyperplasia, are currently collected under the term “adrenal cortical nodular disease,” which is appreciated under three categories: [1] sporadic nodular adrenocortical disease, [2] bilateral nodular micronodular adrenocortical disease, and [3] bilateral macronodular adrenocortical disease [47]. Other adrenal cortical proliferations include bilateral diffuse adrenal cortical hyperplasia, adrenocortical adenoma, and adrenocortical carcinoma.

8.4.1 Hypercortisolism

Hypercortisolism (Cushing syndrome) can arise due to exogenous glucocorticoid utilization, which is also known as iatrogenic Cushing syndrome, or endogenous causes. Most of the endogenous causes are ACTH-dependent. ACTH-secreting pituitary adenoma is the most common cause of Cushing syndrome, followed by ectopic ACTH secretion from nonpituitary tumors, the most common of which is small cell carcinoma of the lung. Hypercortisolism, specifically due to pituitary adenoma that secretes ACTH, is named as Cushing disease [Robbins, Juszczak]. Pituitary adenomas cause enlargement of both adrenal glands due to excess ACTH levels, whereas malignancy prevents prominent adrenocortical hyperplasia in the latter case [1].

ACTH-independent endogenous Cushing syndrome can occur due to adrenocortical adenoma or less commonly to adrenocortical carcinoma. Bilateral macro- or micronodular adrenal hyperplasia and McCune-Albright syndrome are among rare causes of ACTH-independent endogenous Cushing syndrome.

Morphologically, the main lesions of Cushing syndrome are seen in the pituitary and the adrenal glands. In the pituitary glands, high levels of glucocorticoids cause accumulation of intermediate keratin filaments in the cytoplasm of ACTH-producing cells of the adenohypophysis. Granular basophilic cytoplasm of corticotroph cells become pale and homogeneous, which is called Crooke's hyaline change. In the adrenal glands, morphologic appearance depends on the cause of hypercortisolism (Table 8.2). Cushing syndrome

due to exogenous glucocorticoid utilization leads to adrenocortical atrophy, as a result of endogenous ACTH suppression. Endogenous hypercortisolism, on the other hand, causes either diffuse/macronodular/micronodular hyperplasia of the adrenal glands, or primary adrenocortical neoplasm is encountered.

8.4.2 Hyperaldosteronism

Hyperaldosteronism is characterized by chronic overproduction of aldosterone. In primary hyperaldosteronism, excess aldosterone secretion occurs autonomously from the adrenal glands, which leads to sodium and water retention as well as vascular remodeling (stiffening). Increased venous return and increased cardiac output cause hypertension in these patients. Plasma renin levels are low due to feedback suppression. In the most recent WHO classification of adrenal cortical tumors, HISTALDO classification, which uses CYP11B2 immunohistochemistry to identify functional aldosterone-producing sites in primary hyperaldosteronism patients, in order to predict the risk of bilateral disease is endorsed [47]. In secondary hyperaldosteronism, on the other hand, extra-adrenal causes, such as renal artery stenosis, congestive heart failure, cirrhosis, nephrotic syndrome, or pregnancy, induce aldosterone overproduction by stimulating the renin-angiotensin-aldosterone system. Therefore, plasma renin levels are high in these patients. The most common cause of primary hyperaldosteronism is bilateral idiopathic hyperaldosteronism, followed by adrenocortical adenoma, that is also known as Conn syndrome.

Morphologically, aldosterone-producing adenomas are usually solitary, small, well-circumscribed lesions, with typical bright yellow cut surface. Microscopically, the tumor consists of uniform lipid-laden cortical neoplastic cells. The antihypertensive treatment, spironolactone, typically generates eosinophilic laminated cytoplasmic inclusions in the neoplastic cells in these patients, called spironolactone bodies.

Table 8.2 Morphological appearances of the adrenal gland in Cushing syndrome, according to cause of the disease

Cause	Adrenal morphology
Exogenous steroids	Bilateral cortical atrophy
Pituitary adenoma (Cushing disease)	Bilateral diffuse/nodular hyperplasia
Ectopic ACTH	Bilateral hyperplasia
Adrenal adenoma/carcinoma	Tumor on one side, contralateral atrophy

8.4.3 Adrenogenital Syndromes

Adrenogenital syndromes are sexual differentiation disorders, such as virilization or feminization. Androgen overproduction can be due to adrenocortical carcinoma or congenital adrenal hyperplasia (CAH). As opposed to hypercortisolism and hyperaldosteronism, adrenogenital syndromes tend to be more commonly associated with adrenal malignancies, i.e., adrenocortical carcinoma. CAH evolves from a group of autosomal recessive metabolic diseases. The most common cause of CAH is 21-hydroxylase deficiency, in which both cortisol and aldosterone synthesis are impaired, while testosterone synthesis is increased. 21-Hydroxylase deficiency can present as classical (salt-wasting) adrenogenital syndrome, simple virilizing adrenogenital syndrome, or nonclassic adrenal virilism. Classical syndrome is the most aggressive one, which shows total lack of the enzyme, 21-hydroxylase.

Morphologically, the adrenal glands display bilateral hyperplasia in 21-hydroxylase deficiency. The adrenal cortex is thickened with nodule formations. The cut surface of the thickened cortex is brown due to total loss of lipid.

8.4.4 Adrenal Insufficiency

Adrenal insufficiency is a clinical syndrome that occurs due to deficiency of cortisol and occasionally aldosterone. Primary acute adrenocortical insufficiency (adrenal crisis) is an urgent condition that may be fatal. A specific entity that causes acute adrenocortical insufficiency, with massive bilateral adrenal hemorrhage due to bacterial *Neisseria meningitidis* septicemia, is called Waterhouse-Friderichsen syndrome. It is crucial to recognize this entity, since antibiotics are life-saving. Primary chronic adrenal insufficiency, also known as Addison disease, occurs most frequently due to autoimmune adrenalitis. Other rare causes include tuberculosis, various infections, adrenal hemorrhage, metastatic disease, and genetic disorders [48]. Clinical symptoms usually do not appear until nearly 90% of the adrenal cortex is destroyed. Most common symp-

toms occur due to cortisol insufficiency, such as hypotension, weight loss, and weakness; aldosterone insufficiency, such as hyponatremia, hyperkalemia, and dehydration; and excess ACTH levels. Morphologically, in primary autoimmune adrenalitis, the adrenal glands are reduced in size. Microscopically, few scattered cortical cells are seen in the collapsed fibrous tissue of the cortex, and lymphocytic infiltration usually extends into the medulla.

Secondary adrenocortical insufficiency arises either due to pituitary or hypothalamic disorders or more frequently as a result of abrupt discontinuation of long-term glucocorticoid utilization. In this case, only symptoms of cortisol insufficiency are seen, and aldosterone levels are preserved.

8.4.5 Adrenocortical Neoplasms

Adrenocortical neoplasms are mostly sporadic. Nevertheless, there are some familial cancer syndromes which predispose to adrenocortical carcinoma development, the most of which are Li-Fraumeni syndrome, Beckwith-Wiedemann syndrome, and Lynch syndrome. Functional adenomas are usually associated with hyperaldosteronism and Cushing syndrome. The possibility of malignancy in virilizing neoplasms is higher [1, 49].

Adrenocortical adenomas are generally silent tumors that are detected incidentally. Some functional tumors secrete cortisol or aldosterone. They are usually well-circumscribed nodular lesions, the cut surface of which differ according to hormonal production of the tumor (Fig. 8.6). Aldosterone-producing tumors tend to be bright yellowish-orange in color due to lipid deposition, whereas cortisol-producing tumors are often tan to brown. Microscopically, neoplastic cells are similar to adrenocortical cells, with small nucleus and eosinophilic or vacuolated cytoplasm (Fig. 8.7) [47].

Adrenocortical carcinomas, as opposed to adenomas, more often tend to be functional. Particularly in females virilization can be seen due to excess androgen production. These tumors are usually large, invasive lesions which can be

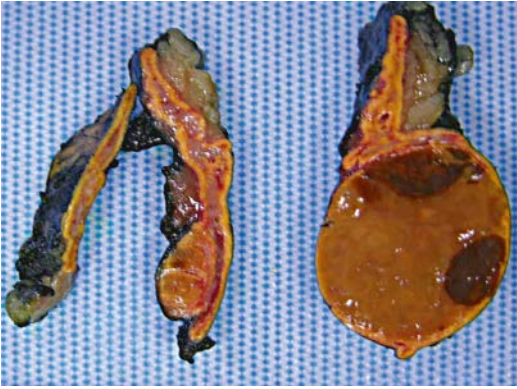


Fig. 8.6 Adrenocortical adenoma. In the serially sectioned adrenalectomy material, the tumor adjacent to the adrenal gland is well-circumscribed and is composed of a yellow firm tissue which is similar to the adrenal cortex. A few hemorrhagic foci within the tumor are seen

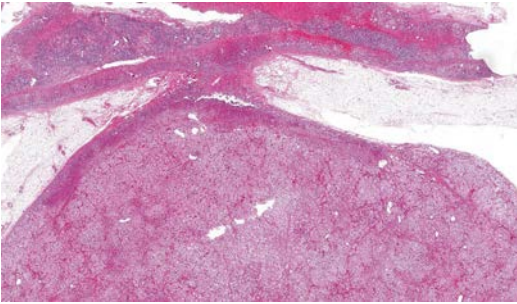


Fig. 8.7 Adrenocortical adenoma. Microscopically, the encapsulated tumor at the bottom of the picture is composed of neoplastic cells with abundant foamy cytoplasm, that resembles normal adrenal fasciculata present at the top (H&E, $\times 250$)



Fig. 8.8 Adrenocortical carcinoma. The cut surface of the tumor adjacent to the adrenal gland is heterogeneous with areas of necrosis, hemorrhage, and cystic spaces

>20 cm in size. The cut surface of the tumors may display necrosis, hemorrhage, and/or cystic changes (Fig. 8.8). Macroscopically, invasion of

the adjacent adipose tissue and/or organs as well as regional veins can be prominent. In diagnosing adrenal cortical carcinomas, classic Weiss criteria described in 1984 and modified in 1989 are used. Histological parameters evaluated in Weiss scoring system are as follows: high Fuhrman nuclear grade, mitotic count $>5/50$ high-power fields, atypical mitosis, necrosis, diffuse architecture $>30\%$ of tumor volume, clear cells $\leq 25\%$ of the tumor volume, and capsular, venous, and sinusoidal (lymphatic) invasion. Other diagnostic systems, such as reticulin algorithm and Lin-Weiss-Bisceglia and Helsinki scoring systems, have also been defined in the recent WHO classification of adrenal cortical tumors [47]. In the pediatric age group, however, the Weiss system is used instead of Weiss criteria, in order to avoid over-diagnosis.

8.4.6 Adrenal Medulla

The adrenal medulla is different than the cortex, in terms of both developmentally, functionally, and structurally. Tumors that arise in the medulla are called pheochromocytoma, meaning “dusky colored tumor” in Latin, because the cut surface of these tumors are usually tan to gray-white. If the fresh tumor tissue is placed into potassium-dichromate solution (Zenker solution), the color of the tumor changes into dark brown, due to a process called chromaffin reaction in which stored catecholamines in neoplastic cells oxidize. Extra-adrenal pheochromocytomas are called paragangliomas.

Microscopically, the tumor consists of polygonal chromaffin cells that form small nests, showing alveolar (Zellballen) pattern. Sustentacular cells are lined at the periphery of cell nests. Neoplastic cells have round to oval nuclei with typical salt and pepper chromatin pattern and vacuolated, granular cytoplasm. These tumors are usually rich in vascular structures.

According to the recent WHO classification system, all pheochromocytomas and paragangliomas are considered malignant. Risk assessment of the tumors is suggested with the following parameters: clinical features including tumor

size, location, and recurrence status; histological features including mitotic activity, necrosis, and vascular invasion; proliferation markers including Ki-67 index; and genetic features such as SDHB mutations [50].

References

- Kumar V, Abbas AK, Aster J. Kumar V, Abbas AK, Aster J, editors. Robbins basic pathology. 10th ed. 2021 Philadelphia: Elsevier.
- Scott IS, Chattopadhyay A, Ansorge O. Development and microscopic anatomy of the pituitary gland. In: Feingold KR, Ahmed SF, Anawalt B, et al., editors. Endotext [internet]. 2025. Dartmouth: MDText.com, Inc.
- Asa SL, Mete O, Perry A, Osamura RY. Overview of the 2022 WHO classification of pituitary tumors. *Endocr Pathol* [Internet]. 2022;33(1):6–26. Available from: <https://doi.org/10.1007/s12022-022-09703-7>
- Sav A. Editorial: diagnosis and treatment of non-functioning pituitary tumors. *Front Endocrinol (Lausanne)*. 2025;16:1–3.
- Mete O, Lopes MB. Overview of the 2017 WHO classification of pituitary tumors. *Endocr Pathol*. 2017;28(3):228–43.
- Tortosa F, Webb SM. Novel aspects in histopathology of the pituitary gland. *Endocrinol Diabetes y Nutr*. 2017;64(3):152–61.
- Gubbiotti MA, Baloch Z. An overview of pituitary neuroendocrine tumors (PitNET) and algorithmic approach to diagnosis. *Adv Anat Pathol*. 2023;30(1):79–83.
- De Sousa SMC, Lenders NF, Lamb LS, Inder WJ, McCormack A. Pituitary tumours: molecular and genetic aspects. *J Endocrinol*. 2023;257(3)
- Asa SL, Mete O. What's new in pituitary pathology? *Histopathology*. 2018;72(1):133–41.
- Wei S, LiVolsi VA, Baloch ZW. Pathology of Thyroglossal duct: an institutional experience. *Endocr Pathol*. 2015;26(1):75–9.
- Oguz A, Tuzun D, Ozdemir E, Ersoy R, Yazgan AK, Cakir B. Importance of ectopic thyroid tissue detected in the midline of the neck: single center experience. *Arch Endocrinol Metab*. 2016;60(3):231–5.
- De Felice M, Di Lauro R. Thyroid development and its disorders: genetics and molecular mechanisms. *Endocr Rev*. 2004;25(5):722–46.
- Manzoni M, Roversi G, Di Bella C, Pincelli AI, Cimino V, Perotti M, et al. Solid cell nests of the thyroid gland: morphological, immunohistochemical and genetic features. *Histopathology*. 2016;68(6):866–74.
- Leo SD, Lee SY, Braverman LE. Unit E, Sciences C. Hyperthyroidism: lancet review. *Lancet*. 2016;388(10047):906–18.
- Batrinis ML. The problem of exogenous subclinical hyperthyroidism. *Hormones (Athens)*. 2006;5(2):119–25.
- Biondi B, Palmieri A, Klain M, Schlumberger M, Filetti S, Lombardi G. Subclinical hyperthyroidism: clinical features and treatment options. *Eur J Endocrinol*. 2005;152(1):1–9.
- Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JI, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American association of clinical endocrinologists and the American Thyroid Association. *Thyroid*. 2012;22(12):1200–35.
- Nair PA, Mishra A, Chaudhary A. Pretibial myxedema associated with euthyroid Hashimoto's thyroiditis: a case report. *J Clin Diagnostic Res*. 2014;8(6):1–2.
- Mizukami Y, Michigishi T, Nonomura A, Hashimoto T, Tonami N, Matsubara F, Takazakura E. Iodine-induced hypothyroidism: a clinical and histological study of 28 patients. *J Clin Endocrinol Metab*. 1993;76(2):466–71.
- Sindoni A, Rodolico C, Pappalardo MA, Portaro S, Benvenga S. Hypothyroid myopathy: a peculiar clinical presentation of thyroid failure. Review of the literature. *Rev Endocr Metab Disord*. 2016;17(4):499–519.
- Caturegli P, De Remigis A, Rose NR. Hashimoto thyroiditis: clinical and diagnostic criteria. *Autoimmun Rev* [Internet]. 2014;13(4–5):391–7. Available from: <https://doi.org/10.1016/j.autrev.2014.01.007>.
- Ragusa F, Fallahi P, Elia G, Gonnella D, Paparo SR, Giusti C, et al. Hashimoto's thyroiditis: epidemiology, pathogenesis, clinic and therapy. *Best Pract Res Clin Endocrinol Metab* [Internet]. 2019;33(6):101367. Available from: <https://doi.org/10.1016/j.beem.2019.101367>
- de Paiva CR, Grønhoj C, Feldt-Rasmussen U, von Buchwald C. Association between Hashimoto's thyroiditis and thyroid cancer in 64,628 patients. *Front Oncologia*. 2017;7:1–10.
- Harigopal M, Sahoo S, Recant WM, DeMay RM. Fine-needle aspiration of Riedel's disease: report of a case and review of the literature. *Diagn Cytopathol*. 2004;30(3):193–7.
- Stasiak M, Lewiński A. New aspects in the pathogenesis and management of subacute thyroiditis. *Rev Endocr Metab Disord* [Internet]. 2021;22(4):1027–39. Available from: <https://doi.org/10.1007/s11154-021-09648-y>.
- Lamichaney R, Sherpa M, Das D, Bhutia CT, Laishram S. Fine-needle aspiration of de quervain's thyroiditis (subacute granulomatous thyroiditis): a cytological review of 20 cases. *J Clin Diagnostic Res*. 2017;11(8):EC09–11.
- Alfadda AA, Sallam RM, Elawad GE, Aldhukair H, Alyahya MM. Subacute thyroiditis: Clinical presentation and long term outcome. *Int J Endocrinol*. 2014;2014:794943.
- Antonelli A, Fallahi P, Elia G, Ragusa F, Paparo SR, Ruffilli I, et al. Graves' disease: clinical manifesta-

- tions, immune pathogenesis (cytokines and chemokines) and therapy. *Best Pract Res Clin Endocrinol Metab.* 2020;34(1):1–13.
29. Viola N, Colleo A, Casula M, Mura C, Boi F, Lanzolla G. Graves' disease: is it time for targeted therapy? A narrative review. *Medicina.* 2025;61(3):1–16.
 30. Baloch ZW, Asa SL, Barletta JA, Ghossein RA, Juhlin CC, Jung CK, et al. Overview of the 2022 WHO classification of thyroid neoplasms [internet]. *Endocr Pathol.* Springer US. 2022;33:27–63. Available from: <https://doi.org/10.1007/s12022-022-09707-3>
 31. Jung CK, Bychkov A, Kakudo K. Update from the 2022 World Health Organization classification of thyroid tumors: a standardized diagnostic approach. *Endocrinol Metab.* 2022;37(5):703–18.
 32. Chiba T. Molecular pathology of thyroid tumors: essential points to comprehend regarding the latest WHO classification. *Biomedicine.* 2024;12(4)
 33. Xu B, Serrette R, Tuttle RM, Alzumaili B, Ganly I, Katabi N, et al. How many papillae in conventional papillary carcinoma? A clinical evidence-based pathology study of 235 unifocal encapsulated papillary thyroid carcinomas, with emphasis on the diagnosis of noninvasive follicular thyroid neoplasm with papillary-like nuclear features. *Thyroid.* 2019;29(12):1792–803.
 34. Christofer Juhlin C, Mete O, Baloch ZW. The 2022 WHO classification of thyroid tumors: novel concepts in nomenclature and grading. *Endocr Relat Cancer.* 2023;30(2)
 35. Nikiforov YE, Seethala RR, Tallini G, Baloch ZW, Basolo F, Thompson LDR, et al. Nomenclature revision for encapsulated follicular variant of papillary thyroid carcinoma: a paradigm shift to reduce overtreatment of indolent tumors. *JAMA. Oncologia.* 2016;2(8):1023–9.
 36. Thompson LD. Ninety-four cases of encapsulated follicular variant of papillary thyroid carcinoma: a name change to noninvasive follicular thyroid neoplasm with papillary-like nuclear features would help prevent overtreatment. *Mod Pathol [Internet].* 2016;29(7):698–707. Available from: <https://doi.org/10.1038/modpathol.2016.65>
 37. Asa SL, Mete O. Medullary thyroid carcinoma in the IARC/WHO neuroendocrine schema. *Endocr Pathol [Internet].* 2022;33(3):346–7. Available from: <https://doi.org/10.1007/s12022-022-09728-y>
 38. Jung CK, Agarwal S, Hang JF, Lim DJ, Bychkov A, Mete O. Update on C-cell neuroendocrine neoplasm: prognostic and predictive histopathologic and molecular features of medullary thyroid carcinoma. *Endocr Pathol [Internet].* 2023;34(1):1–22. Available from: <https://doi.org/10.1007/s12022-023-09753-5>
 39. Volante M, Collini P, Nikiforov YE, Sakamoto A, Kakudo K, Katoh R, et al. Poorly differentiated thyroid carcinoma: the Turin proposal for the use of uniform diagnostic criteria and an algorithmic diagnostic approach. *Am J Surg Pathol.* 2007;31(8):1256–64.
 40. Xu B, Fuchs T, Dogan S, Landa I, Katabi N, Fagin JA, et al. Dissecting anaplastic thyroid carcinoma: a comprehensive clinical, histologic, Immunophenotypic, and molecular study of 360 cases. *Thyroid.* 2020;30(10):1505–17.
 41. Bible KC, Kebebew E, Brierley J, Brito JP, Cabanillas ME, Clark TJ, et al. 2021 American Thyroid Association guidelines for Management of Patients with anaplastic thyroid cancer. *Thyroid.* 2021;31(3):337–86.
 42. Erickson LA, Mete O, Juhlin CC, Perren A, Gill AJ. Overview of the 2022 WHO classification of parathyroid tumors. *Endocr Pathol [Internet].* 2022;33(1):64–89. Available from: <https://doi.org/10.1007/s12022-022-09709-1>
 43. Guilmette J, Sadow PM. Parathyroid pathology. *Surg Pathol Clin.* 2019;12:1007–19.
 44. Akirov A, Asa SL, Larouche V, Mete O, Sawka AM, Jang R, et al. The Clinicopathological Spectrum of parathyroid carcinoma. *Front Endocrinol (Lausanne).* 2019;10:1–10.
 45. Duan K, Mete Ö. Parathyroid carcinoma: diagnosis and clinical implications. *Turk Patoloji Derg.* 2015;31:80–97.
 46. Nicolaides NC, Willenberg HS, Bornstein SR, et al. Adrenal cortex: embryonic development, anatomy, histology and physiology. In: Feingold KR, Ahmed SF, Anawalt B, et al., editors. *Endotext [Internet].* South Dartmouth: MDText.com, Inc.
 47. Mete O, Erickson LA, Juhlin CC, de Krijger RR, Sasano H, Volante M, et al. Overview of the 2022 WHO classification of adrenal cortical tumors [internet]. *Endocr Pathol.* Springer US. 2022;33:155–96. Available from: <https://doi.org/10.1007/s12022-022-09710-8>
 48. Charmandari E, Nicolaides NC, Chrousos GP. Adrenal insufficiency. *Lancet.* 2014;383(9935):2152–67.
 49. Lam AK, Yin. Update on adrenal Tumours in 2017 World Health Organization (WHO) of endocrine Tumours. *Endocr Pathol.* 2017;28(3):213–27.
 50. Mete O, Asa SL, Gill AJ, Kimura N, de Krijger RR, Tischler A. Overview of the 2022 WHO classification of Paragangliomas and Pheochromocytomas. *Endocr Pathol [Internet].* 2022;33(1):90–114. Available from: <https://doi.org/10.1007/s12022-022-09704-6>

Pathology of Nonneoplastic Lung Diseases

9

Gulden Diniz , Nur Yücel, and Berna Kömürçüoğlu

In the general classification of lung diseases, the primary distinction, related to the extent of involvement, is between diffuse and focal lesions. Diffuse diseases are mainly classified as obstructive and restrictive diseases (Table 9.1). Restrictive lung disease is a clinical condition characterized by restricted breathing, exertional dyspnea (shortness of breath that worsens with effort), and decreased lung vital capacity. In all restrictive diseases, there is a reduction in the functional capacity of the affected system. Obstructive diseases are those that block the airways. However, the term “obstructive” is gener-

ally used for chronic lesions. In these diseases, abbreviated as COPD, there is narrowing/obstruction of the airways. The main diagnostic methods for lung lesions include auscultation, radiological examinations (chest X-ray, high-resolution computed tomography of the lungs = HRCT), pulmonary function tests, bronchoscopy or thoracoscopic biopsies, and cytological examinations such as sputum smear, transthoracic needle aspiration, bronchial lavage, and brushing. In general, pathological examination plays an important role in the differential diagnosis of lung diseases.

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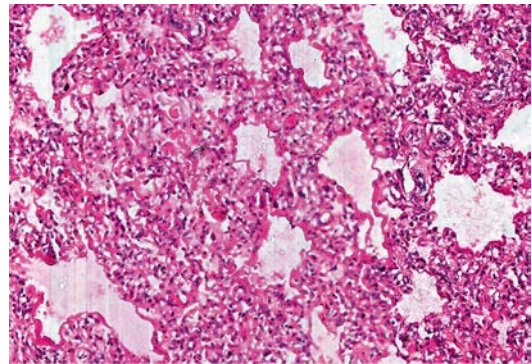
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Table 9.1 Updated classification of nonneoplastic lung diseases

Major group	Examples
Diseases characterized by acute lung injury	Diffuse alveolar damage (DAD), acute respiratory distress syndrome (ARDS), pulmonary edema
Vascular diseases	Pulmonary hypertension, vasculitis (e.g., GPA, EGPA), chronic thromboembolic pulmonary hypertension
Obstructive diseases	Chronic bronchitis, asthma, bronchiolitis obliterans, emphysema
Restrictive diseases	Idiopathic pulmonary fibrosis (UIP), NSIP, AIP, organizing pneumonia, chest wall deformities, and severe obesity
Occupational/environmental diseases	Silicosis, asbestosis, coal worker's pneumoconiosis, berylliosis
Destructive diseases	Emphysema (destructive type), cavitary sequelae of infection, necrotizing bronchiolitis
Infectious diseases	Bacterial pneumonia, viral pneumonitis, tuberculosis, fungal infections
Immune-mediated diseases	Sarcoidosis, hypersensitivity pneumonitis, connective tissue disease–associated ILD, LIP
Miscellaneous nonneoplastic conditions	Pulmonary alveolar proteinosis, eosinophilic pneumonia, lymphangioleiomyomatosis (LAM),

9.1 Diseases Characterized by Acute Lung Injury

Acute lung injury, also referred to by names such as diffuse alveolar damage (DAD) or acute respiratory distress syndrome (ARDS), is defined by the acute onset of noncardiogenic pulmonary edema, hypoxemia, and the need for mechanical ventilation. It is also called hyaline membrane disease in neonates and affects approximately 2% of newborn infants. For neonates, the primary cause is surfactant deficiency. It is more commonly seen in cases of premature birth, prolonged intrauterine asphyxia, and infants born to diabetic mothers. The infant's breathing is rapid, shallow, and labored. Without appropriate treatment, the condition results in cyanosis and death. The formation of hyaline membranes (Fig. 9.1) takes 6–8 hours and peaks at 24–36 hours. Therefore, in infants who die in the very early postnatal period, hyaline membranes may not be observed. Similar lesions are developed in adults and called acute respiratory distress syndrome (ARDS). Both DAD and ARDS are acute restrictive lung diseases. Causes of ARDS include diffuse pulmonary infections, oxygen toxicity, septic shock due to endotoxins, severe trauma, severe burns, massive blood loss, and radiotherapy (Table 9.2).

**Fig. 9.1** Hyaline membranes in DAD**Table 9.2** Causes of ARDS

Infections	Sepsis, <i>Pneumocystis carinii</i> pneumonia, aspiration of gastric fluid
Chemical injury	Heroin, acetylsalicylic acid, barbiturates
Physical injury	Trauma, radiation, fat embolism, drowning, burns, etc.
Hematologic conditions	Disseminated intravascular coagulation (DIC), transfusions, pancreatitis, uremia
Inhaled irritants	Oxygen, cigarette smoke, chemical and irritant gases
Cardiopulmonary bypass	Hypersensitivity reactions, drugs

Clinically dyspnea, tachypnea, cyanosis, and hypoxia are observed. Radiologically, diffuse, bilateral consolidation or reticulonodular infiltration are present. The capillary endothelium and/or alveolar epithelium are damaged, with the involvement of polymorphonuclear leukocytes and the complement system. The characteristic morphological findings are hyaline membranes (fibrin) lining the alveoli in the exudative phase; in the healing phase, there is organization and type II pneumocyte hyperplasia. Mortality is high. In patients over 60 years of age, 90% are lost. The most notable difference between acute interstitial pneumonia and ARDS is that the former occurs without a clearly identifiable antecedent condition such as sepsis or trauma and typically appears in individuals around their 50 s as a worsening illness resembling an upper respiratory tract infection. Hyaline membranes can also be seen in interstitial lung diseases. The most important difference from ARDS is the presence of fibrosis. Because ARDS is an acute process, fibrosis does not occur [1–3].

Another common condition is hydrostatic (hemodynamic) *pulmonary edema*. This condition usually occurs together with congestion, most often due to heart failure. Pulmonary edema due to microvascular injury is less common [4, 5].

9.2 Vascular Diseases

Pulmonary hypertension is an uncommon non-neoplastic disorder which can be primary (idiopathic) or secondary. The four most common causes of secondary pulmonary hypertension are chronic obstructive-interstitial lung diseases such as emphysema, heart diseases such as mitral stenosis, recurrent pulmonary embolism, and autoimmune diseases. Primary pulmonary hypertension is rare and occurs more frequently in young women. In this condition, abnormalities such as reduced prostacyclin and nitric oxide production, increased endothelin production by pulmonary vascular endothelium, and mutations in the bone morphogenetic protein receptor type 2 (BMPR2) gene, which regulates smooth muscle

cell proliferation, are implicated. This gene binds cytokines such as TGF- β and normally, when stimulated, stops smooth muscle proliferation and initiates apoptosis. Vasoconstriction and increased thrombosis occur. Morphologic findings vary depending on the etiology. In primary and postischemic cases, medial hypertrophy is seen initially, followed by intimal fibrosis. In chronic embolism, thrombosis, recanalization, and atheromatous changes are prominent. In primary pulmonary arterial hypertension and secondary cases due to congenital heart diseases with left-to-right shunt, plexogenic pulmonary arteriopathy characterized by glomeruloid structures in the arterial lumen may be observed (Fig. 9.2). In patients with congenital heart disease or pulmonary hypertension, open lung biopsy may be performed to evaluate the condition of the pulmonary vessels and determine the type of surgical approach. According to the Heath-Edwards grading system, the first three groups show reversible changes. In other words, if arterial lesions consist of medial hypertrophy, post-thrombotic fibrosis, and intimal thickening due to smooth muscle hypertrophy, surgery can be performed. If fibrinoid necrosis or plexiform lesions are present (grades 4–6), surgery is not feasible. In addition, in hypertensive pulmonary vascular disease, the number of neuroendocrine cells is also increased [6–8].

9.3 Obstructive Lung Diseases

Emphysema, chronic bronchitis, bronchiectasis, and asthma are studied under the main heading of *chronic obstructive pulmonary disease (COPD)*. The common feature of these diseases is difficulty in expelling inhaled air. Obstructions due to causes such as tumors or foreign bodies are acute and therefore excluded from this group. Obstruction may result from narrowing of the bronchioles and bronchi as in asthma or from loss of the lung's passive elastic recoil after inflation, as in emphysema. The most important etiologic factor is smoking. In addition to bronchiolitis associated with rheumatic diseases and viral infections, bronchiolitis-type obstructive lesions

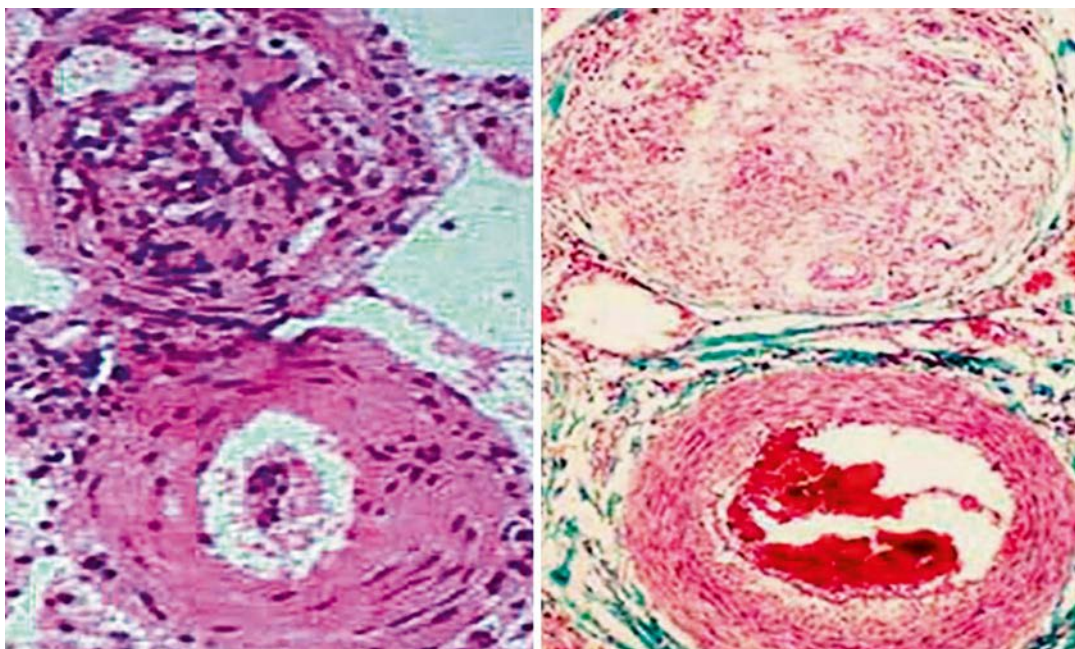


Fig. 9.2 Plexogenic pulmonary arteriopathy with HE (left) and trichrome stain (right)

may also develop after heart-lung transplantation. In pulmonary function tests, the forced expiratory volume in the first second (FEV_1) is below normal. Since emphysema and chronic bronchitis occur together in most patients, the general term **COPD** is used. In some of these patients, asthma may also be present [9–11].

Emphysema is defined as the permanent enlargement of airways and alveoli distal to the terminal bronchioles due to destruction, without accompanying fibrosis (Fig. 9.3). The first clinical signs appear after approximately one-third of the parenchyma is lost. There are four main types: centrilobular, paraseptal, panacinar, and irregular. *Centrilobular (centriacinar) emphysema* is the most common type, associated with cigarette smoking and involves respiratory bronchioles in the center of acini. *Paraseptal emphysema* involves distal acini along the pleura or perilobular septa and may lead to paraseptal scarring and spontaneous pneumothorax. *Panacinar emphysema* is seen in α_1 -antitrypsin deficiency, involving the entire acinus. *Irregular emphysema* cannot be classified under a single pattern, com-

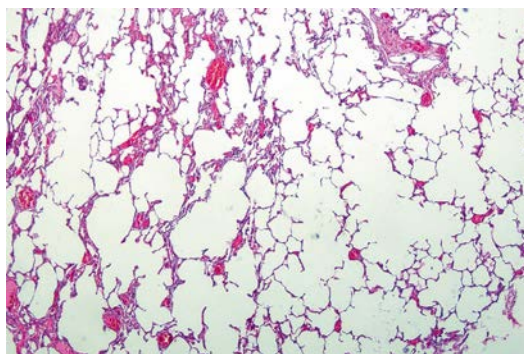


Fig. 9.3 Emphysema

mon in smokers, and generally detected after age 60. Pathogenesis involves excess protease activity (elastase) and/or deficient antiprotease activity (anti-elastase), with free radicals acting as triggers. Morphologic evaluation and classification are based on macroscopic features. Centriacinar affects upper lobes more, while panacinar affects lower lobes more. Air-filled spaces visible grossly, if diameter reaches ≥ 1 cm, are called a bulla. Spontaneous pneumothorax asso-

ciated with paraseptal emphysema occurs especially in tall young men during exercise and tends to recur [12, 13]. *Chronic bronchitis* is defined as cough and sputum production on most days for at least three consecutive months over at least two successive years. Three types with increasing severity are simple chronic bronchitis, chronic asthmatic bronchitis, and obstructive chronic bronchitis. Risk is extremely high in heavy smokers. Chronic irritation etiologically plays primary role, and infections contribute to develop chronic bronchitis. First change is increased bronchial secretions, appearance of goblet cells in airways <3 mm in diameter. Morphologically, bronchial mucous glands are hypertrophic (Fig. 9.4). Bronchiolitis shows goblet cell metaplasia, mucus plugs, inflammation, and fibrosis. Patients experience cough and sputum production for years before developing dyspnea, hypercapnia, hypoxemia, and cyanosis. In advanced stages, cor pulmonale and heart failure occur. Respiratory acidosis is a cause of death. For grading of chronic bronchitis, Reid index (ratio of gland thickness to distance from epithelium to perichondrium) is used. Reid index is found >0.5 in chronic bronchitis [10].

Bronchial asthma is an inflammatory disease characterized by bronchial hyperresponsiveness to various stimuli, resulting in episodic bronchoconstriction. Airway narrowing is initially reversible. During attacks, severe dyspnea, cough, and wheezing are present. It can be extrinsic (allergic) or intrinsic (nonallergic). Extrinsic asthma is

more common in children/young adults and often improves with age. It is associated with family history (atopy). There are elevated serum IgE and peripheral eosinophilia. Intrinsic asthma is more common in older adults and has more severe course. Genetically ADAM-33 gene may play a role in bronchial hyperreactivity. Status asthmaticus is rare, potentially fatal severe attack. Most asthmatics are symptom-free between attacks. Grossly, hyperinflation resembles emphysema with atelectatic areas. Microscopic evaluation, mucus plugs, Curschmann spirals (whorled mucus plugs), eosinophils and Charcot-Leyden crystals (eosinophil breakdown products) are determined. In addition, bronchial epithelial desquamation, thickened basement membrane, subepithelial edema and inflammation rich in eosinophils, submucosal gland hypertrophy, and smooth muscle hypertrophy were seen. Clinical course ranges from minimal symptoms to fatal attacks. Chronic, persistent cases may develop bronchiectasis, cor pulmonale, and pneumonia [14, 15].

Bronchiectasis is a chronic, necrotizing infection that causes irreversible dilation of the bronchi and bronchioles. As the distal airways are narrowed and obstructed, the disease is obstructive in nature. It is a late manifestation of many unrelated diseases. It is characterized by high fever, cough, and copious amounts of foul-smelling sputum. There are two types as obstructive and nonobstructive (post-inflammatory). Obstructive bronchiectasis is due to blockage by a foreign body, tumor, inspissated mucus in cystic fibrosis, or compression from an adjacent lymph node. If the obstruction is removed early, it can be reversible. Post-infectious (nonobstructive) cases are most often caused by adenovirus infections. Nonobstructive forms arise because of repeated pneumonia attacks. It is also common in pertussis. It is observed in sinonasal infections and Kartagener syndrome (immotile cilia syndrome). Nonobstructive bronchiectasis is more common in the left lung because physiological compression of the pulmonary artery on the left bronchus makes drainage more difficult. Lower lobes are more frequently affected. If there is no

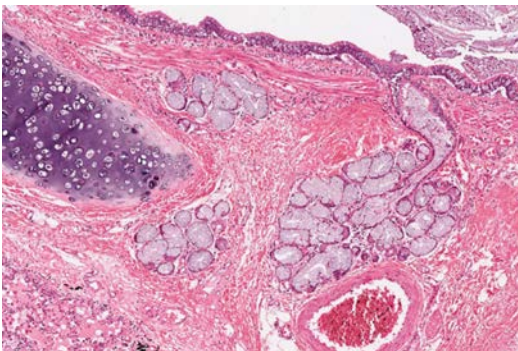


Fig. 9.4 Chronic bronchitis

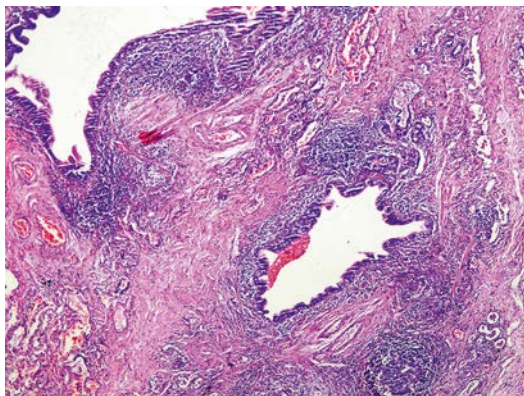


Fig. 9.5 Bronchiectasis

pneumonia attack or atelectasis, it remains localized. Microscopically, chronic inflammation of the bronchial wall is a constant finding, sometimes with lymphoid follicles having germinal centers (Fig. 9.5). Ulceration of the epithelium may be present. Squamous metaplasia is rare. In advanced stages, granulation tissue forms in the lamina propria. Cartilage is destroyed. Muscle is lost. Glands persist longer. The lung parenchyma may appear normal or show organizing pneumonia. Small spindle cell proliferations known as “tumorlets” may be observed; these are nodular hyperplasias of Kulchitsky cells and are associated with carcinoid tumors. Macroscopically, airways are dilated, and even dilated bronchioles near the pleura may be visible to the naked eye. Normally, bronchi within 2–3 cm of the pleura cannot be identified without magnification [16].

9.4 Restrictive Lung Diseases

Idiopathic interstitial pneumonias (IIPs) are a heterogeneous, nonneoplastic group of lung diseases causing damage to the lung parenchyma of unknown cause, with varying degrees of inflammation and fibrosis. Terminology and classification are inconsistent. For example, the same diseases may be grouped under IIP in Japan, but in the USA under idiopathic pulmonary fibrosis (IPF). Like other ILDs, exertional dyspnea and dry cough are the most common symptoms. Early chest X-ray, pulmonary function tests, and arte-

rial blood gases may be normal. However, HRCT may already show changes, diffusion capacity is reduced, and after exercise, oxygen desaturation may be seen. As disease progresses, chest X-ray reveals bilateral diffuse reticular infiltrates, and spirometry shows restrictive patterns. Arterial hypoxia is followed by hypercapnia, and physical exam may show digital clubbing and, in advanced disease, signs of right heart failure. HRCT findings may include ground-glass opacities, nodules, cysts, traction bronchiectasis, reticular densities, bronchovascular thickening, consolidation, and honeycombing. Recent recommendations favor adding the term “pattern” to histopathologic descriptions and using clinico-pathologic diagnosis. Histopathology reveals the most characteristic differences. The new classification defines seven histopathologic subtypes. Surgical lung biopsy (preferably VATS rather than open) may be needed, and it is most helpful before treatment starts. IIPs can be classified in seven groups (Table 9.3). Actually, there are six major IIPs (UIP/IPF, NSIP, COP, DIP, RB-ILD, AIP) while recognizing LIP as a less common entity. The subdivision into chronic fibrosing (UIP, NSIP), smoking-related (RB-ILD, DIP), and acute/subacute organizing (COP, AIP) helps clarify clinical behavior and prognosis [17–20].

Idiopathic pulmonary fibrosis (IPF), also known as usual interstitial pneumonia (UIP), affects older adults and features type II pneumocyte hyperplasia, interstitial fibrosis (Fig. 9.6), and honeycomb lung. Prognosis is poor; there is median survival 2–4 years after diagnosis. Patients usually have ≥ 6 months of symptoms including dyspnea and dry cough, and ~25–50% exhibit clubbing. BAL often shows prominent neutrophilia, but this does not predict prognosis. If eosinophils $>20\%$ or lymphocytes $>15\%$, consider other diagnoses such as NSIP, COP, and hypersensitivity pneumonitis. Radiologically, honeycombing with reticulation and traction bronchiectasis is typical; ground-glass may be present in some areas. *Nonspecific interstitial pneumonia (NSIP)* emerged as a category when biopsies did not fit any known pattern (Fig. 9.7). NSIP has better prognosis than UIP and occurs across a broader age range. Histologically, it has

Table 9.3 Updated classification of idiopathic interstitial pneumonias

Subtype	Clinical features	Histopathology (pattern)	HRCT/radiology findings	Prognosis/notes
UIP (IPF)	≥50 years, progressive dyspnea, dry cough, clubbing	Patchwork fibrosis, fibroblast foci, honeycomb	Basal/subpleural reticulation, traction bronchiectasis, honeycombing	Poor (median ~ 3 years survival)
NSIP	50–60, dyspnea, dry cough; slower than UIP	Uniform inflammation/fibrosis; cellular or fibrosing forms	Bilateral ground-glass, reticulation, possible mild cysts; honeycombing rare	Better prognosis (cellular > fibrosing)
COP (organizing pneumonia)	Subacute onset (<3 months), flu-like symptoms, cough	Masson bodies in bronchioles and alveoli, preserved architecture	Peribronchial/subpleural consolidations, ground-glass halos	Good response to steroids; relapses possible
AIP (Hamman-rich)	Rapid onset dyspnea, fever, myalgias (~weeks)	Diffuse alveolar damage (hyaline membranes, exudative + organizing phases)	Diffuse bilateral ground-glass and consolidation	High mortality (≈50%)
RB-ILD	40–50, smokers, mild dyspnea/cough, clubbing possible	Pigmented macrophages in the bronchioles, minimal fibrosis	Centrilobular nodules, mild ground-glass in the upper lobes	Good prognosis; smoking cessation helps
DIP	40–60, smokers, progressive dyspnea and cough	Alveolar macrophages, minimal fibrosis, intact architecture	Diffuse ground-glass, air bronchogram sign, upper/lower lobes	Generally favorable (survival ~68–94%)
LIP	Middle-aged women, mild dyspnea/cough, sometimes autoimmunity	Diffuse lymphocytic infiltrates, plasma cells, lymphoid follicles in septa	Ground-glass opacities and cysts; peribronchial distribution	Variable; risk of lymphoma, often secondary causes

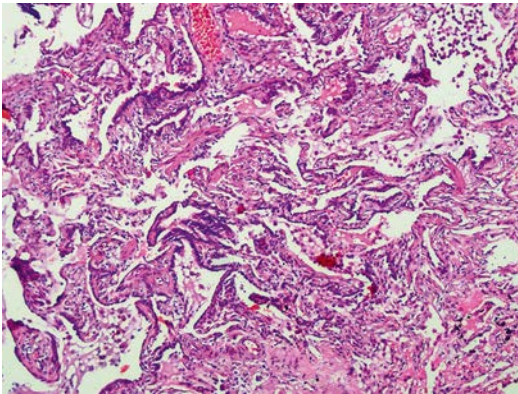


Fig. 9.6 Usual IP

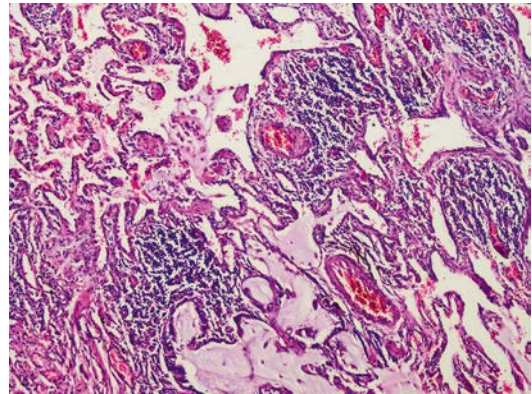


Fig. 9.7 NSIP

either cellular or fibrosing subtypes; BAL often shows lymphocyte predominance. HRCT shows ground-glass (often predominant), patchy bilateral consolidations, lower-zone reticulation, and only occasional traction bronchiectasis; honeycombing is rare. *Cryptogenic organizing pneumonia*

(COP) was first described by Davison in 1983, and in 1985, Epler described the same entity as *bronchiolitis obliterans organizing pneumonia* (BOOP). It presents subacutely (<3 months) with cough, malaise, low-grade fever, and weight loss. Histologically, OP pattern

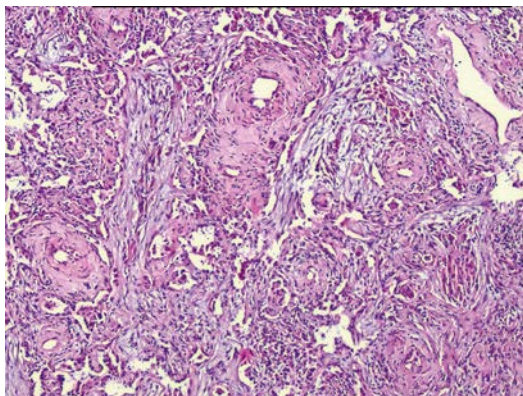


Fig. 9.8 Masson bodies in COP

is characterized with Masson bodies filling the bronchioles and alveoli while lung architecture is preserved (Fig. 9.8). HRCT shows peripheral or peribronchial consolidation, sometimes with ground-glass. Prognosis is good; corticosteroids are effective but relapses common. *Acute interstitial pneumonia (AIP, Hamman-Rich syndrome)* presents rapidly (often <3 weeks) with high fever, myalgias, and dyspnea and leads to diffuse alveolar damage (DAD) indistinguishable from ARDS. Histology shows exudative and then organizing DAD with hyaline membranes. HRCT and chest X-ray reveal diffuse ground-glass and consolidation with high mortality (~50%). *Respiratory bronchiolitis-associated ILD (RB-ILD)* and *desquamative interstitial pneumonia (DIP)* are smoking related. RB-ILD affects middle-aged smokers (~40–50 years) and presents with mild dyspnea and cough; histology shows bronchiolocentric pigmented macrophages and mild fibrosis (Fig. 9.9). HRCT reveals centrilobular nodules, mild ground-glass. DIP has widespread intra-alveolar macrophages causing diffuse ground-glass, minimal fibrosis, and better prognosis. BAL and CT findings are typical. DIP often occurs at similar age in smokers, clubbing is possible, and steroids are effective in many. *Lymphoid interstitial pneumonia (LIP)* is rare and often associated with autoimmune disease or immunodeficiency. It presents in middle age with mild dyspnea and cough. There is histologically diffuse infiltration of the alveolar septa by lymphocytes, plasma cells, and even lymphoid folli-

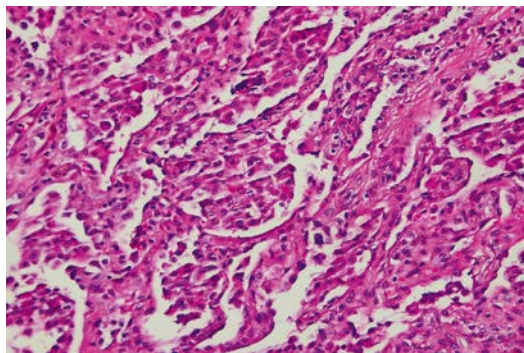


Fig. 9.9 Desquamative IP

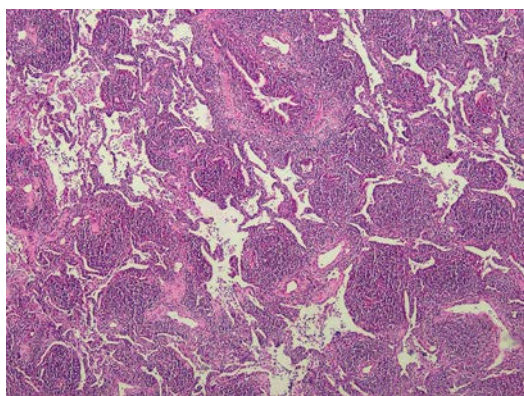


Fig. 9.10 Lymphoid IP

cles (Fig. 9.10). HRCT shows ground-glass opacities and cysts. Prognosis is variable and lymphoma may be developed [17–20].

9.5 Occupational/Environmental Diseases

The most common restrictive lung diseases are *pneumoconioses*. This term, once used to describe dust-related lung diseases, is now also applied to various conditions caused by toxic airborne substances. When inhaled particles less than 5 μm in diameter bypass the mucociliary clearance system, they can reach the terminal bronchioles and alveoli. These fine particles are engulfed by alveolar macrophages through phagocytosis. In all pneumoconiosis, pathogenesis involves stimulation of the macrophages by the toxic agent in the

respiratory tract. Activated macrophages are responsible for recruitment of other leukocytes, damage to pneumocytes, and production/release of cytokines. During this process, activated macrophages release pro-inflammatory mediators (notably IL-1 and TNF- α), lysosomal enzymes, and generate reactive oxygen species, thereby amplifying local cell signaling cascades. Macrophages loaded with these particles tend to accumulate within the interstitial tissue, especially along perivascular and peribronchiolar regions. Once the acute inflammatory response subsides, a fibrotic phase begins, driven by growth factors (e.g., PDGF, TGF- β). Type I pneumocytes are replaced or overlaid by type II pneumocyte proliferation, effectively encapsulating the particles within the interstitium. Fibroblasts are subsequently stimulated to secrete extracellular matrix (ECM) proteins and matrix metalloproteinases (MMPs), resulting in fibrosis and tissue remodeling. Fibrocytes contribute through chemotactic activity, drawing more inflammatory cells to the site and sustaining the immune reaction by releasing additional cytokines and chemokines. In both simple and complicated pneumoconioses, elevated levels of IgG and IgA may be observed. Increased production of fibronectin and collagen leads to the formation of fibrotic scar tissue [21, 22].

Coal worker's pneumoconiosis develops depending on the duration and severity of coal dust exposure and the presence of other contaminants. Three forms of are asymptomatic anthracosis, simple coal worker's pneumoconiosis and complicated coal worker's pneumoconiosis (progressive massive fibrosis). In asymptomatic cases, coal dust accumulates in the interstitium without a cellular reaction. In mild cases, carbon particles are observed in the cytoplasm of macrophages (Fig. 9.11). Sometimes, these macrophages aggregate to form cellular nodules (coal nodules). With increasing severity, fibrotic nodules and interstitial fibrosis appear. The coexistence of rheumatoid arthritis with any pneumoconiosis is called *Caplan's syndrome*. Except in complicated cases, patients are usually asymptomatic. Anthracosis always spreads to regional lymph nodes. *Silicosis* is the most com-

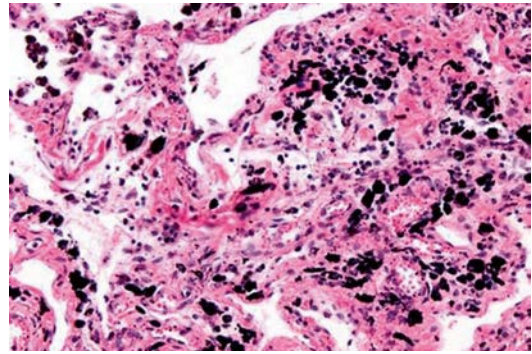


Fig. 9.11 Anthracosis

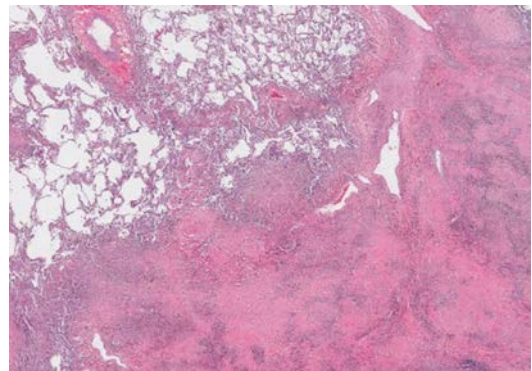


Fig. 9.12 Silicosis

mon chronic occupational disease worldwide, caused by inhalation of *silica* (SiO_2) crystals, which stimulate macrophages. Acute reaction can lead to tachypnea, cough, and cyanosis. It typically involves the *upper lobes*. Among cytokines secreted by macrophages, *TNF* plays a key role in pathogenesis. The lung is characterized by *millimeter-sized fibrotic (silicotic) nodules* (Fig. 9.12). Often, the center contains birefringent silica particles surrounded by whorled bundles of hyalinized collagen. Typical nodules can also be found in hilar lymph nodes and pleura. *Eggshell calcification* of hilar lymph nodes may be visible on chest radiographs. When silica is mixed with other minerals, its fibrogenic effect is reduced. Silicosis may progress to progressive massive fibrosis, increase susceptibility to tuberculosis, and predispose to carcinoma. Silica particles cannot be digested within macrophages, leading to intense macrophage infiltration.

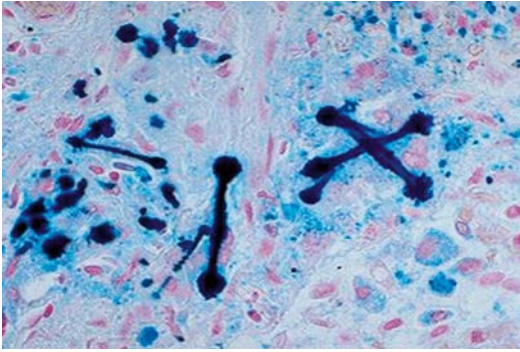


Fig. 9.13 Ferruginous bodies

Asbestosis causes interstitial fibrosis along with fibrous plaques on parietal pleura, pleural effusion, bronchogenic carcinoma, mesothelioma, and other cancers. Among asbestos fibers, the rigid, straight types called amphiboles (e.g., crocidolite, amosite, tremolite) are more pathogenic. Ferruginous bodies are characteristic histologic structures most commonly seen after asbestos exposure. Ferruginous bodies form when asbestos fibers or rarely other inorganic core materials become coated with iron and protein, making them visible under the microscope. Asbestos fibers are phagocytosed by alveolar macrophages; since the fibers cannot be fully digested, macrophages deposit ferritin/hemosiderin around them. On iron stains like Prussian blue, they appear blue-green (Fig. 9.13). The presence of ferruginous bodies indicates exposure to asbestos. Clinically, it is associated with asbestosis, pleural plaques, mesothelioma, and bronchogenic carcinoma risk. Smoking greatly increases the harmful effects of asbestosis—about *tenfold* for bronchogenic carcinoma risk. In asbestos-exposed smokers, lung cancer risk is *~55 times* higher than normal; mesothelioma risk is increased *~1000-fold*. Fibrosis begins in the walls of respiratory bronchioles and spreads to alveolar ducts and sacs. Unlike other common pneumoconioses, asbestosis produces *diffuse* rather than nodular fibrosis. It predominantly involves the *lower lobes* and may progress to *honeycomb lung*. Caplan's syndrome and pulmonary hypertension may also occur. Findings usually appear *15–20 years* after exposure. The most common

finding is *fibrous plaques* on the parietal pleura, particularly on the diaphragmatic surface. Other dust particles causing pneumoconiosis include beryllium dust (*berylliosis*), cotton dust (*byssinosis*), tin dust (*stannosis*), and sugar cane dust (*bagassosis*). Berylliosis, like silicosis, causes acute reaction and late nodular fibrosis. Unlike silicosis, early lesions may include granulomas. *Radioactive dusts* like uranium, thorium, zirconium, and cerium damage the lung tissue by ionizing radiation. Heavy metal dusts like lead, cadmium, and zinc generally cause *systemic toxicity* rather than pneumoconiosis. *Organic dusts* such as pollen and wood dust cause allergic reactions, leading to hypersensitivity pneumonitis [21–23].

9.6 Infectious and Immune-Mediated Lung Diseases

Pulmonary infections are among the most important causes of death. Mortality is particularly high in small children, the elderly, and those in severe clinical condition. Etiological agents cause infection when the lung's defense mechanisms are weakened. The gross morphology of bacterial pneumonias may appear as the more common *bronchopneumonia* or as *lobar pneumonia*. Almost any bacterium can cause pneumonia, especially *Streptococcus pneumoniae* and *Haemophilus influenzae*. Staphylococcus species are particularly responsible for superinfections and hospital-acquired (nosocomial) pneumonias. The most common route of transmission is the airway; however, pneumonia can also occur via the bloodstream. Today, widespread use of antibiotics has decreased the incidence of lobar pneumonia and altered the presentation of its classic stages. The macroscopic stages of lobar pneumonia are parallel to its microscopic features. These stages are red hepatization, gray hepatization, and resolution. Red hepatization is characterized by exudation of neutrophils into alveolar lumens and presence of erythrocytes (congestion). In gray hepatization, the rate of inflammatory cells increases, while erythrocytes decrease. In the resolution stage, clearance of

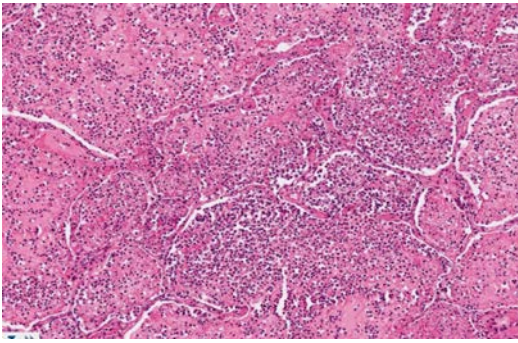


Fig. 9.14 Lobar pneumonia

exudate by macrophages occurs. Histologically, infiltration of the alveoli by neutrophils is the most typical finding (Fig. 9.14). Major complications of bacterial pneumonias include pleural effusion, empyema, lung abscess, organization, and bacteremia. In infants up to two years old, bronchiolitis caused by respiratory syncytial virus (RSV) is common. Influenza, measles, herpes simplex viruses, and adenoviruses are also frequent pathogens. The infiltrate is lymphocytic and interstitial in nature. *Mycoplasma pneumoniae* usually resemble viral pneumonias. Because their symptoms may be mild, pneumonias caused by mycoplasma and viruses are referred to as atypical pneumonias. Lung abscesses most often develop secondary to aspiration. They may arise as a complication of bacterial infection or primarily. Anaerobic bacteria are the most common cause. Obstruction due to a bronchial tumor can impair normal defense mechanisms, leading to abscess formation. Therefore, when an abscess is detected in a smoker over 40 year old, it must be investigated [24].

Tuberculosis is a chronic granulomatous disease. *Mycobacterium tuberculosis*, *M. bovis*, and *M. africanum*, usually cause human tuberculosis. The bacterium belongs to the family Mycobacteriaceae and order Actinomycetales. The TB bacillus is a non-spore-forming, nonmotile, 2–4 μm long pleomorphic microorganism. It appears as chains of beads or clumps. It is an obligate aerobe requiring glycerol, carbon, and ammonium salts for growth, optimally growing at 37–41 $^{\circ}\text{C}$. It produces niacin and contains weak pigments. Important virulence factors

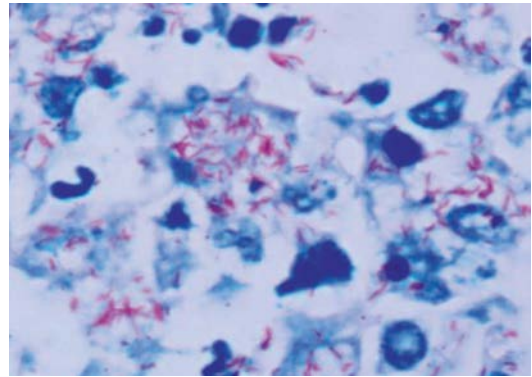


Fig. 9.15 AFB in EZN stain

include cord factor, lipoarabinomannan, and heat-shock proteins. Mycobacteria are acid-fast and stain poorly (Fig. 9.15). Once stained, they resist decolorization with ethanol, HCl, and other acids. They grow slowly, with a generation time of 12–24 hours. Human-to-human transmission occurs through infectious droplets. Droplets smaller than 5 μm may remain suspended in the air for hours and retain viable organisms. Infective droplets contain on average 1–10 bacilli. Theoretically, a single bacillus can cause disease, but usually 5–200 bacilli must be inhaled for infection. Child-to-child transmission is extremely rare. Transmission risk is higher in those with AFB-positive sputum, extensive upper lobe infiltrates or cavities, heavy sputum production, and frequent coughing. Three important factors in transmission are number of bacilli in inhaled air, duration of exposure to contaminated air, and immune status of the individual. Generally, TB affects boys and girls equally. In adults, about two-thirds of cases occur in men. Compared to white Americans, TB incidence is ~10 times higher in Asians, eight times higher in Black populations, and five times higher in Latin Americans. Race itself is not a risk factor; risk correlates with social, economic, and medical conditions. Its pathogenesis is complex, involving a lifelong interplay between mycobacterial virulence factors and the host immune system. Initiation of the immune response to halt bacterial growth does not eliminate the risk, as bacilli can remain dormant for years and reactivate when immune resistance declines. In reactiva-

tion, transmissibility and tissue damage are similar to primary TB. Initial interaction between bacteria and macrophages triggers both helper T cell and cytotoxic T cell responses. As *M. tuberculosis* multiplies within phagocytes, stimulation of antibody production by CD4(+) T cells is ineffective; instead, their release of IFN activates macrophages. IFN also activates endothelial cells, promoting adhesion and migration of T cells into infected tissue. CD8(+) T cells, which release less IFN, kill infected macrophages that cannot destroy the bacteria, allowing released bacilli to be ingested and destroyed by activated macrophages. Macrophages and dendritic cells, in addition to their role in innate immunity during initial infection, contribute to bacterial containment and tissue destruction through a strong TH1-mediated cellular immune response. In healthy adults exposed to a small number of bacilli, activated macrophages contain infection early without significant lung damage. These individuals develop a positive skin test but not symptomatic TB. In infants or adults unable to mount a rapid T cell response, bacilli continue to multiply within pulmonary macrophages until later stages of the disease. Failure of phagocytes to clear infection leads to continued recruitment of T cells, neutrophils, and macrophages to the site of bacterial growth. Macrophages around bacilli fuse to form giant cells and, together with T cells, form a layer around the site of bacterial replication. In some cases, although phagocytes cannot kill the bacilli, T cells and macrophages wall off the focus of replication with a thick fibrin layer known as a tubercle. These tubercles may eventually calcify, producing visible lesions on imaging (Ghon complex). Because tubercles macroscopically resemble granulomas, the cellular immune response that produces them is called a granulomatous response. Mycobacterial regions of difference 1 (RD1) loci encode a specialized secretion system that enhances virulence. RD1-deficient bacteria can still be replicated within macrophages but fail to induce effective granuloma formation. Virulent mycobacteria trigger RD1-dependent signaling in infected macrophages, causing macrophages to aggregate and

form granulomas. Mycobacteria-induced macrophage aggregation is closely linked to intercellular bacterial spread and bacterial proliferation. Mycobacteria can also inhibit sphingosine kinase in macrophages, blocking the Ca^{2+} signaling pathway. This signaling is necessary not for phagocytosis itself, but for later immune mechanisms such as respiratory burst and phagosome maturation. By blocking this signal, *M. tuberculosis* prevents phagosome maturation and survives within the cell. The main structural component of the *M. tuberculosis* cell wall is mycolic acid. Many studies show that functional groups in the acyl chains of mycolic acid are important for pathogenesis and persistence. Disseminated or meningeal TB are early events, appearing 2–6 months after primary infection. Lymph node or endobronchial TB generally occurs between 3–9 months. Joint or bone lesions develop over years. Renal lesions may appear decades after primary infection. Pulmonary TB develops about a year after primary infection, usually due to endogenous reactivation of bacilli within an encapsulated lesion. Secondary TB occurs in 5–10% of those with prior primary TB, often years later, typically involving upper lobes, and follows a more severe course. Complications include hemoptysis, miliary TB, bronchopleural fistula, tuberculous empyema, and extrapulmonary TB. Typical morphology includes granulomas with caseous necrosis (Fig. 9.16) and Langhans giant cells [25–28].

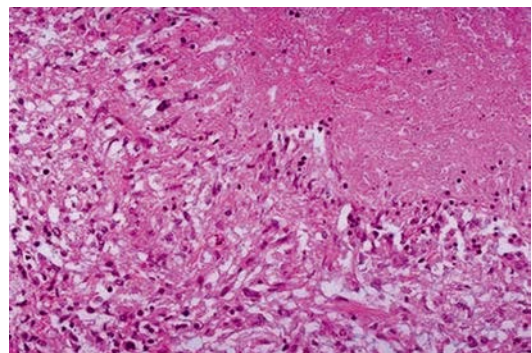


Fig. 9.16 Caseous necrosis in TB

Hypersensitivity pneumonitis (HP) is also called extrinsic allergic alveolitis; HP is a granulomatous inflammation of the alveoli and distal bronchioles caused by allergic reaction to repeat exposure to organic particles or low molecular weight chemicals in susceptible individuals. Lesions are characterized by non-necrotizing granulomas in the interstitium (Fig. 9.17). HP develops after external allergen exposure. Despite the terms “hypersensitivity” and “allergic,” HP is not an atopic disease and is not associated with increased IgE or eosinophilia. Some drug reactions have BAL findings similar to HP, but because they are caused by systemic agents and different mechanisms, they are not classified as HP. Common classic examples of HP are *farmer’s lung* (moldy hay, actinomycetes), *ventilator lung* (actinomycete-contaminated ventilation systems), and *bird fancier’s lung* (avian proteins). *Acute HP* presents dyspnea, nonproductive cough, myalgia, chills, sweating, headache, and malaise. It peaks within 6–24 hours and resolves spontaneously in 1–3 days. There is neutrophilia and lymphopenia, while there isn’t eosinophilia. *Chronic HP* presents progressive severe dyspnea, nonproductive cough, weight loss, and anorexia, and it may last for years. Cor pulmonale may develop. The difference between acute and chronic forms is unclear, but chronic disease is thought to result from low-intensity prolonged exposure, while acute forms follow high-intensity short exposure [29].

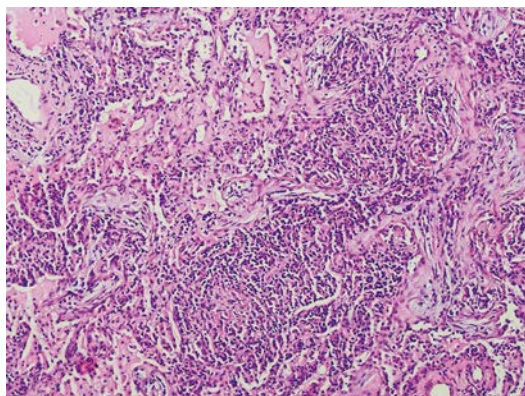


Fig. 9.17 Hypersensitivity pneumonia

9.7 Miscellaneous Nonneoplastic Conditions

Eosinophilic Pneumonia describes all pulmonary infiltrates with eosinophilia, with or without peripheral eosinophilia, involving eosinophilic infiltration of the interstitium. It can be idiopathic or secondary to various causes such as parasitic infections. The *acute form* is known as *Loeffler’s syndrome*. It typically occurs in women aged 20–50 and presents with fever, dyspnea, weight loss, peripheral lung infiltrates, and eosinophilia. Microscopically, there is localized eosinophilic infiltration of the alveoli and interstitium along with plasma cells and histiocytes [30].

Sarcoidosis (Besnier–Boeck disease) remains of unknown etiology. All organs may be affected, but lung involvement and bilateral hilar lymphadenopathy occur in 90% of cases. Disease can be developed in three stages. In stage 1, there is only hilar lymphadenopathy, while in stage 2, parenchymal involvement is also added to hilar lymphadenopathy. In stage 3, there is diffuse parenchymal involvement. The characteristic feature is noncaseating granulomas. Schaumann bodies and asteroid bodies may be seen in the cytoplasm of giant cells (Fig. 9.18). Progressive diffuse interstitial fibrosis occurs in 2–15% of cases, usually in stage 3 patients. About 25% have eye and skin involvement, while 7% have CNS involvement. *Heerfordt syndrome*, often seen in women, is a neurosarcoidosis form char-

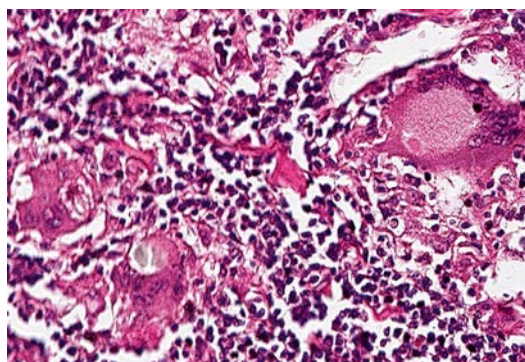


Fig. 9.18 Sarcoidosis

acterized by low-grade fever, uveitis, parotid gland enlargement, and facial nerve palsy. Proposed triggers include pollens, different microorganisms such as *Borrelia*, *Rickettsia helvetica*, *Chlamydia pneumoniae*, EBV, HHV-8, retrovirus, and even mycobacteria. The only consistent finding in sarcoidosis is an aberrant immune response in susceptible individuals, driven primarily by CD4+ T lymphocytes. The disease is often resolved spontaneously without treatment. Drug therapy is used to suppress the immune system and reduce symptoms [31, 32].

Lipoid pneumonia may be exogenous or endogenous. The *exogenous type* is rare and develops when lipid material reaches the lungs, e.g., via nasal sprays. Lipid material is seen throughout the lung, sometimes pooling in certain areas. The *endogenous type* is secondary to destructive lesions like carcinoma causing accumulation of endogenous lipid material. Here, lipid material is usually seen within the macrophages. *Diffuse alveolar hemorrhage* is a syndrome characterized by hemoptysis, anemia, and rapidly progressing bilateral consolidation on radiologic imaging. It may be associated with various vasculitis and autoimmune diseases, such as Wegener's granulomatosis. In Goodpasture syndrome, antibodies against a component of type IV collagen in the basement membrane cause progressive glomerulonephritis, DAD, and hemorrhage. *Idiopathic pulmonary hemosiderosis*, a rare condition, is another cause of diffuse alveolar hemorrhage. It is characterized in young adults by hemoptysis and refractory anemia. Chest X-ray shows perihilar granular infiltrates. Microscopically, hemosiderin-laden macrophages are seen in the alveolar lumens, along

with proliferation of the lining cells. There are no necrosis, vasculitis, granulomas, or lymphoid follicles. The presence of IgG deposits in the basement membrane is important in distinguishing it from Goodpasture syndrome. *Pulmonary embolism* and infarction are common. The most frequent cause is thrombosis in the deep veins of the leg above the knee. Pulmonary embolism may be asymptomatic or present across a spectrum ranging from sudden death to pulmonary hypertension and chronic cor pulmonale. In debilitated or elderly patients, the likelihood of embolism being complicated by infarction is higher. Pulmonary infarction is hemorrhagic when microorganisms colonize the vulnerable infarcted area; septic infarction can occur.

Pulmonary alveolar proteinosis (PAP) is a condition characterized by accumulation of lipid-carbohydrate material in the alveoli, which can persist for years and is associated with progressive dyspnea. It develops secondary to functional deficiency of granulocyte-macrophage colony-stimulating factor (GM-CSF) in the lung, leading to impaired surfactant degradation. There are congenital, acquired (most common), and secondary forms. Radiologically, PAP often mimics pulmonary edema with a perihilar distribution. It usually develops as a response to alveolar injury. It may be seen in immunosuppressed patients, in association with infections and hematologic malignancies. Microscopically, the alveolar lumen contains PAS-positive, amorphous eosinophilic (sometimes basophilic) phospholipid material (Fig. 9.19). There may be hyperplasia of granular pneumocytes, interstitial inflammation, desquamation, and fibrosis [33–35].

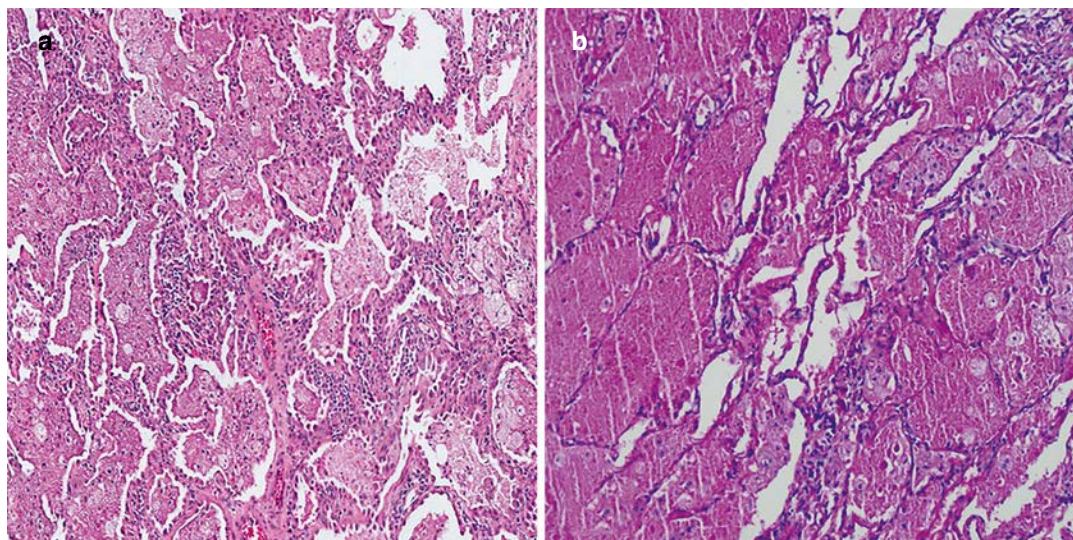


Fig. 9.19 Alveolar Proteinosis (a) H&E stain, (b) PAS stain

References

1. Matthay MA, Zemans RL, Zimmerman GA, Arabi YM, Beitler JR, Mercat A, Herridge M, Randolph AG, Calfee CS. Acute respiratory distress syndrome. *Nat Rev Dis Primers*. 2019;5(1):18. <https://doi.org/10.1038/s41572-019-0069-0>.
2. Kligerman S. Pathogenesis, imaging, and evolution of acute lung injury. *Radiol Clin North Am*. 2022;60(6):925–39. <https://doi.org/10.1016/j.rcl.2022.06.005>.
3. Saguil A, Fargo MV. Acute respiratory distress syndrome: diagnosis and management. *Am Fam Physician*. 2020;101(12):730–8. PMID: 32538594
4. Hsieh PC, Wu YK, Yang MC, Su WL, Kuo CY, Lan CC. Deciphering the role of damage-associated molecular patterns and inflammatory responses in acute lung injury. *Life Sci*. 2022;305:120782. <https://doi.org/10.1016/j.lfs.2022.120782>.
5. Zanza C, Saglietti F, Tesaro M, Longhitano Y, Savioli G, Balzanelli MG, Romenskaya T, Cofone L, Pindinello I, Racca G, Racca F. Cardiogenic Pulmonary Edema in Emergency Medicine. *Adv Respir Med*. 2023;91(5):445–63. <https://doi.org/10.3390/arm91050034>.
6. Mocumbi A, Humbert M, Saxena A, Jing ZC, Sliwa K, Thienemann F, Archer SL, Stewart S. Pulmonary hypertension. *Nat Rev Dis Primers*. 2024;10(1):1. <https://doi.org/10.1038/s41572-023-00486-7>. Erratum in: *Nat Rev Dis Primers*. 2024 Jan 17;10(1):5. doi:10.1038/s41572-024-00493-2
7. Cuthbertson I, Morrell NW, Caruso P. BMPR2 mutation and metabolic reprogramming in pulmonary arterial hypertension. *Circ Res*. 2023;132(1):109–26. <https://doi.org/10.1161/CIRCRESAHA.122.321554>.
8. Poch D, Mandel J. Pulmonary hypertension. *Ann Intern Med*. 2021;174(4):ITC49–64. <https://doi.org/10.7326/AITC202104200>.
9. Ritchie AI, Wedzicha JA. Definition, causes, pathogenesis, and consequences of chronic obstructive pulmonary disease exacerbations. *Clin Chest Med*. 2020;41(3):421–38. <https://doi.org/10.1016/j.ccm.2020.06.007>.
10. Zhang J, Wurzel DF, Perret JL, Lodge CJ, Walters EH, Dharmage SC. Chronic bronchitis in children and adults: definitions, pathophysiology, prevalence, risk factors, and consequences. *J Clin Med*. 2024;13(8):2413. <https://doi.org/10.3390/jcm13082413>.
11. Yang IA, Jenkins CR, Salvi SS. Chronic obstructive pulmonary disease in never-smokers: risk factors, pathogenesis, and implications for prevention and treatment. *Lancet Respir Med*. 2022;10(5):497–511. [https://doi.org/10.1016/S2213-2600\(21\)00506-3](https://doi.org/10.1016/S2213-2600(21)00506-3).
12. Janssen R, Piscaer I, Franssen FME, Wouters EFM. Emphysema: looking beyond alpha-1 antitrypsin deficiency. *Expert Rev Respir Med*. 2019;13(4):381–97. <https://doi.org/10.1080/17476348.2019.1580575>.
13. Alarcon-Calderon A, Vassallo R, Yi ES, Ryu JH. Smoking-related interstitial lung diseases. *Immunol Allergy Clin North Am*. 2023;43(2):273–87. <https://doi.org/10.1016/j.iac.2023.01.007>.

14. Mims JW. Asthma: definitions and pathophysiology. *Int Forum Allergy Rhinol.* 2015;5(Suppl 1):S2–6. <https://doi.org/10.1002/alr.21609>.
15. Sleziaik J, Gawor A, Błażejewska M, Antosz K, Gomułka K. ADAM33's role in asthma pathogenesis: an overview. *Int J Mol Sci.* 2024;25(4):2318. <https://doi.org/10.3390/ijms25042318>.
16. Chalmers JD, Polverino E, Crichton ML, Ringshausen FC, De Soyza A, Vendrell M, Buregel PR, Haworth CS, Loebinger MR, Dimakou K, Murriss M, Wilson R, Hill AT, Menendez R, Torres A, Welte T, Blasi F, Altenburg J, Shteinberg M, Boersma W, Elborn JS, Goeminne PC, Aliberti S, EMBARC Registry Investigators. Bronchiectasis in Europe: data on disease characteristics from the European Bronchiectasis registry (EMBARC). *Lancet Respir Med.* 2023;11(7):637–49. [https://doi.org/10.1016/S2213-2600\(23\)00093-0](https://doi.org/10.1016/S2213-2600(23)00093-0).
17. Althobiani MA, Russell AM, Jacob J, Ranjan Y, Folarin AA, Hurst JR, Porter JC. Interstitial lung disease: a review of classification, etiology, epidemiology, clinical diagnosis, pharmacological and non-pharmacological treatment. *Front Med (Lausanne).* 2024;11:1296890. <https://doi.org/10.3389/fmed.2024.1296890>.
18. Batra K, Adams TN. Imaging features of idiopathic interstitial lung diseases. *J Thorac Imaging.* 2023;38(Suppl 1):S19–29. <https://doi.org/10.1097/RTI.0000000000000728>.
19. Joy GM, Arbiv OA, Wong CK, Lok SD, Adderley NA, Dobosz KM, Johannson KA, Ryerson CJ. Prevalence, imaging patterns and risk factors of interstitial lung disease in connective tissue disease: a systematic review and meta-analysis. *Eur Respir Rev.* 2023 Mar 8;32(167):220210. <https://doi.org/10.1183/16000617.0210-2022>.
20. Smith ML. The histologic diagnosis of usual interstitial pneumonia of idiopathic pulmonary fibrosis. Where we are and where we need to go. *Mod Pathol.* 2022;35(Suppl 1):8–14. <https://doi.org/10.1038/s41379-021-00889-5>.
21. Hua JT, Cool CD, Green FHY. Pathology and mineralogy of the pneumoconioses. *Semin Respir Crit Care Med.* 2023;44(3):327–39. <https://doi.org/10.1055/s-0043-1764406>.
22. Gulumian M, Born PJ, Vallyathan V, Castranova V, Donaldson K, Nelson G, Murray J. Mechanistically identified suitable biomarkers of exposure, effect, and susceptibility for silicosis and coal-worker's pneumoconiosis: a comprehensive review. *J Toxicol Environ Health B Crit Rev.* 2006;9(5):357–95. <https://doi.org/10.1080/15287390500196537>.
23. Caceres JD, Venkata AN. Asbestos-associated pulmonary disease. *Curr Opin Pulm Med.* 2023;29(2):76–82. <https://doi.org/10.1097/MCP.0000000000000939>.
24. Zinserling VA, Swistunov VV, Botvinkin AD, Stepanenko LA, Makarova AE. Lobar (croupous) pneumonia: old and new data. *Infection.* 2022;50(1):235–42. <https://doi.org/10.1007/s15010-021-01689-4>.
25. Cardona PJ. Pathogenesis of tuberculosis and other mycobacteriosis. *Enferm Infecc Microbiol Clin (Engl Ed).* 2018;36(1):38–46. <https://doi.org/10.1016/j.eimc.2017.10.015>.
26. Urbanowski ME, Ordonez AA, Ruiz-Bedoya CA, Jain SK, Bishai WR. Cavitary tuberculosis: the gateway of disease transmission. *Lancet Infect Dis.* 2020;20(6):e117–28. [https://doi.org/10.1016/S1473-3099\(20\)30148-1](https://doi.org/10.1016/S1473-3099(20)30148-1). Pezzella AT. History of pulmonary tuberculosis. *Thorac Surg Clin.* 2019;29(1):1–17. doi:10.1016/j.thorsurg.2018.09.002
27. Mamishi S, Pourakbari B, Hosseinpour Sadeghi R, Marjani M, Mahmoudi S. Diagnostic accuracy of the IFN- γ release assay using RD1 immunodominant T-cell antigens for diagnosis of extrapulmonary tuberculosis. *FEMS Microbiol Lett.* 2024;371:fnae023. <https://doi.org/10.1093/femsle/fnae023>.
28. Phelan JJ, O'Leary S, Keane J. Tuberculosis lymph node granulomas: using transcriptomics to discover immunopathology paradigms and guide host-directed therapy. *J Clin Invest.* 2021;131(15):e151810. <https://doi.org/10.1172/JCI151810>.
29. Churg A. Hypersensitivity pneumonitis: new concepts and classifications. *Mod Pathol.* 2022;35(Suppl 1):15–27. <https://doi.org/10.1038/s41379-021-00866-y>.
30. Cottin V. Eosinophilic lung diseases. *Immunol Allergy Clin North Am.* 2023;43(2):289–322. <https://doi.org/10.1016/j.iac.2023.01.002>.
31. Neves FS, Pereira IA, Sztajnbnok F, Neto NSR. Sarcoidosis: a general overview. *Adv Rheumatol.* 2024;64(1):57. <https://doi.org/10.1186/s42358-024-00381-z>.
32. Esteves T, Aparicio G, Garcia-Patos V. Is there any association between Sarcoidosis and infectious agents?: a systematic review and meta-analysis. *BMC Pulm Med.* 2016;16(1):165. <https://doi.org/10.1186/s12890-016-0332-z>.
33. Kumar V, Abbas AK, Aster JC, Deyrup AT, Das A. Robbins and Kumar basic pathology. 11th ed. Philadelphia: Elsevier; 2023.
34. Huang X, Cao M, Xiao Y. Alveolar macrophages in pulmonary alveolar proteinosis: origin, function, and therapeutic strategies. *Front Immunol.* 2023;14:1195988. <https://doi.org/10.3389/fimmu.2023.1195988>.
35. Morton C, DeBiasi E. Pulmonary alveolar proteinosis. *Clin Chest Med.* 2025;46(2):373–82. <https://doi.org/10.1016/j.ccm.2025.02.014>.

Deniz Nart  and Hafize Ozdemir 

10.1 Tumors of the Lung

10.1.1 Introduction

Approximately 95% of primary lung tumors are carcinomas. Lung carcinoma is the leading cause of cancer-related deaths worldwide. The most significant risk factor is smoking, followed by occupational exposures such as radon and asbestos, as well as air pollution. The remaining 5% of primary lung tumors include carcinoid tumors, mesenchymal malignancies, lymphomas, and benign lesions [1].

10.1.2 Epithelial Tumors

10.1.2.1 Epidemiology

Smoking is the most important risk factor for lung cancer, accounting for approximately 90% of lung cancer deaths in men and 80% in women. The incidence of lung cancer is closely associated with tobacco use. Mortality and incidence rates are particularly high in high-income countries such as the United States and European nations. Although lung cancer has traditionally been more prevalent in men than in women, this gap has been narrowing in recent years.

Tobacco smoke is a complex aerosol containing more than 7000 chemicals, at least 81 of which are known carcinogens in humans or animals. The most potent carcinogens in tobacco smoke are polycyclic aromatic hydrocarbons (PAHs), such as benzo[a]pyrene, which induce mutations in the p53 tumor suppressor gene—mutations that are critical for cell cycle dysregulation and carcinogenesis. Another major group of carcinogens includes tobacco-specific nitrosamines, such as nicotine-derived nitrosoamine ketone. Although nicotine itself is not a direct chemical carcinogen, it is a highly addictive compound that leads to continued exposure to tobacco smoke and its harmful components.

Active smokers have a 15- to 30-fold higher risk of developing and dying from lung cancer compared to nonsmokers. This risk increases with earlier age of smoking initiation, intensity, and duration of smoking. Upon cessation, the risk gradually declines but never returns to the level of those who have never smoked. No form of tobacco is safe—cigars, pipes, and hookahs all pose significant risks for lung cancer development. Among individuals who have never smoked, the incidence of lung cancer is low, estimated at 5–10 cases per 100,000 individuals. Causes include passive smoking, radon exposure, environmental agents, and air pollution; however, in many cases, no specific etiology can be identified. Notably, lung cancer rates among Chinese women are higher than those of European women, despite lower smoking prevalence. This

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has been attributed to indoor air pollution from cooking and heating fuels, as well as high levels of cooking oil vapors. Importantly, the mutation types and patterns differ between cancers in smokers and nonsmokers.

All major histological types of lung cancer are associated with cigarette smoking. However, the relative risk is greatest for squamous cell carcinoma (SqCC) and small cell carcinoma (SCC) compared to adenocarcinoma and large cell carcinoma (LCC). Both SqCC and SCC typically arise in central bronchi heavily exposed to tobacco smoke, whereas ADC and LCC are usually located in the peripheral regions of the lungs.

Among occupational exposures, asbestos is the most well-known cause of lung cancer and significantly potentiates the carcinogenic effects of smoking. While asbestos exposure alone confers a sixfold increased risk of lung cancer, combined exposure to both asbestos and tobacco smoke can increase the risk up to 59-fold. Other recognized risk factors include ionizing radiation—particularly radon gas in indoor settings and mining environments—and occupational or environmental exposure to carcinogens such as arsenic, beryllium, cadmium, chromium, nickel, silica, diesel exhaust, and PAHs. Idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease (COPD), a family history of cancer, and various genetic and hormonal factors may also influence susceptibility to lung cancer.

10.1.2.2 Incidence

The incidence rate of lung cancer increased from 38.4% during 1977–1981 to 43.5% during 1987–1991 and then declined to 33.6% in 2006–2010. Different histological types have been observed at varying frequencies over time. These temporal differences in histological subtype incidences likely reflect changes in cigarette composition, manufacturing methods, and inhalation patterns.

Gender-based differences have also been noted in lung cancer incidence. While the incidence began to decline among men starting in the mid-1980s, it began to increase among women toward the late 1990s. In men, SCC was predominant in the 1970s, followed by SqCC and LCC in

the 1980s, and AC in the 1990s. In women, lung cancer incidence began to rise later, with SCC, SqCC, and LCC increasing in the late 1980s, and adenocarcinoma showing a female-to-male ratio decrease from 2.8 to 1.3 by the late 1990s. The most significant decline was seen in SCC.

These time-dependent histological changes may be associated with modifications in cigarette design. Over the years, filters, ventilation holes, and adjustments aimed at reducing tar and nicotine have been introduced. However, such modifications have led to smoke deposition shifting from central to peripheral lung regions, thereby increasing the risk for adenocarcinoma. Furthermore, the levels of tobacco-specific nitrosamines in cigarette smoke have also changed in these newer types of cigarettes. In animal models, these nitrosamines have been shown to specifically induce adenocarcinoma.

10.1.2.3 Clinical Features

Lung cancer may be asymptomatic or present with a wide range of clinical symptoms. The most commonly observed symptoms include progressive dyspnea, cough, chest pain, hoarseness or voice loss, and hemoptysis. Findings related to disseminated disease may include weight loss, abdominal pain due to involvement of the liver, adrenal glands, or pancreas, neurological symptoms related to brain metastases, and bone pain secondary to skeletal metastases. More than 20% of patients with lung cancer develop brain metastases. The presence and nature of symptoms are generally dependent on the extent of disease and the location of metastases. The majority of patients are diagnosed at a locally advanced or metastatic stage.

At the time of diagnosis, among patients with known staging, approximately 16% have disease confined to a single site, 23% have regional lymph node involvement, and more than 60% present with distant metastases.

Paraneoplastic syndromes are also frequently observed in lung cancer, although they are less common in adenocarcinoma compared to other histological subtypes [2].

10.1.3 Benign Epithelial Tumors

10.1.3.1 Bronchial Papillomas

There are three subtypes: squamous cell, glandular, and mixed squamous and glandular papillomas. Solitary squamous cell papillomas are extremely rare and account for less than 1% of all pulmonary neoplasms. However, among bronchial papillomas, the squamous subtype is the most common.

Squamous and mixed papillomas are three times more frequent in males than in females, while glandular papillomas show an equal sex distribution. These lesions typically occur in the sixth decade of life.

Human papillomavirus (HPV) is detected in less than half of solitary squamous cell papillomas but plays a role in the pathogenesis of nearly all papillomatous lesions.

Solitary papillomas are usually central and endobronchial and only rarely peripheral. Squamous cell papilloma is a papillary tumor composed of loose fibrovascular cores covered by squamous epithelium. It may be solitary or multiple and can exhibit an exophytic or inverted growth pattern. Glandular papilloma is a benign papillary tumor lined by non-ciliated columnar cells, containing variable numbers of cuboidal and goblet cells.

Mixed squamous and glandular papilloma is an endobronchial papillary tumor composed of both squamous and glandular epithelium. Each epithelial component must constitute at least one-third of the total epithelial content.

Complete excision and thorough histopathological evaluation of the entire lesion are essential to exclude malignancy [2, 3].

10.1.3.2 Adenomas

Although each entity is extremely rare, they constitute a group that may pose diagnostic pitfalls, particularly in small biopsies, cytologic specimens, and intraoperative consultation materials.

10.1.3.3 Sclerosing Pneumocytoma

Sclerosing pneumocytoma is a pneumocytic neoplasm characterized by a dual cell population consisting of cuboidal surface cells resembling

type II pneumocytes and round stromal cells. It occurs across a wide age range, with a predominance in females.

Histopathologically, it exhibits a combination of papillary, sclerotic, solid, and hemorrhagic growth patterns.

Both cell populations are immunohistochemically positive for EMA and TTF-1, whereas surface cells show diffuse positivity for pancytokeratin, CAM5.2, CK7, and napsin A; in contrast, round stromal cells are typically negative or only weakly positive for these markers. Neuroendocrine markers are negative.

The primary differential diagnoses include papillary adenocarcinoma and carcinoid tumor. A definitive diagnosis can be challenging, especially in small biopsy, cytology, and intraoperative consultation specimens [2, 4].

10.1.3.4 Alveolar Adenoma

It is extremely rare, typically asymptomatic, and most often identified incidentally. It usually presents as a solitary, peripheral lesion. A slight female predominance has been reported, and cases have been documented in individuals aged 39 to 74 years. Histopathologically, it is composed of cystic spaces lined by a layer of type II pneumocyte-like cells, set against a stroma rich in spindle cells. The cystic spaces resemble alveolar spaces, are filled with granular material, and are lined by flattened to cuboidal cells immunohistochemically consistent with type II pneumocytes. The associated stroma may be myxoid or collagenous and contains spindle cells without cytologic atypia.

10.1.3.5 Papillary Adenoma

These are extremely rare tumors, with fewer than 30 cases have been reported. They are well-circumscribed papillary neoplasms composed of cuboidal to columnar epithelial cells lacking cytologic atypia, lining fibrovascular cores. The most important entity in the differential diagnosis is papillary adenocarcinoma.

10.1.3.6 Bronchiolar Adenoma/Ciliated Muconodular Papillary Tumor

These are benign tumors occurring in middle- to older-aged individuals, typically located in the peripheral lung parenchyma. They are composed of a continuous basal cell layer and luminal cuboidal epithelium of bronchiolar type.

10.1.3.7 Mucinous Cystadenoma

It is a localized cystic lesion lined by columnar mucinous epithelium, lacking cytologic atypia or invasive growth pattern. It is extremely rare, with a slight female predominance. Before establishing the diagnosis, pulmonary colloid carcinoma and metastatic mucinous adenocarcinomas must be carefully excluded.

10.1.3.8 Mucous Gland Adenoma

It is a rare benign tumor arising endobronchially within the proximal airways, exhibiting morphologic resemblance to bronchial seromucinous glands. The primary differential diagnosis includes low-grade mucoepidermoid carcinoma.

10.1.4 Precursor Epithelial Lesions

Preinvasive lesions are locally slow-growing neoplasms that do not exhibit lymphatic/vascular invasion or distant metastasis. With complete surgical resection, the disease-free survival rate is 100%. These lesions are typically located in the peripheral lung parenchyma, often in close proximity to the pleura.

10.1.5 Precursor Glandular Lesions

10.1.5.1 Atypical Adenomatous Hyperplasia

Atypical adenomatous hyperplasia (AAH) is a localized, small (≤ 5 mm) proliferation of type II pneumocytes and/or Clara cells (club cells) exhibiting mild to moderate atypia, typically occurring in the centriacinar regions, lining alveolar walls, and occasionally respiratory bronchioles (Fig. 10.1). Clara cells are columnar with pale eosinophilic cytoplasm, while type II pneu-

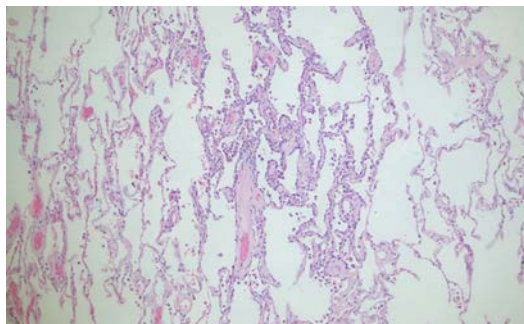


Fig. 10.1 Atypical adenomatous hyperplasia, (≤ 5 mm) showing a proliferation of mildly atypical pneumocytes lining slightly thickened alveolar septa, without evidence of stromal invasion

mocytes appear cuboidal to dome-shaped with finely vacuolated or foamy cytoplasm. There exists a morphologic continuum between AAH and adenocarcinoma in situ (AIS). AAH is often identified incidentally in lung cancer resection specimens.

10.1.5.2 Adenocarcinoma In Situ

Adenocarcinoma in situ (AIS) is a localized adenocarcinoma measuring 3 cm or less in greatest dimension, composed of neoplastic cells growing along preexisting alveolar structures (pure lepidic growth pattern), without evidence of stromal, vascular, or pleural invasion (Fig. 10.2). Thickening of the alveolar septa due to fibrosis and elastosis is commonly observed. Invasive patterns such as acinar, papillary, solid, or

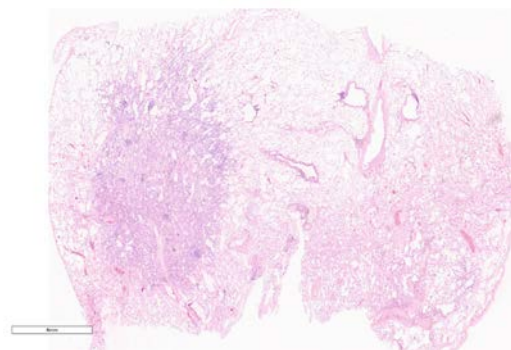


Fig. 10.2 Adenocarcinoma in situ, lepidic growth pattern of neoplastic pneumocytes along preexisting alveolar septa, measuring ≤ 3 cm, without evidence of stromal, vascular, or pleural invasion

micropapillary architecture, as well as intra-alveolar tumor cell proliferation, are absent. This diagnosis can only be rendered following complete evaluation of the entire lesion. AIS is typically located peripherally, often in subpleural regions [2, 5].

10.1.6 Squamous Precursor Lesions

10.1.6.1 Squamous Dysplasia and Carcinoma In Situ

Squamous dysplasia and squamous carcinoma in situ (SCIS) are preinvasive squamous lesions of the bronchial epithelium that are considered precursors to SqCC. These lesions can occur anywhere within the airways and may develop as solitary or multifocal lesions throughout the tracheobronchial tree. They are typically asymptomatic and are often identified incidentally on bronchoscopy.

Squamous dysplasia occurs in approximately 40% of heavy smokers and in patients with obstructive airway diseases. These preinvasive squamous lesions are more frequently observed in males and in individuals exposed to asbestos or other occupational carcinogens. They arise due to sequential genetic and epigenetic alterations associated with field cancerization involving the entire tracheobronchial tree. Early events include loss of heterozygosity at 3p and 9p21, starting from morphologically normal epithelium. TP53 mutations occur at variable stages.

SCIS often develops near bifurcations of segmental bronchi and may extend into adjacent lobar and subsegmental branches. In response to irritants and carcinogens, bronchial epithelium may undergo basal cell hyperplasia or squamous metaplasia, accompanied by loss of goblet and ciliated cells; however, these changes are not considered preneoplastic. Ongoing exposure may lead to progression from mild to moderate and severe dysplasia and eventually to SCIS.

Dysplasia is graded as low grade (mild and moderate dysplasia) or high grade (severe dysplasia). Dysplastic lesions may show angiogenic or papillary features, though these have no established prognostic significance. Severe dysplasia

progresses or persists in approximately 37% of cases, whereas SCIS progresses or persists in about 88%. At this stage, complete excision is typically curative, although there is a risk of multifocality.

Mild dysplasia should be distinguished from basal cell hyperplasia and squamous metaplasia. Differentiating SCIS from invasive carcinoma may be challenging, especially in small biopsy samples. The presence of necrosis and an endoscopically visible mass may suggest an invasive disease [2, 6].

10.1.7 Malignant Epithelial Tumors

10.1.7.1 Adenocarcinomas

10.1.7.1.1 Minimally Invasive Adenocarcinoma

Minimally invasive adenocarcinoma (MIA) is a lepidic-predominant adenocarcinoma measuring 3 cm or less in size, with an invasive component of 5 mm or less. Similar to AIS, the diagnosis of MIA can only be made on resection specimens. Macroscopically, the tumor is typically peripherally located, with collapsed fibrosis and alveolar air spaces observed in the central region. For accurate tumor size assessment, correlation between CT imaging and gross pathology findings is essential. Like AIS, MIA is most often non-mucinous. Non-mucinous MIA typically consists of type II pneumocytes or Clara (club) cells, while mucinous MIA is composed of columnar cells with prominent apical mucin and basally located small nuclei, resembling goblet cell morphology. The invasive component consists of histologic subtypes other than lepidic (e.g., acinar, papillary, micropapillary, and/or solid patterns). Tumor cells invade myofibroblastic stroma. If the tumor shows invasion into lymphatics, blood vessels, air spaces (spread through air spaces, STAS), or pleura, or if tumor necrosis is present, a diagnosis of MIA cannot be made.

According to the updated staging, MIA is classified as T1a(mi). The main differential diagnosis is invasive adenocarcinoma. The size of the

invasive component is the key criterion for distinction [2, 7].

10.1.7.1.2 Invasive Non-mucinous Adenocarcinoma

Invasive pulmonary adenocarcinoma is a malignant epithelial tumor characterized by glandular differentiation and the production of mucin or expression of pneumocyte markers. These tumors exhibit one or more growth patterns including acinar, papillary, micropapillary, lepidic, or solid. A tumor displaying only a single growth pattern is extremely rare, as invasive adenocarcinomas are typically composed of a complex, heterogeneous mixture of histologic subtypes. Unlike other lung cancer types, pulmonary adenocarcinoma can also occur in nonsmokers, although no definitive environmental or genetic factors have been consistently identified in these patients.

In invasive non-mucinous adenocarcinoma, the tumor may appear on computed tomography (CT) as completely solid, mixed solid and ground-glass opacity (GGO). Histologically, the solid component corresponds more frequently to invasive adenocarcinoma, while GGO reflects lepidic growth. The most common location for invasive adenocarcinoma is the peripheral lung.

Macroscopically, most invasive adenocarcinomas present as gray-white nodules with a central fibrotic scar, anthracotic pigmentation, and pleural retraction. If a peripheral lepidic component is present, the tumor margins may appear ill-defined, and even preserved alveolar parenchyma may be discernible at the lesion's edge. In fresh, unfixed tissue, identifying the lepidic component can be particularly difficult.

Microscopically, according to the 2021 WHO Classification of Thoracic Tumors, five major histologic patterns are defined: lepidic, acinar, papillary, micropapillary, and solid. It is recommended to quantify these patterns semiquantitatively in 5% increments, identify the predominant pattern for subtype classification, and report the proportion of each component after reviewing all available tumor sections. Although two patterns may theoretically be present in equal proportions, in practice, a dominant pattern must be chosen.

Spread through air spaces (STAS) may be observed in the form of micropapillary clusters, solid nests, or single tumor cells. STAS is associated with a higher risk of recurrence and poor prognosis, particularly in stage I adenocarcinoma patients undergoing limited resection. Since STAS is considered a form of tumor spread, it should not be included in the percentage estimates of histologic subtypes [2, 8].

10.1.7.1.3 Lepidic Adenocarcinoma

Lepidic adenocarcinoma is composed of pneumocytic cells (type II pneumocytes, Clara cells) growing along the alveolar walls, similar in morphology to that observed in AIS and MIA. For a diagnosis of invasive adenocarcinoma, the invasive component must be present in at least one focus exceeding 5 mm in greatest dimension.

In cases where there are multiple foci or if measuring a single invasive focus is challenging, it is recommended to estimate the invasive size by multiplying the total tumor size by the percentage of invasive component. If this calculated dimension exceeds 5 mm, the diagnosis should be reported as lepidic predominant adenocarcinoma.

The diagnosis of invasion is based on at least one of the following features:

1. Presence of a histologic subtype other than lepidic.
2. Tumor cells infiltrating a myofibroblastic stroma.
3. Vascular or pleural invasion.
4. Spread through air spaces (STAS).
5. Tumor necrosis.

If any of these features are present, the tumor should be classified as lepidic predominant adenocarcinoma.

The lepidic growth pattern can also be seen in tumors metastatic to the lung and in invasive mucinous adenocarcinomas. However, the term "lepidic predominant adenocarcinoma" in this classification specifically refers to non-mucinous adenocarcinomas with a predominant lepidic growth pattern and should not be used for invasive mucinous adenocarcinomas.

10.1.7.1.4 Acinar Adenocarcinoma

In pulmonary adenocarcinoma, the most commonly observed predominant pattern is the acinar pattern. It is composed of round or oval-shaped glandular structures formed by tumor cells surrounding a central lumen. The neoplastic cells and/or glandular lumina may contain mucin. When lepidic growth becomes trapped in collapsed alveoli forming nests, it may be challenging to distinguish from the acinar pattern. However, the absence of alveolar framework and/or the presence of myofibroblastic stroma favors a diagnosis of acinar adenocarcinoma (Fig. 10.3a). Cribriform architecture is considered a variant of the acinar pattern and is associated with poor prognosis. Recent studies recommend that if the cribriform component constitutes more than 10% of the tumor, this should be explicitly reported in the pathology report.

10.1.7.1.5 Papillary Adenocarcinoma

Papillary adenocarcinoma consists of cuboidal to columnar glandular cells growing along a central fibrovascular core. This tumor should be distinguished from lepidic adenocarcinoma with tangential sectioning of alveolar walls. If a tumor exhibits lepidic growth but the alveolar spaces are filled with papillary structures, the tumor should be classified as papillary adenocarcinoma. In this pattern, myofibroblastic stroma is not required for diagnosis.

10.1.7.1.6 Micropapillary Adenocarcinoma

Micropapillary adenocarcinoma consists of tumor cells forming flower-like papillary clusters without a fibrovascular core (Fig. 10.3b). These structures may appear detached from or attached to the alveolar walls.

Tumor cells are small cuboidal cells with variable nuclear atypia. Ring-like glandular structures may be seen floating within alveolar spaces. Vascular and stromal invasion is common. Psammoma bodies may also be observed.

10.1.7.1.7 Solid Adenocarcinoma

Solid adenocarcinoma lacks the recognizable patterns of acinar, papillary, micropapillary, or lepidic growth and is composed of polygonal tumor cells forming solid sheets or nests. If the tumor is 100% solid, intracellular mucin must be present in at least five tumor cells in two high-power fields, and this must be confirmed by histochemical mucin staining.

Immunohistochemically, the most commonly used pneumocyte markers are TTF-1 and Napsin A. Approximately 75% of invasive adenocarcinomas are positive for TTF-1. Among the adenocarcinoma patterns, lepidic and papillary types most frequently show TTF-1 positivity, while the solid type shows the least. There is a strong correlation between TTF-1 positivity and EGFR mutation. Although Napsin A has similar sensitivity to TTF-1, some studies suggest TTF-1 is superior to Napsin A in distinguishing

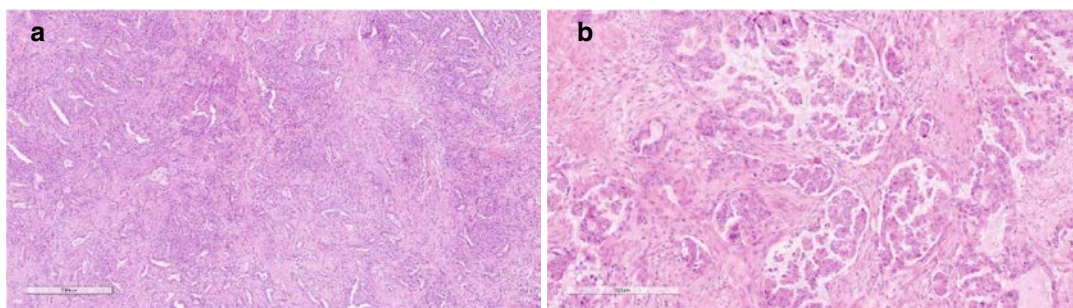


Fig. 10.3 (a) Acinar pattern is characterized by well-formed malignant glandular structures with central lumina, lined by cuboidal to columnar atypical epithelial cells, infiltrating fibrotic stroma. (b) Micropapillary pat-

tern is characterized by small, tight clusters of neoplastic epithelial cells lacking fibrovascular cores, often appearing to float within alveolar spaces or retraction clefts in the stroma

adenocarcinoma from SqCC. While evaluating immunostaining, entrapped pneumocytes that may show positivity should be carefully excluded.

Napsin A may also be positive in tumors such as renal cell carcinoma. P40 is a highly specific squamous marker showing strong and diffuse staining in SqCC and is more specific than p63, which may be positive in approximately 30% of adenocarcinomas.

The differential diagnosis includes other types of lung carcinoma, mesothelioma, and extrapulmonary metastases. SqCC and SCC are the most common tumors that pose diagnostic challenges against adenocarcinoma. Some solid adenocarcinomas have dense eosinophilic cytoplasm, which can resemble SqCC. In resected, poorly differentiated tumors, squamous morphology may be seen, but keratinization, pearl formation, or intercellular bridges are absent. Diagnosis is confirmed using TTF-1 and p40 immunostaining.

Some solid adenocarcinomas may mimic SCC, especially when peripheral palisading is present. However, negative staining with neuroendocrine markers supports a diagnosis of adenocarcinoma.

A tumor diameter >25 mm, as well as solid and micropapillary patterns, is associated with poor prognosis. Lung tumors often harbor driver mutations such as EGFR mutations, ALK, ROS1, RET rearrangements, MET exon 14 skipping, and BRAF p.V600E. The presence of these mutations is strongly correlated with response to tyrosine kinase inhibitors.

10.1.7.1.8 Invasive Mucinous Adenocarcinoma

Invasive mucinous adenocarcinoma (IMA) has been placed in a separate category in the new classification due to its distinct clinical, pathological, and genetic characteristics. Radiologically, it typically presents as lobar or multilobar involvement. It may appear as a GGO, either isolated or accompanied by a solid component.

Microscopically, tumor cells contain abundant intracytoplasmic mucin and display goblet and/or columnar cell morphology, with small, basally located nuclei. Characteristically, nuclear atypia

is absent or minimal. The surrounding alveolar spaces are filled with mucin. All patterns (acinar, papillary, micropapillary, and lepidic) except solid growth may be observed in a heterogeneous mixture, similar to non-mucinous tumors. However, it is important to distinguish IMA from other mucin-producing adenocarcinomas that lack goblet or columnar cells. Although lepidic pattern is the most common dominant pattern, invasive foci with desmoplastic stroma may be seen, especially when extensive sampling of resection specimens is performed. If the tumor in a resection specimen meets the criteria for AIS or MIA and has the characteristic mucinous cell morphology, then the diagnosis should be mucinous AIS or MIA. However, these tumors are extremely rare.

The coexistence of mucinous and non-mucinous adenocarcinoma is also rare. If each component constitutes $\geq 10\%$ of the tumor, then the tumor should be classified as a mixed adenocarcinoma, with both components described in the report.

10.1.7.1.9 Colloid Adenocarcinoma

Previously classified as “mucinous cystic tumor of borderline malignancy” and “mucinous cystadenocarcinoma,” colloid adenocarcinoma (CA) is characterized by abundant extracellular mucin accumulation, which expands alveolar spaces and destroys alveolar walls. It exhibits an invasive growth pattern toward alveolar spaces. Mucin deposits expand and dissect through the lung parenchyma, forming mucin-rich matrix lakes. The tumor cells are arranged in a lepidic pattern foci, composed of tall columnar cells with goblet-like features. These tumor cells and glandular structures are seen to float within mucinous material. The mucinous tumor cells are highly well differentiated and do not fully line the alveolar walls. This appearance can pose diagnostic challenges, especially in small biopsies or intraoperative evaluations. Epithelial stratification and nuclear atypia may be observed. Mitotic activity is extremely low, and necrosis is absent. Inflammatory cells, including histiocytes and giant cells, may be seen.

Immunohistochemically, tumor cells express intestinal markers such as CDX2, MUC2, and cytokeratin 20 (CK20). Focal and weak staining with TTF-1 and CK7 may be seen. Differential diagnosis includes IMA. In colloid adenocarcinoma, mucin completely eliminates the alveolar framework, and tumor cells are extremely sparse. Clinical correlation is crucial to exclude metastasis from the gastrointestinal tract, pancreas, ovary, or breast.

10.1.7.1.10 Fetal Adenocarcinoma

Previously, this tumor was termed “pulmonary blastoma.” It consists of glycogen-rich, non-ciliated cells resembling the epithelium of the pseudoglandular phase of fetal lung development (Fig. 10.4a). Both low-grade and high-grade fetal adenocarcinomas have been described.

Low-grade tumors exhibit mild nuclear atypia and morule formation. The neoplastic glandular structures are surrounded by a loose, fibromyxoid stroma.

High-grade tumors show marked nuclear atypia, and morules are absent. Transitional areas into conventional adenocarcinoma and necrosis are prominent features.

Immunohistochemically, low-grade fetal adenocarcinoma expresses TTF-1 and demonstrates aberrant nuclear localization of β -catenin. More than 90% of low-grade tumors contain neuroendocrine cells that express chromogranin A and/or synaptophysin. About 50% of high-grade tumors

also contain such cells. High-grade tumors frequently express AFP, glypican-3, and SALL4.

10.1.7.1.11 Enteric-Type Adenocarcinoma

This tumor, previously referred to as “pulmonary intestinal-type adenocarcinoma,” resembles colorectal adenocarcinomas. It consists of acinar and/or cribriform as well as papillotubular structures similar to colorectal adenocarcinoma (Fig. 10.4b). Cytologically, the tumor is composed of eosinophilic, tall columnar cells with brush borders and vesicular nuclei. Central dirty necrosis is commonly observed. Since lung adenocarcinomas are typically heterogeneous, this pattern must constitute more than 50% of the tumor for this diagnosis to be made.

Immunohistochemically, variable expression of CDX2, CK20, and CK7 is seen. TTF-1 expression is rare, making it challenging to differentiate this tumor from metastatic colorectal adenocarcinoma [2, 8].

10.1.8 Squamous Cell Carcinomas

10.1.8.1 Squamous Cell Carcinoma

SqCC is a malignant epithelial tumor demonstrating squamous cell differentiation either morphologically (e.g., keratinization, intercellular bridges) or immunophenotypically. Compared to adenocarcinomas, SqCC is more strongly associated with smoking. Over 90% of patients with

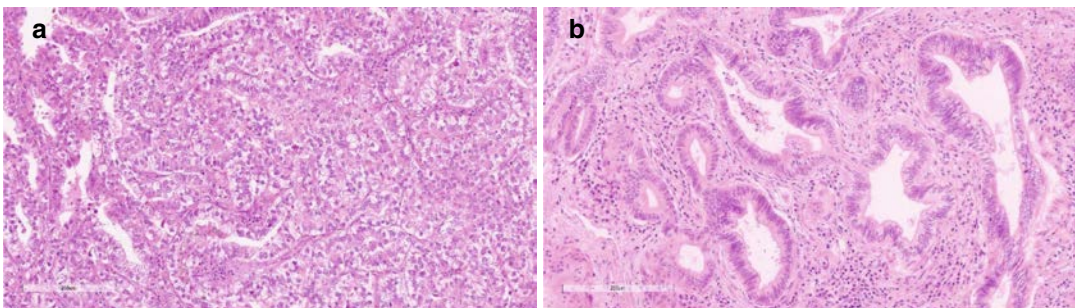


Fig. 10.4 (a) Fetal adenocarcinoma is characterized by glands resembling developing fetal lung tubules, lined by non-ciliated columnar cells with clear or glycogen-rich cytoplasm. (b) Enteric type adenocarcinoma is morpho-

logically resembling colorectal adenocarcinoma, composed of tall columnar cells with eosinophilic cytoplasm forming irregular glands

SqCC have a history of heavy smoking. Other risk factors include radon gas, metals (e.g., arsenic, cadmium, chromium), radiation, air pollution, infections, age, family history, and passive smoking. SqCC develops through a multistep transformation characterized by progressive accumulation of genetic and epigenetic alterations and increasing morphological dysplasia. The role of HPV in lung SqCC pathogenesis remains unclear. It is more common in males and accounts for approximately 20% of all lung cancers, making it the second most common subtype. It is the most frequently seen histologic type in patients with idiopathic pulmonary fibrosis and interstitial lung disease.

Macroscopically, the cut surface appears white, light brown, or gray, sometimes with central carbon pigment accumulation and starlike retraction at the periphery. Cavitation may develop centrally in large tumors due to necrosis. Central tumors often grow endobronchially and exophytically in a papillary pattern, leading to frequent bronchial obstruction and subsequent secondary atelectasis, obstructive pneumonia, and fungal and/or bacterial infections.

Histopathologically, keratinizing, nonkeratinizing, and basaloid subtypes have been described:

Keratinizing SqCC is characterized by keratinization features such as keratin pearls and intercellular bridges. The extent of keratinization

correlates with the degree of tumor differentiation (Fig. 10.5a).

Nonkeratinizing SqCC lacks keratinization and appears as a solid tumor. Squamous differentiation can be demonstrated via immunohistochemical markers (Fig. 10.5b).

Basaloid SqCC is composed of small-to-medium-sized cells with scant cytoplasm, high mitotic activity, lobular architecture, and peripheral palisading. Diagnosis requires >50% of the tumor to show basaloid morphology. It expresses squamous markers immunohistochemically.

Immunohistochemically, the most specific marker of squamous cell differentiation is p40. Other markers like p63, high molecular weight cytokeratins, desmoglein, and desmocollin are less specific. Diffuse positivity for squamous markers supports a diagnosis of SqCC.

Differential diagnosis depends on the histologic subtype. As differentiation decreases, the range of entities in the differential increases. These include adenocarcinoma, LCC, mucoepidermoid carcinoma, and especially for the basaloid subtype, large cell neuroendocrine carcinoma (LCNEC), SCC, and NUT carcinoma. In morphologically ambiguous tumors, immunophenotyping is necessary. However, in small biopsy samples, judicious use of limited immunohistochemical markers is crucial to preserve tissue for potential downstream molecular testing. Additionally, distinguishing metastatic

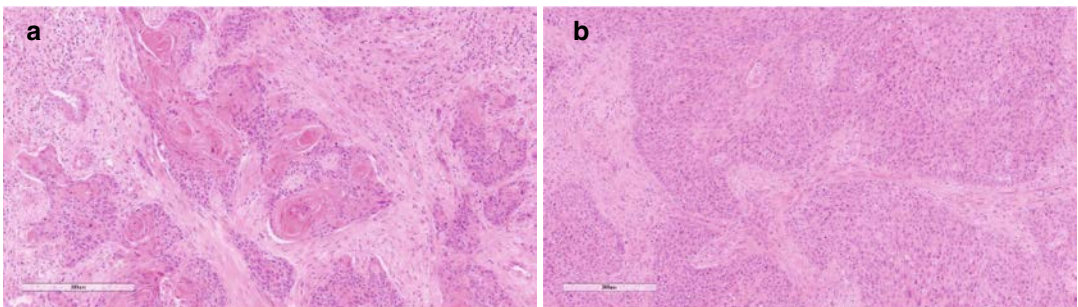


Fig. 10.5 (a) Keratinizing squamous cell carcinoma is characterized by nests and sheets of malignant squamous epithelial cells exhibiting intercellular bridges and prominent keratinization, often forming keratin pearls within the tumor nests. (b) Nonkeratinizing squamous cell carcinoma

is composed of malignant squamous epithelial cells forming nests or solid sheets, with evident intercellular bridges but lacking overt keratinization or keratin pearl formation

SqCC from primary pulmonary SqCC is morphologically and immunohistochemically difficult; therefore, clinical and radiological data are of great importance [2, 8].

10.1.8.2 Lymphoepithelial Carcinoma

Lymphoepithelioma-like carcinoma (LELC) is a poorly differentiated variant of SqCC, often associated with Epstein-Barr virus (EBV) and accompanied by variable lymphoplasmacytic infiltration. It is a rare tumor and shows a female predominance. In patients of Asian descent, >90% of cases are EBV related, whereas this association is lower in individuals of European ancestry.

The absence of TP53, KRAS, EGFR mutations, and ALK or ROS1 translocations, which are commonly observed in non-small cell carcinomas, suggests a distinct pathogenetic pathway in the development of this tumor.

Macroscopically, these tumors appear as round to oval, well-circumscribed, pink-white, fleshy masses on cut surface. Microscopically, they exhibit a syncytial growth pattern with prominent lymphoplasmacytic infiltration. In a small portion of tumors, this lymphoid infiltration may be minimal, resulting in a morphology resembling poorly differentiated SqCC. The tumor cells have eosinophilic cytoplasm and large vesicular nuclei with prominent eosinophilic nucleoli. Focal keratinization and amyloid deposition may be seen. Non-necrotizing granulomatous inflammation can also be present in the stroma.

Immunohistochemically, tumor cells show diffuse positivity for pancytokeratin, CK5/6, p40, and p63. The associated lymphoid infiltrate is composed of CD3-positive T cells and CD20-positive B cells. In EBV-associated tumors, *in situ* hybridization can demonstrate EBV positivity.

The differential diagnosis includes nasopharyngeal nonkeratinizing carcinoma, poorly differentiated non-small cell carcinoma, NUT carcinoma, and non-Hodgkin lymphoma. This diagnosis should be considered when encountering nonkeratinizing SqCC in a young, nonsmoking Asian patient.

Prognosis is generally better than that of conventional non-small cell carcinomas in both early and late stages. Poor prognostic factors include tumor necrosis, low lymphocytic infiltration, and high baseline plasma EBV DNA concentration [2, 9].

10.1.9 Large Cell Carcinoma

These are non-small cell carcinomas that cannot be subtyped cytologically, architecturally, immunohistochemically, or histochemically. They account for approximately 1.5% of all lung carcinomas. The average age at diagnosis is 65, with a marked male predominance, and most patients are smokers. Its etiology is similar to that of other non-small cell carcinomas. Pathogenesis parallels that of other lung cancers. Some mutations associated with adenocarcinoma can also be found in large cell carcinomas. Gene expression profiling often reveals features of epithelial-mesenchymal transition, indicating that LCCs are less differentiated than other non-small cell carcinomas.

Macroscopically, they present as large, solid masses, frequently exhibiting necrosis. Microscopically, diagnosis of LCC requires examination of the entire tumor. Morphological, immunohistochemical, and histochemical

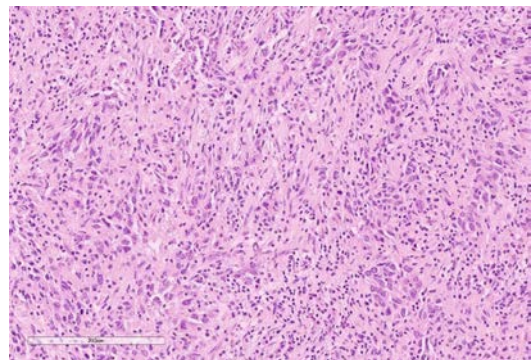


Fig. 10.6 Large cell carcinoma is an undifferentiated non-small cell carcinoma composed of large polygonal cells with abundant cytoplasm, prominent nucleoli, and vesicular nuclei, lacking morphological and immunohistochemical features of glandular, squamous, or neuroendocrine differentiation

exclusion of SCC, adenocarcinoma, SqCC, and giant cell, spindle cell, or pleomorphic carcinomas is necessary. The tumor consists of sheets and nests of large polygonal cells with prominent nucleoli, vesicular chromatin, and visible cytoplasm (Fig. 10.6). Clear cell and/or rhabdoid features may be present, and their proportions should be specified.

Immunohistochemically, the first-line markers for identifying adenocarcinomatous and squamous differentiation are TTF-1 and p40, respectively. Cytokeratins can be used to confirm epithelial differentiation. A mucin stain must show positivity in fewer than five cells in two high-power fields; otherwise, the tumor should be diagnosed as an adenocarcinoma.

Differential diagnosis includes solid type adenocarcinoma, nonkeratinizing SqCC, adenosquamous carcinoma, LCNEC, carcinosarcoma, thoracic SMARCA4-deficient undifferentiated tumors, metastatic carcinomas, lymphoma, melanoma, and mesothelioma. If spindle and/or giant cells are present and constitute more than 10% of the tumor, it should be classified as a pleomorphic carcinoma [2, 10].

10.1.10 Adenosquamous Carcinoma

These are tumors containing both adenocarcinoma and SqCC components, each constituting at least 10% of the tumor. They account for approximately 2–3% of all lung cancers. There is a male predominance, with a median age around 65–67 years. It is associated with smoking, but like adenocarcinomas, it may also occur in never-smokers, particularly in females within that group. Although the tumor morphologically contains both squamous and adenocarcinoma components, they share identical driver mutations, suggesting a clonal origin. This indicates that adenosquamous carcinoma is not a collision tumor. Two proposed pathogenic mechanisms include:

1. Origin from multipotent tissue stem cells.
2. Transdifferentiation from adenocarcinoma or SqCC.

The gross appearance is similar to other non-small cell carcinomas. These tumors show varying proportions of adenocarcinoma and SqCC components. The adenocarcinoma component may exhibit various histological patterns, while the squamous component may be keratinizing or nonkeratinizing. In tumors combining solid adenocarcinoma and nonkeratinizing squamous components, distinguishing the two morphologically may be challenging.

The best immunohistochemical marker for the adenocarcinoma component is TTF-1. For the squamous component, p40 is preferred. When TTF-1 is negative in a solid adenocarcinoma component, mucin positivity must be demonstrated to confirm adenocarcinomatous differentiation.

Differential diagnosis includes adenocarcinoma, SqCC, and high-grade mucoepidermoid carcinoma. Special attention should be paid to squamoid solid adenocarcinomas and pseudoglandular structures in squamous cell carcinomas, which can mimic gland formation. Compared to other non-small cell carcinoma subtypes, adenosquamous carcinoma is more aggressive [2, 11].

10.1.11 Sarcomatoid Carcinomas

10.1.11.1 Pleomorphic Carcinoma

This is a poorly differentiated non-small cell lung carcinoma (NSCLC) that contains at least 10% spindle and/or giant cell components, or it is composed entirely of spindle and/or neoplastic giant cells. A definitive diagnosis of pleomorphic carcinoma can only be made on surgical specimens. In surgical series, it accounts for approximately 2–3% of NSCLCs. It most commonly occurs in the seventh decade of life and shows male predominance, most patients are current or former smokers. It is believed that the sarcomatoid component arises through epithelial-mesenchymal transition (EMT) of carcinoma cells.

Macroscopically, tumors are usually well-circumscribed, with an average diameter of 50 mm. Invasion of the mediastinum and chest

wall is frequent. Microscopically, the tumor consists of components of adenocarcinoma, SqCC, or LCC. More than 10% of the tumor should consist of spindle and/or giant cell components with these histological patterns. These components may be intermixed or sharply demarcated. Necrosis, hemorrhage, and vascular invasion are common.

The giant cell carcinoma component is composed of pleomorphic neoplastic giant cells with irregular, multilobulated nuclei and abundant eosinophilic-granular cytoplasm (Fig. 10.7).

The spindle cell carcinoma component is composed of pure neoplastic spindle cells. A variable amount of chronic inflammatory infiltrate may be present.

Immunohistochemistry is useful to demonstrate the various components: pancytokeratin is positive in the NSCLC component, but expression in the spindle/giant cell component is variable. Multiple epithelial markers may be required to demonstrate epithelial differentiation.

Differential diagnosis includes carcinosarcoma, pulmonary blastoma, metastatic sarcomatoid carcinomas, primary sarcomas, inflammatory myofibroblastic tumor, germ cell tumors, melanoma, dendritic cell sarcoma, and biphasic/sarcomatoid mesothelioma.

If adenocarcinoma, SqCC, or LCC components are present, the tumor is considered pleomorphic carcinoma, even if keratin expression is completely negative in the spindle and/or giant

cell components. This is because a diagnosis of *carcinosarcoma* requires the presence of malignant heterologous elements (e.g., osteosarcoma, chondrosarcoma, rhabdomyosarcoma).

Rarely, reactive fibrotic processes with prominent inflammation can mimic spindle cell carcinoma. Tumors with spindle and/or giant cell components that are part of SCC or LCNEC should be classified accordingly. Compared to other NSCLC subtypes, pleomorphic carcinoma follows a more aggressive clinical course [2, 12, 13].

10.1.11.2 Pulmonary Blastoma

Pulmonary blastoma is a biphasic tumor composed of a low-grade fetal adenocarcinoma and a primitive mesenchymal stroma. Areas showing specific mesenchymal differentiation may be present but are not required for diagnosis. This tumor is extremely rare. Pulmonary blastomas frequently harbor missense mutations in exon 3 of the CTNNB1 gene, leading to activation of the WNT signaling pathway and aberrant nuclear localization of β -catenin. Macroscopic features of these tumors are typically large peripheral masses and often show necrosis and hemorrhage. Microscopically, they exhibit a biphasic pattern composed of branching glandular structures and primitive mesenchymal cells: the glandular component is made up of small, monotonous cells with subnuclear vacuolization, resembling secretory endometrium. Morule formation is seen in approximately 40% of cases. The glandular morphology is identical to low-grade fetal adenocarcinoma. In about one-third of cases, atypical glands with a less differentiated morphology resembling conventional adenocarcinoma may be present. The mesenchymal component consists of oval to spindle-shaped primitive blastema-like cells, along with more mature fibroblast-like cells.

Immunohistochemically, the epithelial component expresses markers similar to low-grade fetal adenocarcinoma. The mesenchymal component shows vimentin positivity and may express tissue-specific antigens depending on the type of differentiation. Both the glandular and blastemal

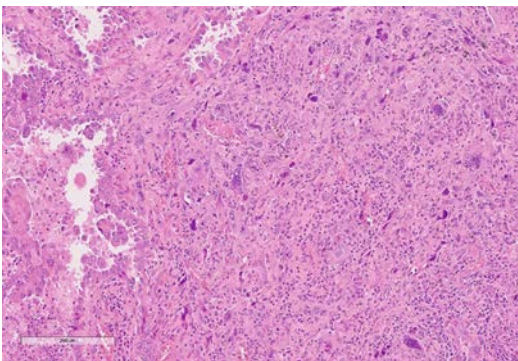


Fig. 10.7 Giant cell carcinoma admixed with an adenocarcinoma component, showing gland formation on the left side and a giant cell component on the right side with numerous multinucleated giant bizarre cells

components exhibit nuclear and cytoplasmic beta-catenin expression.

Differential diagnosis includes fetal adenocarcinoma, pleomorphic carcinoma, and carcinosarcoma.

Distant metastasis and recurrence are common. The prognosis is poor [2, 8].

10.1.11.3 Carcinosarcoma

Pulmonary carcinosarcoma is a malignant tumor containing at least one sarcomatous heterologous element in association with non-small cell carcinoma. It is extremely rare and shows a male predominance. Most patients are heavy smokers. Molecular studies have demonstrated that both the carcinomatous and sarcomatous components arise from a common clonal origin, classifying these tumors as carcinomas with sarcomatoid differentiation.

Microscopically, it presents a biphasic morphology composed of carcinomatous and sarcomatous components. The carcinomatous component is most frequently SqCC, followed by adenocarcinoma and LCC. The sarcomatous component may include elements of rhabdomyosarcoma, chondrosarcoma, and/or osteosarcoma.

The presence of heterologous elements is a key feature distinguishing carcinosarcoma from pleomorphic carcinoma. When diagnosing carcinosarcoma, the specific histological subtypes of both epithelial and mesenchymal components should be specified.

Immunohistochemically, the carcinomatous and sarcomatous components express their respective subtype-specific markers. Spindle cell areas may be positive or negative for pancytokeratin. β -catenin typically shows membranous expression.

Differential diagnosis includes pleomorphic carcinoma, pulmonary blastoma (which contains fetal adenocarcinoma and blastema-like areas with nuclear β -catenin positivity), sarcomas (which may have high-grade epithelioid areas but lack gland formation or keratinization), synovial sarcoma (whose glandular component is TTF-1 negative), and biphasic mesothelioma (epithelioid component expresses mesothelial markers).

Like other sarcomatoid carcinomas, pulmonary carcinosarcoma has a poor prognosis [2, 8].

10.1.12 Other Epithelial Tumors

10.1.12.1 NUT Carcinoma

NUT carcinoma is a poorly differentiated carcinoma with an aggressive clinical course characterized by NUTM1 gene rearrangement. It shows no gender predominance and can occur at any age. Approximately 51% of all NUT carcinoma cases are located in the thoracic/mediastinal region, followed by the head and neck region.

It is characterized by a chromosomal translocation, t(15;19)(q14;p13.1), resulting in a fusion of NUTM1 with BRD4 or other genes encoding BRD4-interacting proteins.

Macroscopically, it appears as one or more large pulmonary or mediastinal masses involving the hilum, pleura, and/or mediastinum, often with extensive necrosis.

Microscopically, it consists of monomorphic, small- to medium-sized undifferentiated cells arranged in sheets and nests, with vesicular chromatin, prominent nucleoli, and uniform nuclei. Frequent mitoses and necrosis are present. In about one-third of cases, there are abrupt foci of keratinization emerging from the undifferentiated morphology—a hallmark feature of NUT carcinoma. Glandular differentiation is not observed.

Immunohistochemistry: NUT antibody shows punctate nuclear staining in 87% of cases; staining in >50% of cells is diagnostic. Pancytokeratin and squamous differentiation markers (p63/p40) are positive in most cases. Rarely, NUT carcinomas may express chromogranin, synaptophysin, and TTF-1. CD34 positivity can also be seen. Markers for germ cell, lymphoid, or myeloid lineages are negative. Ki-67 proliferation index is typically very high.

Differential diagnosis includes poorly differentiated SqCC, SCC, combined small cell and squamous cell carcinoma, undifferentiated carcinomas, and other small round blue cell tumors [2, 14].

10.1.12.2 Thoracic SMARCA4-Deficient Undifferentiated Tumor (SMARCA4-UT)

SMARCA4-UT is a high-grade malignant neoplasm seen in adults involving the thorax, showing an undifferentiated or rhabdoid phenotype, with loss of SMARCA4, a key component of the BAF chromatin-remodeling complex. It typically affects young to middle-aged adults but has a wide age range (27–90 years). It shows a marked male predominance and is strongly associated with heavy smoking. It develops due to biallelic inactivation of SMARCA4. These tumors commonly involve the mediastinum, pulmonary hilum, and/or pleura, presenting as large, aggressive masses compressing adjacent structures. Grossly, they appear as large, gray-white tumors with extensive necrosis. Microscopically, they consist of sheets of large round-to-epithelioid cells with vesicular chromatin, prominent nucleoli, and relatively monotonous nuclei, though some cells may show mild to moderate pleomorphism. Rhabdoid morphology may also be present. Frequent mitoses and necrosis are common. About 5% of cases have combined morphology with conventional NSCLC.

Immunohistochemically, complete loss of SMARCA4 expression is typical. In 25% of cases, there is a diffuse reduction in SMARCA4 expression. Cytokeratin expression is often focal or weak. Most cases express CD34, SOX2, and/or SALL4, with p53 overexpression frequently observed.

The differential diagnosis includes lymphoma, NUT carcinoma, germ cell tumor, neuroendocrine carcinoma, LCC, melanoma, and various sarcomas. SMARCA4 loss can also be seen in ~5% of NSCLC cases. Although morphologic clues such as epithelial architecture and cellular cohesion, along with markers like CD34, SOX2, and SALL4, are helpful, none are fully sensitive or specific. Additionally, metastases from morphologically identical tumors of other origins must be clinically excluded. These tumors exhibit aggressive behavior and have a poor prognosis. Cytotoxic chemotherapy regimens are generally reported to be ineffective [2, 15].

10.1.13 Salivary Gland-Type Tumors of the Lung

Mucoepidermoid carcinoma and adenoid cystic carcinoma are the most common pulmonary salivary gland-type tumors. Other rare examples reported include epithelial-myoepithelial carcinoma, hyalinizing clear cell carcinoma, and pleomorphic adenoma. Salivary gland-type tumors account for less than 1% of all pulmonary neoplasms. They can occur across a wide age range and show no sex predilection.

These tumors originate from submucosal glands of the tracheobronchial system and typically present as slow-growing, centrally located, well-circumscribed endobronchial masses.

Macroscopically and microscopically, they exhibit an identical morphology to their counterparts found in the salivary glands.

In the differential diagnosis, the main consideration is metastasis from malignant salivary gland tumors of the head and neck region. Morphological distinction is not possible, so clinical correlation is essential. Additionally, in small biopsy or cytology specimens, it may be difficult to distinguish them from conventional NSCLC. However, because these tumors have a different clinical behavior compared to NSCLC, this distinction is important. Compared to conventional NSCLCs, most salivary gland-type tumors have a better prognosis. They typically follow an indolent course. Surgery is the primary treatment approach. Recurrence and metastasis are rare [2].

10.1.14 Neuroendocrine Neoplasms of the Lung

In the lung, approximately 95% of neuroendocrine neoplasms are high-grade tumors, consisting of SCC (79%) and LCNEC (16%). Carcinoid tumors make up a small portion of this group.

High-grade neuroendocrine carcinomas are typically seen in older patients and have a strong association with smoking. Their prognosis is poor. In contrast, carcinoid tumors tend to occur at younger ages and have a weaker association

with smoking. High-grade neuroendocrine carcinomas (SCC and LCNEC) exhibit more genetic alterations, including amplifications, deletions, and mutations, compared to pulmonary carcinoids. Biallelic inactivation of TP53 and RB1 is characteristic of SCC. In about 25% of cases, inactivating mutations are observed in the NOTCH gene family. Large cell neuroendocrine carcinomas show greater genetic heterogeneity compared to SCC, with one group resembling SCC (with TP53 and RB1 biallelic inactivation) and another group resembling NSCLC with mutations in KRAS and STK11/KEAP1.

Pulmonary carcinoids do not exhibit the mutations found in high-grade neuroendocrine carcinomas.

In summary, carcinoids and high-grade neuroendocrine carcinomas differ significantly in clinical, epidemiological, histological, genetic, and prognostic aspects [2, 16].

10.1.14.1 Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia (DIPNECH)

DIPNECH is a multifocal proliferation of pulmonary neuroendocrine cells. It is considered a pre-invasive condition that can transform into carcinoid tumors. DIPNECH is not associated with high-grade neuroendocrine carcinomas. It usually occurs in nonsmokers during the fifth or sixth decade of life. The pathogenesis of DIPNECH is unclear, but chronic lung diseases, interstitial fibrosis, airway inflammation and/or fibrosis, infections, and hypoxemia may contribute to neuroendocrine cell hyperplasia. Rare cases have been associated with multiple endocrine neoplasia type 1 (MEN1).

Macroscopically, DIPNECH is not visible, but when tumorlets reach 5 mm in diameter, they may appear as gray-white nodules.

Microscopically, DIPNECH is characterized by proliferation of neuroendocrine cells involving small airways and/or the presence of tumorlets. A nodular proliferation of neuroendocrine cells measuring less than 5 mm that extends beyond the bronchiolar wall is classified as a tumorlet (Fig. 10.8). Nodular proliferations greater than 5 mm are classified as carcinoid

tumors. Neuroendocrine cell hyperplasia is defined as more than five neuroendocrine cells present singly or in clusters along the basement membrane of the bronchiolar epithelium. In DIPNECH syndrome, bronchiolar fibrosis with luminal narrowing or constrictive bronchiolitis is seen.

DIPNECH associated with carcinoid tumors is defined as the presence of one or more carcinoid tumors in the lung parenchyma along with neuroendocrine cell hyperplasia and tumorlets.

Immunohistochemically, DIPNECH shows positive expression for neuroendocrine markers such as chromogranin, synaptophysin, and CD56, as well as pancytokeratin and TTF-1. It is negative for p40/p63 and high molecular weight cytokeratins.

DIPNECH should be distinguished from localized reactive neuroendocrine cell hyperplasia. In patients with carcinoid tumors, neuroendocrine cell hyperplasia and/or tumorlets may also be found in the surrounding lung parenchyma.

10.1.14.2 Carcinoid/Neuroendocrine Tumor

Carcinoid tumors are well-differentiated neuroendocrine malignancies with organoid architecture. They are classified into two subtypes: typical and atypical carcinoids. These tumors account for less than 2% of all pulmonary malignancies. The incidence is higher in women, in the White population, and most commonly occurs in the fifth and sixth decades of life. Pulmonary carcinoids represent a significant portion of lung tumors in childhood. Typical carcinoids are more frequently located centrally, whereas atypical carcinoids are more often peripherally located.

In terms of pathogenesis, DIPNECH, as well as localized or widespread neuroendocrine cell hyperplasia, plays important roles. The orthopedia homeobox protein (OTP) is expressed in both DIPNECH and carcinoid tumors, but not in isolated neuroendocrine cells. This suggests that OTP may contribute to abnormal proliferation in the development of pulmonary carcinoids. In contrast to SCC and LCNEC, mutations in the

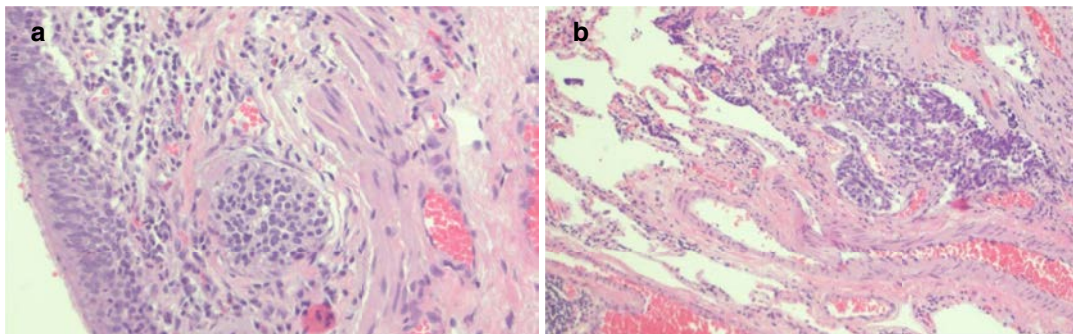


Fig. 10.8 Neuroendocrine cell hyperplasia within the bronchiolar wall and tumorlet foci extending beyond the basement membrane into the adjacent lung parenchyma

TP53 and RB1 genes are exceedingly rare in carcinoids.

Macroscopically, central carcinoids usually present as well-circumscribed, round to oval, endobronchial masses. In peripheral tumors, a clear relationship with the airways may not be evident. Neuroendocrine proliferations larger than 5 mm are classified as carcinoid tumors, while those smaller than 5 mm are considered tumorlets. Typical carcinoids are generally smaller in size than atypical carcinoids.

Microscopically, both typical and atypical carcinoids are well-differentiated neuroendocrine tumors in terms of architecture and cytology (Fig. 10.9). Clinically, typical carcinoids are classified as low-grade, while atypical carcinoids are considered intermediate-grade. Typical carcinoids contain fewer than 2 mitoses per 2 mm² and do not exhibit necrosis. Atypical carcinoids display between 2 and 10 mitoses per 2 mm² and/or

focal or punctate necrosis. Neuroendocrine morphology may be observed in trabecular, rosette, insular, palisading, pseudoglandular, or solid patterns. Tumor cells characteristically have eosinophilic cytoplasm, granular chromatin and nuclei with either prominent or inconspicuous nucleoli. They are generally uniform in appearance and may be cuboidal, polygonal, or spindle-shaped, especially in peripheral locations.

Immunohistochemically, these tumors are positive for low molecular weight cytokeratins and negative for high molecular weight cytokeratins. They strongly express neuroendocrine markers such as chromogranin A, synaptophysin, CD56, and INSM1. TTF-1 is typically positive in peripheral tumors and negative in central tumors. Although the Ki-67 proliferation index is not used as a diagnostic criterion to differentiate between typical and atypical carcinoids in the lung, it is useful in distinguishing carcinoids

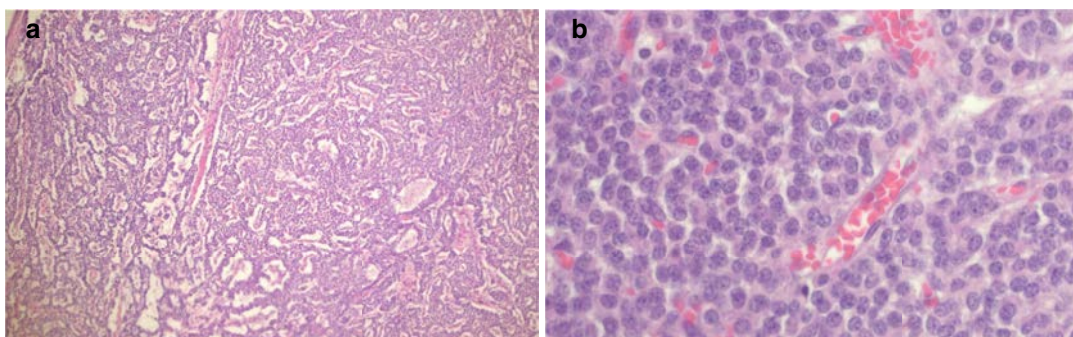


Fig. 10.9 Carcinoid tumor displaying a pseudoglandular architecture and trabecular cords of uniform neuroendocrine cells with finely granular chromatin and moderate amounts of cytoplasm

from high-grade neuroendocrine carcinomas in cytologic specimens or small biopsies.

The differential diagnosis includes metastatic carcinoids, SCC, LCNEC, salivary gland-type tumors, paraganglioma, melanoma, glomus tumor, lobular carcinoma of the breast, and metastatic thyroid carcinoma. Gastrointestinal carcinoids often show glandular architecture, are negative for TTF-1, and express CDX2 and PAX8. Counting mitotic figures is essential for distinguishing high-grade neuroendocrine carcinomas. However, in small or crushed biopsy samples where mitoses cannot be counted, a Ki-67 proliferation index greater than 30% is a strong indicator of high-grade neuroendocrine carcinoma. Differentiation from other entities may require the use of immunohistochemical and/or molecular panels. Mitotic count is the most important predictive factor for survival. Reported five-year survival rates are 82–100% for typical carcinoids and 50–68% for atypical carcinoids.

10.1.14.3 Neuroendocrine Carcinomas

10.1.14.3.1 Small Cell Carcinoma of the Lung (SCC)

SCC is an aggressive, malignant epithelial tumor composed of small-sized cells with scant cytoplasm, finely granular nuclear chromatin, inconspicuous nucleoli, high mitotic activity, and extensive necrosis. These tumors demonstrate neuroendocrine marker expression and account for approximately 15% of all lung carcinomas. SCC is strongly associated with heavy cigarette smoking, although it may rarely occur in never-smokers. In cases of epidermal growth factor receptor (EGFR)-mutant NSCLC, small cell transformation can emerge as a mechanism of resistance to tyrosine kinase inhibitor (TKI) therapy.

Biallelic inactivation of *TP53* and *RB1* is considered obligatory in the pathogenesis of SCC. No well-defined precursor lesions have been established. Clinically, SCC has a rapid onset and course, with frequent local invasion, extrapulmonary dissemination, and paraneoplastic syndromes.

Macroscopically, SCCs typically present as large, unresectable perihilar masses. Approximately 5% of cases are peripherally located.

Microscopically, the tumor consists of cells with scant cytoplasm, finely granular nuclear chromatin with absent or inconspicuous nucleoli (Fig. 10.10). Cells are oval to spindle shaped and typically smaller than three times the diameter of a mature lymphocyte. Nuclear molding, frequent necrosis, and apoptosis are characteristic findings. The expected mitotic rate is >10 per 2 mm^2 , with an average of around 60 mitoses per 2 mm^2 . Azzopardi phenomenon, in which basophilic tumor DNA encrusts blood vessels due to crush artifact, may be observed. Neuroendocrine growth patterns are often seen in resection specimens.

10.1.14.3.2 Combined Small Cell Carcinoma

Combined SCC includes tumors with a small cell component along with components of LCNEC or any NSCLC subtype. The most common non-small cell elements seen are LCC, adenocarcinoma, and SqCC. Although classic morphology may suffice for diagnosis in many cases, immunohistochemical stains are frequently employed for confirmation, exclusion of differential diagnoses, and definitive diagnosis. Cytokeratin expression is often dot-like or in a delicate rim pattern. High molecular weight cytokeratins are

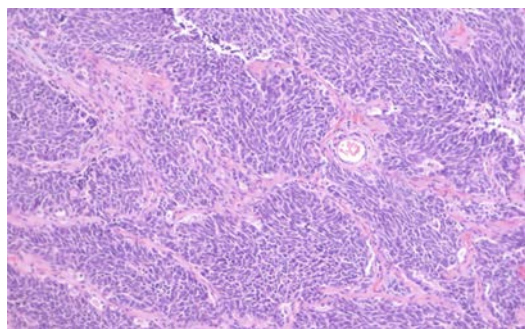


Fig. 10.10 Resection specimen showing small cell carcinoma composed of sheets and nests of small to intermediate-sized cells with scant cytoplasm, finely granular chromatin, inconspicuous nucleoli, nuclear molding, and frequent mitotic figures

typically negative. Neuroendocrine markers such as *chromogranin A*, *synaptophysin*, and *CD56* are usually positive; *CD56* is the most sensitive but least specific. *INSM1* is also a reliable neuroendocrine marker for SCC. However, 5–10% of cases may be negative for neuroendocrine markers. Most tumors exhibit loss of *RB1* protein expression and either loss or overexpression of *p53*. The *Ki-67 proliferation index* is typically high, ranging from 65% to 100%.

The differential diagnosis includes LCNEC, carcinoid tumors, basaloid SqCC, lymphoma, and small round blue cell sarcomas. There are no specific immunohistochemical or molecular markers that definitively distinguish SCC from LCNEC; the distinction is made solely on morphological grounds. Basaloid SqCC may closely resemble SCC in both cytologic and architectural aspects; in such cases, p63 and p40 immunostaining may assist in the diagnosis. Small round cell sarcomas may focally express neuroendocrine markers and should be considered, especially when cytokeratin staining is negative or there is no smoking history. Rarely, SCC may also be cytokeratin negative. In such cases, diagnosis should be based on a combination of characteristic morphology, positive neuroendocrine marker expression, *RB1* loss, and *p53* staining patterns.

10.1.14.3.3 Large Cell Neuroendocrine Carcinoma (LCNEC) of the Lung

LCNEC is a high-grade non-small cell carcinoma characterized by neuroendocrine morphology, a mitotic rate >10 per 2 mm², and expression of at least one neuroendocrine immunohistochemical marker. Combined LCNEC refers to tumors that harbor components of adenocarcinoma, SqCC, or spindle/giant cell carcinoma in addition to the LCNEC component. LCNEC accounts for approximately 3% of resected lung carcinomas. It predominantly affects males over the age of 65. More than 90% of patients have a history of heavy tobacco use, making smoking the most significant etiological factor. LCNEC comprises two distinct genomic subgroups: one resembling SCC and the other adenocarcinoma. Transcriptomic analyses have demonstrated that

these two subtypes of LCNEC are molecularly distinct entities from both conventional SCC and non-small cell carcinoma.

Macroscopically, LCNECs are typically large, peripherally located, well-circumscribed tumors with areas of necrosis.

Microscopically, LCNEC is composed of large cells with abundant cytoplasm, well-defined cell borders, coarse granular nuclear chromatin, and prominent nucleoli (Fig. 10.11). Architectural features include trabecular growth, peripheral palisading, and rosette formation. Some LCNECs may show nuclear features similar to SCC; however, the presence of abundant cytoplasm supports a diagnosis of LCNEC. Extensive necrosis is common. Stromal desmoplasia and inflammatory infiltrates are frequently observed.

Diagnosis of LCNEC requires expression of at least one neuroendocrine marker. Most tumors express two or all three of the following: *chromogranin A*, *synaptophysin*, and *CD56*. If morphology is consistent with LCNEC, focal positivity of a single marker may support the diagnosis. However, due to its lower specificity, *CD56* should be interpreted with caution. TTF-1 is expressed in approximately half of LCNEC cases. Pancytokeratin is typically strongly positive, sometimes displaying a dot-like staining pattern. The *Ki-67* proliferation index is expected to be >30% and may exceed 80% in some cases.

The differential diagnosis includes SCC, LCC, non-small cell carcinomas with neuroendocrine differentiation, basaloid SqCC, carcinoid tumors, metastatic neuroendocrine tumors, and thoracic SMARCA4-deficient undifferentiated tumors. LCNEC is differentiated from SCC by the presence of prominent nucleoli and/or abundant cytoplasm and generally larger cell size. However, the cytological overlap between these entities can make the distinction difficult in certain cases. Currently, no immunohistochemical or molecular marker definitively separates LCNEC from SCC. When LCNEC contains a component of SCC, the diagnosis is combined SCC and LCNEC. LCNEC exhibits an aggressive clinical course. Even in early-stage disease, survival rates are lower compared to

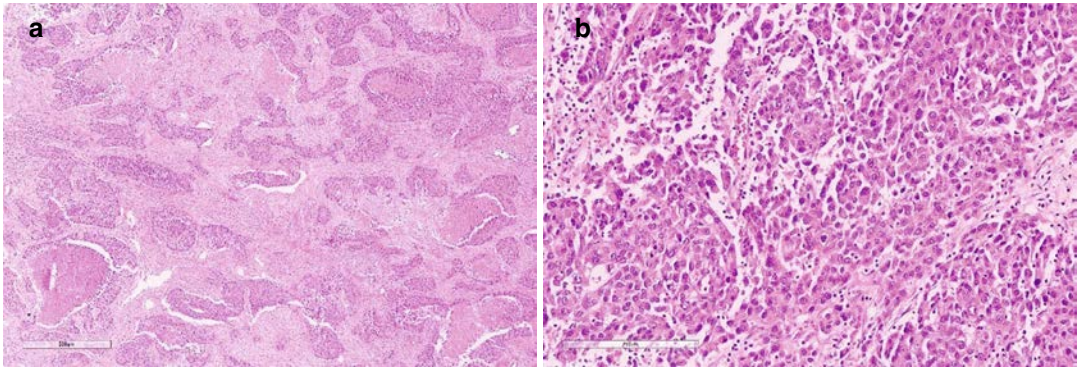


Fig. 10.11 Large cell neuroendocrine carcinoma is composed of solid nests and areas of necrosis, with large polygonal tumor cells containing abundant cytoplasm,

coarse granular nuclear chromatin, and prominent nucleoli, arranged in organoid, trabecular, or rosette-like patterns, and showing high mitotic activity

other non-small cell carcinoma subtypes [2, 16, 17].

10.1.15 Mesenchymal Tumors Specific to the Lung

10.1.15.1 Pulmonary Hamartoma

Pulmonary hamartomas are benign mesenchymal neoplasms composed of at least two mesenchymal components in varying proportions, accompanied by entrapped respiratory epithelium. They represent the most common benign pulmonary neoplasm and account for approximately 8% of radiologically detected pulmonary “coin lesions.” Hamartomas show a male predominance and most frequently occur in the sixth decade of life. They are usually peripherally located but can be found in any pulmonary lobe. Although the presence of “popcorn” calcification on imaging can be a helpful diagnostic clue, it is observed in only a minority of cases. Detection of fat density on CT is a more specific radiological feature. Pulmonary hamartomas frequently harbor the translocation $t(3;12)(q27-q28; q14-q15)$.

Macroscopically, hamartomas appear as firm, round, well-circumscribed nodules, most commonly measuring less than 4 cm in diameter.

Microscopically, they are predominantly composed of hyaline cartilage admixed with varying amounts of other mesenchymal elements such as adipose tissue, smooth muscle, fibrous tissue,

bone, and benign myxoid cells. Entrapped respiratory epithelium is typically observed between lobules of cartilage and connective tissue, often in a cleft-like pattern (Fig. 10.12). Immunohistochemical staining is generally not required for diagnosis.

The differential diagnosis includes other soft tissue tumors. While hamartomas are typically distinguishable from monomorphic soft tissue tumors by the presence of multiple mesenchymal components, they may pose diagnostic challenges in small biopsy specimens. In particular, when only the myxoid component is sampled, differentiation from myxoid sarcomas may be difficult. Compared to sarcomas, hamartomas exhibit much lower cellularity and lack cytologic atypia [2, 18].

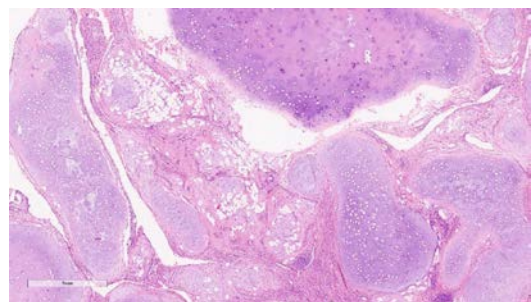


Fig. 10.12 Pulmonary hamartoma composed of a disorganized mixture of mature cartilage, fibrous tissue, and adipose tissue with entrapped respiratory epithelium

10.1.15.2 Pulmonary Chondroma

Pulmonary chondroma is a benign neoplasm of hyaline cartilage origin. Most patients with pulmonary chondroma are young females and often have Carney's triad—a nonhereditary tumor syndrome characterized by the presence of gastrointestinal stromal tumors (GISTs), paragangliomas, and pulmonary chondromas.

These tumors are well-circumscribed nodules composed of pure hyaline cartilage, often exhibiting myxoid changes. Calcification and ossification are common histological features. Unlike pulmonary hamartomas, invagination of respiratory epithelium into the tumor is not observed.

10.1.15.3 Diffuse Pulmonary Lymphangiomatosis

Diffuse pulmonary lymphangiomatosis is characterized by diffuse proliferation of lymphatic vessels and smooth muscle along the lymphatic channels of the lungs, pleura, and mediastinum. It most commonly affects children.

Histologically, it is defined by endothelium-lined, anastomosing lymphatic channels of variable caliber that follow lymphatic pathways. These dilated lymphatics frequently contain acellular eosinophilic material. Between the lymphatic channels, collagenous stroma or spindle-shaped cells resembling smooth muscle are present. The disease leads to progressive respiratory failure and currently lacks a curative treatment.

10.1.15.4 Pleuropulmonary Blastoma

Pleuropulmonary blastoma is an embryonal tumor arising from immature pulmonary mesenchyme, presenting as cystic and/or solid masses during infancy and early childhood. It is the most common primary lung neoplasm in children. Various mutations resulting in loss of function of the *DICER1* gene play a central role in its pathogenesis.

Macroscopically, it is classified into three types:

Type I: Purely cystic, with approximately 40% of cases being multifocal.

Type II: Exhibits both cystic and solid components.

Type III: Entirely solid in nature.

Microscopically:

Type I is characterized by cystic air spaces lined by alveolar or bronchiolar epithelium, with thickened alveolar septa. Classic cases show nodular aggregates of primitive mesenchymal cells beneath the epithelial lining of the cyst wall. Nodules composed of immature cartilage or mature spindle cells may be found within the septa, not always accompanied by primitive cells. Since primitive mesenchymal foci may be focal, thorough sampling of the entire cystic lesion is essential.

Type II contains solid nodules of primitive mesenchymal cells alongside cystic spaces.

Type III tumors are completely solid and can display various microscopic patterns. These include:

1. *Blastemal pattern:* solid nests of undifferentiated, hyperchromatic cells with high nuclear-to-cytoplasmic ratios.
2. *Embryonal rhabdomyosarcomatous pattern:* stellate to ovoid cells embedded in myxoid stroma with variable eosinophilic cytoplasm.
3. *Fibrosarcomatous pattern:* fascicular or herringbone arrangements.
4. *Chondrosarcomatous pattern.*

One or more of these components may predominate in any given case. Prognosis is primarily determined by histologic type, with survival decreasing as the tumor progresses from type I to type III. Reported survival rates are approximately 91% for type I, 74% for type II, and 53% for type III.

10.1.15.5 Pulmonary Artery Intimal Sarcoma

Pulmonary artery sarcoma is a malignant mesenchymal tumor arising in the major vessels of the pulmonary circulation. Due to its intraluminal growth, it leads to obstruction of the vascular lumen. The tumor shows a slight female predominance, with a median age at diagnosis of 48 years. Histologically, it is composed of spindle cells with varying degrees of atypia and cellularity. The prognosis is poor.

10.1.15.6 Pulmonary Lymphangioliomyomatosis (LAM)

Pulmonary lymphangioliomyomatosis (LAM) is a rare, locally destructive, slow-growing mesenchymal neoplasm characterized by bilateral interstitial infiltration and cystic changes in the airspaces due to abnormal smooth muscle proliferation along lymphatic pathways. It occurs almost exclusively in women and may be sporadic or associated with tuberous sclerosis. Sporadic cases characteristically exhibit biallelic inactivating mutations in the *TSC2* gene.

Macroscopically, the lungs exhibit numerous thin-walled cysts distributed throughout the parenchyma.

Microscopically, spindle cells are present within the walls of the cysts, either in nodular aggregates or interstitially distributed. These spindle cells have finely dispersed chromatin, small nucleoli, and granular eosinophilic cytoplasm. They may infiltrate venous walls.

Immunohistochemically, the spindle cells are positive for SMA and HMB45. ER, PR, and Melan-A are also frequently positive, while S100 is negative.

10.1.16 Primary Hematolymphoid Neoplasms of the Lung

Primary hematolymphoid neoplasms of the lung are rare, with extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) lymphoma being the most common type. Secondary involvement due to systemic disease is more frequently encountered, often affecting the hilar lymph nodes. Hematolymphoid neoplasms that may present as primary lung tumors include MALT lymphoma, diffuse large B-cell lymphoma (DLBCL), lymphomatoid granulomatosis, intravascular large B-cell lymphoma, Langerhans cell histiocytosis, and Erdheim-Chester disease.

In addition to hematolymphoid neoplasms, benign lymphoproliferative conditions such as reactive lymphoid hyperplasia, Castleman disease, and IgG4-related disease are also frequently

observed in the lung. Due to the broad spectrum of lymphoid proliferations, definitive diagnosis often requires collaborative evaluation by both pulmonary and hematopathologists.

10.2 Tumors of the Pleura

10.2.1 Mesothelial Tumors

10.2.1.1 Adenomatoid Tumor

This is a benign tumor of mesothelial origin that arises from the visceral or parietal pleura. It is exceedingly rare, with fewer than 20 cases reported in the literature. These tumors typically present as well-circumscribed masses on the pleural surface. Although generally localized, the tumor may show focal infiltration into adjacent soft tissue.

Microscopically, the tumor exhibits a combination of pseudoglandular structures, pseudovascular spaces, tubules, and papillary formations. Lymphoid aggregates are commonly observed in association. Immunohistochemically, the tumor expresses mesothelial markers and retains nuclear expression of BAP1, which helps to distinguish it from malignant mesothelioma [2, 19].

10.2.1.2 Well-Differentiated Papillary Mesothelial Tumor

This is a noninvasive pleural mesothelial neoplasm characterized by papillary stromal formations lined by mesothelial cells without cytologic atypia. It is exceedingly rare.

Microscopically, the lesion arises from the pleural surface and demonstrates papillary proliferation without evidence of stromal invasion. The papillae are lined by a single layer of flat to cuboidal mesothelial cells with inconspicuous nucleoli, lacking atypia, and with absent or rare mitoses. Occasionally, the papillae may exhibit back-to-back complex architecture that can mimic invasion. Therefore, thorough sampling of the entire tumor is required to confidently exclude stromal invasion.

10.2.1.3 Mesothelioma In Situ

This entity represents a preinvasive, single-layered proliferation of neoplastic mesothelial cells. Only a limited number of cases have been reported, and there is a male predominance. In its pathogenesis, early molecular alterations implicated in mesothelioma development—such as *BAP1* inactivation and homozygous deletion of *CDKN2A*—have been described. Diagnosis requires immunohistochemical and/or molecular support. It has the potential to progress to invasive epithelioid mesothelioma.

10.2.1.4 Localized Mesothelioma

A rare malignant neoplasm of mesothelial origin that arises as a circumscribed mass without diffuse serosal spread. Mutations in *BAP1* and *TRAF7* have been implicated in its pathogenesis.

Histopathological, ultrastructural, and immunophenotypic features are identical to those of diffuse malignant mesothelioma.

10.2.1.5 Malignant Mesothelioma (Pleural)

Malignant mesothelioma is a neoplasm of mesothelial cell origin characterized by diffuse involvement of the pleura. It accounts for less than 2% of all malignancies. The most significant etiologic factor is asbestos exposure, with the carcinogenic potential varying according to fiber type. Amphibole asbestos fibers are more carcinogenic than serpentine types. Other mineral fibers (such as erionite) and therapeutic or occupational radiation exposure are also considered etiologic factors.

The pathogenesis of malignant mesothelioma is complex. Frequently mutated genes include *BAP1*, *NF2*, *TP53*, *SETD2*, *DDX3X*, *ULK2*, *RYR2*, *CFAP45*, *SETDB1*, and *DDX51*. Homozygous deletion of *CDKN2A* is observed in 67–83% of epithelioid and biphasic mesotheliomas, and this rate approaches 100% in sarcomatoid subtypes. *CDKN2A* is often co-deleted with the adjacent *MTAP* gene located at 9p21.

Macroscopically, the tumor presents as multiple nodules in the parietal or visceral pleura in the early stages. As the disease progresses, these nodules coalesce to form a rind encasing the lung

and infiltrating the lung parenchyma or thoracic wall.

Microscopically, malignant mesothelioma is classified into three subtypes: epithelioid, sarcomatoid, and biphasic.

Epithelioid mesothelioma is composed of cells with vesicular chromatin, small nucleoli, and eosinophilic cytoplasm (Fig. 10.13a). It may exhibit various architectural patterns including tubulopapillary, trabecular, micropapillary, solid, and adenomatoid. Cytological variants such as rhabdoid, deciduoid, pleomorphic, signet ring-like, small cell, and clear cell features can also be observed. Additionally, a lymphohistiocytoid morphology characterized by malignant mesothelial cells obscured by CD8-positive T lymphocytes may be present. The presence of pleomorphic features in epithelioid mesothelioma is associated with a prognosis similar to sarcomatoid subtypes and thus should be reported.

Sarcomatoid mesothelioma is characterized by irregular or fascicular spindle cell proliferation infiltrating the adipose tissue and/or lung parenchyma (Fig. 10.13b). It may contain heterologous elements such as rhabdomyosarcoma, osteosarcoma, or chondrosarcoma. The desmoplastic variant consists of spindle cells with minimal atypia within dense hyalinized stroma and is diagnosed when more than 50% of the tumor displays desmoplastic features.

Biphasic mesothelioma contains both epithelioid and sarcomatoid components, each constituting at least 10% of the tumor.

Immunohistochemically, to distinguish epithelioid mesothelioma from metastatic carcinomas, at least two mesothelial and two carcinoma markers should be employed. Recommended mesothelial markers include calretinin, WT1, D2–40, and CK5/6, while carcinoma markers frequently used are claudin-4, BerEP4, MOC31, B72.3, CEA, CD15, and BG8. Claudin-4 has superior specificity and sensitivity among carcinoma markers. Sarcomatoid and desmoplastic mesotheliomas show at least focal positivity for cytokeratins; however, sarcomatoid subtypes may be cytokeratin negative. Calretinin is positive in approximately 30% of cases, while D2–40 positivity is more frequent. Expression of actin,

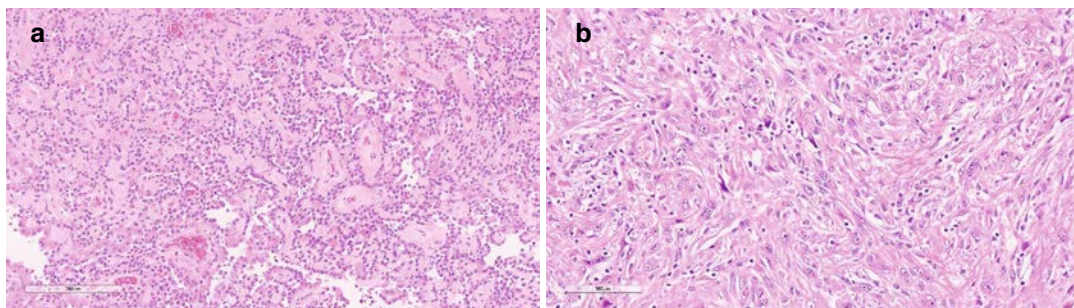


Fig. 10.13 (a) Epithelioid mesothelioma is composed of uniform polygonal to cuboidal tumor cells with eosinophilic cytoplasm and round nuclei, arranged in papillary structures. (b) Sarcomatoid mesothelioma is

composed of spindle-shaped malignant cells arranged in fascicles, with elongated nuclei, prominent nucleoli, and cytologic atypia, associated with collagen deposition

desmin, and S100 may occasionally be seen. CK5/6 and WT1 have lower sensitivity. Vimentin is typically positive in sarcomatoid mesotheliomas but generally negative in the epithelioid subtype. Loss of nuclear BAP1 expression and cytoplasmic MTAP expression may help differentiate mesothelioma from reactive mesothelial proliferations and reactive fibrous pleuritis. Nonetheless, molecular testing may be required for confirmation in some cases.

The primary differential diagnosis for epithelioid mesothelioma includes pleural carcinoma. Clinical history, mesothelial markers, carcinoma markers, and organ-specific markers aid in differentiation. Other differential considerations include tumors with pseudomesotheliomatous morphology such as epithelioid hemangioendothelioma, angiosarcoma, intrapleural thymoma, melanoma, lymphoma, and monophasic synovial sarcoma. Severe atypical reactive mesothelial hyperplasias may mimic epithelioid mesothelioma in the context of infections, collagen vascular diseases, or pulmonary embolism. In such cases, evidence of invasion into the chest wall, soft tissue, or lung parenchyma supports a diagnosis of mesothelioma, and markers such as BAP1 and MTAP can be helpful. Differential diagnoses for sarcomatoid mesothelioma include sarcomatoid carcinomas of the lung and other organs, primary thoracic or metastatic sarcomas, and organizing pleuritis. In challenging cases, morphology and

immunohistochemistry should be supplemented by clinical history, radiologic findings, and molecular tests.

Prognosis varies by subtype. Long-term survival is generally poor. However, younger age, epithelioid subtype, and early-stage disease are associated with longer survival. Micropapillary pattern, pleomorphic morphology, epithelioid-sarcomatoid transition areas, and solid growth patterns are associated with poorer outcomes [2, 20, 21].

10.2.2 Hematolymphoid Tumors

Pleural involvement is not uncommon in disseminated or pulmonary lymphomas. However, primary pleural lymphoma is rare. Primary effusion lymphoma and DLBCL associated with chronic inflammation are the main lymphoid malignancies primarily involving the pleura or pericardium. Rarely, follicular lymphoma, extranodal marginal zone lymphoma, and anaplastic large cell lymphoma may present with primary pleural involvement.

10.2.2.1 Primary Effusion Lymphoma

These are HHV8-associated large B-cell lymphomas that frequently coinfect with EBV, presenting as serous effusions without lymph node involvement or solid mass formation, and can develop in all serous cavities. Extracavitary pri-

mary effusion lymphoma, on the other hand, appears as solid masses in regions such as the lungs or gastrointestinal tract. It occurs in immunosuppressed individuals, including HIV-positive patients or those who have undergone organ transplantation. The most commonly affected group comprises HIV-positive males in their fifth decade with low CD4 cell counts.

Diagnosis is typically made from cytologic specimens. The cells display a range of morphologies, from immunoblastic or plasmablastic features to pleomorphic or anaplastic nuclei. Nucleoli are prominent; cytoplasm is abundant and may contain a perinuclear hof.

Immunohistochemically, B-cell markers are negative, while markers such as CD38, CD138, EMA, and CD30 are expressed [2, 22].

10.2.2.2 Diffuse Large B-Cell Lymphoma (DLBCL)

This is an EBV-associated mature B-cell neoplasm that develops secondary to long-standing chronic inflammation confined to a specific anatomical site. The most commonly affected site is the pleura, and it is referred to as pyothorax-associated lymphoma. At the time of diagnosis, the disease is usually confined to the thoracic cavity. Histopathologically and immunophenotypically, it resembles DLBCL, not otherwise specified (DLBCL-NOS).

References

1. Robbins & Kumar Basic Pathology, 11th ed; 2023.
2. WHO Classification of Tumours: Thoracic Tumours, 5th ed. Edited by the WHO Classification of Tumours Editorial Board; 2021.
3. Tryfon S, Dramba V, Zoglopitis F, et al. Solitary papillomas of the lower airways: epidemiological, clinical, and therapeutic data during a 22-year period and review of the literature. *J Thorac Oncol*. 2012;7(4):643–8.
4. Lovrenski A, Vasilijevic M, Panjkovic M, et al. Sclerosing pneumocytoma: a ten-year experience at a western Balkan university hospital. *Medicina (Kaunas)*. 2019;55(2):E27.
5. Hu X, Fujimoto J, Ying L, et al. Multi-region exome sequencing reveals genomic evolution from pre-neoplasia to lung adenocarcinoma. *Nat Commun*. 2019;10(1):2978.
6. Gupta A, Harris K, Dhillon SS. Role of bronchoscopy in management of central squamous cell lung carcinoma in situ. *Ann Transl Med*. 2019;7:354.
7. Kadota K, Villena-Vargas J, Yoshizawa A, et al. Prognostic significance of adenocarcinoma in situ, minimally invasive adenocarcinoma, and nonmucinous lepidic predominant invasive adenocarcinoma of the lung in patients with stage I disease. *Am J Surg Pathol*. 2014;38:448.
8. Travis WD, Brambilla E, Burke AP, et al., editors. WHO classification of tumours of the lung, pleura, thymus and heart. Lyon (France): International Agency for Research on Cancer; 2015. (WHO classification of tumours series, 4th ed.)
9. Yeh YC, Kao HL, Lee KL, et al. Epstein-Barr virus-associated pulmonary carcinoma: proposing an alternative term and expanding the histologic spectrum of lymphoepithelioma-like carcinoma of the lung. *Am J Surg Pathol*. 2019;43(2):211.
10. Travis WD. Lung cancer pathology: current concepts. *Clin Chest Med*. 2020;41(1):67–85.
11. Mordant P, Grand B, Cazes A, et al. Adenosquamous carcinoma of the lung: surgical management, pathologic characteristics, and prognostic implications. *Ann Thorac Surg*. 2013;95(4):1189–95.
12. Pelosi G, Sonzogni A, De Pas T, et al. Review article: pulmonary sarcomatoid carcinomas: a practical overview. *Int J Surg Pathol*. 2010;18(2):103–20.
13. Terra SB, Jang JS, Bi L, et al. Molecular characterization of pulmonary sarcomatoid carcinoma: analysis of 33 cases. *Mod Pathol*. 2016;29(8):824–31.
14. Chau NG, Ma C, Danga K, et al. An anatomical site and genetic-based prognostic model for patients with nuclear protein in testis (NUT) midline carcinoma: analysis of 124 patients. *JNCI Cancer Spectr*. 2019;4(2)
15. Nambirajan A, Singh V, Bhardwaj N, et al. SMARCA4/BRG1-deficient non-small cell lung carcinomas: a case series and review of the literature. *Arch Pathol Lab Med*. 2020;145:90.
16. Travis WD. Pathology and diagnosis of neuroendocrine tumors: lung neuroendocrine. *Thorac Surg Clin*. 2014;24(3):257–66.
17. Wang J, Ye L, Cai H, et al. Comparative study of large cell neuroendocrine carcinoma and small cell lung carcinoma in high-grade neuroendocrine tumors of the lung: a large population-based study. *J Cancer*. 2019;10(18):4226–36.
18. Von Ahsen I, Rogalla P, Bullerdiek J. Expression patterns of the LPP-HMGA2 fusion transcript in pulmonary chondroid hamartomas with t(3;12)(q27 approximately 28;q14 approximately 15). *Cancer Genet Cytogenet*. 2005;163:68.
19. Minato H, Nojima T, Kurose N, et al. Adenomatoid tumor of the pleura. *Pathol Int*. 2009;59(8):567–71.

20. Minami K, Jimbo N, Tanaka Y, et al. Malignant mesothelioma in situ diagnosed by methylthioadenosine phosphorylase loss and homozygous deletion of CDKN2A: a case report. *Virchows Arch.* 2020;476:469.
21. Ohar JA, Cheung M, Talarchek J, et al. Germline BAP1 mutational landscape of asbestos- exposed malignant mesothelioma patients with family history of cancer. *Cancer Res.* 2016;76(2):206–15.
22. Lurain K, Polizzotto MN, Aleman K, et al. Viral, immunologic, and clinical features of primary effusion lymphoma. *Blood.* 2019;133:1753.

Pathology of the Prostate and Bladder

11

Ender Düzcan

11.1 Prostate

11.1.1 Anatomy and Histology

The prostate gland is situated between the bladder neck and the urogenital diaphragm, anterior to the rectum. It assumes an inverted conical shape, with its base positioned at the bladder neck and at the entry points of the seminal vesicles, and its apex directed distally toward the urogenital diaphragm. As the urethra traverses the prostate, it exhibits an anterior angulation of approximately 35 degrees at the level of the verumontanum. A thin connective tissue structure known as Denonvilliers' fascia separates the prostate from the rectum.

Although the prostate is often clinically referred to in terms of right and left lobes, McNeal's zonal anatomy, which is based on the glandular components of the prostate, is the most widely accepted model for morphological evaluation [1]. According to this model, the prostate consists of three primary zones: central, peripheral, and transitional. The central zone, comprising approximately 25% of the prostate volume, forms an inverted cone with its base at the bladder neck and its apex at the verumontanum, encasing the ejaculatory ducts. Tumors originating from the central zone constitute about 10% of all prostate carcinomas, although it is not uncommon

for peripheral zone tumors to invade this region. The peripheral zone accounts for roughly 70% of the prostate and surrounds the central and transitional zones basally, extending posteriorly and laterally to encircle the distal prostatic urethra. The acini in this zone are small and round, with stroma composed of loosely arranged smooth muscle fibers. The majority of prostate carcinomas and PIN lesions arise in this zone. Inflammatory and atrophic changes are also more frequently observed here, whereas hyperplastic changes are rare. The transitional zone, which surrounds the proximal prostatic urethra, consists of two small lobes. Its glands are small, simple, and round, and their ducts open just proximal to the urethral angulation. This zone is the primary site of benign prostatic hyperplasia (BPH) and is the origin of approximately 15–20% of prostate carcinomas. Due to the difficulty in distinguishing between the central and peripheral zones, some classification systems consider the prostate in terms of transitional and non-transitional zones. The anterior fibromuscular stroma, accounting for approximately one-third of the prostate, contains minimal glandular elements, and its muscle fibers are continuous with those of the bladder neck proximally and the external sphincter distally (Fig. 11.1).

The epithelial component of the prostate comprises large ducts that open into the urethra and their branching terminal acini. These glandular structures are lined by a combination of urothelial, secretory, basal, and neuroendocrine cells.

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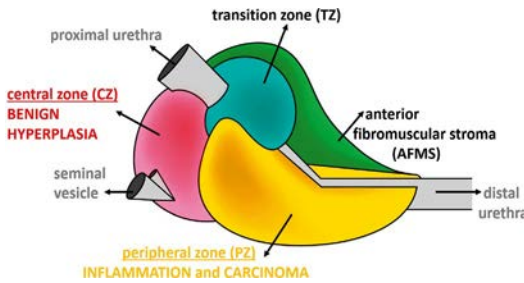


Fig. 11.1 McNeal's zonal anatomy of prostate and the zones where the primary lesions of the prostate originate

The proximal portions of the ducts are lined by urothelial epithelium. However, instead of umbrella cells, a columnar cell arrangement showing PSA and PSAP reactivity is observed. The distal ducts and acini display a bilayered architecture consisting of secretory and basal cells. Secretory cells stain positively with PSA and PSAP immunohistochemically but are negative for high molecular weight cytokeratins. Basal cells, situated directly beneath secretory cells, possess round to oval nuclei and are arranged parallel to the basement membrane. The absence of basal cells supports the diagnosis of carcinoma and is a critical criterion in differentiating benign mimics of malignancy. When conventional histopathological methods are insufficient, immunohistochemical markers such as p63 or high molecular weight cytokeratins are employed for accurate identification.

11.1.2 Prostatitis

Prostatitis encompasses a spectrum of acute and chronic inflammatory conditions of the prostate, which may arise due to various etiological factors. In acute and chronic bacterial prostatitis, the most frequently encountered pathogens are Gram-negative bacteria, primarily *Escherichia coli*. *Neisseria gonorrhoeae* and *Chlamydia trachomatis* may also be responsible for acute infections. Nonspecific granulomatous prostatitis is considered a reaction to material released from obstructed ducts, bacterial products, or urinary reflux. Postprocedural prostatitis arises as a consequence of traumatic injury.

According to the 1999 NIH classification, the definitive diagnosis of prostatitis necessitates an integrated assessment of clinical symptoms, microbiological analysis, and other laboratory data [2]. Consequently, incidental histological findings of acute or chronic prostatitis in prostate biopsies should not be generically labeled as “prostatitis” in pathology reports; instead, they should be described in a more descriptive, detailed manner. However, granulomatous prostatitis—although not explicitly included in the NIH classification—may be reported as a distinct histopathological diagnosis.

Granulomatous prostatitis presents clinically with symptoms such as dysuria, urinary urgency, and fever. The detection of firm and fixed nodules on digital rectal examination frequently leads to suspicion of prostate carcinoma, prompting biopsy. Indeed, coexistent carcinoma is identified in approximately 10–15% of these patients. Microscopically, nonspecific granulomatous prostatitis demonstrates epithelioid histiocytes with granular cytoplasm concentrated around prostatic ducts. The presence of other inflammatory cells within these histiocytes is a critical feature for differential diagnosis. Cribriform-patterned nonneoplastic glands are often seen in the background. Importantly, microorganisms and caseous necrosis are absent [3].

Postprocedural granulomatous prostatitis microscopically resembles a rheumatoid nodule. Noncaseating granulomas composed of histiocytes and giant cells surrounding degenerated, necrobiotic collagen are observed.

The prostate is the most commonly affected organ in male genital tuberculosis. The infection may spread hematogenously from the lungs or bones or extend locally from the urethra. In early stages, multiple cavitory lesions with caseous necrosis are noted, whereas late stages show fibrosis and calcification.

Eosinophilic prostatitis occurs in individuals with peripheral eosinophilia and a history of asthma or allergic conditions. Xanthogranulomatous prostatitis is characterized by the dominance of lipid-laden histiocytes. Malakoplakia, frequently associated with bladder involvement, may also extend to the prostate.

11.1.3 Hyperplastic and Nonneoplastic Lesions

Benign prostatic hyperplasia (BPH) is a nonneoplastic nodular enlargement of the prostate resulting from hyperplasia of both glandular and stromal components, typically associated with lower urinary tract symptoms. The correlation between the degree of hyperplasia and the severity of clinical symptoms is generally weak. The pathological diagnosis of BPH is established using specimens obtained from procedures that sample a substantial amount of prostatic tissue, such as transurethral resection (TUR) or open prostatectomy. Since transrectal needle biopsies do not sample the transitional zone, a diagnosis of BPH should be avoided in such specimens. Most importantly, because a definitive diagnosis of BPH relies on both pathological findings and clinical parameters, the presence of stromal or glandular nodules in transrectal biopsy specimens, in isolation, is of limited diagnostic significance. The macroscopic appearance of benign prostatic hyperplasia (BPH) is characterized by the formation of nodules. Initially, BPH nodules are stromal in nature, composed predominantly of fibrous connective tissue and smooth muscle. These nodules are typically located submucosally in the periurethral region and do not usually reach large sizes. These nodules, which exhibit a predominantly glandular composition, exert pressure on the prostatic urethra. On cut surface, stromal nodules resemble leiomyomas, whereas those with a predominant epithelial component display a spongy appearance. Benign prostatic hyperplasia (BPH) nodules are microscopically characterized either as purely stromal nodules or as lesions exhibiting a combined proliferation of glandular and stromal elements. Stromal nodules consist of spindle cells arranged in short fascicles and whorled patterns within a myxoid or hyalinized matrix. No cytologic atypia or mitotic activity is observed. Nodules with a predominant epithelial component are composed of glands of varying shapes and sizes, lined by secretory and basal cells. Certain nodules may show additional changes such as squamous metaplasia or infarction. In the acute phase, infarcted areas manifest

as coagulative necrosis, which is gradually replaced by fibrous scar tissue over time. In regions adjacent to the infarct, cell clusters may mimic squamous cell carcinoma or urothelial carcinoma. These foci can exhibit marked cytologic atypia, which may resemble malignancy. However, the most critical distinguishing feature in the differential diagnosis is that such atypical changes are confined to the periphery of the infarcted area.

In addition to benign prostatic hyperplasia (BPH), the prostate can present with other hyperplastic lesions. These lesions may display microscopic features that closely resemble those of premalignant and malignant conditions. Therefore, recognizing their histopathological characteristics is crucial in minimizing the risk of overdiagnosis.

Adenosis (atypical adenomatous hyperplasia) is a hyperplastic lesion arising from the transitional zone. Consequently, it is rarely encountered in needle biopsy specimens and is usually detected incidentally. The proliferative glands forming the lesion are of small caliber, which distinguishes them from BPH nodules; however, differential diagnosis from low-grade adenocarcinomas is crucial. Histopathologically, these lesions display a lobular architecture, and minimal stromal infiltration may be observed in approximately 20% of cases. Within the lobular structure, benign glands with intraluminal papillary infoldings are commonly seen, surrounded by small-caliber proliferative glands. Although not present in all glands, the identification of flattened basal cells in some is a helpful feature for differential diagnosis [4].

Clear cell cribriform hyperplasia is a rare lesion that typically occurs in association with BPH nodules. It is composed of cells with clear cytoplasm, well-defined cytoplasmic membranes, and small nuclei. The lesion is characterized by exaggerated papillary proliferation and a cribriform architecture with bridging patterns. Due to these features, it may be misinterpreted as high-grade adenocarcinoma if not carefully evaluated histologically.

Basal cell lesions of the prostate encompass a spectrum ranging from benign hyperplasia to

carcinoma. These lesions are most commonly located in the transitional zone and are frequently identified in transurethral resection (TUR) specimens. Focal or diffuse areas of basal cell hyperplasia may be seen within BPH nodules. In TUR specimens, the preserved lobular configuration often facilitates recognition of the lesion's benign nature. However, they may occasionally present diagnostic challenges in needle biopsy specimens. Microscopically, the most notable feature is a basaloid appearance created by the multilayered arrangement of basal cells with scant cytoplasm. Desmoplastic stromal reactions are absent around these glands. A distinguishing histological feature is the presence of intracytoplasmic eosinophilic globules. In some cases, when findings such as prominent nucleoli, nuclear enlargement, or single-cell necrosis are observed, the diagnosis of atypical basal cell hyperplasia may be considered.

Also, there are mesenchymal lesions that should be considered in the differential diagnosis of BPH nodules with purely stromal characteristics. These may include nonneoplastic reactive lesions as well as true neoplastic masses. A reactive lesion that may develop following a prior TUR procedure is the postoperative spindle cell nodule. In this lesion, the fibroblasts demonstrate an infiltrative growth pattern, with prominent nucleoli and increased mitotic activity; however, nuclear pleomorphism and atypical mitotic figures are absent. Another nonneoplastic lesion arising from the transitional zone is the inflammatory myofibroblastic tumor, in which both cellular and myxoid areas composed of spindle cells are observed concurrently.

In addition to hyperplastic lesions, age-related atrophic changes that develop in the peripheral zone are also of significance, particularly because they may pose diagnostic challenges in needle biopsies when evaluating for carcinoma. Among the various patterns of atrophy, partial atrophy may necessitate immunohistochemical analysis and expert consultation. These lesions are composed of small- to medium-sized acini lined by epithelial cells with pale or clear scant cytoplasm and prominent nucleoli, while basal cells may be observed in a discontinuous pattern [5].

11.1.4 Preneoplastic and Neoplastic Lesions

High-grade prostatic intraepithelial neoplasia (HGPIN) is defined as a proliferation of secretory epithelial cells lining the ducts and acini of the prostate, characterized by nuclear atypia. It is considered the earliest histologically recognizable precursor lesion of prostatic adenocarcinoma. In contrast, low-grade prostatic intraepithelial neoplasia is no longer regarded as a reportable or clinically relevant entity due to its poor reproducibility and its morphological overlap with benign hyperplastic glands. HGPIN predominantly arises in the peripheral zone of the prostate and is typically detected incidentally in needle biopsy specimens performed for prostate cancer evaluation. Its prevalence increases with advancing age and varies significantly by race and geographic region, highlighting the combined roles of genetic predisposition and environmental influences in its pathogenesis. Exposure to dietary carcinogens and chronic inflammatory processes promotes an oxidative stress-related microenvironment, which facilitates the accumulation of genetic and epigenetic alterations. Many of these molecular alterations are also observed in prostatic adenocarcinoma. Histologically, HGPIN is characterized by cytological atypia of the secretory epithelium, including cellular crowding, stratification, nuclear hyperchromasia, nuclear overlapping, amphophilic cytoplasm, and the presence of prominent nucleoli (Fig. 11.2). Although the basal cell layer remains present, it is often reduced in number and discontinuous. Crucially, HGPIN lacks features such as necrosis, marked nuclear pleomorphism, and increased mitotic activity, which are typical of intraductal carcinoma of the prostate (IDC-P). The most commonly observed histological patterns are tufting, micropapillary, and flat, though these patterns lack prognostic significance and are not required for routine diagnostic reporting. Immunohistochemical staining for basal cell markers, including high molecular weight cytokeratin (34 β E12) and p63, can assist in differentiating HGPIN from invasive adenocarcinoma, particularly in cases with pseudohyperplastic or

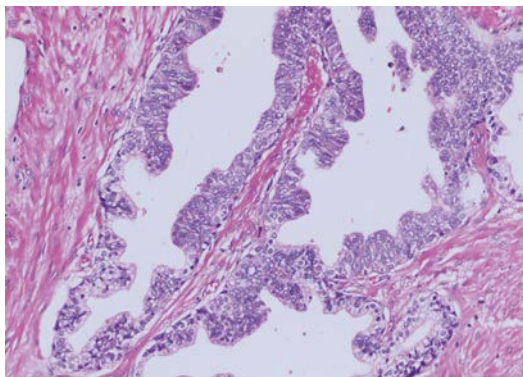


Fig. 11.2 High-grade prostatic intraepithelial neoplasia with tufted pattern. Stratified epithelium with prominent nucleoli creating small luminal protrusions. (HE×100)

foamy gland features. Importantly, the cribriform pattern previously attributed to HGPIN is now excluded from this category and is instead classified under atypical intraductal proliferation or IDC-P. From a clinical management perspective, the presence of a single focus of HGPIN on needle biopsy does not independently warrant repeat biopsy. However, when multifocal HGPIN is identified, the risk of an underlying or subsequent diagnosis of prostatic adenocarcinoma is significantly increased, and repeat biopsy within a year is generally recommended for appropriate patient surveillance [6, 7].

Intraductal carcinoma of the prostate (IDC-P) is a neoplastic epithelial proliferation characterized by the formation of solid or cribriform patterns of severely atypical epithelial cells within expanded prostatic ducts. These lesions retain at least a partial basal cell layer and are most commonly associated with high-grade and high-stage prostatic adenocarcinomas. Atypical intraductal proliferation (AIP) refers to intraductal lesions that demonstrate cytological atypia more severe than that seen in high-grade prostatic intraepithelial neoplasia (HGPIN), but that do not meet the full morphological criteria for IDC-P. Both IDC-P and AIP are genetically distinct from HGPIN and share molecular alterations that are commonly observed in high-grade invasive prostate carcinomas. IDC-P and high Gleason score adenocarcinomas are frequently characterized by substantial genomic instability, as well as recur-

rent molecular alterations including *ERG* gene fusions, *PTEN* loss, and mutations in *SPOP*, *TP53*, and *FOXA1*, whereas these alterations are less commonly observed in Gleason pattern 3 carcinomas and HGPIN [8]. For the microscopic diagnosis of IDC-P, the presence of solid or dense cribriform growth patterns is considered definitive. In cases exhibiting loose cribriform or micropapillary architecture, the presence of more pronounced cytological atypia is required for diagnosis. Comedonecrosis is an important ancillary feature that strongly supports the diagnosis of IDC-P. Given its strong correlation with adverse pathological features—including high Gleason score, large tumor volume, extraprostatic extension, seminal vesicle invasion, and pelvic lymph node metastasis—IDC-P should always be reported in both radical prostatectomy and needle biopsy specimens due to its significant prognostic implications.

Prostate cancer is the most common malignancy in men. Established risk factors include advancing age, family history, genetic predisposition, and race. Both incidence and cancer-specific mortality rates increase dramatically with age. A family history of prostate cancer increases the risk by approximately 1.5 to 2.5 times. If two or more first-degree relatives are affected, the risk increases by five- to tenfold. In these individuals, germline mutations in genes such as *HOXB13*, *BRCA2*, and *ATM* exhibit high penetrance, with variants involving *BRCA2* and *ATM* particularly associated with an increased risk of lethal disease.

Molecular alterations observed in the early stages of prostate carcinogenesis include *MYC* amplification, telomere shortening, CpG island hypermethylation affecting *GSTP1* and other genes, and gene fusions involving ETS transcription factors (e.g., *TMPS2::ERG*). As the disease progresses, additional alterations such as 8q24 gain (*MYC*), *PTEN* loss, *TP53* inactivation, and various other mutations become more prevalent. Metastatic prostate cancer is initially sensitive to androgen deprivation therapy (ADT) or androgen receptor (AR) blockade; however, the majority of cases eventually progress to castration-resistant prostate cancer (CRPC) due

to mechanisms including *AR* gene amplification, mutation, or structural rearrangement. Germline or somatic alterations in DNA repair genes are present in approximately 20% of aggressive primary and metastatic prostate cancers. Such tumors may exhibit therapeutic sensitivity to poly (ADP-ribose) polymerase (PARP) inhibitors or, in cases of mismatch repair deficiency, to immune checkpoint inhibitors [9].

Environmental and lifestyle factors also play a significant role in the development of prostate cancer. Diets high in saturated and animal fats are associated with accelerated disease progression, whereas the consumption of tomatoes and cooked vegetables rich in lycopene, along with low-carbohydrate diets, has been associated with a reduced risk of aggressive prostate cancer. Conversely, the intake of red meat and meats cooked at high temperatures is linked to an increased risk of prostate cancer.

Prostatic cancers are broadly classified into two major categories based on their site of origin and morphological characteristics: acinar adenocarcinomas, which arise from the peripheral zone, and ductal adenocarcinomas, which are predominantly located in the periurethral region. Acinar adenocarcinomas, derived from secretory epithelial cells, along with their subtypes, account for approximately 95% of all prostatic malignancies. Macroscopically, they generally do not form a well-defined mass lesion. However, in advanced-stage and extensive tumors, they may appear as solid, poorly circumscribed, firm, yellow-white areas that can be distinguished from the surrounding prostatic parenchyma.

Acinar adenocarcinomas are most commonly diagnosed on needle biopsies. Microscopically, they exhibit a broad histological spectrum, ranging from well-differentiated glandular structures that closely resemble normal prostatic glands to poorly differentiated carcinomas. Accurate diagnosis and grading rely on the combined assessment of both architectural and cytological features. A key diagnostic criterion is the presence of an infiltrative growth pattern, characterized by small acinar structures demonstrating cytological atypia, dispersed among benign glandular components. The loss of the natural undulations of the inner luminal

contours, which are typical in normal glands, serves as an important histological clue. Tumor acini tend to adopt a more regular, tubular configuration (Fig. 11.3). The most significant cytological indicators are nuclear enlargement and prominent nucleoli. The absence of a basal cell layer, as demonstrated by immunohistochemical staining, is a critical diagnostic marker. In limited tissue samples, such as needle biopsies, evaluating the infiltrative pattern can occasionally be challenging. Certain microscopic features are considered virtually pathognomonic, including perineural invasion, glomeruloid formations, and mucinous fibroplasia (Fig. 11.4) [10]. Additional supportive findings include amphophilic cytoplasm, intraluminal amorphous eosinophilic material, intraluminal crystalloids, blue-tinged mucinous secretions, and the presence of adjacent high-grade prostatic intraepithelial neoplasia (HGPIN).

Acinar adenocarcinomas may sometimes exhibit atypical morphological patterns that pose diagnostic challenges, including atrophic adenocarcinoma, pseudohyperplastic adenocarcinoma, microcystic adenocarcinoma, foamy gland adenocarcinoma, and mucinous adenocarcinoma.

Rare and morphologically distinct subtypes of acinar adenocarcinoma are clinically significant due to their association with poor prognosis. These include signet ring cell-like adenocarcinoma, sarcomatoid carcinoma, pleomorphic giant cell adenocarcinoma, and PIN-like adenocarcinoma, which was previously catego-

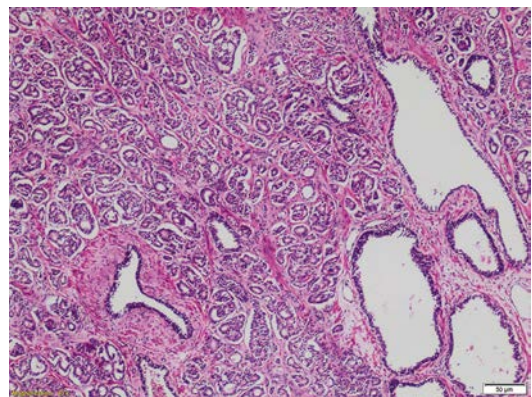


Fig. 11.3 Acinar adenocarcinoma with glandular crowding and infiltrative growth pattern. (HE×40)

rized as a subtype of ductal adenocarcinoma but has since been reclassified under the acinar adenocarcinoma group due to its distinct biological behavior and molecular features [9].

The Gleason grading system is the fundamental method used for grading prostate cancer. It has undergone multiple revisions, and subsequent validation studies have demonstrated that the

Gleason score is an independent predictor of recurrence, metastasis, and prostate cancer-specific mortality. The Gleason system evaluates the architectural growth pattern, while nuclear and cytoplasmic features are not incorporated into the score. Growth patterns are graded on a scale from 1 (well-differentiated) to 5 (poorly differentiated) (Fig. 11.5). The total Gleason

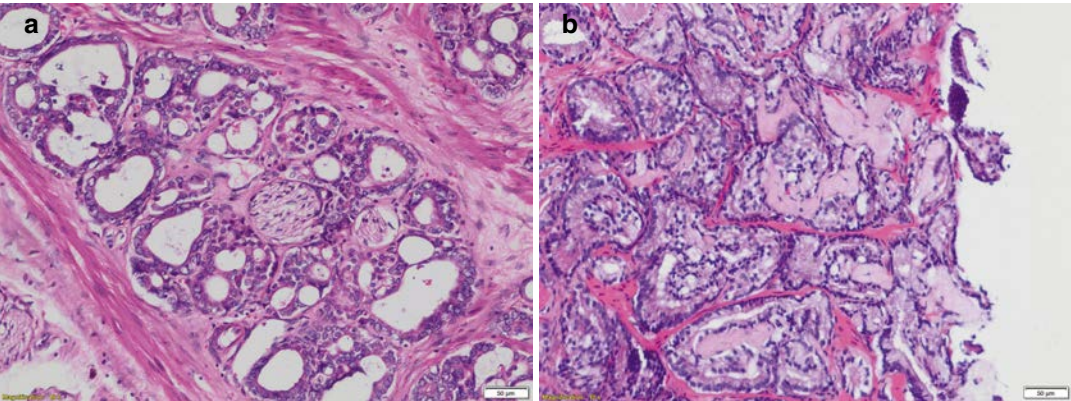


Fig. 11.4 (a) Perineural invasion characterized by malignant glands surrounding nerves. (HEX100). (b) Adenocarcinoma associated with collagenous micronodules (mucinous fibroplasia). (HEX100)

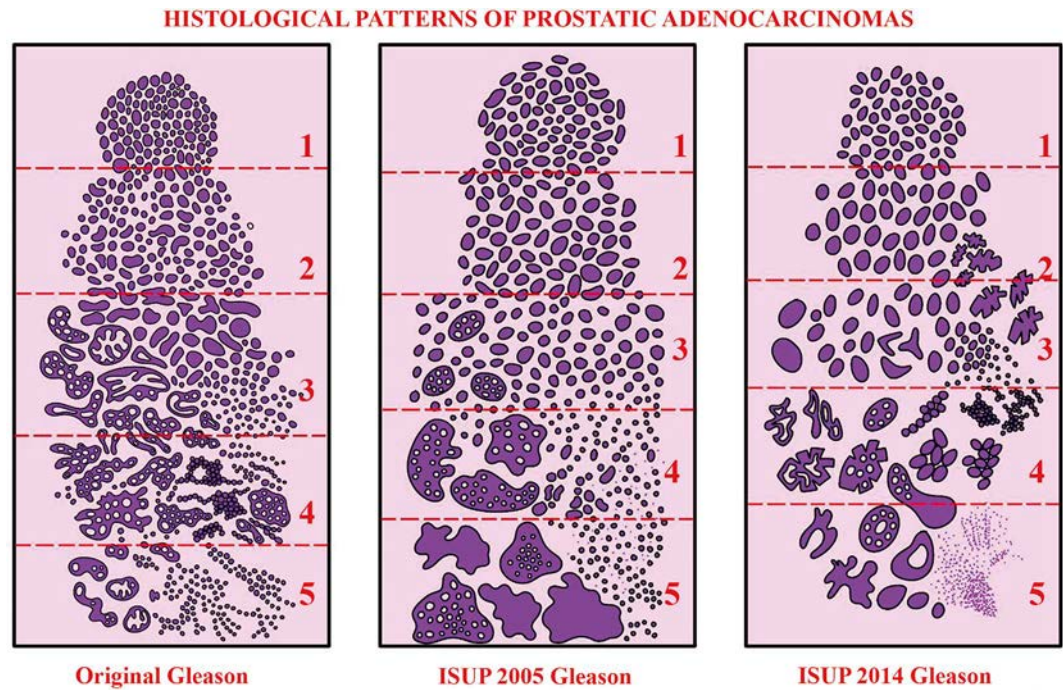


Fig. 11.5 Historical evolution of the Gleason scoring system

Table 11.1 Grade Group system (ISUP/WHO 2014)

Gleason score	Grade group	Outcome
3 + 3 = 6	GG1	Low risk, good prognosis
3 + 4 = 7	GG2	Intermediate risk
4 + 3 = 7	GG3	Intermediate risk
4 + 4 = 8	GG4	High risk
3 + 5 = 8		
5 + 3 = 8		
4 + 5 = 9	GG5	Very high risk
5 + 4 = 9		
5 + 5 = 10		

score is the sum of the most predominant (primary pattern) and the second most common (secondary pattern) growth patterns (e.g., 3 + 4 = 7). If only a single pattern is present, the score is calculated by multiplying that pattern by two. In the 2005 revision by the International Society of Urological Pathology (ISUP), it was recommended that patterns 1 and 2 should not be assigned in needle biopsies, resulting in the currently applicable Gleason score range of 6 to 10. The same revision also established that, for biopsies, the Gleason score should be composed of the primary pattern plus the highest-grade present, whereas for prostatectomy specimens, it should consist of the primary and secondary most prevalent patterns [11]. Given its strong correlation with prognosis, pattern 5 is reported as the secondary pattern if it comprises more than 5% of the tumor volume, even if it is not the second most common pattern. In the 2014 ISUP consensus, the more prognostically relevant Grade Group system was introduced and has since been widely adopted (Table 11.1).

Ductal adenocarcinomas, which rarely occur in pure form, most commonly arise in the peripheral zone, with a subset developing in the transitional zone surrounding the prostatic urethra. Given their immunohistochemical and molecular profiles, which closely resemble those of acinar adenocarcinomas, and their frequent coexistence, they are believed to originate from prostatic glandular epithelial cells. Microscopically, they are composed of papillary and cribriform structures lined by pseudostratified epithelial cells with amphophilic or pale cytoplasm and prominent

nucleoli. Foci of intraductal carcinoma and high-grade prostatic intraepithelial neoplasia are commonly associated. According to the 2005 ISUP consensus, all ductal adenocarcinomas are graded as pattern 4, except in the presence of comedonecrosis, which warrants assignment to pattern 5 [11].

Prostatic stromal sarcomas, which originate from specialized prostatic stroma, are extremely rare tumors that may arise in both the peripheral and transitional zones of the prostate. Microscopically, they are characterized by hypercellularity, cytological atypia, increased mitotic activity, and atypical mitoses. Necrosis may also be present. Accurate diagnosis requires identification of characteristic morphological and immunohistochemical features. Stromal sarcomas are positive for vimentin and CD34, while they are negative for SMA and desmin. Epithelial markers such as pancytokeratin are only rarely expressed [9].

11.2 Urinary Bladder

11.2.1 Anatomy, Histology and Morphological Variations

The urinary bladder is a part of the urinary system and is located in the pelvis, posterior to the pubic symphysis. It is situated above the prostate gland and anterior to the rectum in males. In females, it is anterior to the vagina and uterus. It has a posterior surface known as the bladder base (or fundus) and two inferolateral surfaces. Posterior anatomic relationships are important, because most bladder neoplasms arise in the posterior wall adjacent to ureteral orifices and may extend into those tissues and organs. Trigone is a triangular area at the base formed by two ureteric orifices and one internal urethral orifice. It continues with the bladder neck, funnel-like part that leads into the urethra. The anterior and lateral walls of the bladder are formed by the internal obturator and levator ani muscles as well as the pubic bones. Cloacal exstrophy is a congenital anomaly characterized by the absence of the

anterior bladder and lower abdominal wall, along with eversion of the posterior bladder wall. These defects can be partial or complete and are often accompanied by other urogenital anomalies. Apex (bladder dome) is connected to umbilicus via the median umbilical ligament, a fibrous cord occurring by the involution of urachus, which is a structure that connects bladder to umbilicus during fetal development. When the involution process is incomplete, its lumen may remain connected to the bladder wall and cavity, and various urachal anomalies can occur. The failure of its closure may lead to patent urachus (persistent connection between the bladder and umbilicus, causing urine leakage from the umbilicus), urachal cyst (a fluid-filled cyst in the midline between the umbilicus and bladder), urachal sinus (a blind-ending tract extending from the umbilicus) and urachal diverticulum (an out-pouching of the bladder due to partial closure of the urachus) as well as it may cause infections or be asymptomatic. Very rarely, adenocarcinoma can develop from these remnants localized in the bladder wall or abdominal wall beneath the peritoneum. The bladder wall consists of three layers: mucosa, muscularis propria, and adventitia. The bladder mucosa consists of urothelium, lamina propria, and, in some cases, muscularis mucosae, which is more frequently observed in females. Urothelium has ability to transform its morphology. This condition may develop as a result of a local stimulus or may occur without any signs of inflammation. Ultimately, a series of morphological changes emerge, which are benign in nature and can be considered histological variants of the urothelium. The most common proliferative change is called von Brunn nests, formed by the invagination of surface urothelium into the underlying lamina propria. Such proliferations may mimic nested variant of urothelial carcinoma, especially when they lie deep in lamina propria. Distinguishing features are the noninfiltrative lobular array of the nests and lack of cytologic atypia [12]. Von Brunn nests may become cystic, and if lined by urothelial-like cells, they are called cystitis cystica. It is referred to as cystitis glandularis, if the lining epithelium resem-

bles colonic epithelium. All of these proliferative changes may be seen in the same specimen, and the high incidence (85–90%) of these changes in normal bladder suggests that they are not premalignant [13].

Lamina propria is a heterogenous network of structural proteins and cells. Small fascicles of smooth muscle may be found within the superficial lamina propria forming a complete or incomplete muscularis mucosae. They are frequently seen in association with medium-sized vessels and must not be confused with muscle bundles of the muscularis propria, because this might result in errors of tumor staging. Similarly, we should keep in mind that there may be fat in the lamina propria. This is also important because the presence of invasive tumor at the level of fat in a transurethral resection specimen does not warrant a diagnosis of extravesical extension. Muscularis propria, also known as the detrusor muscle, consists of three sublayers: inner longitudinal, middle circular, and outer longitudinal. The bladder's body has a higher smooth muscle content than the trigone. Serosa is a thin connective tissue layer that covers the bladder dome and is continuous with the peritoneal layer of the abdominal wall. Benign metaplastic changes can be observed in the bladder. They frequently develop in the presence of irritations such as stones and long-term catheter use. The squamous metaplasia of the urothelium may be vaginal type or keratinized. Vaginal epithelium is seen exclusively in women and is quite common. The keratinized type, known as leukoplakia, is more frequent in men and is associated with chronic irritation [14].

Nephrogenic adenoma is considered a metaplastic change that can develop due to traumatic factors as well as following renal transplantation. It can arise in any part of the bladder and typically presents as fragile, papillary, or polypoid lesions smaller than 1 cm. Microscopically, tubular/glandular pattern lined by low columnar or cuboidal epithelium is common. Nuclear atypia and mitosis are not observed. The most important lesion to consider in the differential diagnosis is clear cell adenocarcinoma of the bladder [15].

11.2.2 Inflammatory Lesions

It is possible to classify inflammatory lesions of the urinary bladder according to their etiologies; however, in daily pathology practice, we often encounter nonspecific findings of acute and chronic inflammation in tissue samples. Although many bacterial, viral, and fungal microorganisms can cause cystitis, the most commonly observed pathogens are coliform bacteria, particularly *Escherichia coli*. Less frequently, urea-splitting bacteria, gas-forming bacteria, tuberculosis, schistosomiasis (which is more prevalent in the Middle Eastern region), and papillomavirus (which can also affect different parts of the urogenital system) may be identified as causative agents of cystitis. For many years, urine was believed to be sterile; however, we now know that it is not. The urinary microbiome, which has been found to include not only bacteria but also fungi, viruses, and even archaea, may be influenced by many variables, such as gender, infections, smoking status, diet, antibiotic therapy, and numerous other factors [16].

Encrusted cystitis, characterized by calcium deposition on the mucosal surface and within the lamina propria of the bladder, is a form of cystitis caused by urea-splitting bacteria. Emphysematous cystitis is a lesion caused by gas-forming bacteria such as *Clostridium perfringens*. In this condition, gas-filled vesicles form within the bladder wall, particularly in the lamina propria, which can be observed both cystoscopically and macroscopically. Diabetes, neurogenic bladder, malignant hematologic diseases, and chronic urinary infections predispose individuals to this condition. Among the granulomatous infections of the bladder, tuberculosis is the most common across a wide geographic range. Bladder infection, which usually develops secondary to renal tuberculosis, initially presents as superficial ulcerations around the ureteral orifices. Subsequently, caseating granulomas form, leading to fibrosis and ultimately resulting in ureteral strictures. However, in modern clinical practice, such granulomas are most frequently observed as a consequence of intravesical BCG immunotherapy or posttransurethral resection. Malakoplakia is a

lesion characterized by mucosal nodular thickening, most commonly observed in the bladder, although it can also affect other organs. Microscopically, clusters of histiocytes with granular, eosinophilic cytoplasm are found beneath the surface epithelium. Some of these cells contain intracellular, concentrically layered, targetoid Michaelis-Gutmann bodies or calcospherites. If Michaelis-Gutmann bodies are absent, the lesion is classified as xanthogranulomatous cystitis. Noninfectious causes of cystitis include traumatic factors such as bladder stones and catheterization, as well as the effects of chemotherapy and radiotherapy, nutritional deficiencies, and immune system alterations. Polypoid cystitis is a benign reactive lesion that macroscopically mimics a neoplasm. The most well-established cause of polypoid cystitis is catheterization. Eosinophilic cystitis can present in two clinical forms. The first form is observed in children and women, typically associated with allergic diseases and eosinophilia. The second form occurs in older men, often accompanying bladder injury related to bladder or prostate diseases. Microscopically, eosinophilic cystitis is defined by a dense inflammatory infiltration rich in eosinophils, frequently accompanied by fibrosis, muscle necrosis, and occasionally, the formation of giant cells. Radiation cystitis is a form of cystitis that typically develops around 4–6 weeks after treatment. Microscopically, the earliest findings include pronounced mucosal edema, leading to thickening of mucosal folds. This may be accompanied by atypical changes in the urothelial epithelium, which can sometimes be mistaken for carcinoma in situ [17].

Interstitial cystitis (Hunner's cystitis) is a condition that predominantly affects adult or elderly women. It is a form of cystitis that presents with urinary frequency, urgency, suprapubic pressure, and bladder pain. Clinical and pathological correlation is essential for a definitive diagnosis. The primary role of the pathologist is to contribute to the differential diagnosis of lesions that may be clinically and cystoscopically confused with interstitial cystitis, especially urothelial carcinoma in situ. There are no characteristic histologic features for interstitial cystitis. The term

Hunner's ulcer refers to ulcers covered with fibrin and necrotic material, which can appear in any part of the bladder. Mast cells are frequently observed, and mononuclear inflammatory cells with perineural localization may be present. Differentiating between ulcerative and non-ulcerative disease is important. Although the pathogenesis of them is similar, the disease severity and treatment strategy differ [18]. Other rare forms of cystitis include giant cell cystitis, follicular cystitis, and gangrenous cystitis.

11.2.3 Nonneoplastic Lesions

Diverticulosis is an acquired lesion that most often develops as a result of partial obstruction of the urethra or bladder neck, commonly due to benign prostatic hyperplasia (BPH). To overcome the obstruction and facilitate bladder emptying, prolonged detrusor contractions occur, leading to muscular hypertrophy and herniation of the mucosa through weakened areas. The remaining cases are congenital. Diverticula are most frequently located on the posterior wall of the bladder, above the trigone, in the region of the ureteral orifice, or at the dome near the obliterated urachus. The wall of the diverticulum consists of fibrous tissue with little or no muscular component. Complications include stone formation, perforation into the peritoneal cavity, and development of adenocarcinoma, usually of the intestinal type.

11.2.4 Neoplastic Lesions

Bladder cancer commonly occurs in individuals over the age of 60. It has been linked to various environmental factors. These include smoking, exposure to aniline dyes, aromatic amines, naphthylamine, consumption of drinking water containing arsenic, chronic inflammation caused by bladder stones, radiation exposure to the pelvic region, and long-term use of certain medications such as the anticancer drug cyclophosphamide and analgesics containing phenacetin. It has been shown that smokers have increased levels of tryptophan metabolites, naphthylamine, nitrosamines, and benzidine in their urine. The risk is directly related to the duration and intensity of smoking. Aromatic amines, which are widely used in the paint, tar, rubber, leather, petroleum, chemical, metal, and textile industries, enter the body through inhalation, ingestion, and skin absorption. The most classic example of chronic irritation and infection is schistosomiasis. *Schistosoma haematobium*, a trematode, causes squamous metaplasia, precancerous changes, and squamous cell carcinoma in the urothelium. The molecular mechanisms identified in the development of urothelial carcinomas are consistent with histopathological classifications. Low-grade papillary carcinomas, which exhibit high recurrence rates but low risk of progression, and high-grade papillary carcinomas with muscle-invasive potential, which carry a higher risk of progression, share overlapping mutational spectra yet differ in the prevalence of specific genetic alterations. Bladder carcinomas, which are etiologically associated with exposure to multiple carcinogenic agents, characteristically display a high burden of somatic mutations. These mutations predominantly affect genes involved in cell cycle regulation, chromatin modification, receptor tyrosine kinase/RAS signaling, and the PI3K/AKT pathway. Among these, mutations in the TERT promoter region are the most frequently observed alterations in urothelial carcinoma, present across all grades and stages of the disease, but absent in benign conditions. The detection of TERT promoter mutations even in early-stage and low-grade tumors suggests that this alteration represents an early genetic event in urothelial tumorigenesis. The clinical relevance of these genetic alterations lies in their potential as biomarkers for patient selection in chemotherapy, for mutation profiling of invasive tumor samples, and for evaluating bladder-sparing therapeutic strategies in tumors that exhibit favorable molecular features [19, 20].

Most bladder tumors originate from the urothelium. The classification of urothelial tumors is based on growth patterns and structural changes in the epithelium. These tumors can present in three different growth patterns: flat, papillary

(exophytic), and inverted (endophytic). Structural changes in the urothelium are graded using a similar approach across all growth patterns. Cytologic features encompassed in grading include nuclear shape and size, number and site of mitosis, prominence of nucleoli, and polarization of cells. The grading system that is widely accepted and commonly used today for urothelial tumors is the WHO/ISUP (International Society of Urological Pathology) system, proposed in 2004/2016. This two-tiered system classifies tumors as low grade and high grade, which provides high interobserver reproducibility and improves risk stratification.

Flat lesions can appear as dysplasia, reactive urothelial atypia, urothelial atypia of unknown significance, or carcinoma in situ. Reactive urothelial atypia is a benign regenerative epithelial change secondary to therapy or infection. Urothelial atypia of unknown significance and dysplasia are controversial categories with poor reproducibility in which the urothelium shows some loss of polarization and mild cytologic atypia. Dysplasia is defined as cytological atypia that is interpreted as neoplastic in nature but not definitive for the diagnosis of CIS. Urothelial carcinoma in situ, which is common in men, is often associated with high-grade papillary or invasive carcinomas. Primary cases (*de novo*) are rare, being less than 3%. Clinical behavior is variable; however, approximately half of the cases progress to invasion in 5 years. Multifocality is fre-

quently observed. Histopathological changes in the urothelial epithelium include disordered proliferation, loss of polarity, and marked cytological atypia. The epithelial thickness can vary from a single-layer arrangement to hyperplasia. Nucleomegaly, prominent nucleoli, condensed nuclear chromatin, dyscohesion, and mitoses with atypical forms are the main features of cytological atypia. Different morphological patterns such as pleomorphic, nonpleomorphic, small cell, Pagetoid, and clinging are described. In urothelial carcinoma in situ, full-thickness cytoplasmic staining is observed for CK20 and AMACR, whereas CD44 staining is absent or limited to basal cells (Fig. 11.6) [21, 22].

Urothelial papilloma is a group of tumors more commonly observed in young adults. These tumors appear as small exophytic papillary structures. They have low recurrence rate and the architecture of the urothelial epithelium remains intact. There is no increased cellularity or cytological atypia. Mitoses are absent [23, 24]. Papillary urothelial neoplasms of low malignant potential (PUNLMP) are typically observed as papillary exophytic masses measuring 1–2 cm in diameter. Recurrence is observed in approximately 20% of cases, while progression to a higher-grade lesion occurs in less than 5% of cases. Microscopically, they appear as papillary structures composed of hyperplastic urothelium with preserved polarization. Cytological atypia is absent or minimal. Umbrella cells are generally

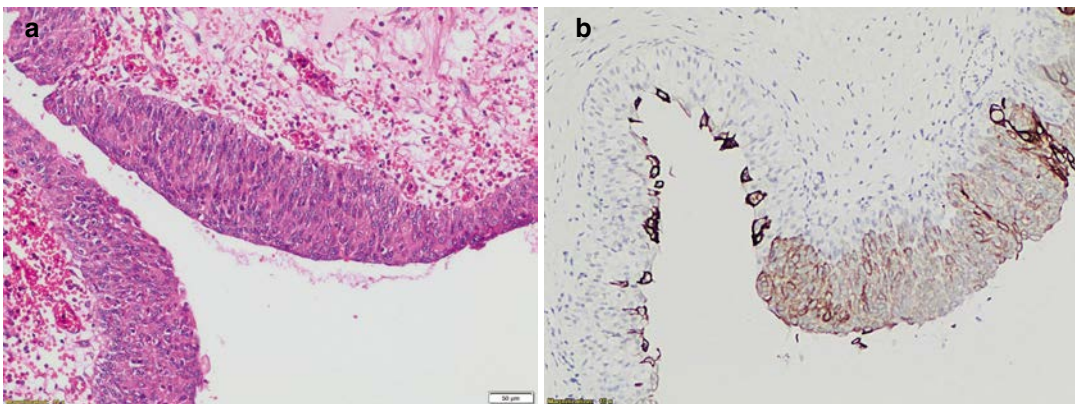


Fig. 11.6 (a) Urothelial carcinoma in situ. Loss of cellular polarity, nuclear crowding, and enlargement with prominent nucleoli. (HE $\times 40$). (b) Full thickness staining of CK20 despite normal urothelium. (DAB $\times 40$)

preserved. Mitoses are very rare and localized to the basal layer. Some cases may exhibit partial or complete inverted growth [25]. Low-grade papillary urothelial carcinomas are more frequently seen in older adults and males. Although these tumors have a high recurrence rate (50–70%), the progression and disease-related mortality rate remains below 5%. The papillary structures are composed of urothelial cells with mildly enlarged, uniform, round nuclei, with occasional nuclear contour irregularities. Loss of polarity, characterized by disruption of linear perpendicular orientation, is a notable feature. Mitoses are rare and are typically observed in the lower half of the epithelium [23]. High-grade papillary urothelial carcinomas frequently exhibit recurrence and progression to invasive disease. Macroscopically, they appear as exophytic papillary tumors. Microscopically, they consist of urothelial cells forming complex papillary structures with varying degrees of nuclear atypia, ranging from mild pleomorphism to marked anaplasia, along with loss of cellular cohesion. Disorganized proliferation and loss of order are observed in the urothelial epithelium. Mitotic activity is prominent, including in the upper layers. These tumors may coexist with low-grade tumors, and grading is based on the highest-grade areas (Fig. 11.7) [23].

All papillary tumors may show an inverted growth pattern. Inverted papilloma consists of trabeculae formed by neoplastic urothelial epithelium without atypia, invaginating into the lamina propria. The cells surrounding the trabec-

ulae display a palisading arrangement, while the central cells may have a spindle-shaped morphology. The recurrence rate is very low. In invasive urothelial carcinomas, the primary factor determining treatment and prognosis is the depth of invasion. Therefore, understanding the heterogeneity in bladder histology is crucial for accurate pathological staging. In cases showing lamina propria invasion, intravesical therapies are employed, whereas in cases with muscularis propria invasion, treatment options include radical cystectomy followed by chemotherapy, radiotherapy, or targeted therapy. The depth of invasion is also a key determinant in the course of the disease. Invasive urothelial carcinomas are macroscopically observed as papillary, solid, nodular, or polypoid masses, either solitary or multifocal. Ulceration is a common finding. Microscopically, in early invasive cases, epithelial cells are seen in small nests or groups within the lamina propria. One of the most challenging aspects for specialists in the pathological evaluation of bladder biopsies is the assessment of tumor invasion. Although numerous studies have been conducted and various criteria proposed to address this issue, certain factors continue to complicate the diagnostic process. These include the structural characteristics of tissue fragments, misleading morphologies arising during tissue processing, and the often-subtle nature of invasion patterns. In some cases, reaching a definitive conclusion remains particularly difficult. Invasive urothelial carcinomas are largely composed of high-grade

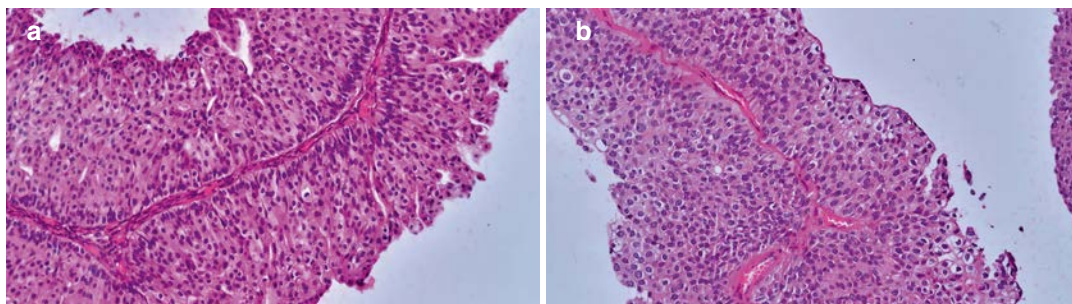


Fig. 11.7 (a) Low-grade urothelial carcinoma. Neoplastic epithelium with orderly architecture and mild pleomorphism. Cells are generally uniform in size. (HEx200). (b) High-grade urothelial carcinoma.

Disordered proliferation with crowded overlapping cells and nuclear pleomorphism. Irregular contours, nucleomegaly, and mitoses are present. (HEx200)

tumors. However, histological grade does not significantly influence recurrence rate, metastatic potential, or prognosis. Another important aspect in microscopic evaluation is the potential presence of variant histological patterns or other divergent differentiations. In cases showing divergent differentiation, classical papillary, in situ, or invasive urothelial carcinoma components are present, even if only focally. These tumors exhibit squamous, glandular, or trophoblastic differentiation. Histological subtypes or variants may present with various morphologies such as nested, micropapillary, tubular and microcystic, plasmacytoid, sarcomatoid, small cell, lymphoepithelioma-like, or lipid-rich patterns (Fig. 11.8). The clinical treatment and follow-up of histological subtypes or cases with divergent differentiation are planned based on staging, similar to classical urothelial carcinomas. However, the characteristics of certain variants may influence treatment approaches. For example, lymphoepithelioma-like carcinomas are notable for their low metastatic potential and favorable response to cisplatin-based chemotherapy. In contrast, sarcomatoid variants do not respond well to neoadjuvant or adjuvant chemotherapy. Small cell tumors are characterized by their tendency to metastasize early and their sensitivity to chemotherapy [26, 27].

Villous adenoma is a benign glandular tumor originating from the urothelial epithelium. Microscopically, pseudostratified columnar epithelium surrounding a central fibrovascular core can be seen. In rare cases, invasive adenocarci-

noma may develop; therefore, the entire excised tissue should be thoroughly examined. Invasive adenocarcinomas of the bladder are defined as tumors without accompanying squamous or urothelial components. Bladder exstrophy is the most significant developmental anomaly that increases the risk of adenocarcinoma. Glandular morphology can present in various patterns, such as enteric or mucinous adenocarcinoma, signet-ring cell carcinoma, and clear cell adenocarcinoma. In these cases, direct invasion of prostatic adenocarcinoma or colorectal adenocarcinoma must be excluded. Therefore, immunohistochemical analysis is essential. Primary bladder adenocarcinoma typically exhibits a CK20(+), CK7(-), CDX2(+), SATB2(+) expression pattern. PSAP may be positive; however, PSA and nuclear beta-catenin are negative [28].

Squamous cell carcinomas of the bladder are strongly associated with smoking and schistosomal infections. For diagnosis, the tumor must show pure squamous cell histology, without components of urothelial carcinoma or adenocarcinoma. They are more frequently found in areas other than the bladder base. It can be challenging to distinguish nonkeratinizing tumors from high-grade urothelial carcinomas. Except for the verrucous variant, the majority of squamous cell carcinomas exhibit deep invasion at the time of diagnosis. Therefore, the value of histological grading in these tumors is considered debatable. Verrucous carcinoma is a variant of squamous cell carcinoma that almost always occurs in association with *Schistosoma* infection and typically arises in endemic regions. It generally presents as exophytic, papillary masses and exhibits minimal cytologic atypia. A characteristic feature is the presence of pushing and rounded microscopic borders. Diagnosing this tumor on TUR specimens can be challenging. If a focus of invasion is identified, the case should be reported as squamous cell carcinoma, even if the overall architecture is consistent with verrucous carcinoma.

The TNM system is used for staging of bladder tumors. Accordingly, primary tumors are classified as superficial (noninvasive) and invasive. Superficial bladder tumors include Ta (defines noninvasive papillary carcinoma), Tis

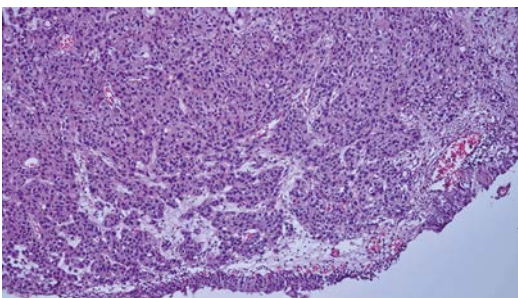


Fig. 11.8 Invasive urothelial carcinoma. Neoplastic cells with high-grade nuclear features arranged in irregular nests invading the lamina propria. (HEx100)

(carcinoma in situ), and T1 (tumor invades the lamina propria). The term invasive bladder tumors refers to T2 tumors, which are characterized by invasion into the muscular layer of the bladder wall. Superficial bladder tumors have a very good prognosis. In cases with muscle invasion, the 5-year survival rate is approximately 50%, while in those with distant metastases, it drops to around 10–17%.

In bladder carcinoma, tumor dissemination occurs via local invasion, lymphatic spread, and hematogenous metastasis. Local extension typically begins with invasion beyond the submucosal layer into the muscularis propria and subsequently the serosal layer, involving the full thickness of the bladder wall. Further progression leads to infiltration of the perivesical fat and adjacent pelvic organs (Fig. 11.9). Tumors located near the ureteric orifices may extend into the ureters, while those involving the bladder neck may invade the urethra and prostate. Lymphatic dissemination follows a predictable pathway, initially involving the obturator, internal iliac, external iliac, prevesical, and presacral lymph nodes. Hematogenous metastasis can result in the involvement of distant organs, most commonly the liver, lungs, bones, and brain.

Nonepithelial bladder tumors are rare. Lesions referred to as pseudosarcomatous myofibroblastic proliferation, inflammatory myofibroblastic tumor, postoperative spindle cell nodule, and inflammatory pseudotumor—demonstrating similar features—can collectively be classified under the term “myofibroblastic proliferations.” These rare lesions are typically observed in young adults. They present as polypoid masses or sub-

mucosal nodules. Microscopically, they are characterized by loose fascicular arrangements of spindle cells, often accompanied by large, nucleated cells [29].

Leiomyomas are the most commonly encountered benign mesenchymal tumors of the bladder. These tumors typically develop as intramural nodules smaller than 2 cm and are composed of cells with eosinophilic cytoplasm and elongated, spindle-shaped nuclei. Nuclear pleomorphism, necrosis, and mitotic activity are absent. Cases showing mitotic figures should be evaluated as low-grade leiomyosarcomas. Leiomyosarcomas, though rare, are the most frequently observed malignant mesenchymal tumors of the genitourinary system. Key diagnostic criteria include nuclear atypia, an infiltrative growth pattern, and necrosis. Based on mitotic activity, they are categorized into low-grade (<5 mitoses/10 HPF) and high-grade leiomyosarcomas. These tumors are typically positive for smooth muscle actin and caldesmon. Rhabdomyosarcomas represent a heterogeneous group of tumors in terms of clinical, morphological, and molecular characteristics. Histopathologically, they are classified into four subtypes: embryonal, alveolar, spindle cell, and pleomorphic rhabdomyosarcomas. These tumors commonly express desmin, myogenin, and MyoD1. Other mesenchymal tumors that may be observed in the bladder include neurofibroma, solitary fibrous tumor, hemangioma, postradiation sarcoma, pleomorphic undifferentiated sarcoma, and PEComa [30].

Another rare tumor of the bladder, typically seen in younger patients, is paraganglioma. Microscopically, these tumors display the characteristic nested “zellballen” pattern. They are immunohistochemically positive for synaptophysin, chromogranin A, and CD56 and typically show nuclear GATA3 expression. Cases with loss of SDHB expression tend to exhibit more aggressive behavior. Approximately 10% of these tumors behave malignantly, and recurrence is common in cases where surgical excision is incomplete [31].

Secondary tumors involving the bladder, either by direct extension or metastasis, may also be encountered. The most common primary

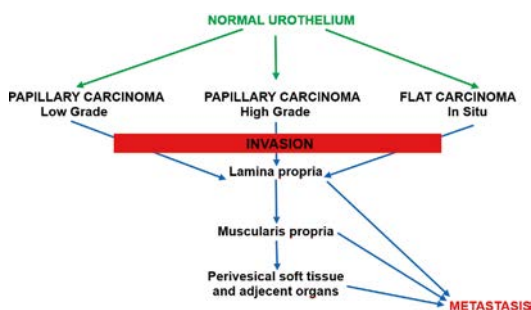


Fig. 11.9 Pathogenesis

sources include prostate, colorectal, and gynecological malignancies. During cystoscopic sampling of bladder tumors, in addition to the tumor tissue itself, it is recommended to obtain specimens from the tumor base and adjacent mucosal areas, when feasible. The pathology report should include a detailed assessment comprising the histologic type and grade of the tumor, histologic variant (e.g., papillary, micropapillary, nested), depth of invasion, presence of muscularis propria, evidence of divergent differentiation (if present), lymphovascular invasion, and any alterations observed in the surrounding urothelium. Examination of voided urine for exfoliated malignant cells demonstrates high sensitivity and specificity in the screening, diagnosis, and surveillance of high-grade urothelial carcinomas. In contrast, the detection of low-grade neoplasms remains challenging due to the cytological resemblance of low-grade tumor cells to benign urothelial cells. The diagnostic criteria defined by The Paris System (TPS) for high-grade urothelial carcinoma require the identification of a minimum of 5–10 well-preserved urothelial cells exhibiting a nuclear-to-cytoplasmic (N:C) ratio of ≥ 0.7 , moderate to severe hyperchromasia, coarse chromatin texture, and irregular nuclear membrane contours [32].

References

- McNeal JE. Normal and pathologic anatomy of prostate. *Urology*. 1981;17(suppl):11–6.
- Krieger JN, Nyberg L Jr, Nickel JC. NIH consensus definition and classification of prostatitis. *JAMA*. 1999;282(3):236–7.
- Bryan RL, Newman J, Campbell A, Fitzgerald G, Kadow C, O'Brien JM. Granulomatous prostatitis: a clinicopathological study. *Histopathology*. 1991;19(5):453–7.
- Srigley JR. Benign mimickers of prostatic adenocarcinoma. *Mod Pathol*. 2004;17:328–48.
- Egevad L, Delahunt B, Furusato B, Tsuzuki T, Yaxley J, Samaratunga H. Benign mimics of prostate cancer. *Pathology*. 2021;53(1):26–35.
- Bostwick DG, Cheng L. Precursors of prostate cancer. *Histopathology*. 2012;60(1):4–27.
- Epstein JI, et al. The 2019 Genitourinary Pathology Society (GUPS) White Paper on contemporary grading of prostate cancer. *Arch Pathol Lab Med*. 2021;145(4):461–93.
- Bettendorf O, Schmidt H, Staebler A, Grobholz R, Heinecke A, Boecker W, Hertle L, Semjonow A. Chromosomal imbalances, loss of heterozygosity, and immunohistochemical expression of TP53, RB1, and PTEN in intraductal cancer, intraepithelial neoplasia, and invasive adenocarcinoma of the prostate. *Genes Chromosomes Cancer*. 2008;47(7):565–72.
- Kench JG, Kristiansen G, Berney DM, Netto GJ, De Marzo A, Litjens GJS, Magi-Galluzzi C, Yang XJ, Egevad L. Prostatic acinar adenocarcinoma. In: Srigley JR, Amin MB, Rubin MA, Tsuzuki T, editors. *WHO classification of tumours: urinary and male genital tumours*. 5th ed. International Agency for Research on Cancer; 2022.
- Baisden BL, Kahane H, Epstein JI. Perineural invasion, mucinous fibroplasia, and glomerulations: diagnostic features of limited cancer on prostate needle biopsy. *Am J Surg Pathol*. 1999;23(8):918–24.
- Epstein JI, Allsbrook WC Jr, Amin MB, Egevad L, ISUP Grading Committee. The 2005 International Society of Urological Pathology (ISUP) Consensus conference on Gleason grading of prostatic carcinoma. *Am J Surg Pathol*. 2005;29(9):1228–42.
- Volmar KE, Chan TY, De Marzo AM, Epstein JI. Florid von Brunn nests mimicking urothelial carcinoma: a morphologic and immunohistochemical comparison to the nested variant of urothelial carcinoma. *Am J Surg Pathol*. 2003;27(9):1243–52.
- Amin A, Murati-Amador B, Lombardo KA, Jackson CL, Grada Z, Palsgrove DN, Matoso A. Analysis of intestinal metaplasia without dysplasia in the urinary bladder reveal only rare mutations associated with colorectal adenocarcinoma. *Appl Immunohistochem Mol Morphol*. 2020;28(10):786–90.
- Ahmad I, Barnetson RJ, Krishna NS. Keratinizing squamous metaplasia of the bladder: a review. *Urol Int*. 2008;81(3):247–51.
- Santi R, Angulo JC, Nesi G, Petris G, Kuroda N, Hes O, López JJ. Common and uncommon features of nephrogenic adenoma revisited. *Pathol Res Pract*. 2019;215(10):152561.
- Kim DS, Lee JW. Urinary tract infection and microbiome. *Diagnostics*. 2021;2023:1–13.
- Smith SC. Overview of cystitis. In: Amin MB, Tickoo SK, editors. *Diagnostic pathology genitourinary*. 3rd ed. Elsevier; 2022. p. 286–91.
- Akiyama Y, Homma Y, Maeda D. Pathology and terminology of interstitial cystitis/bladder pain syndrome: a review. *Histol Histopathol*. 2019;34(1):25–32.
- Williamson SR, et al. Chapter 3: Invasive urothelial carcinoma. In: Comperat EM, Netto GJ, Tsuzki T, editors. *WHO classification of tumours: urinary and*

- male genital tumours. 5th ed. International Agency for Research on Cancer; 2022.
20. Peng S, Yang Y, Zheng H. Review of recent molecular pathology of bladder urothelial carcinoma. *Discov Oncol*. 2025;16:424.
 21. McKenney JK. Urothelial carcinoma in situ: diagnostic update. *Pathology*. 2021;53(1):86–95.
 22. Neal DJ, Amin MB, Smith SC. CK20 versus AMACR and p53 immunostains in evaluation of urothelial carcinoma in situ and reactive atypia. *Diagnol Pathol*. 2020;15(1):61.
 23. Amin MB, et al. The Genitourinary Pathology Society update on classification and grading of flat and papillary urothelial neoplasia with new reporting recommendations and approach to lesions with mixed and early patterns of neoplasia. *Adv Anat Pathol*. 2021;28(4):179–95.
 24. Raspollini MR, et al. Chapter 3: Urothelial papilloma. In: Comperat EM, Netto GJ, Tsuzki T, editors. WHO classification of tumours: urinary and male genital tumours. 5th ed. International Agency for Research on Cancer; 2022.
 25. Jones TD, Cheng L. Reappraisal of the papillary urothelial neoplasm of low malignant potential (PUNLMP). *Histopathology*. 2020;77(4):525–35.
 26. Gandhi J, Chen JF, Al-Ahmadie H. Urothelial carcinoma: divergent differentiation and morphologic subtypes. *Surg Pathol Clin*. 2022;15(4):641–59.
 27. Kwon W-A, Seo HK, Song G, Lee M-K, Park WS. Advances in therapy for urothelial and non-urothelial subtype histologies of advanced bladder cancer: from etiology to current development. *Biomedicines*. 2025;13(1):86.
 28. Wang HL, Lu DW, Yerian LM, Alsikafi N, Steinberg G, Hart J, Yang XJ. Immunohistochemical distinction between primary adenocarcinoma of the bladder and secondary colorectal adenocarcinoma. *Am J Surg Pathol*. 2001;25(11):1380–7.
 29. Harik LR, Merino C, Coindre JM, Amin MB, Pedetour F, Weiss SW. Pseudosarcomatous myofibroblastic proliferations of the bladder: a clinicopathologic study of 42 cases. *Am J Surg Pathol*. 2006;30(7):787–94.
 30. Kunze E, Theuring F, Krüger G. Primary mesenchymal tumours of the urinary bladder. A histological and immunohistochemical study of 30 cases. *Pathol Res Pract*. 1994;190(4):311–32.
 31. So JS, Epstein JI. GATA3 expression in paragangliomas: a pitfall potentially leading to misdiagnosis of urothelial carcinoma. *Mod Pathol*. 2013;26(10):1365–70.
 32. Raspollini MR, et al. Chapter 3: Tumours of the urinary tract: Introduction. In: Comperat EM, Netto GJ, Tsuzki T, editors. WHO classification of tumours: urinary and male genital tumours. 5th ed. International Agency for Research on Cancer; 2022.

12.1 Introduction to Tumors of the Testis

Tumors of the testis are relatively uncommon compared to other malignancies in the genitourinary tract, accounting for approximately 1–2% of all tumors, within the age range of 15–35, with an incidence rate of about 6 cases per 100,000 men annually [1]. It is crucial to differentiate these testicular tumors from other forms of neoplasms, such as lymphomas or sarcomas, due to distinct histological features and varying degrees of aggressive behavior. The formation and progression of testicular neoplasms are impacted by a range of factors, including genetic predispositions, environmental exposures, and lifestyle choices. The majority of solid testicular neoplasms (95%) are classified as seminomatous and non-seminomatous germ cell tumors. Only 5% of testicular neoplasms are the rather rare testicular sex cord-stromal tumors (SCSTs). Usually benign, these tumors are diverse collections of neoplasms that originate from the testes' hormone-producing and supporting structures [2].

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12.2 Normal Structural and Microscopic Anatomy of the Testis

The testis is normally an oval, firm, and smooth structure. In a normal adult man, it measures 4–6 cm in length and 3–4 cm in width, and the testis weights 14–25 g (average 20 g). The scrotum is a pouch of skin that contains the testicles and are attended to by the cremaster and dartos muscles. The testis consists of interstitium and seminiferous tubules. Interstitium constitutes 5% of the testis and consists of the interstitial cells, which are derived from the stroma of the mesonephros (testosterone-secreting Leydig cells), blood vessels, lymphatics, and connective tissue. Seminiferous tubules make up about 90% of the volume of the testis. These are the sites of spermatogenesis. Each testis is composed of lobules containing seminiferous tubules, each of which contains germ cells and supporting cells [3]. Each lobule has convoluted seminiferous tubules lined by spermatogenic cells and sustentacular cells and contains small interstitial cells of Leydig which secrete testosterone. Inside these lobules, the convoluted seminiferous tubules are lined Sertoli cells (sustentacular cells), which are tall columnar cells extending from the basement membrane to the lumen. They feature a prominently rounded nucleus with a noticeable nucleolus and appear pale under hematoxylin and eosin staining. Essential for the development of male gametes are typically round to polygonal with a

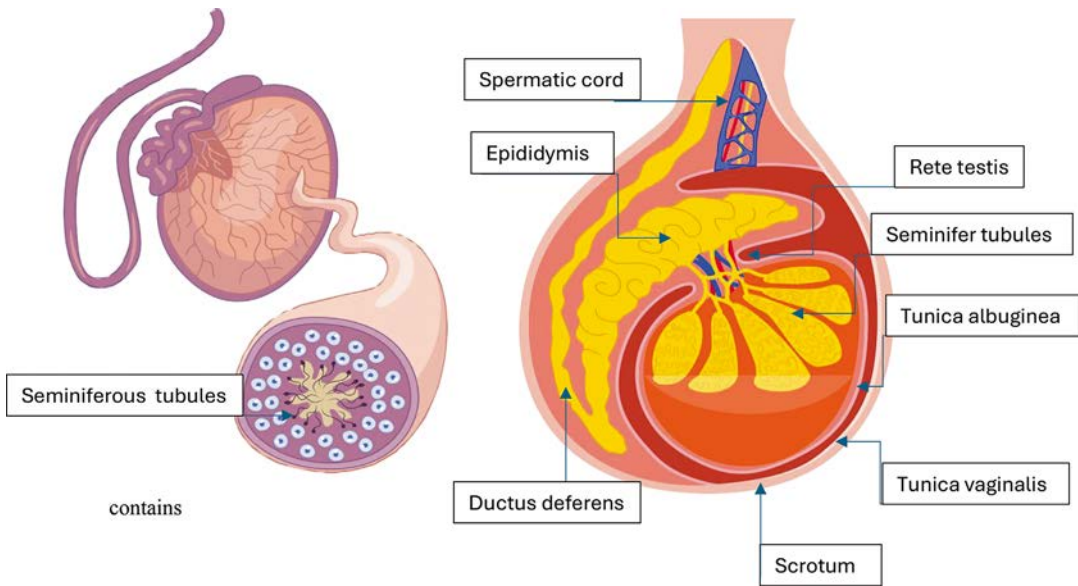


Fig. 12.1 Testicular Anatomy: Structural features and spatial orientation

large, darkly stained, clumped nucleus. These cells not only provide structural support but also create an environment that fosters the maturation of sperm cells throughout their developmental stages. The Leydig cells are round to oval, lipid-laden cells with low N/C ratio and lightly stained cytoplasm. They produce testosterone and play an important role in the development of male sexual organs. This is an abundant hormone during puberty and promotes development and maintenance of male secondary sexual characteristics [4] (Fig. 12.1).

12.3 Testicular Lesions: Epidemiology

Testicular cancer arises from the germinal epithelium and predominantly impacts young adults, while testicular teratomas are frequently encountered in pediatric patients. Multilocular cysts can occur in different areas of the testis, occasionally resembling tumors. Inflammatory lesions, ranging in severity, like epididymitis and orchitis, can pretend tumor conditions. Benign conditions, such as hydrocele, varicocele, and spermatocele, result from the enlargement or inflammation of

blood vessels. Other benign formations include soft tissue tumors, fibromas, lipomas, and hemangiomas. Evaluating epididymal, spermatic cord, and testicular adnexal lesions are crucial, focusing on solid tumors and hamartomas, with a differential diagnosis encompassing a range of tumors [5–7]. Congenital anomalies affecting male genitalia include cryptorchidism and complex testicular dysgenesis syndromes [8].

However, testicular cancer is a relatively uncommon disease, accounting for approximately 1% of all cancers and ranking 26th in the incidence of cancer among males [9]. Family history is a key risk factor, with men who have a brother or father diagnosed with testicular cancer at a higher risk, with 2–5% of testicular cancers occurring in a familial pattern. In Australia, testicular cancer is the most common cancer in males aged 15–39, while in New Zealand, it is the second most common after prostate cancer. Australia sees around 830 new cases each year and about 20 deaths. New Zealand has an annual incidence rate of 4.9 per 100,000, the highest worldwide, particularly in males aged 15–30. From 1990 to 2018, the incidence rose by 3.1% overall, with increases of 3.1% in Australia, 4.2% in New Zealand, and 0.08% in Japan [10, 11].

12.4 Congenital and Cystic Disorders of the Testis

12.4.1 Cryptorchidism

Cryptorchidism is a common urological condition where one or both testicles fail to descend into the scrotum. Cryptorchidism affects about 1–4% of male births. This rate rises considerably with low birth weight. Typically, the peak descent occurs between 8 and 9 months after birth, with a high chance of spontaneous descent within the first 2 years. Following a one-year observation, if descent hasn't occurred, surgical intervention may be considered. The timing of surgery is debated, with suggestions for intervention at ages 2–3 years, before assessing fertility or cancer risk. Histological characteristics of cryptorchid testis include reduced germ cells due to impaired gonocyte maturation, interstitial fibrosis, and decreased Sertoli cells. Notably, there is significant atrophy of Leydig cells, suggesting endocrinopathy plays a role in cryptorchidism [12–14].

12.4.2 Hydrocele and Hematocele

A hydrocele is defined as the accumulation of fluid between the visceral and parietal layers of the tunica vaginalis surrounding the testicle, which gives fluctuation and is partially translucent. Only approximately 1% of adult males have hydroceles, whereas the incidence of neonatal hydroceles is as high as 4.7% [14]. The testicle cannot be palpated because it is surrounded by fluid. Hydrocele may be congenital or secondary to trauma, inflammatory, and neoplastic causes. Typically, both conditions can present with similar symptoms, such as scrotal swelling and discomfort. However, the treatment approach may vary, with hydroceles frequently managed through surgical techniques or sclerotherapy, while hematocele may require addressing the source of bleeding in addition to fluid drainage. The distinction between the two conditions is crucial for appropriate management and treatment [15].

12.4.3 Testicular Hypoplasia and Agenesis

Testicular hypoplasia is characterized by reduced testicular volume due to inadequate descent and developmental anomalies in the testicular tissue. Testicular agenesis can be defined as the total absence of a testis, mediastinum testis, ductus deferens, or epididymis. Such a complete absence or agenesis may occur as the result of environmental disruptors during the embryological development of the urogenital system. Cryptorchidism, developmental abnormalities, testicular torsion, orchitis, trauma, and genetic anomalies (such as Turner and Klinefelter syndromes) are all associated with these entities [16, 17].

12.5 Infections of the Testis

12.5.1 Orchitis

Parenchymal testis infection, known as orchitis, is less common than epididymitis. Testicular parenchyma involvement in the acute presentation (testicular orchitis) is rather an uncommon diagnosis and usually referred to in conjunction with a concomitant epididymal disorder (classic epididymal-orchitis). Orchitis in isolation without concurrent epididymitis is a much rarer entity (1–11% of all scrotal pathology), even rarer than in the pediatric population. Isolated acute orchitis is unusual and presents with the clinical picture of testicular swelling and pain, which may be preceded by febrile illness. The onset is typically rapid. The disease can be unilateral or bilateral (a much rarer disease). Mumps virus, specifically the paramyxovirus, is the most common causative infectious agent. Mumps orchitis occurs 10 days after the onset of parotitis (this complication may be bilaterally) in 15–20% of patients and in males who get the disease after puberty as 40–60% (from the group of evaluable resistant pubescent males). Nonparotid complications include epididymo-orchitis and meningoencephalitis.

Chronic granulomatous testicular involvement may occur in systemic conditions such as tuberculosis, sarcoidosis, or specific infections. Diffuse granulomatous inflammation can result from either the gradual entry of low-virulence organisms into the testicular tissue or from local tissue responses to specific microbes or endogenous compounds. It usually occurs as a late complication and is associated with the older age group. Clinicians may misdiagnose granulomatous orchitis as a neoplastic condition [18].

12.5.2 Tuberculosis of the Testis

Tuberculosis of the testis, though rare, is the most common extrapulmonary site of tuberculosis infection in the male genitourinary system. It presents as a painless scrotal swelling or as a mass that involves the epididymis and later the testis. The epididymis is the most prevalent site of genital tuberculosis in men, with the seminal vesicles, prostate, testis, and vas deferens following in that order. This results in epididymo-orchitis and, if untreated, hydrocele. However, the primary TB of the testis is rare and may result from hematogenous and lymphatic spread of bacilli to the gland. The majority of cases of tuberculosis epididymo-orchitis are believed to be the result of the retrograde spread of tubercle bacilli from the affected urinary tract into the prostate through reflux. In the differential diagnosis, it is important to consider testicular tumors, infarctions, and other granulomatous infections [19].



Fig. 12.2 Macroscopic appearance of dilated epididymis filled with pus

rhoeae. Subsequently, it may also be due to bacterial urinary tract infection, which may be associated with benign prostatic hyperplasia (BPH) in older patients (over 35). Rare noninfectious conditions can cause epididymitis, including trauma, catheterization, and hematogenous spread of infection [20]. Boys under the age of 14 should be evaluated for noninfectious reasons such as post viral inflammation or Henoch-Schönlein vasculitis. Chemical epididymitis can be caused by certain medications, including amiodarone [20] (Fig. 12.2).

12.6 Epididymis and Cord

12.6.1 Epididymitis

Epididymitis is categorized based on duration, with acute cases lasting less than 6 weeks, subacute lasting 6–12 weeks, and chronic cases lasting over 3 months. Acute epididymitis primarily affects young men and is predominantly caused by sexually transmitted diseases caused by *Chlamydia trachomatis* and *Neisseria gonor-*

12.6.2 Spermatocele

Spermatocele is a benign cystic structure that forms in the epididymis, typically arising from the proximal segment of the epididymal duct and is filled with a clear or milky fluid containing spermatozoa. The exact etiology of spermatocele formation remains unclear, but it is believed to be associated with obstructive processes in the epididymis that lead to dilatation of the ductules. Most cases are asymptomatic and are often discovered incidentally during imaging tests for

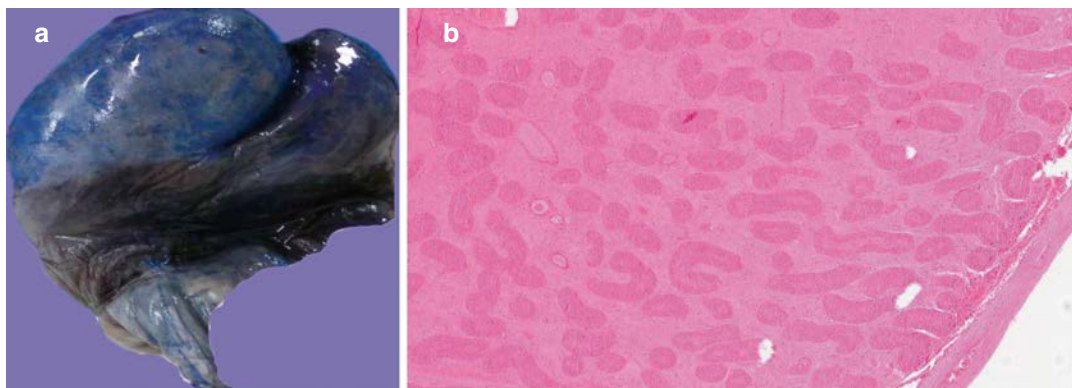


Fig. 12.3 Testicular torsion gross: red and dark testis; on H&E section, necrotic parenchyma is seen

other conditions. However, larger spermatoceles can present as palpable scrotal masses and may cause discomfort or pain, especially if they become torsed [21]. In histology, a single layer of cuboidal to ciliated columnar epithelium flattens as fluid accumulates. Proteinaceous fluid and spermatozoa are present in the lumen, cyst wall, and soft tissue. The soft tissue wall is composed of thin fibromuscular fibers [22].

12.6.3 Varicocele

Varicocele has a higher prevalence in developing nations, leading to low fertility rates. Varicocele is characterized by the abnormal enlargement of the pampiniform plexus veins in the scrotum, primarily affecting the left side (90%) due to its unique venous drainage into the left renal vein. The underlying mechanism involves valve incompetence leading to retrograde blood flow and increased venous pressure [23, 24].

12.6.4 Testicular Torsion

Testicular torsion is a urological emergency characterized by the twisting of the spermatic cord, which compromises blood flow to the testis. It primarily affects adolescents and neonates, with a bimodal incidence observed between the first year of life and ages 13–16 years. There are risk factors such as increase intrauterine pressure,

long spermatic cord, and undescended testicle. The condition presents with acute scrotal pain, which may be accompanied by nausea, vomiting, and abdominal pain. Prompt diagnosis is critical, as delayed treatment can lead to irreversible damage and loss of the affected testis due to ischemia and necrosis, which can occur within hours of onset. Ultrasonographic findings play a crucial role in the diagnosis of testicular torsion. Key indicators include the presence of spermatic cord twisting or the “whirlpool sign,” as well as a decrease or absence of blood flow to the affected testis. In cases where torsion is suspected, surgical intervention should be considered urgently, ideally within 6 h of the onset of symptoms, to maximize the chances of salvaging the testis [25–28] (Fig. 12.3).

12.7 Tumors of the Testis

This is the third most frequent malignant neoplasm in the pediatric population after leukemias and CNS tumors. Testicular cancers are rare neoplasms that arise primarily from germ cells, with an incidence rate of about five cases per 100,000 persons worldwide; tumors of the testis account for only 1–2% of all cancers in males. Of these neoplasms, germ cells tumors are the most frequent tumors representing over 95% of tumors [29–31]. Family history is a key risk factor, family members of affected men have a 2–10 times greater risk than the general population, but

genetic factors are not yet well understood [31]. Testicular cancer is the most diagnosed solid tumor in males between the ages of 18 and 50. The prevalence of this malignancy has increased twofold over the last 40 years, with testicular cancer mortality being highest in developing countries due to delayed diagnosis and restricted healthcare access [32].

Germ cells are the source of 95% of testicular tumors, and nearly all of them are malignant. Conversely, sex cord-stromal tumors that develop from Sertoli or Leydig cells are uncommon and generally benign. Spermatogenic tumors represent the most common testicular neoplasm in men aged between 15 and 30 years. Germ cell tumors (GCTs) can be broadly subdivided into seminomas and non-seminomatous germ cell tumors (NSGCTs). They may occur purely or as a mixture of different subtypes. Non-seminomatous tumors include embryonal carcinoma, yolk sac tumor, choriocarcinoma, and teratoma [33]. Testicular germ cell tumors (TGCTs) in young adults originate from a common precursor, germ cell neoplasia in situ (GCNIS), formerly known as carcinoma in situ (CIS) (Fig. 12.4). GCNIS arises from developmentally arrested gonocytes that fail to differentiate into spermatogonia. Morphologically, GCNIS cells resemble fetal gonocytes but display more irregular nuclear chromatin. They are typically arranged in a single row along the basement membrane of seminiferous tubules. GCNIS is linked to all types of germ cell tumors in adolescents and adults, except spermatocytic tumors (Table 12.1). In contrast, prepubertal-type testicular teratomas are benign and unrelated to GCNIS [34].

Germ cell tumors are the most prevalent malignancy in young males, with rising incidence rates in the developed world. Cryptorchidism (undescended testis) significantly raises the risk of these tumors, indicating that abnormal developmental pathways may contribute to testicular germ cell cancer’s onset. Factors like maternal diethylstilbestrol exposure and a family history of testicular cancer are also associated with increased risk [35]. Genetic predisposition is recognized as a critical risk factor, with familial patterns observed in siblings and

Table 12.1 Testicular germ cell tumors (TGCTs) are grouped according to the presence or absence of germ cell neoplasia in situ (GCNIS) [38]

WHO 2022—Testicular Germ Cell Tumors (TGCTs)	
GCNIS-related TGCTs	Non-GCNIS-related TGCTs
Seminomas	Yolk sac tumor, prepubertal type
Nonseminomatous mixed germ cell tumors:	Teratoma, prepubertal type and associated tumors:
Embryonal carcinoma	Dermoid cyst
Yolk sac tumor, postpubertal type	Epidermoid cyst
Choriocarcinoma and other trophoblastic tumors	Well-differentiated tumors
	Neuroendocrine tumors
Burned-out (regressed) germ cell tumors	Spermatocytic tumor

identical twins. Chromosome 12p aberrations have been identified as early events, and genes such as *KIT*, *RAS*, *TP53*, and epigenetics-related genes are implicated [36]. Up to 25% of tumors contain oncogenic mutations in *KIT* [37]. Additionally, testicular germ cell tumors are associated with mutations in the *TERT* promoter and polymorphisms (SNPs) in some genes [38]. Numerous recurrent chromosomal alterations (in particular, the gain of chromosome arm 12p) were observed in cytogenetic studies of pure types of testis tumor. Additionally, frequent large-scale copy number gains were observed in chromosomes 7, 21, 22, and X, which were not present in testicular sex cord-stromal tumors or paratesticular tumor. These findings suggested different biological behavior in the various tumors originating in the testis [39]. Also, *P53/MDM2* axis, which is inactivation of *P53* and overexpression of *MDM2*, is responsible for chemotherapy resistance [40] (Fig. 12.4).

12.7.1 Germ Cell Tumors

Table 12.2 delineates the subclassification of testicular germ cell tumors into seminoma and non-seminomatous tumors. The most prevalent kind of testicular germ cell neoplasm is the sem-

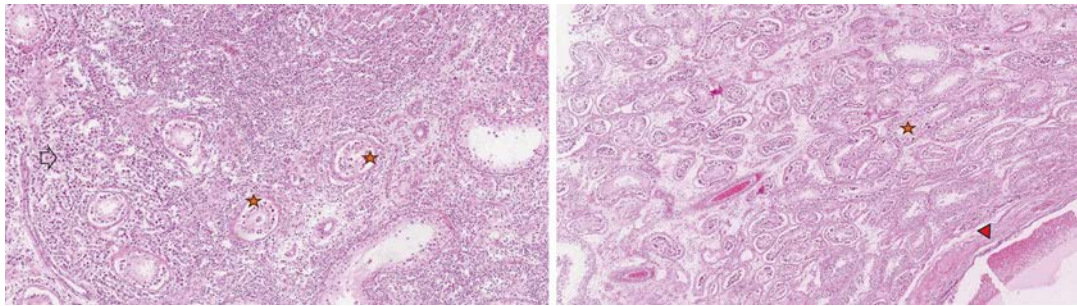


Fig. 12.4 These figures depict an in situ germ cell tumor region (stars) in many areas, alongside invasive seminomatous tumor regions (arrow), and in one area, ciliated epithelium (arrowhead) associated with the teratomatous component

Table 12.2 Comparison table between *seminomatous* and *non-seminomatous germ cell tumors (NSGCT)* of the testis [41, 42]

Feature	Seminomatous tumors	Non-seminomatous tumors
Definition	Germ cell tumors primarily composed of seminoma cells, resembling primordial germ cells	Germ cell tumors include embryonal carcinoma, yolk sac tumor, choriocarcinoma, or teratoma
Prevalence	~50% of testicular GCTs	~50% of testicular GCTs, often mixed components
Age group	Typically, 30–40 years	Typically, 20–30 years, slightly younger
Histology	Uniform cells, clear cytoplasm, lymphoid infiltrates, central nuclei, syncytiotrophoblasts in some cases	Diverse: embryonal (immature cells), yolk sac (Schiller-Duval bodies), choriocarcinoma (syncytiotrophoblasts), teratoma (mixed tissues)
Gross pathology	Homogeneous, gray-white, lobulated	Heterogeneous: hemorrhage, necrosis, cystic areas
Tumor markers	Elevated hCG in ~10–15%; AFP rarely elevated	Often elevated AFP (yolk sac), hCG (choriocarcinoma, embryonal); LDH in both
Radiosensitivity	Highly radiosensitive	Less radiosensitive; chemotherapy preferred
Chemosensitivity	Highly chemosensitive, but slightly less aggressive regimens	Highly chemosensitive, often requires more aggressive regimens
Metastatic pattern	Primarily lymphatic spread (retroperitoneal nodes)	Lymphatic and hematogenous spread (lungs, liver, brain)
Prognosis	Excellent prognosis; 5-year survival >95% for early stages	Good prognosis, but slightly worse than seminoma; 5-year survival ~90% for early stages. Depends on subtype and stage
Stage at diagnosis	Often localized (stage I) at presentation	More likely to present at advanced stages (II or III)
Treatment	Orchiectomy, surveillance (stage I), radiotherapy, or chemotherapy for advanced stages	Orchiectomy, chemotherapy (e.g., BEP regimen), RPLND for residual disease, surveillance
Risk of recurrence	Lower risk, especially with radiotherapy	Higher risk, especially if teratoma component present
Pathologic features	Slow growing, homogenous, no hemorrhage/necrosis	Faster growing, often heterogeneous with hemorrhage/necrosis

inoma, which accounts for approximately 50% of cases. They are histologically indistinguishable from tumors known as dysgerminomas, found in the ovary, and germinomas, located in the central nervous system and other extragonadal regions.

Seminoma

Seminoma is typically soft, well-circumscribed white and gray mass. It often presents as a painless testicular mass. It may show hemorrhage and necrosis in larger tumors. Histologically, it comprises large, uniform cells characterized by clear,

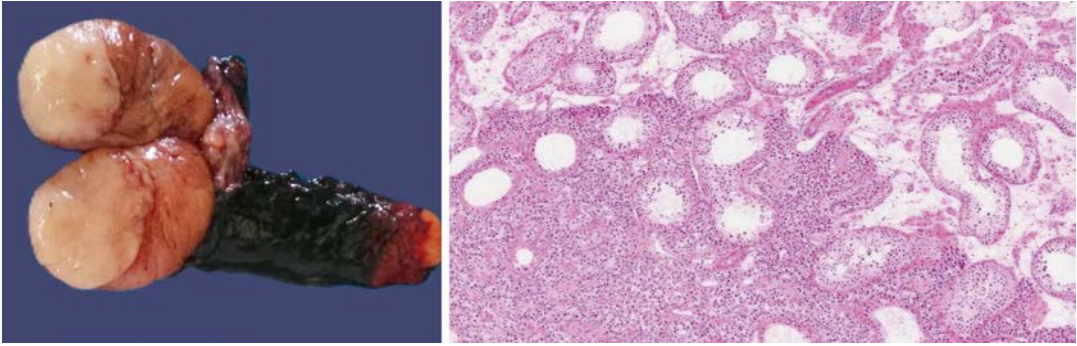


Fig. 12.5 Macroscopically and microscopically, an appearance of seminoma is observed. Macroscopically, a well-circumscribed, shiny-surfaced, cream-colored tumor

is observed. Microscopically, an invasive tumor area accompanied by in situ areas is seen in the figure

glycogen-laden cytoplasm, well-defined borders, round nuclei, and prominent nucleoli. The cells are organized into lobules divided by fibrous septa, frequently exhibiting lymphocytic infiltration and, at times, a granulomatous response. Elevated tumor markers that are frequently monitored include β -hCG (beta-human chorionic gonadotropin) and LDH (lactate dehydrogenase), although seminomas typically do not elevate alpha-fetoprotein (AFP). Syncytiotrophoblasts are present and leading to a minor increase in hCG, which does not affect prognosis [40]. The prognosis for seminomas is typically favorable, with high cure rates due to their sensitivity to chemotherapy and radiation therapy (Fig. 12.5).

Spermatocytic Tumor

Spermatocytic tumor is a rare type of testicular germ cell tumor that primarily affects older males, typically over the age of 50. It is distinct from typical seminomas and non-seminomatous germ cell tumors due to its unique histopathological features and clinical behavior. Spermatocytic tumors are classified as low-grade tumors and have different prognostic implications compared to other germ cell tumors. Histologically, spermatocytic tumors are characterized by the presence of three distinct cell types: small, intermediate, and large cells. These tumors typically exhibit a well-circumscribed pattern with a solid or trabecular architecture. The small cells are round with scant cytoplasm,

while the intermediate cells are larger, have abundant cytoplasm, and often display prominent nucleoli. The large cells are polygonal and have abundant eosinophilic cytoplasm. An important feature of spermatocytic tumors is the absence of lymphocytic infiltration and lack of fibrous septa, which is frequently seen in classic seminomas [43].

Embryonal Carcinoma

It is most commonly seen in young males, typically between the ages of 15 and 35. Embryonal carcinoma is known for its aggressive behavior and ability to metastasize, making early diagnosis and treatment critical. Histologically, embryonal carcinoma is characterized by the presence of primitive, undifferentiated cells that resemble embryonic tissue. The tumor typically exhibits a heterogeneous architecture with areas of poorly differentiated cells, as well as regions that may show glandular or cystic differentiation. The cells are large, with abundant cytoplasm, irregular nuclei, and prominent nucleoli. Mitotic figures are often abundant, reflecting the tumor's aggressive nature. In most cases, the embryonal areas are mixed with cells that are specific to other types of germ cell tumors, like yolk sac tumor, teratoma, and choriocarcinoma. Additionally, necrosis and hemorrhage are common features within the tumor. It is typically diagnosed via histopathological and immunohistochemical analysis (CD30 and OCT3/4), often presenting as a

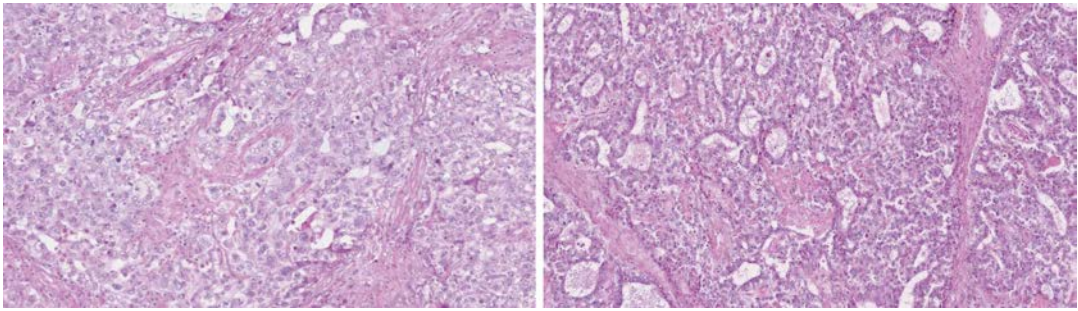


Fig. 12.6 Microscopic figure shows a solid tumor composed of poorly differentiated pleomorphic cells belonging to embryonic carcinoma. In the other area, more glandular differentiation is observed

painless testicular mass with rapid progression and early metastasis. Despite their rarity, especially in pure form (3–4%), they are clinically significant due to their potential for early hematogenous spread, often presenting with metastasis at diagnosis, emphasizing the need for early and accurate detection [44, 45] (Fig. 12.6).

Yolk Sac Tumor

Yolk sac tumors (YSTs), also known as endodermal sinus tumors, are malignant germ cell neoplasms that primarily arise in the gonads but can also occur in extragonadal locations such as the mediastinum, retroperitoneum, and even the liver. These tumors are most commonly diagnosed in children and young adults, with a median age of diagnosis around 19 years. YSTs are characterized by their aggressive growth and a high potential for metastasis, often spreading via lymphatic and hematogenous routes. Histologically, yolk sac tumors exhibit a variety of patterns, including the endodermal sinus or pseudopapillary pattern: lacelike (reticular) network of medium-sized cuboidal or flattened cells. A distinctive feature is the presence of Schiller-Duval bodies, which are glomerular-like structures found in approximately 20% of cases, though their presence is not essential for diagnosis. The tumor cells typically express alpha-fetoprotein (AFP), which serves as a critical tumor marker for diagnosis and monitoring treatment response [46, 47] (Fig. 12.7).

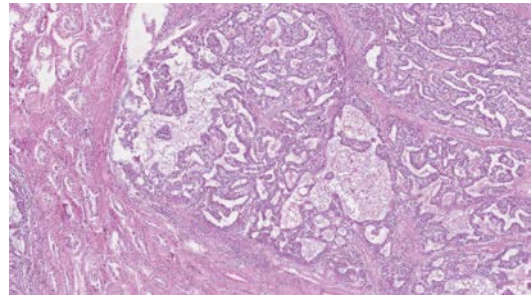


Fig. 12.7 Microscopically, the yolk sac tumor exhibits pseudopapillary characteristics and localized cystic regions

Choriocarcinoma

Choriocarcinoma is a highly malignant tumor that arises from trophoblastic tissue and can be either gestational (GC) or nongestational (NGC) in origin. Histologically, it is characterized by anaplastic cytotrophoblasts and syncytiotrophoblasts without chorionic villi, and it produces high levels of human chorionic gonadotropin (hCG). It spreads rapidly via the bloodstream and can present with metastases in the lungs, liver, or brain. The tumor is often hemorrhagic and necrotic, and pathology may be confirmed through biopsy and immunohistochemical staining for hCG. Choriocarcinoma can also appear in unusual extragonadal locations such as the lung, brain, gastrointestinal tract, and breast, often mimicking other malignancies and complicating diagnosis [48, 49].

Teratoma

Teratomas are germ cell tumors that can contain a variety of tissues, including hair, muscle, fat, and sometimes even more complex structures like teeth and bone. These tumors can arise in the as well as in extragonadal sites such as the mediastinum, sacrococcygeal region, and retroperitoneum. The “prepubertal type” of pure teratoma is relatively prevalent in neonates and children. In neonates and children, teratomas are the second most common germ cell tumor after yolk sac tumors. In adults, pure teratomas are rare, comprising merely 2–3% of germ cell tumors. Teratomas are more frequently encountered in combination with other types of tumors, such as embryonal carcinoma or yolk sac tumor. Molecular studies have shown that postpubertal malignant teratomas often exhibit cytogenetic abnormalities like isochromosome 12p, a marker of malignant germ cell tumors. Postpubertal adult teratomas are typically considered malignant, irrespective of the presence of immature components. Non-germ cell cancers may infrequently develop within teratomas, a condition known as teratoma with somatic-type malignancy. Examples of such neoplasms include squamous cell carcinoma originating from squamous epithelium, adenocarcinoma derived from glandular epithelium, osteosarcoma arising from bone tissue, and various sarcomas [50–53] (Fig. 12.8).

12.7.2 Non-germ Cell Tumors (Stromal Tumors)

Sertoli Cell Tumors

Sertoli cell tumors comprise 1–2% of all testicular tumors. They can be found at any age but mainly from the fetus to middle age. These tumors typically present as painless, slow-growing testicular masses and are often benign, though about 10% may behave malignantly. Characteristics of malignancy in SCT encompass extratesticular dissemination, size exceeding 5 cm, pronounced cytologic atypia, more than five mitotic figures per ten high-power fields, necrosis, or lymphovascular invasion. Histologically, they are characterized by tubular or trabecular patterns of bland epithelial-like cells and may show features like “coffee bean” nuclei or stromal sclerosis depending on the subtype. Subtypes include classic, large-cell calcifying, and sclerosing variants, each with different clinical and prognostic features [54, 55].

Leydig Cell Tumors

Leydig cell tumors (LCTs) are rare sex cord-stromal tumors of the testis, accounting for 1–3% of all testicular neoplasms. They commonly occur in men aged 30–60 but can also be found in children, where they are almost always benign, usually unilateral, rarely 3% bilateral. LCTs often present as painless testicular masses and

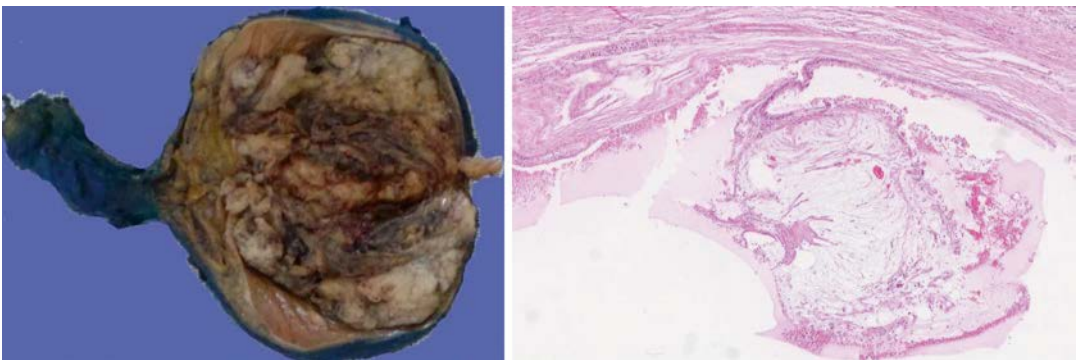


Fig. 12.8 This figure illustrates a macroscopically heterogeneous mass of a mixed germ cell tumor, with a teratomatous component observed microscopically in certain

regions of the gross section. Teratomatous component exhibiting mucinous epithelium and mucin synthesis observed

may be associated with hormonal symptoms such as gynecomastia or precocious puberty due to estrogen or androgen secretion. Histologically, LCTs consist of large polygonal cells with eosinophilic cytoplasm and round nuclei. They are typically positive for markers like inhibin, WT1, calretinin, and Melan-A and do not express germ cell markers such as OCT4. Although 90% of adult LCTs are benign, about 10–20% can be malignant in adults, identified by features such as size >5 cm, necrosis, mitotic activity, vascular invasion, and nuclear atypia [56, 57].

12.8 Other Tumors of the Testis

12.8.1 Mesothelial

Mesothelial tumors of the testis, primarily malignant mesothelioma, arise from mesothelial cells lining the tunica vaginalis and are often linked to asbestos exposure and extremely rare neoplasia (0.3–5%). Patients may present with scrotal swelling, pain, and possibly hydrocele. These tumors typically appear as firm, lobulated masses and require a high index of suspicion for diagnosis, which is confirmed through imaging, cytological analysis, and histopathological examination following surgical resection. Management of mesothelial tumors is challenging due to their aggressive nature. Surgical treatment, such as radical orchiectomy, is the primary approach, often followed by chemotherapy or radiation, depending on the tumor's grade and stage [58].

12.8.2 Adenomatoid Tumors and Adenocarcinoma of Rete Testis (Epididymis)

Adenomatoid tumor is a benign tumor that originates from the mesothelial tissue, typically located in the epididymis and well-defined, the benign paratesticular tumor that is most frequently encountered, and comprises approximately one-third of all paratesticular tumors and 60% of benign paratesticular tumors [59]. Primary adenocarcinoma of the collecting ducts

and rete testis is a rare, aggressive neoplasm that is characterized by an aggressive clinical behavior and is derived from the epithelium of the rete testis. The differential diagnosis includes mesothelioma, metastatic adenocarcinoma, and germ cell malignancies, among other entities and is an exclusionary diagnosis. Histopathologic examinations frequently reveal a diverse array of architectural patterns, such as complex tubulopapillary, glandular, solid, and cribriform [60].

12.8.3 Testicular Lymphoma and Plasmacytoma

In lymphoma and plasmacytoma, the testicular parenchyma is partially or completely replaced by a diffuse or lobulated mass. Tan, pale yellow, or slightly pink homogeneous cut surface that is fleshy and creamy in color. As a primary lymphoma that affects the testis, diffuse large B-cell lymphoma is the most prevalent. Tumoral and intratubular replacement are also possible. Effacement and infiltration of seminiferous tubules by lymphoma may be noticed. Other lymphomas include follicular, extranodal NK/T-cell, anaplastic large cell, Burkitt, and plasmablastic lymphoma, as well as MALT. Neoplastic plasma cells that are monomorphic and variably differentiated are the hallmarks of plasmacytoma. Three testicular tumors—malignant lymphoma, spermatocytic seminoma, and metastatic tumors—occur in patients aged 50–60. Only 2–5% of all testicular neoplasms are malignant lymphoma. Secondary involvement is more common than primary lymphoma. The primary plasmacytoma of the testis is exceedingly uncommon. Secondary plasmacytoma is diagnosed in up to 2% of patients with multiple myeloma during autopsy, although it is typically undetected clinically [61–63] (Fig. 12.9).

12.8.4 Metastatic Carcinoma

Testicular metastatic carcinomas are rare and only recorded in autopsy series or case reports. Metastatic tumors in the testis are frequently uni-



Fig. 12.9 Gross specimen of the testis showing diffuse infiltration by lymphoma. The testis is markedly enlarged, and the cut surface demonstrates a homogeneous tan-white appearance with areas of hemorrhage and focal necrosis. The normal architecture of the testicular parenchyma is completely effaced. The tumor appears well circumscribed but infiltrative, involving the tunica albuginea and potentially extending into the epididymis and spermatic cord. This gross morphology is characteristic of testicular involvement by non-Hodgkin lymphoma, most commonly diffuse large B-cell lymphoma (DLBCL)

lateral and solitary and may exhibit growth patterns and cytological features similar to original testicular cancers. When there is no history of a primary tumor elsewhere, it makes diagnosis difficult. About 50% of testis metastatic carcinomas are caused by metastatic prostatic adenocarcinoma, which is followed by colorectal and renal cell carcinomas [64].

References

1. Siegmund SE, Mehra R, Acosta AM. An update on diagnostic tissue-based biomarkers in testicular tumors. *Hum Pathol.* 2023;133:32–55.
2. Henriques D, Mota Pinto A, Donato H, Leão R. Prevalence and management of incidental testicular masses-a systematic review. *J Clin Med.* 2022;11:5770.
3. Mega Obukohwo O, Eze Kingsley N, Arientare Rume R, Victor E. The concept of male reproductive anatomy. In: *Male reproductive anatomy.* London: IntechOpen; 2022.
4. Li L, Lin W, Wang Z, et al. Hormone regulation in testicular development and function. *Int J Mol Sci.* 2024;25:5805.
5. Kutsal C, Baloglu İH, Albayrak AT. Hydrocele accompanying testicular cavernous hemangioma: a infant case report. *Int J Surg Case Rep.* 2021;82:105844.
6. Sosnowska-Sienkiewicz P, Januszkiewicz-Lewandowska D, Mańkowski P. Testicular and scrotal abnormalities in pediatric and adult patients. *Pol Przegl Chir.* 2023;96:88–96.
7. Kantarci F, Mihmanli İ, MacLennan GT. Neoplasms of the spermatic cord and testicular adnexae. In: *Genitourinary radiology: male genital tract, adrenal and retroperitoneum.* London: Springer; 2013. p. 95–105.
8. Toppari J, Virtanen HE, Main KM, Skakkebaek NE. Cryptorchidism and hypospadias as a sign of testicular dysgenesis syndrome (TDS): environmental connection. *Birth Defects Res A Clin Mol Teratol.* 2010;88:910–9.
9. Yazici S, Del Biondo D, Napodano G, et al. Risk factors for testicular cancer: environment, genes and infections-is it all? *Medicina (Kaunas).* 2023;59. <https://doi.org/10.3390/medicina59040724>.
10. Huang J, Chan SC, Tin MS, et al. Worldwide distribution, risk factors, and temporal trends of testicular cancer incidence and mortality: a global analysis. *Eur Urol Oncol.* 2022;5:566–76.
11. Tateo V, Thompson ZJ, Gilbert SM, et al. Epidemiology and risk factors for testicular cancer: a systematic review. *Eur Urol.* 2025;87:427–41.
12. Hadziselimovic F. On the descent of the epididymo-testicular unit, cryptorchidism, and prevention of infertility. *Basic Clin Androl.* 2017;27:21.
13. Chung JM, Lee SD. Individualized treatment guidelines for postpubertal cryptorchidism. *World J Mens Health.* 2015;33:161–6.
14. Wampler SM, Llanes M. Common scrotal and testicular problems. *Prim Care.* 2010;37:613–26, x.
15. Huzaifa M, Moreno MA. Hydrocele. In: *StatPearls.* Treasure Island (FL): StatPearls Publishing; 2025.
16. Yu YD, Hong YK. A case of cryptorchidism with ipsilateral congenital unilateral absence of the Vas deferens and contralateral renal agenesis. *Case Rep Urol.* 2016;2016:2379793.
17. Pirgon Ö, Dündar BN. Vanishing testes: a literature review. *J Clin Res Pediatr Endocrinol.* 2012;4:116–20.
18. Civelli VF, Heidari A, Valdez MC, et al. A case of testicular granulomatous inflammation mistaken for malignancy: tuberculosis identified post orchiectomy. *J Investig Med High Impact Case Rep.* 2020;8:2324709620938947.
19. Das A, Batabyal S, Bhattacharjee S, Sengupta A. A rare case of isolated testicular tuberculosis and review of literature. *J Family Med Prim Care.* 2016;5:468–70.
20. Norton SM, Saies A, Browne E, et al. Outcome of acute epididymo-orchitis: risk factors for testicular loss. *World J Urol.* 2023;41:2421–8.
21. Gebreselassie KH, Berhanu E, Akkasa SS, Woldehawariat BY. Torsed spermatocele, a rare cause of acute scrotum: report of a case and review of literature. *Urol Case Rep.* 2022;45:102172.

22. Spermatocoele. <https://www.pathologyoutlines.com/topic/testisspermatocoele.html>. Accessed 25 May 2025.
23. Mohammed A, Chinegwundoh F. Testicular varicocele: an overview. *Urol Int*. 2009;82:373–9.
24. Park YW, Lee JH. Varicocele secondary to spermatic cord hematoma related to blunt trauma. *Urogenit Tract Infect*. 2020;15:79–82.
25. Riaz-Ul-Haq M, Mahdi DEA, Elhassan EU. Neonatal testicular torsion; a review article. *Iran J Pediatr*. 2012;22:281–9.
26. Hosokawa T, Tanami Y, Sato Y, Oguma E. Point-of-care ultrasonography for the diagnosis and manual detorsion of testicular torsion. *J Med Ultrason* (2001). 2024;51:59–70.
27. Schick MA, Sternard BT. Testicular torsion. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; 2025.
28. Bhardwaj R, Chakravarthy S, Misra S. Testicular torsion: successful management of a late-diagnosed case. *Cureus*. 2021;13:e16845.
29. Xavier R, de Carvalho RC, Fraietta R. Semen quality from patients affected by seminomatous and non-seminomatous testicular tumor. *Int Braz J Urol*. 2021;47:495–502.
30. Gilligan T, Lin DW, Adra N, et al. NCCN guidelines® insights: testicular cancer, version 2.2025. *J Natl Compr Cancer Netw*. 2025;23. <https://doi.org/10.6004/jnccn.2025.0018>.
31. Berney DM, Cree I, Rao V, et al. An introduction to the WHO 5th edition 2022 classification of testicular tumours. *Histopathology*. 2022;81:459–66.
32. Saab MM, Hegarty J, Landers M. Testicular awareness: the what, the why, and the how. *Int J Men's Soc Community Health*. 2019;2:e1–e10.
33. Katabathina VS, Vargas-Zapata D, Monge RA, et al. Testicular germ cell tumors: classification, pathologic features, imaging findings, and management. *Radiographics*. 2021;41:1698–716.
34. Rajpert-De Meyts E, Aksglaede L, Bandak M, et al. Testicular cancer: pathogenesis, diagnosis and management with focus on endocrine aspects. In: *Endotext*. South Dartmouth (MA): MDText.com, Inc.; 2000.
35. Latini JM, Faerber GJ, Schuster TG, Roberts WW. Urology. In: *Clinical men's health*. Philadelphia: Elsevier; 2008. p. 278–320.
36. Skotheim RI, Autio R, Lind GE, et al. Novel genomic aberrations in testicular germ cell tumors by array-CGH, and associated gene expression changes. *Cell Oncol*. 2006;28:315–26.
37. Kumar V, Abbas AK, Aster JC. Robbins basic pathology. Moscow: OOO “GEOTAR-Media” Publishing Group; 2022. p. 1–1136.
38. Pinto MT, Cárcano FM, Vieira AGS, et al. Molecular biology of pediatric and adult male germ cell tumors. *Cancers (Basel)*. 2021;13:2349.
39. Litchfield K, Summersgill B, Yost S, et al. Whole-exome sequencing reveals the mutational spectrum of testicular germ cell tumours. *Nat Commun*. 2015;6:5973.
40. Lobo J, Jerónimo C, Henrique R. Cisplatin resistance in testicular germ cell tumors: current challenges from various perspectives. *Cancers (Basel)*. 2020;12:1601.
41. Gilligan T, Lin DW, Adra N, Bagrodia A, Feldman DR, Yamoah K, Aggarwal R, Chandrasekar T, Costa D, Drakaki A, Eggener S, Enamekhoo H, Geynisman DM, Graham L, Humphrey P, Leuva H, Levine EG, Luckenbaugh A, Maughan BL, McGregor B, Monk P, Picus J, Pierorazio P, Rais-Bahrami S, Reichert Z, Rwigema JC, Saylor P, Shah A, Shah S, Singla N, Sircar K, VanderWeele D, Zhumkhawala A, Montgomery S, Sliker B. NCCN guidelines® insights: Testicular Cancer, Version 2.2025. *J Natl Compr Cancer Netw* [Internet]. National Comprehensive Cancer Network; 2025 Apr 1 [cited 2025 May 27];23(4). Available from: <https://jnccn.org/view/journals/jnccn/23/4/article-e250018.xml> PMID: 40203876
42. Nicol D, Berney DM, Boormans JL, Di Nardo D, Fankhauser CD, Fischer S, Gremmels H, Cornes R, Heidenreich A, Leão R, Nicolai N, Oing C, Patrikidou A, Tandstad T, Papachristofilou A, Haugnes HS. EAU Guidelines on Testicular Cancer. (2025, April 1) <https://d56bochlfluxqz.cloudfront.net/documents/full-guideline/EAU-Guidelines-on-Testicular-Cancer-2025.pdf>
43. Secondino S, Viglio A, Neri G, et al. Spermatocytic tumor: a review. *Int J Mol Sci*. 2023;24. <https://doi.org/10.3390/ijms24119529>.
44. Jagtap S, Bisht T, Jagtap S, Huddedar A. Pure embryonal carcinoma of testis presenting with extensive metastasis. *Int J Med Sci Public Health*. 2015;4:145.
45. Kao C-S, Ulbright TM, Young RH, Idrees MT. Testicular embryonal carcinoma: a morphologic study of 180 cases highlighting unusual and unemphasized aspects. *Am J Surg Pathol*. 2014;38:689–97.
46. Mushtaq K, Khan MU, Al Soub D, et al. Metastatic yolk sac tumor masquerading as multifocal hepatocellular carcinoma in a young adult: a case report. *Clin Case Reports*. 2023;11:e6861.
47. Song L, Wei X, Wang D, et al. Primary yolk sac tumor originating from the endometrium: a case report and literature review. *Medicine (Baltimore)*. 2019;98:e15144.
48. Xusheng Z, Yuke Y, Yun M, et al. Primary gastric choriocarcinoma: a case report. *Front Surg*. 2022;9:1009119.
49. Lei N, Lei L-L, Wang C-H, Mei C-R. Pure testicular choriocarcinoma, a rare and highly malignant subtype with challenging treatment: a case report and review of the literature. *Mol Clin Oncol*. 2024;20:1.
50. Harms D, Zahn S, Göbel U, Schneider DT. Pathology and molecular biology of teratomas in childhood and adolescence. *Klin Padiatr*. 2006;218:296–302.
51. Yoon HM, Byeon S-J, Hwang J-Y, et al. Sacrococcygeal teratomas in newborns: a comprehensive review for the radiologists. *Acta Radiol*. 2018;59:236–46.

52. Moraru L, Mitranovici M-I, Chiorean DM, et al. Immature teratoma: diagnosis and management-a review of the literature. *Diagnostics (Basel)*. 2023;13. <https://doi.org/10.3390/diagnostics13091516>.
53. Hwang MJ, Hamza A, Zhang M, et al. Somatic-type malignancies in testicular germ cell tumors: a clinicopathologic study of 63 cases: a clinicopathologic study of 63 cases. *Am J Surg Pathol*. 2022;46:11–7.
54. Allameh F, Alinejad Khorram A, Hojjati SA, Rastian N. Sertoli cell tumor in patient with multiple intratesticular cysts. *Urol Case Rep*. 2022;44:102153.
55. Terayama K, Hirokawa M, Shimizu M, et al. Sertoli cell tumor of the testis. Report of a case with imprint cytology findings. *Acta Cytol*. 1998;42:1458–60.
56. Kim I, Young R, Scully R. Leydig cell tumors of the testis: a clinicopathological analysis of 40 cases and review of the literature. *Am J Surg Pathol*. 1985;9:177–92.
57. Geminiani JJ, Marshall SD, Ho TS, Brandes SB. Testicular Leydig cell tumor with metachronous lesions: outcomes after metastasis resection and cryo-ablation. *Case Rep Urol*. 2015;2015:748495.
58. Chekol SS, Sun C-C. Malignant mesothelioma of the tunica vaginalis testis: diagnostic studies and differential diagnosis. *Arch Pathol Lab Med*. 2012;136:113–7.
59. Amin W, Parwani AV. Adenomatoid tumor of testis. *Clin Med Pathol*. 2009;2:17–22.
60. Tian Y, Yao W, Yang L, et al. Primary adenocarcinoma of the rete testis: a case report and review of the literature. *Oncol Lett*. 2014;7:455–7.
61. Mooney KL, Kao C-S. A contemporary review of common adult non-germ cell tumors of the testis and paratestis. *Surg Pathol Clin*. 2018;11:739–58.
62. Khan M, Rajarubendra N, Azer S, et al. Plasmacytoma of the testis in a patient with relapsed and refractory multiple myeloma: case report and review of the literature. *Urol Ann*. 2015;7:530–3.
63. Alnemer M, Felemban JM, Mansoor A, Butt SA. Primary testicular lymphoma mimicking germ-cell tumor: a case report. *Cureus*. 2023;15:e48990.
64. Wang G. Metastatic carcinoma to the testis – a mini review. *J Rare Dis Res Treat*. 2019;4:16–22.

Nonneoplastic Diseases of the Kidney

13

Gulden Diniz , Funda Taşlı, and Emel Yaldir

13.1 Introduction

Renal diseases are broadly classified according to their clinical syndromes, and the compartment is predominantly affected. Despite diverse etiologies, the histopathological response of the kidney is limited, necessitating careful correlation of clinical findings, laboratory data, and morphological evaluation using light microscopy, immunofluorescence, and electron microscopy. Renal biopsy remains the cornerstone of diagnosis, and adequate sampling is essential. The adequacy of material depends on the disease. For example, in conditions diffusely affecting glomeruli, a biopsy containing a single glomerulus may be sufficient for diagnosis, whereas in lesions with focal and segmental involvement, even ten glomeruli may be inadequate. However, 8–10 glomeruli are generally required to evaluate severity and distribution of disease [1].

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13.2 Structure of the Glomerulus

During nephron development, the metanephros appears as a blind-ending tubule lined by a single layer of cuboidal epithelium. Dilation of one end allows invagination of a capillary tuft, thereby forming the glomerulus. The epithelial cells drawn in during invagination form the podocyte layer. The epithelial cells covering the glomerular capillaries are called podocytes because of their thin footlike projections. Together with the endothelial basement membrane, they form the glomerular basement membrane (GBM). Connective tissue trapped during invagination remains as supporting tissue, composed of mesangial cells and matrix, termed the mesangium. EM enables clear identification of podocytes, endothelial cells, and mesangial cells (Fig. 13.1). The average diameter of the glomeruli is 200 μm ; juxtamedullary glomeruli are about 20% larger. Mesangial cells, of mesenchymal origin, are contractile and phagocytic with proliferative capacity and secrete bioactive mediators. They contain α -smooth muscle actin and myosin, resembling pericytes and vascular smooth muscle cells. Visceral epithelial cells (podocytes), located on the urinary side of the GBM, synthesize basement membrane components. Their foot processes embed into the lamina rara externa. Between foot processes (pedicels) are filtration slits 20–30 nm wide, bridged by a thin diaphragm. Within these slit diaphragms, transmembrane proteins called

Fig. 13.1 Structure of glomerulus

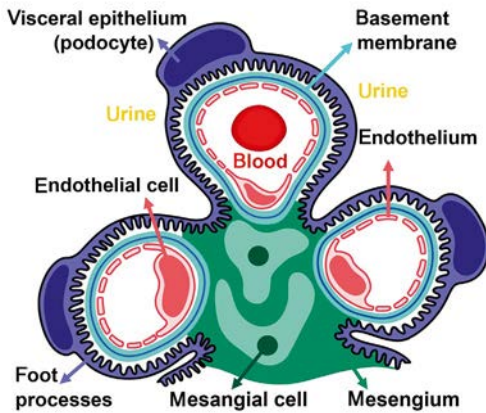
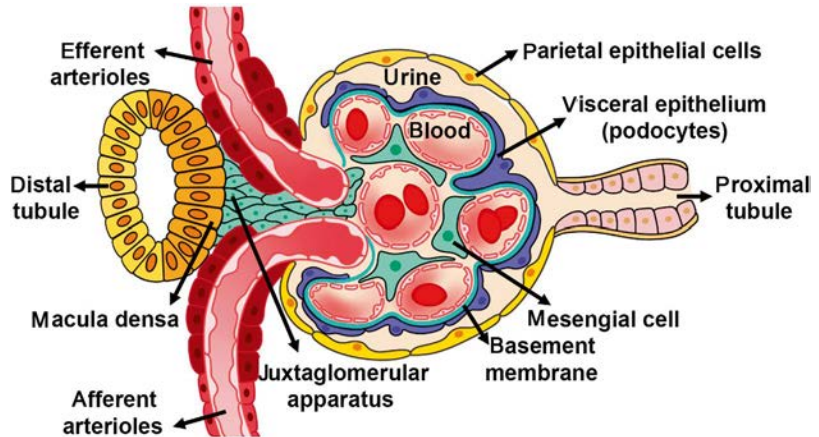


Fig. 13.2 Glomerular filtration barrier

nephrin extend; their extracellular domains resemble immunoglobulin-like adhesion molecules mediating cell-cell and cell-matrix interactions, while intracellularly, they associate with podocin, CD2-associated protein, and actin. This complex allows passage of water and small molecules but acts as a critical barrier to proteins. Podocytes are keratin negative but positive for vimentin and desmin, whereas the flat parietal epithelial cells lining Bowman's capsule are keratin positive [1, 2] (Fig. 13.2).

13.3 Molecular Basis of the Glomerular Basement Membrane (GBM)

The basement membrane provides mechanical support for proliferating cells and serves as a semipermeable, electrochemical, and structural barrier between tissue compartments. Its main components are type IV collagen, laminin, fibronectin, nidogen (entactin), polyanionic proteoglycans rich in heparan sulfate, and other glycoproteins. Under EM, basement membranes show two amorphous layers: lamina lucida and lamina densa. However, in some basement membranes such as the GBM, cells are present on both sides. In other words, the GBM is formed by the fusion of the endothelial and epithelial basement membranes. This creates a three-layered structure with a central electron-dense zone (lamina densa) flanked by two electron-lucent layers, the lamina rara externa and interna. Due to the unique three-layered shape of the glomerular basement membrane and its greater thickness than the basement membranes of the renal tubular epithelium, the basement membrane within the glomerulus is clearly visible in kidney biopsies. Type IV collagen forms the backbone of the GBM. Six

different α chains ($\alpha 1$ – $\alpha 6$, encoded by COL4A1–COL4A6) assemble into triple-helical protomers. The most frequent combinations are $\alpha 1.1.2/\alpha 1.1.2$ in all basement membranes; $\alpha 3.4.5/\alpha 3.4.5$ in the GBM, some tubular basement membranes, cochlea, eye, lung, and testis; and $\alpha 1.1.2/\alpha 5.5.6$ in the skin, smooth muscle, and Bowman's capsule. At their N-terminus, protomers contain a 7S domain, while their C-terminus carries a globular NC1 trimer (Fig. 13.3). Glycoproteins such as laminin and entactin, and acidic proteoglycans like heparan sulfate and perlecan, attach to this collagen network. The NC1 domain plays a crucial role in collagen network assembly and attachment of other components. The $\alpha 3\alpha 4\alpha 5$ network

predominates in the GBM, and mutations lead to hereditary diseases such as Alport syndrome and thin basement membrane nephropathy. The NC1 domain of collagen IV is critical for network assembly and represents the target of pathogenic autoantibodies in anti-GBM disease [2–4].

13.4 Development and Structure of the Nephrons

Each functional unit of the kidney, composed of the renal corpuscle (glomerulus) and renal tubules, is called a nephron (Fig. 13.4). The nephron is the basic structural and functional unit of the kidney. They are responsible for the processes of filtration, reabsorption, secretion, and excretion that maintain fluid and electrolyte balance. The proximal end of each nephron forms Bowman's cap-

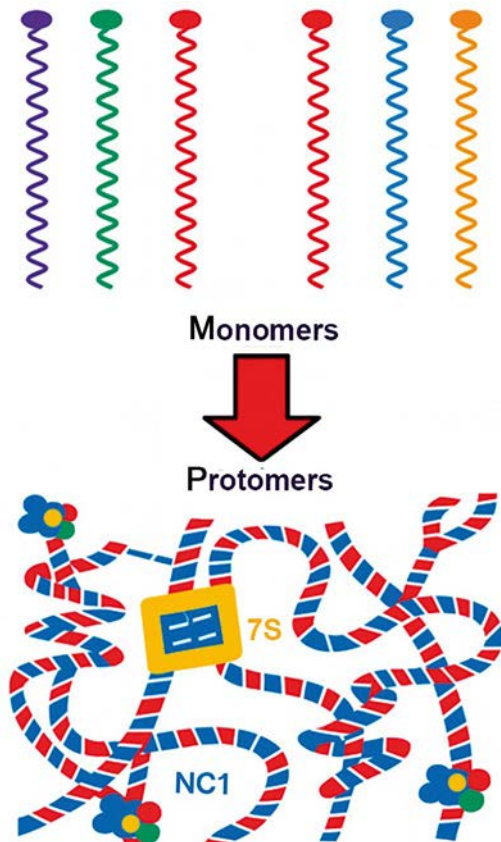


Fig. 13.3 Structure of collagen

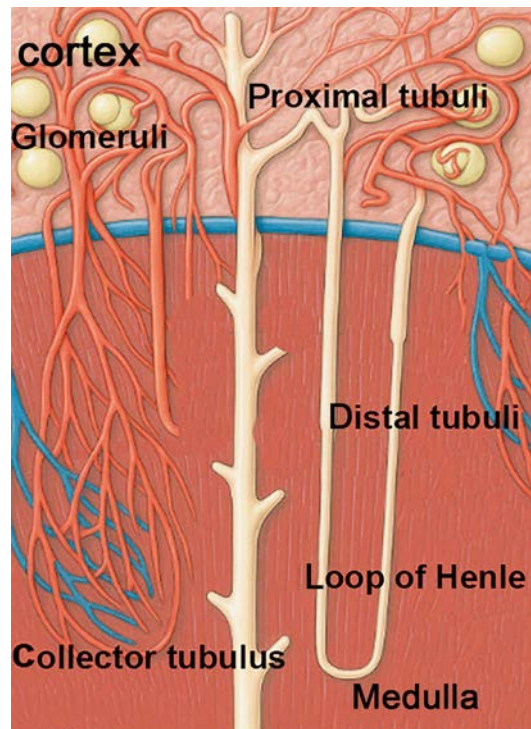


Fig. 13.4 Structure of the nephron

sule, deeply indented by the glomerulus, while the distal end connects to a collecting duct. Continued elongation of the excretory tubules gives rise to the proximal convoluted tubules, loop of Henle, and distal convoluted tubules. The excretory unit of the urinary system derives from the metanephric mesoderm, whereas the collecting system originates from the ureteric bud, an outgrowth of the Wolffian duct. Nephrons are sufficiently mature to produce urine by the tenth gestational week, and by 12–14 weeks, they can excrete sodium and concentrate urea. By the end of the first trimester, the fetus begins to pass urine, which at this stage is essentially an ultrafiltrate of plasma. From the fourth month onward, amniotic fluid is almost entirely composed of fetal urine. Swallowed amniotic fluid is absorbed in the gastrointestinal tract, enters the fetal circulation, is filtered by the kidneys, and returns to the amniotic cavity. In the second trimester, tubular reabsorption is still immature, resulting in a high urine volume. Urine production increases progressively throughout gestation, but near term, improved tubular reabsorption of water and salts leads to a slight decline in urine output. During intrauterine life, the placenta, rather than the kidneys, serves as the major excretory organ. The primary role of the fetal kidney is to produce amniotic fluid, which is essential for fetal lung development. By 34–36 weeks, nephron development is complete, and each newborn kidney contains over one million nephrons. At birth, kidneys weigh about 25 g, compared to ~300 g in adults. A term infant's kidney contains only about 17% of the adult number of cells. DNA synthesis continues for 6 months postnatally, after which renal growth occurs mainly by cellular hypertrophy rather than proliferation. At birth, kidneys are lobulated; this lobulation gradually disappears during infancy as nephrons continue to enlarge [5, 6].

13.5 Early Development of the Kidneys

The first excretory system is called the pronephros (pronephric system), which develops from the dorsal mesenchyme during the third week of

gestation. This cord-like structure soon canalizes into a tubular form and connects distally to the cloaca. In primitive vertebrates, the pronephros functions as the kidney, whereas in the human embryo, it is a rudimentary structure that persists until the fourth gestational week. Its function in humans is poorly understood. Since the earliest nephrotomes regress before caudal ones appear, all traces of the pronephric system disappear by the end of the fourth week. From the fourth week onward, the mesonephros (mesonephric or Wolffian system) develops from specialized mesenchyme of the intermediate mesoderm, known as nephrostomes or nephrotomes. On either side of the midline, a cord-like structure forms the mesonephros, which rapidly canalizes into the mesonephric duct and connects to the distal segment of the pronephric system. The mesonephros can persist until the eighth gestational week and may function transiently. By the end of the second month, however, most of it has regressed completely. Although temporary, the mesonephros plays a critical role in the development of the urinary system. Disturbances in its development can lead to various congenital urinary anomalies, highlighting its importance in embryogenesis. The third and final urinary organ, the metanephros (metanephric system, or permanent kidney), appears in the fifth week. The ureteric bud penetrates the metanephric mesenchyme, initiating the inductive interactions necessary for the blastema to differentiate into the permanent kidney. In turn, the metanephric mesenchyme stimulates the ureteric bud to branch and form the collecting system. If the ureteric bud fails to establish contact with the metanephric blastema, the blastema cannot differentiate into a permanent kidney. Thus, the reciprocal interaction between the ureteric bud and metanephric tissue is fundamental to normal renal development. Following penetration, the ureteric bud expands and branches progressively, ultimately giving rise to the ureter, renal pelvis, calyces, and collecting ducts. Simultaneously, the metanephric mesenchyme differentiates into the excretory units of the nephron [5, 6].

13.6 Congenital Anomalies of the Kidney

The development of the metanephros depends on precise reciprocal signaling between the ureteric bud and metanephric blastema. Any disruption in this process can give rise to a wide spectrum of anomalies, ranging from agenesis to dysplastic kidneys. Recognition of these developmental disorders is important in neonatology, pediatrics, and nephrology, since their impact may vary from incidental findings to life-threatening conditions. Renal agenesis occurs when the ureteric bud fails to develop or does not establish contact with the metanephric blastema. Unilateral agenesis is usually asymptomatic and discovered incidentally, whereas bilateral agenesis results in oligohydramnios and pulmonary hypoplasia and is incompatible with life, a condition known as Potter sequence. Renal hypoplasia refers to kidneys that are present but smaller in size and contain fewer nephrons, usually less than half the normal number. It may affect one kidney or both. An ectopic kidney develops when normal ascent fails, leaving the kidney in the pelvis or lower abdomen. Although often asymptomatic, this anomaly can predispose to obstruction or infection. A horseshoe kidney forms when the lower poles of both kidneys fuse during ascent. The fused organ becomes trapped beneath the inferior mesenteric artery and remains lower than normal. While frequently asymptomatic, it is associated with an increased risk of kidney stones, hydronephrosis, and certain genetic syndromes, including Turner syndrome and trisomy 18. Duplications of the collecting system result from early branching of the ureteric bud. This may produce double ureters or a bifid pelvis. A multicystic dysplastic kidney develops due to abnormal interaction between the ureteric bud and the metanephric mesenchyme. The normal renal parenchyma is replaced by nonfunctioning cysts. This condition is often unilateral but can occasionally be bilateral, leading to renal failure in infancy [6].

13.7 The Role of Complement System in Renal Diseases

Complement levels are of great importance in the differential diagnosis of renal diseases. The complement system is an ancient defense mechanism, composed of more than 30 proteins, most of which are enzymes, circulating in plasma in inactive form and activated upon encountering pathogens. Despite its evolutionary antiquity, it plays a crucial role in modern immune defense. Complement activation occurs through three main pathways: the classical pathway, triggered by antigen-antibody complexes (particularly IgG and IgM binding to C1q); the alternative pathway, activated directly by microbial lipopolysaccharides, cobra venom, or endotoxin-like molecules; and the lectin pathway, initiated by mannose-binding lectin (MBL) or C-reactive protein binding to microbial carbohydrate structures. All three converge on the cleavage of C3 into C3a and C3b. The early phase culminates in formation of C3 convertase, while the late phase activates C5 and downstream components C6–C9, forming the membrane attack complex (MAC), which creates pores in microbial membranes and leads to cell lysis. The biological functions of the complement system include inflammation (via anaphylatoxins C3a, C5a), opsonization (facilitating phagocytosis of encapsulated bacteria), and direct cytolysis through MAC formation. Deficiency in complement proteins predisposes to recurrent bacterial infections, especially with encapsulated organisms such as *Neisseria* species. Hepatocytes are the major site of synthesis, but production also occurs in monocytes/macrophages, endothelial cells, fibroblasts, adipocytes, and even neurons. Tight regulation is essential, as uncontrolled activation is detrimental. Plasma inhibitors include C1 inhibitor (C1-INH), which prevents spontaneous classical pathway activation. Its deficiency results in hereditary angioedema, characterized by recurrent swelling and inflammation, reversible with C1-INH replacement. Cell surface regulators

such as decay accelerating factor (DAF/CD55) and CD59 block formation of the terminal MAC. Their deficiency underlies paroxysmal nocturnal hemoglobinuria (PNH), in which red blood cells undergo recurrent complement-mediated lysis [7, 8]. The complement system is described in detail in Volume 1, Chap. 8.

13.8 Renal Tubules and Juxtaglomerular Apparatus

Renal tubular epithelial cells vary according to their segment. Proximal tubule cells are rich in mitochondria and have long apical microvilli forming a brush border. They reabsorb nearly two-thirds of filtered sodium and water, in addition to glucose, phosphate, potassium, and proteins. The *juxtaglomerular apparatus (JGA)* is located where the afferent arteriole enters Bowman's capsule, and the distal tubule passes by the same glomerulus. It acts like a small endocrine organ. It includes juxtaglomerular (granular) cells, which contain renin granules and

secrete renin when blood pressure falls; macula densa cells of the distal tubule, which sense sodium concentration; and lacis (Polkissen) cells, thought to be extraglomerular mesangial cells. Decreased blood pressure, filtration, or sodium levels trigger macula densa signaling, which stimulates renin release and activates the renin-angiotensin-aldosterone system [5, 6].

13.9 Patterns of Glomerular Involvement

Glomerular disease is described by its distribution and extent. In focal disease, less than half of the glomeruli are affected, while in diffuse disease, most are involved. If only part of the glomerular tuft is affected, it is called segmental, and if the entire tuft is involved, it is global (Fig. 13.5). Histological injury patterns include increased cellularity, thickened basement membranes, and hyalinization or sclerosis. Hypercellularity may result from mesangial or endothelial proliferation, inflammatory infiltration, or crescent formation. Glomeruli can be damaged by many causes.

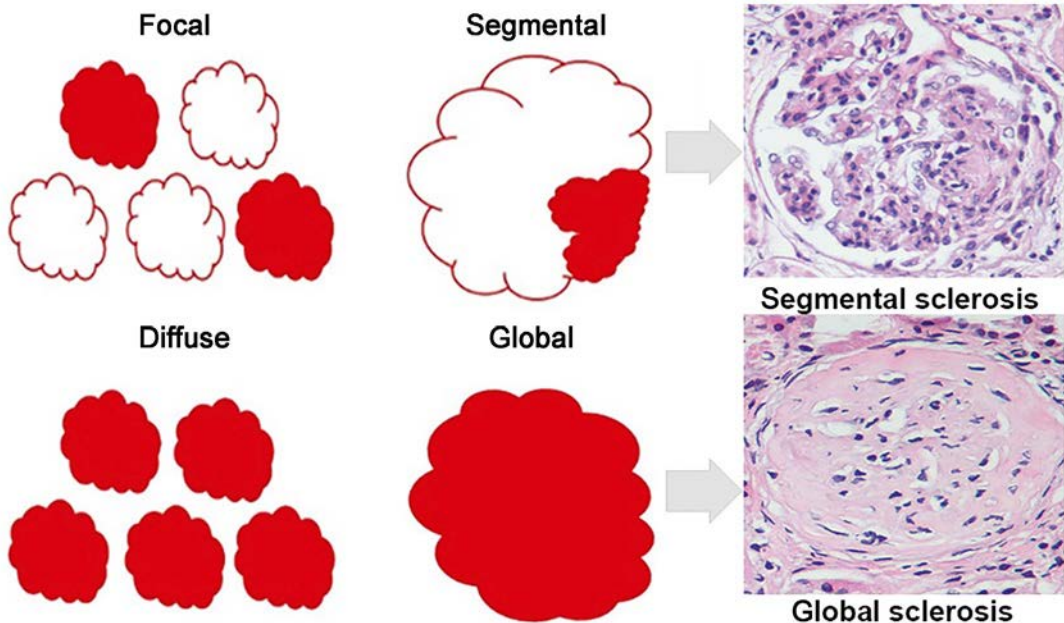


Fig. 13.5 The distribution of sclerosis in the glomeruli in the biopsy (left) and the distribution pattern in a single glomerular tuft (right)

Secondary glomerular disease occurs as part of systemic illnesses such as lupus erythematosus, hypertension, polyarteritis nodosa, diabetes mellitus, or hereditary syndromes. In primary glomerular disease, the kidney is the only organ affected, and no systemic disorder is identified. If the glomerulus is predominantly affected, the

condition is termed a glomerular disease (Table 13.1). When the interstitium or tubules are the main target, the condition is classified as tubulointerstitial disease (Table 13.2). Despite different causes, most glomerular and tubulointerstitial diseases converge to similar late-stage findings such as chronic renal failure.

Table 13.1 Glomerular diseases

Clinical syndrome	Diseases/conditions
Nephrotic syndrome (Proteinuria, hypoproteinemia, edema, hyperlipidemia, common pathology: podocyte injury)	1. Minimal change disease 2. Focal segmental glomerulosclerosis 3. Membranous glomerulonephritis 4. Membranoproliferative GN 5. Diabetic nephropathy 6. Amyloidosis 7. Other secondary causes (e.g., lupus, hepatitis B, hepatitis C, HIV, malignancy, drugs such as gold, penicillamine, NSAIDs, bisphosphonates)
Acute nephritic syndrome (Hematuria, edema, hypertension, azotemia)	1. Diffuse endocapillary proliferative GN/post-streptococcal GN 2. Membranoproliferative GN 3. Diffuse mesangioproliferative GN 4. Crescentic GN (may be idiopathic or secondary) 5. Rapidly progressive GN (RPGN): anti-GBM, ANCA-associated vasculitis, lupus nephritis
Vasculitis related	1. Polyarteritis nodosa (PAN) 2. Wegener's granulomatosis (granulomatosis with polyangiitis) 3. Churg-Strauss syndrome (eosinophilic granulomatosis with polyangiitis) 4. Cryoglobulinemia
DIC (disseminated intravascular coagulation) and hypertension related	1. Hemolytic uremic syndrome (HUS) 2. Thrombotic thrombocytopenic purpura (TTP) 3. Purpura (systemic infections, sepsis, toxemia, viral infections) 4. Benign and malignant nephrosclerosis
Pregnancy related	1. Preeclampsia (toxemia of pregnancy) 2. HELLP syndrome 3. Other pregnancy-related glomerulopathies
Hereditary glomerular diseases	1. Alport syndrome (progressive hematuria, sensorineural deafness, ocular abnormalities; X-linked or autosomal dominant/recessive) 2. Thin basement membrane nephropathy 3. Fabry disease 4. Nail-patella syndrome 5. Other rare hereditary conditions (e.g., fibrillary GN, immunotactoid GN, collagen-related disorders)

Table 13.2 Oxford Classification of IgA nephropathy (MEST-C)

Parameter	Definition	Scoring
M, mesangial hypercellularity	Average >50% of glomeruli with >4 mesangial cells per mesangial area	M0, absent; M1, present
E, endocapillary hypercellularity	Presence of increased cells within glomerular capillary lumina	E0, absent; E1, present
S, segmental glomerulosclerosis	Presence of segmental sclerosis/adhesion in any glomerulus	S0, absent; S1, present
T, tubular atrophy/interstitial fibrosis	Percent of cortical area affected	T0, 0–25%; T1, 26–50%; T2, >50%
C, crescents (added 2016)	Cellular/fibrocellular crescents in ≥1 glomerulus	C0, absent; C1, 1–24% of glomeruli; C2, ≥25%

13.10 Glomerular Diseases

In primary glomerular disease, the kidney is the only organ affected, and no systemic disorder is identified. If the glomerulus is predominantly affected, the condition is termed a glomerular disease (Table 13.1). When the interstitium or tubules are the main target, the condition is classified as tubulointerstitial disease. Despite different causes, most glomerular and tubulointerstitial diseases converge to similar late-stage findings such as chronic renal failure. There are three basic mechanisms for development of glomerular diseases. In circulating immune complex nephritis (e.g., post-streptococcal GN, SLE), antigen-antibody complexes form systemically and deposit in the glomerulus, invoking complement-mediated type III hypersensitivity injury. During in situ immune complex nephritis (e.g., anti-GBM), glomerular antigens target a type II hypersensitivity reaction. Cell-mediated injury includes complement pathway activation via alternative routes and cytotoxic T-cell-mediated damage in certain glomerulonephritis. In glomerular diseases, the glomerulus is the primary site of injury, and the location of immune complex deposits varies by disease type (Fig. 13.6). In acute glomerulonephritis, they are subepithelial (between the podocytes and the lamina rara externa). Membranous glomerulonephritis and Heymann nephritis show epimembranous deposits (within foot processes facing Bowman's

space). In SLE-associated nephritis and membranoproliferative GN, deposits are subendothelial (between capillary endothelium and lamina rara interna). IgA nephropathy features mesangial deposition, while anti-GBM disease demonstrates deposits along the basement membrane [9].

13.10.1 Glomerular Diseases Leading to Nephrotic Syndrome

Nonproliferative glomerulonephritis often manifests as nephrotic syndrome. Hallmark features are heavy proteinuria (>3.5 g/day), hypoproteinemia (<3 g/dL), and edema. In advanced stages, azotemia, hematuria, and hypertension may develop. The initial insult involves structural or physicochemical disruption of the glomerular filtration barrier, often with podocyte foot process effacement. Hypoalbuminemia activates compensatory synthesis of proteins including lipoproteins, leading to hyperlipidemia and lipiduria. Fluid shifts into the interstitium reduce glomerular filtration rate, promote aldosterone-mediated sodium and water retention, and exacerbate edema in a self-perpetuating cycle. In children, 95% of nephrotic syndrome cases are primary glomerular diseases; in adults, this figure drops to 60%, with nearly half being secondary to systemic diseases such as diabetes mellitus, SLE, or amyloidosis. In children, minimal change disease is the most common cause of nephrotic syndrome, accounting for 60–70% of cases. The incidence of other glomerular diseases, such as FSGS, membranoproliferative glomerulonephritis (MPGN), and other proliferative GNs, which lead to nephrotic syndrome is around 10% in childhood. Membranous glomerulonephritis and secondary glomerulonephritis, which lead to nephrotic syndrome, do not exceed 5% in children. Until the 2000s, the most common primary glomerular disease-causing nephrotic syndrome was known as membranous glomerulonephritis. However, today, FSGS is considered the most prevalent disease, particularly in countries with reliable health statistics, such as the United States [10, 11].

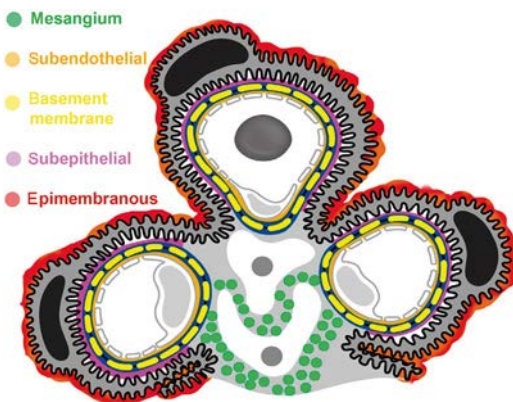


Fig. 13.6 The location of immune complex deposits according to the disease type

13.10.1.1 Minimal Change Disease (MCD)

Minimal change disease (MCD) also known as minimal change glomerulopathy, is the most common cause of nephrotic syndrome in children, typically between the ages of 2 and 6 years. In MCD, lipoproteins leak through the damaged glomerular filtration barrier and are reabsorbed by the proximal tubular cells, leading to lipid accumulation in tubular epithelium. This process manifests clinically as lipiduria, characterized by the presence of fatty casts or oval fat bodies in urine. It was first described in 1913, when intracytoplasmic lipid and protein droplets were observed in renal tubular epithelium. Based on these findings, the term “lipoid nephrosis” was coined, long before the immunopathological basis of the disease was understood. Today, the preferred term is MCD, which reflects the nearly normal appearance of glomeruli under light microscopy and the characteristic podocyte foot process effacement identified by electron microscopy. Because MCD is the most common cause of childhood nephrotic syndrome and glomeruli may appear normal under light microscopy, electron microscopy is particularly important for the diagnosis of native kidney biopsies in children. This technique allows identification of the characteristic diffuse effacement of podocyte foot processes, which is not visible on light microscopy or immunofluorescence. The male-to-female ratio in children is approximately 2–3:1, while in adults, it is equal. MCD accounts for two-thirds of idiopathic nephrotic syndrome in children and about 10–15% of cases in adults. The disease often follows upper respiratory tract infections, allergic reactions, or routine immunizations. A hallmark of MCD is its dramatic response to corticosteroid therapy. Immunologic mechanisms are believed to play a central role, as suggested by the absence of immune deposits on immunofluorescence, its association with atopic conditions, and its increased incidence in Hodgkin lymphoma. Experimental models support that T-cell-derived permeability factors may damage the glomerular basement membrane (GBM) by altering its polyanionic charge, leading to selective albuminuria. Despite massive

proteinuria, renal function is typically preserved, and hypertension or gross hematuria is uncommon. Hypercholesterolemia is frequent and complement levels remain normal. Most children achieve complete remission with corticosteroids, and even steroid-dependent cases are often resolved by adolescence. The prognosis is excellent, with progression to end-stage renal disease (ESRD) occurring in <5% of cases, usually over decades [10–13].

13.10.1.2 Focal Segmental Glomerulosclerosis (FSGS)

Focal segmental glomerulosclerosis (FSGS) is characterized by sclerosis affecting some glomeruli (focal) and involving only a portion of the affected tuft (segmental). First described in 1957 by Rich, FSGS often presents with nephrotic syndrome or heavy proteinuria. It can be idiopathic (primary) or secondary to conditions such as heroin use, HIV infection, obesity, or sickle cell disease. FSGS arises through diverse mechanisms. Primary (idiopathic) forms are often thought to result from circulating podocyte-permeability factors, while secondary FSGS are due to hyperfiltration stress (e.g., obesity, reduced nephron number), infections, drugs, or genetic mutations. Genetic FSGS associated with mutations in genes like *NPHS2* (podocin), *INF2*, *TRPC6*, and others highlights the role of podocyte structural proteins in disease susceptibility. FSGS is also the most common kidney disease associated with AIDS and may also arise in reflux nephropathy, analgesic nephropathy, or congenital nephron loss. Mutations in podocyte-associated genes (e.g., *nephrin* on 19q13, *podocin* on 1q25–31) are also implicated. Idiopathic FSGS accounts for ~10% of nephrotic syndrome in children. Although earlier estimates placed FSGS as responsible for only 10–15% of adult nephrotic syndrome cases, its incidence has risen significantly. In many developed countries today, FSGS is the leading cause of nephrotic syndrome in adults. Hematuria, reduced glomerular filtration rate, and hypertension are more common than in MCD. Proteinuria is typically nonselective. Immunofluorescence often shows IgM, C3, and fibrin deposition within sclerotic segments. Because it affects a subset of

glomeruli, biopsy sampling may miss the lesion. Histological variants include the not otherwise specified (NOS), perihilar (located in vascular pole), cellular, tip lesion variant (located near the proximal tubule) and collapsing forms. Collapsing variant is the most aggressive with poor response to therapy, while tip lesion variant is often steroid responsive with better outcomes. Primary FSGS is thought to result from circulating permeability factors, while secondary forms reflect adaptive responses to hyperfiltration injury. Spontaneous remission is rare, and corticosteroid responsiveness is limited. FSGS frequently progresses to end-stage kidney disease (ESKD); up to 50% of patients develop ESRD within 5–10 years, particularly in aggressive variants. Malignant FSGS, particularly in HIV-associated cases, progresses rapidly, sometimes causing renal failure within 2 years. Recurrence after kidney transplantation occurs in 25–50% of cases [13–17].

13.10.1.3 C1q Nephropathy

C1q nephropathy was first described in 1985 as a morphological variant of FSGS. It is defined by dominant or codominant mesangial deposition of C1q on immunofluorescence, with electron-dense mesangial deposits visible on electron microscopy. Light microscopy findings vary and may resemble MCD, FSGS, or proliferative glomerulonephritis. C1q nephropathy is seen predominantly in children and young adults, presenting with nephrotic syndrome and often impaired renal function. Unlike lupus nephritis, it occurs in the absence of serologic evidence of systemic lupus erythematosus or HIV infection. Prognosis is variable, and progression to renal insufficiency is not uncommon. Recent data suggest it may be underrecognized in adults, occurs across age groups, and can respond to targeted immunosuppressive therapies such as calcineurin inhibitors in pediatric cases [18].

13.10.1.4 Membranous Glomerulonephritis (MGN)

Membranous glomerulonephritis (MGN) is characterized by diffuse thickening of the glomerular basement membrane (GBM) due to subepithelial,

intramembranous, or occasionally subendothelial immune complex deposits, in the absence of significant mesangial proliferation or inflammatory cell infiltration. Approximately 85% of cases are idiopathic, while secondary causes include malignancies (lung, stomach, colon, and breast carcinoma, melanoma, lymphoma), autoimmune diseases such as systemic lupus erythematosus (SLE), infections (hepatitis B virus, hepatitis C virus, syphilis, schistosomiasis, malaria), certain drugs (penicillamine, captopril, NSAIDs), heavy metals (gold, mercury), and thyroiditis. MGN is seen in ~15% of patients with SLE. The pathogenesis involves chronic immune complex deposition, which may form against endogenous glomerular antigens or exogenous agents (e.g., hepatitis B virus, *Treponema*). Geographic variations exist, with higher incidence in Japan and other parts of Asia, attributed to endemic HBV infection and parasitic diseases. The absence of neutrophils and monocytes within deposits, but the presence of complement—particularly C5b-C9 membrane attack complex (MAC)—indicates complement-mediated podocyte and capillary wall injury, leading to proteinuria. Light microscopy typically reveals uniform, diffuse GBM thickening. Early cases may lack obvious LM changes, but later stages show spikelike protrusions and irregular thickening highlighted by PAS or silver stains (Fig. 13.7). Immunofluorescence demonstrates granular subepithelial deposits, predominantly IgG, often accompanied by C3; IgM and IgA may also be present in some cases. The finding of granular deposits along the GBM is pathognomonic for immune complex disease. In lupus nephritis, deposits of IgA, C1q, and C4, along with involvement of tubular basement membranes, help distinguish secondary causes. Electron microscopy shows subepithelial and intramembranous electron-dense deposits with reactive GBM changes, while mesangial deposits are rare in idiopathic MGN. Clinically, MGN is a major cause of nephrotic syndrome in adults, accounting for 20–40% of idiopathic cases, but is less common in children (1–9%). Until the 2000s, it was known as the most common cause of nephrotic syndrome in adults, but today, mem-

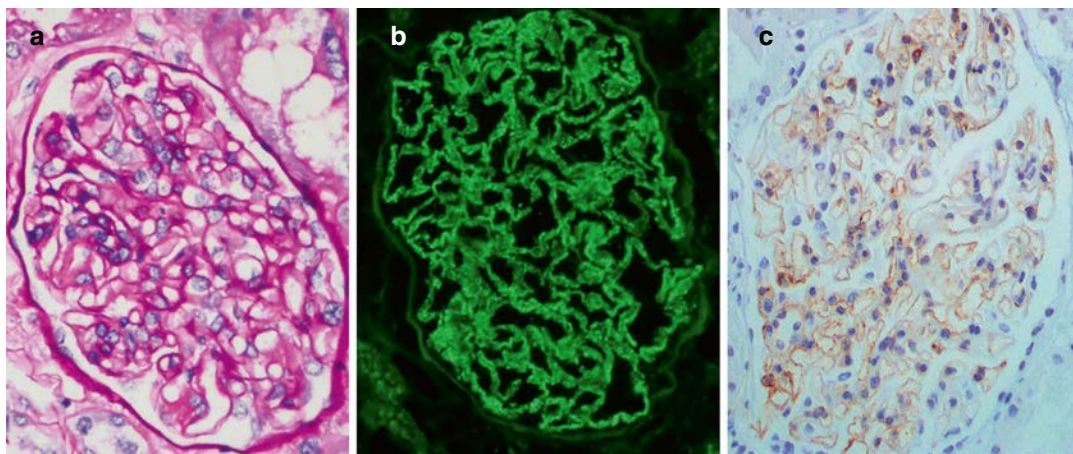


Fig. 13.7 (a) Irregular thickening of basement membrane is highlighted by PAS, (b) granular IgG deposits along basement membrane can be seen by direct immuno-

fluorescence (DIF), and (c) similar membranous deposits are highlighted by C4d staining

branous glomerulonephritis is the second most common cause of nephrotic syndrome in adults, following FSGS. It usually presents in the fourth to fifth decade, more often in men, with insidious-onset nephrotic syndrome, proteinuria, microscopic hematuria, and sometimes hypertension. Approximately 10–15% of cases have subnephrotic proteinuria, and 15–35% develop hematuria and mild hypertension. The clinical course is variable: some cases experience recurrent proteinuric relapses, while others progress to chronic renal failure. Spontaneous remission occurs in 20–65% of patients, especially in children, women, and early-stage cases. About 20–25% progress to end-stage renal disease over 10–15 years. Corticosteroids and immunosuppressive therapy have limited efficacy in altering prognosis, although newer targeted approaches are emerging. Recurrence after transplantation is uncommon [19].

13.10.1.5 Diabetic Nephropathy

Diabetic nephropathy, also known as Kimmelstiel-Wilson syndrome, is classically defined by the triad of diabetes mellitus, nephrotic syndrome, and hypertension. Histologically, it is characterized by acellular nodular hyaline deposits within the glomeruli (nodular glomerulosclerosis). Approximately 30% of patients with diabetes die

from chronic kidney failure. Nonselective proteinuria is the most consistent finding and represents the earliest marker of renal involvement. Nephrotic syndrome is reported in 6–40% of series, while microscopic hematuria may also be observed. Hypertension usually develops in later stages, and at least 10 years of diabetes is typically required before clinically significant nephropathy develops, with higher incidence in patients with childhood-onset diabetes. The characteristic vascular change is thickening of the vascular and tubular basement membranes, reflecting the systemic nature of diabetic microangiopathy. Both diffuse and nodular glomerulosclerosis occur, often simultaneously in the same patient. The nodular form is considered pathognomonic for diabetes. Mesangial matrix expansion, GBM thickening, and hyaline deposition are prominent, with affected mesangial nodules appearing eosinophilic, argyrophilic, PAS positive, and staining blue-green with trichrome. Similar appearances may be seen in light-chain nephropathy, where deposits consist of κ and λ chains, or in amyloidosis, though the latter shows Congo red positivity and birefringence. Rare, atypical lesions, including crescent formation, may also occur. Tubular basement membrane thickening is the most typical collecting system change, followed in advanced disease by tubular

atrophy and interstitial scarring. Intracytoplasmic glycogen accumulation in tubular epithelium, termed the Armani-Ebstein lesion, was historically frequent in uncontrolled diabetes but is now uncommon. On immunofluorescence, linear IgG deposition along tubular and glomerular basement membranes and Bowman's capsule is typical, without evidence of anti-GBM antibodies [20] (Fig. 13.8).

13.10.1.6 Renal Amyloidosis

Amyloidosis is characterized by extracellular deposition of fibrillar proteins with a distinctive β -pleated sheet configuration, producing apple-

green birefringence on Congo red staining under polarized light (Fig. 13.9). When multiple organs are involved, the condition is termed systemic amyloidosis, whereas localized amyloidosis refers to single-organ involvement. Secondary (AA) amyloidosis arises in association with chronic inflammatory disorders such as leprosy, osteomyelitis, Crohn's disease, or rheumatoid arthritis. More than 15 amyloid proteins have been identified, but the three most frequent are AL (light chain), AA (amyloid associated), and A β (beta-amyloid). AL amyloidosis results from monoclonal plasma cell disorders, typically using immunoglobulin light chains (mostly λ). AA

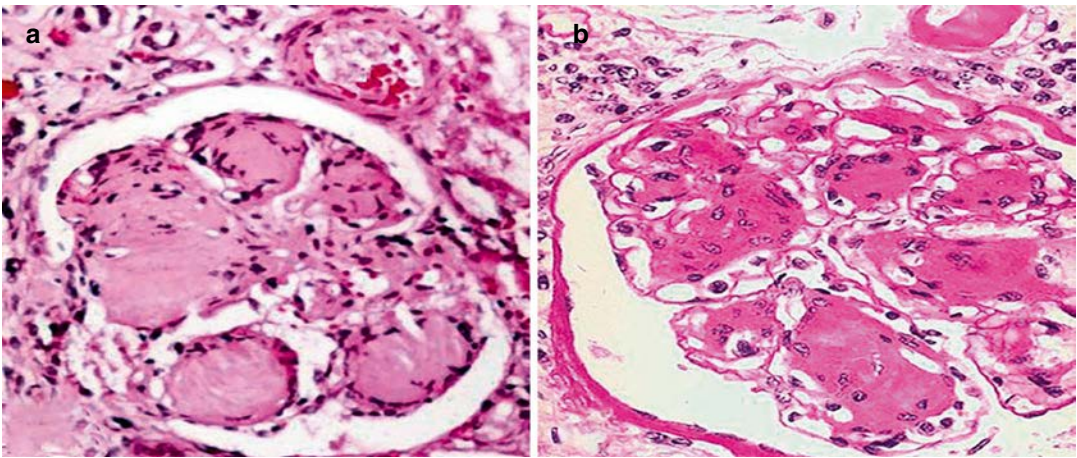


Fig. 13.8 (a, b) Nodular glomerulosclerosis of diabetic nephropathy

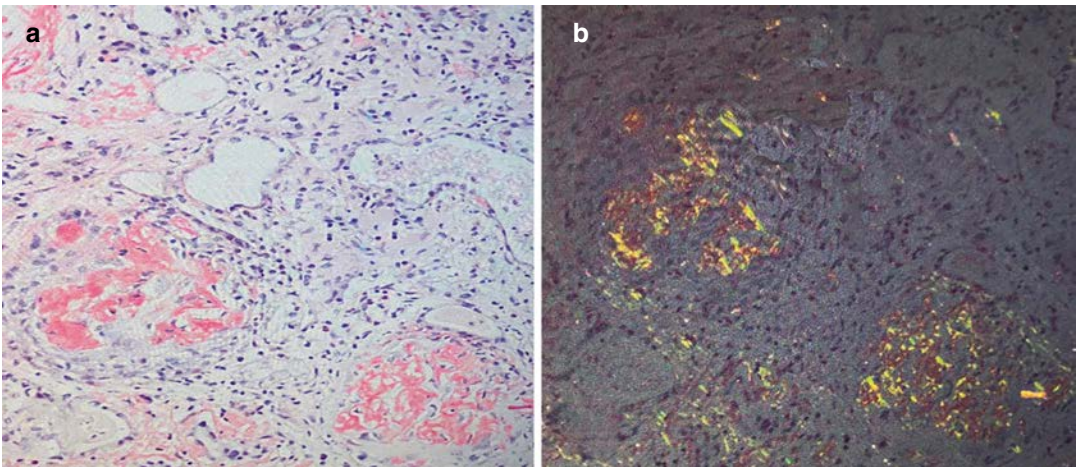


Fig. 13.9 (a) Amyloidosis by Congo red staining, (b) amyloid deposits under polarized light microscope

amyloid originates from serum amyloid A (SAA), an acute-phase reactant produced by the liver under the influence of cytokines such as IL-1 and IL-6. A β amyloid accumulates in Alzheimer's disease. Other types include transthyretin-derived ATTR amyloidosis, which may be hereditary (due to TTR gene mutations) or senile systemic (wild-type TTR). In senile systemic (or cardiac) amyloidosis, the deposited protein is wild-type transthyretin (ATTRwt). Unlike hereditary transthyretin amyloidosis, the transthyretin here has no mutation. The deposits primarily accumulate in the heart, leading to restrictive cardiomyopathy and heart failure, most commonly in elderly men. β 2-microglobulin amyloidosis occurs in long-term dialysis patients, often manifesting in joints and synovia. β 2M is normally cleared by the kidneys, accumulates in long-term dialysis patients, forming amyloid fibrils that preferentially deposit in the joints, synovia, bones, and tendon sheaths, leading to complications such as carpal tunnel syndrome, bone cysts, and arthritis-like symptoms. Endocrine amyloid (AE) is found in tumors such as pancreatic islet cell tumors or medullary thyroid carcinoma. Renal involvement of amyloidosis is common, and amyloid deposits are found in about two-thirds of secondary amyloidosis, one-quarter of primary amyloidosis, and 10–15% of multiple myeloma cases. Nonselective proteinuria is the most consistent finding, and nephrotic syndrome is present in ~50% of AA and ~30% of AL amyloidosis cases. Prognosis is generally poor in primary AL amyloidosis. In the kidney, deposits begin in the mesangium and extend into capillary walls, obliterating foot processes. Immunofluorescence helps distinguish AL from AA, while electron microscopy confirms the fibrillar nature of deposits. Congo red, crystal violet, and thioflavin stains are used for diagnosis. Amyloid deposits may also involve tubulointerstitium and vessel walls. If glomerular proliferative or crescentic changes are present, the diagnosis should be reconsidered [21].

13.10.1.7 Fibrillary Glomerulonephritis (FGN)

Fibrillary glomerulonephritis (FGN) is a relatively newly recognized entity. At first glance, the

lesion resembles amyloidosis; however, the extracellular fibrils are thicker, and unlike amyloid, they are Congo red and thioflavin negative but PAS positive. Most cases occur in middle-aged adults, without extrarenal involvement. Clinically, patients present with heavy proteinuria and hypertension in approximately 70% of cases. Unlike multiple myeloma, there is no evidence of Bence-Jones proteinuria, serum paraproteins, or associated lymphoproliferative disease. Prognosis is poor, with nearly half of patients progressing to chronic kidney failure within 2 years. Histologically, mesangial expansion and GBM thickening are seen, without necrosis or inflammation. Mesangial hypercellularity is common. Immunofluorescence demonstrates IgG (most frequently IgG4), light chains, and C3 deposits along capillary walls and within mesangium. These fibrils are considered highly organized immune deposits [22].

13.10.1.8 Light Chain Deposition Disease (LCDD)

Light chain deposition disease (LCDD) shows κ light chain accumulation in about 80% of reported cases. The male-to-female ratio is approximately 4:1. Nearly 60% of patients have underlying multiple myeloma or other lymphoplasma-cytic disorders. Although predominantly affecting older adults, rare cases have been reported in HIV-infected children under 2 years. Heavy proteinuria is a hallmark. The disease is systemic, with deposits found in multiple organs, not only the kidney [23].

13.10.1.9 Congenital Nephrotic Syndrome (CNS)

Congenital nephrotic syndrome (CNS) refers to lesions present at birth or developing within the first 3 months of life. It may appear as Finnish-type CNS (NPHS1 mutation) or *diffuse mesangial sclerosis (DMS)*. Finnish-type disease accounts for <1.5% of childhood nephrotic syndrome but is common in Finland (1/10,000 live births). It is inherited in an autosomal recessive manner due to mutations in the NPHS1 gene (chromosome 19q13.1), encoding nephrin, a slit diaphragm protein. Additional studies suggest

mutations in NPHS2 (encoding podocin) may also contribute, indicating genetic heterogeneity. Clinically, Finnish-type CNS is associated with prematurity, asphyxia, placentomegaly, and congenital anomalies. Proteinuria begins in utero, is initially selective, and is resistant to steroids or immunosuppressants. Most children develop chronic renal failure within 3–4 years without renal replacement therapy (Fig. 13.10). Transplantation leads to dramatic improvement, and recurrence does not occur. DMS may occur in isolation or in association with Denys-Drash syndrome (male pseudohermaphroditism and Wilms tumor), caused by *de novo* mutations in the WT1 gene. Unlike Finnish-type disease, placentomegaly and prematurity are not typical. Patients usually develop renal failure and hypertension within the first months of life, progressing to end-stage renal disease before age three. Histologically, CNS shows enlarged glomeruli, mesangial expansion, and diffuse tubulointerstitial microcysts in the deep cortex. DMS is characterized by expansion of mesangial matrix without marked proliferation, obliteration of capillary lumina, and diffuse glomerulosclerosis. Tubular atrophy and interstitial fibrosis are common. Immunofluorescence shows nonspecific mesangial deposits (IgM, C3, occasionally C1q), while electron microscopy demonstrates podocyte foot process effacement, cytoplasmic vacuolization, and mesangial matrix expansion [24, 25].

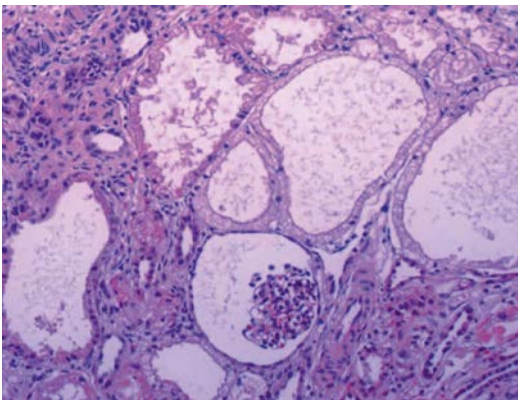


Fig. 13.10 Cystic dilated tubules in Finnish-type congenital nephrotic syndrome

13.10.2 Acute Nephritic Syndrome and Associated Lesions

Acute nephritic syndrome is characterized by hematuria, azotemia, oliguria, and mild-to-moderate hypertension. Urine commonly contains numerous red and white blood cells, and proteinuria may occur, though not at nephrotic range. Mild edema, often facial, may be present. While classification can be clinical, histopathologic patterns provide greater precision. Diffuse glomerulonephritides are broadly divided into membranous and proliferative types, with proliferative lesions further subclassified as endocapillary proliferative, membranoproliferative type I, dense deposit disease (type II MPGN), mesangioproliferative, and crescentic glomerulonephritis. In proliferative glomerulopathies, inflammation and repair mechanisms contribute to injury beyond the reversible filtration barrier changes seen in minimal change disease or membranous nephropathy. Consequently, these lesions more often present with nephritic syndrome, although some nonproliferative lesions may lead to irreversible injury.

13.10.2.1 Diffuse Endocapillary Proliferative Glomerulonephritis (Postinfectious GN)

Classically represented by post-streptococcal glomerulonephritis (PSGN), diffuse endocapillary proliferative GN may follow infections with various bacterial, viral, or parasitic agents. The term refers to proliferation of mesangial and endothelial cells accompanied by marked hypercellularity due to infiltration of neutrophils, macrophages, lymphocytes, or plasma cells. The hallmark is obliteration of glomerular capillary lumina. Epidemiology: PSGN occurs most often in children 5–15 years, though it may appear at any age. It follows infections with nephritogenic strains of group A β -hemolytic streptococci, particularly M types 1, 2, 12, 49, 55, 57, and 60. Risk varies with infection site: M49 pharyngitis carries ~5% risk of GN, whereas impetigo due to the same strain increases risk fivefold. Latency is 7–10 days after pharyngitis and up to 6 weeks

after skin infection. Pathogenesis: PSGN is an immune complex-mediated disease. Strong glomerular C3 positivity with absent C1q and C4 suggests alternative complement pathway activation. Characteristic subepithelial “hump-like” electron-dense deposits on EM confirm the diagnosis. Patients present acutely with gross hematuria, proteinuria, edema, hypertension, and variable renal impairment. Serum C3 levels decreased in the acute phase but normalize within 8 weeks. Most children recover fully within 6–8 weeks, whereas prognosis in adults is less favorable, particularly in those with crescents or severe acute renal failure. Rarely, the disease progresses to rapidly progressive GN or chronic kidney disease. Pathologically, there are diffuse global hypercellularity with mesangial and endothelial proliferation, neutrophilic infiltration, lobular accentuation, and narrowed capillary lumina. Interstitial edema and mild mononuclear infiltration may be present. In direct immunofluorescence investigation, there are granular deposits of IgG and C3 along the glomerular capillary walls, showing patterns such as “starry sky,” mesangial, or garland-type staining (Fig. 13.11). In electron microscopy, subepithelial humps surrounded by podocyte foot process effacement are observed [26].

13.10.2.2 Membranoproliferative Glomerulonephritis (MPGN)

Membranoproliferative glomerulonephritis (MPGN), also known as mesangiocapillary GN, is characterized by mesangial cell proliferation and thickening of capillary walls. It is classified into idiopathic (primary) and secondary forms, the latter arising in the context of other conditions such as infections (e.g., HBV, HCV, endocarditis, visceral abscesses, parasitic diseases, EBV, HIV), autoimmune disorders (SLE, RA, Sjögren’s), immunoglobulinopathies (light- and heavy-chain deposition, cryoglobulinemia, Waldenström’s macroglobulinemia), chronic liver disease (cirrhosis, α 1-antitrypsin deficiency), thrombotic microangiopathies (HUS/TTP, antiphospholipid syndrome), radiation nephropathy, sickle cell anemia, and posttransplant states. Idiopathic MPGN is further subdivided based on electron microscopy patterns into:

- *Type I MPGN*, involving subendothelial immune complex deposits
- *Type II (dense deposit disease, DDD)*, characterized by intramembranous dense complement deposits

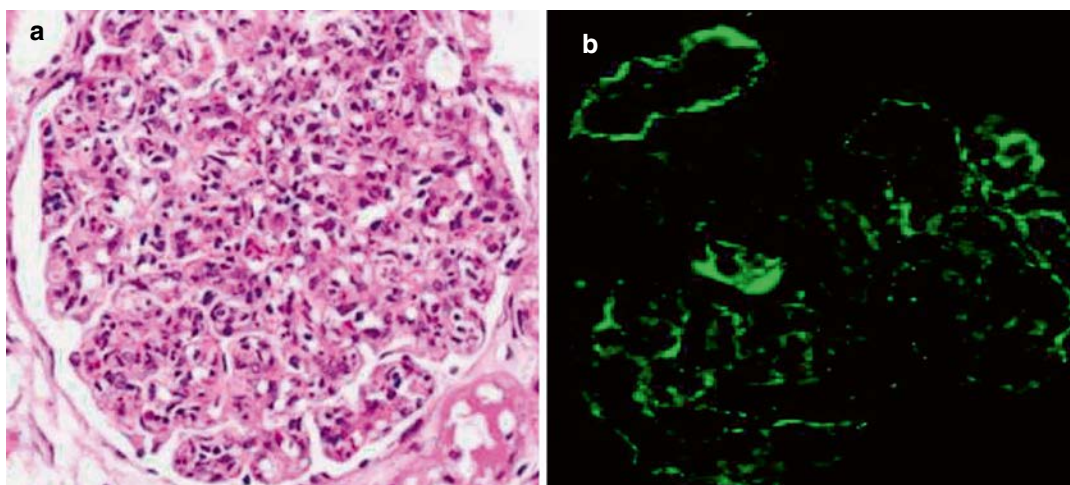


Fig. 13.11 (a) A hypercellular glomerulus, (b) Garland-type staining in DIF

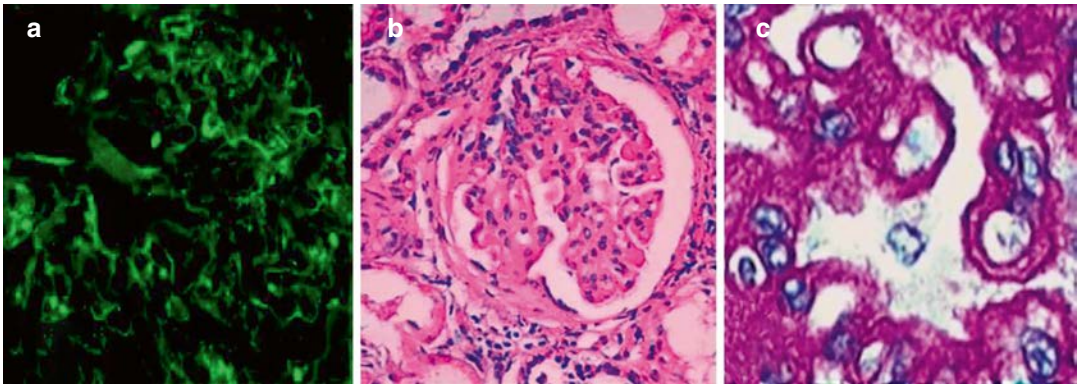


Fig. 13.12 (a) IgG deposition forming mesangial rings in DIF, (b) lobular architecture, and (c) tram-track appearance with PAS

In MPGN, both the classical and alternative complement activation pathways are implicated. Type I is considered an immune complex-mediated disease, while type II stems from dysregulation of the alternative complement pathway. A strong association exists between HBV infection and MPGN. Type I is the most common primary form, accounting for roughly 5–13% of childhood idiopathic nephrotic syndromes and approximately 6% in adults. While more prevalent in children, MPGN can occur at any age (M-F ratio $\approx 1.5:1$). Clinical presentations include nephritic and/or nephrotic features. A consistent laboratory finding in all forms of MPGN is hypocomplementemia, primarily due to decreased levels or consumption of C3 driven by immune complex activity. On immunofluorescence, granular deposits of IgG, C3, C1q, and C4 are seen within glomeruli. In type II, deposition of C3 and IgG along the GBM occurs without classical complement components (C1q/C4), giving rise to the pathognomonic “mesangial C3 ring” appearance. Alternative pathway activation is prominent in type II, often with involvement of properdin and factor B, and its serum levels correspondingly decrease. The presence of C3 nephritic factor (C3NeF)—an autoantibody stabilizing C3 convertase—is frequently observed in type II patients. Light microscopy reveals diffusely enlarged glomerular tufts and lobular architecture, with marked hypercellularity and GBM duplication (“tram-track” appearance) (Fig. 13.12). Mesangial interposition contributes

to new basement membrane formation, and crescents may be present. Chronic injury manifests with tubular atrophy, interstitial fibrosis, and sclerosis. Clinical course and prognosis are variable. Idiopathic MPGN in adults carries a poor prognosis; up to 50% of patients progress to renal failure within 5 years and 64% within 10 years. Interstitial/tubulointerstitial fibrosis predicts a worse outcome. Recurrence posttransplantation occurs in 20–30% of type I cases and a striking 80–90% of type II cases, particularly in repeat transplants [27, 28].

13.10.2.3 Diffuse Mesangioproliferative Glomerulonephritis (MesPGN)

Diffuse mesangioproliferative glomerulonephritis (MesPGN) refers to a heterogeneous group of disorders characterized by diffuse proliferation of mesangial cells and expansion of the mesangial matrix, while glomerular capillary lumina remain patent and capillary walls appear thin. By convention, a mesangial area containing ≥ 4 mesangial cells is considered proliferative. Neutrophilic infiltration is absent. Importantly, diffuse mesangial cell proliferation is a nonspecific finding and may be observed artifactually in thick biopsy sections or in the resolution phase of postinfectious glomerulonephritis. Diseases such as IgA nephropathy, systemic lupus erythematosus (SLE), and Henoch-Schönlein purpura (IgA vasculitis) belong to this category. In some

patients, the clinical presentation may overlap with nephrotic syndrome [29–31].

13.10.2.3.1 IgM Nephropathy

IgM nephropathy is a distinct form of MesPGN that arises in individuals without systemic disease or other primary glomerulopathies. It is typically seen in older children and young adults, presenting with proteinuria or nephrotic syndrome. Histologically, there is mesangial cell proliferation and matrix expansion. Immunofluorescence reveals mesangial deposition of IgM and C3, while electron microscopy demonstrates mesangial electron-dense deposits. The presence of IgM deposition has led to its designation as IgM nephropathy. However, IgM nephropathy remains a controversial entity, considered a variant of the FSGS spectrum by some authors. Because up to 70% of cases also show focal segmental glomerulosclerosis (FSGS). Corticosteroid responsiveness is generally favorable; however, a subset of patients may progress slowly to chronic kidney disease despite treatment [29].

13.10.2.3.2 IgA Nephropathy

IgA nephropathy (IgAN/Berger's disease) represents the prototype of primary MesPGN, although focal forms also occur. It is defined by diffuse mesangial IgA and C3 deposition on immunofluorescence and mesangial electron-dense deposits on electron microscopy (Fig. 13.13). The disease is usually latent and becomes clini-

cally apparent when gross hematuria develops. Recurrent gross or microscopic hematuria is typical. First described by Berger in 1968, IgAN is characterized by mesangial proliferation on light microscopy and mesangial IgA deposition (often accompanied by IgG and C3). It can also occur secondarily in conditions such as Henoch-Schönlein purpura, alcoholic liver disease, celiac disease, dermatitis herpetiformis, and HIV infection. The primary form (*Berger's disease*) typically affects adolescents and young adults (10–30 years), with a male predominance of 2–3:1. Lesions range from minimal mesangial proliferation to crescentic glomerulonephritis. Hematuria episodes usually follow upper respiratory infections (synpharyngitic hematuria). Isolated macroscopic hematuria is often accompanied by mild proteinuria (<1 g/day). Approximately 10% of patients develop nephrotic syndrome, while 25–40% progress to end-stage kidney disease requiring transplantation. Posttransplant recurrence is well documented. The diagnosis requires immunofluorescence microscopy; no specific serologic test exists. The frequent presence of C3 but absence of C1q and C4 supports the role of alternative complement pathway activation. Serum IgA levels are elevated in 50–70% of cases, particularly in Henoch-Schönlein nephritis, though elevated IgA alone is not diagnostic. Some studies suggest high serum IgA may indicate poor prognosis. About one-third of patients are rheumatoid factor positive. Importantly, the presence of gross hematuria

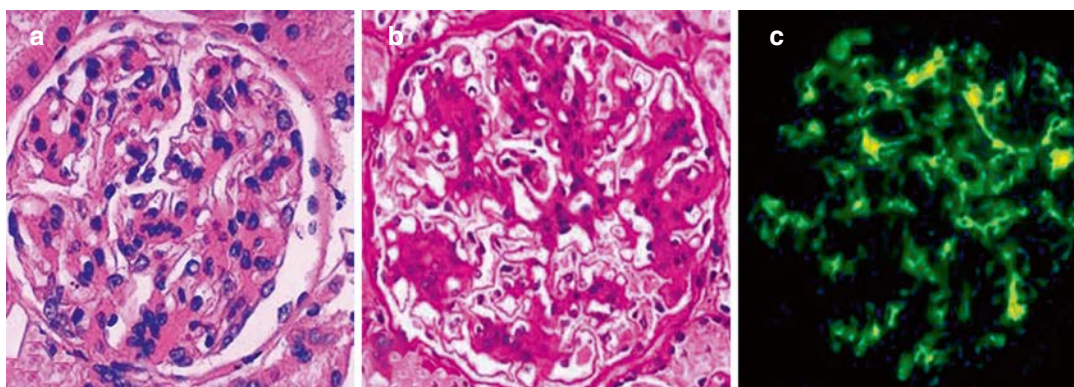


Fig. 13.13 (a) Mesangial proliferation in IgAN, (b) mesangial matrix increase with PAS, and (c) mesangial IgA deposition with DIF

does not correlate with histologic severity. Instead, tubulointerstitial changes and the extent of glomerular lesions are better predictors of renal outcome. Patients with purely mesangial pathology or focal segmental lesions generally recover with minimal urinary abnormalities, whereas those with endocapillary or extra capillary (crescentic) lesions often progress to renal failure. In 2009, the Oxford Classification introduced a reproducible histopathologic scoring system for IgA nephropathy, later refined in 2016. The system evaluates five key morphologic parameters, summarized as MEST-C (Table 13.2) [30, 31].

13.10.2.4 Crescentic Glomerulonephritis

Crescentic (rapidly progressive) glomerulonephritis (RPGN) is a histopathological lesion defined by the presence of crescents, which represent proliferating cells within Bowman's space that form a crescent-like configuration. Clinically, it corresponds a syndrome characterized by acute and progressive loss of renal function that leads to end-stage kidney failure and death within weeks or months if untreated. Although the proliferating cells were once thought to arise from the parietal epithelium of Bowman's capsule, it is now clear that infiltrating monocytes and macrophages play a major role and that immune-mediated mechanisms drive crescent formation.

The proliferating cells are oval or spindle shaped, often admixed with neutrophils and fibrin, while glomerular basement membrane (GBM) ruptures, best demonstrated by methenamine silver stain or electron microscopy, are a typical finding. Morphology of crescent reflects the stage and activity of glomerular injury. A cellular crescent represents the earliest and most active stage. It is composed predominantly of proliferating parietal epithelial cells and infiltrating monocytes or macrophages, often accompanied by fibrin and occasional neutrophils. The lesion appears hypercellular and crowded, indicating ongoing immune-mediated damage. Because it reflects acute activity, cellular crescents may partially regress with prompt and effective immunosuppressive treatment. As the process evolves, fibrous tissue gradually replaces the proliferating cells. When both cellular elements and fibrous matrix coexist, the lesion is called a fibrocellular crescent, an intermediate form between active and chronic stages. A sclerotic (fibrous) crescent is the end stage, in which Bowman's space is filled by dense collagen and scar tissue with few or no viable cells. This stage represents chronic, irreversible damage and is strongly associated with permanent loss of renal function. In summary, cellular crescents indicate acute and potentially reversible injury, while sclerotic crescents reflect chronic, irreversible scarring (Fig. 13.14). Crescentic GN is not a single disease entity but a

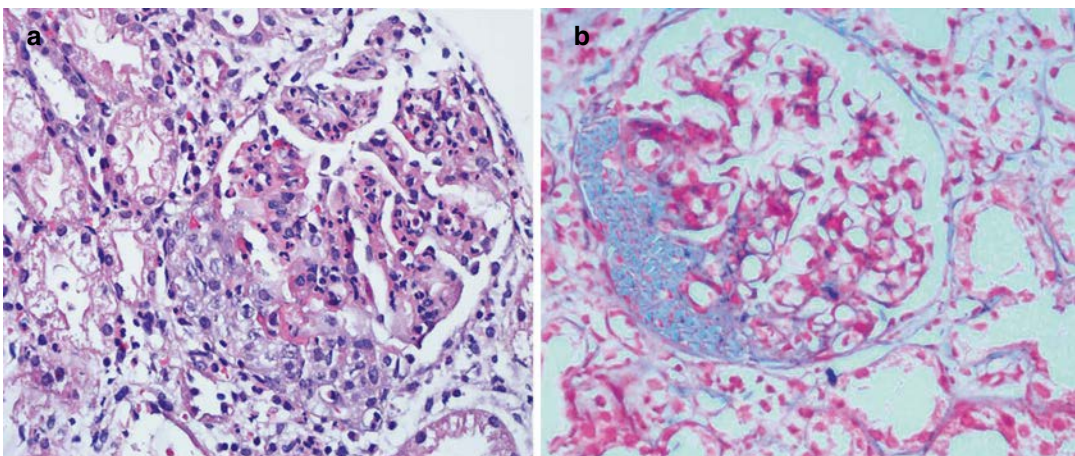


Fig. 13.14 (a) Cellular crescent, (b) sclerotic (fibrous) crescent

morphological pattern that may occur in many glomerular disorders. If an underlying systemic disease such as systemic lupus erythematosus is identified, the lesion is best referred to as the crescentic form of that disease. In large biopsy series, crescentic GN accounts for only 2–5% of cases. Based on immunopathological features, three major categories of RPGN are recognized [32–35].

13.10.2.4.1 Type I RPGN

Type I RPGN also known as *anti-GBM disease*, is characterized by linear deposition of IgG, often with C3, along the GBM. The underlying mechanism involves autoantibodies against the non-collagenous NC1 domain of the $\alpha 3$ chain of type IV collagen. These antibodies may also cross-react with alveolar basement membranes, resulting in the pulmonary-renal syndrome known as *Goodpasture's disease*. In this setting, patients develop pulmonary hemorrhage and rapidly progressive glomerulonephritis, and a significant proportion may also be positive for antineutrophil cytoplasmic antibodies (ANCA). Electron microscopy typically reveals GBM breaks, while immunofluorescence demonstrates continuous linear IgG deposition. Prognosis is poor unless treatment is initiated early, and combined immunosuppression with plasma exchange has become the standard of care [33].

13.10.2.4.2 Type II RPGN

Type II RPGN is immune complex mediated and results from deposition of circulating immune complexes within the glomeruli. Immunofluorescence shows granular IgG and C3 deposition along the GBM and mesangium. This pattern is seen in postinfectious glomerulonephritis, lupus nephritis, and Henoch-Schönlein purpura. Serum complement levels are often reduced. The clinical course and prognosis are variable and depend largely on the underlying disease process [32, 34].

13.10.2.4.3 Type III RPGN

Type III RPGN also called pauci-immune crescentic GN, is the most common form, accounting for more than half of cases. Immunofluorescence

studies show little or no deposition, but most patients have circulating ANCAs directed against neutrophil cytoplasmic enzymes. The two main antigenic targets are proteinase 3 (PR3), corresponding to c-ANCA with a cytoplasmic staining pattern, and myeloperoxidase (MPO), corresponding to p-ANCA with a perinuclear pattern. These autoantibodies are detected either by indirect immunofluorescence or more specifically by ELISA. Pauci-immune RPGN is strongly associated with systemic small-vessel vasculitis, including *granulomatosis with polyangiitis*, which was known as *Wegener's granulomatosis*, *microscopic polyangiitis*, and *eosinophilic granulomatosis with polyangiitis* (formerly Churg-Strauss syndrome). Prognosis is generally better than in anti-GBM disease, and many patients respond to immunosuppressive therapy. The clinical presentation of RPGN typically includes hematuria, sub-nephrotic proteinuria, and rapidly worsening renal function. Prognosis varies according to the immunopathological type, with anti-GBM disease having the worst outcome and pauci-immune forms showing the most favorable response to treatment. Early diagnosis and prompt initiation of high-dose corticosteroids, cyclophosphamide, and, in the case of anti-GBM disease, plasma exchange, are essential for preserving renal function and improving survival [34, 35].

13.10.2.5 Lupus Nephritis

Renal involvement during the course of systemic lupus erythematosus (SLE) is referred to as lupus nephritis. SLE is a chronic systemic autoimmune disease that can occur at any age, although the initial manifestations usually appear between 16 and 30 years. Renal involvement is one of the most common and clinically significant features of SLE, affecting up to 80% of adult patients at some point in their disease course. The spectrum of renal disease is broad, ranging from minimal mesangial alterations with an excellent prognosis to diffuse proliferative or sclerosing glomerulonephritis that may progress to end-stage kidney disease and death within a few years if untreated. The underlying lesion in lupus nephritis is an immune complex-mediated glomerulonephritis.

The histopathological changes may involve glomeruli, tubulointerstitial compartments, and renal vessels. According to the ISN/RPS classification (2003, revised in 2018), lupus nephritis is divided into six classes:

- Class I: Minimal mesangial lupus nephritis
- Class II: Mesangial proliferative lupus nephritis
- Class III: Focal lupus nephritis (<50% of glomeruli affected)
- Class IV: Diffuse lupus nephritis (≥50% of glomeruli affected)
- Class V: Membranous lupus nephritis
- Class VI: Advanced sclerosing lupus nephritis

In class I and II, the light microscopic appearance may be unremarkable, and diagnosis requires immunofluorescence or electron microscopy. Class IV is the most frequent and severe form, associated with widespread immune complex deposition and a high risk of progression. Class V disease often follows a rapidly progressive course, particularly when combined with proliferative lesions. Transitions between classes occur in approximately 15% of patients over the disease course, especially from class III to IV. Tubulointerstitial inflammation and fibrosis frequently accompany proliferative lesions and correlate with poor prognosis. Necrotizing vasculitis is rare but may occur in severe cases.

The immunopathological hallmark of lupus nephritis is the so-called “full house” pattern on immunofluorescence microscopy, characterized by deposition of multiple immunoglobulins and complement components within glomeruli. IgG and IgM are most prominent, but IgA, IgE, C1q, C3, C4, fibrinogen, and properdin are often present as well. Among the different classes, class IV shows the most abundant and diverse immune deposits [36, 37].

13.10.3 Vasculitis-Associated Glomerulonephritis

Vasculitis refers to inflammation of blood vessels, most often accompanied by fibrinoid necro-

sis. While the term generally implies arterial involvement, venous or lymphatic inflammation is usually described with different terms. The classification of vasculitis remains complex, but the most widely adopted systems categorize them according to vessel size and pathogenic mechanisms, distinguishing between infectious and immune-mediated forms [38–40].

13.10.3.1 Infectious Vasculitis

Infectious vasculitis can be caused by bacteria (e.g., pneumococcus, meningococcus, tuberculosis), rickettsiae (Rocky Mountain spotted fever), spirochetes (syphilis), fungi (aspergillosis, mucormycosis), and viruses (e.g., herpes). These forms usually involve necrosis of arterial walls, are prone to thrombosis, and may lead to aneurysm formation.

13.10.3.2 Immune-Mediated Vasculitis

Immune-mediated vasculitis occurs when humoral or cellular immune mechanisms contribute to vascular injury. Examples include cryoglobulinemic vasculitis, in which IgG-IgM-complement immune complexes deposit; lupus vasculitis due to DNA-anti-DNA immune complexes; hepatitis B- and C-related vasculitis associated with viral antigen-antibody complexes; and anti-basement membrane antibody-mediated vascular damage in Goodpasture’s disease. In Kawasaki disease, anti-endothelial cell antibodies have been implicated. Mechanisms include immune complex deposition, direct antibody binding, T-cell-mediated injury, and autoantibodies against neutrophil cytoplasmic antigens (ANCA). ANCAs are autoantibodies directed against neutrophil granule proteins, primarily proteinase 3 (PR3) and myeloperoxidase (MPO). PR3 is present in neutrophil lysosomes and plays a role in neutrophil maturation and tissue infiltration, while MPO contributes to bactericidal activity by generating reactive oxygen species. On indirect immunofluorescence (IFAT), ANCAs produce two major staining patterns: cytoplasmic (c-ANCA, usually directed against PR3) and perinuclear (p-ANCA, typically targeting MPO). ELISA is used to distinguish PR3-ANCA from MPO-ANCA (Fig. 13.15). ANCA titers often correlate with disease activity.

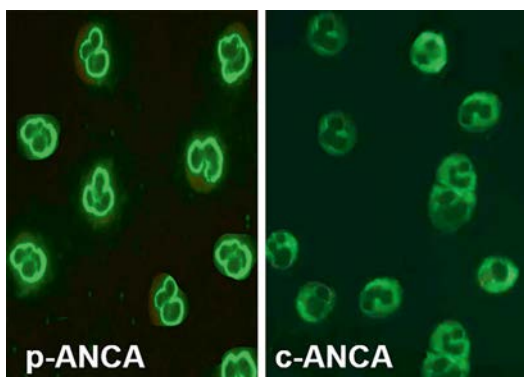


Fig. 13.15 ANCA staining patterns with IFAT

Pathogenetically, ANCAs are thought to activate neutrophils, leading to oxidative burst, degranulation, and release of lytic enzymes and free radicals, which cause endothelial damage. Infection-induced cytokines may potentiate this process, and PR3-ANCA may further promote injury by inactivating α 1-antitrypsin. Vasculitis may be secondary to systemic autoimmune diseases such as systemic lupus erythematosus (SLE) or rheumatoid arthritis, to infections, or to drug-induced hypersensitivity reactions. Primary idiopathic systemic vasculitis also occurs, and clinical manifestations vary according to the size of the vessels involved and the organs affected.

13.10.3.2.1 Polyarteritis Nodosa (PAN)

Polyarteritis nodosa (PAN) is a necrotizing systemic vasculitis of medium-sized arteries. The classic form, described by Kussmaul and Maier, involves transmural acute necrotizing inflammation with fibrinoid necrosis, polymorphonuclear infiltration, and subsequent fibrosis. Lesions are focal, segmental, and frequently accompanied by aneurysms or occlusion. PAN typically spares arterioles, capillaries, and venules, and the lungs are characteristically uninvolved. About one-third of patients are carriers of hepatitis B virus, suggesting an immune complex-mediated pathogenesis. ANCA is generally negative. Renal involvement, with necrotizing arteritis of interlobular arteries and arterioles, is a major determinant of prognosis. Microscopically, healed lesions show fibrous thickening and periarterial nodules, with lesions of different stages often coexisting, a feature characteristic of PAN.

13.10.3.2.2 Microscopic polyangiitis (MPA)

Microscopic polyangiitis (MPA), previously referred to as hypersensitivity angiitis, differs from classic PAN by its involvement of small vessels including capillaries and venules, its ability to involve the lung, and the fact that lesions are usually in a uniform stage.

13.10.3.2.3 Granulomatosis with Polyangiitis (GPA)

Granulomatosis with polyangiitis (GPA), formerly *Wegener's granulomatosis*, is a necrotizing systemic vasculitis characterized by the triad of necrotizing granulomatous inflammation of the respiratory tract, systemic vasculitis of small to medium vessels, and necrotizing crescentic glomerulonephritis. It most often affects adults between 30 and 50 years of age, with a male predominance. Renal involvement occurs in the majority of patients, typically as focal necrotizing glomerulonephritis, often with crescents. Immunofluorescence may show scant Ig or complement deposition, while fibrinogen is more prominent. More than 90% of patients are c-ANCA positive (anti-PR3). Without treatment, GPA is usually fatal; however, corticosteroids combined with cyclophosphamide or newer immunosuppressive agents can induce remission, although relapses are common.

13.10.3.2.4 Eosinophilic Granulomatosis with Polyangiitis (EGPA)

Eosinophilic granulomatosis with polyangiitis (EGPA), formerly *Churg-Strauss syndrome*, is an allergic granulomatous vasculitis that often involves the lungs but only rarely the kidneys. Renal lesions, when present, are usually necrotizing glomerulonephritis. The pathology is distinguished by prominent eosinophilic infiltrates. The disease is strongly associated with asthma and peripheral eosinophilia. Unlike GPA, ANCA positivity is more commonly p-ANCA/MPO-ANCA, while c-ANCA is typically negative. Corticosteroids are effective, but cytotoxic drugs used in GPA are less successful.

13.10.3.2.5 IgA Vasculitis

IgA vasculitis (Henoch-Schönlein purpura, now more often termed *IgA vasculitis*) is a leukocytoclastic small-vessel vasculitis most frequently seen in children. It manifests clinically with purpuric rash, abdominal pain, gastrointestinal bleeding, arthralgia, and renal involvement. Histologically, mesangioproliferative glomerulonephritis, sometimes with crescents, is typical. Immunofluorescence demonstrates IgA deposition in glomeruli and dermal vessels, resembling IgA nephropathy. The prognosis is generally favorable, with about half of patients achieving complete remission within 1 year, though severe cases may progress to chronic kidney disease.

13.10.3.2.6 Cryoglobulinemic Vasculitis

Cryoglobulinemic vasculitis results from circulating cryoglobulins—immunoglobulins that precipitate at cold temperatures and dissolve upon warming. Three types are recognized: type I, consisting of a single monoclonal immunoglobulin, usually associated with hematological malignancies; type II, composed of a monoclonal IgM with rheumatoid factor activity against polyclonal IgG; and type III, consisting of mixtures of polyclonal immunoglobulins. Mixed cryoglobulinemia (types II and III) is most often associated with autoimmune diseases, chronic infections, or liver disease, especially hepatitis C virus infection. Renal manifestations typically include membranoproliferative glomerulonephritis with subendothelial cryoglobulin deposits, as well as small-vessel vasculitis. Clinically, patients often present with purpura, arthralgia, hepatosplenomegaly, lymphadenopathy, and renal disease, usually years after the onset of systemic symptoms.

13.10.4 Disseminated Intravascular Coagulation or Hypertension-Related Lesions

13.10.4.1 Hemolytic Uremic Syndrome (HUS)

Hemolytic uremic syndrome (HUS) is a heterogeneous disorder characterized by the triad of

microangiopathic hemolytic anemia, thrombocytopenia, and azotemia. It is the leading cause of acute kidney injury in children and can be classified into several categories. The classic childhood form is most common in children aged 2–3 years, without sex predilection. It frequently occurs in North America, particularly in summer months, and may appear in epidemic clusters. A prodromal diarrheal illness, sometimes bloody, is typical. Prognosis is usually favorable, although about one-third of cases develop neurological symptoms. The disease is strongly associated with infection by *Escherichia coli* O157:H7 producing Shiga-like (verocytotoxin). The adult form includes postinfectious, secondary, and postpartum HUS-like syndromes. Postinfectious HUS may occur at any age and is often associated with *Shigella dysenteriae* type 1, *Streptococcus pneumoniae*, *Salmonella typhi*, and various viral infections. Secondary HUS arises in systemic lupus erythematosus, scleroderma, malignant hypertension, and certain malignancies or as a complication of chemotherapy (e.g., mitomycin C, cyclosporine) or radiotherapy. The postpartum form is particularly severe, with a mortality rate exceeding 50%, and oral contraceptives have also been implicated via estrogenic mechanisms. Hereditary and recurrent forms may occur at any age and frequently progress to chronic kidney disease.

The relationship between HUS and thrombotic thrombocytopenic purpura (TTP) remains debated. Both conditions may share a common pathogenesis involving endothelial injury, leading to impaired cleavage of von Willebrand factor (vWF) multimers. Normally, vWF multimers are degraded by the metalloprotease ADAMTS-13. In congenital or acquired ADAMTS-13 deficiency, uncleaved large multimers promote platelet aggregation and microthrombus formation. This triggers tissue ischemia, endothelial dysfunction, and reduced production of vasodilatory mediators such as prostacyclin (PGI₂) and nitric oxide [41].

13.10.4.2 Thrombotic Microangiopathy (TMA)

Thrombotic microangiopathy (TMA) is an acute clinical syndrome characterized by microangio-

pathic hemolytic anemia, thrombocytopenia, and widespread platelet-rich thrombi in the microcirculation, leading to ischemic organ injury. The kidney is most frequently affected, but other organs such as the brain and heart may also be involved. The classical triad of TMA is microangiopathic hemolytic anemia, thrombocytopenia, and renal failure. Von Willebrand factor (vWF), a key molecule in hemostasis, is synthesized by endothelial cells and megakaryocytes. Following synthesis, it is stored in Weibel-Palade bodies within endothelial cells and in the α -granules of platelets. A portion of vWF is secreted into the subendothelial matrix, where it mediates platelet adhesion after vascular injury. Upon endothelial stimulation, large vWF multimers are released into the plasma. In the circulation, these ultra large multimers are normally cleaved into smaller fragments by ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13), a zinc-containing metalloprotease also known as vWF-cleaving protease. The smaller fragments function in secondary hemostasis as carrier proteins for coagulation factor VIII. When the endothelium is excessively stimulated, vWF release is markedly increased. If ADAMTS13 activity is quantitatively deficient or functionally impaired, cleavage of ultra large vWF multimers does not occur. These uncleaved multimers adhere to the endothelium and form long strings, to which platelets rapidly bind, resulting in platelet aggregation and the formation of microvascular thrombi. The accumulation of these thrombi within the microcirculation leads to ischemic organ injury, thrombocytopenia due to consumption, and microangiopathic hemolytic anemia due to mechanical fragmentation of red blood cells (Fig. 13.16). The clinical picture that emerges—characterized by thrombocytopenia, hemolytic anemia, neurological symptoms, and renal dysfunction—is typical of thrombotic thrombocytopenic purpura (TTP), one of the best-recognized forms of TMA [42].

13.10.4.3 Systemic sclerosis

Systemic sclerosis (progressive systemic sclerosis, PSS) is a connective tissue disorder of unknown etiology, with renal involvement in up to 60–70% of patients. Women are affected more

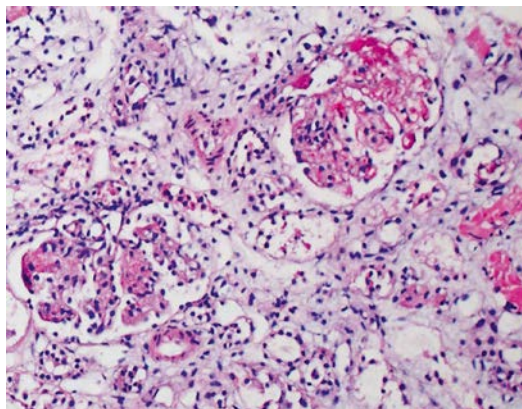


Fig. 13.16 Thrombi and absence of erythrocytes in TMA

frequently, typically between ages 30 and 60. Renal lesions range from rapidly progressive to indolent forms. Acute renal disease shows fibrinoid necrosis, thrombosis, and myxoid intimal thickening of interlobular arteries, while chronic lesions include glomerulosclerosis, tubular atrophy, and interstitial fibrosis. Immunofluorescence often demonstrates deposition of fibrinogen, with or without IgM and C3, in the glomeruli and vessels. Differentiation of scleroderma renal crisis from HUS and malignant hypertension requires careful clinicopathological correlation.

13.10.4.4 Hypertension

Hypertension is both a cause and consequence of renal injury, and chronic elevation of blood pressure induces progressive vascular and glomerular damage. The vascular lesions of hypertension fall into three categories: hyaline arteriosclerosis, myointimal hyperplasia, and fibrinoid necrosis. Benign nephrosclerosis refers to the renal changes of long-standing mild or moderate hypertension. The kidneys are symmetrically atrophic with finely granular surfaces. Small arteries and arterioles show hyaline wall thickening due to accumulation of PAS-positive, eosinophilic glycoproteinaceous material that reacts with IgM and complement. This predominantly affects afferent arterioles. Myointimal hyperplasia, more prominent in interlobular arteries, is characterized by concentric thickening due to smooth muscle cell proliferation and deposition of basement membrane-like material, producing an “onion-skin” appearance. These chronic isch-

emic changes result in glomerulosclerosis, tubular atrophy, and interstitial fibrosis. Malignant hypertension and malignant nephrosclerosis represent acute, life-threatening vascular lesions. Grossly, the kidneys may show pinpoint petechial hemorrhages, described as a “flea-bitten” appearance. Histologically, arterioles demonstrate fibrinoid necrosis and thrombosis (necrotizing arteriolitis), often superimposed on preexisting benign lesions. Immunofluorescence reveals deposition of fibrin, fibrinogen, IgM, and complement. Interlobular arteries show onion-skin lesions, while the glomeruli may display necrotizing glomerulitis and microthrombi. Clinically, malignant hypertension is defined by diastolic blood pressure >130 mmHg and presents with hypertensive encephalopathy, papilledema, and cardiovascular abnormalities. Without urgent treatment, renal failure and death occur within months; however, effective antihypertensive therapy can dramatically improve survival.

13.10.5 Pregnancy-Related Glomerulopathies

Pregnancy may be complicated by the development of new kidney disease or by the activation of preexisting renal disorders. The most characteristic entity is preeclampsia, a syndrome defined by hypertension, proteinuria, and edema, sometimes accompanied by coagulopathy and hepatic dysfunction. Preeclampsia usually appears after the 20th week of gestation and occurs 6–8 times more frequently in primigravid women than in multiparous women. Although historically referred to as “toxemia of pregnancy,” no specific toxin is responsible. Toxemia encompasses both preeclampsia and its more severe manifestation, eclampsia, which is characterized by seizures and may progress to coma. Preeclampsia typically develops after the 32nd week of gestation, but it may arise earlier in molar pregnancies or in women with preexisting renal disease or chronic hypertension. The overall incidence is approximately 6% of all pregnancies, with a higher frequency among primiparas. The earliest manifestations are hypertension and

edema, often followed by headache, visual disturbances, and, in severe cases, neurological complications such as seizures and coma. Mild disease may resolve with bed rest, dietary management, and antihypertensive therapy. In previously healthy women, clinical findings usually disappear within 1–2 weeks after delivery. In contrast, eclampsia can involve multiorgan injury, including the liver, kidney, heart, placenta, and brain, and is frequently complicated by disseminated intravascular coagulation (DIC). The pathogenesis of preeclampsia remains incompletely understood. The most widely accepted model implicates inadequate trophoblastic invasion of the maternal spiral arteries, leading to poor placental perfusion. Normally, invading trophoblasts remodel the spiral arteries into high-capacitance vessels, but in preeclampsia, this process is incomplete. The resulting placental ischemia stimulates production of vasoconstrictors such as thromboxane, angiotensin II, and endothelin, while vasodilators including prostacyclin, prostaglandin E₂, and nitric oxide are suppressed. Dysregulation of the renin-angiotensin and prostaglandin systems has also been described, with loss of the normal resistance to angiotensin II. More recently, anti-angiogenic factors have been implicated: increased levels of soluble fms-like tyrosine kinase-1 (sFlt-1), which binds and inactivates placental growth factor (PlGF) and vascular endothelial growth factor (VEGF), lead to reduced angiogenesis and endothelial dysfunction. DIC in preeclampsia and eclampsia is driven by endothelial injury, abnormal coagulation factor activity, and platelet consumption. Elevated synthesis of thromboplastic substances and decreased antithrombin III activity contribute to the procoagulant state. The characteristic lesion of eclampsia is thrombosis of renal arterioles and capillaries, and in severe cases, bilateral renal cortical necrosis may occur. The renal lesion of preeclamptic nephropathy primarily involves the glomeruli. Glomeruli appear enlarged due to endothelial cell swelling rather than hypercellularity. The visceral epithelial cells (podocytes) and capillary endothelium often display vacuolated cytoplasm due to lipid accumulation. Immunofluorescence typically

demonstrates fibrinogen deposition in mesangial and subendothelial regions, sometimes with associated basement membrane proteins. The prognosis is generally favorable, as hypertension and proteinuria regress within a few weeks after delivery [43].

13.10.6 Hereditary Glomerular Diseases

13.10.6.1 Alport Syndrome (AS)

Alport syndrome (AS) is a progressive hereditary nephritis characterized by hematuria, high-tone sensorineural hearing loss, and ocular abnormalities such as lens dislocation, posterior cataracts, and corneal or macular changes. The fundamental defect is in type IV collagen synthesis. Three genetic forms are recognized. The X-linked recessive form, caused by mutations in the COL4A5 gene, accounts for about 85% of cases. It affects males almost exclusively, with over 300 mutations described to date. In males, type IV collagen $\alpha 5$ chain is absent in glomerular and epidermal basement membranes, while females typically show segmental defects. Diagnosis can be supported by immunohistochemistry for COL4A5 in skin biopsies, which reveals absent or discontinuous staining in about 80% of cases. Autosomal recessive AS results from biallelic mutations in COL4A3 or COL4A4, affecting both sexes, whereas autosomal dominant AS is due to heterozygous mutations in the same genes. Hematuria, either microscopic or macroscopic, usually begins in childhood, and progression to renal failure varies by sex and genetic type. In men, all patients eventually develop end-stage renal disease (ESRD), either in the juvenile form around 20 years of age or the adult/nonprogressive form around 40 years. Women usually present with intermittent hematuria and rarely progress to renal failure. Prognostic indicators include early-onset gross hematuria, heavy proteinuria, nephrotic syndrome, and diffuse glomerular basement membrane (GBM) thickening. Extrarenal features include bilateral sensorineural hearing loss, typically developing after the first decade, and ocular lesions. The hallmark

ultrastructural lesion is irregular GBM thickening with a characteristic “basket-weave” pattern on electron microscopy. Immunofluorescence is typically negative [44].

13.10.6.2 Epstein Syndrome

Epstein syndrome is considered a variant of autosomal dominant Alport syndrome, associated with platelet dysfunction.

13.10.6.3 Thin Basement Membrane Nephropathy

Thin basement membrane nephropathy (benign familial hematuria) is a hereditary condition characterized by persistent microscopic hematuria, minimal proteinuria (≤ 500 mg/day), and preserved renal function. It is one of the most common causes of asymptomatic hematuria in both children and adults. While many cases show familial inheritance, often autosomal dominant, up to one-third are sporadic. Electron microscopy reveals uniformly thin GBM, but type IV collagen chains are preserved. If proteinuria, hypertension, and renal failure are absent, prognosis is excellent and no treatment is required. Affected individuals may serve as kidney donors.

13.10.6.4 Fabry Disease

Fabry disease is an X-linked recessive lysosomal storage disorder caused by deficiency of α -galactosidase A, leading to accumulation of glycosphingolipids in endothelial, epithelial, neuronal, and smooth muscle cells. Clinical manifestations begin in childhood or adolescence with neuropathic pain, angiokeratomas, corneal deposits, abdominal pain, and hypohidrosis. Progressive renal, cardiac, and cerebrovascular involvement occurs in adulthood, often leading to premature death. Renal manifestations typically appear in the second decade with hematuria and proteinuria, followed by renal dysfunction in the third decade. Podocytes are particularly affected, leading to proteinuria and, in some cases, nephrotic syndrome. About one-quarter of patients develop ESRD by their 40s. Hypertension occurs in about 30% of cases. Light microscopy shows lipid-laden podocytes, with additional deposits in tubular and endothelial cells. Electron

microscopy reveals characteristic lamellar inclusions (“zebra bodies” or myeloid bodies). Diagnosis is confirmed by α -galactosidase activity measurement in leukocytes or fibroblasts, along with family history and systemic findings.

13.10.6.5 Nail-Patella Syndrome

Nail-patella syndrome (hereditary onychoosteodysplasia) is an autosomal dominant disorder caused by mutations in the LMX1B gene on chromosome 9. It is characterized by nail dysplasia, patellar hypoplasia or aplasia, iliac horns, and elbow anomalies such as radial head dislocation. Renal involvement occurs in 30–50% of cases, presenting with hematuria, proteinuria, hypertension, or nephrotic syndrome, and may progress to ESRD in 10–30%. Histological findings range from normal glomeruli to focal or global glomerulosclerosis, with associated interstitial fibrosis and tubular atrophy. Immunofluorescence is usually negative, though IgM, C3, and C1q may be found in sclerotic lesions. Electron microscopy shows irregular GBM thickening with a moth-eaten appearance, lucent areas, collagen fibrils, and foot process effacement.

13.10.6.6 Collagen Type III Glomerulopathy

Collagen type III glomerulopathy is a rare hereditary disorder, more common in Japan, characterized by deposition of type III collagen fibrils in the mesangium and GBM. Both sporadic and familial (autosomal recessive) cases occur. Clinical manifestations include proteinuria, hypertension, and progressive renal failure, sometimes beginning in childhood. Elevated serum procollagen type III peptide is a consistent laboratory finding. Histology shows mesangial expansion and GBM thickening, while electron microscopy confirms subendothelial and mesangial fibrillar collagen deposition.

13.10.6.7 Fibronectin Glomerulopathy

Fibronectin glomerulopathy is a slowly progressive, autosomal dominant disease characterized

by massive deposition of fibronectin in the mesangium and subendothelial regions. Light microscopy reveals homogeneous PAS-positive, Congo red-negative deposits, which are immunohistochemically positive for fibronectin. Clinically, patients present with proteinuria, hematuria, hypertension, and gradual progression to ESRD. Altered podocyte VEGF-A expression has been implicated in the pathogenesis.

13.11 Tubulointerstitial Diseases

Tubulointerstitial diseases are a heterogeneous group of disorders in which the primary site of injury is the renal interstitium and tubules, although glomerular involvement may occur secondarily. Despite diverse etiologies, they share common functional disturbances, including impaired urinary concentration, defective acid secretion, reduced sodium reabsorption, hyperkalemia, and azotemia. Clinical presentations may be acute or chronic, depending on the underlying pathology [45] (Table 13.3).

13.11.1 Pyelonephritis

Pyelonephritis is defined as inflammation of the renal parenchyma and collecting system. It presents with three incidence peaks: infancy and early childhood, women of childbearing age, and both sexes after age 60. Acute pyelonephritis typically arises from ascending infections, often due to *Escherichia coli* and other coliform bacteria, sometimes staphylococci or fungi such as *Candida* or *Aspergillus*. It manifests cortical and medullary inflammation with neutrophil infiltration, abscesses, and tubular necrosis. Hematogenous spread, more common in immunocompromised hosts, results in cortical microabscesses with minimal medullary involvement. Chronic pyelonephritis is associated with obstructive uropathy or vesicoureteral reflux, leading to cortical thinning, calyceal dilation, tubular atrophy, and interstitial fibrosis.

Table 13.3 Classification of tubulointerstitial nephritis

Category	Subtypes/examples
Infectious	Acute pyelonephritis Chronic pyelonephritis: Obstructive Nonobstructive Xanthogranulomatous Malakoplakia
Obstructive	Hydronephrosis, nephrolithiasis, reflux
Allergic	Drug induced, vasculitis associated Associated with systemic lupus erythematosus (SLE) Anti-tubular basement membrane antibodies
Toxic	Aminoglycosides, cyclosporine, cisplatin, lithium, analgesics Heavy metals
Other	Radiotherapy, sarcoidosis, idiopathic

Complication of all these conditions is renal papillary necrosis. Its morphological stages are as follows:

Stage 1: Cortex appears normal; papillae are firm and gray.

Stage 2: Integrity of papillae is lost, and they become brownish. The medulla shows confluent necrotic foci, while the cortex demonstrates tubular atrophy, interstitial fibrosis, and inflammatory infiltrates.

Stage 3: Resembles chronic pyelonephritis. If necrotic papillae cannot be eliminated, urinary outflow is obstructed, leading to secondary glomerulosclerosis.

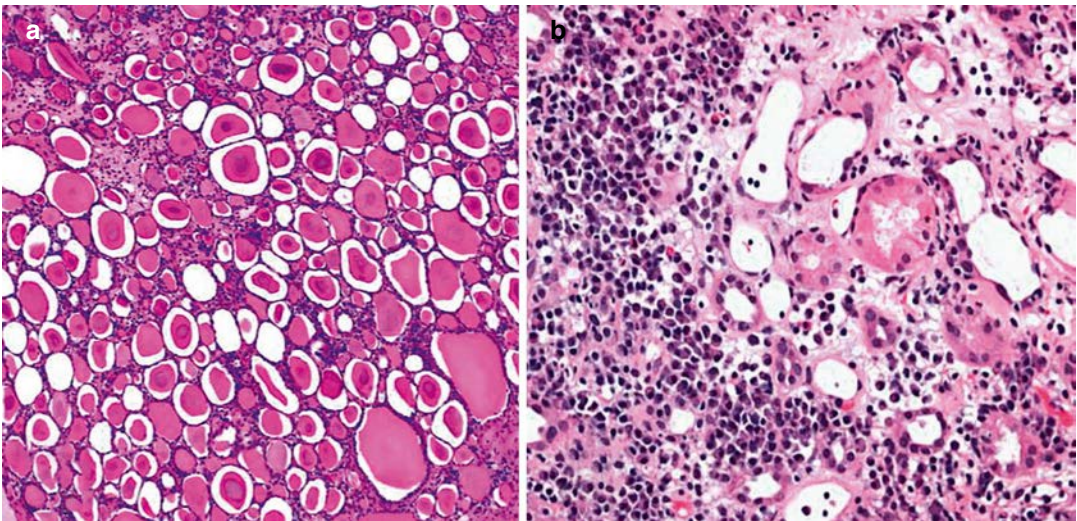


Fig. 13.17 (a) Thyroidization, (b) tubulointerstitial nephritis

Thyroidization, characterized by colloid-filled dilated tubules, is a distinctive feature (Fig. 13.17). Xanthogranulomatous pyelonephritis presents as a yellow, lobulated renal mass mimicking malignancy, usually unilateral and associated with obstruction, most often by calculi. The lesion consists of sheets of lipid-laden macrophages with inflammatory infiltrates. Michaelis-Gutmann bodies may be present, distinguishing it from malakoplakia.

13.11.2 Hydronephrosis

Hydronephrosis is dilation of the renal pelvis and calyces with parenchymal atrophy due to urinary tract obstruction. Causes may be congenital or acquired, including calculi, tumors, inflammatory strictures, pregnancy, or neurogenic bladder. Complete obstruction for 3 weeks or partial obstruction for 3 months produces irreversible renal damage.

13.11.3 Nephrolithiasis

Nephrolithiasis (renal calculi) arises in the renal pelvis or calyces, most commonly calcium oxalate or phosphate stones (65%), followed by uric acid, xanthine, cystine (20%), and magnesium ammonium phosphate (15%). Risk factors include genetic predisposition, male sex, age 25–45 years, low fluid intake, climate, and metabolic disorders such as hyperparathyroidism or renal tubular acidosis. Uric acid and cystine stones form in acidic urine, whereas struvite stones result from infection with urease-producing bacteria. Stones cause renal colic and may obstruct at narrow points such as the ureterovesical junction. Radiopacity varies by stone composition, with uric acid and xanthine stones being radiolucent.

13.11.4 Myeloma Kidney

Myeloma kidney results from light chain cast nephropathy, in which tubular lumina are obstructed by eosinophilic, laminated proteinaceous casts composed of immunoglobulin light chains and Tamm-Horsfall protein, often surrounded by multinucleated giant cells and associated with interstitial inflammation and fibrosis.

13.11.5 Acute Interstitial Nephritis

Acute interstitial nephritis most often follows exposure to drugs, including β -lactam antibiotics, rifampin, diuretics, and nonsteroidal anti-inflammatory drugs. Symptoms include fever, rash, and acute renal dysfunction. Histology shows interstitial edema, mixed inflammatory infiltrates with lymphocytes, plasma cells, macrophages, and eosinophils, and tubular epithelial injury. Removal of the offending agent usually leads to recovery.

13.11.6 Analgesic Nephropathy

Analgesic nephropathy results from long-term use of analgesics such as phenacetin, leading to papillary necrosis, chronic interstitial nephritis, anemia, and increased risk of urothelial carcinoma.

13.11.7 Calcineurin Inhibitor Nephrotoxicity

Calcineurin inhibitor nephrotoxicity (cyclosporine, tacrolimus) is a major cause of drug-induced renal injury, presenting with arteriolar lesions, striped interstitial fibrosis, tubular atrophy, and secondary focal segmental glomerulosclerosis. Acute toxicity may resemble hemolytic uremic syndrome, while chronic toxicity is characterized by interstitial fibrosis and is often irreversible.

13.11.8 Radiation Nephritis

Radiation nephritis occurs after therapeutic irradiation (>2300 rad) and may be acute, presenting weeks after exposure, or chronic, developing years later. Histological findings include glomerulosclerosis, vascular fibrosis, tubular atrophy, and sometimes fibrinoid necrosis.

13.11.9 Renal Papillary Necrosis

Renal papillary necrosis may complicate pyelonephritis or arise in association with obstruction, diabetes, sickle cell disease, analgesic abuse, vascular thrombosis, or long-term rifampin therapy. It progresses from focal necrosis with calcification to sloughing of papillae into the pelvis, potentially causing obstruction. Chronic cases resemble pyelonephritis with interstitial fibrosis and calcification.

13.11.10 Other Disorders

13.11.10.1 Acute Kidney Injury (AKI)

Acute kidney injury (AKI) is defined as sudden impairment of renal function with oliguria (<400 mL/day). Causes include acute tubular necrosis (ATN), rapidly progressive glomerulonephritis, vasculitis, papillary necrosis, and drug-induced nephritis. ATN, the most common cause, results from ischemic or toxic injury to tubular epithelial cells. Ischemic ATN is associated with shock and hypotension, while toxic ATN follows exposure to agents such as heavy metals, antibiotics, or radiocontrast. Histology shows loss of brush border, epithelial necrosis, tubular casts (composed of Tamm-Horsfall protein and plasma proteins), and regenerative changes. ATN is potentially reversible with supportive therapy.

13.11.10.2 Diffuse Cortical Necrosis

Diffuse cortical necrosis is a rare but catastrophic lesion usually seen in obstetric complications such as placental abruption or septic shock, often associated with disseminated intravascular coagulation. It produces widespread cortical ischemia and acute anuria, with rapid progression to uremia and high mortality without dialysis.

13.11.10.3 Chronic Glomerulonephritis

Chronic glomerulonephritis represents the end stage of many glomerular diseases and accounts for about 60% of chronic renal failure. The kidneys are small and granular, with diffuse scarring and obliteration of the glomeruli. Secondary vascular and tubular lesions accompany interstitial fibrosis and tubular atrophy. At this stage, the initiating lesion is no longer recognizable, and the kidneys are termed “end-stage kidneys.”

References

1. Nissen CJ, Moreno V, Davis VG, Walker PD. Increasing incidence of inadequate kidney biopsy samples over time: a 16-year retrospective analysis

- from a large national renal biopsy laboratory. *Kidney Int Rep.* 2021;7(2):251–8. <https://doi.org/10.1016/j.ekir.2021.11.026>.
2. Bersie-Larson LM, Gyoneva L, Goodman DJ, Dorfman KD, Segal Y, Barocas VH. Glomerular filtration and podocyte tensional homeostasis: importance of the minor type IV collagen network. *Biomech Model Mechanobiol.* 2020;19(6):2433–42. <https://doi.org/10.1007/s10237-020-01347-y>.
3. Naylor RW, Morais MRPT, Lennon R. Complexities of the glomerular basement membrane. *Nat Rev Nephrol.* 2021;17(2):112–27. <https://doi.org/10.1038/s41581-020-0329-y>.
4. Quinlan C, Rheault MN. Genetic basis of type IV collagen disorders of the kidney. *Clin J Am Soc Nephrol.* 2021;16(7):1101–9. <https://doi.org/10.2215/CJN.19171220>.
5. Taguchi A, Nishinakamura R. Higher-order kidney organogenesis from pluripotent stem cells. *Cell Stem Cell.* 2017;21(6):730–746.e6. <https://doi.org/10.1016/j.stem.2017.10.011>.
6. Kuure S, Sariola H. Mouse models of congenital kidney anomalies. *Adv Exp Med Biol.* 2020;1236:109–36. https://doi.org/10.1007/978-981-15-2389-2_5.
7. Messias N. Immunofluorescence use and techniques in glomerular diseases: a review. *Glomerular Dis.* 2024;4(1):227–40. <https://doi.org/10.1159/000542497>.
8. Shami GJ, Chen Z, Cheng D, Wisse E, Braet F, Shami GJ, Chen Z, Cheng D, et al. On the long-term storage of tissue for fluorescence and electron microscopy: lessons learned from rat liver samples. *Histochem Cell Biol.* 2025;163:12. <https://doi.org/10.1007/s00418-024-02334-5>.
9. Agrawal V, Sharma A. Diagnostic immunostaining of renal biopsies: an overview of markers for glomerular diseases. *Glomerular Dis.* 2025;5(1):176–90. <https://doi.org/10.1159/000545311>.
10. Haas M, et al. Consensus definitions for glomerular lesions by light and electron microscopy: recommendations from a working group of the Renal Pathology Society. *Kidney Int.* 2020;98(5):1120–34.
11. Vivarelli M, Massella L, Ruggiero B, Emma F. Minimal change disease. *Clin J Am Soc Nephrol.* 2017;12(2):332–45. <https://doi.org/10.2215/CJN.05000516>.
12. Glassock RJ. The pathogenesis of minimal change disease: a 100-year perspective. *Kidney Int.* 2019;96(2):274–6. <https://doi.org/10.1016/j.kint.2019.04.016>.
13. Zee J, et al. Kidney biopsy features most predictive of clinical outcomes in the spectrum of minimal change disease and focal segmental glomerulosclerosis. *J Am Soc Nephrol.* 2022;33(7):1411–26.
14. Altintas MM, Agarwal S, Sudhini Y, Zhu K, Wei C, Reiser J. Pathogenesis of focal segmental glomerulosclerosis and related disorders. *Annu Rev*

- Pathol. 2025;20(1):329–53. <https://doi.org/10.1146/annurev-pathol-051220-092001>.
15. Morales-Alvarez MC, Knob A, Rennke HG, Pollak MR, Denker BM. Clinical and pathological heterogeneity in FSGS due to INF2 mutations. *Kidney Int Rep.* 2022;7(12):2741–5. <https://doi.org/10.1016/j.ekir.2022.08.033>.
 16. Jungraithmayr TC, Hofer K, Cochat P, Chernin G, Cortina G, Fargue S, Grimm P, Kneuppel T, Kowarsch A, Neuhaus T, Pagel P, Pfeiffer KP, Schäfer F, Schönermarck U, Seeman T, Toenshoff B, Weber S, Winn MP, Zschocke J, Zimmerhackl LB. Screening for NPHS2 mutations may help predict FSGS recurrence after transplantation. *J Am Soc Nephrol.* 2011;22(3):579–85. <https://doi.org/10.1681/ASN.2010010029>.
 17. Riehle M, Büscher AK, Gohlke BO, Kaßmann M, Kolatsi-Joannou M, Bräsen JH, Nagel M, Becker JU, Winyard P, Hoyer PF, Preissner R, Krautwurst D, Gollasch M, Weber S, Harteneck C. TRPC6 G757D loss-of-function mutation associates with FSGS. *J Am Soc Nephrol.* 2016;27(9):2771–83. <https://doi.org/10.1681/ASN.2015030318>.
 18. Omar Faroque, Sultana N, Rahaman A, Islam SF, Alam MR, Ahmed AHH, Islam MN, Hossain RM. A clinicopathological study of C1q nephropathy: a single center experience. *Arch Nephrol Urol.* 2025;8(2):68–73. <https://doi.org/10.26502/anu.2644-2833097>.
 19. Sethi S, Madden B, Debiec H. Membranous nephropathy: pathogenesis, diagnosis, and treatment. *Lancet.* 2022;400(10366):911–25. [https://doi.org/10.1016/S0140-6736\(22\)01261-9](https://doi.org/10.1016/S0140-6736(22)01261-9).
 20. Alicic RZ, Rooney MT, Tuttle KR. Diabetic kidney disease: challenges, progress, and possibilities. *Clin J Am Soc Nephrol.* 2017;12(12):2032–45. <https://doi.org/10.2215/CJN.11491116>.
 21. Sethi S, Vrana JA, Theis JD, Dogan A. Amyloidosis: clinical pathologic correlation and classification. *Kidney Int.* 2022;101(1):43–59. <https://doi.org/10.1016/j.kint.2021.09.020>.
 22. Nasr SH, Sethi S. Fibrillary glomerulonephritis and related entities. *Kidney Int.* 2021;100(2):252–65. <https://doi.org/10.1016/j.kint.2021.03.015>.
 23. Herrera GA. Renal lesions associated with plasma cell dyscrasias: practical approach to diagnosis, new concepts, and challenges. *Arch Pathol Lab Med.* 2020;144(2):227–46. <https://doi.org/10.5858/arpa.2018-0337-RA>.
 24. Holmberg C, Antikainen M, Rönholm K. Congenital nephrotic syndrome: recent advances. *Pediatr Nephrol.* 2021;36(9):2649–62. <https://doi.org/10.1007/s00467-020-04850-8>.
 25. Niaudet P. Genetic forms of nephrotic syndrome. *Nephrol Dial Transplant.* 2020;35(8):1350–6. <https://doi.org/10.1093/ndt/gfaa040>.
 26. Satoskar AA, Nadasdy T, Nadasdy G. Postinfectious glomerulonephritis in the modern era: experience from a North American center. *Am J Kidney Dis.* 2020;76(3):398–407. <https://doi.org/10.1053/j.ajkd.2020.02.435>.
 27. Bomback AS, Appel GB. Updates on the complement system in glomerular disease. *Semin Nephrol.* 2018;38(5):467–74. <https://doi.org/10.1016/j.semnephrol.2018.07.003>.
 28. Larsen CP, Cossey LN, De Vriese AS, et al. DDD (Dense Deposit Disease) and C3 glomerulonephritis: reorganizing classification. *Kidney Int.* 2014;86(2):371–7. <https://doi.org/10.1038/ki.2014.112>.
 29. Coppo R. IgM nephropathy revisited: diagnostic considerations and pathogenesis. *Nephrol Dial Transplant.* 2019;34(4):546–53. <https://doi.org/10.1093/ndt/gfy171>.
 30. Rodrigues JC, Haas M, Reich HN. IgA nephropathy. *Clin J Am Soc Nephrol.* 2017;12(4):677–86. <https://doi.org/10.2215/CJN.07420716>.
 31. Trimarchi H, Barratt J, Catran DC, et al. Oxford classification of IgA nephropathy 2016: an update. *Kidney Int.* 2017;91(5):1014–21.
 32. Jennette JC, Falk RJ. Crescentic glomerulonephritis and rapidly progressive glomerulonephritis. *Kidney Int.* 2017;92(2):297–314. <https://doi.org/10.1016/j.kint.2017.01.033>.
 33. McAdoo SP, Pusey CD. Anti-GBM disease: clinical features and treatment. *Semin Nephrol.* 2017;37(5):494–503. <https://doi.org/10.1016/j.semnephrol.2017.07.004>.
 34. Ponticelli C, Glasscock RJ. Rapidly progressive crescentic glomerulonephritis: an update. *Nephrol Dial Transplant.* 2020;35(3):389–95. <https://doi.org/10.1093/ndt/gfz287>.
 35. Kitching AR, Anders HJ, Basu N, et al. ANCA-associated vasculitis. *Nat Rev Dis Primers.* 2020;6(1):71. <https://doi.org/10.1038/s41572-020-0204-y>.
 36. Anders HJ, Saxena R, Zhao MH, Parodis I, Salmon JE, Mohan C. Lupus nephritis. *Nat Rev Dis Primers.* 2020;6(1):7. <https://doi.org/10.1038/s41572-019-0141-9>.
 37. Tektonidou MG, Dasgupta A, Ward MM. Risk of end-stage renal disease in patients with lupus nephritis, 1971–2015: a systematic review and Bayesian meta-analysis. *Arthritis Rheumatol.* 2016;68(6):1432–41. <https://doi.org/10.1002/art.39594>.
 38. Ecclestone T, Watts RA. Classification and epidemiology of vasculitis: emerging concepts. *Best Pract Res Clin Rheumatol.* 2023;37(1):101845. <https://doi.org/10.1016/j.berh.2023.101845>.
 39. Sharma P, Zonozi R, Geetha D. ANCA-associated vasculitis. *Adv Kidney Dis Health.* 2024;31(3):194–205. <https://doi.org/10.1053/j.akdh.2024.04.005>.

40. Parums DV. A review of IgA vasculitis (Henoch-Schönlein purpura) past, present, and future. *Med Sci Monit.* 2024;30:e943912. <https://doi.org/10.12659/MSM.943912>.
41. Loirat C, Fakhouri F, Ariceta G, et al. An international consensus approach to the management of atypical hemolytic uremic syndrome in children. *Pediatr Nephrol.* 2016;31(1):15–39.
42. George JN, Nester CM. Syndromes of thrombotic microangiopathy. *N Engl J Med.* 2014;371(7):654–66.
43. Rana S, Lemoine E, Granger JP, Karumanchi SA. Preeclampsia: pathophysiology, challenges, and perspectives. *Circ Res.* 2019;124(7):1094–112.
44. Blasco M, Quiroga B, García-Aznar JM, Castro-Alonso C, Fernández-Granados SJ, Luna E, et al. Genetic characterization of kidney failure of unknown etiology in Spain: findings from the GENSEN study. *Am J Kidney Dis.* 2024;84(6):719–730.e1. <https://doi.org/10.1053/j.ajkd.2024.04.021>.
45. Rodríguez-Iturbe B, Johnson RJ. Tubulointerstitial disease. In: Tisher CC, Brenner BM, editors. *Brenner and Rector's the kidney*. 11th ed. Philadelphia: Elsevier; 2020. p. 1045–100.

A. Cysts of the Kidney

Cystic diseases of the kidney are discussed briefly in this chapter because, although they primarily cause renal dysfunction, they also present as space-occupying lesions that may mimic or coexist with neoplasms. The spectrum includes hereditary malformation complexes with renal cysts, multicystic dysplastic kidney, autosomal recessive and autosomal dominant polycystic kidney disease, medullary sponge kidney, the nephronophthisis-medullary cystic disease spectrum, simple (localized) renal cysts, acquired cystic kidney disease related to long-term dialysis, and syndromic renal cyst (Table 14.1). Correct classification matters for clinical counseling, prognosis, and tumor risk [1–3].

- *Multicystic dysplastic kidney* typically presents in infancy, often unilaterally, as a grapelike cluster of variable cysts without corticomedullary differentiation. Microscopy shows immature, dysplastic tubules and cysts within cellular mesenchyme, frequently accompanied by cartilage islands; ureteral atresia or stenosis and contralateral urinary tract anomalies

are common. Many lesions involute with growth, while early nephrectomy is reserved for symptomatic masses.

- *Polycystic kidney disease* occurs in two broad genetic forms. *Autosomal recessive polycystic kidney disease (ARPKD)*, usually related to PKHD1 alterations, reflects collecting-duct derived cysts and is part of a hepatorenal fibrocystic spectrum with periportal fibrosis and bile duct proliferation; prenatal or infantile presentation with enlarged echogenic kidneys is typical. *Autosomal dominant polycystic kidney disease (ADPKD)*, most often due to PKD1 or PKD2, usually manifests later with massively enlarged, “spongy” kidneys containing innumerable cortical and medullary cysts lined by cuboidal epithelium; extrarenal cysts are frequent. In both forms, compressed native tubules and glomeruli may be seen between cysts, underscoring the developmental role of the affected proteins in nephrogenesis.
- *Medullary sponge kidney* consists of congenital ectasia of collecting ducts, most often discovered incidentally in adults; renal function is usually preserved, but infection, nephrocalcinosis, and stones may complicate the course.
- *Nephronophthisis-medullary cystic disease complex* is a *hereditary tubulointerstitial process* characterized by corticomedullary junction cysts, cortical

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Table 14.1 Cystic kidney diseases

Entity	Presentation	Pathology	Genetics/assoc.	Tumor risk/notes
Multicystic dysplastic kidney (MCDK)	Prenatal/infancy; unilateral mass; contralateral anomalies common	Grapelike cysts; no corticomedullary differentiation; dysplastic/immature tubules ± cartilage	Developmental; ureteral atresia/stenosis; vesicoureteral reflux	Low risk; many involute; nephrectomy if symptomatic; US ± DMSA/MAG3 for function
Autosomal recessive PKD (ARPKD)	Perinatal/infantile; enlarged echogenic kidneys; hepatic disease/portal HTN	Collecting-duct derived radial cortical cysts; dilated medullary channels; congenital hepatic fibrosis	PKHD1; hepatorenal fibrocystic spectrum	Tumor risk not primary; outcomes driven by hepatic/renal complications
Autosomal dominant PKD (ADPKD)	Adolescence-adulthood; flank pain, hematuria, HTN; extrarenal cysts	Massively enlarged kidneys; innumerable cortical/medullary cysts; compressed parenchyma	PKD1, PKD2; systemic cystic disease	RCC risk debated; manage BP/complications; screen family
Medullary sponge kidney (MSK)	Often adult incidental; stones/infection/hematuria possible	Congenital ectasia of medullary collecting ducts; preserved function	Usually sporadic	No inherent RCC predisposition; prevent stones; treat infections
Nephronophthisis/medullary cystic disease	Childhood-adolescence (NPH) or adult (MCD); polyuria/polydipsia; progressive renal failure	Corticomedullary cysts; interstitial fibrosis/inflammation; tubular atrophy; glomerulosclerosis	NPHP (AR) or MCD (AD) genes; renal-retinal variants	Not a tumor-predisposition disorder; genetic testing; plan for renal replacement
Simple renal cyst	Incidental; thin-walled cortical lesion	Solitary, benign cyst	Non-syndromic	Benign; complex lesions by Bosniak; radiology-led follow-up
Acquired cystic kidney disease (ACKD)	ESRD on long-term dialysis; often asymptomatic	Multiple cortical/medullary cysts; flattened/hyperplastic lining; calcium oxalate crystals	Acquired in ESRD	↑ RCC risk (cyst wall carcinomas) with dialysis duration; individualized surveillance
Syndromic cysts (TSC, VHL)	Variable; cysts may precede tumors	TSC, hyperplastic eosinophilic lining; VHL, clear-cell-like lining	TSC1/TSC2; VHL	High renal neoplasia risk; protocolized imaging; genetic counseling

interstitial fibrosis and chronic inflammation, tubular atrophy, and secondary glomerulosclerosis. Patients develop an early concentrating defect with polyuria and polydipsia and may progress to kidney failure; ocular findings occur in some renal-retinal variants.

- *Simple renal cysts* are usually incidental, solitary cortical lesions with thin walls; management is radiology driven.

- *Acquired cystic kidney disease* arises in end-stage kidney disease after prolonged dialysis, with multiple cortical and medullary cysts lined by flattened or hyperplastic epithelium; calcium oxalate crystals are common within the lumina. Importantly, this setting confers an increased risk of renal cell carcinoma arising in cyst walls, so follow-up should be individualized.

- *Syndromic renal cysts*: Some conditions—especially tuberous sclerosis complex caused by pathogenic variants in TSC1 or TSC2 and von Hippel-Lindau disease due to VHL alterations—carry a well-established predisposition to renal neoplasia; renal cysts in these settings may show hyperplastic or clear-cell-like epithelium and warrant surveillance.

Nuclear medicine studies are often used to support differential diagnosis and functional assessment. Technetium-99 m dimercaptosuccinic acid (DMSA) binds to the cortical tubular cell fraction and provides high-resolution static images of cortical morphology; technetium-99 m diethylenetriamine pentaacetic acid (DTPA) is purely filtered and is used to estimate glomerular filtration rate; technetium-99 m mercaptoacetyl-triglycine (MAG3) and technetium-99 m ethylenedicycysteine are filtered and tubularly secreted and are preferred for effective renal plasma flow estimation and dynamic studies, particularly when obstruction or reduced function is suspected. In practice, correlation of imaging with clinical context and histopathology (when indicated) clarifies whether a cystic lesion is a developmental malformation, a hereditary cystic disease with systemic implications, a benign incidental finding, or an acquired process with increased neoplastic risk [1–3] (Fig. 14.1).

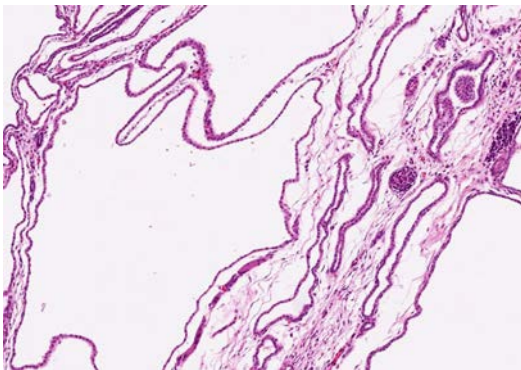


Fig. 14.1 Note the cysts covered with cuboidal epithelium without atypia and the occasional rudimentary glomeruli in ARPKD

- B. *Kidney tumors in adult*: In the adult population, epithelial-derived benign renal tumors include papillary adenoma, oncocytoma, and metanephric adenoma [4].

14.1 Benign Neoplasms

- *Papillary adenomas* are the most common benign renal tumors and are defined by the WHO as tumors measuring ≤ 15 mm in diameter, originating from the renal tubular epithelium [1]. These tumors are asymptomatic and are typically detected incidentally in nephrectomy specimens performed for unrelated reasons. Cytogenetically, trisomy 7 and 17 and loss of the Y chromosome are frequently observed [1]. Macroscopically, they appear as well-circumscribed, nonencapsulated, yellow-white nodules. Microscopically, they consist of low-grade cells forming papillary and tubular structures. Differential diagnosis from papillary renal cell carcinoma (RCC) is critical, although immunohistochemistry is not helpful in this distinction. Key distinguishing features include small size, low nuclear grade, and absence of a capsule [4, 5].
- *Renal oncocytomas* are benign, well-circumscribed, nonencapsulated, and typically asymptomatic masses. They may be multifocal and, rarely, bilateral. Their gross appearance is characteristic: mahogany brown or yellowish-colored masses. The absence of gross necrosis is a diagnostic criterion. A central stellate scar is observed in approximately one-third of cases. Histopathologically, oncocytomas are composed of uniform large cells with eosinophilic, granular cytoplasm and prominent central nucleoli, arranged in solid nests, micro- or macrocystic spaces, and tubules (Fig. 14.2). The stroma is hypocellular, and mitotic activity is low [4, 6].

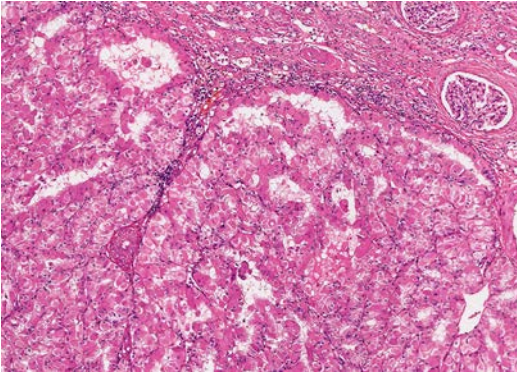


Fig. 14.2 Oncocytoma

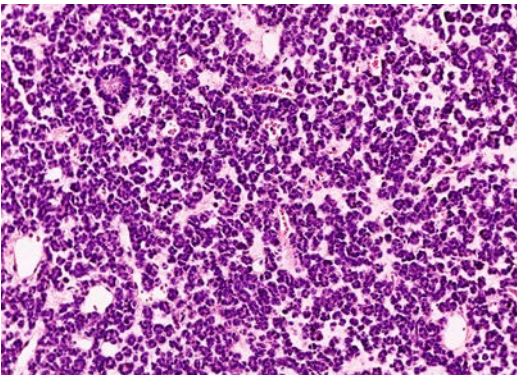


Fig. 14.3 Metanephric adenoma

- *Metanephric adenomas* are benign tumors that typically occur in young- or middle-aged women and are composed of fine tubules or papillary structures, histologically resembling but distinct from papillary adenomas (Fig. 14.3) [4, 7, 8].

14.2 Malignant Neoplasms

The diagnosis of malignant renal tumors is usually straightforward. Although microscopic metastases may occasionally be identified at autopsy, the kidney is not a common site for clinically evident metastatic deposits. Clinically detectable renal metastases are considerably rarer, despite the fact that the kidneys receive nearly 20% of the total cardiac output. Data from autopsy series indicates an incidence ranging between 2.4% and 12.6% among patients who

die of metastatic malignancy, most of which originated from another primary renal carcinoma. Consequently, nearly all malignant tumors of the kidney are primary in origin. Apart from the contralateral kidney, the most frequent primary sources of metastases to the kidney include the lung, breast, and gastrointestinal tract, especially from the esophagus, stomach, and colon, as well as from malignant melanoma of skin. When only primary renal tumors are considered, a consistent age-related pattern is observed: about 85% of malignant renal tumors in childhood are Wilms tumors, whereas 80–90% of adult renal malignancies correspond to renal cell carcinoma (RCC). The increased availability of cross-sectional imaging, particularly computed tomography (CT) and magnetic resonance imaging (MRI), together with improvements in oncologic therapies, has led to a rising number of reported cases of metastatic deposits to the kidney in recent years [4, 9].

Renal cell carcinoma (RCC) accounts for approximately 2% of all cancers worldwide. Risk factors include obesity (in both men and women), smoking, hypertension, use of certain antihypertensive drugs, long-term dialysis, exposure to heavy metals, petroleum products, and genetic predispositions. Approximately one-third of renal cell carcinoma (RCC) cases are diagnosed at the metastatic stage. In recent years, the introduction of targeted therapies such as tyrosine kinase inhibitors and immune checkpoint inhibitors like PD-L1 has significantly improved outcomes, with 5-year survival rates reaching up to 75%. RCC has traditionally been classified based on architectural and cytological features. However, recent molecular studies have revealed chromosomal and molecular alterations involved in tumor pathogenesis, necessitating updated classification systems. Nevertheless, it is noteworthy that RCC subtypes often lack clear genotype-phenotype correlations. Even RCC subtypes that fall within the same morphological classification may differ significantly in terms of etiology, pathogenesis, and prognosis. Despite these molecular insights, current evidence suggests that it is still premature to adopt a purely molecular classification for RCC. As such, RCCs

are currently classified into two groups: those defined by morphological and those by molecular characteristics. Grading of RCCs is still recommended to be based on nuclear pleomorphism and nucleolar prominence, although this grading system has only demonstrated clinical relevance in clear cell RCC and papillary RCC (Table 14.2). Pathological tumor stage significantly impacts prognosis and is primarily determined by the size of the primary tumor (Table 14.3). In radical nephrectomy specimens, the Gerota fascia, which is resected along with the renal parenchyma, lacks a distinct histological architecture.

Table 14.2 WHO/International Society of Urological Pathology (ISUP) grading system for clear cell renal cell carcinoma

Grade	Description
Grade 1	Nucleoli absent or inconspicuous and basophilic at ×400 magnification
Grade 2	Eosinophilic nucleoli observed at ×400 but not prominent at ×100 magnification
Grade 3	Nucleoli prominent and eosinophilic at ×100 magnification
Grade 4	Carcinoma cells display extreme nuclear pleomorphism, tumor giant cells, and/or any amount of sarcomatoid or rhabdoid differentiation

Table 14.3 TNM staging of renal tumors’ antibodies used in the differential diagnosis of renal neoplasms

<i>Primary tumor (pT)</i>
pTX: primary tumor cannot be assessed
pT0: no evidence of primary tumor
pT1a: ≤4 cm, limited to the kidney
pT1b: >4 cm and ≤7 cm, limited to the kidney
pT2a: >7 cm and ≤10 cm, limited to the kidney
pT2b: >10 cm, limited to the kidney
pT3a: invades renal vein/branches, perirenal fat, renal sinus fat, or pelvicalyceal system
pT3b: extends into the vena cava below the diaphragm
pT3c: extends into the vena cava above the diaphragm or invades the vena cava wall
pT4: invades beyond the Gerota fascia, including direct extension to the adrenal gland
<i>Regional lymph nodes (pN)</i>
pNX: cannot be assessed
pN0: no regional lymph node metastasis
pN1: regional lymph node metastasis
<i>Distant metastasis (pM)</i>
pM1: distant metastasis, including noncontiguous adrenal involvement

Therefore, in cases where microscopic tumor involvement is identified at the soft tissue surgical margin, it is interpreted as invasion of the Gerota fascia and thus corresponds to a pT4 stage. Expansile growth of renal cell carcinomas (RCCs) into the perinephric adipose tissue is commonly observed. These foci are typically surrounded by a well-demarcated fibrovascular capsule and should not be interpreted as extracapsular extension. In tumors larger than 7 cm in diameter, invasion into the renal sinus and renal veins are frequently encountered. Consequently, although tumors exceeding 10 cm are classified as pT2b, the potential for concomitant invasion of the renal sinus or renal pelvis should be taken into consideration [4, 10, 11]. Some specific antibodies are used for differential diagnosis of renal neoplasms (Table 14.4). These antibodies are summarized as follows:

- PAX8, nuclear positivity, is seen in all renal epithelial neoplasms. It is a reliable marker for renal origin.
- CAIX, strong membranous expression, is typical for clear cell RCC, but usually negative in others.
- CD10 is common in clear cell and papillary RCC; luminal staining pattern is seen in papillary type.
- CK7 is expressed in papillary, chromophobe, oncocytoma, and collecting duct carcinoma.
- AMACR is positive in papillary RCC but variably in metanephric adenoma.
- CD117 is useful to distinguish chromophobe RCC and oncocytoma (both positive) from clear cell RCC.
- Vimentin is positive in clear cell and papillary RCC, while negative in chromophobe and oncocytoma.
- INI1 is lost in renal medullary carcinoma, retained in others.
- p63/HMWCK is positive in collecting duct carcinoma and renal medullary carcinoma.
- CD57 is often positive in metanephric adenoma.

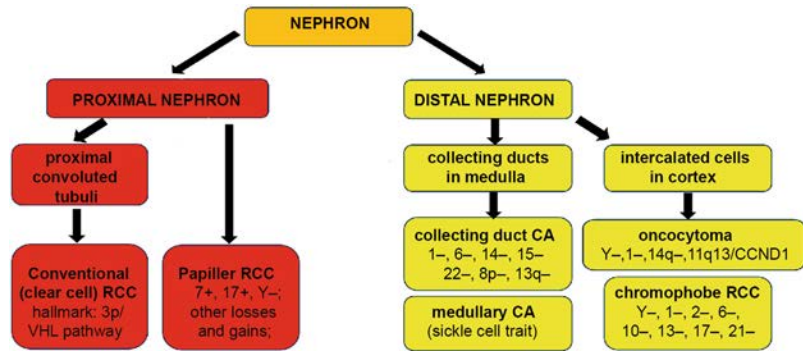
Approximately 60–75% of RCCs are of the *clear cell subtype (CCRCC)* and they originate from epithelium of proximal convoluted tubule

Table 14.4 Antibodies used in the differential diagnosis of renal neoplasms

Antibody	Clear cell RCC	Papillary RCC	Chromophobe RCC	Oncocytoma	Metanephric adenoma	Collecting duct carcinoma	Renal medullary carcinoma
PAX8	+	+	+	+	+	+	+
CAIX (membranous)	+	±	—	—	—	—	—
CD10	+	+	±	—	+	—	—
CK7	—	+	+	±	+	+	+
AMACR (P504S)	+	+	—	—	±	—	—
CD117 (KIT)	—	—	+	+	—	—	—
Vimentin	±	+	—	—	—	+	+
TFE3	—	—	—	—	—	—	—
HMB45	—	—	—	—	—	—	—
Cathepsin K	—	—	—	—	—	—	—
HMWCK	—	—	+	+	—	+	+
P63	—	—	—	—	—	+	+
INI1	+	+	+	+	+	+	—
OCT4	—	—	—	—	—	?	?
CD57	—	—	—	—	+	—	—

+ positive, — negative, ± variable expression, ? data is limited

Fig. 14.4 Origins of renal neoplasms



(Fig. 14.4). While most cases are sporadic, some occur as components of hereditary syndromes such as Von Hippel-Lindau (VHL) and Cowden syndrome. In the majority of CCRCCs, loss of the short arm of chromosome 3 (3p) and inactivation of the VHL gene via mutation or methylation are observed. In hypoxic tumor regions where necrosis occurs, the absence or dysfunction of pVHL leads to overexpression of HIF1- α , which, in cooperation with HIF2, translocates to the nucleus and activates downstream effectors including VEGF, GLUT1, CA9, EDGF, PDGF, and EPO. These molecules enable tumor cells to evade the deleterious effects of hypoxia and contribute to CCRCC progression. Additionally, losses of genes such as PBRM1, BAP1, and SETD2, which are also located on chromosome 3p, play important roles in CCRCC pathogenesis. Tumors with BAP1 mutations tend to exhibit more aggressive behavior. Macroscopically, CCRCCs appear as masses ranging from 1 to 25 cm in diameter, with a yellow cut surface. Cystic areas are more frequently observed in low-grade tumors, while necrosis and hemorrhage become more prominent with increasing grade. The classic microscopic pattern includes tubular structures, solid nests, and alveolar arrangements composed of cells with abundant clear cytoplasm. Some tumors exhibit marked histological heterogeneity, and as the grade increases, eosinophilic cytoplasm, giant cells, and spindle or rhabdoid morphology may be observed. Immunohistochemically, CCRCCs are positive for AE1/AE3, vimentin, CD10, CAIX, and RCC marker, while AMACR, CK7, and CD117 are typically negative. CCRCCs com-

monly metastasize via hematogenous routes. Prognostic parameters include tumor stage, nuclear grade, presence of sarcomatoid or rhabdoid differentiation, and tumor necrosis [10, 11].

Clear cell renal cell carcinomas with *fibromyxomatous stroma* typically present as small, well-circumscribed masses. The presence of fibromuscular bands surrounding both the mass and tumor cells gives rise to a multinodular appearance. Microscopically, the tumors are composed of tubular, papillary, and acinar structures formed by cells with abundant clear or finely granular cytoplasm (Fig. 14.5). Immunohistochemically, the tumor cells show diffuse positivity with CA IX and focal or diffuse positivity with CK7. Somatic mutations are frequently identified in the *ELOC* gene located on chromosome 8 and in *TSC1* and *TSC2* genes located on chromosomes 9 and 16, respectively [12].

Multilocular cystic renal neoplasms of low malignant potential (MCNLMPs) are renal tumors that present as multiloculated, cystic masses. They account for approximately 10% of all cystic renal tumors and harbor VHL gene alterations. The cysts lack solid nodules or areas of necrosis within their walls. In most cases, the tumor diameter is 7 cm or less (pT1). Microscopically, the cysts are lined by cells with clear cytoplasm and low nuclear grade (WHO grade 1 or 2). These cells may form small clusters within the fibrous septa between cysts or in the surrounding fibrous pseudocapsule. The presence of necrosis, frequent mitoses, lymphovascular invasion, or features of rhabdoid or sarcomatoid differentiation argues against the diagnosis. The

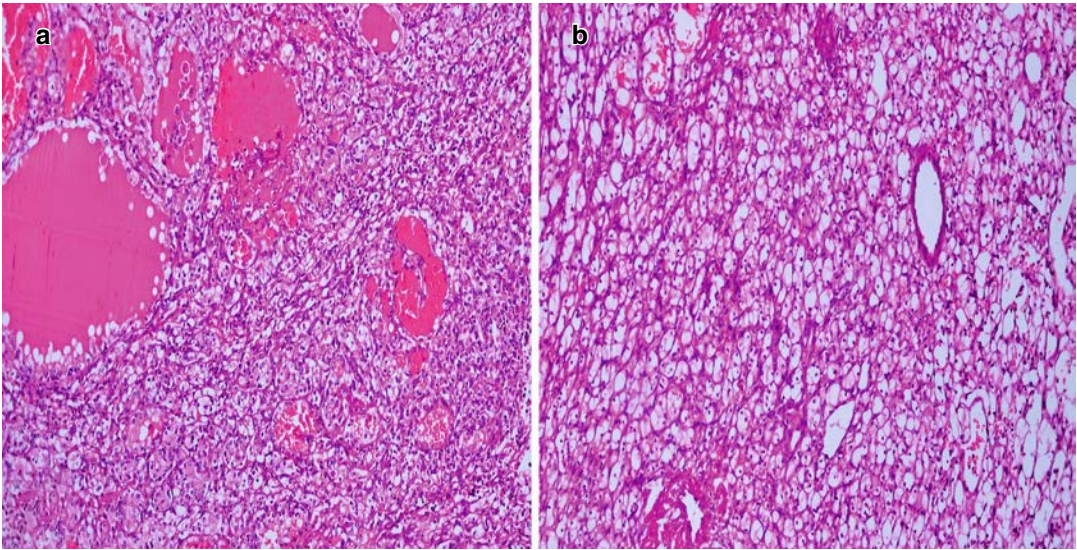


Fig. 14.5 (a) Clear cell RCC with cystic changes, nested architecture, and thin-walled vessels (HE, $\times 100$), (b) clear cell RCC ISUP grade 1 with inconspicuous nucleoli (HE $\times 200$)

absence of papillary architecture is also essential for the differential diagnosis of clear cell papillary renal cell tumors. A definitive diagnosis should be avoided on needle biopsy specimens due to limited sampling, as distinction from cystic CCRCC and clear cell papillary renal cell tumors may be impossible. Long-term follow-up studies have reported no cases of progression or metastasis associated with MCNLMP [13].

Clear cell papillary renal cell tumor (CCPRCT) is characterized as a low-grade, low-stage neoplasm exhibiting focal papillary architecture lined by cuboidal to flat cells with clear cytoplasm, in the absence of VHL gene alterations. Approximately one-fourth of cases demonstrate multifocal and bilateral involvement, and more than half are associated with a concurrent, histologically distinct subtype of renal cell carcinoma. Despite their low mutational burden, these tumors display a unique metabolic phenotype marked by mitochondrial DNA depletion, consequent oxidative stress, and sorbitol accumulation. Grossly, they typically present as small (<4 cm), well-circumscribed, and encapsulated masses, often containing cystic areas. Histologically, the tumors show focal papillary and tubular architecture composed of clear cells with a distinctive luminal orientation of the nuclei. Immunohistochemically, they exhibit dif-

fuse expressions of CAIX and CK7, while staining for CD10 and AMACR is negative. A characteristic “cuplike” staining pattern for CAIX is a diagnostic hallmark [14].

Papillary renal cell carcinoma (PRCC) represents the second most prevalent histological subtype of renal cell carcinoma. It exhibits marked molecular heterogeneity, with recurrent chromosomal abnormalities including trisomy of chromosomes 7 and 17 and loss of the Y chromosome. Alterations in the *MET* proto-oncogene are predominantly associated with low-grade tumors. In contrast, high-grade PRCCs frequently harbor aberrations in *CDKN2A*, components of the MYC signaling axis, and genes involved in the NRF2/ARE oxidative stress response pathway. Grossly, PRCCs are typically well-circumscribed neoplasms, often exhibiting multifocal and bilateral distribution. Their macroscopic appearance can vary considerably due to secondary changes such as hemorrhage, necrosis, and cystic degeneration. Histologically, the classic architecture is characterized by papillary and tubulopapillary structures lined by cuboidal cells with scant basophilic cytoplasm. Although not pathognomonic, the presence of stromal foamy macrophages and psammoma bodies can support the diagnosis. Approximately 50% of PRCCs display a heterogeneous architectural profile, incorporat-

ing patterns beyond the classic morphology. These may include solid, microcystic, micropapillary, hobnail, Warthin-like, and biphasic configurations. Emerging evidence suggests that such patterns, some of which are associated with adverse clinicopathological features, and grading provide prognostically relevant information. As a result, the traditional binary classification into type 1 and type 2 PRCC is no longer endorsed. While these morphologic variants should not be regarded as discrete subtypes, their documentation in diagnostic reports is recommended due to their potential clinical implications. Among these, the papillary neoplasm with reverse polarity has garnered attention owing to its distinctive morphologic and immunophenotypic characteristics. These tumors are composed of delicate papillae lined by low-grade oncocyctic cells demonstrating nuclear polarization away from the basement membrane. Immunohistochemically, these tumors typically exhibit diffuse GATA3 positivity, are negative for vimentin and CA9, and show weak expression of AMACR. Notably, KRAS mutations have been frequently reported in RPPNs, distinguishing them from conventional PRCCs. The WHO/International Society of Urological Pathology (WHO/ISUP) grading

system is applicable to PRCC and has been validated as a robust prognostic tool. While diagnostic challenges are uncommon in low-grade tumors, the differential diagnosis of high-grade PRCCs may include a spectrum of other renal neoplasms. Immunohistochemical evaluation often reveals diffuse and strong AMACR positivity across all architectural patterns. CK7 is typically diffusely expressed, although this reactivity may be diminished or absent in eosinophilic tumors. In addition, vimentin and CD10 expression is commonly observed [15–17].

TFE3-rearranged renal cell carcinomas (RCCs) are characterized by gene fusions involving TFE3 with various partner genes. Microscopically, these tumors often exhibit morphological features that can mimic several subtypes of renal cell carcinoma; however, the characteristic histology typically comprises papillary architecture composed of clear cells accompanied by psammoma bodies. A definitive diagnosis is supported by strong nuclear immunoreactivity for TFE3. In addition, cathepsin K expression, observed in more than half of the cases, serves as a valuable ancillary diagnostic marker. Clinically, these tumors demonstrate a course similar to that of clear cell renal cell carcinoma [17] (Fig. 14.6).

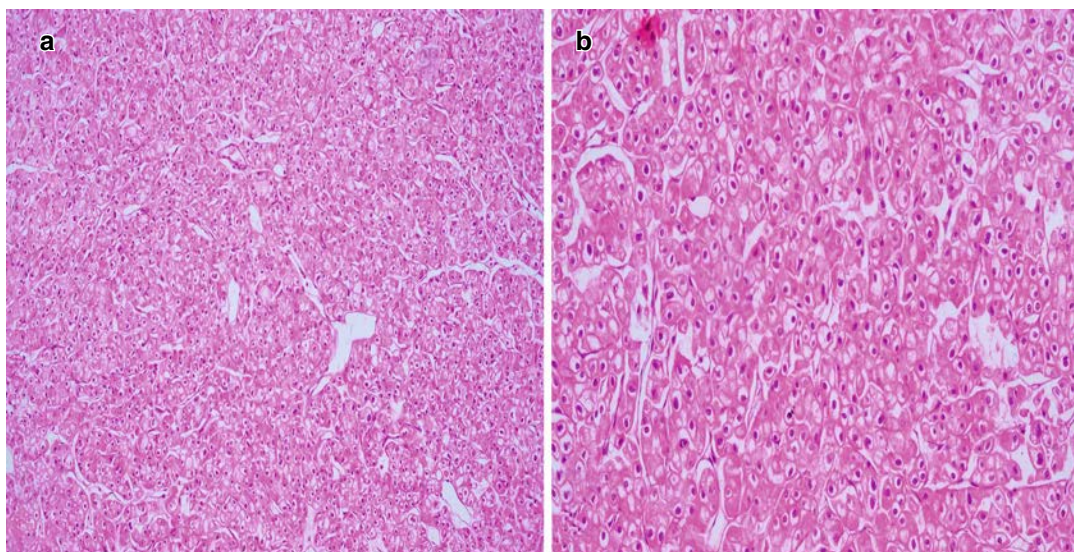


Fig. 14.6 (a) Chromophobe RCC growing in solid confluent sheets separated by thin septa (HE× 100), (b) chromophobe RCC showing characteristic hyperchromatic

nuclei with irregular contours (raisinoid/koilocytic-like) and perinuclear clear halos (HE× 400)

Chromophobe renal cell carcinoma (ChRCC), accounting for approximately 5% of all renal cell carcinomas, is typically a well-circumscribed tumor with a characteristic gross appearance, exhibiting a cut surface that ranges in color from yellow to mahogany red. In a subset of cases, a central stellate scar may be observed within the mass. These tumors generally form solid masses. Microscopically, ChRCCs are composed of solid nests of tumor cells characterized by distinct cytoplasmic borders, pale foamy or brightly eosinophilic cytoplasm, and hyperchromatic nuclei often accompanied by perinuclear clearing (haloes). Alveolar, papillary, or sarcomatoid patterns may occasionally be seen. Nuclear features frequently include multinucleation and a wrinkled, raisinoid appearance. The tumor nests are surrounded by a thin, vascular stroma. Immunohistochemically, the majority of ChRCCs exhibit strong and diffuse staining with cytokeratin 7 (CK7), a feature that aids in the differential diagnosis from oncocytoma. In contrast, oncocytomas are either negative for CK7 or show only limited staining in small clusters of cells. In addition to CK7, ChRCCs also commonly express KIT (CD117). They are typically negative for AMACR, CA9, and vimentin. CD10 may show focal positivity in some cases. Histological grading is not recommended for ChRCC. Among the most important prognostic parameters is the tumor stage. The presence of tumor necrosis and sarcomatoid differentiation are also associated with unfavorable prognosis. ChRCCs are characterized by a low somatic mutation rate [8]. Although mitochondrial DNA mutations are frequently observed, they are not specific to ChRCC [18].

Collecting duct carcinomas (CDCs), which constitute a very small subset (<1%) of malignant renal tumors, are centrally located, clinically aggressive neoplasms arising from the Bellini ducts of the renal medulla. Nearly half of the cases present distant metastases involving organs such as the lungs, liver, and bones. Cytogenetic and molecular studies have revealed chromosomal aberrations and molecular alterations distinct from those observed in other subtypes of renal cell carcinoma (RCC) and urothelial carcinoma. Macroscopically, CDCs appear as large,

ill-defined, multinodular masses within the renal parenchyma, frequently extending into the cortex and renal sinus. Satellite nodules, hemorrhage, and necrosis are commonly observed. Histologically, the typical appearance consists of irregular glandular structures exhibiting an infiltrative growth pattern within a desmoplastic fibrous stroma. In addition to this classic architecture, solid, trabecular, and microcystic patterns may also be present. Tumor cells display large, pleomorphic vesicular nuclei with prominent nucleoli and eosinophilic cytoplasm. Mitotic activity is usually high. Necrosis, as well as areas of sarcomatoid and rhabdoid differentiation, may be seen. The diagnosis of collecting duct carcinoma requires the exclusion of other RCC subtypes, urothelial carcinoma, and metastatic tumors. The presence of any component within the tumor demonstrating the classic morphology of clear cell RCC, papillary RCC, or mucinous tubular and spindle cell carcinoma supports a diagnosis of the corresponding entity. Immunohistochemically, CDCs typically exhibit positive staining for both high-molecular-weight cytokeratins (such as 34 β E12) and low-molecular-weight cytokeratins (CK7, CK19), as well as PAX8, fumarate hydratase, and SMARCB1 [19].

SMARCB1-deficient renal medullary carcinoma and *medullary-like renal cell carcinoma* are aggressive neoplasms that share morphological similarities with collecting duct carcinomas. Histologically, they exhibit infiltrative cribriform, solid, and tubular structures within a desmoplastic stroma. The key distinguishing feature between the two is the association of renal medullary carcinoma with hemoglobinopathies, which is not observed in medullary-like renal cell carcinoma.

Tubulocystic renal cell carcinomas (TcRCCs) are well-circumscribed tumors typically presenting as solitary masses. Microscopically, they are composed of variably sized tubules lined by a single layer of flattened to cuboidal epithelial cells. A characteristic feature is the prominent nucleoli, which obviates the need for histological grading. Clinically, TcRCCs are indolent neoplasms with a favorable prognosis.

Mucinous tubular and spindle cell carcinomas, which are observed slightly more frequently in females, are microscopically composed of tubular structures formed by epithelial cells exhibiting low-grade nuclear features within a myxoid stroma containing spindle-shaped cells. In some cases, either the epithelial or spindle cell component may be more predominant. Tumors with this classic morphology tend to follow an indolent clinical course and rarely metastasize. However, cases exhibiting high-grade features with sarcomatoid transformation are associated with a more aggressive clinical behavior. Immunohistochemically, these tumors are positive for CK7, PAX8, and AMACR [20]. Although rare, the presence of oncocytic or clear cell changes in some cells, as well as papillary architecture, may pose diagnostic challenges in the differential diagnosis.

Angiomyolipomas, which originate from perivascular epithelioid cells (PEComa family), are sporadic in approximately 80% of cases. The remaining 20% are mostly associated with tuberous sclerosis complex (TSC), characterized predominantly by *TSC2* gene mutations. Clinically benign, these tumors form well-circumscribed, nonencapsulated masses and are composed microscopically of varying proportions of adipose tissue, smooth muscle, and dysmorphic blood vessels. Smooth muscle cells may appear spindle shaped or epithelioid and, in some cases, may display marked cellular atypia mimicking malignancy. Mitoses are rare. Tumors may exhibit a dominant lipomatous or leiomyomatous component, and rare variants may contain oncocytoma-like areas, sclerotic regions, or epithelial cysts. Although vascular invasion into the renal sinus or renal vein may be observed, it has not been shown to adversely affect prognosis. Immunohistochemically, these tumors are defined by the expression of melanocytic markers—particularly in epithelioid cells—including HMB-45, Melan-A, MiTF, and cathepsin K, while epithelial markers are negative. Angiomyolipomas with a predominant epithelioid morphology (>80%) are considered to have malignant potential. These tumors demonstrate a metastatic rate of approximately 5%, most com-

monly to the liver and lymph nodes. Along with the proportion of epithelioid cells, other factors influencing metastatic risk include mitotic count, presence of atypical mitoses, necrosis, tumor size, and perinephric invasion.

Juxtaglomerular cell tumors typically present in young adults with medically refractory hypertension. They are usually small, encapsulated, unilateral, and solitary masses. Microscopically, they are composed of sheets of round, uniform cells within a vascular-rich stroma. Immunohistochemically, they are positive for renin, CD34, CD117, and vimentin [20].

In summary, the most primary malignant tumors of kidney originate from the proximal nephron. Clear cell, papillary, and chromophobe RCCs develop from the epithelium of proximal convoluted tubule, while oncocytoma develops from intercalated cells, confirmed by ultrastructural and mitochondrial features. Mucinous tubular/spindle cell RCCs are from the loop of Henle-distal nephron hybrid phenotype (CK7+, AMACR+). Medullary, and collecting duct carcinomas have medullary collecting duct lineage. Xp11.2/TFEB RCCs have a proximal tubular phenotype with TFE3/TFEB fusions.

C. Primary Renal Tumors of Childhood

Malignant renal tumors in childhood are relatively uncommon but represent a distinct group with characteristic histological and genetic features. The majority—approximately 85% of pediatric renal malignancies—are Wilms tumors (nephroblastomas). Other notable entities include congenital mesoblastic nephroma ($\approx 5\%$), clear cell sarcoma of the kidney ($\approx 4\%$), and malignant rhabdoid tumor ($\approx 2\%$). Renal cell carcinoma (RCC) is rare in children, accounting for less than 5% of cases and often appears under the “miscellaneous” category, alongside lymphoma, primitive neuroectodermal tumor (PNET), angiomyolipoma, and renal medullary carcinoma. In practice, when a spindle cell renal tumor occurs in a child, Wilms tumor is the most probable diagnosis, whereas RCC should be considered only after other possibilities have been excluded. Wilms tumor typically arises between 2 and

5 years of age, with 90% of cases diagnosed before 7 years. Although the tumor classically shows a triphasic pattern (blastemal, epithelial, and stromal components), it may occasionally be biphasic or monophasic, mimicking other pediatric neoplasms such as neuroblastoma or even RCC in older patients. Monophasic epithelial tumors in adults can pose diagnostic difficulties, which are often resolved after nephrectomy when the other components are identified [21, 22].

Wilms tumor (nephroblastoma) is the most common malignant renal neoplasm of childhood, first described by Max Wilms. It almost always occurs in patients under 10 years old, though rare adult cases have been reported. About 5–10% are bilateral, either synchronous or metachronous. The clinical presentation typically includes a palpable abdominal mass, hematuria, abdominal pain, hypertension, or fever. Although environmental risk factors have been proposed, none are clearly established. Importantly, several genetic syndromes are associated with WT, collectively accounting for about 10% of cases and offering valuable insights into tumor pathogenesis. These include [21–24]:

- WAGR syndrome (Wilms tumor, aniridia, genital anomalies, retardation): deletion involving WT1 (11p13) and PAX6.

- Denys-Drash syndrome: missense mutation in WT1, characterized by gonadal dysgenesis and nephropathy.
- Perlman syndrome: associated with prenatal overgrowth, facial dysmorphism, and renal dysplasia.
- Fanconi anemia type D1: biallelic BRCA2 mutation.
- Simpson-Golabi-Behmel syndrome: GPC3 (Xq26) mutation.
- Beckwith-Wiedemann syndrome: imprinting defect at 11p15 (WT2 locus) affecting IGF2 and H19, leading to IGF2 overexpression.
- In addition to WT1 and WT2, other genes implicated include WTX (X chromosome), HACE1 (6q21), and CTNNB1 (β -catenin), emphasizing the genetic heterogeneity of WT. The classic two-hit hypothesis by Knudson is applicable to syndromic cases such as WAGR and Denys-Drash, where loss or mutation of both WT1 alleles is necessary for tumor development.

Wilms tumor arises from primitive metanephric blastemal cells, showing aberrant differentiation reminiscent of developing kidney tissue. Histologically, it demonstrates varying proportions of blastemal, epithelial, and stromal components (Fig. 14.7a), with possible heterologous

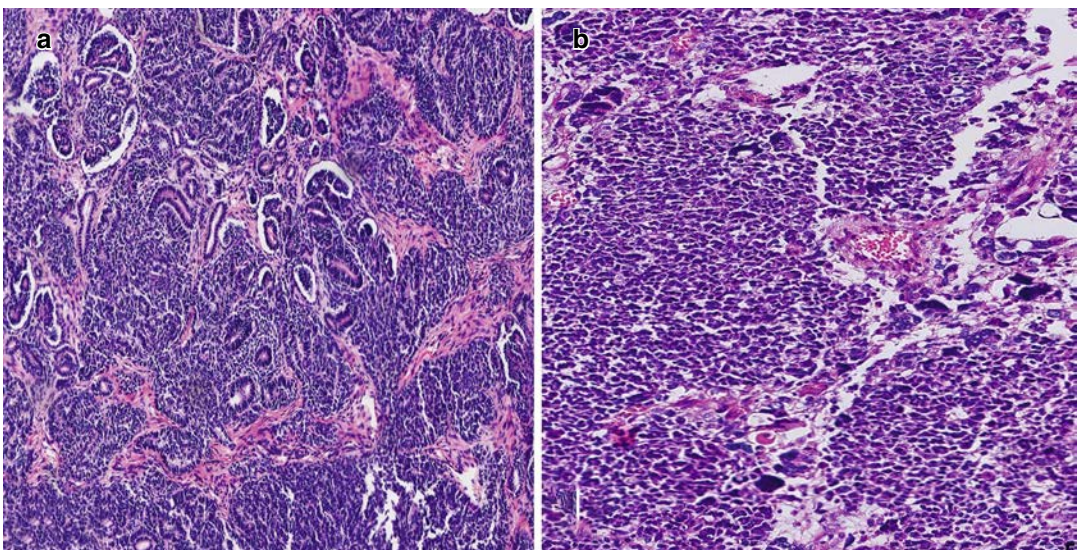


Fig. 14.7 (a) Classical triphasic Wilms tumor, (b) anaplastic Wilms tumor

differentiation (e.g., skeletal muscle, cartilage, bone). Macroscopically, tumors are large, lobulated, and soft, often with necrosis, hemorrhage, or cystic change. The presence of nephrogenic rests—either perilobar or intralobar—supports a developmental origin and may indicate a risk for bilateral disease. Anaplasia, defined by markedly enlarged, hyperchromatic nuclei and atypical multipolar mitoses, is an adverse prognostic feature (Fig. 14.7b). Focal anaplasia is confined to some areas, whereas diffuse anaplasia is associated with TP53 mutations and indicates resistance to chemotherapy and poorer prognosis [21–24].

Staging and Prognosis: The Children's Oncology Group (COG) staging system parallels the earlier NWTSG classification:

- Stage I: confined to the kidney, completely excised
- Stage II: extends beyond the kidney but completely resected
- Stage III: residual non-hematogenous tumor confined to the abdomen
- Stage IV: distant metastases (lung, liver, bone, or brain)
- Stage V: bilateral renal involvement

Treatment combines surgery, chemotherapy (vincristine, actinomycin D, doxorubicin), and radiotherapy in advanced cases. Prognosis is excellent for localized disease—>90% 5-year survival—and approximately 80% even in stage IV with modern multimodal therapy. Poor prognostic factors include advanced stage, diffuse anaplasia, LOH at 1p or 16q, and DNA aneuploidy [21–24].

Congenital mesoblastic nephroma: Also termed *congenital leiomyomatous hamartoma*, mesoblastic nephroma is a monomorphic spindle cell tumor seen almost exclusively in infants under 1 year. It arises from embryonic renal stromal cells of the developing nephrogenic zone. It exhibits myofibroblastic differentiation and is typically cured by nephrectomy. Late recurrence or metastasis is rare but reported, particularly in infants older than 3 months or with the cellular variant. There is no specific alteration like infantile fibromatosis in classic type, while cellular

variant has the ETV6–NTRK3 fusion/ t(12;15) (p13;q25), and it is associated with recurrence and even metastases [25].

Clear cell sarcoma of the kidney (CCSK): Clear cell sarcoma, historically regarded as a variant of WT, is a distinct malignant neoplasm with a propensity for bone metastasis. CCSK is a malignant mesenchymal neoplasm of the kidney that primarily affects children. It originates from the primitive nephrogenic mesenchyme, which represents the embryonic stromal component of the developing kidney. Unlike Wilms tumor, which exhibits epithelial and blastemal differentiation, CCSK shows pure mesenchymal differentiation without epithelial or blastemal elements. At the molecular level, most CCSKs harbor characteristic genetic alterations involving BCOR or YWHAE genes. The BCOR internal tandem duplication (BCOR ITD) is the most frequent genetic abnormality. A subset of cases shows YWHAE–NUTM2B/E fusion, which is also seen in certain high-grade endometrial stromal sarcomas, indicating a shared mesenchymal oncogenic pathway. These molecular findings support that CCSK arises from primitive renal mesenchymal precursor cells rather than epithelial or neuroectodermal lineages. It commonly affects children aged 2–3 years, presenting as a medullary, well-circumscribed, gray-white mass. Microscopically, tumor cells have clear cytoplasm and indistinct borders, arranged in cords or nests within a delicate vascular network (Fig. 14.8). Prognosis has improved with doxorubicin-based chemotherapy, though late recurrences and bone metastases remain common [25, 26].

Malignant rhabdoid tumor (MRT) is a highly aggressive embryonal neoplasm of early childhood, arising most commonly in the kidney, but also in the central nervous system (as atypical teratoid/rhabdoid tumor, ATRT) and in soft tissues. Histologically, it was once thought to represent a variant of Wilms tumor showing rhabdomyoblastic differentiation. However, subsequent immunohistochemical and molecular studies demonstrated that MRT has a distinct histogenesis and is not myogenic in origin. MRT arises from primitive pluripotent cells of the renal medullary or cortical mesenchyme. These cells possess the potential for epithelial, mesenchy-

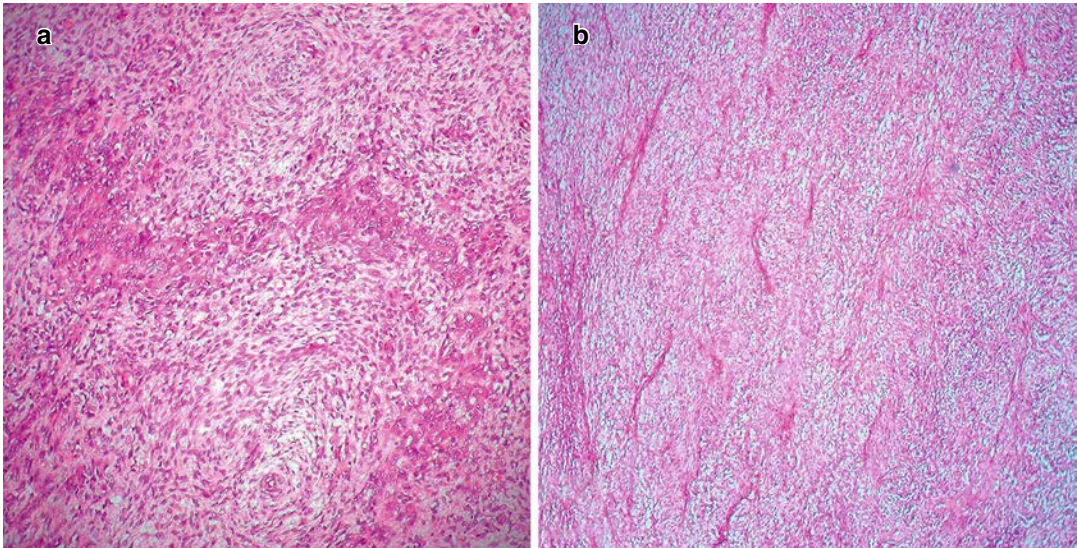


Fig. 14.8 (a) Tumor cells with clear cytoplasm and indistinct borders of CCSK, (b) note the delicate vascular network

mal, and even neural differentiation, which explains the tumor's variable immunophenotype (e.g., coexpression of vimentin, cytokeratin, and EMA). Therefore, its exact lineage remains ambiguous, but it is considered to derive from an undifferentiated embryonic stemlike cell of mesenchymal origin. The defining genetic event in MRT is biallelic inactivation of the SMARCB1 (INI1, hSNF5, BAF47) gene located on chromosome 22q11.2. This gene encodes a core subunit of the SWI/SNF chromatin-remodeling complex, which regulates transcriptional control and cellular differentiation. Loss of SMARCB1 results in epigenetic dysregulation and uncontrolled proliferation of undifferentiated progenitor cells. Rarely, SMARCA4 (BRG1) mutations may substitute for SMARCB1 loss, especially in extrarenal rhabdoid tumors. This aggressive infantile renal neoplasm, typically presenting at <2 years of age, composed of large cells with eccentric nuclei and eosinophilic cytoplasmic inclusions representing intermediate filaments. Immunohistochemically, tumor cells are INI1 negative but positive for cytokeratin and vimentin. The prognosis is extremely poor, with most patients dying within a year of diagnosis [25, 27].

Translocation renal cell carcinoma (Xp11.2 RCC): Pediatric RCCs differ genetically and

morphologically from adult cases. The most common subtype is Xp11.2 translocation RCC, characterized by TFE3 gene fusions, most frequently PRCC-TFE3 t(X;1)(p11.2;q21) and ASPL-TFE3 t(X;17)(p11;q25). Histologically, these tumors exhibit papillary, tubular, or nested growth with clear to eosinophilic cytoplasm and psammoma bodies. Immunohistochemistry shows nuclear TFE3 positivity, along with reactivity for CD10 and RCC marker. They are typically negative or focally positive for cytokeratin and EMA. Clinically, they tend to occur in adolescents and young adults and may overlap with alveolar soft part sarcoma due to shared molecular events [25].

Juxtaglomerular cell tumor (reninoma): This renin-producing neoplasm usually affects young adults, presenting with hypertension and elevated plasma renin levels. Histologically, it resembles hemangiopericytoma, composed of uniform polygonal to spindle cells with PAS-positive cytoplasmic granules. The tumor is benign, and surgical excision is curative [21, 25].

Anaplastic sarcoma of the kidney (ASK), first described by Vujančić et al. in 2007, is a rare, highly aggressive spindle cell sarcoma affecting mainly children and adolescents (mean age,

5 years). Tumors are large (4–12 cm), negative for epithelial markers (keratin, WT1, CD99), but positive for vimentin and occasionally desmin. No WT-associated genetic defects have been demonstrated. Prognosis is poor despite aggressive multimodal therapy [21, 25].

In summary, renal neoplasms encompass a diverse group of benign and malignant tumors derived from the nephrogenic blastema, renal tubular epithelium, or mesenchymal stromal elements. In the pediatric population, most renal tumors originate from embryonic or mesenchymal precursor cells, reflecting aberrant differentiation of the developing nephrogenic zone. Wilms tumor (nephroblastoma) is by far the most frequent lesion, followed by clear cell sarcoma, malignant rhabdoid tumor, and congenital mesoblastic nephroma. Each entity displays distinctive histologic, immunophenotypic, and molecular characteristics that aid in accurate classification and prognostication. Advances in molecular pathology have defined specific driver alterations—such as WT1, WT2/IGF2, BCOR, SMARCB1, and ETV6-NTRK3 fusions—clarifying the histogenesis of these neoplasms and supporting more refined diagnostic criteria. Pediatric renal tumors differ significantly from their adult counterparts, such as renal cell carcinoma, in both genetic background and clinical behavior. Recognition of these distinctions, combined with integrated histopathologic and molecular evaluation, is essential for accurate diagnosis, risk stratification, and targeted therapeutic approaches.

References

- Sexton SJ. Renal and urinary conditions: kidney cysts and tumors. *FP Essent.* 2024;543:12–7.
- Reiterová J, Tesař V. Autosomal dominant polycystic kidney disease: from pathophysiology of cystogenesis to advances in the treatment. *Int J Mol Sci.* 2022;23(6):3317. <https://doi.org/10.3390/ijms23063317>.
- Thomas CC, Jana M, Sinha A, Bagga A, Ramachandran A, Sudhakaran D, Gupta AK. Ultrasound imaging of renal cysts in children. *J Ultrasound Med.* 2021;40(3):621–35. <https://doi.org/10.1002/jum.15435>.
- Raspolini MR, Amin MB, Moch H, Tan PH, Turajlic S. Renal cell tumours: introduction. In: Amin MB, Gill AJ, Hartman A, Lazar AJ, Moch H, Tickoo SK, Turajlic S, editors. *WHO classification of tumours: urinary and male genital tumours.* 5th ed. Ch 2. International Agency for Research on Cancer; 2022.
- Tickoo SK, Reuter VE. Papillary adenoma. In: Amin MB, Tickoo SK, editors. *diagnostic pathology genitourinary.* 3rd ed. Elsevier; 2022. p. 44–7.
- Mirkheshti N, Farrukh N, Legesse T, Rowe SP, Gordetsky J, Hussain A. Renal oncocytoma: a challenging. *Curr Opin Oncol.* 2022;34(3):243–52. Hsieh JJ, Le VH, Oyama T, Ricketts CJ, Ho TH, Cheng EH. Chromosome 3p loss-orchestrated VHL, HIF, and epigenetic deregulation in clear cell renal cell carcinoma. *J Clin Oncol* 2018;36(36):JCO2018792549. <https://doi.org/10.1200/JCO.2018.79.2549>.
- Hu X, Li W, Bai J, Li D, Wang P, Cai J. Metanephric adenoma in children: a case report and literature review. *Oncol Lett.* 2023;26(5):486. <https://doi.org/10.3892/ol.2023.14073>.
- Calìò A, Eble JN, Hes O, Martignoni G, Harari SE, Williamson SR, Brunelli M, Osunkoya AO, Wang L, Comperat E, Lopez-Beltran A, Wang M, Zhang S, Curless KL, Post KM, Chang HY, Luchini C, Baldrige LA, MacLennan GT, Montironi R, Grignon DJ, Cheng L. Distinct clinicopathological features in metanephric adenoma harboring BRAF mutation. *Oncotarget.* 2016;8(33):54096–105. <https://doi.org/10.18632/oncotarget.11117>.
- Cazacu SM, SÂndulescu LD, Mitroi G, Neagoe DC, Streba C, Albulescu DM. Metastases to the kidney: a case report and review of the literature. *Curr Health Sci J.* 2020;46(1):80–9. <https://doi.org/10.12865/CHSJ.46.01.11>.
- Ishihara H, Yamashita S, Liu YY, Hattori N, El-Omar O, Ikeda T, Fukuda H, Yoshida K, Takagi T, Taneda S, Kondo T, Nagashima Y, Tanabe K, Ushijima T. Genetic and epigenetic profiling indicates the proximal tubule origin of renal cancers in end-stage renal disease. *Cancer Sci.* 2020;111(11):4276–87. <https://doi.org/10.1111/cas.14633>.
- Tickoo SK, Reuter VE. Renal cell carcinoma. In: Amin MB, Tickoo SK, editors. *Diagnostic pathology genitourinary.* 3rd ed. Elsevier; 2022. p. 54–63.
- Shah RB. Renal cell carcinoma with fibromyxomatous stroma—the whole story. *Adv Anat Pathol.* 2022;29(3):168–77.
- Tretiakova M, Kwon JW, Paner GP. Cystic features in renal epithelial neoplasms and their increasing clinical and pathologic significance. *Adv Anat Pathol.* 2024;31(3):157–68.
- Tickoo SK, Reuter VE. Clear cell papillary renal cell tumor. In: Amin MB, Tickoo SK, editors. *Diagnostic pathology genitourinary.* 3rd ed. Elsevier; 2022. p. 74–83.
- Castillo VF, Trpkov K, Saleeb R. Contemporary review of papillary renal cell carcinoma-current state and future directions. *Virchows Arch.*

- 2024;485(3):391–405. <https://doi.org/10.1007/s00428-024-03865-x>.
16. Angori S, Lobo J, Moch H. Papillary renal cell carcinoma: current and controversial issues. *Curr Opin Urol.* 2022;32(4):344–51. <https://doi.org/10.1097/MOU.0000000000001000>.
 17. Williamson SR. Papillary renal cell carcinoma. In: Amin MB, Gill AJ, Hartman A, Lazar AJ, Moch H, Tickoo SK, Turajlic S, editors. *WHO classification of tumours: urinary and male genital tumours*. 5th ed. Ch 2. International Agency for Research on Cancer; 2022.
 18. Amin MB, Paner GP, Alvarado-Cabrero I, Young AN, Stricker HJ, Lyles RH, Moch H. Chromophobe renal cell carcinoma: histomorphologic characteristics and evaluation of conventional pathologic prognostic parameters in 145 cases. *Am J Surg Pathol.* 2008;32(12):1822–34.
 19. Kobayashi N, Matsuzaki O, Shirai S, Aoki I, Yao M, Nagashima Y. Collecting duct carcinoma of the kidney: an immunohistochemical evaluation of the use of antibodies for differential diagnosis. *Hum Pathol.* 2008;39(9):1350–9.
 20. Nathany S, Monappa V. Mucinous tubular and spindle cell carcinoma: a review of histopathology and clinical and prognostic implications. *Arch Pathol Lab Med.* 2020;144(1):115–8.
 21. Royer-Pokora B. Genetics of pediatric renal tumors. *Pediatr Nephrol.* 2013;28(1):13–23. <https://doi.org/10.1007/s00467-012-2146-4>.
 22. Diniz G. Histopathological and molecular characteristics of Wilms tumor. In: van den Heuvel-Eibrink MM, editor. *Wilms tumor* [internet]. Brisbane: Codon Publications; 2016. Chapter 3.
 23. Dome JS, Perlman EJ, Graf N. Clinical features and biology of Wilms tumor. *N Engl J Med.* 2023;389(14):1302–17.
 24. Diniz G, Baskin Y, Çalibaşı G, Aktaş S. Relationship of c-Kit Gene and microsatellit instability in the pathogenesis of Wilms tumors. *Turk Patoloji Derg.* 2016;32(2):139–40. English. <https://doi.org/10.5146/tjpath.2015.01347>.
 25. Perotti D, O’Sullivan MJ, Walz AL, Davick J, Al-Saadi R, Benedetti DJ, Brzezinski J, Ciceri S, Cost NG, Dome JS, Drost J, Evageliou N, Furtwängler R, Graf N, Maschietto M, Mullen EA, Murphy AJ, Ortiz MV, van der Beek JN, Verschuur A, Wegert J, Williams R, Spreafico F, Geller JJ, van den Heuvel-Eibrink MM, Hong AL. Hallmark discoveries in the biology of non-Wilms tumour childhood kidney cancers. *Nat Rev Urol.* 2025;22(8):526–43. <https://doi.org/10.1038/s41585-024-00993-6>.
 26. Alchahin AM, Mei S, Tsea I, Hirz T, Kfoury Y, Dahl D, Wu CL, Subtelny AO, Wu S, Scadden DT, Shin JH, Saylor PJ, Sykes DB, Kharchenko PV, Baryawno N. A transcriptional metastatic signature predicts survival in clear cell renal cell carcinoma. *Nat Commun.* 2022;13(1):5747. <https://doi.org/10.1038/s41467-022-33375-w>.
 27. Pawel BR. SMARCB1-deficient tumors of childhood: a practical guide. *Pediatr Dev Pathol.* 2018;21(1):6–28. <https://doi.org/10.1177/1093526617749671>.

Neoplasms of the Vulva, Vagina, Uterus, and Tuba Uterina

15

Seyran Yiğit and Sevil Sayhan

15.1 Vulva

The vulva is the external female genital organ consisting of the labia majora, labia minora, mons pubis, and vestibule. The labia majora and mons pubis are covered with keratinized stratified squamous epithelium and skin appendages. The labia minora is lined with nonkeratinized stratified squamous epithelium and contains minor sweat glands and sebaceous glands. Inflammatory and neoplastic diseases of the skin are seen in the vulva due to its lining epithelium. Diseases of the vulva can be grouped as vulvitis, nonneoplastic epithelial disorders, and neoplastic lesions.

15.1.1 Vulvitis

Symptoms of vulvitis are pruritus and traumatic erosion. Under the vulvitis umbrella, acute-chronic dermatitis, bacterial (bacterial vaginosis, *N. gonorrhea*, *T. pallidum*), mycotic (candidiasis), and viral (human papillomavirus, pox virus, Herpes simplex virus) infections are included.

The most important complication of vulvitis is the Bartholin cyst and Bartholin abscess, which occur as a result of dilation and obstruction of the Bartholin gland duct, which has very painful symptoms [1–3].

15.1.2 Nonneoplastic Epithelial Disorders

In this group of diseases, pruritus and scaling result in the formation of white plaques, clinically called leukoplakia. Leukoplakia, inflammatory dermatoses (e.g., psoriasis, chronic dermatitis), nonneoplastic epithelial disorders (Lichen sclerosus and squamous cell hyperplasia), and neoplasia, (e.g., vulvar intraepithelial neoplasia (VIN), Paget's disease, and invasive carcinoma) are observed. Microscopic examination is essential in cases of leukoplakia, which is seen in many benign, premalignant, and malignant lesions [1–3].

- *Lichen sclerosus*: Although it is seen in all age groups, it is frequently seen in postmenopausal women and prepubertal girls. Clinically, it is characterized by pruritus and leukoplakia. Microscopically, it is characterized by thinning of the epidermis, disappearance of rete pegs, in papillary dermis, a zone of acellular, homogenized, dermal fibrosis, and a bandlike mononuclear inflammatory cell infiltrate (Fig. 15.1). Its pathogenesis is uncertain, but

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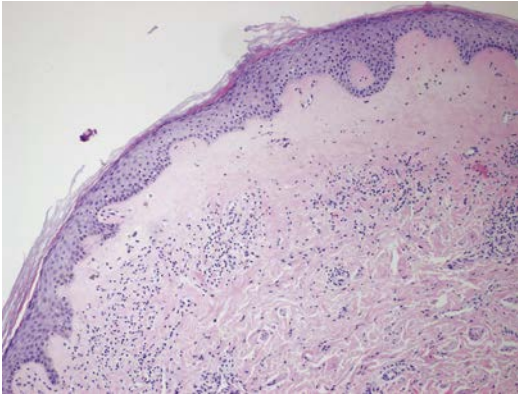


Fig. 15.1 Lichen sclerosus (HE x 40)

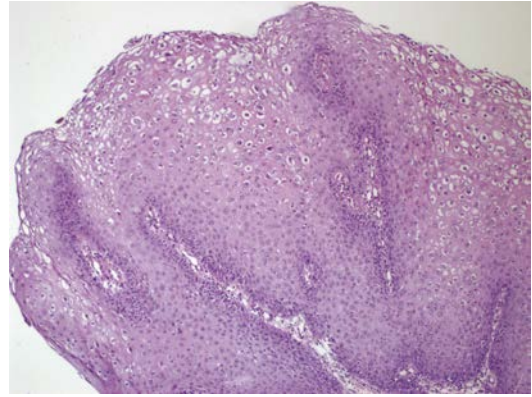


Fig. 15.2 Condyloma acuminatum (HE x 40)

the increased frequency of autoimmune disorders in affected women suggests an autoimmune etiology. Lichen sclerosus itself is benign but associated with a slightly increased (1%–5%) risk for HPV-negative squamous cell carcinoma of vulva [1–3].

- *Squamous cell hyperplasia*: Clinically, it is a nonspecific lesion characterized by pruritus and leukoplakia. Microscopically squamous cell hyperplasia is seen with marked stratum granulosum, epithelial thickening, and hyperkeratosis. Increased mitotic activity is seen in the basal and suprabasal layers; however, there is no epithelial atypia. Squamous cell hyperplasia is a benign lesion and does not predispose to malignancy [1–3].
- *Condyloma acuminatum*: It is a benign squamous proliferation in which human papillomavirus (HPV) genotypes 6 and 11 play a role in its etiology. Histologically, HPV-associated condylomas are characterized by koilocytes (Fig. 15.2). Prognosis is excellent. Recurrence is common in people with weak immune systems and smokers. It may be associated with squamous neoplasms.

15.1.3 Neoplastic Lesions

Neoplastic lesions of the vulva can be divided into three groups as epithelial neoplastic lesions (squamous and glandular neoplastic lesions), malignant melanoma, and mesenchymal neoplastic lesions [1, 5, 6]

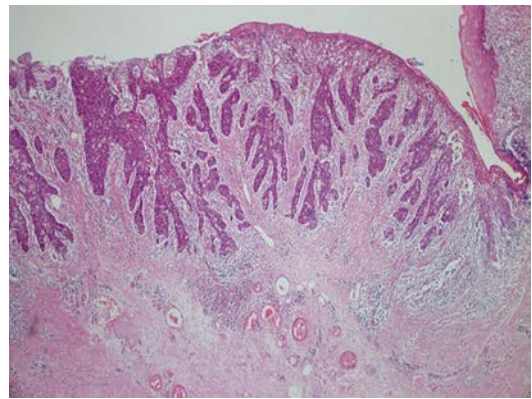


Fig. 15.3 Basaloid SCC (HE x 40)

• Epithelial Neoplastic Lesions

- *Squamous neoplastic lesions*: Vulvar carcinomas account for about 5% of female genital system cancers. Squamous cell carcinomas account for 90% of vulvar carcinomas. Squamous cell neoplastic lesions are divided into HPV-associated and HPV-independent lesions. Premalignant lesions are called vulvar intraepithelial neoplasia (VIN). The lesions of classic VIN are associated HPV. Microscopically, it is characterized by epidermal thickening, nuclear atypia, increased mitoses, and lack of cellular maturation. Invasive carcinomas develop from classic VIN. Microscopically basaloid carcinoma consists of nests and cords of small, tightly packed cells that lack maturation and resemble the basal layer of the normal epithelium (Fig. 15.3).

Table 15.1 Features of vulvar squamous cell carcinomas (SCCs)

	HPV-unrelated SCC	HPV-related SCC
Prevalence	80%	20%
Age	Older	Young
Focality	Unifocal	Multifocal
Risk factors	Long standing lichen sclerosus, chronic inflammation, and irritation	Multiple partners, early first age of intercourse
Morphology	keratinizing	Warty-basaloid
Relationship with VIN	Rare; differentiated-type VIN	Often; classical (usual)
Relationship with HPV	HPV 5, 8 (cutaneous)	HPV 16, 18
Relationship with vulvar dysplasia	Often	Rare
Immunohistochemistry	P 53 sometimes (+), P 16 (–)	P 53 (–), P 16 (+)

The tumor may have foci of central necrosis. Despite this, warty carcinoma is characterized by papillary architecture and prominent koilocytotic atypia [1, 5, 6]. Differentiated VIN is independent HPV. Microscopically characterized by marked atypia of the basal layer of the squamous epithelium. Invasive keratinizing squamous cell carcinomas that develop in differentiated VIN contain nests and tongues of malignant squamous epithelium with prominent keratin pearls [1, 5, 6] (Table 15.1 and Fig. 15.4).

- *Glandular neoplastic lesions:* The vulva contains apocrine glands, like the breast. These causes include papillary hidradenoma and extramammary Paget’s disease, which are also seen in the vulva.
 - A. *Papillary hidradenomas* are well-circumscribed nodular lesions characterized by a papillary growth pattern containing two layers of cells, similar to intraductal papilloma of the breast [1, 2, 5].
 - B. *Extramammary Paget’s disease:* Clinically, the appearance is similar to Paget’s disease of the breast, and extramammary Paget’s disease presents with pruritus, redness, and ulceration. In Paget’s disease of the nipple, ductal breast carcinoma is seen in almost 100% of the breast, while invasive carcinoma of the vulva is rare and the tumor is localized to the epidermis of the vulva. Intraepithelial Paget’s

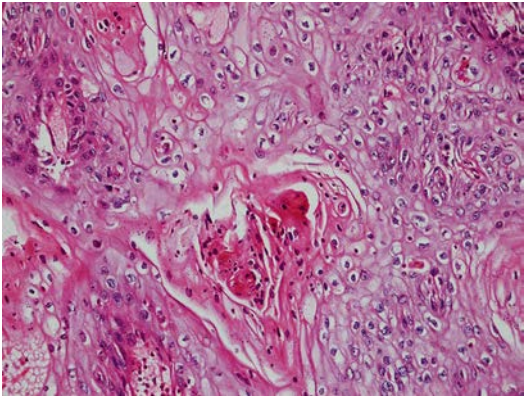


Fig. 15.4 Keratinizing SCC (HEx 100)

- disease persists for years without invasion or metastasis. Microscopically, it is characterized by atypical cells that are larger than the epithelial cells, either individually or in small groups, among the epithelial cells (Fig. 15.5). The cytoplasm of the cells contains mucopolysaccharide that stains with periodic acid-Schiff (PAS), Alcian blue, or mucicarmine stains. Additionally, neoplastic cells stain with cytokeratin 7, whereas squamous epithelium does not [1–3, 5] (Fig. 15.6).
 - *Malignant melanoma* is the second most common malignant vulvar neoplasm after squamous cell carcinoma (8–11%). It is most commonly localized on the labia majora and is more common in women in the postmenopausal period (6th–8th decade).

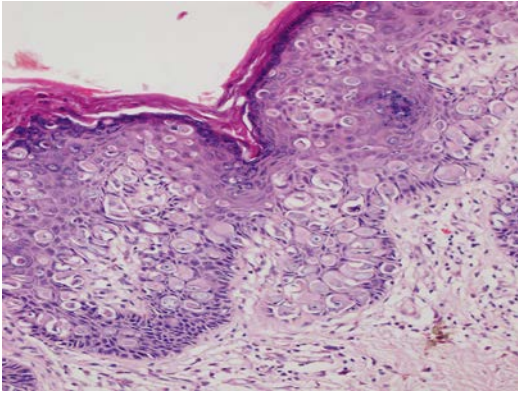


Fig. 15.5 Extramammary Paget's disease (HEx 200)

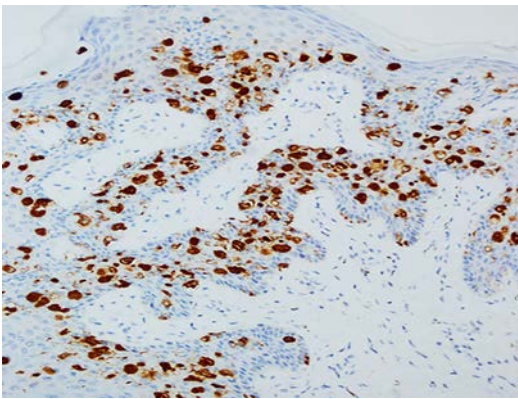


Fig. 15.6 CK 7 positivity Paget's disease (DABx 40)

Macroscopically, it is in the form of an irregularly bordered macule or papule. Plaque or nodule form indicates an invasive tumor. It has a poor prognosis because it is diagnosed late and recurs frequently. 5-year survival is 37–54% [1–3, 5, 6]. Extramammary Paget's disease is important in differential diagnosis. Malignant melanoma is S-100(+), keratin (–), and PAS (–), while extramammary Paget's disease is S-100(–), keratin (+), and PAS (+).

- **Mesenchymal neoplastic lesions:** Benign mesenchymal tumors of the vulva include angio-myofibroblastoma and cellular angiofibroma. Angiomyofibroblastoma is well-circumscribed myofibroblastic tumor composed of numerous capillaries and stromal cells distinctive to vulvovaginal mesenchyme. Cellular angiofibroma is typically cellular mesenchymal neoplasm

composed of spindle cells with prominent vascular component [1–5]. Superficial angio-myxoma is often a polypoid, multilobulated myxomatous neoplasm with thin-walled curvilinear vessels. Deep (aggressive) angio-myxoma is infiltrative, no metastasizing, hypocellular myxoid neoplasm of vulvovaginal and pelvic region with potential for local, destructive recurrence(s). In cases where complete excision is not possible, there is a 30–40% risk of local destructive recurrence [5, 6].

15.2 Vagina

The vagina is a tubular structure originating from the double Mullerian duct and extending from the vulva vestibule to the uterus. The vaginal mucosa is lined with nonkeratinized squamous epithelium. Under the epithelium is a muscular layer and adventitia. The Gartner ducts, which are remnants of the Wolffian duct, are located deep along the lateral wall. All of these ducts are lined with simple cuboidal epithelium and the eosinophilic secretion in their lumens is characteristic. Vaginal diseases can be grouped as vaginitis, nonneoplastic lesions, and tumors.

15.2.1 Vaginitis

Vaginitis is a common condition that is usually temporary. The etiology includes bacteria, fungi and parasites.

15.2.2 Nonneoplastic Lesions

- **Vaginal cysts** are named as Müllerian cyst, squamous cyst, and Gartner duct (mesonephric) cyst according to their lining epithelium [1, 3, 6]. Müllerian cysts are lined with a single layer of columnar endocervical-type epithelium. Squamous cysts are lined with stratified non-coalescing epithelium, and Gartner duct cysts are lined with a single layer of columnar-cuboidal epithelium with scant eosinophilic cytoplasm [1, 3, 6].

- **Adenosis:** Vaginal adenosis occurs in one-third of individuals exposed to diethylstilbestrol (DES) prenatally. Adenosis is characterized by the presence of columnar mucinous epithelium or tuboendometrioid-type epithelium of the endocervix instead of the squamous epithelium of the vagina. Vaginal clear cell carcinoma may rarely develop in cases of vaginal adenosis [1, 3, 6].
- **Polyps:** This group includes fibroepithelial stromal polyp and tubulosquamous polyp.
 - *Fibroepithelial polyp* causes post coital bleeding or mass in the reproductive and postmenopausal period. Microscopically, there is squamous epithelium on the surface and fibrous or edematous stroma under the epithelium. There are thin- or thick-walled vessels in the stroma [1, 3, 6].
 - *Tubulosquamous polyp* is seen in late reproductive and postmenopausal period. Well-defined epithelial nests are observed in hypocellular fibrous stroma. In the middle of the epithelial nests, there are necrosis, keratinization, classification, and squamous epithelium around it [1, 3, 6].

15.2.3 Tumors

Tumors of the vagina are epithelial, mesenchymal, malignant melanoma and secondary tumors.

- **Epithelial Tumors**
 - *Vaginal intraepithelial neoplasia (VAIN):* It is a preinvasive tumor and HPV infection plays a role in etiology. VaIN is called VaIN 1 (mild dysplasia), VaIN 2 (moderate dysplasia), and VaIN 3 (severe dysplasia/carcinoma in situ) according to the rate of involvement of the intraepithelial similar epithelium of the cervix. According to the 2014 WHO classification, VaIN 1 is considered low-grade squamous dysplasia (LGSIL); VaIN 2 and VaIN 3 are considered high-grade dysplasia (HGSIL) [1, 3, 4, 6].
 - A. *LGSIL (VaIN 1):* There are koilocytotic changes characterized by cyto-

megaly, cytoplasmic clearing, nuclear membrane irregularity, and binucleation in the upper layers of the epithelium.

- B. *HGSIL (VaIN 2 and VaIN 3):* There are full-thickness epithelial involvement, loss of maturation, dyskeratotic cells, and cells with large nuclei, narrow cytoplasm, and coarse chromatin. While LGSIL usually regresses, ablative or excisional biopsy is applied to HGSIL [1, 3, 4, 6].
- *Squamous cell carcinoma* constitutes 1–2% of all gynecological malignancies and 85% of vaginal malignancies. It is more common in the postmenopausal period. Although HPV 16 is involved in etiology, tumors developing in the lower part of the vagina are HPV independent. Microscopically, keratinizing SCCs are HPV independent; nonkeratinizing-basaloid subtypes are HPV associated. Tumor stage, size, age, and histological type are important prognostic factors. Radiotherapy and surgery are applied in treatment [1, 3, 4, 6].
- *Clear cell carcinoma (CCC):* It was seen in women who used diethylstilbestrol (DES) in utero to prevent early pregnancy loss in the 1950s and 1960s. It was determined that clear cell carcinoma developed because of adenosis in women exposed to DES. It develops based on adenosis or endometriosis in those without a history of DES. CCC shows bimodal age distribution, including young and postmenopausal. Vaginal bleeding is the most common symptom. Microscopically, it is a Mullerian type adenocarcinoma and can be tubulocystic, papillary solid, and mixed pattern. The cytoplasm of tumor cells is eosinophilic, clear, or hobnail. Stage is important in prognosis. Survival in stage I tumors is 90%, and in metastatic tumors, it is 35% [1, 3, 4, 6].
- **Mesenchymal Tumors**
 - *Leiomyomas* originating from smooth muscle and *rhabdomyomas* originating from

striated muscle are benign mesenchymal tumors.

- *Rhabdomyosarcoma (RMS)* is a malignant tumor originating from striated muscle. The embryonal type (sarcoma botryoides) is the most common type and is the most common vaginal cancer seen in infants and children. Ninety percent of patients are under the age of 5. Clinically, it presents with vaginal bleeding and mass. Macroscopically, it is in the form of soft edematous nodular multiple polypoid masses protruding from the introitus. Microscopically, there is a “cambium layer” consisting of primitive, small, mitotic cells under the squamous epithelium. Under this layer, there are inflammatory cells and rhabdomyoblasts in a loose edematous and fibromyxomatous stroma. It is reported that over 90% cure is achieved with chemotherapy and radiotherapy in addition to surgery. It is reported that recurrence may occur within the first 5 years after diagnosis [1, 3, 4, 6].
- *Malignant Melanoma (MM)*: It constitutes <0.3% of all malignant melanomas and <3% of malignant tumors of the vagina. It is common in the peri- and postmenopausal period (mean, 57 years). It frequently develops in the distal 1/3 (anterior) part of the vagina [1–4]. Microscopically, it consists of diffuse, nested, trabecular, and/or fascicular patterns formed by atypical epithelioid (most frequent) ± spindled cells melanocytes. Since these tumors remain asymptomatic for a long time, most of the cases have deep invasion and/or are advanced. Therefore, the prognosis is generally poor [1, 3, 4, 7].
- *Yolk Sac Tumor*: It is a malignant primitive germ cell tumor with histological features that repeat different developmental stages of the normal yolk sac. It is seen in children younger than 3 years of age. Vaginal bleeding and mass are among the symptoms. Serum alpha fetoprotein is high. Macroscopically, it resembles embryonal RMS. Microscopically, it has different patterns. It can be confused

with CCC and embryonal RMS. PAX8, EMA, and cytokeratin 7 positivity supports CCC; desmin, myoglobin, etc. muscle marker positivity supports embryonal RMS. Chemotherapy in addition to surgery is effective in treatment and is reported to be >95% cured [1, 3, 4, 7].

- *Secondary Neoplasms*: Although metastatic tumors of the vagina are rare, they are more common than primary cancers. These tumors reach the vagina by hematogenous spread or direct spread. The most common organs of origin are the cervix (50%), endometrium (13%), and kidney (1%). Ninety percent of vaginal adenocarcinomas originate from the gynecologic tract. The order of frequency is the cervix, endometrium, ovary, and vulva. Adenocarcinomas from outside the gynecologic tract originate from the colorectal, breast, and urinary tract. Twenty-five percent of vaginal SCCs originate from the cervix and vulva. Trophoblastic neoplasms (mostly choriocarcinoma) metastasize to the vagina [1, 3, 5, 7].

15.3 Uterine Cervix

The cervix is the 2.5–3 cm long fibromuscular part of the uterus. The portion that protrudes into the vagina and is lined by stratified squamous epithelium is called the ectocervix. The opening into the vagina is termed the external os. The region from the external os to the internal os is lined by mucus-secreting simple columnar epithelium and is called the endocervix. The opening into the uterine cavity is called internal os. The junction where the squamous and columnar epithelium meet is referred to as the squamocolumnar junction, which shifts over time depending on age and hormonal status, often moving upward into the endocervical canal. The process by which the endocervical epithelium transforms into squamous epithelium is called squamous metaplasia. The area where columnar and squamous epithelium coexist is termed the transformation zone. The

immature squamous metaplastic cells in this zone are particularly susceptible to HPV infection, which plays a major role in cervical carcinogenesis.

15.3.1 Acute and Chronic Cervicitis

With menarche, estrogen production matures the cervical and vaginal mucosa (glycogenation). As these cells shed, glycogen serves as a substrate for bacterial growth. Normal vaginal and cervical flora, particularly lactobacilli, produce lactic acid to maintain a vaginal pH of 4.5. At low pH, lactobacilli also produce bacteriotoxic hydrogen peroxide (H_2O_2). Factors such as bleeding, antibiotic use, or vaginal douching can decrease H_2O_2 production, raise pH, and allow microbial overgrowth. This can lead to purulent vaginal discharge. In overt infections, epithelial reactive and reparative changes are observed. Although difficult to distinguish from the normal flora, cervicitis can be classified as infectious or non-infectious. Etiological agents include bacteria (*Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Treponema pallidum*), viruses (HSV1, HSV2, CMV, molluscum contagiosum), and others (*Trichomonas vaginalis*, *Mycobacterium tuberculosis*, *Schistosoma haematobium*). Most (e.g., *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Treponema pallidum*, HSV2, *Trichomonas vaginalis*) are sexually transmitted. HSV2 infections can be transmitted from the mother to fetus during birth, leading to fatal systemic neonatal infections. Treatment depends on the specific pathogen and usually involves antibiotics [3, 7, 8].

15.3.2 Nonneoplastic Lesions of the Cervix

- *Endocervical Polyp*: Although seen at all ages, it is more common after the age of 40. Most are smaller than 1 cm. It is an exophytic lesion with fibrovascular stroma lined with cuboidal-columnar endocervical epithelium on the surface [3, 7, 8].
- *Müllerian Papilloma*: Rare in the cervix. It consists of branching thin fibrous papillary structures lined with single-layered cuboidal columnar epithelium [3, 7, 8].
- *Nabothian Cyst*: These are cystic structures with mucus and tissue inside located in the endocervical wall. It is common in multiparous women. It develops secondary obstruction in the neck part of the endocervical glands. Cysts are lined with single-layered cuboidal, columnar flattened endocervical epithelium. Deeply located nabothian cysts can be confused with gastric-type endocervical adenocarcinoma [3, 7, 8].
- *Tunnel Clusters*: Well-defined rounded lobular proliferation of endocervical glands within the cervical wall. The glands are lined with single-layered cuboidal, columnar endocervical cells. There are no atypia and mitosis. It can be confused with gastric-type endocervical adenocarcinoma [3, 7, 8].
- *Microglandular Hyperplasia (MGH)*: It is a benign lesion characterized by the proliferation of back-to-back endocervical glands showing subnuclear vacuolization. The stroma is scanty and is characterized by acute and chronic inflammatory cell infiltration infiltrating the glands. It can be confused with clear cell carcinoma and endometrial adenocarcinoma [3, 7, 8].
- *Lobular Endocervical Hyperplasia (LGEH)*: It is a lobular proliferation of endocervical glands that give the impression of being scattered around a large gland in the middle. The glands may show gastric differentiation. Minimal atypia and mitosis can be seen. It can be confused with gastric-type endocervical adenocarcinomas [3, 7, 8].
- *Diffuse Lamellar Endocervical Hyperplasia (DLEH)*: It is a gland proliferation seen as a band just below the surface in the endocervical canal. It is seen incidentally in the premenopausal period [3, 7, 8].
- *Mesonephric Remnants and Hyperplasia*: It is frequently seen in the reproductive period and postmenopausal period. They are well-defined aggregates formed by tubular glands lined with cuboidal epithelium containing eosino-

philic secretion in their lumens. It is typically located around a duct located in the center. Focal atopy and rare mitoses may be seen. Differential diagnosis may be necessary with mesonephric carcinoma and clear cell carcinoma [3, 7, 8].

- *Arias-Stella Reaction*: It is associated with pregnancy. Endocervical glandular epithelial cells have enlarged vacuolated clear/oxyphilic cytoplasm, hyperchromatic nucleus, and hob-nail appearance, similar to those in the endometrium. Differential diagnosis includes clear cell carcinoma and adenocarcinoma in situ [3, 7, 8].
- *Endocervicosis*: The presence of benign endocervical glands in the outer half of the cervix. They cause pelvic pain or dysmenorrhea. It is thought to be associated to a cesarean section. They are localized to the anterior wall of the cervix in the form of masses [3, 7, 8].
- *Endometriosis*: The presence of endometrial type glands and stroma in the cervix. Although endometriosis is a benign lesion, clear cell carcinoma and endometrioid carcinoma may develop on the basis of endometriosis [3].
- *Tuboendometrioid Metaplasia*: It is defined as the replacement of the endocervical epithelium by tubal-endometrioid type epithelium. It is the metaplastic event most often confused with adenocarcinoma in situ [1–3].
- *Ectopic Prostate Tissue*: The replacement of the endocervical epithelium by benign-looking prostate glands containing basal cells and squamous metaplasia [3, 7, 8].
- *Reactive Atypia*: It is confused with adenocarcinoma in situ due to the enlargement of the nuclei in endocervical epithelial cells. Acute and chronic inflammation often accompanies the event. Since nonneoplastic lesions of the cervix can be confused with cervical adenocarcinoma and carcinoma in situ, it is important to recognize and know these entities [3, 7, 8].

15.3.3 Neoplasms of the Cervix

- *Epithelial tumors* are categorized into preinvasive and invasive types. Although human papillomavirus (HPV) plays a significant role in

the development of epithelial neoplasms, as with vulvar tumors, some cervical epithelial tumors are independent to HPV [9, 10].

- *Preinvasive tumors*: The classification of premalignant squamous cell lesions has evolved. Previously, the terminology CIN (cervical intraepithelial neoplasia) 1, 2, 3 was used. In 2014, World Health Organization (WHO) introduced a two-tiered system [10]. This system includes low-grade squamous intraepithelial lesion (LGSIL = CIN1, flat/exophytic condyloma) and high-grade squamous intraepithelial lesion (HGSIL = CIN 2 and 3).

A. *Low-grade squamous intraepithelial lesion (LGSIL/CINI)*: LGSILs are seen at a rate of 80% in the early 20s, while this rate drops to 5% in the 50s. Low oncogenic risk HPV (such as HPV 6,11) is responsible for etiology. Low oncogenic risk HPVs are transmitted sexually and cause vulvar, perineal, and perianal warts (condyloma acuminatum). Most HPV infections are transient and 50% clear up within 8 months and 90% within two years. HPV enters the cervix epithelium through microscopic cracks and infects the basal cells. There is no genomic integration of HPV in LGSIL cases. It is evaluated as an “HPV infection” rather than a precancerous lesion. They do not show macroscopic findings. Microscopically, increased nuclear size, nuclear contour irregularities, and hyperchromasia, binucleated or multinucleated cells with distinct perinuclear halos (koilocytotic atypia), are typical in the upper layers of the epithelium. There is no atypia in the basal layer, or it is reduced. Mitoses are typically confined to the lower 1/3 of the epithelium (Fig. 15.7). Histomorphological evaluation is the gold standard in the diagnosis of LGSIL. The use of p16, an immunohistochemical marker, is recommended in cases with HGSIL

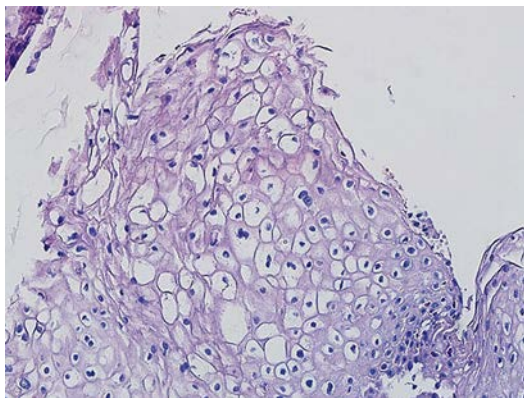


Fig. 15.7 Low-grade SIL (HEx 400)

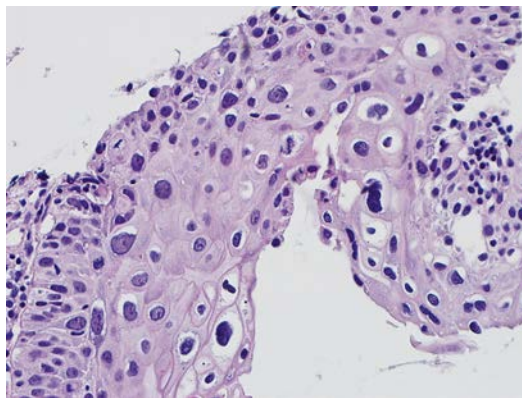


Fig. 15.8 High-grade SIL (HEx 400)

(CIN 2). Treatment is generally conservative (watch and wait), as most lesions regress within a year [3, 7–10].

- B. *High-grade squamous intraepithelial lesion (HGSIL/CIN2 and CIN3)*: High oncogenic risk HPV (such as HPV 16, 18) is responsible for etiology. It is 20 years earlier than invasive carcinomas. In the pathogenesis of HGSIL, unlike the pathogenesis of LGSIL, there is integration of HPV into the host genome. E1 and E2 proteins in the HPV genome control viral replication together. E2 protein ensures that viral DNA is transported to the host nucleus and binds to the genome. E5 protein increases proliferation by acting through E6 and E7 proteins. E6 protein binds to p53 and provides its degradation, exhibiting an antiapoptotic effect and ensuring continuous cell division. E7 protein binds to retinoblastoma protein, activates E2F transcription factor, and ensures cell division. With the disruption of the cell cycle, continuously dividing cells become vulnerable to mutation. As a result of these changes, normal cell cycle is disrupted, and as a result of these changes, proliferation and cytological changes are seen in basal squamous epithelial cells [3, 4, 7–10]. They do not show macroscopic findings.

Microscopically, dysplastic cells with narrow cytoplasm and hyperchromatic nuclei are characterized by involvement of 2/3 or all of the epithelium. Abnormal tripolar, tetrapolar mitotic figures are seen (Fig. 15.8). Immunohistochemically, p16 and Ki67 can be used to distinguish HGSIL from its mimickers. Block staining is seen in neoplastic epithelium with p16, and high proliferation is seen with Ki67. Treatment requires removal of the entire cervical transformation zone [3, 7–10].

- *Premalignant glandular tumor (adenocarcinoma in situ (AIS))*: The incidence of this lesion is increasing like invasive adenocarcinomas. While the etiology of premalignant squamous cell tumors of the cervix is completely HPV associated according to our current knowledge, glandular lesions are rare but HPV-independent types have also been defined. The most common types that play a role in the etiology of HPV-associated types are HPV 16 and 18. The incidence of AIS and invasive adenocarcinomas is rising. While all premalignant squamous tumors are HPV associated, some glandular lesions may not be. HPV 16 and 18 are most commonly involved. The mean age in HPV-associated AIS cases is 38, while the age spectrum is wide in HPV-independent cases. It is generally

asymptomatic and is detected via atypical glandular cells in abnormal PAP smear [10–15].

A. Microscopically, in *HPV-associated AIS*, normal glandular structure is preserved. There is a sharp difference between normal tissue and lesion. Mucus loss in the epithelium, pseudostratified cells with large hyperchromatic nuclei, is seen. Apoptotic cells and luminal mitosis are typical (Fig. 15.9). Block staining in neoplastic epithelium with P 16 and Ki 67 high proliferation is seen (Fig. 15.10). HPV-associated AIS, *stratified mucin-producing intraepithelial lesion (SMILE)*, consists of multilayered polyhedral to columnar cells with

abundant eosinophilic, mucinous, or vacuolated cytoplasm. Mitosis is not evident [10–13].

B. There are *subtypes of HPV-independent AIS* such as gastric-type, tubal/ciliated, atypical lobular endocervical gland hyperplasia. In the *gastric type*, there may be an appearance resembling gastric foveolar mucosa, goblet cells. There are mitosis and apoptosis, but it is not as striking as in HPV-associated AIS. It is important to distinguish AIS from nonneoplastic benign cervical glandular lesions that mimic it (tubal-tuba endometrioid metaplasia, endometriosis, reactive atypia, Arias-Stella reaction, cautery artifact, radiation atypia, etc.), and the distinction is made with the help of immunohistochemical markers. Treatment options are cold conization or hysterectomy [10–13].

- *Invasive Tumors*

- *Squamous cell carcinoma (SCC)* is the second most common cancer in women after breast cancer. It is responsible for 14% of deaths from female genital system cancers. Cervical cancer incidence and mortality have decreased in developed countries with the screening method with cervical cytology. In addition to high oncogenic risk HPVs [16, 18] are key etiologic agents, cofactors (such as smoking, number of pregnancies, oral contraceptive use, chlamydia infection, HSV type 2 infection) are also important. Human papillomavirus (HPV) gene expression is tightly linked to the differentiation state of the squamous epithelium. Early (E) genes, including E1, E2, E5, E6, and E7, are expressed in the basal and parabasal layers, where viral replication and oncogenic transformation occur. These proteins regulate viral genome replication, transcription, and interference with host cell-cycle control. In contrast, late (L) genes, L1 and L2, which encode structural capsid proteins, are expressed only in the superficial, ter-

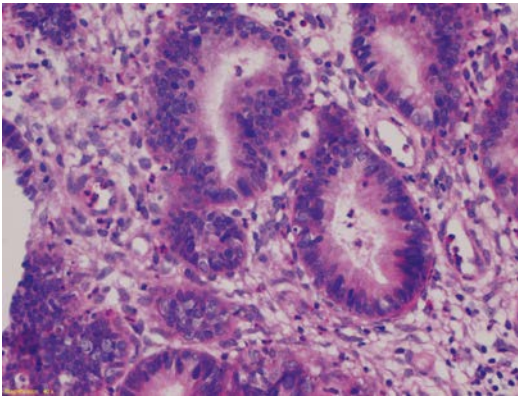


Fig. 15.9 Cervical adenocarcinoma in situ (HEEx 400)

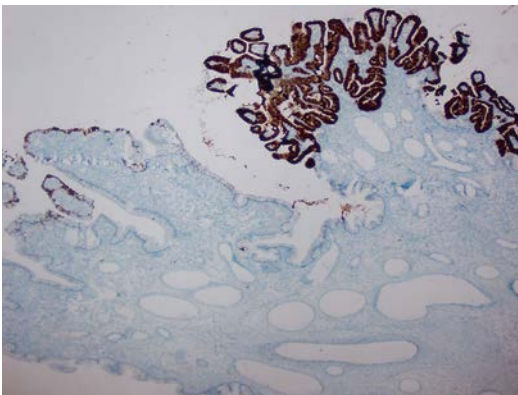
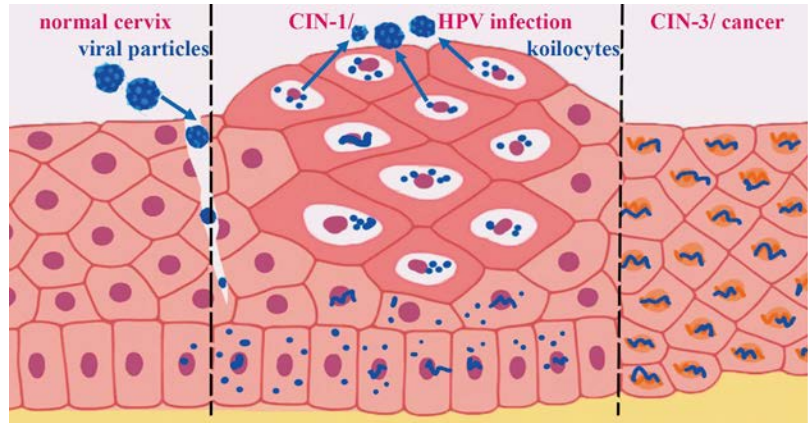


Fig. 15.10 P16 staining (DABx 40)

Fig. 15.11 Changes in HPV components according to the degree of cervical intraepithelial neoplasia



minally differentiated epithelial cells, where viral assembly takes place (Fig. 15.11). This differentiation-dependent expression pattern allows HPV to complete its life cycle without triggering strong immune responses. High-risk human papillomaviruses (HPV), particularly types 16 and 18, promote cervical carcinogenesis through the viral oncoproteins E6 and E7. The E6 protein binds to and induces the degradation of the p53 tumor suppressor, impairing DNA damage-induced apoptosis and allowing the accumulation of mutations. The E7 protein binds to the retinoblastoma protein (pRb), leading to its inactivation and uncontrolled progression through the G1/S cell-cycle checkpoint. Together, these actions cause deregulated cell proliferation, genomic instability, and malignant transformation of cervical epithelial cells (Fig. 15.12). P16 is a cyclin-dependent kinase inhibitor that regulates the G1/S cell-cycle checkpoint by inhibiting CDK4/6-mediated phosphorylation of the retinoblastoma protein (pRb). Immunohistochemical 16 positivity in tumor cells indicates HPV association because the viral E7 oncoprotein functionally inactivates pRb, leading to compensatory overexpression and diffuse nuclear-cytoplasmic accumulation of p16 protein. In 2020, The WHO divided squamous cell carcinomas into three groups as HPV-associated, HPV-independent, and

squamous cell carcinoma NOS [4, 5, 8–10, 16, 17].

A. HPV-associated SCCs constitute 90–95% of all SCCs. They develop in the setting of HGSIL and are p16 diffuse positive. Macroscopically, they may be ulcerated, polypoid barrel-shaped cervix. Microscopically, they have nonkeratinizing, keratinizing, basaloid, warty, papillary, lymphoepithelial-like patterns [4, 5].

- *Keratinizing*: Keratin pearls, eosinophilic cytoplasm, intercellular bridges.
- *Nonkeratinizing*: Lacks keratin pearls (Fig. 15.13)
- *Basaloid*: Nests of small basaloid cells
- *Warty*: Shows condylomatous changes
- *Papillary*: Fibrovascular cores lined by stratified squamous/transitional epithelium
- *Lymphoepithelial like*: Dense lymphoid infiltrate

B. HPV-independent SCCs constitute 5–7% of all SCCs. These tumors are cases where HPV cannot be detected despite the most sensitive HPV detection techniques [1, 8]. Etiology is unknown. Microscopically, it is usually keratinized type, but other types can be seen. Prognosis is associated to FIGO stage and lymph node. HPV-

Fig. 15.12 Mechanism of carcinogenic effect of HPV on cell cycle [17]

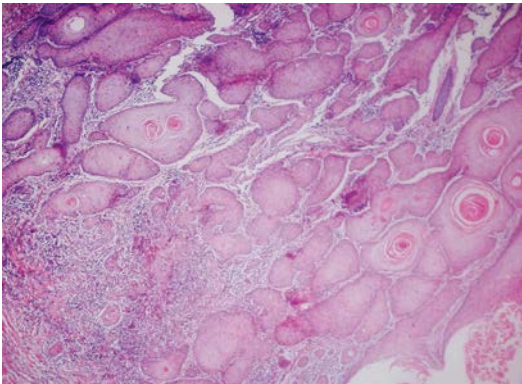
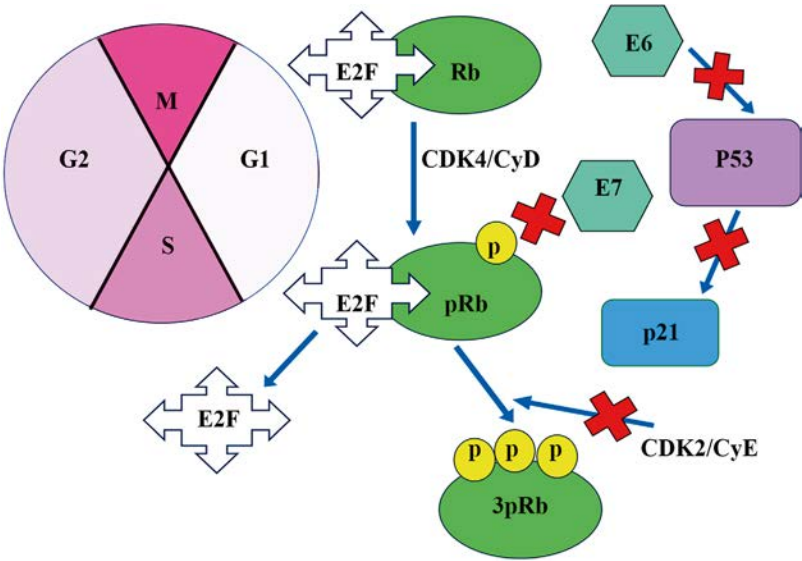


Fig. 15.13 Nonkeratinizing cervical squamous cell carcinoma (HEX 100)

independent tumors have been reported to have a worse prognosis. Five-year disease-free survival is 95% in stage IA and 5–15% in stage IV [4, 5].

- **Adenocarcinoma:** Cervical adenocarcinomas constitute 15–20% of cervical cancers. The WHO 2022 [10] divided cervical adenocarcinomas into two groups as HPV associated (85%) and HPV independent (15%).
 - A. *HPV-associated adenocarcinomas:* The average age of occurrence is 40–42, and they are seen at slightly

younger ages than HPV-independent ones. HPV 16, 18, 45 plays the most role in etiology. In pathogenesis, HPV integration into the host genome, genomic instability, and somatic mutation accumulation occur as a result of p53 and RB1 inactivation of HPV's E6 and E7 oncoproteins. Macroscopically, they are in the form of exophytic, ulcerated masses in the distal part of the cervix. Microscopically, apical mitosis, apoptotic body, and karyorrhexis seen at low magnification are important features. Nuclei are large, elongated, and hyperchromatic. In well-differentiated and moderately differentiated areas, glandular luminal borders are smooth and lined with pseudostratified columnar epithelium (Fig. 15.14). Histologically, there are two groups: classical type and mucin-producing type [5]. Classic type constitutes 75% of all endocervical adenocarcinomas and mucin-producing type constitutes 10%. Classical type includes villoglandular and micropapillary type. Mucin-producing type includes mucinous NOS (>50% intracytoplasmic mucin of cells),

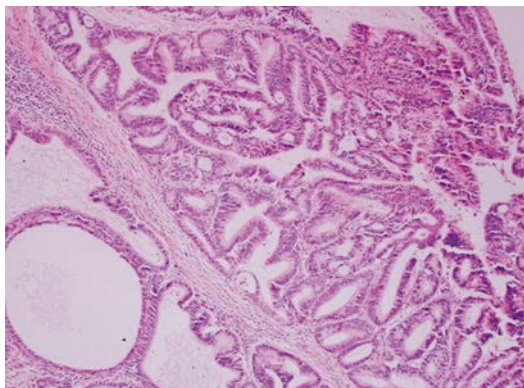


Fig. 15.14 Endocervical adenocarcinoma (HEX 200)

intestinal (>50% goblet cell of cells), signet ring (>50% signet ring cell), and invasive stratified mucin-producing carcinoma (iSMILE). HPV-associated adenocarcinomas may have destructive and nondestructive invasion patterns. Pattern-based classification (Silva system) has been reported to be associated with nodal metastasis risk, recurrence, and survival [13]. Stromal invasion is divided into three groups according to its pattern. Pattern A represents nondestructive stromal invasion, Pattern B shows early or focal destructive invasion, and Pattern C is characterized by diffuse destructive stromal invasion. Lymph node metastasis, recurrence, and mortality risk are stated as 0% in Pattern A, 4% in Pattern B, and ~20% in Pattern C. Since lymph node metastasis is not seen in Pattern A, it is stated that lymph node dissection is not necessary. Immunohistochemically, there is block staining with p16. While ER, PR, CK20, and vimentin SATB2 are negative, CDX2 may be positive in intestinal type [1, 5]. Differential diagnosis includes low-grade endometrioid endometrial adenocarcinoma and HPV-independent endocervical adenocarcinomas (gastric, clear, mesonephric). In microscopic adenocarcinomas,

measurement of invasion depth is very important for staging. Five-year overall survival is 77%. Stage is the most important prognostic parameter. In early invasive tumors (stage IA1), it is 100%, while in stage I A2, stage III, and stage IV, it is 93%, 34%, and 3%, respectively [13–15].

- B. *HPV-independent adenocarcinomas:* The average age of occurrence is 50–55 (range 37–84). Their etiology and pathogenesis are not fully known. Gastric-type adenocarcinomas may be associated with Peutz-Jeghers syndrome (germline STK 11 mutation). Five types of HPV-unrelated adenocarcinomas have been defined. These are gastric type, clear cell type, mesonephric type, NOS, and other types (endometrioid, carcinosarcoma, adenosquamous, adenoid basal, undifferentiated). Microscopically, gastric type constitutes tubular-cystic-papillary pattern and consists of clear-pale-foamy abundant cytoplasm and sharp cell borders. Atypia is variable and mitosis and apoptosis are not remarkable. Clear cell type represents solid, tubular, and cystic growth pattern tumors consisting of cells containing intracellular glycogen and intraluminal eosinophilic/mucinous secretion. Intracellular mucin is not seen. Mesonephric type represents several patterns. Although there are many different growth patterns, the most typical pattern is tubular with eosinophilic secretion in the lumen. The cells are uniform and have coarse or vesicular chromatin or grooved nucleus structure. Nucleolus is not noticeable. In endometrioid type, patterns ranging from simple tubular galls to complex glandular structures are seen. Glandular structures are lined with pseudostratified columnar cells with round nuclei. Squamous metaplasia may be seen. Differential diagnosis

- includes cervical nonneoplastic lesions, HPV-independent adenocarcinoma types, HPV-related endocervical adenocarcinomas, endometrial adenocarcinoma types extending to the cervix, and metastatic carcinomas. A wide immunohistochemical panel may be required for differentiation. HPV-independent adenocarcinomas represent worse prognosis than HPV-related adenocarcinomas. Overall survival is related to surgical type, stage, and lymph node metastasis status. Stage I tumors have an excellent prognosis (90%). Recurrence is seen in the first 2–3 years in advanced stage tumors [13–15].
- *Neuroendocrine tumors (NET)*: They are epithelial tumors with different prognosis originating from neuroendocrine cells. They constitute ~2% of cervical neoplasms. The mean age of occurrence is 36–42. High oncogenic risk HPV [16, 18] plays a role in etiology. According to histological features, there are types such as low-grade neuroendocrine tumors (NET) grade 1 (carcinoid), grade 2 (atypical carcinoid), small cell neuroendocrine carcinoma (SCNEC), and large cell neuroendocrine carcinoma (LGNEC). Immunohistochemically, synaptophysin, chromogranin, NSE, CD56 positivity is required. Differential diagnosis includes metastatic small cell carcinoma (vs. SCNEC), HPV-associated squamous cell carcinoma (vs. SCNEC), and lymphoma/leukemia (vs. SCNEC, LCNEC). Prognosis: NET grade 1 tumors have a good prognosis but have metastatic potential. NET grade 2 tumors have a similar prognosis to high-grade neuroendocrine carcinoma. SCNEC and LCNEC have poor prognoses [3, 5, 8].
 - *Mixed epithelial and mesenchymal tumors of the cervix*: Adenomyoma and adenofibroma have both epithelial and mesenchymal components and are benign. In Müllerian adenosarcoma, the epithelial component is benign, while the mesenchymal component is malignant. Primary cervical adenosarcoma is rare [3, 5, 8].
 - *Melanocytic tumors of the cervix*: The frequency of pigmented lesions of the cervix is 1–2%. Blue nevus is a benign melanocytic tumor. Primary cervical malignant melanoma is very rare and has a poor prognosis. It is often seen in the postmenopausal period. It can be confused with poorly differentiated carcinoma, sarcoma, and lymphoma histologically [3, 5, 8].
 - *Secondary tumors of the cervix* usually originate from the endometrium and ovary. Advanced-stage tumors originating from the rectum and bladder show direct extension to the cervix. Most metastatic tumors of the cervix originate from the stomach and breast [3, 5, 8].

15.4 Endometrium (Uterine Corpus)

15.4.1 Neoplasms of the Endometrium

- *Benign endometrial neoplasms* are mainly represented by endometrial polyps and leiomyomas (when extending from the myometrium into the endometrial cavity). Endometrial polyps are localized overgrowths of endometrial glands and stroma covered by epithelium; they may occur at any age but are most common in perimenopausal women. These lesions are usually hormonally responsive and may present with abnormal uterine bleeding. Histologically, polyps show irregularly shaped glands, often with fibrotic stroma and thick-walled vessels. Although typically benign, they can occasionally harbor foci of hyperplasia or carcinoma. Other rare benign lesions include adenofibroma and adenomyoma, which show both glandular and stromal components without destructive invasion [18–20].

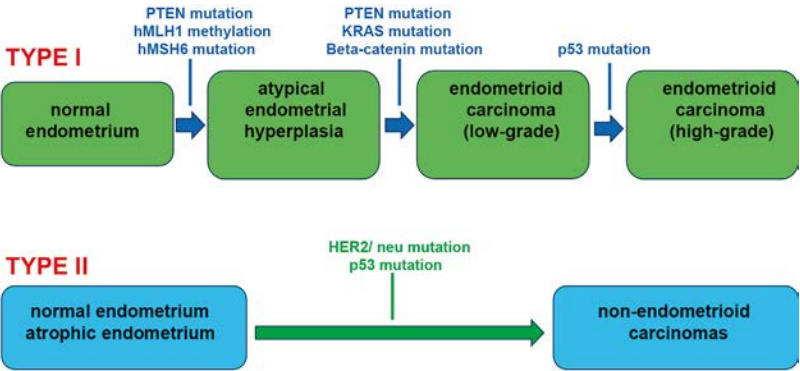
- *Carcinoma of the endometrium*: Endometrial carcinoma is the most common female genital tract cancer, especially in developed countries. According to Globocan 2022 data, approximately 420,000 new cases have been reported each year, and it is the sixth most common in women (4.3%). Endometrial carcinomas are divided into two pathogenetic types (Table 15.2). Type I tumors are low-grade, estrogen-related, clinically indolent endometrioid carcinomas. It is the most common type. Type II tumors are non-endometrioid, clinically aggressive, not related to estrogen, serous, clear cell, carcinosarcoma types. There

are overlapping features between these two types of tumors at the clinical, pathological, and molecular levels (Fig. 15.15). Diagnosing low-grade endometrial carcinomas based on their histopathological appearance does not cause any problems among pathologists. However, there is high interobserver variability in high-grade endometrial carcinomas [21–23]. The most next-generation sequencing studies put forward to differences between endometrioid and serous carcinomas. The Cancer Genome Atlas (TCGA) has defined four molecular subtypes. These subtypes are summarized as follows:

Table 15.2 Features of type I and type II endometrial carcinomas

Features	Type I	Type II
Clinic	Obesity Hypertension Diabetes Unopposed estrogen	Atrophy
Morphology	Endometrioid	Serous Clear cell Carcinosarcoma
Precursor	Hyperplasia	Serous or endometrial intraepithelial carcinoma
Mutated/abnormal genes	PTEN ARID 1A PIK3CA (PI3K) KRAS FGF2 MSI CTNNB 1(Wnt signaling) POLE TP53	TP53 Aneuploidy PIK3CA(PI3K) FBXW7 CCN 1 PPP2RIA
Progression	Indolent Spreads via lymphatics	Aggressive Spreads intraperitoneal and via lymphatics

Fig. 15.15 Genetic mutations in the carcinogenesis of endometrial carcinomas



- I. *Ultramutated-POLE mutated tumors*: They have good prognosis. There is a mutation in DNA polymerase ϵ and a high somatic mutation burden.
 - II. *Hypermutated/MSI (microsatellite instability) tumors*: They have an intermediate prognosis. There is a mutation or epigenetic silencing in mismatch repair genes. A high somatic mutation burden is seen.
 - III. *Tumors showing low-copy-number changes/MSS (microsatellite stable)*: They have an intermediate prognosis. They are characterized by mutations in the PI3K/AKT pathway.
 - IV. *High copy-number changes/serous-like tumors*: These tumors show poor prognosis. They are serous or high-grade endometrioid types. They usually show TP53 mutation and high copy number.
- *Endometrioid carcinoma of the endometrium* is the most common endometrial carcinoma. They constitute approximately 80–90% of the cases. The majority are well-differentiated and pathogenetically type I tumors. They are associated with excessive unopposed estrogenic stimulation of the endometrium such as early menarche, late menopause, nulliparity, tamoxifen, polycystic ovary syndrome, and estrogen-producing ovarian tumors. It can be seen together with some hereditary syndromes such as Lynch and Cowden. Endometrioid carcinoma develops because of a series of changes in tumor suppressor genes and oncogenes. Identical PTEN mutations have been detected in atypical endometrial hyperplasia and endometrioid carcinoma. The fact that this mutation is seen before carcinoma develops supports the view that atypical hyperplasia is a precursor lesion of endometrial carcinoma. Sequencing of genomes studies, especially in endometrioid carcinoma, have revealed mutations that most frequently lead to increased signaling in the PI3K/AKT pathway. PI3K/AKT signals increase the expression of estrogen receptor-dependent target genes in the endometrial epithelium. Mutations affecting the PI3K/AKT pathway in endometrial carcinoma are as follows [23–25]:
 - Mutations in the PTEN suppressor gene (in 30–80% of cases).
 - PIK3CA is an oncogene that encodes the catalytic subunit of PI3K. It is the source of activating mutations in approximately 40% of endometrioid carcinomas. However, it is generally not seen in atypical hyperplasia, suggesting that PIK3CA may play a role in malignant transformation.
 - KRAS activating mutations are seen in 25% of cases. These mutations also stimulate PI3K/AKT signals.
 - There are loss-of-function mutations in ARID 1A. It is seen in one-third of carcinomas. ARID 1A is a regulator of chromatin structure. This mutation has also been frequently detected in ovarian endometrioid and clear cell carcinomas developing on the basis of endometriosis.
 - Defects of DNA mismatch repair genes are frequently found in 20% of sporadic tumors and in endometrioid carcinomas of women with hereditary nonpolyposis colorectal carcinoma syndrome (Lynch syndrome).
 - A small number of mutations (less than 10% of cases) are detected that impair the proofreading function of DNA polymerase ϵ , encoded by the POLE gene.
 - Approximately half of poorly differentiated carcinomas have mutations in the TP53 gene that cause loss of function.
- Macroscopically, endometrial carcinomas may be exophytic or diffusely infiltrative. Necrosis and hemorrhage may be observed. Histologically, endometrioid carcinoma is characterized by pseudostratified nuclei and columnar cells forming villoglandular structures (Fig. 15.16). There is nuclear atypia. Squamous differentiation can be seen in approximately 25% of cases (Fig. 15.17). The degree of tumor differentiation and the degree of squamous differentiation are usually parallel. When determining the degree of differentiation in the tumor, only glandular differentiation is considered, squamous areas are not considered. Tumors with POLE

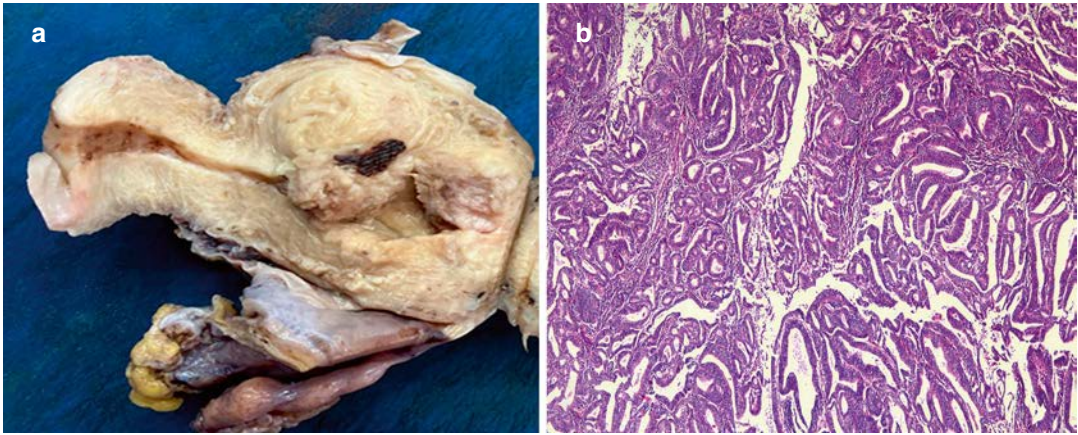


Fig. 15.16 (a) Gross view of endometrioid carcinoma, (b) Microscopic view of well-differentiated endometrioid carcinoma

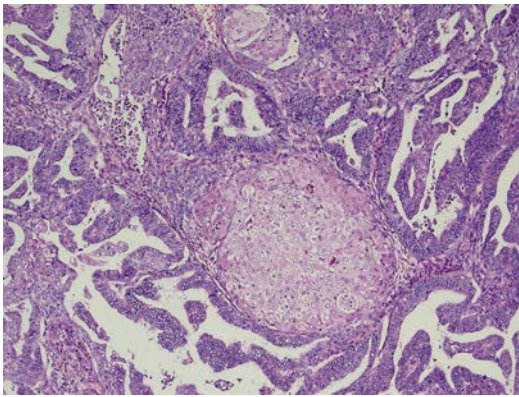


Fig. 15.17 Area of squamous differentiation

mutation and defects in DNA mismatch genes show intense T lymphocyte infiltration. Endometrial carcinomas are determined by a FIGO (International Federation of Gynecology and Obstetrics) grade based on the degree of glandular differentiation and fall into three histologic groups [26–29]:

1. *Well-differentiated (grade 1) tumors* represent well-formed glands resembling atypical endometrial hyperplasia, but separated from it by stromal invasion and desmoplastic stroma.
2. *Moderately differentiated (grade 2) tumors* represent well-formed glands are together with nonglandular solid areas. However, solid areas constitute less than 50% of the tumor.

3. *Poorly differentiated (grade 3) tumors* represent solid nonglandular, and non-squamous areas constitute more than 50% of the tumor.

- *Serous carcinoma of the endometrium* constitutes approximately 10% of endometrial carcinomas. They are seen on the basis of endometrial atrophy. They occur at later ages compared to the endometrioid type. They show widespread, distinct nuclear pleomorphism with papillary or glandular development (Fig. 15.18a). They are classified as type II carcinoma and poorly differentiated. In pathogenesis, mutations in the TP53 tumor suppressor gene were detected in most serous carcinomas. Therefore, nuclear p53 protein expressions are positive. In addition, genetic alterations in PIK3CA, PP2R1A, and FBXW7 and genetic amplifications in ERBB2 (HER2) were observed. Molecularly, all serous carcinomas are in the high copy number subgroup and show significant chromosomal instability. TP 53 mutation is also seen in most serous intraepithelial carcinomas involving the glands or surface epithelium of atrophic endometrium (Fig. 15.18b). Although noninvasive, serous intraepithelial carcinoma may metastasize to extrauterine organs such as the fallopian tube or omentum early with exfoliation. Therefore, it should be considered as potentially malignant. Macroscopically, serous

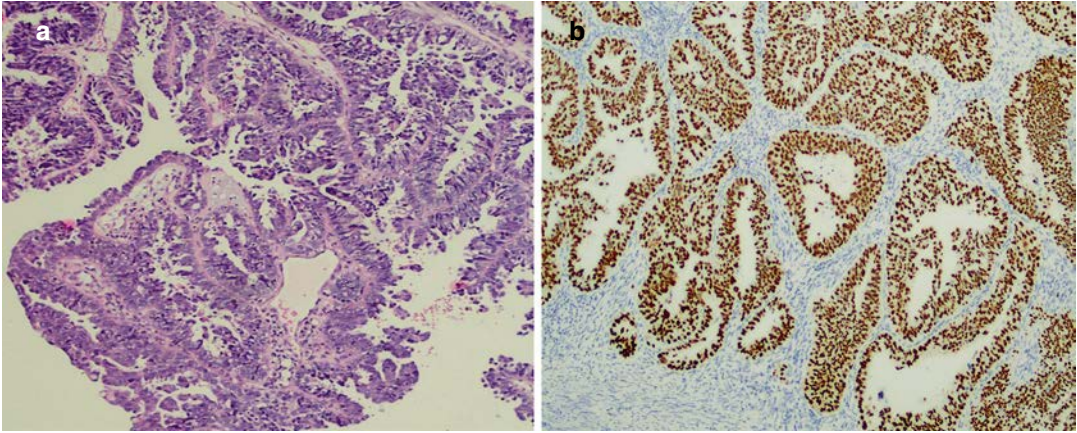


Fig. 15.18 Serous endometrial carcinoma: (a) Papillary growth pattern, (b) p53 nuclear protein accumulation

tumors may have an invasive appearance originating from an exophytic or atrophic base. When diagnosed, cervix invasion or adnexal involvement may be detected. Microscopically, it may be papillary, glandular, or solid pattern. Cells with clear or eosinophilic cytoplasm showing marked nuclear atypia are characteristic. Mitotic activity is increased and there are occasional atypical mitoses.

Prognosis of uterine cancer is related to the FIGO stage of the disease [30]:

- Stage I—Uterine cancer is confined to the uterus.
- Stage II—Uterine cancer has spread to the cervix.
- Stage III—Uterine cancer has spread to the vagina, ovaries, and/or lymph nodes.
- Stage IV—Uterine cancer has spread to the urinary bladder, rectum, or organs located far from the uterus, such as the lungs or bones [30].

Surgery alone or in combination with radiotherapy is applied for low-stage (stage I–II) and low-grade (grade I–II endometrioid type) endometrial carcinomas. Treatment for stage III–IV and high-grade (grade III endometrioid, serous, clear cell type) carcinomas is surgery plus radiotherapy and chemotherapy. In addition to PI3K/AKT pathway inhibitors, immune checkpoint inhibitor therapy is being tried, especially in

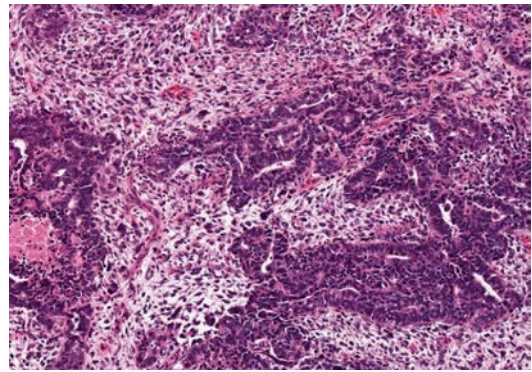


Fig. 15.19 Carcinosarcoma

tumors showing hypermutated MSI and ultramutated polymerase ϵ molecular characteristics. The majority of endometrial cancers are diagnosed early stage (80% in stage I), with 5-year survival rates over 95% [5, 10, 30].

- *Carcinosarcoma (malignant mixed Mullerian tumor)*: It is a biphasic tumor containing high-grade carcinomatous and sarcomatous components. The epithelial component may be high-grade endometrioid, serous, clear cell, or undifferentiated carcinoma. The sarcomatous component is mostly of uterine origin and is high grade (Fig. 15.19). However, heterologous elements (rhabdomyosarcoma, osteosarcoma) may also be seen. Since similar molecular changes have been detected in the sarcomatous and carcinomatous components,

it is accepted that sarcoma develops from carcinoma through the epithelial-mesenchymal transition mechanism. Macroscopically, carcinosarcomas are exophytic lesions. They are polypoid and may prolapse from the cervix to the vagina. They may show hemorrhage, necrosis, or cystic degeneration. Causes are typically postmenopausal and usually present with complaints of vaginal bleeding or a pelvic mass. Prognosis depends on the stage. In stages I and II, 5-year survival is approximately 60%, while in stage IV, it is 10%. In addition, a mass larger than 5 cm, deeper myometrial invasion than 50%, lymphovascular invasion, dominant sarcomatous component, heterologous element, and the presence of serous carcinoma are associated with poor prognosis [5, 10, 30].

- *Tumors of Endometrial Stroma*

- *Adenosarcoma* is a rare gynecologic malignancy representing approximately 1% of female genital tract malignancies and 8% of uterine sarcomas [13]. Abnormal uterine bleeding or tissue protruding through the cervical os may occur in the clinic. Patients are mostly postmenopausal. It is biphasic neoplasm composed of a benign epithelial component and a malignant stromal component. The epithelial component consists of benign endometrial or ciliated epithelium-lined phylloidiform cleft-like or dilated glands. Neoplastic stroma is diagnostic, especially with hypercellularity around the glands. The sarcomatous component is usually of uterine origin (homologous) but may rarely show heterologous features such as rhabdomyosarcoma [27, 28].
- *Stromal tumors*: Endometrial stromal tumors are uterine mesenchymal tumors, which histologically resemble endometrial stroma of the functioning endometrium. These are classified as endometrial stromal nodule, low-grade endometrial stromal sarcoma (LG-ESS), high-grade endometrial stromal sarcoma (HG-ESS), and undifferentiated uterine sarcoma (UUS). Molecular studies have revealed specific gene fusions

in these tumors. Now, correlation of specific molecular findings with morphological and immunohistochemical features has allowed better differential diagnosis between these tumors. Stage is the most important prognostic factor. Prognosis is better in low-grade sarcoma, while prognosis is worse in high-grade sarcoma and undifferentiated sarcoma [23, 31].

- *Tumors of the Myometrium*

- *Smooth muscle neoplasms of the uterus* are common, and most are *leiomyomas*. They are most frequently seen in middle-aged women. Progestin, progesterone, hormone replacement therapy, and pregnancy occasionally are associated with rapid leiomyoma growth. They are single or frequently multiple. They may carry simple chromosomal abnormalities. Approximately 70% of leiomyomas have mutations in the MED12 gene. The MED12 gene encodes a mediator component that stimulates gene expression by acting as a bridge between transcription factors and RNA polymerase. Macroscopically, leiomyomas are well circumscribed but unencapsulated. Their size is variable. They have characteristically firm, whorled, white cut surface. Large tumors may have hemorrhage and infarction. They are frequently within the myometrium of the corpus, as intramural, submucosal, or subserosal. But, occasionally, they occur in uterine ligaments, lower uterine segments, or cervix. Microscopically, leiomyomas are composed of spindle cells arranged with intersecting fascicles. Cells have uniform size and shape eosinophilic fibrillary cytoplasm and oval nucleus with small nucleoli. Mitotic figures are rare (Fig. 15.20). Histologically, there are many subtypes. Cellular leiomyoma and leiomyoma with bizarre nuclei which has nuclear atypia and giant cells can be confused with leiomyosarcoma. A low mitotic index distinguishes it from malignancy. They are mostly embedded in veins, especially the vena cava. Hematogenous disseminated

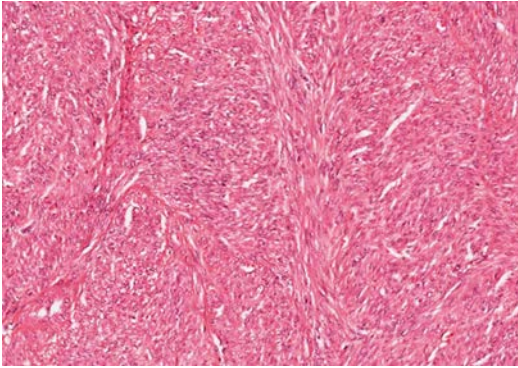


Fig. 15.20 Leiomyoma

intravenous leiomyomatosis, fumarate hydratase-deficient leiomyoma, and disseminated peritoneal leiomyomatosis seen as widespread small nodules in the peritoneum are rare variants. Leiomyomas are usually asymptomatic. Depending on their size and location, they may cause bleeding, pelvic pain, infertility, or spontaneous abortion in pregnant women. They may recur after myomectomy. Malignant transformation is quite rare [23, 27].

- *Leiomyosarcoma* is a malignant mesenchymal tumor showing uterine myometrial derivation. Leiomyosarcomas constitute approximately 1.3% of uterine malignancies. It is seen at an average age of 50–55. There are symptoms of abnormal vaginal bleeding, lower abdominal pain, or abdominal mass. Macroscopically, they are seen as single, large, soft mass or a polypoid mass protruding from the cervical os into the vagina. The cut surface usually contains hemorrhage and necrosis. Microscopically, interlacing, disorganized fascicles formed by cells with eosinophilic cytoplasm showing marked nuclear atypia are seen. There are spindle, epithelioid, and myxoid subtypes. They are distinguished from leiomyoma by the presence of high mitotic index, nuclear atypia, and tumor necrosis. In the spindle type, if nuclear atypia and/or necrosis are present, ten or more mitoses per ten high-power fields (HPF) are diagnostic of leiomyosarcoma.

In the epithelioid and myxoid types, nuclear atypia and/or necrosis as well as fewer mitoses per 10 high-power fields (≤ 4 and ≥ 1 , respectively) are diagnostic of malignancy. A small number of tumors of smooth muscle origin exceed the morphologic criteria for leiomyoma or its subtypes but do not meet the criteria for the diagnosis of leiomyosarcoma. These tumors are called “smooth muscle tumors of uncertain malignant potential.” Leiomyosarcomas have poor prognosis. Following surgery, they often recur and metastasize hematogenously to distant organs. The overall 5-year survival rate for all stages combined ranges from 15% to 25%. Response to chemotherapy is limited [23, 31].

15.5 Fallopian Tubes

- Disorders of the fallopian tube include infections, ectopic pregnancy, endometriosis, and torsion. Infections may be acute, chronic, or granulomatous/histiocytic. Acute infection is purulent. *Neisseria gonorrhoeae* and *Chlamydia trachomatis* have been suggested as the most common causative organisms of the acute salpingitis. On the other hand, *Mycobacterium tuberculosis* is the most common cause of granulomatous salpingitis, especially in low-income communities. The most common lesion is paratubal cysts (hydatids of Morgagni) with a diameter of 0.5–2 cm lined with serous epithelium [27].
- *Tumors of the fallopian tubes*: The most common benign tumor is adenomatoid tumor. It is usually a yellow-white nodule with a diameter of 1–2 cm and located subserosal. In addition, adenofibroma and papilloma are among other benign tumors. More detailed macroscopic and microscopic examination of the fallopian tubes today has shown that serous tubal intraepithelial carcinoma in the epithelium is the origin of high-grade serous carcinoma in the ovary and peritoneum as well as the tube. TP53 mutation in the tubal epithelium is an

early finding in high-grade serous carcinogenesis and has been shown in more than 90% of cases. Tubal carcinoma is staged according to the TNM classification. Five-year survival in stage I is >80% [23, 27].

References

- Nucci MR, Oiva E. Diagnostic pathology gynecological. 3rd ed. Philadelphia: Elsevier; 2024. p. 1–162.
- Wilkinson EJ, Rush DS, Kurman RJ, Ellenson LH, Ronnett BM, editors. Blaustein's pathology of female genital tract. 7th ed. New York: Springer; 2019. p. 1–116.
- Koyuncuoğlu M. Jinekolojik Tümörlerin Patolojisi. 1st ed. İzmir: O tip Kitapevi; 2018. p. 1–82.
- Kumar V, Abbash AK, Aster JC, editors. Robbins & Cotran Pathologic basis of disease. 10th ed. Philadelphia: Elsevier; 2020. p. 986–93.
- Cree IA. WHO classification of tumors female genital tumors. 5th ed; 2020. p. 419–49.
- Sanchez I, Raffi J, Kraus CN. Vulvar neoplasms (Part II). Urology. 2022;2022(165):31–5.
- Nucci MR, Zaino RJ, Kurman E, Kurman RJ, Ellenson LH, Ronnett BM. Blaustein's pathology of female genital tract. 7th ed. New York: Springer; 2019. p. 180–93.
- Nucci MR, Oiva E. Diagnostic pathology gynecological. 3rd ed. Philadelphia: Elsevier; 2024. p. 208–338.
- Wright TC, Ronnett MB, Kurman RJ, Ellenson LH, Ronnett BM. Blaustein's pathology of the female genital tract. 7th ed. Cham: Springer; 2019. p. 193–369.
- Kurman RJ, Carcangiu ML, Herrington CS, Young RH. WHO classification of tumours of female reproductive organs. 4th ed. World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Breast and Female Genital Organs; 2014.
- Mikami Y, McCluggage WG. Endocervical glandular lesions exhibiting gastric differentiation: an emerging spectrum of benign, premalignant, and malignant lesions. Adv Anat Pathol. 2013;20:227–37.
- Nicolás I, Marimon L, Barnadas E, Saco A, Rodríguez-Carunchio L, Fusté P, Martí C, et al. HPV-negative tumors of the uterine cervix. Mod Pathol. 32(8):1189–96. <https://doi.org/10.1038/s41379-019-0249-1>.
- Alvarado-Cabrero, Parra-Herran C, Stolnicu S, Roma A, Oliva E, Malpica A. The Silva Pattern-based Classification for HPV-associated Invasive Endocervical Adenocarcinoma and the Distinction Between In Situ and Invasive Adenocarcinoma: relevant issues and recommendations from the international society of gynecological pathologists. Int J Gynecol Pathol. 2021;40:S48–65.
- De Vivar AD, Roma AA, Park KJ, Alvarado-Cabrero I, Rasty G, Chanona-Vilchis JG, Mikami Y, et al. Invasive endocervical adenocarcinoma: proposal for a new pattern-based classification system with significant clinical implications: a multi-institutional study. Int J of Gynecol Path. 2013;32:592–601.
- Park KJ. Cervical adenocarcinoma: integration of HPV status, pattern of invasion, morphology and molecular markers into classification. Histopathology. 2020;76:112–27. <https://doi.org/10.1111/his.13995>.
- Doorbar J, Egawa N, Griffin H, Kranjec C, Murakami I. Human papillomavirus molecular biology and disease association. Rev Med Virol. 2015;25 Suppl 1(S1):2–23.
- Uysal Yantur G, Sezak N, Diniz G. The role of immunohistochemical P16 tissue expression in determining the presence of the main oncoproteins E6 and E7 of human papilloma virus: a systematic review. Int J Adv Multidisc Res Stud. 2024;4(6):789–96. <https://doi.org/10.62225/2583049X.2024.4.6.3512>.
- Sahoo SS, Aguilar MXY, et al. Endometrial polyps are non-neoplastic but harbor epithelial mutations in endometrial cancer drivers at low allelic frequencies. Mod Pathol. 2022;35:1702–12. <https://doi.org/10.1038/s41379-022-01124-5>.
- Wang X, Zhang H, Xu J, et al. The typical polypoid adenomyoma is a special form of endometrial polyp: a case-controlled study with a large sample size. Eur J Med Res. 2023;28:308. <https://doi.org/10.1186/s40001-023-01286-1>.
- Watanabe H, Harada N, Nobuhara I, Haruta N, Higashiura Y, Watanabe S. Magnetic resonance imaging and flexible hysteroscopic findings of a uterine adenofibroma: case report and literature review. Case Rep Obstet Gynecol. 2018;2018:9685683. <https://doi.org/10.1155/2018/9685683>.
- Tai YJ, Chiang CJ, Chiang YC, Wu CY, Lee WC, Cheng WF. Age specific trend and birth cohort effect on different histologic types of uterine corpus cancers. Sci Rep. 2023;13:1019.
- Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74:229–63.
- WHO Classification of Tumours Editorial Board. Female genital tumours. WHO classification of tumours. 5th ed. IARC; 2020.
- Huang J, Chan WC, Ngai CH, Lok V, Zhang L, Lucero-Prisno DE III, Xu W, Zheng ZJ, Elcarte E, Withers M, Wong MCS. Global incidence and mortality trends of corpus uteri cancer and associations with gross domestic product, human development index, lifestyle, and metabolic risk factors. Int J Gynecol Obstet. 2023;162:998–1009.
- Galant N, Krawczyk P, Monist M, Obara A, Gajek L, Grenda A, Nicoś M, Kalinka E, Milanowski J. Molecular classification of endometrial cancer

- and its impact on therapy selection. *Int J Mol Sci.* 2024;25:5893.
26. Saglam O. Uncommon morphologic types of endometrial cancer and their mimickers: how much does molecular classification improve the practice for challenging cases? *Life.* 2024;14:387.
 27. Ellenson LH, Ronnet BM, Soslow RA, Lastra RR, Kurman RJ. Endometrial Carcinoma. In: Kurman RJ, Ellenson RH, Ronnet BM, editors. *Blaustein's pathology of the female genital tract.* 7th ed. Cham: Springer; 2019.
 28. Brierley JD, Gospodarowicz MK, Wittekind C, editors. *TNM classification of malignant tumours.* 8th ed. Oxford: Wiley-Blackwell; 2017.
 29. Trojano G, Olivieri C, Tinelli R, Damiani GR, Pellegrino A, Cicinelli E. Conservative treatment in early stage endometrial cancer: a review. *Acta Biomed.* 2019;90:405–10.
 30. Koskas M, Amant F, Mirza MR, Creutzberg CL. Cancer of the corpus uteri: 2021 update. *FIGO CANCER REPORT 2021.* *Int J Gynecol Obstet.* 2021;155:45–60.
 31. Kostov S, Kornovski Y, Ivanova V, Dzhakov D, Metodiev D, Watrowski R, Ivanova Y, Slavchev S, Mitev D, Angel YA. New aspects of sarcomas of uterine corpus – a brief narrative review. *Clin Pract.* 2021;11:878–900.

16.1 Introduction

The ovaries are a pair of organs located on either side of the uterus, adjacent to the lateral pelvic wall, behind the broad ligament and in front of the rectum. It is suspended to the broad ligament by the mesovarium formed by peritoneal folds, to the uterine cornu by the utero-ovarian ligament and to the lateral pelvic wall by the infundibulopelvic (suspensor) ligament. The size of the ovary in infants and childhood expands approximately 30 times in puberty and changes shape, taking on the weight, size, and shape of the ovary in adulthood. In the reproductive age, it has an average size of $4 \times 2 \times 1$ cm and weighs 5–8 g. It consists of three layers with unclear borders: outer cortex layer, inner medulla layer, and hilus. Follicular structures are seen in the cortex and medulla. In the postmenopausal period, their size is almost halved. The cross-sectional surface is usually firm and solid. Occasionally cysts a few millimeters in diameter can be seen in the cortex. Corpus albicans are seen in the medulla, and thick-walled vessels are seen in the medulla and hilus. The

main ovarian lymph ducts tangle at the hilus and drain through the mesovarium to the para-aortic lymph nodes, while accessory branches drain to the internal, external, and common iliac, inter-aortic, and inguinal lymph nodes. The ovaries are covered by a single layer of modified mesothelial cells known as the surface epithelium, also referred to as the coelomic or germinal epithelium. This epithelium typically expresses keratin, epithelial membrane antigen (EMA), EpCAM (with the mesothelial Ber-EP4 subtype being negative), CA-125, desmoplakin, vimentin, epidermal growth factor (EGF), estrogen, and progesterone receptors, as well as follicle-stimulating hormone (FSH) immunoreactivity. Embryologically and functionally, this surface epithelium is closely related to the Müllerian duct-derived lining epithelium of the fallopian tube, endometrium, and endocervix, which helps explain the morphological and biological similarities among the female genital organs and the tumors that arise from them. In women, the pelvic and lower abdominal mesothelium, together with the adjacent mesenchyme, are collectively referred to as the secondary Müllerian system, reflecting their shared developmental potential to give rise to similar epithelial and mesenchymal lesions [1–4].

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16.2 Ovarian Cysts

The ovaries are organs in which cystic lesions with very different pathogenesis are very common. Surface epithelial inclusion glands and cysts are formed by invagination of the surface epithelium and loss of its relationship with the surface. These cysts are less than 1 cm in diameter. It is lined with flat, cubic, or columnar epithelium. Psammoma bodies may be seen in the lumen or adjacent stroma. They have no clinical significance. Developmental cysts may also occur in the mesonephric/paramesonephric remnants in the ovarian hilus. Mesonephric ones are lined with cuboidal, non-ciliated epithelium; paramesonephric ones are lined with columnar and ciliated cells. Morgagni cyst is paramesonephric. Most paraovarian cysts and Gardner's cysts in the vagina are thought to be mesonephric in origin [5].

Follicular and luteal cysts of the ovary are variants of the normal physiologic structure. Solitary follicular and luteal cysts are very common in reproductive age. They usually present with a palpable mass or symptoms associated with excessive estrogen production. Rarely, they rupture and cause hemoperitoneum and abdominal pain. Macroscopically, the cyst is thin-walled and 3–8 cm in diameter. When less than 2.5 cm in diameter, they are called cystic follicles and cystic corpus luteum. They have serous or clot-like contents. Microscopically, follicular cysts are lined with granulosa cell layer on the inside and theca interna cell layer on the outside. The wall of lutein cysts contains luteinized granulosa and luteinized theca cells and the innermost layer of connective tissue is prominent. Most cysts regress spontaneously. Otherwise, excision may be necessary. Multiple luteinized follicular cysts (theca-lutein cyst) are seen in conditions such as mole hydatidiform, choriocarcinoma, and twin pregnancy [1, 5].

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women of reproductive age, affecting 5–10% of the female population. Although pathophysiology is complex and the initiating factor is not fully understood, the main finding is elevated LH or elevated LH/FSH

ratio. It presents with oligomenorrhea/amenorrhea, hyperandrogenism, infertility, hirsutism, and obesity in girls and young adults after menarche. Most patients have hyperinsulinemia and impaired glucose tolerance test. Macroscopically, both ovaries are usually round shaped and 3–5 times the normal ovarian size. Ovarian sections show multiple cysts, usually less than 1 cm in size, under a fibrotic and hypocellular capsule-like cortex. The cysts are atretic cystic follicles lined with several rows of granulosa cells on the inside and luteinized theca interna cells on the outside [3–5].

Luteoma of pregnancy is a solid proliferation of luteinized cells in the ovarian stroma associated with HCG. It is usually asymptomatic and is detected incidentally, close to delivery or postpartum. It may be microscopic in size and may reach 15–20 cm in diameter. It consists of limited, diffuse solid masses of luteinized cells. It is a benign lesion and regresses after delivery [5].

Stromal hyperplasia is seen in women in the 6th–9th decade. It is characterized by diffuse or nodular proliferation of ovarian stromal cells in the cortex and medulla of bilateral ovaries. In stromal hyperthecosis, luteinized stromal cells form single cells, nests, or islands, more common in the medulla [5].

16.3 Ovarian Tumors

Primary ovarian tumors originate from cells with endocrine functions, characterized as surface epithelium, germ cells, or sex cords that develop from the Müllerian epithelium (Fig. 16.1). Ovarian cancers are the seventh most common cancer in women worldwide and the eighth leading cause of cancer deaths. Twenty-five percent of cancers of the female genital area originate from the ovary. Except for germ cell tumors, most of them are observed in advanced age. The average age of development is 60 years. Most ovarian tumors seen in young people and children are germ cell tumors. Epithelial ovarian tumors constitute many ovarian tumors and approximately 90% of malignant ovarian tumors. Germ cell and sex cord-stromal tumors are less

Fig. 16.1 Origins of ovarian tumors

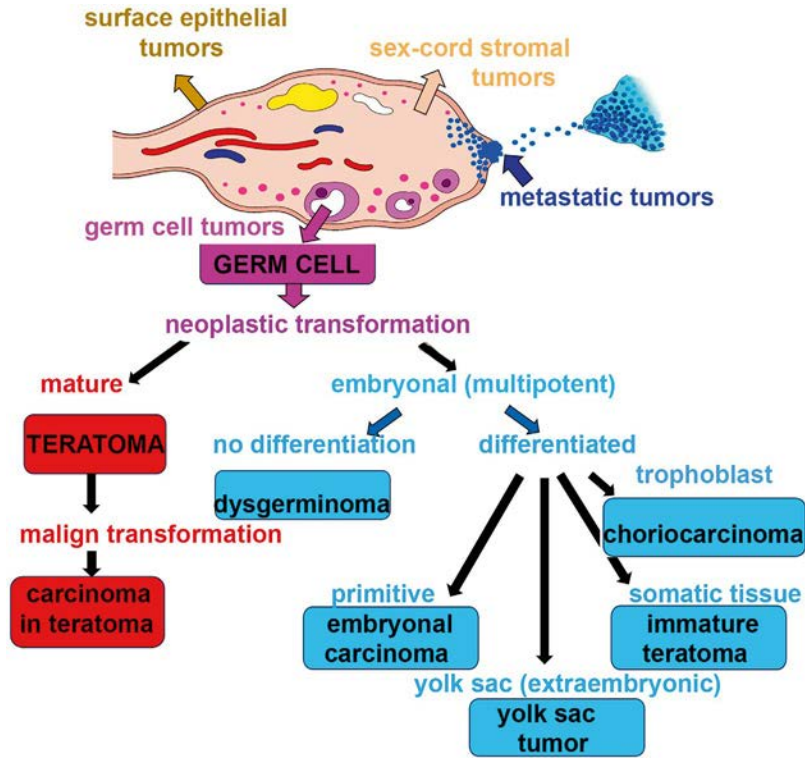


Table 16.1 Frequency, age of occurrence, and types of ovarian tumors according to their origin

	Surface epithelial tumors	Sex cord–stromal tumors	Germ cell tumors	Metastasis
Incidence	65–70%	5–10%	15–20%	5%
Age (years)	>20	All age	<25	Variable
Type	Serous Mucinous Endometrioid Clear cell Brenner Undifferentiated Mesonephric-like carcinoma Carcinosarcoma	Fibroma Thecoma Sclerosing stromal tumor Granulosa cell tumor Steroid cell tumors Sertoli–Leydig cell tumor Gynandroblastoma Gonadoblastoma	Teratoma Dysgerminoma Embryonal carcinoma Yolk sac tumor Choriocarcinoma	

common and comprise 20–30% of ovarian tumors and 10% of malignant tumors [5–7]. Types, ages of onset, and incidence of ovarian tumors are shown in Table 16.1.

The presence of hormonal factors, familial predisposition, and tumor suppressor gene mutations in the *etiology of ovarian cancer* has been definitively proven. In addition, a diet rich in animal fat and red meat, obesity, excessive coffee and alcohol consumption, a diet low in fiber and vitamin A, asbestosis, and viral agents are

claimed to be effective in the development of ovarian tumors. Among hormonal factors, *ovulation* is the most frequently reported risk factor. Early puberty, late menopause, and low number of pregnancies and births increase the risk of ovarian cancer. Multiple pregnancies and oral contraceptive use decrease the risk [5]. Approximately 5–10% of ovarian cancers are familial. The majority of these cases are associated with mutations in the *BRCA1* and *BRCA2* tumor suppressor genes. *BRCA1* is localized on

chromosome 17q and BRCA2 on chromosome 13. The lifetime risk of developing ovarian cancer is approximately 30% in BRCA1 carriers and lower in BRCA2 carriers. The rates of BRCA1 and BRCA2 mutations in sporadic ovarian cancers are 8% and 10%. There are three types of hereditary ovarian cancer: site-specific ovarian cancer, breast-ovarian cancer syndrome, and Lynch 2 syndrome. Hereditary ovarian cancer develops on average 10 years earlier (approximately 50 years of age) compared to sporadic cases. In breast-ovarian cancer syndrome, the defect is reported to be associated with the BRCA-1 gene. Lynch 2 syndrome is a combination of familial colon cancer (hereditary non-polyposis coli = Lynch 1 syndrome) and a high incidence of ovarian, as well as endometrial, breast, some gastrointestinal, and genitourinary system tumors. In this syndrome, the incidence of epithelial type ovarian tumors is higher [8]. There is an association between some genetic diseases and some ovarian tumors. For example, the frequency of fibroma in basal cell nevus syndrome characterized by nevoid basal cell carcinomas, granulosa cell tumors, and benign serous tumors in Peutz–Jeghers syndrome, gonadoblastoma, and dysgerminoma in patients with gonadal dysgenesis is increased [7].

Tumor markers used in the diagnosis and monitoring of ovarian cancers are macromolecules with protein–carbohydrate or protein–lipid structures. They are classified into three groups according to their origin: oncofetal or embryonic (α -fetoprotein, AFP), placental (β -human chorionic gonadotropin, β -hCG), and tumor-specific markers (cancer antigen 125, CA-125). CA-125 is a mucinous glycoprotein encoded by the MUC16 gene and remains the most widely used marker for epithelial ovarian carcinoma. However, its serum level may also be elevated in malignancies of the endometrium, fallopian tube, breast, lung, and gastrointestinal tract, as well as in certain benign conditions such as endometriosis and peritonitis. It is particularly useful in non-mucinous epithelial tumors of the ovary and in carcinomas of the endometrium and fallopian tube for assessing metastatic spread and monitor-

ing response to chemotherapy. Human epididymal protein 4 (HE4), encoded by the WFDC2 gene, is a glycoprotein expressed mainly in the epithelium of the distal epididymis, fallopian tube, and endometrium. In ovarian cancer, particularly high-grade serous carcinoma, serum HE4 levels are frequently elevated. It has higher specificity than CA-125 in distinguishing malignant from benign adnexal masses, especially in peri- and postmenopausal women. In clinical use, HE4 is combined with CA-125 in the risk of ovarian malignancy algorithm (ROMA), which provides a more accurate preoperative prediction of malignancy risk. Unlike CA-125, HE4 levels are less affected by benign gynecologic conditions such as endometriosis, leiomyoma, or pelvic inflammatory disease. Therefore, current guidelines recommend using both HE4 and CA-125 together for diagnosis, risk stratification, and follow-up of epithelial ovarian tumors. β -hCG is secreted by trophoblastic cells of the placenta and serves as an important marker in choriocarcinoma and other trophoblastic tumors. AFP is produced by the fetal liver, yolk sac, and gastrointestinal tract, and its level is increased in about half of ovarian germ cell tumors, most often yolk sac tumors, making it valuable for prognosis and treatment monitoring. Placental alkaline phosphatase (PLAP) is an enzyme produced by the placenta from the ninth week of gestation and normally exists only in trace amounts in adult serum; however, its concentration may increase markedly in ovarian germ cell tumors such as dysgerminomas and seminomas [5, 9, 10].

FIGO staging system is used in the *staging of ovarian tumors*. According to this system, *stage 1* defines limited disease in the ovary. In 1A, there is a tumor in one ovary/tuba uterina, and in 1B there is a tumor in both ovaries and tuba uterina. In 1C, the capsule is ruptured, and/or malignant cells are found in ascites or peritoneal fluid. In stage 2, the tumor has spread into the pelvis. In 2A, the tumor has invaded or implanted in the uterus, ovary, or tuba uterina. In 2B, there is spread to other pelvic organs. In stage 3, there is extra-pelvic spread. In 3A, implants up to 10 mm

in diameter are found on the abdominal peritoneal surfaces. In 3B, the abdominal peritoneal implants are smaller than 2 cm, and in 3C they are larger. Retroperitoneal lymph node involvement may also be present. Capsular invasion of the liver and spleen is considered stage 3C. Stage 4 is distant metastasized disease. Metastasis to the liver and splenic parenchyma is considered stage 4. In the presence of pleural effusion, malignant cytology is required to be considered stage 4 [3, 5].

16.3.1 Epithelial Tumors of the Ovary

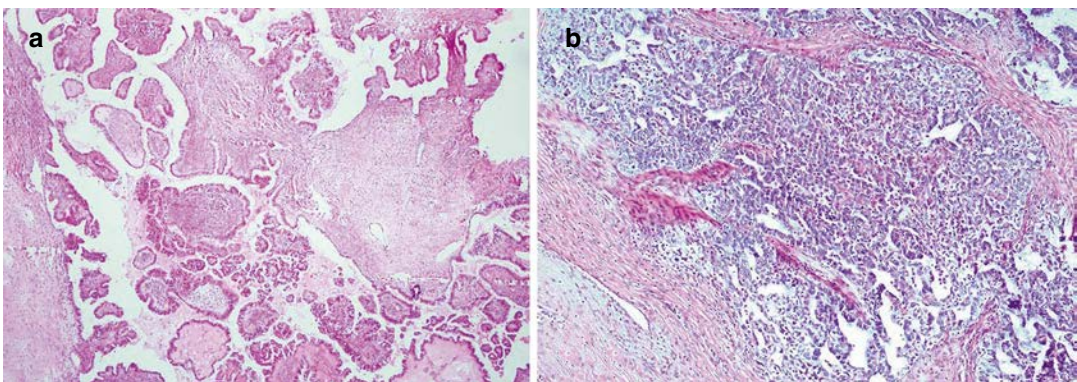
Epithelial tumors of the ovary originating from the Müllerian epithelium constitute 50% of all ovarian tumors, 40% of benign ovarian tumors, and 90% of malignant ovarian tumors. Approximately half of epithelial tumors are serous and 1/3 are mucinous. Endometrioid (7%), clear cell (3%), and transitional type (2%) are other microscopic types. Tumors containing at least two different components are called mixed epithelial carcinomas and are very rare (<1% of ovarian carcinomas). Almost all surface epithelial tumors have benign, borderline/low malignant potential and malignant forms. Those of the transitional type are usually benign. Approximately 80% of mucinous tumors are benign. In the serous type, the proportion of benign tumors with low malignant potential and malignant tumors is almost equal. Benign and borderline forms of endometrioid and clear cell tumors are very rare, and the majority are malignant. In addition, the rate of bilaterality is quite high in this group of tumors. 25–65% of serous tumors and 40% of endometrioid and clear cell carcinoma are bilateral. These tumors have a high bilaterality rate, just like metastatic ovarian tumors. In the other group of primary ovarian tumors and mucinous tumors, this rate is around 5–15% [4, 5]. Ovarian carcinoma histotypes have different characteristics (Table 16.2).

The most common ovarian tumor is a *serous tumor* (Fig. 16.2). Half of serous tumors are benign. Benign serous tumors, also known as

serous cystadenomas, have the appearance of a cyst with a mean diameter of 10 cm, smooth inner and outer surface, and clear, sometimes mucoid fluid inside, and are usually uniloculated. Rarely, a few small papillary formations may be observed. The solid type of benign serous tumors consisting of fibrous stroma-rich areas with glands and cysts as minor components is called cystadenofibroma or adenofibroma. While the bilaterality rate is 10% in benign tumors, this rate reaches 30% in borderline and 70% in malignant tumors. The cell type of serous tumors is high columnar ciliated epithelial cells of the normal tuba uterina in most tumors or non-cylindrical cuboidal epithelial cells similar to the surface epithelium of the ovary. In benign tumors, concentric calcifications, which are observed rarely and inconspicuously, are called psammoma bodies [5]. Borderline serous tumors are large-sized and multiloculated cystic tumors. Endophytic papillary structures are observed on the inner surface and exophytic papillary structures on the serosal surface. Necrosis and hemorrhage are rare. They rarely have a solid appearance. Papillae are more numerous and more complex as a result of epithelial proliferation. Microscopic examination shows increased alignment, budding, and clustering-like changes in the epithelium. Clusters can be found free in the cyst cavity. The cells lining the cysts and forming the papillae are columnar cells, ciliated or eosinophilic metaplastic cells. Nuclear atypia is mild or moderate. Mitosis is rare and not atypical. Microinvasions may be seen. Although they may be seen in several foci, as a rule, a single focus should not exceed 5 mm. Microinvasion has no negative effect on prognosis [5, 7]. Extraovarian spread and peritoneal implants may be observed in serous tumors. It is more common in borderline tumors (20–59%) and those with exophytic development. These are divided into noninvasive and invasive implants according to whether they invade the underlying normal tissue stroma. Noninvasive implants account for 88% of all implants. Invasive implants are considered as extraovarian low-grade serous carcinoma. Haphazard infiltration of solid epithelial nests

Table 16.2 Clinicopathologic features of surface epithelial tumors of the ovary

Feature	High-grade serous carcinoma	Clear cell carcinoma	Endometrioid carcinoma	Mucinous carcinoma	Low-grade serous carcinoma
Typical stage at diagnosis	Mostly advanced stage (III–IV)	Usually early stage (I–II)	Usually early stage	Usually early stage	Often advanced stage
Genetic risk factor	<i>BRCA1</i> , <i>BRCA2</i> mutations	<i>Lynch syndrome</i> (MMR genes)	<i>Lynch syndrome</i> (MMR genes)	Rare, uncertain	Rare, uncertain
Environmental/hormonal risk factors	Risk decreases with oral contraceptive use and tubal ligation; increases with hormone replacement therapy	Possible association with endometriosis	Associated with endometriosis; decreased risk with oral contraceptives	Possible link with smoking	Decreased risk with oral contraceptive use
Precursor lesion	Serous tubal intraepithelial carcinoma (STIC)	Endometriosis, atypical endometriosis	Endometriosis, atypical endometrioid proliferation	Benign or borderline mucinous cystadenoma	Serous borderline tumor
Clinical presentation	Ascites, abdominal distension, gastrointestinal symptoms	Pelvic mass, pain, endometriosis symptoms	Pelvic mass, abnormal uterine bleeding	Pelvic mass, pressure symptoms	Gastrointestinal or pelvic symptoms
Pattern of spread	Peritoneal and nodal dissemination	Peritoneal, nodal, hematogenous	Peritoneal, nodal, hematogenous	Peritoneal, pseudomyxoma peritonei (rare)	Peritoneal and nodal
Chemotherapy response	Usually platinum-sensitive (responsive)	Relatively chemoresistant	Moderately responsive	Relatively chemoresistant	Relatively chemoresistant
Major molecular alterations	<i>TP53</i> , <i>BRCA1/2</i>	<i>PIK3CA</i> , <i>ARID1A</i> , <i>PTEN</i> , <i>MMR</i>	<i>PTEN</i> , <i>ARID1A</i> , <i>CTNNB1</i> (β -catenin), <i>MMR</i>	<i>KRAS</i> , <i>HER2</i> amplification	<i>KRAS</i> , <i>BRAF</i> , <i>NRAS</i>
Potential therapeutic targets	PARP inhibitors (for <i>BRCA</i> -mutated tumors), anti-angiogenic therapy (VEGF inhibitors)	PI3K/AKT/mTOR pathway, anti-angiogenic therapy	Hormone receptor modulation, PI3K/AKT/mTOR pathway inhibitors	HER2-targeted therapy	MAPK pathway inhibitors (BRAF/MEK), hormone receptor modulation

**Fig. 16.2** (a) Borderline serous tumor, (b) serous carcinoma

with surrounding spaces and marked cytologic atypia is diagnostic. Glandular inclusions lined with single rows of columnar serous cells with no obvious cytologic atypia are considered as endosalpingiosis [5].

Malignant serous tumors contain papillary structures and a stroma of immature connective tissue according to their differentiation. Psammoma bodies are seen in 60–70% of cases. Some contain small amounts of mucin. Diagnostic serous papillary tumor features are faint in poorly differentiated tumors. Therefore, differential diagnosis especially with endometrioid carcinoma may be difficult. The average age of presentation is 63 years. 2/3 of the tumors are bilateral. Sometimes papillary serous carcinoma may develop in the peritoneum (extra ovarian) without ovarian involvement. It should be differentiated from mesothelioma [7]. Serous carcinomas are composed of columnar–cuboidal cells with marked nuclear atypia and nuclear pleomorphism (size difference between nuclei $> \times 3$). Mitosis is very high and often atypical. Immunohistochemically, CK7, PAX-8, WT-1, p16 positivity, and aberrant p53 expression are detected. CK 20 and Napsin A are negative [5].

Mucinous tumor is the second most common epithelial tumor of the ovary. 75–85% are benign [3]. The bilaterality rate of benign ones is very low. They are typically multilocular cysts containing myxoid material. It is the ovarian tumor with the highest incidence of acute torsion because they can reach a large size and are frequently seen in pregnancy. Cell type is endocervical (Müllerian) or intestinal cell-like. Mucinous

cystadenoma characteristically has a single-layered, uniform, highly cylindrical epithelium. Their cytoplasm is transparent and they have basally located hyperchromatic nuclei (Fig. 16.3a). Most contain diastase-resistant PAS(+) neutral mucin. Other intra-abdominal organs, especially the ovary and appendix, should be reviewed to exclude the possibility of bilaterality and not to miss cases associated with low-grade mucinous neoplasm of the appendix [5, 7]. Borderline mucinous tumors are large (15–30 cm), cystic, smooth tumors. 90% are unilateral. More than 10% of the tumor has budding, increased stratification of the epithelium and papillary structuring (Fig. 16.3b). Mild atypia is seen in the epithelium. Areas with high degree of atypia (intraepithelial carcinoma) and microinvasion may be present. Stromal invasion may be in the form of single cells or tumor nests not exceeding 5 mm in size [5].

Only 25% of mucinous ovarian carcinomas are primary (Fig. 16.4). Features supporting primary ovarian carcinoma include unilateral tumor, tumor size greater than 10 cm, complex papillary pattern, expansile invasion pattern, smooth serosal surface, presence of mural nodules, presence of concomitant teratoma, adenofibroma, endometriosis, and Brenner tumor. Carcinomas are usually intermixed with benign and borderline tumor areas. Glands are almost always lined with intestinal type epithelium. Rarely, signet ring cells may be seen. Mucinous carcinomas show two types of invasion patterns. Expansile invasion is associated with good prognosis. Infiltrative invasion pattern indicates malignant behavior.

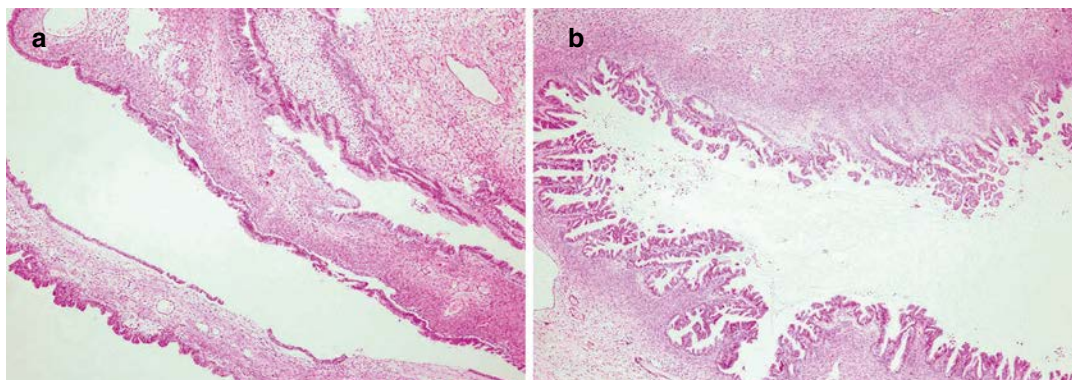


Fig. 16.3 (a) Mucinous cystadenoma, (b) borderline mucinous tumor

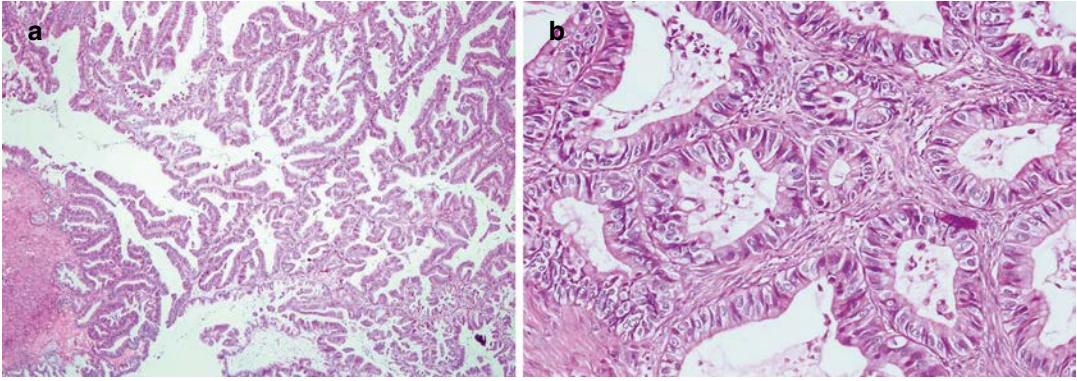


Fig. 16.4 (a) Expansile and (b) infiltrative invasion pattern in mucinous carcinoma

Immunohistochemically, CK7, CK20, and CEA are positive in the tumor [3, 5].

Endometrioid tumors are the third most common surface epithelial tumor of the ovary. Benign and borderline forms are rare. Benign forms have the appearance of adenofibroma or cystadenofibroma. Accompanying endometriosis is present in 20–30% of cases [5]. 15–30% of patients have endometrial carcinoma. Microscopically, tubular glands and cystic structures lined with pseudostratified epithelium similar to proliferative endometrial epithelium are observed. The stroma has a fibromatous appearance. Endometrial stroma is not detected. Serous, mucinous differentiation and squamous metaplasia may be seen in the epithelium [5].

Borderline endometrioid tumors are very rare. In approximately half of the cases, endometrioid adenofibroma is seen in the background. It is characterized by mild glandular crowding, increased stratification of the laying epithelium, and mild to moderate nuclear atypia compared to endometrioid adenofibroma. Severe nuclear atypia of the epithelium may indicate intraepithelial carcinoma. In some areas, the glands merge to form complex structures and show cribriformity. These areas are considered microinvasion when less than 5 mm in diameter. In the presence of invasion exceeding 5 mm, endometrioid carcinoma is diagnosed [7]. Eighty percent of endometrioid tumors are malignant. When malignant epithelial tumors are considered, it is the second most common malignant tumor after serous carcinoma among surface epithelial tumors of the

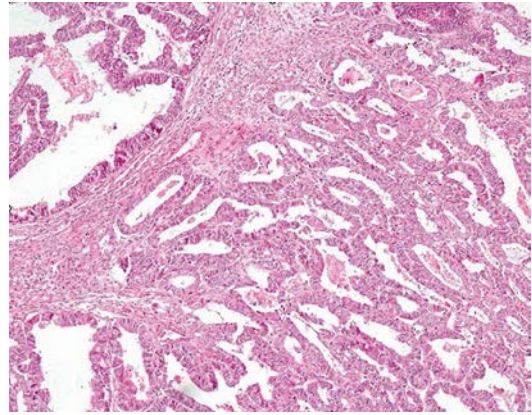


Fig. 16.5 Complex glands lined stratified epithelium in endometrioid carcinoma

ovary. It usually occurs in the fifth to sixth decade. Endometrioid carcinoma associated with endometriosis occurs at a younger age. Approximately half of the cases are stage 1 at the time of diagnosis. Most of them are low stage and low histological grade, and prognosis is good. In 15–25% of cases, endometrioid adenocarcinoma is present in the endometrium. The tumor size is larger compared to benign and borderline. Bilaterality rate is 10–30%. Macroscopically, it contains solid and cystic areas and polypoid lesions developing toward the cyst lumen are detected. There is hemorrhagic fluid in the cyst lumen. Microscopically, in well and moderately differentiated tumors, complex glandular and papillary structures lined with pseudostratified or multi-row columnar epithelium are observed (Fig. 16.5). There is necrotic material in the gland

lumen and squamous differentiation and secretory changes in the epithelium. There may also be a foreign body reaction to keratin. Mitosis is usually $<1/10$ BBA. Moderately differentiated tumors are distinguished by more complex glandular and microglandular structures. Nuclear atypia is more prominent, and tumoral giant cells are more frequent. Poorly differentiated endometrioid carcinomas are very rare. Most areas are solid islands or microglandular. Foci of hemorrhage and necrosis are common. Squamous differentiation and secretory changes are rare. Mitosis number is very increased. Immunohistochemically, cytokeratin and EMA and estrogen and progesterone receptors are positive in all cases; B72.3, vimentin, and CA 19.9 are positive in most cases. CEA is positive in half of the cases, and CA 125 is positive in 25%. Inhibin is negative. Sex cord–stromal tumors may be included in the differential diagnosis due to the similarity of microglandular areas to granulosa cells and trabecular areas to Sertoli cells. In such cases, cellular pleomorphism, true glandular structures, squamous differentiation, and mitosis are in favor of endometrioid carcinoma. EMA positivity and inhibin negativity also rule out sex cord–stromal tumor. Differential diagnosis with yolk sac tumor with secretory changes may be difficult. Yolk sac tumor is seen in younger women, and AFP positivity is helpful. Colon carcinoma metastases should also be kept in mind. These do not have squamous metaplasia, and CEA and CDX-2 are positive [5, 7].

Brenner's tumor accounts for 1–2% of all epithelial ovarian tumors. Most patients are in the fifth to seventh decade. Most of them are benign. Macroscopically, it is usually a unilateral, small, well-circumscribed solid nodule. Microscopically, it consists of islands of uniform transitional epithelium in a fibrous stroma. These islands resemble Walthard islands, epithelial inclusions that can be found in the serosa of the tuba or ovarian hilus. In the center of the epithelial islands, microcysts and nuclear grooves can be seen in the cells. Cells with defined borders and nuclear grooves resemble coffee beans. Mitosis is very rare. The stroma shows luteinization, hyalinization, dystrophic calcification, and rarely bone formation (Fig. 16.6). Associations with mucinous neoplasms (mostly mucinous cystadenomas) may be seen. Borderline and malignant Brenner tumor is very rare. It develops at an older age. The coffee bean-like identifying features of the cells are lost. Mitosis is high [5, 11].

Clear Cell Tumors Sixty percent of these tumors are associated with pelvic endometriosis. They constitute approximately 10% of ovarian tumors. Benign and borderline forms are rare. Benign forms are unilateral, 3–15 cm in diameter, microscopically adenofibroma-like tumors with a honeycomb appearance on the cross-sectional surface. Small tubule or cystic spaces are lined by hobnail cells and cubic cells with clear or eosinophilic cytoplasm. Cellular atypia is absent or minimal,

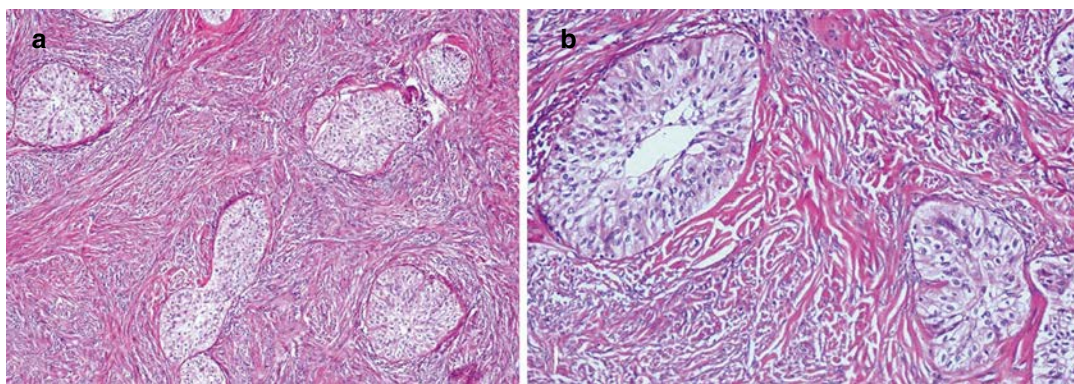


Fig. 16.6 (a) Tumor island in fibrous stroma. (b) Nuclear features in Brenner tumor

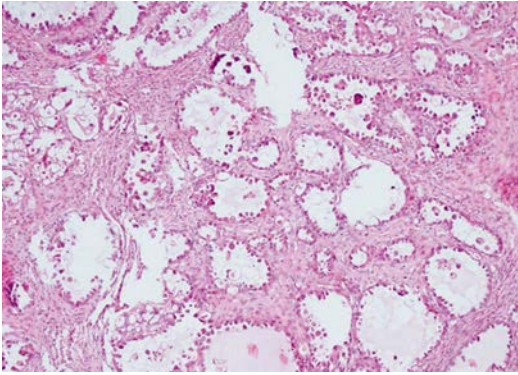


Fig. 16.7 Hobnail cells and tumor cells with clear cytoplasm lining the tubules and cystic structures in clear cell carcinoma

and mitosis is not seen. Mucin may be present in the cystic cavities. The stroma is fibrocollagenous. Borderline forms are unilateral and slightly larger in size than the benign form. Microscopically, atypia findings, increased sorting, budding, and solid proliferation rate are higher in epithelial cells compared to benign form. Mitosis is low [5, 7]. Clear cell carcinoma is seen at an older age (50–60 years). Most of them have endometriosis in the ovary or pelvis. Macroscopically, it is a unilateral, large cystic mass with soft nodular structures bulging toward the inner surface. Microscopically, tubulocystic, papillary and solid patterns are seen in different proportions. The cells lining the tubules, cysts, and papillary structures are cuboidal and/or hobnail shaped and arranged in a single row (Fig. 16.7). Cells are usually monomorphic. Nuclear pleomorphism is seen focally. Mitosis is usually low. Glycogen-rich clear cytoplasm stains positively with PAS and fades with diastasis. With mucicarmen and diastase PAS, focal staining of the apical cell membrane mucin can be seen. Immunohistochemically, PAX8, Napsin A, and HNF1 β are positive; WT1, ER, and PR are negative. WT1, ER, and Napsin A stains can be used in differentiation from high-grade serous carcinoma, and PR and Napsin A stains can be used in differentiation from endometrioid carcinoma. In differential diagnosis, renal cell carcinoma metastasis, yolk sac tumor, and dysgerminoma should also be considered [5, 12].

Other rare subtypes of surface epithelial tumors are mesonephric-like carcinoma, carcinosarcoma, undifferentiated and dedifferentiated carcinoma, and mixed carcinoma [5].

16.3.2 Sex Cord–Stromal Tumors

They include tumors containing granulosa cells, theca cells, Sertoli cells, Leydig cells, and fibroblasts, either singly or in various combinations and degrees of differentiation. It has been suggested that the cells forming these tumors originate from the mesenchyme or specialized stroma of the genital ridge or are formed by the participation of cholomic and mesonephric epithelium as the sex cord develops. In tumors originating from these cells, the tumor cells may maintain the function of normal cells and secrete estrogen or androgen. Most hormone-secreting ovarian tumors are in this group. Sex cord-stromal tumors constitute 5–10% of all ovarian tumors. Sex cord–stromal tumors are classified into three major groups: pure stromal tumors, pure sex cord tumors, and mixed sex cord–stromal tumors (Table 16.3) [5].

Fibroma is the most common ovarian stromal tumor. It is composed of spindle cells producing collagen at different rates (Fig. 16.8). It is mostly seen in middle age. Rarely luteinized cells and minor sex cord elements may be seen. Abdominal ascites is detected in 40% of cases, especially in those with a tumor diameter of more than 6 cm. In the rare Meigs syndrome, pleural effusion, ascites, and ovarian fibroma are present. In Gorlin syndrome, ovarian fibroma accompanies basal cell nevus syndrome. It usually has a good prognosis. Rarely, mitosis-active tumors with high nucleo-cytoplasmic ratio can be seen. Those with malignant course are called fibrosarcoma [3, 5].

Thecomas are of two types: typical and luteinized. Typical thecomas are composed of stromal cells forming diffuse syncytial layers with pale cytoplasm similar to lipid-bearing theca cells. Fibroblasts and hyaline plaques are observed in variable proportions. It is seen in advanced age. Almost all are unilateral. There is a reticulum

Table 16.3 WHO classification of sex cord–stromal tumors of the ovary (WHO 2020)

Pure stromal tumors	Pure sex cord tumors	Mixed sex cord–stromal tumors
Fibroma	Adult granulosa cell tumor	Sertoli–Leydig cell tumor
Cellular fibroma	Juvenile granulosa cell tumor	Sex cord–stromal tumor, NOS
Thecoma	Sertoli cell tumor	
Luteinized thecoma associated with sclerosing peritonitis	Sex cord tumor with annular tubules	
Fibrosarcoma		
Sclerosing stromal tumor		
Signet-ring stromal tumor		
Microcystic stromal tumor		
Leydig cell tumor		
Steroid cell tumor		
Steroid cell tumor, malignant		

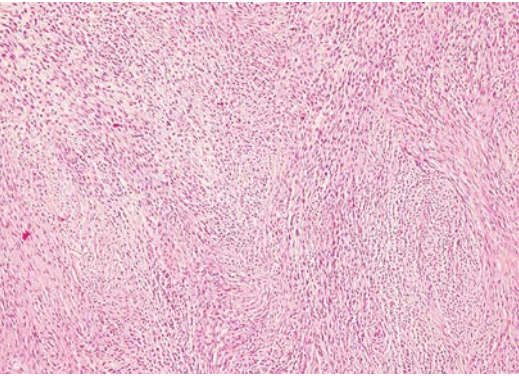


Fig. 16.8 Spindle cell bundles extending in different directions in the collagenized stroma of fibroma

network surrounding the individual cells. The luteinized thecoma form, which is composed of luteinized theca cells, occurs at a younger age. Since they are hormone active, vaginal bleeding may occur in most cases, and endometrial hyperplasia-carcinoma may occur in some [5].

Sclerosing stromal tumor is a clinically and pathologically distinct tumor from fibroma and thecoma. Fibromas and thecomas are almost never seen before the age of 30. However, sclerosing stromal tumors occur between the ages of 10 and 30. In contrast to a thecoma, very few of them produce estrogen. It is usually a solid, white tumor with a nodular pattern. Microscopically, it has a pseudobubular appearance. It consists of cellular nodules separated by hypocellular, edematous, collagenized stroma.

Numerous thin walled, branching vascular structures like antlers, fibroblasts, and round cells with vacuoles are observed in the nodules (Fig. 16.9). The nodules are sclerosed. The tumor has benign behavior [5, 7].

Granulosa Cell Tumors There are adult and juvenile forms. Adult granulosa cell tumors constitute 1 to 2% of all ovarian tumors. Most are estrogenic (3/4 of them); others are nonfunctioning, rarely androgenic. They are usually unilateral, encapsulated, solid tumors with a mean diameter of 12 cm, with occasional cystic formations. Abdominal pain may occur due to tumor rupture. Adult type occurs most commonly in the perimenopausal period, juvenile type in children and under 20 years of age. Most of them are adult types. If the proportion of theca cells is high and they are composed of luteinized cells, they are more yellow in color. Adult granulosa cell tumor is one of the tumors with low malignant potential due to a 5–25% chance of recurrence and invasion. 10-year survival is around 85%. However, long-term follow-up is essential as recurrence may occur even after 20 years. In addition, estrogen produced in abundance in most granulosa cell tumors increases the risk of endometrial hyperplasia and adenocarcinoma. Adenocarcinoma develops in 10–15% of cases with estrogen producing tumors [5]. Microscopically, it shows different structural patterns. The diffuse pattern is most common. Cells

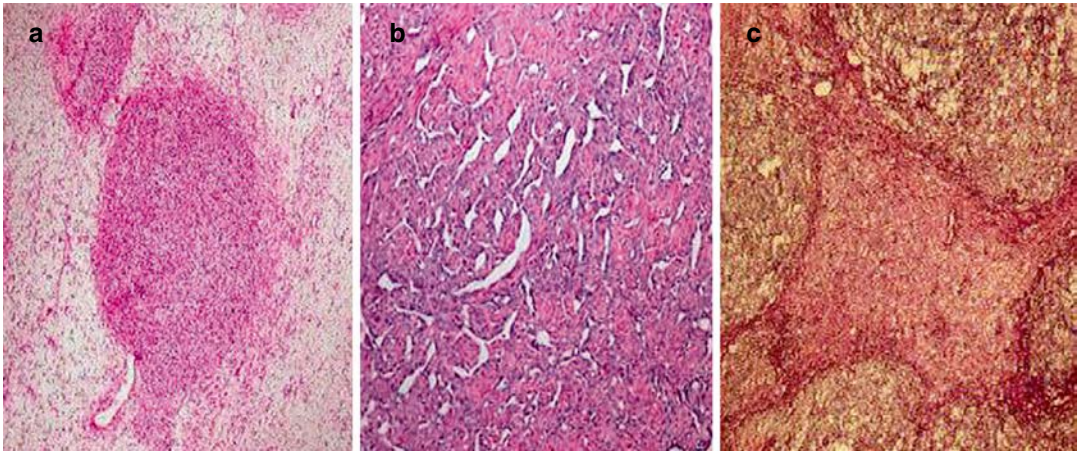


Fig. 16.9 (a) Pseudolobular appearance. (b) Branching vascular structure. (c) Variable reticular network in sclerosing stromal tumor

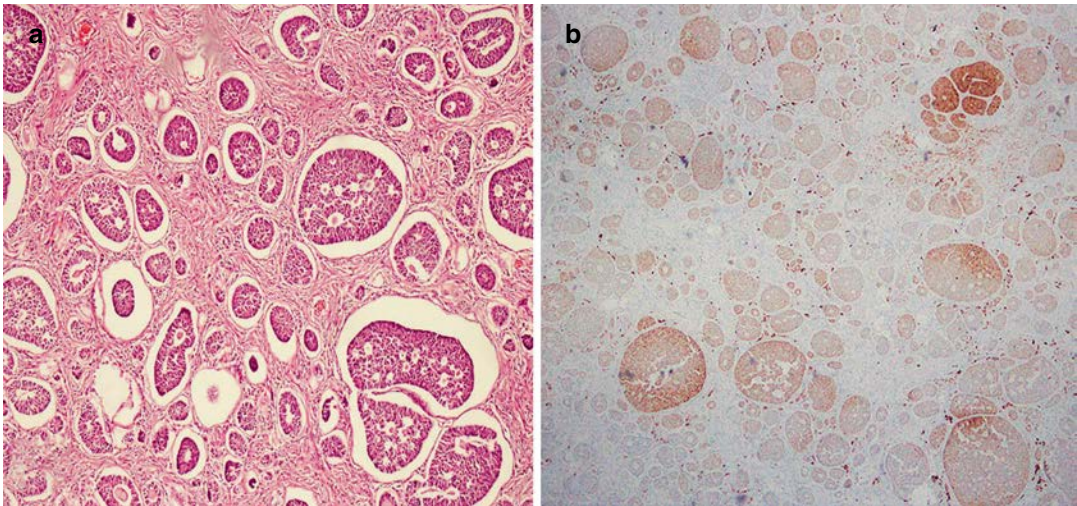


Fig. 16.10 (a) Microfollicular pattern and typical Call-Exner bodies in granulosa cell tumor. (b) Inhibin positivity in granulosa cell tumor

may show a macrofollicular pattern consisting of cords, large follicles resembling Graafian follicles, or a microfollicular pattern with typical Call-Exner bodies. Call-Exner bodies look like cystic formations filled with eosinophilic material surrounded by 1–2 rows of granulosa cells arranged in a radial pattern. Less common patterns are watered silk, gyriform, sarcomatoid, and pseudopapillary. The appearance of the nucleus is typical in granulosa cell tumors. In some of the oval, uniform, pale stained nuclei, a

longitudinal groove in the middle gives the nucleus a coffee bean appearance (Fig. 16.10). In luteinized type, cells with abundant eosinophilic cytoplasm are seen. In the adult form, fibromatous group tumors and endometrioid, clear cell, and undifferentiated carcinoma from surface epithelial ovarian tumors should be considered in the differential diagnosis. Immunohistochemical positivity for inhibin, FOXL2, CD99, and calretinin is important in the differential diagnosis. The most important parameter in prognosis is

stage. Tumor rupture, >5 cm diameter, atypia, and increased mitosis rate are also associated with prognosis. Juvenile granulosa cell tumors usually develop in the first three decades, 50% of them prepubertal. Clinically, it causes estrogenic or androgenic symptoms such as puberty precocity and menstrual irregularities. Microscopically, follicles with irregular contours, varying sizes, and basophilic secretions in the lumen are seen. Tumor cells have round vesicular nucleoli. Nuclear clefts are not seen. Mitosis is numerous. Prognosis is very good in ovarian limited tumors [5, 7].

Steroid cell tumors (stromal luteomas) constitute 20% of this group. They are usually smaller than 3 cm and have a benign course. There are androgenic, estrogenic, or progesterone-producing tumors. Polygonal cells clustered around vessels are found in the ovarian hilus. Tumors known as *hilus cell or pure Leydig cell tumors* originate from polygonal cells clustered around vessels in the ovarian hilus. They are benign and constitute 15% of steroid cell tumors. Tumor cells have distinct cell borders and large cytoplasm containing lipofuscin pigment. The presence of cytoplasmic formations called Reinke crystals are typical features. 17 ketosteroid release and masculinization are observed in cases. *Unspecified steroid cell tumors* constitute 60% of the cases. Nest, cord, pseudoglandular, and follicle-like structures formed by large polygonal cells are observed. Malignant course is

observed in 25–43% of cases. Tumor diameter over 7 cm, prominent mitotic activity, and presence of necrosis are features suggestive of malignancy [7].

Mixed sex cord–stromal tumors contain Sertoli and Leydig cells and fibroblasts in different proportions and differentiation. Pure Sertoli cell or pure Leydig cell tumors are very rare. Most of them are composed of *Sertoli and Leydig cell tumors*. It constitutes less than 1% of all ovarian tumors. It is common between 20 and 40 years of age. 40–60% of the patients show androgenic, and a few shows estrogenic symptoms. There are well, moderately differentiated, poorly differentiated, and retiform types. Tumor grade is given according to the degree of tubular differentiation of Sertoli cell component. As the grade increases, tubule structures decrease, and primitive gonadal stroma increases. Leydig cells decrease as the grade increases. In the well-differentiated type, there are tubules lined with Sertoli cells without nuclear atypia and mitotic activity and Leydig cell groups in the thin fibrous stroma in between. These cells may have vacuolated cytoplasm. They contain lipofuscin pigment and Reinke crystals. In moderately differentiated tumors, Sertoli cells form nests, cords, and tubules. There is mild to moderate nuclear atypia and moderate mitosis (Fig. 16.11). In poorly differentiated Sertoli–Leydig cell tumor, sarcomatoid stroma similar to primitive gonadal stroma is detected. Mitosis is prominent. Heterologous elements

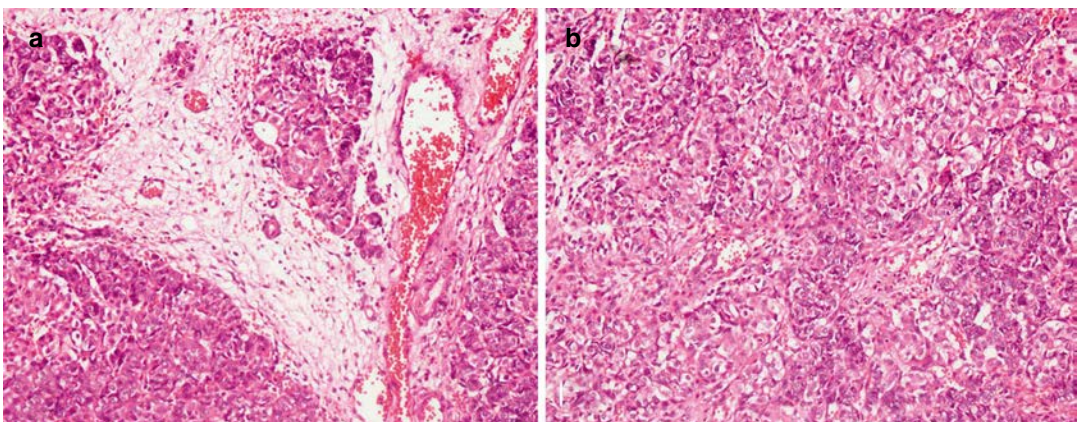


Fig. 16.11 Sertoli cells and Leydig cell groups form solid layers and tubule structures in Sertoli–Leydig cell tumors

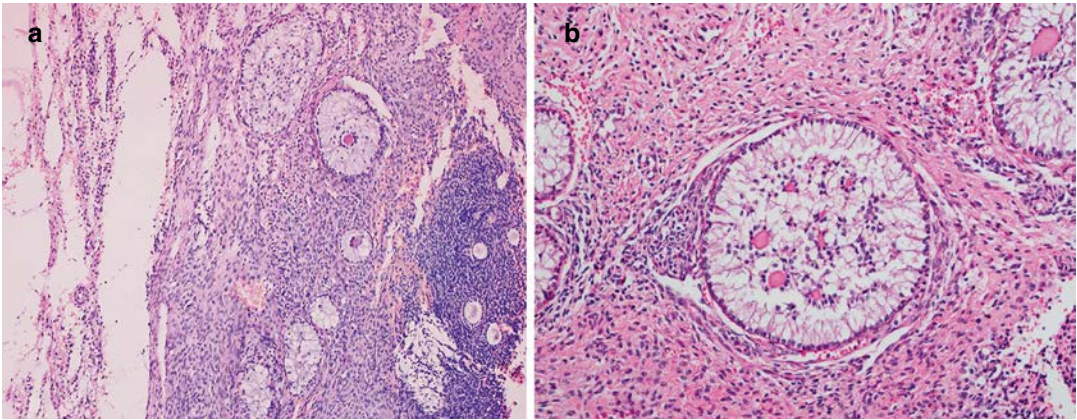


Fig. 16.12 Annular tubular sex cord–stromal tumor

which may be epithelial or mesenchymal may be seen in 20% of intermediate and poorly differentiated tumors. Retiform type constitutes 15% of cases. It resembles the retina of the testis. Hyalinized or edematous papillae and slit-like spaces are lined with low cuboidal cells. Malignant prognosis is higher in heterologous elements, retiform, and poorly differentiated types [5, 7].

Gynandroblastoma is a mixed sex cord–stromal tumor with Sertoli–Leydig cell and granulosa cell tumor areas and has benign behavior. On the other hand, 20% of annular tubular sex cord tumors have a malignant course. 1/3 of the tumors are associated with Peutz–Jeghers syndrome. Microscopically, round tubules and tubule groups surrounded by hyalinized basement membrane-like material are observed (Fig. 16.12). The cells forming the tubules have transparent cytoplasm rich in lipids. In the center of annular tubules, there may be pink staining and cytoplasm-like material, or the cells may have grown toward the center and filled the lumen. Focal calcification is observed in most cases. *Gonadoblastoma* is a member of the group of mixed germ cell–sex cord–stromal tumors. It is always seen in patients with abnormal gonadal development. This disorder takes the form of pure or mixed gonadal dysgenesis or male pseudohermaphroditism. The most common karyotype is 46XY. Patients typically have a female phenotype. They present with amenorrhea and virilization. The pure form has a

benign course. It is seen in child–adolescent period. 1/3 of the tumors are bilateral. In 25% of cases, the tumor is in the form of microscopic foci. It is important because half of them develop malignant germ cell tumors, especially dysgerminoma. It should be considered as an in situ form of carcinoma because of the high risk of malignant tumor development. Microscopically, islands of germ cells and smaller sex cord-type epithelial cells separated by fibrous stroma are observed. These cells surround cavities filled with basement membrane-like material. Epithelial cells resemble immature Sertoli or granulosa cells and are usually inhibin positive. Germ cells resemble dysgerminoma cells and are PLAP positive. Dysgerminoma and sex cord tumor with annular tubules should be considered in the differential diagnosis [3, 5].

16.3.3 Germ Cell Tumors

They are the second most common ovarian neoplasms after surface epithelial tumors. They are more common in Asia and Africa than on the surface epithelial tumors. In children and adolescents, more than 60% of ovarian tumors are of germ cell origin, and 1/3 of them are malignant. In adulthood, 95% are benign. It can develop at any age. However, the majority are seen in the first two decades. It is usually unilateral [5, 13].

Ovarian teratomas are divided into three main groups: mature teratoma, immature teratoma, and monodermal/specialized teratomas. Tumors originating from two or three germ layers, known as *mature cystic teratoma* or *dermoid cyst*, constitute 99% of cases. The tumor contains mature tissue fragments, most commonly cartilage, bone, teeth, skin, and skin appendages (Fig. 16.13). Mature solid teratoma is rare. In very few cases (10%), the tumor is bilateral. It usually develops during active reproductive age. The major complication is torsion (15%) and associated rupture. Simple excision is usually curative. Malignant transformation and recurrence rates are very low (1–2%). In *struma ovarii*, almost all of the mature

teratoma is composed of thyroid tissue. It constitutes 2–3% of all ovarian teratomas. Ascites is observed in approximately 20% of cases. The most important complications of monodermal teratomas are malignant transformation and ascites formation [5, 7, 13].

In *immature teratomas*, the tumor originated from three germ leaves. However, it contains immature or embryonal structures in between. Unlike mature teratoma which can be seen at any age; it is observed in the first two decades (0–20 years). It may develop in pure form or as a malignant mixed germ cell tumor component. It produces mass and pressure findings due to rapid growth of the tumor. The immature component is usually immature neuroepithelial tissues (Fig. 16.14). Tumor grading is based on the microscopic, small-magnification area (4.5 mm diameter, $\times 40$) containing immature neuroepithelium in each preparation. According to this assessment, grade 0 indicates a mature teratoma. Grade 1 has foci of immature tissue not exceeding 1 small magnification in each preparation. Grade 2 tumors have immature foci not exceeding three small-magnification fields in each preparation. In grade 3, there are immature foci exceeding four small-magnification areas in each preparation. The main prognostic factors are the stage and grade of the primary tumor and the extent of metastasis. The prognosis is very good in stage I tumors [5, 7].

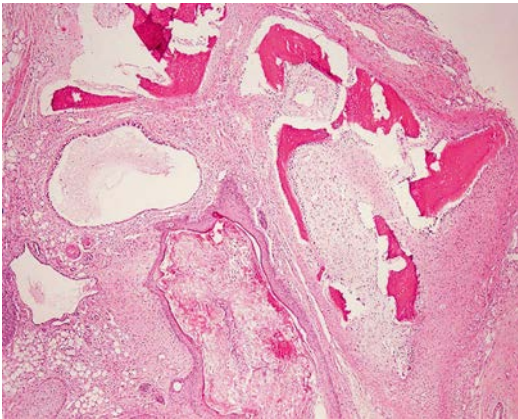


Fig. 16.13 Mature cystic teratoma

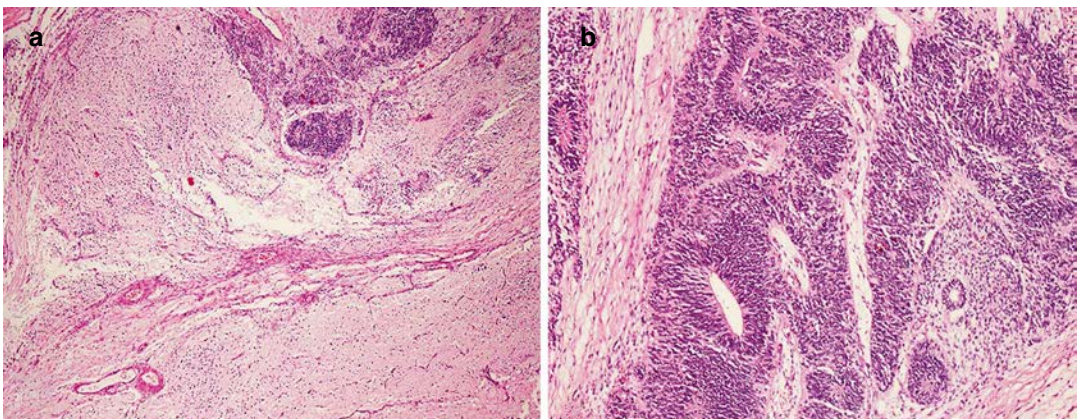


Fig. 16.14 Immature neuroepithelial structures in immature teratoma

Polyembryoma is a rare tumor seen in association with other germ cell tumors. It is malignant. Microscopically, it is characterized by embryoid structures resembling human embryos [7].

Dysgerminoma is a primitive germ cell tumor without specific differentiation. Although it constitutes 3–5% of ovarian malignancies, it is the most common pure germ cell tumor. Like other germ cell tumors, the rate of bilaterality is low. 80% of tumors are seen under the age of 30. It does not give endocrine findings. Macroscopically, it looks like a gray–yellow solid mass. Cystic degeneration, hemorrhage, and necrosis may be observed. Dysgerminoma accompanies gonadoblastoma in half of the cases. In these cases, the bilaterality rate increases, but the tumor is smaller in diameter. The most common ovarian tumors in pregnancy are dysgerminoma and benign serous cystadenoma. Microscopically, cords or islands of monotonous cells with well-defined borders, polygonal shape, and transparent cytoplasm are detected. The cells have round vesicular nuclei (Fig. 16.15). Mitosis is common. Scattered syncytiotrophoblastic cells can be seen. Thin fibrous septa separate the tumor groups. In the fibrous stroma, lymphocyte infiltration, mostly of T phenotype, forming follicles is detected. Immunohistochemically, tumor cells stain positively with PLAP, OCT 4, CD 117, and D2-40. Stage is the most important prognostic factor.

Due to its radiosensitivity, 10-year recurrence-free survival has reached 90% in ovarian limited tumors [5, 7, 13].

Embryonal carcinoma is a primitive malignant germ cell tumor with somatic or extraembryonal differentiation. It usually occurs in association with other germ cell tumors. It is seen in children and adolescents (average age 14 years). Serum hCG and/or AFP levels are high. Macroscopically, it has a solid, hemorrhagic, necrotic appearance. Microscopically, the tumor is composed of polygonal shaped, mitotic active cells with severe atypia, forming solid nests and gland-like, papillary structures (Fig. 16.16). Differential diagnosis includes indifferentiated carcinoma. Tumor cells are immunohistochemically positive for OCT4 and CD30 [5, 7].

Ovarian choriocarcinomas can develop in three ways. *Gestational choriocarcinoma* occurs following ovarian pregnancy or more commonly as ovarian metastasis of a tumor that develops in the uterus. Very rarely, it may develop with trophoblastic differentiation of germ cells, i.e., unrelated to pregnancy. The pure form of these tumors, called *non-gestational choriocarcinoma*, is very rare and is more commonly found as a component of a mixed germ cell tumor. It is seen in children and young adults. The tumor is large and unilateral. Serum β HCG levels are high. Microscopically, the tumor consists of mononu-

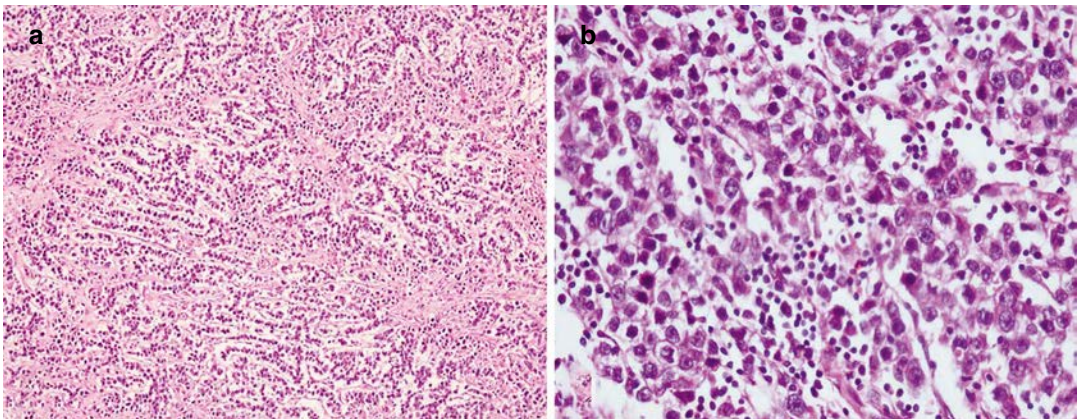


Fig. 16.15 (a) Tumor cell cords in dysgerminoma. (b) Monotonous tumor cells with clear cytoplasm

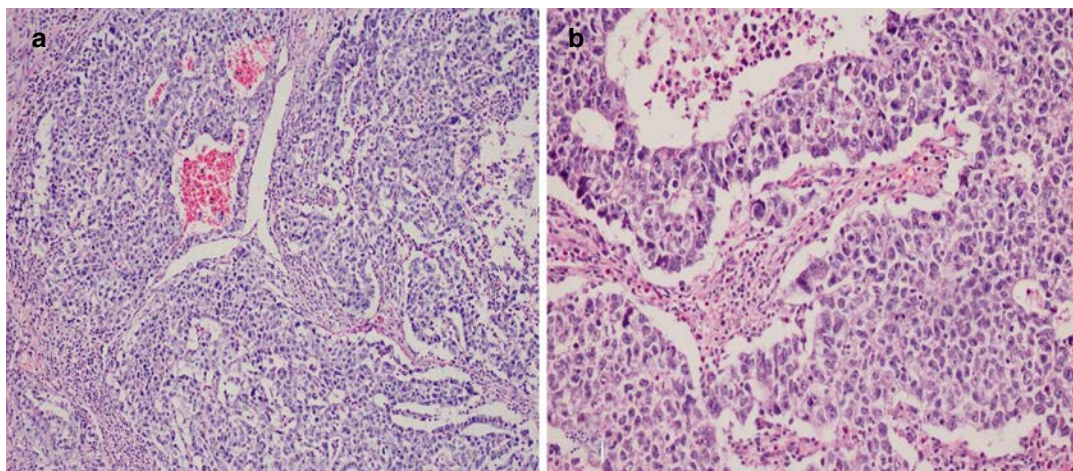


Fig. 16.16 Gland-like structures (a) and solid layer (b) formed by cells showing marked atypia in embryonal carcinoma

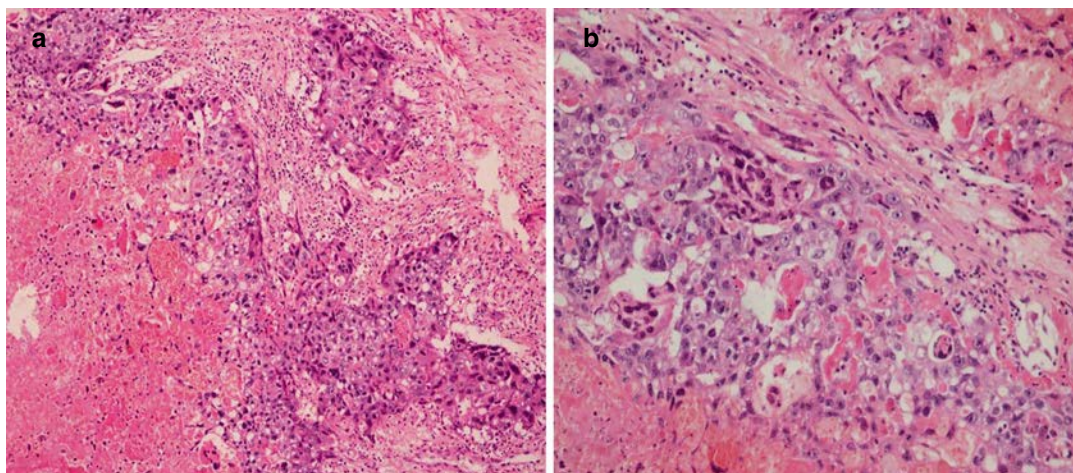


Fig. 16.17 Non-gestational choriocarcinoma

clear cytotrophoblasts and multinuclear syncytiotrophoblasts (Fig. 16.17). Diffuse hemorrhage and necrosis areas are observed. *Gestational choriocarcinomas* mostly metastasize to distant organs, especially the lung, by hematogenous spread. However, non-gestational choriocarcinoma spreads to the surrounding lymph nodes or abdominal cavities via the lymphatic route and is less sensitive to chemotherapy than gestational choriocarcinoma [7].

Yolk sac (vitellus sac, endodermal sinus) tumor is the second most common malignant germ cell tumor after dysgerminoma. It is usually in pure form. Sometimes it may have a mixed germ cell tumor component. It is most common in the second to third decade. Serum alpha fetoprotein (AFP) levels are high. Patients are present with abdominal pain and a rapidly growing mass. It is almost always unilateral. Bilaterality is an indicator of dissemination. Histopathologically,

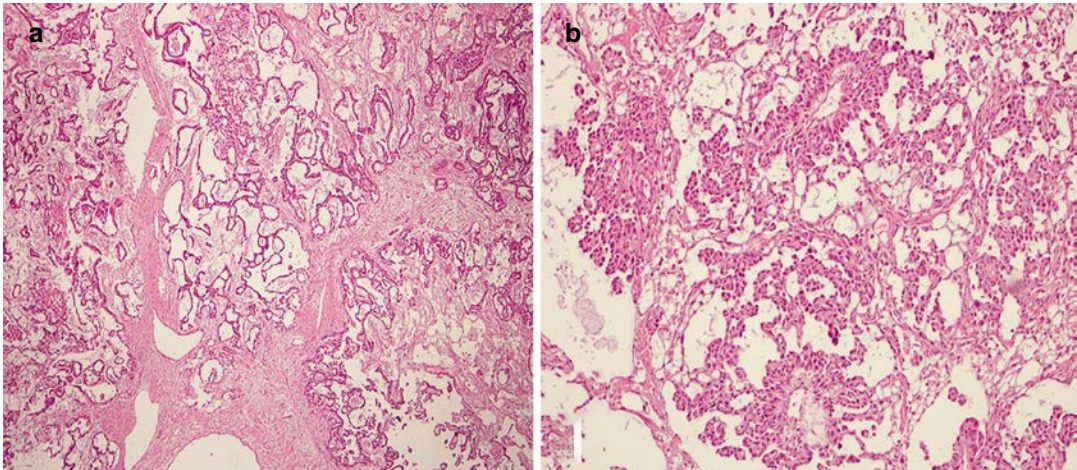


Fig. 16.18 (a) Reticular–microcystic pattern in yolk sac tumor. (b) Papillary pattern and Schiller–Duval body

many different patterns are found together. The most common patterns are reticular/microcystic patterns. It is in the form of small cysts and anastomosing network-like structures lined with single-row tumor cells. Loose or myxoid stroma is seen. Other patterns include endodermal sinus, papillary, solid, festoon, and glandular patterns. Schiller–Duval bodies, which are structures extending into cystic spaces surrounded by tumor cells around a central core containing a single vessel in the endodermal sinus pattern is seen (Fig. 16.18). It is helpful in the diagnosis of yolk sac tumor. Polyvesicular vitelline, parietal, mesenchyme-like, and hepatoid patterns are less common. Nuclear atypia and mitosis are variable in tumor cells. Their cytoplasm is pale eosinophilic or clear. Clear cytoplasm and hyaline globules stained positively with PAS are seen. The coexistence of histological 3 to 4 patterns is a good prognostic indicator. Clinical stage is important in prognosis. Multi-agent chemotherapy is used in treatment [5, 7, 14].

16.3.4 Metastatic Tumors of the Ovary

The ovary is the most frequently metastasized organ in the female genital system. Most of them are metastases of tumors from organs of Müllerian origin. In other words, tumors of the uterus, tuba uterina, other ovaries, or pelvic peritoneum often

metastasize to the ovary. Apart from these organs, metastases from tumors of the breast and gastrointestinal tract, especially the colon, stomach, biliary tract, and pancreas, are common. Macroscopically, bilateral involvement, size less than 10 cm, nodular development, and superficial cortex involvement suggest metastasis. Metastases may develop via direct invasion, lymphovascular/hematogenous invasion, and transperitoneal or transtubal route. Krukenberg tumors are bilateral metastatic ovarian tumors originating from the gastrointestinal tract and most commonly from the stomach, usually involving signet ring cells (Fig. 16.19) [5, 7].

16.3.5 Hemopoietic Neoplasms of Ovary

Ovarian lymphoma refers to a rare condition in which lymphoid tissue malignancy either originates in or involves the ovary. It can occur as a primary ovarian lymphoma, when the disease is initially confined to the ovary (with no prior nodal lymphoma), or as secondary involvement, when systemic lymphoma spreads to the ovary. Clinically, patients may present with abdominal or pelvic pain, a pelvic mass, bloating, or systemic “B-symptoms” (fever, night sweats, weight loss) though these are less common. Because the presentation overlaps with more common ovarian cancers, correct diagnosis often requires tissue

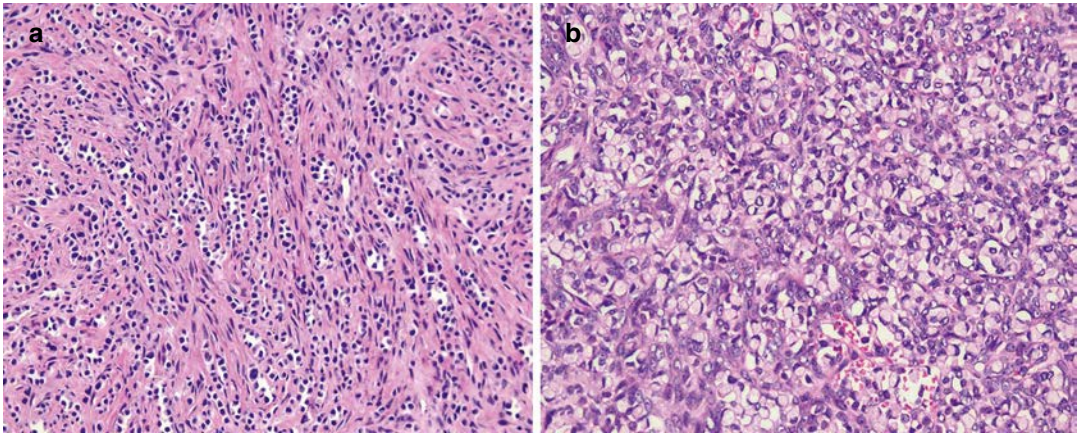


Fig. 16.19 (a) Ovarian metastasis of an invasive lobular carcinoma of breast. (b) Metastatic signed-ring carcinoma from the stomach (Krukenberg tumor)

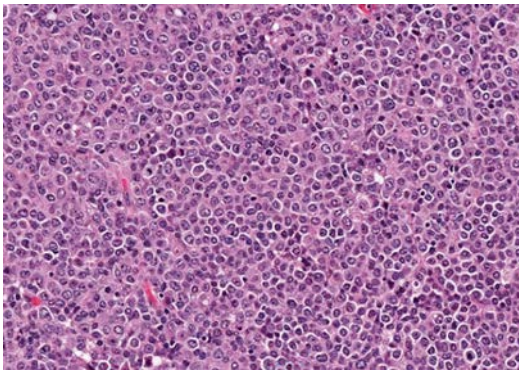


Fig. 16.20 Primary diffuse large B-cell lymphoma of ovary

biopsy and immunohistochemical studies. Primary ovarian lymphoma is very rare—it has been estimated to represent around 0.5% of all non-Hodgkin lymphomas (NHL) and about 1.5% of all ovarian neoplasms (Fig. 16.20). The prognosis depends on whether it is primary vs secondary, the histologic subtype (e.g., diffuse large B-cell lymphoma is common), extent of disease (unilateral vs bilateral, nodal involvement), and responsiveness to chemotherapy. Management typically involves systemic chemotherapy (often like other NHL protocols), and surgery may be used when the diagnosis is only made after excision of an ovarian mass. Early-stage primary cases tend to have better outcomes compared to secondary cases.

References

1. Mills SE. Histology for pathologist. 5th ed. Philadelphia: Wolters Kluwer; 2020.
2. Lindberg MR, Lamps LW. Diagnostic pathology normal histology. 2nd ed. Salt Lake City: Elsevier; 2018.
3. Yokoi A, Matsumoto T, Watanabe G, Tochimoto M, Saegusa M. Immunophenotypic profile as a predictor of prognosis in advanced ovarian carcinoma. *Hum Pathol.* 2019;85:210–20. <https://doi.org/10.1016/j.humpath.2018.10.036>.
4. Kurman RJ, LeM S. The dualistic model of ovarian carcinogenesis: revisited, revised, and expanded. *Am J Pathol.* 2016;186(4):733–47. <https://doi.org/10.1016/j.ajpath.2015.11.011>.
5. Kurman RJ. Blaustein's pathology of female genital tract. 7th ed. New York: Springer; 2019.
6. Kumar V, Abbas AK, Aster JC. Robbins basic pathology. 10th ed. Philadelphia: Elsevier Saunders; 2018.
7. Lokuhetty D, White VA, Cree IA. WHO classification of tumours. Female genital tumours. 5th ed. Lyon: IARC; 2020.
8. Ponti G, De Angelis C, Ponti R, Pongetti L, Losi L, Sticchi A. Hereditary breast and ovarian cancer: from genes to molecular targeted therapies. *Crit Rev Clin Lab Sci.* 2023;60(8):640–50.
9. Zhang M, Cheng S, Jin Y, Zhao Y, Wang Y. Roles of CA125 in diagnosis, prediction, and oncogenesis of ovarian cancer. *Biochim Biophys Acta Rev Cancer.* 2021;1875(2):188503.
10. Qiao L, Chen X, Xi X, Chen X, Zhang P, Dong H, Wu X, Chen X. Correlation analysis and clinical significance of CA125, HE4, DDI, and FDP in type II epithelial ovarian cancer. *Medicine (Baltimore).* 2020;99(49):e23329. <https://doi.org/10.1097/MD.00000000000023329>.

11. Yüksel D, Kılıç Ç, Çakır C, Kimyon GK, Turan T, et al. Brenner tumors of the ovary: clinical features and outcomes in a single-center cohort. *J Turk Ger Gynecol Assoc.* 2022;23(1):22–7.
12. Gadducci A, Multinu F, Cosio S, Carinelli S, Ghioni M, Aletti GD. Clear cell carcinoma of the ovary: epidemiology, pathological and biological features, treatment options and clinical outcomes. *Gynecol Oncol.* 2021;162(3):741–50.
13. Ramalingam P. Germ cell tumors of the ovary: a review. *Semin Diagn Pathol.* 2023;40(1):22–36.
14. Young RH, Wong A, Stall J. Yolk Sac tumor of the ovary: a report of 150 cases and review of the literature. *Am J Surg Pathol.* 2022;46:309–25.

Pathology of the Placenta and Gestational Diseases

17

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17.1 Introduction

The placenta is a unique organ which develops during pregnancy and is discarded at labor. It originates from fertilized ovum implanting into endometrium and evolves according to needs of developing fetus; it is possible to examine its full life span. Decidualization of endometrial stromal cells play crucial role during the implantation, and this process not only serves placental development, but decidua also acts as a defense mechanism for extreme invasion of the embryo [1]. Abnormal invasion patterns (placenta accreta spectrum) or aberrant implantation site (e.g., placenta previa) have clinical associations and problems [2].

The placenta is an interchange hub between mother and fetus; thus, any problem either in the mother or the fetus is reflected in the placenta and interferes with ongoing pregnancy and fetal well-being. Several polypeptide hormones and ste-

roids and galactogen produced by placenta affect regulation of decidualization and angiogenesis (placental development) as well as fetal growth and survival. Trophoblasts residing over the basal membrane constitute a barrier and allow passive (through trophoblast cytoplasm) or active (using complex network of transporters) transport for nutrients and other maternal endogenous substances [3]. Thus, the placenta plays a fundamental role in the pregnancy outcome, and placental examination is crucial to explain the clinical problems encountered during pregnancy and/or labor or in the newborn. Also essential is the clinical context for submitted placentas as clinic-pathologic correlation is easily achieved in the final placental report [4, 5]. Thus, it is important to set up a request form using the guidelines and standardized for the center [6]. Table 17.1 shows defined indications for placental examination [7–9]. Many centers ask for at least macroscopic evaluation of *all* placentas delivered.

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Table 17.1 Indication for placental examination

Maternal diseases	Coagulopathy (thrombophilias, HELLP syndrome, systemic autoimmune diseases) HT (primary, pregnancy induced) DM Infections (TORCH, COVID-19 or other viral diseases) Metastatic malignancies
History of reproductive problems	Spontaneous abortions Premature deliveries Stillbirths Neonatal deaths IVF treatment
Antenatal indications	Prematurity (<32 gw) Postmaturity (>42 gw) Oligo-/polyhydramnios Fever or infection Abruptio placenta Repetitive bleeding (second and third trimester) Invasive procedures during pregnancy Ruptured membranes >24 h
Gross anomaly	Placental shape and weight anomalies Umbilical cord anomalies Presence of masses, hematoma, etc.

17.2 Development of the Placenta

Around the third day after fertilization, trophoblastic cells in the morula begin to differentiate. Syncytiotrophoblasts are large, multinucleated cells with eosinophilic cytoplasm that show strong reactivity for human chorionic gonadotropin (hCG). Cytotrophoblasts, which are the progenitor cells of the syncytiotrophoblasts, are hCG-negative, small, mononuclear cells with distinct cell borders and clear cytoplasm. Intermediate trophoblasts, also known as extravillous or interstitial trophoblasts (formerly referred to as “X cells”), are characterized by positivity for human placental lactogen (hPL). All three trophoblast lineages express cytokeratin. In addition, they typically express CD66a and CD146; HNK-1 expression is confined to villous trophoblasts, while EMA and HLA-G expression are characteristic of the chorionic (extravillous) trophoblasts. Trophoblastic cells originate from the

trophectoderm, the outer epithelial layer of the blastocyst. Around the sixth day, they invade the uterine mucosa—which has become receptive to implantation through proliferative glandular activity, stromal edema, and decidual transformation. The amniotic cavity and yolk sac, bounded by an endodermal and mesodermal lining, appear by the seventh day. The yolk sac corresponds functionally to the yolk of avian eggs. By the 16th day, an allantoic diverticulum (tubercle) forms between the caudal part of the embryo and the yolk sac, while trophoblastic cells have already penetrated the endometrium. During the second week, trophoblasts erode maternal vascular endothelium, and the lacunae observed within the syncytiotrophoblastic layer fill with maternal blood—an event marking the beginning of the materno-placental circulation (Fig. 17.1). At the start of development, the embryo possesses two stalks: the vitelline stalk on the ventral side and the embryonic (allantoic) stalk on the caudal side. As the embryo folds ventrally during further development, both stalks assume a ventral position and fuse to form the umbilical cord. From the third month onward, the vitelline vesicle (yolk sac) completely regresses, leaving only remnants of the vitelline duct and allantois together with the umbilical vessels within the cord. The umbilical cord is covered by the amnion membrane, which consists of a single layer of flattened epithelial cells resting on a basement membrane. Near the point of attachment of the cord, squamous metaplasia of the amniotic epithelium is commonly observed [1, 2, 10–12].

17.3 Gross Evaluation of the Placenta

The placenta is a disc-shaped organ with a smooth, membranous surface at one side and a fleshy and bloody surface at the opposite side. Membranous facet is the fetal surface; membranes surround the fetus and ruptures during labor. This surface also contains an umbilical cord. Fleshy facet is maternal surface and composed of roundish bulks called cotyledons. Cotyledons are demarcated by fibrous septa, and

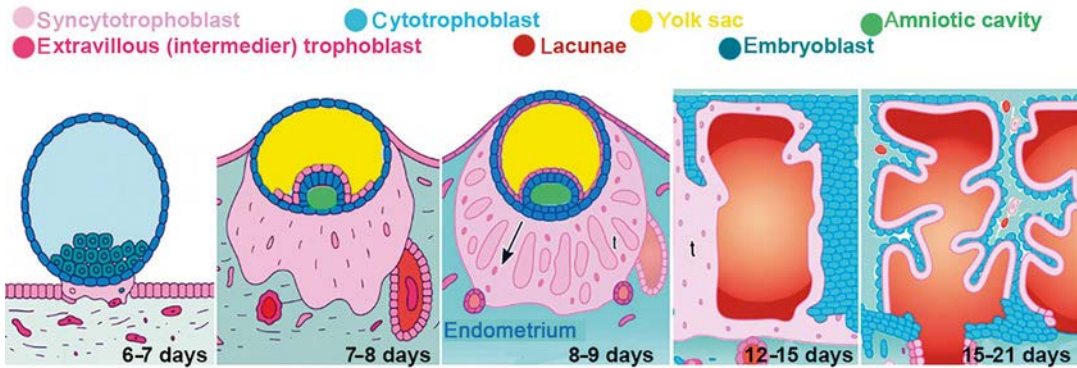


Fig. 17.1 Schematic development of the placenta

each cotyledon can be accepted as functional unit for fetomaternal exchange. The term placenta is composed of 15–20 cotyledons. Predominant form of the placenta is a single lobe, round, or oval in shape (Fig. 17.2a and b). There may be two almost similar size lobes both of which supply nutrients to fetal circulation, no matter where the cord inserts. These bilobed placentas inevitably contain velamentous vessels. In a succenturiate placenta, there is another smaller lobe (accessory lobe) besides the major lobe. These multilobed placentas are associated with perfusion problems in the uterus (leiomyomas, cornu, etc.). A rare placental shape anomaly is placenta membranacea which is excessively large but thin as all fetal sac contains villous structures. Other rare abnormalities cover placenta fenestrata where a central focal area is totally composed of membranes (beware to rule out missing cotyledon) and annular placenta which has a ring shape (Fig. 17.3).

Macroscopic examination begins with orientation. Observation of both sides, including the umbilical cord is important: integrity and appearances of both surfaces, area of membrane insertion and rupture, presence of masses or defects, hematomas, etc. Measurements and weight after cord removal are noted, to be compared with normal values for the gestational age (Table 17.2). If the placental measurements and weight are significantly high (above 95% of normal—placentomegaly), the most common associations are maternal diabetes, hydrops fetalis, and Beckwith-

Wiedemann syndrome [10]. Associated placental diseases are mesenchymal dysplasia and chorangioma, particularly when diffuse and/or multifocal [11–14]. In mesenchymal dysplasia, cystic areas can be observed macroscopically at the cut surface as chorionic vessels are dilated and tortuous [11, 13]. Birth weight to placental weight ratios also supply important clues for placental efficiency for fetal needs [15]. Low placental measurements and weight (below 10% of normal) can be associated with maternal and paternal BMI as well as high altitude residency, maternal anemia, gestational hypertension, maternal addictions (tobacco, alcohol, etc.), or maternal autoimmune diseases [11]. Placental thickness differs in certain circumstances. For example, it is significantly reduced in intrauterine death cases compared to placentas of livebirths. Placental thickness is increased in placentomegaly (see above).

The placenta is full of blood and show a soft, spongy feeling when handling. Firm consistency of the placenta suggests extensive fibrin deposition (to be confirmed histologically) [11]. In normal configuration, membranes insert into the edge of placental disc. When there is a distance between cord insertion and placental margin, it is a circummarginate or circumvallate placenta, the later defined by presence of circumferential plica of membranes. Area of rupture is also important to mention especially when too close to the margin. If membranes have no free margin and edge of the placenta is disfigured with hemorrhage and

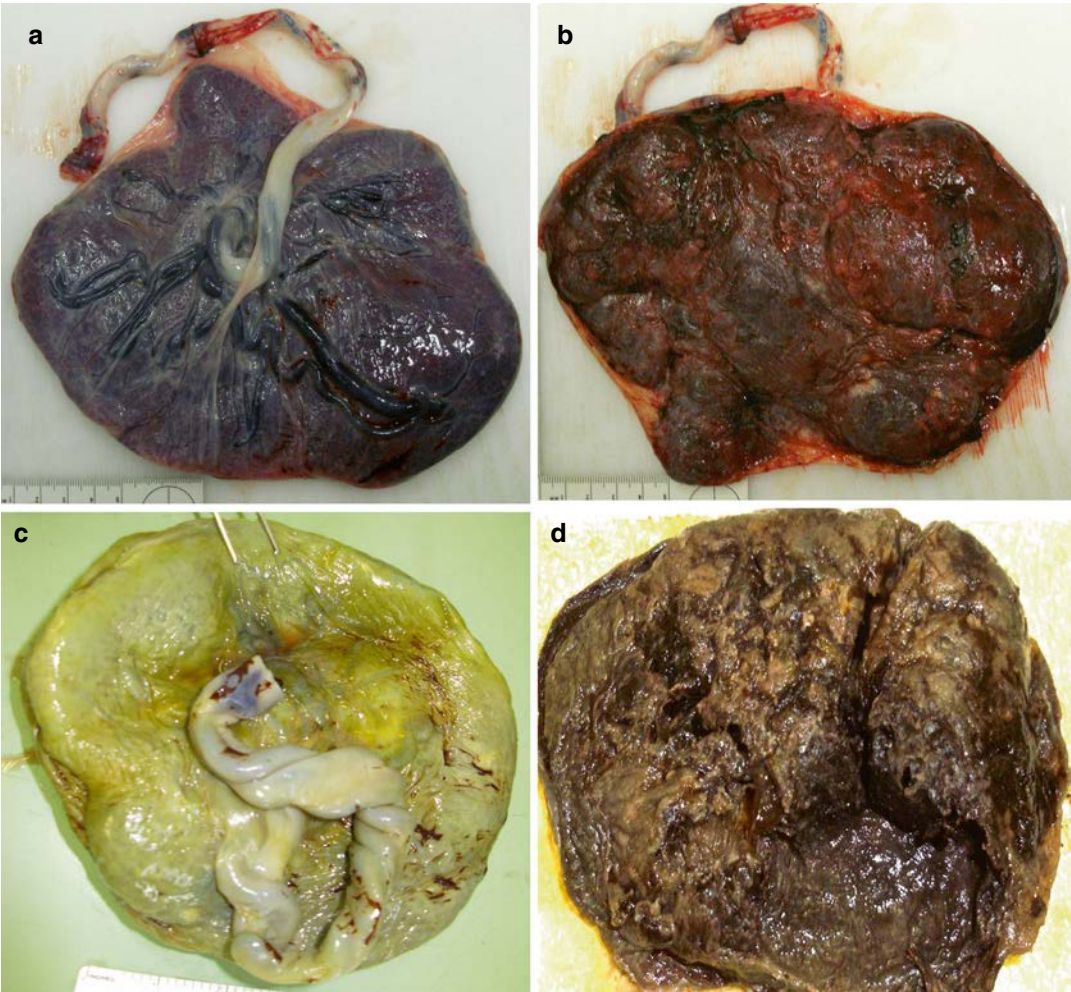


Fig. 17.2 Appearance of the fetal surface (a) and maternal surface (b) of a normal placenta and umbilical cord. (c) Meconium-stained placental membranes also showing

acute chorioamnionitis. (d) Large hallow in the maternal surface representing retroplacental hematoma.

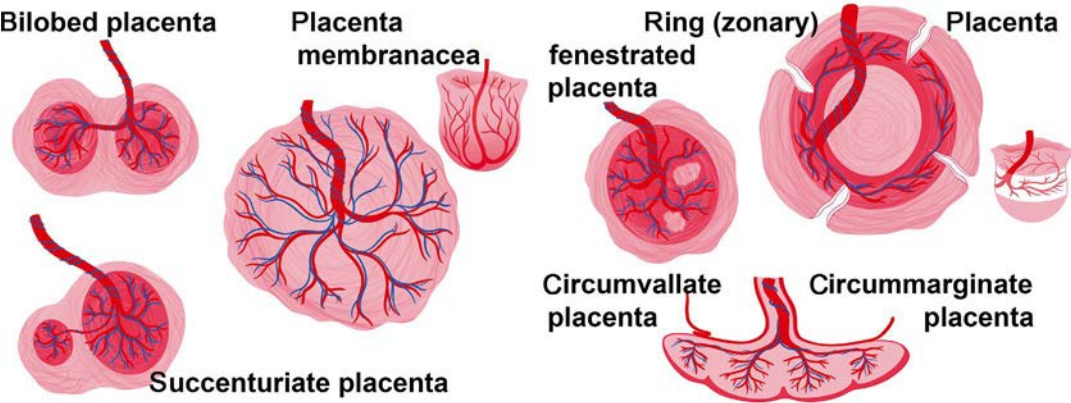


Fig. 17.3 Placental shape anomalies [11]

Table 17.2 Control values of placenta

Gestational week (from last menstruation)	Crown- rump length (mm)	Embryo/ fetus weight (g)	Placental weight (g)	Postpartum placental thickness (mm)	Umbilical cord length (mm)	Umbilical cord diameter (mm, by USG)
2	—	—	—	—	2	—
3	—	—	—	—	4	—
4	2.5	—	—	—	—	—
5	5	—	—	—	12	2.5
6	9	—	—	—	20	3.3
8	14	1.1	6	—	35	3.3
9	20	2	8	—	53	4.4
10	26	3	11	—	79	5.3
11	33	7	17	6	125	6.1
12	46	14	26	8	162	7.0
13	63	28	41	10	188	8.2
14	85	50	60	11	215	9.1
15	110	80	81	13	249	10.1
16	120	130	100	14	309	10.5
17	135	250	126	15	330	11.1
18	152	320	144	15	350	12.8
19	163	480	162	17	367	13.9
20	176	560	180	18	384	13.9
21	188	650	194	19	405	15.2
22	200	750	216	19	430	15.2
23	216	900	232	20	455	15.5
24	230	1160	252	20	474	16.9
25	250	1400	280	21	490	16.3
26	263	1750	306	21	502	16.5
27	276	1950	324	22	520	17.4
28	289	2100	342	22	530	17.4
29	303	2300	358	23	549	17.4
30	318	2500	376	23	562	17.4
31	334	2750	394	24	572	18.0
32	347	3000	414	24	575	18.0
33	357	3200	431	25	582	17.0
34	367	3400	451	25	585	17.0

Source: Benirschke et al. [12]

hematoma, placenta previa should be considered. An early rupture of the membranes (before 12th week) will result in formation of amniotic bands that might entangle with parts of fetus or umbilical cord, leading to fetal amputations, anomalies, or even demise. Membranes are normally transparent and clear. If they are thickened and blurred showing a yellowish-white discoloration, **chorioamnionitis** is considered and greenish hue indicates **meconium staining** (Fig. 17.2c); brownish discoloration old hemorrhage. In cases of retromembraneous hematomas, decidual necrosis, or fetus papyraceous, membranes are necrotic [11, 12].

Cysts can be identified on the fetal surface. Most common ones are subchorionic cysts with no clinical significance though they can be associated with hemorrhage. Others are **inclusion cysts**; not clinically significant, either [11, 12]. White/yellowish-white nodules of different sizes and shapes can be observed over the fetal surface. **Amnion nodosum** is disseminated small nodules and is associated with oligohydramnios. Slightly elevated, circumscribed yellowish white, pinpoint nodules can indicate candida infection, particularly if similar lesions are present over the umbilical cord. Single nodules can be **embryologic remnants** or vernix caseosa (to be

confirmed histologically). Occasionally old hematomas also appear as white nodules. Another mass in the membranes is defined as teratoma, most probably representing **acardiac twin** [11, 12]. The received placenta usually contains several hematomas attached to the extraplacental membranes and/or maternal surface. Recent ones can be washed away and easily removed. Retromembranous hematomas are usually secondary to amniocentesis and have no clinical significance. **Subchorionic hematomas (SCH)** are associated with preterm delivery, spontaneous abortion, elevated alpha fetoprotein levels, intrauterine growth restriction, and fetal demise; however, great majority of SCH detected before 20 weeks occurring in mothers with circulatory disorders (antinuclear antibodies, thrombophilia, or complex heart disease) result in normal term delivery. A special type of SCH which is located close to cord insertion is Breus' mole and shows sacculations due to its fibrin-rich content; it can be associated with missed abortion [11].

The umbilical cord needs special attention [16]; its insertion site and pattern, its length and diameter (any changes—torsion, stricture, etc.), coiling index (number of coils in 10 cm), vascular features (number of vessels, dilatation, thrombus, wall thickening, etc.), and masses or defects. The umbilical cord usually inserts the placenta with structural integrity; insertion site being central, eccentric, or marginal. However, in some cases, one or more vessels can have separate traces and/or insertion points: velamentous vessels will travel along the membranes and branching of vessels before insertion will lead to furcate insertion. In both circumstances, vessels are

devoid of surrounding protective stroma and vulnerable to trauma (Fig. 17.4).

Cord length, particularly too short and too long cords, can interfere with fetal well-being (compare with control tables). But beware that the entire cord is usually not submitted to pathology (at least a segment is left attached to the fetus). Main clinical problems with long cords are entanglement (nuchal cord) and prolapse; true knots can be formed. **Short cords** are associated with clinical or placental problems causing decreased fetal movements and result in fetal distress and low Apgar scores sometimes due to rupture and hemorrhage in the cord [11, 12]. **Coiling index** of the cord correlates with fetal movements. Hypercoiling might need special attention for thrombus formation, etc., as it can interfere with blood flow through the cord. It is associated with multiparity and drug usage as well as fetal structural or chromosomal abnormalities (Fig. 17.5a). Hypocoiling is common in multiple pregnancy and in chromosomal anomalies [11].

The cord is examined carefully for presence of attached membranes (either free or limiting the cord at insertion—interpositioned) and knots (true or false). False knots are kinking of vessels and usually do not interfere with fetal circulation. **True knots** (Fig. 17.5b) can interfere with circulation, particularly when tight and of long duration; untie the knot and check for thrombus formation, etc. [11, 12]. The cord contains two arteries and one vein. A **single umbilical artery** (Fig. 17.5c) is the commonest anomaly. Beware that sometimes placental end of the cord might have two vessels (and a remnant), whereas the fetal end contains three vessels. In cases of funisi-

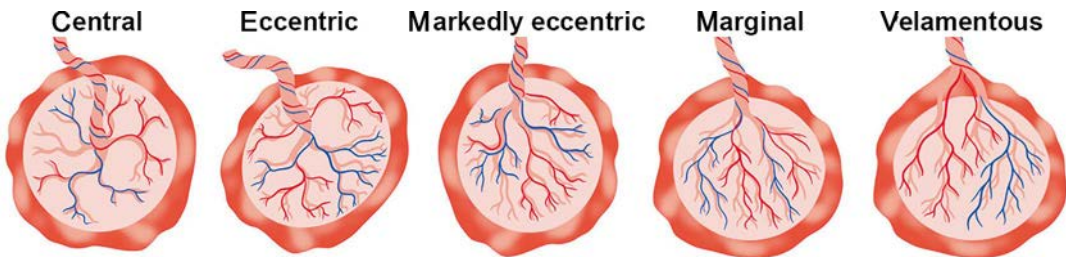


Fig. 17.4 Insertion patterns of the umbilical cord

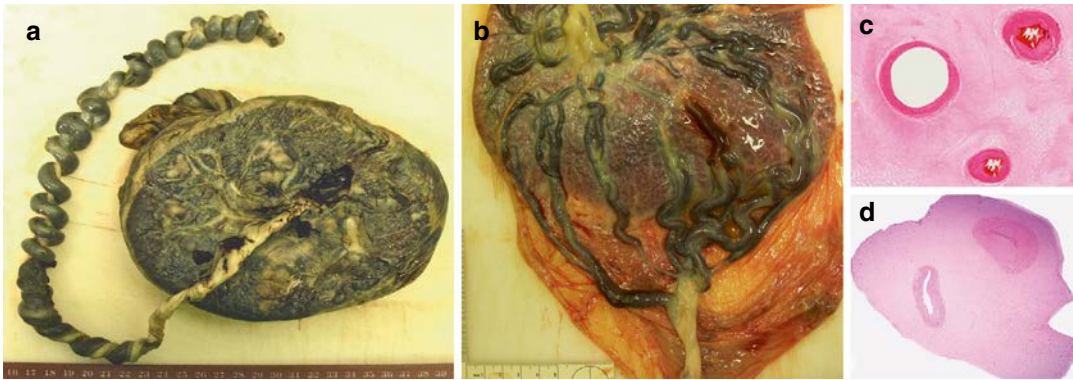


Fig. 17.5 (a) Hypercoiling umbilical cord. (b) Velamentous insertion of the umbilical cord. (c) Normal vessels (two arteries and one vein). (d) Single umbilical artery

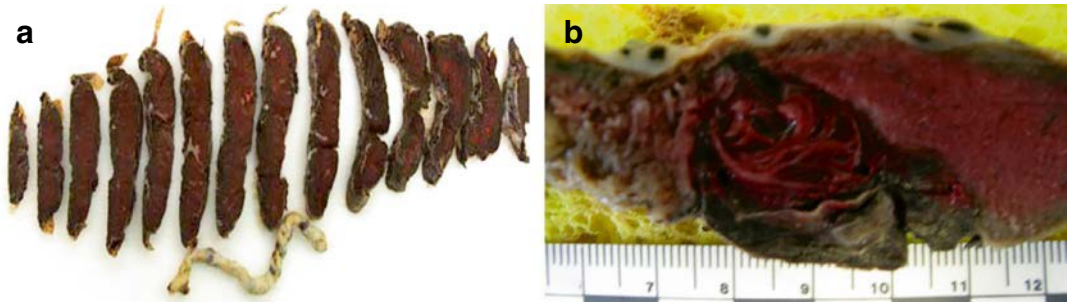


Fig. 17.6 (a) The placenta sliced for cross-sectional examination and photography. (b) An intra-placental hematoma is present

tis, vessel walls are thickened and easily observed as whitish borders [11]. Tumors or polyps of the cord are rare and occur at the placental end of the cord. Capillary hemangioma is the most common mass, at times showing a myxoid stroma (angio-myxoma). Teratomas are also described [11].

If microbiological or fetal vascular studies are planned, these must be done in fresh tissue and are initial procedures. Then the placenta is serially sliced and each cut-surface is observed (Fig. 17.6). Usually, it is so bloody that at least overnight fixation is advised as observation and sampling might be easier the next day and for sure better blocks and slides will be obtained. Appearance of placental cut surface can vary with pale areas admixed with congested areas, suggesting perfusion problems. Large yellowish-white areas with well-defined borders suggest areas of **infarct** (necrosis), and if it occupies more than 50% of total surface area, it will cause

significant placental insufficiency (Fig. 17.7). Smaller yellowish-white lesions with less-defined borders suggest septic infarct [11]. Single or a few separate small cysts at the cut surface usually represent septal cyst of no clinical significance. However, a collection of cysts (even if small) suggests partial or complete mole [11, 12]. **Hematomas** can be identified at the cut surface and named according to their site. Marginal hematoma resides at the edge and usually of least significance unless associated with placenta previa or circummarginate placenta. **Intraplacental hematomas** (Fig. 17.6b) can sometimes occupy the full thickness and rather called as massive subchorial hematoma; clinical significance of intraplacental hematoma is its association with fetomaternal hemorrhage. **Retroplacental hematoma** (Fig. 17.2d) indicates abruptio placenta. Grossly identified retroplacental hematomas will be more than 2 h old, adherent to the



Fig. 17.7 In fixed material, a focus of old hematoma is surrounded by sharply demarcated, dirty yellow (infarcted) areas, occupying more than half of the placenta

maternal surface and compress the underlying villous tissue. Occasionally, retroplacental hematoma is concealed and causes less or no clinical problems [11, 12].

In cases of multiple pregnancies, placental examination is essentially similar but includes some other features requiring special attention. It is important to determine the distribution pattern of membranes in order to define the type of placenta thus, dividing membranes are sampled. Another essential observation is about fetal vessels, particularly for the presence of anastomosis. Twin placentas can be monochorionic monoamniotic (least common; single disc and single set of membranes but two umbilical cords), monochorionic diamniotic (single disc but thin dividing membranes which can easily be separated from each other) and dichorionic diamniotic (two fused placentas). Triplets or other multiple pregnancy placentas are defined accordingly, e.g., trichorionic diamniotic triplet placenta. Sampling should include the common membrane roll for exact identification [17]. Placental fetal surface of the multiple pregnancy must be carefully examined for vascular anastomosis, and type of the anastomosis (artery-artery, artery-vein, vein-vein) is determined [11, 12]. Special injection studies can be performed to evaluate such anastomosis in a detailed manner. Similarly, interaction of two umbilical cords is important (e.g., entanglement). When one placental compartment of multiple pregnancies look paler than the other, twin-twin transfusion is considered, and search for anastomosis is done more carefully and if needed in a detailed manner [11, 12]. Iatrogenic changes can

also be observed, e.g., laser blockage of a chorionic vessel for twin-twin transfusion treatment. Blockage will result in a pale area representing the watershed area of the vessel [11].

17.4 Microscopic Evaluation of Placenta

It is important to orientate yourself while examining the placental slide. Routine sampling allows you to see either fetal or maternal surface of the placenta at one border of the section; the rest is parenchyma composed of villi and intervillous space (Fig. 17.8 and 17.9). Fetal surface is lined by fetal membranes. Fetal membranes have two components: amnion and chorion (Fig. 17.10). Amnion is characterized by simple columnar epithelium over a thin mesoderm which is composed of compact fibrous tissue and a thin network of fibroblasts. Underlying chorion begins with a spongy layer which sometimes allows amnion component of the membranes to slide easily and be removed. The other component of chorion is mainly fibrous tissue where extravillous trophoblastic cells, lymphocytes, and macrophages can be seen. The outermost thin layer is capsular decidua where decidual cells, extravillous trophoblastic cells, and few inflammatory cells are interwoven with Langhans' fibrinoid. At the edge of the placenta (marginal sinus), capsular decidua continues with parietal and basal decidua. Amniotic columnar epithelium reacts to chemical or physical processes. Multi-layering or squamous metaplasia represent direct physical trauma, usually secondary to oligohydramnios. Anhydramnios will lead to nodules of squames (amnion nodosum) which can also be detected macroscopically. Cytoplasmic features also change: foamy (vacuolated) appearance of the cytoplasm can be due to gastroschisis or meconium discharge, later particularly if associated with eosinophilic globules and/or chorionic pigmented macrophages. Duration of meconium discharge changes, and both tissue reactions and associated clinical outcomes correlate with it. Fetal (post) maturity as well as fetal distress can cause meconium discharge [11].

Fig. 17.8 Schematic appearance of human placentas

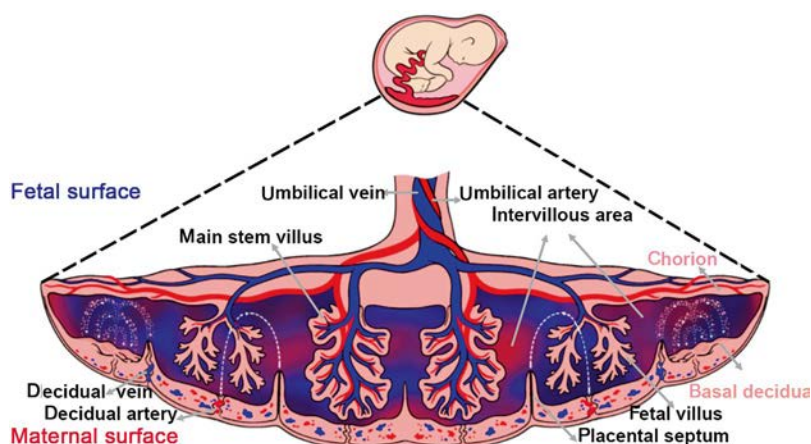
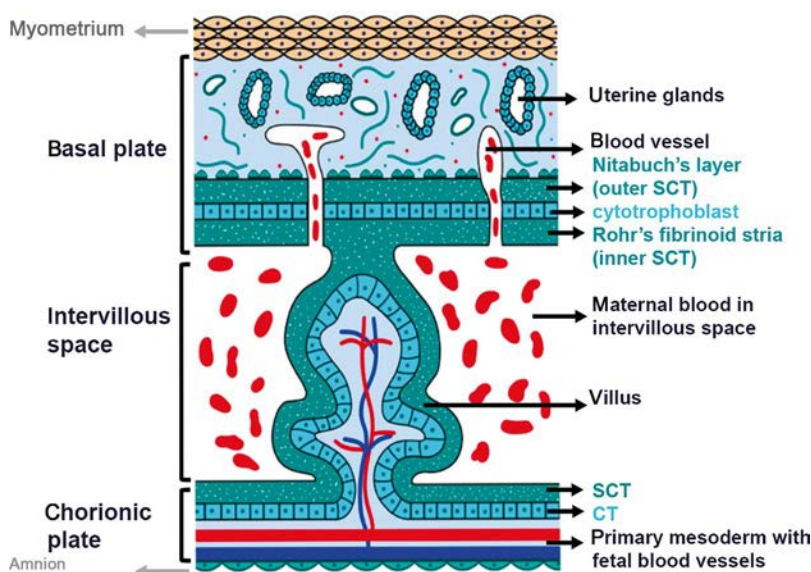


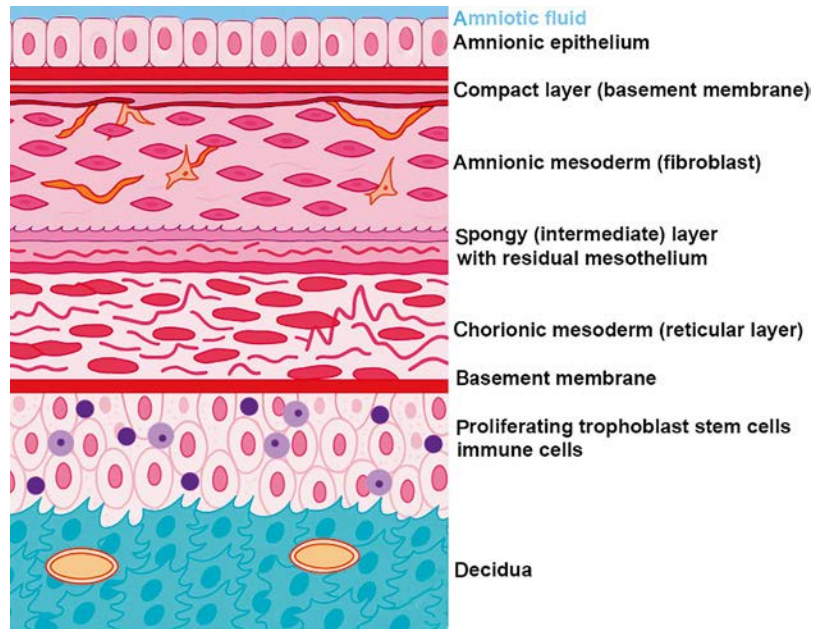
Fig. 17.9 Schematic appearance of chorionic villi



Teratomas (reminiscent of acardiac twins) and embryonic rests (most commonly cartilage) or yolk sac remnants (sometimes as totally calcified mass) can be seen in fetal membranes. Spontaneous rupture of membranes might result in dissection of amnion and chorion by vernix (skin secretions of the fetus) and accumulate there with no clinical significance even if in remarkable amounts [11, 12]. A need for unity in diagnostic terminology and systemic approach for placental studies led an international workshop in Amsterdam, and this group's consensus provided a guideline for pathologic evaluation and diagnostic criteria [18]. Major categories of microscopic evaluation are ascending intrauter-

ine infection (ACA, **acute chorioamnionitis**), **villitis of unknown etiology** (VUE), **maternal vascular malperfusion** (MVM), and **fetal vascular malperfusion** (FVM). Later studies for inter-observer reproducibility showed good agreement in inflammations but fair to poor agreement in MVM and FVM [19]. Acute chorioamnionitis is common, with an incidence of 20%–24% of livebirths and up to 67% of preterm deliveries [11, 12]. It is called amniotic sac infection syndrome and is known to be an ascending infection. It is associated with membrane rupture which is the result of infection rather than the cause. Neutrophils are the major inflammatory cells in acute placental inflammation, but eosino-

Fig. 17.10 Schematic appearance of fetal membranes



phils might be seen particularly in preterm placentas [20]. Grading and staging of acute chorioamnionitis are advised for clinical correlations: low- or high-grade maternal and fetal inflammatory responses (Table 17.3) [18, 21]. Higher stages correspond to longer exposure to insult: Stage 1 refers 6–12 h, Stage 2 12–36 h, and Stage 3 >36 h. In presence of fetal inflammatory response, early-onset sepsis can occur as well as retinopathy, necrotizing enterocolitis and spontaneous intestinal perforation in preterm [20]. Amsterdam consensus emphasizes that clinical chorioamnionitis is not equivalent to histologic chorioamnionitis. Sometimes, subchorionic area is the only place where substantial number of neutrophils present and should be diagnosed as **subchorionitis** only, indicating an early phase of maternal inflammatory response but not established chorioamnionitis [18]. There is a special acute inflammatory condition where maternal inflammatory response is missing: eosinophilic **T-cell vasculitis**. Here histiocytes and T cells accompany eosinophils, all infiltrating the wall and lumen of large fetal vessels. It usually involves a single chorionic vessel which often shows thrombus formation. Although usually seen as an isolated finding, association with VUE is common [11, 12, 20].

The umbilical cord is also lined by simple columnar amniotic epithelium and reacts similarly. Stroma, called Wharton jelly, is composed of “stem cells” ultrastructurally resembling myofibroblasts residing in a mucopolysaccharide-rich background. There are usually two fetal arteries and one vein in the cord. **Single umbilical artery** (SUA) (Fig. 17.5c) is a common anomaly/variation and reported to be associated with maternal diabetes, chromosomal abnormalities (particularly trisomies), congenital malformations, growth restriction, poly-/oligohydramnios and increased perinatal mortality [11, 12]. Sometimes a vascular remnant at the placental end of umbilical cord section suggests normal vessel number at the opposite end. Hyrtl anastomosis of the arteries in cord insertion might cause increased numbers of arteries in the section if cord sample is taken deep at the insertion. Thrombosis of umbilical vessels frequently occurs near term and more common in veins. It can be due to mechanical factors (torsion, knots, etc.) or coagulation problems (e.g., thrombophilia of the mother or fetus). It has clinical significance if blood flow is significantly disturbed/diminished. Similar findings can be seen in outflow branching vessels and detected in villi. This is the main pattern in fetal vascular malperfusion (FVM) and will be discussed further.

Table 17.3 Grading and staging ascending intrauterine infection (acute chorioamnionitis)

<i>Maternal inflammatory response</i>	
Stage 1—Acute subchorionitis or chorionitis	Polymorphonuclear leukocytes in subchorion and chorion
Stage 2—Acute chorioamnionitis	Polymorphonuclear leukocytes in fibrous chorion and/or amnion
Stage 3—Necrotizing chorioamnionitis	Karyorrhexis of polymorphonuclear leukocytes, amniotic epithelial necrosis, amniotic basement membrane hypereosinophilia
Grade 1	Not severe as defined for Grade 2
Grade 2	Confluent polymorphonuclear leukocytes in chorion or subchorionic microabscess formation
<i>Fetal inflammatory response</i>	
Stage 1	Acute inflammation of chorionic fetal vessels or umbilical vein only
Stage 2	Acute inflammation of umbilical vein and one or both umbilical arteries
Stage 3—Necrotizing funisitis	Karyorrhexis of polymorphonuclear leukocytes in umbilical vessel walls or Wharton jelly
Grade 1	Not severe as defined for Grade 2
Grade 2	Near-confluent polymorphonuclear leukocytes disrupting and destroying vascular smooth muscle

Rarely, emboli formation leading to CNS lesions in infants can be encountered [16]. Remnants of allantoic duct, yolk sac, or vitellino-intestinal (omphalomesenteric) duct can be seen in cord sections. Both remnants are lined by simple columnar epithelium, but vitellino-intestinal duct contains smooth muscle fibers in its wall [11, 12]. Inflammation in the cord is fetal response and should not be missed as it would alert clinicians for medical evaluation and if necessary treatment of the infant. Particularly, a fungal infection diagnosis is much easier histologically. Candida can be an incidental finding at term but will cause serious clinical problems in premature (cutaneous candidiasis, sepsis, pneumonia, perinatal death) [20]. Maternal surface is composed of basal decidua containing decidual cells, extra-villous trophoblastic cells, and maternal vessels with extremely thin walls and dilated lumina. In areas corresponding the demarcation of cotyledons, basal decidua extends into parenchyma forming septa, all showing similar features to basal decidua. The maternal vessels in the basal decidua can give clue about maternal hypertension/hypercholesterolemia when lined by foamy endothelial cells (**acute atherosclerosis**) generally associated with fibrin deposition.

Chorion leave of the peripheral sample might contain unadapted maternal vessels, but this is

within normal limits. Inflammatory cells, particularly lymphocytes, and NK cells are common in the basal decidua. However, if extensive or includes plasma cells, presence of inflammation in the villous/intervillous area and/or fetal membranes should be carefully searched [11, 12]. Well-formed basal decidua with decidualization of endometrial stromal cells is a key factor for normal implantation and ongoing pregnancy. Decidual cells limit the invasion of extravillous trophoblasts. If decidualization is defective, trophoblastic invasion continues deeper into myometrium. Histological correspondence is villous structures and trophoblasts in direct relation to myometrial fibers. It is called **placenta accreta** and presents as a spectrum [1]. If superficial parts of myometrium are invaded by villous structures, this is placenta increta, and invasion of myometrial full thickness is placenta percreta [11, 12]. All of these will cause some clinical problems in correlation with depth of invasion. However, a simple or focal accreta will show insignificant clinical findings and can be diagnosed by careful sampling of rough irregular area in the basal plate. Parenchyma is composed of villi and intervillous areas. Villous development is gradual and villous structure changes in association with branching vessels and transforming trophoblastic cells [5]. Villi are lined by trophoblastic cells and

initially have a loose connective tissue stroma where vessels are difficult to discover (mesenchymal villi). During first trimester, Hofbauer cells (the macrophages) appear in the stroma, and trophoblastic cells show double layering (cyto- and syncytiotrophoblasts—immature intermediate or primary villi). From primary villi, two types of villi are transformed: stem villi and peripheral (mature intermediate and terminal) villi. Stem villi have a compact stroma and carry the large arteries/arterioles and veins/venules of the fetus. Peripheral villi reside in the area where primary exchange is done between maternal and fetal circulatory systems and are mainly composed of fetal capillaries which migrate and attach to the basement membrane of the villi (trophoblastic basement membrane) forming vaso-

syncytial membranes and trophoblastic knots (occurring after 13 weeks gestation) (Fig. 17.11).

Features of villi represent the developmental stage of the placenta [11, 12]. For practical purposes, mature placenta (third trimester) will be composed of slender villi rich in capillaries (>50%) surrounded by syncytiotrophoblasts forming syncytial knots in places. Villi with abundant (primitive) stroma rich in Hofbauer cells and surrounded by two layers of trophoblastic cells with well-defined cytotrophoblasts will point an immature placenta. Although maturation is a developmental process evolving throughout pregnancy, maturation can be delayed or accelerated according to maternal conditions and/or fetal needs. Thus, features of villi for the stated gestational age have to be known in order to com-

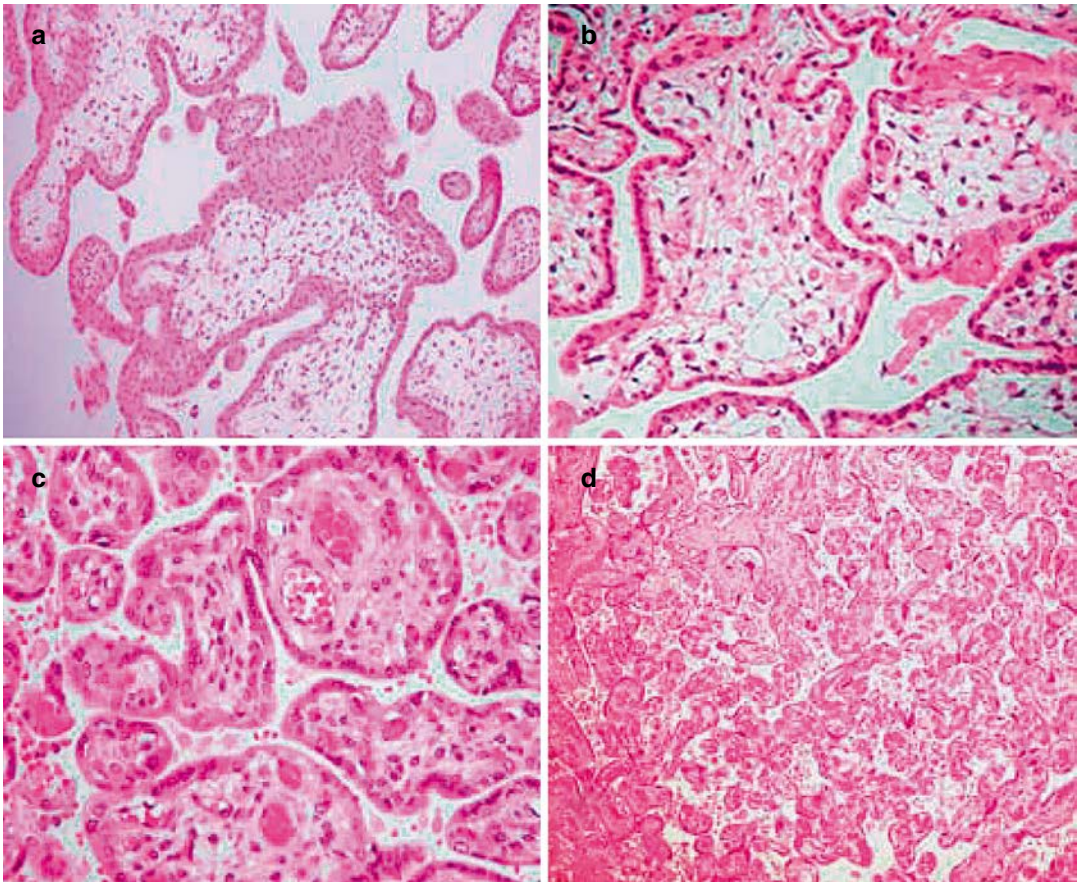


Fig. 17.11 (a) Budding of trophoblastic cells. (b) Immature intermediate villi where Hofbauer cells are easily detected. (c) Mature intermediate villi. (d) Terminal villi

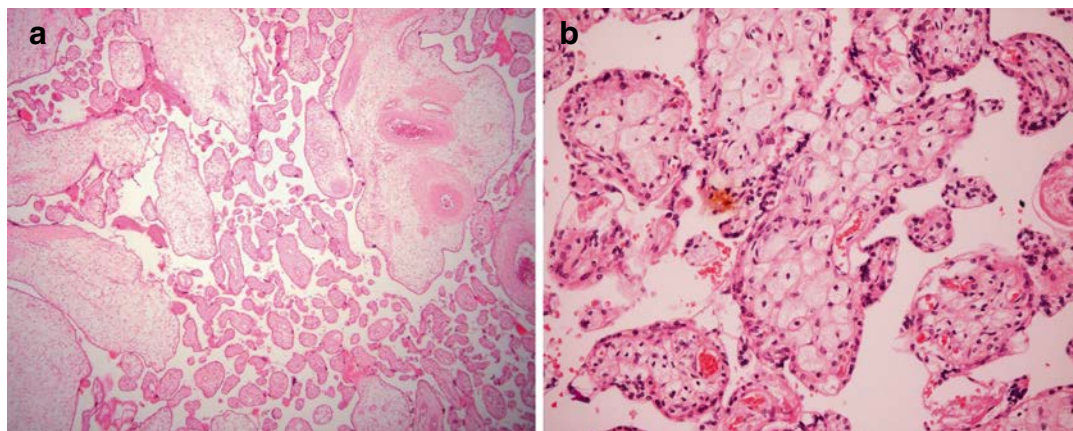


Fig. 17.12 (a) Mesenchymal dysplasia featuring stem villi with oedematous stroma and dysplastic vessels due to concentric medial hyperplasia (fibromuscular sclero-

sis), (b) Foamy appearances of Hofbauer cells in villous stroma compatible with lysosomal storage disease.

ment on maturation observed. **Delayed villous maturation** is suggested by Amsterdam Consensus as a preferred term for villous dysmaturity or villous maturation defect [18]. This lesion is best observed after 36 weeks and characterized by villi all showing no vasosyncytial membrane or trophoblastic knot formation. Another pathology of villous origin is **mesenchymal dysplasia** (Fig. 17.12a). It is a rare entity representing as a huge placenta with long tortuous umbilical cord and increased maternal alpha-fetoprotein. Main pathology is in stem villi which show expansion of stroma with cistern formation initially and later dysplastic thick-walled vessels, some with thrombus formations. Terminal villi might show stromal hypercellularity and fibrosis. Aneurysmal dilatation of chorionic vessels and edematous villi create a cystic placenta at ultrasonography suggesting molar diseases. About 1/5 of mesenchymal dysplasia fetuses will have Beckwith-Wiedemann syndrome. Clinical problems are fetal growth restriction, hydrops fetalis, or intrauterine fetal death. Color Doppler and MRI are diagnostic tools helpful for differential diagnosis of multicystic placentas [13].

In early gestational ages, there are Hofbauer cells and small-sized vessels in the villous stroma. Vessels are fetal in origin, and **nucleated red blood cells** (NRBC) can be seen as a normal component. An excess of NRBC is an indication of

fetal anemia and/or hemorrhage (feto-maternal or feto-fetal in multiple pregnancies). Fetal anemia might be due to erythroblastosis fetalis (immune fetal hydrops). Although placental findings are not specific in **erythroblastosis fetalis**, significant findings are pallor, friable tissue and both macroscopic (placental) and microscopic (villous) edema/enlargement commonly associated with intervillous thrombus [12]. Trophoblastic cells can be a harbinger for fetal metabolic diseases when their cytoplasm has a foamy appearance [12]. Additional clue for metabolic diseases will be similar vacuolization in either Hofbauer cells, fibroblasts, or capillary endothelial cells (Fig. 17.12b). They can also carry viral inclusions such as SARS [22]. Their cellular features disappear when villi are embedded within fibrinoid/fibrin (silhouettes) indicating functional loss (necrosis); main cause will be inflammation [12]. Basement membrane is the border between trophoblastic cells and villous stroma. Mineralization of the basement membrane can be seen in cases of intrauterine death as well as chromosomal abnormalities; the latter is associated with hyperconvoluted villi resulting in trophoblastic pseudo-inclusions in villus stroma [12].

Intervillous area is like a delta for maternal blood; thus, maternal blood cells are present. Fibrin/fibrinoid is also a common finding in intervillous area as there are areas of turbulence and represents a clue for areas where maternal

blood flow slows. Similar eosinophilic deposits are seen in placental sections, and many studies are done to evaluate or sub-classify these accumulations. Briefly, fibrin is maternal in origin and fibrinoid (particularly matrix-type) is a product of post proliferative, invasive extra-villous trophoblastic cells. This is the reason for many authors preferring to use the term “fibrinoid” in placental sections. However, fibrinoid is usually associated with fibrin, leading to description of fibrin-type fibrinoid. Certain parts of the placenta show fibrin/fibrinoid accumulations as part of normal development. Special names have been given to these: “**Langhans fibrinoid**” is in the subchorionic area; “**Rohr’s and Nitabuch’s layers**” are in the basal decidua, Rohr’s being closer to villi [11, 12]. At times, intervillous areas can show extensive fibrin deposition. If deposition is mainly in the basal decidua, this is called maternal floor infarction. If deposition is more diffuse and extends into deeper parts, surrounding villi in a netlike pattern, this is called **massive perivillous fibrin deposition (MPFD)**. Placentas are stiff and pale. MPFD correlates with IUGR, IUFD, and neurologic impairment of baby [11, 12]. Another component of the parenchyma is “Cell Islands” composed of extravillous trophoblastic cells and fibrinoid, occasionally associated with decidual cells suggesting to be part of placental septa. Cysts can be observed in these islands, but no direct clinical correlation is mentioned [11, 12]. Inflammatory cells can be seen in all parenchymal areas and named accordingly: acute or chronic villitis or intervillitis. **Acute villitis** is associated with maternal sepsis from listeriosis or usually bacterial infections (e.g., Group B streptococci, *Klebsiella*, *E. coli*) and indicates fetal sepsis through hematogenous dissemination [20]. **Chronic villitis** contains mainly lymphocytes associated with histiocytes and occasionally plasma cells (Fig. 17.13a). There are two main groups of chronic villitis. One etiologic agent can be identified and will be diagnosed accordingly, e.g., cytomegalovirus, parvovirus B19, Mpox, *Toxoplasma gondii*, herpes simplex virus, mycobacteria, *Treponema pallidum*, or plasmodia (Fig. 17.13b). In such cases, the agent can be

identified by careful analysis in H&E sections, but special stains, immunohistochemical studies, or PCR are also performed [22, 23]. In the other more frequent (>95%) type, chronic villitis, no specific etiology can be obtained and, thus, named as **villitis of unknown etiology (VUE)**. A complement-mediated process is suggested as deposition of complement component C4d is seen on villous surface and fetal vascular endothelium [20]. VUE has a high recurrence rate and is associated with poor outcome (miscarriage, fetal demise, premature delivery, fetal growth restriction) [11, 12, 20]. Histologic associations are thrombus formation in fetal vasculature resulting in avascular villi, hemosiderin deposition, and increased numbers of NRBC. VUE is multifocal and concentrates in areas close to basal plate. Grading is performed as low and high grade: in low grade, <10 villi per focus are involved [24].

In **chronic histiocytic intervillitis (CHI)**, there is an excess accumulation of histiocytes in the intervillous area, but it is usually associated with fibrin deposition (Fig. 17.13c). It is also graded as low and high grade: high grade is when >50% of the intervillous space is involved [24]. All these intervillous changes (MPFD, VUE, and CHI) usually present a spectrum, occur in the second or third trimester, can be seen in normal pregnancies to some extent, and can be discordant in dichorionic twins. However, they have a recurrence capacity and result in adverse outcomes (pregnancy loss). They are all reported to be associated with immune mediated diseases (e.g., SLE) [24]. Another inflammatory reaction type is granulomatous. Granulomas with giant cells can be part of some VUE but more specific etiology such as mycobacteria, toxoplasmosis, or sarcoidosis can also be of concern [11, 12].

Maternal malperfusion (MVM) include a set of findings caused by maternal insufficient blood supply for the placenta. Prototype is preeclampsia [25]. Placenta is small and show infarcts and/or retroplacental hematoma. There is **distal villous hypoplasia (DVH)** and **accelerated villous maturation (AVM)**. AVM, decidual arteriopathy, infarcts, and retroplacental hematoma are more frequently associated with stillbirth compared to

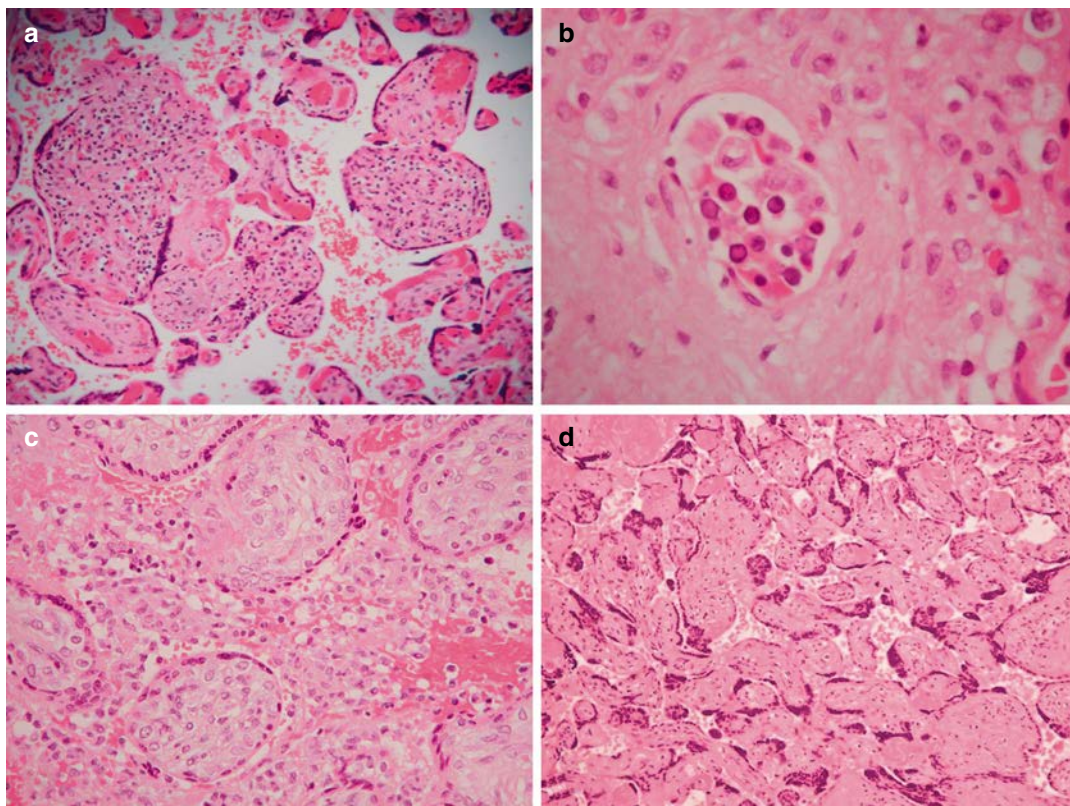


Fig. 17.13 (a) Chronic villitis . (b) Parvovirus inclusions. (c) Chronic histiocytic intervillitis. (d) Increased syncytial knots.

livebirths. Although DVH is more common in early pregnancy (before 32 gestational age), these two entities are usually seen together as intermingled areas. Changes can be focal (in one full-thickness slide) or diffuse (in two or more full-thickness slide). In DVH, villi are small and slender, with areas of decreased number of villi around the stem villi in the lower 2/3 of placental slide. In AVM (formerly Tenney-Parker change), villi show increased numbers of syncytial knots at least in 1/3 of the examined area (Fig. 17.13d). (Beware that increased syncytial knots are also present around infarcts.) Other associated findings are vascular changes in the basal decidua: acute atherosclerosis, fibrinoid necrosis, and mural hypertrophy. Chronic perivasculitis, arterial thrombosis, and persistence of intramural endovascular trophoblast in the third trimester can also be seen.

Another term suggested by Amsterdam Group is **delayed villous maturation** (DVM), corre-

sponding to villous developmental features in contrast to accelerated maturation and replacing the terms such as villous dysmaturity or villous maturation defect [18]. Here villous morphology is not compatible with gestational age and show earlier gestational age features, e.g., presence of immature villi whereas mature forms should dominate. **Fetal vascular malperfusion** (FVM) has replaced the term fetal thrombotic vasculopathy [18]. Findings describe results of obstruction in the fetal blood circulation: thrombus formation in fetal vessels, groups of avascular villi, and karyorrhexis in the stroma or fetal vasculature of the villi, usually accompanied by erythrocyte extravasation (Associated findings such as dilated vessels, intravascular fibrin deposition, and hyperplastic vascular wall changes in stem villi are also reported. If main thrombus is in the umbilical vessel, then this is global FVM, and if occlusion is at a lower level (branches of umbilical cord vessel,

such as stem villous vessel), this is segmental FVM. Both can be low or high grade. High-grade FVM is defined by multiple groups of avascular villi (an average of 15 or more avascular villi in each slide with or without thrombus formation and at least three slides should be examined) or two or more vessels in chorion or major stem villi either partially or totally thrombosed or multiple nonocclusive thrombus in fetal vessels. Apart from thrombi in villous vasculature, there is an associated pattern used to be described as hemorrhagic endovasculitis (HEV). This is mainly extravasation and fragmentation of erythrocytes due to wall injury of small vessels (microangiopathy) in villous stroma. It is important to remind that this is a common finding in stillbirth deliveries as this would be the prototype for cessation of fetal blood flow. Intravillous hemorrhage is suggested as the acute phase of HEV where other evidence for vascular injury is missing. Clinical associations with FVM are gestational diabetes, marginal or velamentous cord insertion, SUA, and stillbirth [26].

17.5 Gestational Trophoblastic Diseases

Gestational trophoblastic diseases (GTDs) are rare tumors originating from trophoblasts and compose a heterogeneous group. Benign forms are more common and constitute molar diseases: **partial or complete hydatidiform moles** (HMs). HMs originate from cytotrophoblasts and are considered pre-neoplastic lesions [27]. Another recently defined benign form is **atypical placental site nodule** (APSN) and about 15% of APSN undergo malignant transformation, showing the need for medical monitoring. Malignant forms originate from intermediate, generally extravillous trophoblasts and are referred as **gestational trophoblastic neoplasia** (GTN). GTN cover invasive mole, choriocarcinoma, placental-site trophoblastic tumor, and epithelioid trophoblastic tumor. **Hydatidiform moles** are usually sporadic diseases but familial forms with recurrent molar pregnancies are also seen. There is high incidence in Southeast Asia, and incidence increases

in advanced ages (2.5-fold >35 years and 5-fold >40 years) and adolescent pregnancies. They have a high recurrence rate and higher risk of developing other GTDs [27]. Clinically human chorionic gonadotropin (hCG) levels can be used at both stages: markedly raised during diagnosis and declining after treatment, during follow-up. Mean interval for hCG normalization is 6 weeks in partial moles and slightly longer in complete moles. Monitoring hCG levels after normalization continues up to 6 months in CHM. Hydatidiform moles are classified as partial and complete according to histopathologic examination and genetics. Macroscopic finding (also seen in ultrasonography) is cystic structures either focal (partial) or global forming grape-like structures (complete) (Fig. 17.14a). Microscopic examination reveals edematous villi with central cisterns showing no fetal vessels and proliferation of trophoblasts (Fig. 17.14b). Trophoblast proliferation is more extensive and circumferential in CHM and is associated with cytologic atypia and stromal apoptotic bodies. Large hydropic villi of PHM have scalloped contours resulting in trophoblastic pseudo-inclusions in villous stroma [11, 27]. A great challenge is diagnosis of early CHM as pathologic features are not fully developed. Differential diagnosis will be PHM and hydropic abortus. As the edema is less, cauliflower-shaped villi are small and show a light blue discoloration of stroma; trophoblastic proliferation is not pronounced [12]. Other diagnostic tools and clinicopathologic correlation are needed for definite diagnosis. Some ancillary techniques are developed to overcome diagnostic pitfalls and intra-/interobserver variability: immunohistochemistry using p57 and ploidy studies are suggested. Conventional cytogenetics, flow cytometry, or FISH can detect ploidy but not maternal or paternal origin of chromosomes. Recently suggested DNA genotyping of short tandem repeat (STR) technique is costly (not allowing routine application), and its interpretation has challenges; thus, it is advised to be used in a selective group of patients. Next-generation sequencing (NGS) technique is used to search for microRNAs as potential biomarker for differential diagnosis of HMs and suggested as a diag-

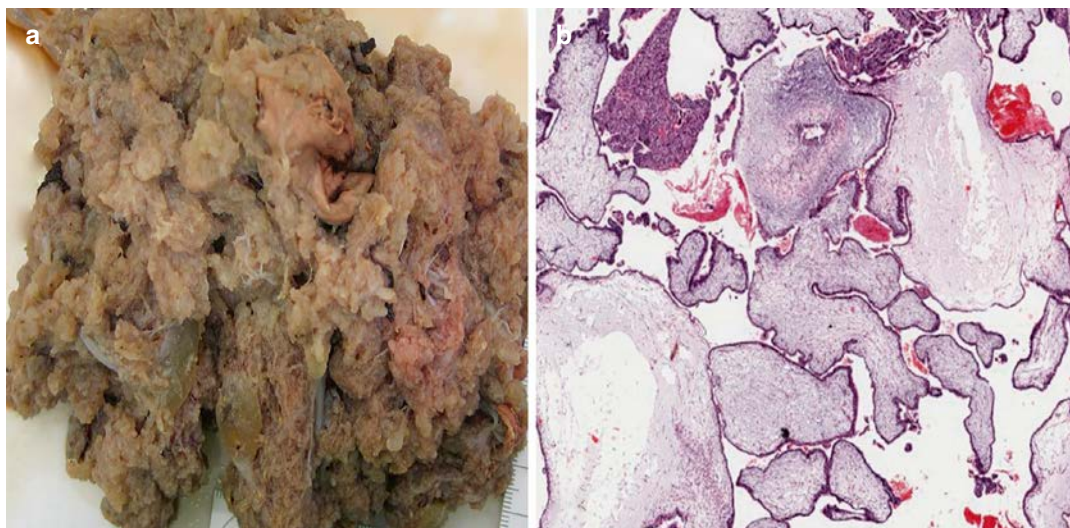


Fig. 17.14 Gross appearance (a) and microscopic features (b) of hydatidiform mole

nostic tool for CM [28]. Nuclear staining of p57 is very helpful for histologic diagnosis of CHM as it is easily performed and evaluated: extravillous trophoblasts and decidua serve as internal control; cytotrophoblasts and villous stroma cells are negative in CHM, allowing to differentiate CHM from PHM and HM [27]. Apart from staining technique or tissue processing related unequivocal results in p57 staining, it is important to remember other conditions where p57 is negative (false negatives): loss of maternal chromosome 11 in non-CHM, mutation of maternal p57 allele (e.g., Beckwith-Wiedemann syndrome) in non-molar pregnancy, and paternal uniparental disomy of chromosome 11.

Fetal parts are absent in complete hydatidiform mole (CHM) (exception is presence of diploid twin) and CHM has paternal diploid karyotype. Some evidence of fetal development (such as amniotic fetal vessels) is seen in partial hydatidiform mole (PHM), and it almost always shows triploidy with one set of maternal and two sets of paternal chromosomes. Approximately 15%–20% of CHMs and <5% of PHMs have malignant potential and progress to gestational trophoblastic neoplasia. Familial recurrent hydatidiform mole is autosomal recessive disorder, and their genetic profile is most often diploid biparental but gener-

ally show biallelic mutations NLRP7 resulting in imprinting defects. Other germline mutations such as KHDC3L, ME11, TOP6BL, and REC114 have also been described in recurrent moles. Recent molecular studies show a wide range of mutations and chromosomal rearrangements, but none can be used as definitive marker as yet. All invasive moles but about half of choriocarcinomas (CC) and a quarter of placental-site trophoblastic tumor (PSTT) or epitheloid trophoblastic tumor (ETT) develop after a molar pregnancy; the rest can develop after any pregnancy, including normal or ectopic pregnancy. FIGO has set diagnostic criteria for post-molar gestational trophoblastic neoplasia. Invasive mole rarely metastasizes and is usually locally destructive invading myometrium to a variable thickness. On the other hand, CC develops systemic metastasis at an early stage. It is also important to mention placental choriocarcinoma in situ which was described as an incidental finding and not metastasizing. Recently preferred approach is to name all as intraplacental choriocarcinomas to emphasize the need for clinical follow-up of hCG levels with the possibility of metastases [29]. Fetomaternal hemorrhage can be a complication in some intraplacental CCs, and perinatal mortality is high (%36.8) in such cases [30]. Beware that primary choriocarcinoma can develop

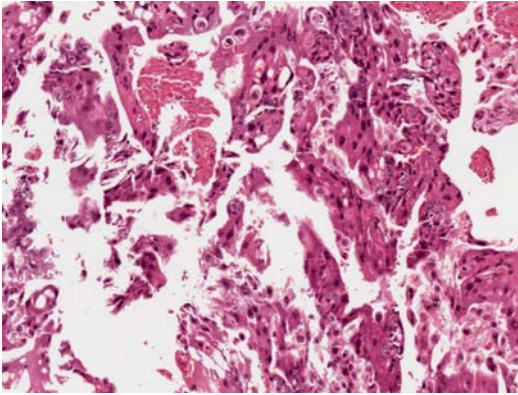


Fig. 17.15 Uterine choriocarcinoma

in other organs and is non-gestational. Macroscopically hemorrhagic and/or necrotic foci in the placenta can be a clue for CC. Microscopic features are characterized by aggregates/groups of trophoblasts with hyperchromatic and pleomorphic nuclei in a hemorrhagic and necrotic background (Fig. 17.15). Some CCs are complicated by fetomaternal hemorrhage and is associated with high perinatal mortality [30, 31].

Even rarer types of gestational trophoblastic neoplasia (GTN) are placental-site trophoblastic tumor (PSTT) and epitheloid trophoblastic tumor (ETT) in order of frequency [31]. PSTT, as the name implies, develops at the placental bed; it originates from intermediate trophoblasts and invades the myometrium without formation of villi. Compared to choriocarcinoma, PSTT is less hemorrhagic but excessively necrotic. ETT also originates from intermediate trophoblasts and has a nodular expansive growth pattern and usually resides in lower uterus or cervix causing diagnostic problems with cervical cancer [31]. They are both slow growing tumors and can be detected months to years after a pregnancy; neither hCG levels nor metastatic rate is exuberant.

17.6 Miscellaneous Placental Lesions

Confined Placental Mosaicism After broad practice of in vitro fertilization (IVF) and chorionic villous sampling (CVS) procedures genetic

studies are more detailed. Chromosomal alterations can be detected even pre-implantation stages and ploidy status of each cell can be driven, informing about mosaicism or chimerism. Confined placental mosaicism (CPM) refers to mosaicism in placental tissue only and is detected in 1%–2% of CVS. It is more common than true fetal mosaicism [32]. According to abnormal cell population, CPM is defined in three groups: in CPM-I, cytotrophoblasts have abnormal cell population, in CPM-II fibroblasts have abnormal cell population, and in CPM-III both cytotrophoblasts and fibroblasts are affected. Different trisomies are the most common abnormality in all CPM types. It is not clear whether CPM develops at pre- or postimplantation stage [32]. It has low recurrence risk. Histopathologic findings of CPM are not clearly described [12]. It is usually subtle. The placenta will often be both macroscopically and microscopically normal. Some will be small in correlation with fetal growth restriction. Some will show heterogenous villous morphology with basement membrane mineralization or groups of edematous villi.

Angiomatous Lesions All these lesions originate from villous capillaries. Chorangioma is a compensatory reaction of terminal or distal villi, and its capillaries lack the continuous perivascular lining of pericytes as identified by muscle-specific actin and reticulin stains [14]. Its diagnosis relies on the presence of ten or more capillaries in ten or more terminal villi in several sections examined. Neoplastic nature of chorangioma and chorangiomatosis is still debatable; although usually accepted as a reactive or hyperplastic disorder, a recent study showed TP53 mutations suggesting a neoplastic nature [33]. They are histologically similar but present different TP53 profile. Chorangioma forms a well-defined nodular lesion on the fetal surface or within the placenta. If inside the placenta, cut surface shows a pale nodular lesion. It can be single or multiple. Main clinical problems arise usually in large/giant (above 5 cm) or multiple (multinodular) forms and are secondary to increased blood volume circulating within the

lesion. It can occasionally show hyperplasia of trophoblasts [14]. Chorangiomas cannot be detected macroscopically. It resides usually at the peripheral parts of the placenta. There is hyperplasia of villous capillaries and sometimes associated with nonspecific proliferation of trophoblasts at villous periphery. If localized, it involves stem villi. If multifocal, it is associated with FVM in more than half of the cases. Placentomegaly and MVM are seen in all these villous capillary lesions. Clinical associations with chorangiosis are maternal diabetes and chronic villitis; those with chorangioma and chorangiomas are preeclampsia, multiple gestation, premature rupture of membranes, congenital malformations, and fetal growth restriction [14]. Chorangiocarcinoma is also a nodular lesion detected incidentally at term or near term. It is a disputable lesion described as a hybrid neoplasm where constitutional villous stroma show proliferation of vessels surrounded by atypical trophoblasts associated with mitotic figures and apoptotic bodies [11]. Main challenge is about the trophoblasts: how atypical are they?

17.7 Other Tumors and Tumor-Like Lesions

There are reported cases of placental leiomyomas either attached to membranes or within the parenchyma. Their origin is ambiguous in former reports but proved to be maternal in recent articles [11]. A similar discussion is carried for inflammatory myofibroblastic tumor [34]. Microscopic incidental findings are heterotopic tissues in the placenta. Most common ones are hepatic and adreno-cortical tissues [11, 12]. Also seen is adipose tissue or fetal pigmented melanocytic nevus [34]. Metastatic tumors can be fetal or maternal origin. Fetal ones will be within the villous fetal vasculature; maternal ones will be in the intervillous area. Most common fetal tumor is neuroblastoma, and maternal tumor is malignant melanoma [11, 34]. A diagnostic challenge here is presence of nevus cell aggregates within the placenta (even in the intervillous area) in cases of giant congenital melanocytic nevus [11, 34].

Other reported fetal malignancies are hepatoblastoma, sarcomas, teratomas, and leukemia; maternal ones are hematologic malignancies and carcinomas of several organs (lung, stomach, breast, etc.) [34, 35].

References

1. Deryabin PI, Borodkina AV. The role of the endometrium in implantation: a modern view. *Int J Mol Sci*. 2024;25(17):9746.
2. Fan D, Lin D, Rao J, Li P, Chen G, Zhou Z, Sun L, Liu L, Ma Y, Guo X, Liu Z. Factors and outcomes for placental anomalies: an umbrella review of systematic reviews and meta-analyses. *J Glob Health*. 2024;14:04013.
3. Kotta-Loizou I, Pritsa A, Antasouras G, Vasilopoulos SN, Voulgaridou G, Papadopoulou SK, Coutts RHA, Lechouritis E, Giaginis C. Fetus exposure to drugs and chemicals: a holistic overview on the assessment of their transport and metabolism across the human placental barrier. *Diseases*. 2024;12(6):114.
4. Redline RW, Ravishankar S, Bagby CM, Saab ST, Zarei S. Four major patterns of placental injury: a stepwise guide for understanding and implementing the 2016 Amsterdam consensus. *Mod Pathol*. 2021;34(6):1074–92.
5. Redline RW, Roberts DJ, Parast MM, Ernst LM, Morgan TK, Greene MF, Gyamfi-Bannerman C, Louis JM, Maltepe E, Mestan KK, Romero R, Stone J. Placental pathology is necessary to understand common pregnancy complications and achieve an improved taxonomy of obstetrical disease. *Am J Obstet Gynecol*. 2023;228(2):187–202.
6. Strahler L, Horky A, Spahn S, Bahlmann F, Gradhand E. Unveiling clinical relevance: investigating placentas submitted for histological examination and their correlation with clinical indications and histological findings. *Life (Basel)*. 2024;14(8):927.
7. Baergen RN. Indications for submission and macroscopic examination of the placenta. *APMIS*. 2018;126(7):544–50.
8. Langston C, Kaplan C, Macpherson T, Mancini E, Peevy K, Clark B, Murtagh C, Cox S, Glenn G. Practice guideline for examination of the placenta: developed by the Placental Pathology Practice Guideline Development Task Force of the College of American Pathologists. *Arch Pathol Lab Med*. 1997;121(5):449–76.
9. Zhou YY, Ravishankar S, Luo G, Redline RW. Predictors of high grade and other clinically significant placental findings by indication for submission in singleton placentas from term births. *Pediatr Dev Pathol*. 2020;23(4):274–84.
10. Liang X, Zhang J, Wang Y, Wu Y, Liu H, Feng W, Si Z, Sun R, Hao Z, Guo H, Li X, Xu T, Wang M, Nan Z,

- Lv Y, Shang X. Comparative study of microvascular structural changes in the gestational diabetic placenta. *Diab Vasc Dis Res.* 2023;20(3):14791641231173627.
11. Baergen RN. Manual of Benirschke and Kaufmann's pathology of the human placenta. New York: Springer; 2005.
12. Benirschke K, Kaufmann P, Baergen RN. Pathology of the human placenta. 5th ed. New York: Springer; 2006.
13. Mehedintu C, Frincu F, Ionescu OM, Cirstoiu MM, Sajin M, Olinca M, Bratila E, Petca A, Carp-Veliscu A. A challenging diagnosis: placental mesenchymal dysplasia-literature review and case report. *Diagnostics (Basel).* 2022;12(2):293.
14. Ogino S, Redline RW. Villous capillary lesions of the placenta: distinctions between chorangioma, chorangiomatosis, and chorangiosis. *Hum Pathol.* 2000;31(8):945–54.
15. Choo S, de Vrijer B, Regnault TRH, Brown HK, Stitt L, Richardson BS. The impact of maternal diabetes on birth to placental weight ratio and umbilical cord oxygen values with implications for fetal-placental development. *Placenta.* 2023;136:18–24.
16. Sánchez-Trujillo L, García-Montero C, Fraile-Martínez O, Guijarro LG, Bravo C, De Leon-Luis JA, Saez JV, Bujan J, Alvarez-Mon M, García-Honduvilla N, Saez MA, Ortega MA. Considering the effects and maternofoetal implications of vascular disorders and the umbilical cord. *Medicina (Kaunas).* 2022;58(12):1754.
17. Fitzgerald B. Histopathological examination of the placenta in twin pregnancies. *APMIS.* 2018;126(7):626–37.
18. Khong TY, Mooney EE, Ariel I, Balmus NC, Boyd TK, Brundler MA, Derricott H, Evans MJ, Faye-Petersen OM, Gillan JE, Heazell AE, Heller DS, Jacques SM, Keating S, Kelehan P, Maes A, McKay EM, Morgan TK, Nikkels PG, Parks WT, Redline RW, Scheimberg I, Schoots MH, Sebire NJ, Timmer A, Turowski G, van der Voorn JP, van Lijnschoten I, Gordijn SJ. Sampling and definitions of placental lesions: Amsterdam placental workshop group consensus statement. *Arch Pathol Lab Med.* 2016;140(7):698–713.
19. Redline RW, Vik T, Heerema-McKenney A, Jamtoy AH, Ravishankar S, Ton Nu TN, Vogt C, Ng P, Nelson KB, Lydersen S, Oskoui M. Interobserver reliability for identifying specific patterns of placental injury as defined by the Amsterdam Classification. *Arch Pathol Lab Med.* 2022;146(3):372–8.
20. Goldstein JA, Gallagher K, Beck C, Kumar R, Gernand AD. Maternal-fetal inflammation in the placenta and the developmental origins of health and disease. *Front Immunol.* 2020;11:531543.
21. Redline RW, Faye-Petersen O, Heller D, Qureshi F, Savell V, Vogler C, Society for Pediatric Pathology, Perinatal Section, Amniotic Fluid Infection Nosology Committee. Amniotic infection syndrome: nosology and reproducibility of placental reaction patterns. *Pediatr Dev Pathol.* 2003;6(5):435–48.
22. Kotiloglu-Karaa E, Kele B, Kulasegaran-Shylini R, Broad CE, Owoyemi D, Martin J, MacPhail G, Iliodromiti S, Riddell A, Alexander E, Cutino-Moguel T. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) placental infection is associated with massive perivillous fibrin deposition at the maternal-fetal Interface: a preliminary study. *Clin Infect Dis.* 2022;75(1):e1176–9.
23. Auriti C, De Rose DU, Santisi A, Martini L, Piersigilli F, Bersani I, Ronchetti MP, Caforio L. Pregnancy and viral infections: mechanisms of fetal damage, diagnosis and prevention of neonatal adverse outcomes from cytomegalovirus to SARS-CoV-2 and Zika virus. *Biochim Biophys Acta Mol basis Dis.* 2021;1867(10):166198.
24. Cornish EF, McDonnell T, Williams DJ. Chronic inflammatory placental disorders associated with recurrent adverse pregnancy outcome. *Front Immunol.* 2022;13:825075.
25. Jung E, Romero R, Yeo L, Gomez-Lopez N, Chaemsathong P, Jaovisidha A, Gotsch F, Erez O. The etiology of preeclampsia. *Am J Obstet Gynecol.* 2022;226(2S):S844–66.
26. Stanek J. Placental fetal vascular malperfusion in maternal diabetes mellitus. *J Perinat Med.* 2024;53(2):179–87.
27. Gonzalez J, Popp M, Oejo S, Abreu A, Bahmad HF, Poppiti R. Gestational trophoblastic disease: complete versus partial hydatidiform moles. *Diseases.* 2024;12(7):159.
28. Chia WK, Yeoh HXY, Mustangin M, Khong TY, Wong YP, Tan GC. MicroRNA profiling in complete and partial hydatidiform moles. *Malays J Pathol.* 2023;45(3):353–62.
29. Dahl J. Intraplacental gestational neoplasms: a review of clinically relevant diagnostically challenging lesions. *Arch Pathol Lab Med.* 2024;148(4):398–408.
30. Stabile G, Gentile RM, Carlucci S, Stampalija T, Biffi S, Oletto G, Guido M, Bruno M. Maternal and fetal outcomes of intraplacental chorioncarcinoma complicated by fetomaternal hemorrhage: a systematic review. *J Matern Fetal Neonatal Med.* 2023;36(2):2285238.
31. Kurt S, Ilgen O, Ulukus EC, Yuzuguldu RI, Celiloglu M. Evaluation of epithelioid trophoblastic tumor in the light of literature. *Arch Iran Med.* 2021;24(7):579–82.
32. West JD, Everett CA. Preimplantation chromosomal mosaics, chimaeras and confined placental mosaicism. *Reprod Fertil.* 2022;3(2):R66–90.
33. Luo Y. Mutation of the TP53 gene in placental chorangiomatosis. *Fetal Pediatr Pathol.* 2023;42(3):400–9.
34. Sebire NJ, Jauniaux E. Fetal and placental malignancies: prenatal diagnosis and management. *Ultrasound Obstet Gynecol.* 2009;33(2):235–44.
35. Wolters V, Lok CAR, Gordijn SJ, Wiltshagen EA, Sebire NJ, Khong TY, van der Voorn JP, Amant F. Placental pathology in cancer during pregnancy and after cancer treatment exposure. *Placenta.* 2021;111:33–46.

Non-neoplastic Disorders of the Breast

18

Nuket Ozkavruk Eliyatkin and Çiğdem Selli 

18.1 Structure of the Breast

18.1.1 Anatomy and Histology of the Breast

The breast is a modified sweat gland of ectodermal origin. Bilateral mammary ridges begin forming during the 5th week of intrauterine life, and epithelial buds develop between the 10th and 12th weeks, continuing their growth until birth. Hormones such as insulin and growth hormone play essential roles in breast development. Prior to puberty, breast morphology is similar in both sexes. The breast tissue lies between the subcutaneous fat and the pectoralis major muscle. Approximately half of the breast volume is located in the upper outer quadrant, explaining why the majority of primary breast tumors arise in this region. Lymphatic drainage differs by location: the lateral (outer) breast drains into the axillary lymph nodes, while the medial (inner) portion drains into the internal mammary chain [1–3].

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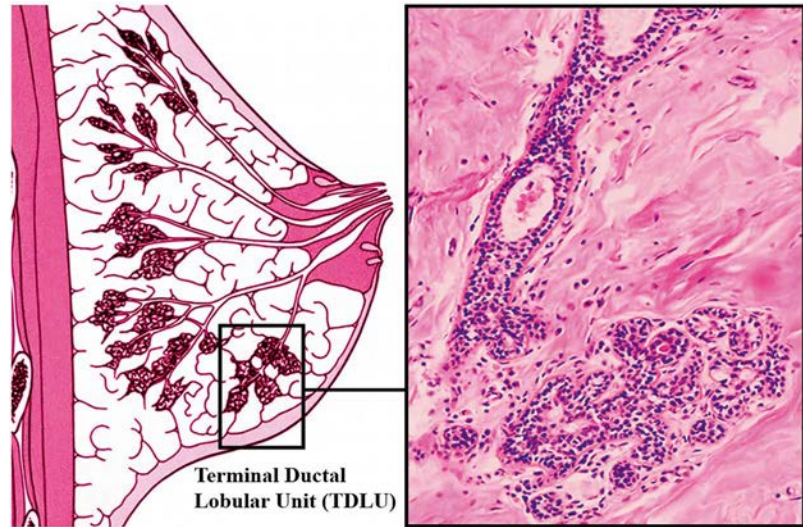
18.1.2 Lobular and Ductal Structure

The breast is composed of 15–25 pyramid-shaped lobes that converge toward the areola. Each lobule is connected to a single collecting duct, known as a lactiferous duct or sinus, which dilates subareolarly and opens at the nipple. The terminal ductal lobular unit (TDLU) consists of terminal ducts and acini and represents the gland's functional secretory unit (Fig. 18.1). Milk produced in the TDLU passes through subsegmental ducts and then segmental (lactiferous) ducts and finally exits via the lactiferous sinuses at the nipple [1–3].

18.1.3 Stromal Compartments

Breast stroma is divided into interlobular and intralobular components. Interlobular stroma constitutes most of the breast volume and expands during puberty, contributing to breast enlargement. It contains fibroblasts, myofibroblasts, adipocytes, blood vessels, and lymphatics, with abundant elastic fibers but minimal hormone-sensitive stroma. Neoplasms such as lipoma, angiolipoma, nodular fasciitis, and angiosarcoma can originate from this component and may also occur in extramammary sites. Intralobular stroma surrounds and supports acini within the TDLU. It lacks elastic fibers but is hormonally responsive. Lesions from this stromal type are specific to the breast [1–3].

Fig. 18.1 Schematic structure of the breast



18.1.4 Epithelial and Myoepithelial Cells

Each duct and lobule is lined by luminal epithelial cells, which are cuboidal or low columnar and externally surrounded by myoepithelial cells. Luminal cells express low molecular weight cytokeratins (CK7, CK8, CK18, CK19), α -lactalbumin, and mammaglobin. Their apical surfaces are positive for epithelial membrane antigen (EMA) and human milk fat globule membrane antigen 2 (HMFG-2). Gross cystic disease fluid protein-15 (GCDFP-15) was originally isolated from breast cyst fluid. In normal breast epithelium, it shows focal staining. It is also present in all apocrine cells in the body and in cells exhibiting apocrine metaplasia in the breast. GCDFP-15 is positive in a subset of breast carcinomas, particularly in more than half of those with apocrine histological features. Its expression is generally associated with lower-grade breast cancers [4–6].

Myoepithelial cells reside between luminal cells and the basement membrane. They are contractile and may appear flattened, spindle-shaped, or clear. These cells express high molecular weight cytokeratin (CK5/6, CK14, CK17), smooth muscle actin, calponin, smooth muscle myosin heavy chain, CD10, S-100, P-cadherin, mammary serine protease inhibitor (maspin), and

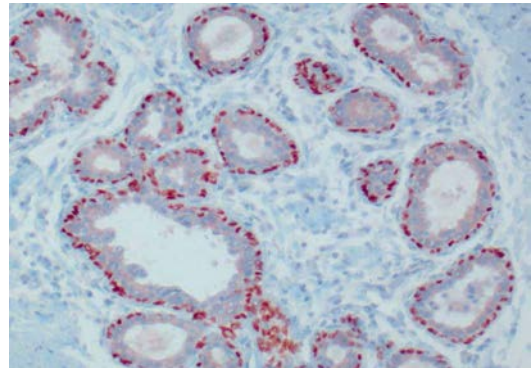


Fig. 18.2 Nuclear P63 expression in myoepithelial cells

nuclear markers such as p63 (Fig. 18.2) and p75NTR. CD109 demonstrates membranous staining. CK14 is limited to myoepithelial cells of large or terminal ducts. Laminin and type IV collagen are present in the glandular basement membrane. Pankeratin stains both epithelial and myoepithelial cells [7].

18.1.5 Nipple and Montgomery Glands

The nipple contains sebaceous glands, hair follicles, dense fibrous stroma, and 10–12 terminal collecting ducts, as well as specialized sebaceous structures known as Montgomery tubercles,

which are located around the areola. These structures play a role in lubrication and protection of the nipple during breastfeeding [1, 2].

18.2 Developmental and Structural Changes in the Breast

18.2.1 Prepubertal, Pubertal, and Senescent Breast

Before puberty, mammary ducts terminate in blind ends. During adolescence, lobules composed of acini begin to develop distally from these ducts. In advanced age, lobular acini and the associated stroma undergo complete atrophy, leaving a breast structure composed primarily of ducts, resembling that of children or males. At puberty, epithelial proliferation is the most prominent morphological change. During pregnancy, all cellular components of the breast—epithelial, stromal, and myoepithelial—undergo marked proliferation. Postmenopausal regression affects both epithelial and stromal compartments. The lobular glands often become cystically dilated, a process known as cystic lobular involution (Fig. 18.3). In some conditions, such as usual ductal hyperplasia, the epithelial lining becomes multilayered (2–4 cell layers), and the intralobular stroma may exhibit increased fibrosis or collagenization [8, 9].

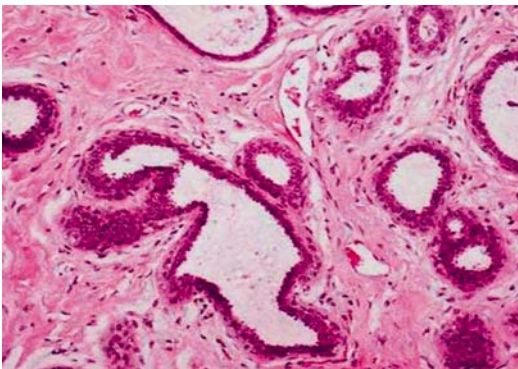


Fig. 18.3 Cystic lobular involution

18.2.2 Ectopic Breast Tissue and Congenital Anomalies

Ectopic (accessory) breast tissue may develop anywhere along the “milk line,” a linear embryologic structure that extends from the axilla to the groin. The most common location is the axilla, where accessory breast tissue may mimic lymphadenopathy or metastatic carcinoma. This tissue can undergo all physiological and pathological changes seen in normal breast tissue, including cyclical changes, lactational changes, and neoplastic transformation. Hidradenoma papilliferum, a tumor found in the vulva, is hypothesized to originate from ectopic mammary tissue.

There are several congenital anomalies of breast. For example, athelia is absence of the nipple, polythelia is presence of supernumerary nipples, and amastia is complete absence of breast tissue and nipple [1–3, 9].

18.2.3 Hormonal Influence on the Terminal Duct Lobular Unit (TDLU)

Breast development and lactation are regulated by a complex interplay of hormones such as estrogen, progesterone, prolactin, and insulin. The terminal duct lobular unit (TDLU) is particularly sensitive to hormonal changes associated with the menstrual cycle, pregnancy, lactation, and menopause. During proliferative (follicular) phase, lobules remain quiescent. In luteal phase, acinar proliferation, stromal edema, and myoepithelial vacuolization occur. Apoptosis of epithelial cells and resolution of edema dominate in menstruation. During pregnancy, proliferation of secretory acini from terminal ducts becomes prominent. By the third trimester, secretory vacuoles are well developed, and the breast appears almost entirely lobular. By the end of pregnancy, the breast becomes densely lobulated with tightly packed back-to-back acini, this appearance (Fig. 18.4) is known as lactating

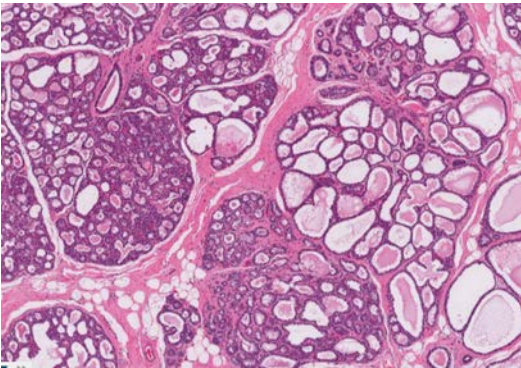


Fig. 18.4 Lactating breast

breast. In approximately half of middle-aged and elderly women, stromal elastosis may be observed around blood vessels and ducts. Occasionally, the breast exhibits morphologic changes resembling pregnancy, referred to as pregnancy-like change, even in the absence of pregnancy or exogenous hormones. These changes are characterized with prominent cytoplasmic vacuolization, luminal dilation, and enlarged, apically placed nuclei (reminiscent of the Arias-Stella reaction). Clear cell change, on the other hand, is characterized by epithelial cells with optically clear cytoplasm, forming structures distinct from classic lobules [1–3, 10–12].

18.3 Histogenetic Origin of Breast Lesions

Each type of benign or malignant breast lesion originates from a specific anatomical or histological compartment of the breast such as TDLU, ducts, and stroma (Table 18.1). This classification is essential for predicting behavior, guiding diagnostic strategies, and informing clinical management decisions (Fig. 18.5). Fibrocystic changes (FCC) are detected in 40% of biopsies performed on breast masses. No pathology is found in up to 30% of biopsies. Benign lesions other than FCC account for 13%, malignancies for 10%, and fibroadenomas for 7% [13, 14].

Table 18.1 Anatomical origin of breast lesions

Anatomic structure	Inflammatory lesions	Hyperplasia/tumor
Nipple/areola	Squamous metaplasia of lactiferous ducts	Nipple adenoma, leiomyoma, Paget disease
Large duct system	Duct ectasia	Papilloma, encapsulated papillary carcinoma
Terminal ductal lobular unit	Cysts, granulomatous lobular mastitis	Epithelial hyperplasia, sclerosing adenosis, carcinomas
Interlobular stroma	Fat necrosis, bacterial infection	Lipoma, angiolipoma, fibromatosis, sarcoma
Intralobular stroma	Granulomatous lobular mastitis, lymphocytic mastopathy	Fibroadenoma, phyllodes tumor

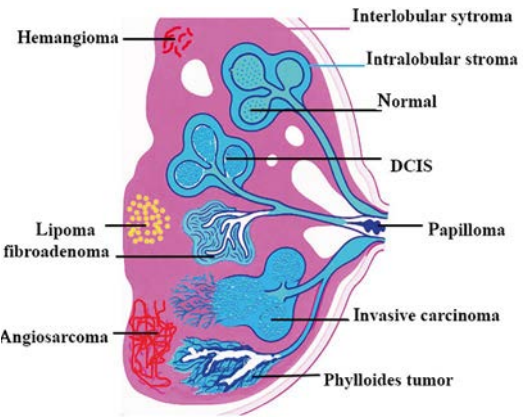


Fig. 18.5 Components of the breast and tumors developing from them

18.4 Non-neoplastic Inflammatory and Reactive Lesions of the Breast [15–19]

18.4.1 Breast Abscess and Acute Mastitis

Breast abscesses most commonly occur during lactation and are typically caused by the rupture of mammary ducts, accompanied by secondary

bacterial infection. *Staphylococcus aureus* usually produces localized abscesses, while *Streptococcus* spp. more commonly causes diffuse mastitis with breast-wide pain, swelling, and tenderness. Histologically, a central cavity filled with neutrophils and necrotic debris is surrounded by inflamed parenchyma, which may become fibrotic in later stages. The lobular architecture is typically effaced. Due to its mass-forming nature, a localized abscess may clinically mimic carcinoma, underscoring its diagnostic relevance.

18.4.2 Post-biopsy and Post-surgical Changes

Patients with a history of biopsy or breast surgery often exhibit hemorrhagic and reparative changes. Common findings include hemosiderin-laden macrophages, granulation tissue with organized hemorrhage, fat necrosis, and presence of foreign material like suture fragments. Later stages show fibrosis and scarring. Epithelial displacement—epithelial cells found outside their normal ductal or lobular locations—is often seen, particularly in association with papillary lesions. This artifact must be recognized to avoid misdiagnosing malignancy.

18.4.3 Foreign Body Reactions

Reactions to silicone or implant materials can manifest as silicone granulomas, with cystic spaces containing empty or pale material surrounded by histiocytes (often multinucleated), and synovial metaplasia, where the implant capsule is lined by epithelium resembling synovium. In addition, silicone leakage can occur even without overt implant rupture, and the leaked material may also involve lymph nodes.

18.4.4 Ductal Ectasia and Plasma Cell Mastitis

Ductal ectasia typically affects premenopausal women aged 40–50 and results from the accumulation of secretions in large ducts. In ~20% of cases, it presents with nipple retraction or inversion, clinically mimicking carcinoma. Histologically, dilated ducts with secretions are surrounded by fibrotic stroma rich in elastic fibers, sometimes containing calcifications. There is no epithelial proliferation within the ducts (Fig. 18.6). If a duct ruptures, luminal contents can incite an inflammatory response in adjacent tissue, resulting in plasma cell mastitis. This

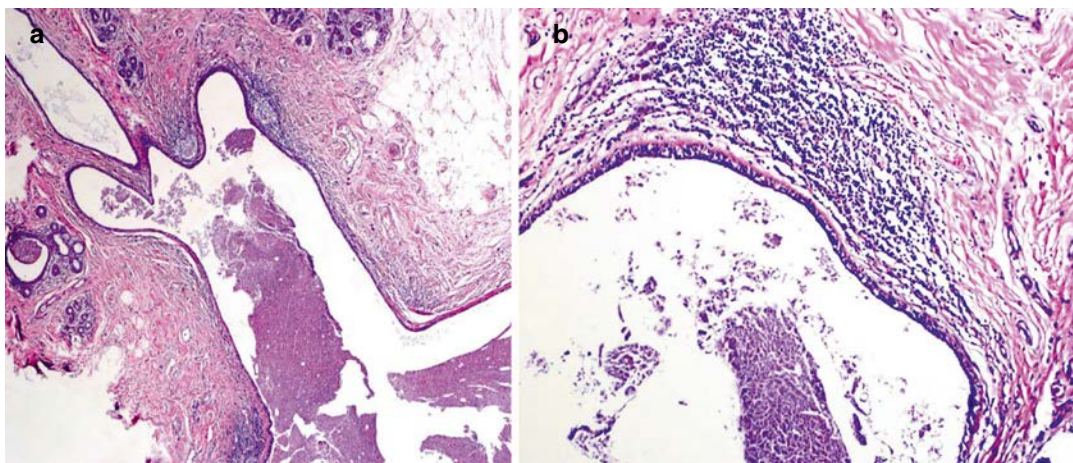


Fig. 18.6 (a) Ductal ectasia is characterized by dilated ducts with secretions. (b) Lymphoplasmacytic inflammation in the wall

entity differs from periductal mastitis in that it is not associated with smoking or squamous metaplasia and typically occurs in multiparous women.

18.4.5 Periductal Mastitis (Zuska's Disease)

It is seen in both men and women of various ages; periductal mastitis—also known as recurrent subareolar abscess or Zuska's disease—features squamous metaplasia of the lactiferous ducts and periareolar inflammation. A history of smoking is frequent. Keratin debris induces a foreign body reaction, and secondary bacterial infection may lead to abscess formation.

18.4.6 Fat Necrosis

Fat necrosis may result from trauma, prior surgery, radiation therapy, or underlying ductal ectasia or fibrocystic changes. Clinically and radiologically, it may mimic carcinoma due to skin retraction or mass effects. Chronic lesions show fibrosis and calcification. Histologically, foamy macrophages infiltrate necrotic fat lobules (Fig. 18.7). While the diagnosis is typically straightforward on paraffin sections, it may be challenging on frozen sections.

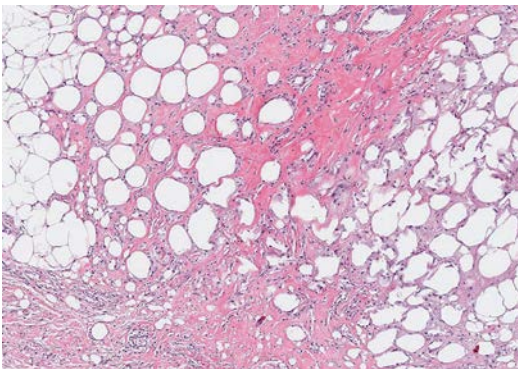


Fig. 18.7 Fat necrosis

18.4.7 Lymphocytic Mastitis (Diabetic Mastopathy)

Most associated with type 1 diabetes and autoimmune thyroiditis, this condition is believed to have an autoimmune etiology. Also known as sclerosing lymphocytic lobulitis, it presents as one or more firm, palpable masses. Histological features include lobular atrophy; keloid-like stromal fibrosis; dense periductal, perilobular, and perivascular B-cell-predominant lymphocytic infiltrates; and presence of stromal epithelioid myofibroblasts. Fine-needle aspiration may be inconclusive due to stromal density.

18.4.8 Granulomatous Mastitis

Seen in ~1% of all breast biopsies, granulomatous mastitis may be secondary to infections (e.g., tuberculosis, fungal, nipple piercings), autoimmune disorders (e.g., sarcoidosis), and implants or other iatrogenic sources. The idiopathic form, termed granulomatous lobular mastitis, presents as non-caseating granulomas confined to lobules. It is more common in parous women and may represent a hypersensitivity reaction to changes in epithelial antigens during lactation.

18.4.9 IgG4-Related Mastitis

This rare inflammatory condition is characterized by painless breast masses, dense lymphoplasmacytic infiltrates, storiform fibrosis, and obliterative phlebitis. Immunohistochemistry reveals increased IgG4-positive plasma cells. Lobular atrophy is a frequent finding.

18.4.10 Other Uncommon Inflammatory Lesions

- *Breast infarction* may result from ischemic changes due to underlying breast lesions,

trauma, or systemic diseases like mitral stenosis.

- *Mondor's disease* is a rare form of superficial thrombophlebitis of subcutaneous veins in the breast and thoracoabdominal wall. It presents with a sudden-onset, firm, cord-like lesion that may mimic malignancy. Histology shows phlebitis with intraluminal thrombus, which may later recanalize.

18.5 Hyperplastic Lesions of the Breast (Benign Epithelial Lesions of the Breast)

Benign epithelial lesions of the breast include a broad spectrum of histologically distinct entities, some of which are associated with an increased risk of carcinoma, while others are not. Given their clinical implications, these lesions are best categorized by their associated risk of developing breast carcinoma, as recommended in current consensus classifications [15–19].

18.5.1 Risk-Based Classification of Benign Breast Lesions

- *Nonproliferative breast disease* (no increased risk) includes mild ductal hyperplasia (3–4 cell layers), cysts (gross or microscopic), apocrine metaplasia, ductal ectasia, squamous metaplasia, fibroadenoma (without complex features), parenchymal atrophy, and stromal fibrosis and mastitis. Nonproliferative lesions are the most common findings in benign breast biopsies, historically grouped under the term “fibrocystic disease,” now replaced with *fibrocystic changes (FCC)* (Fig. 18.8). These changes are often bilateral and multifocal, peak between ages 25 and 45 and are rare before menarche or after menopause. Estrogen-progesterone imbalance is consid-

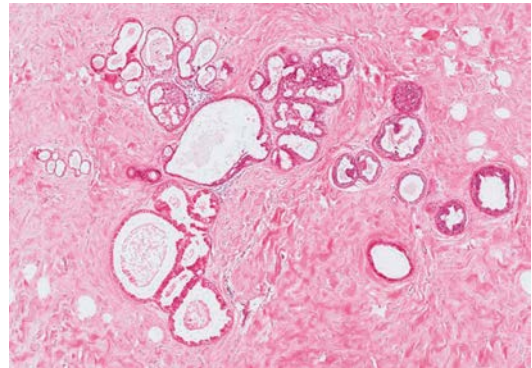


Fig. 18.8 Fibrocystic changes (FCC)

ered a key etiological factor. Oral contraceptive use has been shown to reduce FCC risk. FCC may include both proliferative and non-proliferative elements. When ≥ 2 of the following are present—apocrine metaplasia, apocrine adenosis, sclerosing adenosis, microglandular adenosis, radial scar, epithelial hyperplasia, and small duct papilloma—the diagnosis of FCC is favored. Common histologic components of FCC are listed below:

- *Cysts* are frequent and may be solitary, multifocal, or bilateral. They originate from TDLUs, not from larger ducts. Large cysts can present as palpable firm masses. Contents may be clear or hemorrhagic, and secretory debris often contains calcifications.
- *Calcifications* are less common than in ductal carcinoma in situ (DCIS). Benign calcifications in FCC often appear as coarse, amorphous calcium oxalate crystals with low to moderate density on mammography. These are almost always benign. In contrast, malignant microcalcifications are typically fine, linear, or branching with higher density.
- Stromal fibrosis may result from chronic cyst rupture and inflammation. Histologically, dense collagen replaces normal parenchyma and compresses ducts and lobules.
- *Apocrine metaplasia* involves the replacement of normal ductal or cyst-lining epi-

thelium with large polygonal cells that have abundant eosinophilic granular cytoplasm and prominent nucleoli (Fig. 18.9). These cells are ER/PR negative, but positive for androgen receptor and GCDFP-15. Although apocrine epithelium is not native to the breast, it may arise in terminal duct lobular units (TDLU) and is termed *apocrine adenosis* when associated with glandular proliferation. Simple apocrine metaplasia is not associated with malignancy. Atypical or papillary apocrine changes, particularly in women >45 years, may indicate increased cancer risk [20].

- *Adenosis* refers to an increased number of acini within a terminal duct lobular unit (TDLU) without a lobular size increase that exceeds normal variation (Fig. 18.10). Diagnosis relies on comparison with adjacent lobules. These lesions are usually non-

palpable and detected incidentally during histological examination. There are several types of adenosis. *Ductal adenosis* is a variant in which acinar lumens are dilated. *Nodular adenosis* refers to the coexistence of ductal and sclerosing adenosis and may represent an early form of sclerosing adenosis. *Sclerosing adenosis* is a benign but potentially misleading lesion due to its clinical and radiological resemblance to invasive carcinoma. Key features for diagnosis of adenosis are increased number of distorted and compressed acini within TDLUs. They may present as a palpable mass or mammographic abnormality (e.g., calcifications or architectural distortion). Radiologically, small lesions appear as microcalcifications, while larger lesions show increased parenchymal density. Grossly firm with irregular borders but lacks the chalky or striated appearance of carcinoma. Microscopically, there is at least twofold increase in acini per lobule. Compressed, lumen-poor acini are located centrally, while patent lumens are located peripherally. Maintained lobulocentric architecture is a useful clue to benignity. They may mimic invasive carcinoma, particularly in cases with pronounced fibrosis forming double-layered cords without visible lumens (Fig. 18.11). *Microglandular adenosis (MGA)* is a rare benign epithelial lesion notable for the absence of myoepithelial cells, which typically serve as a key

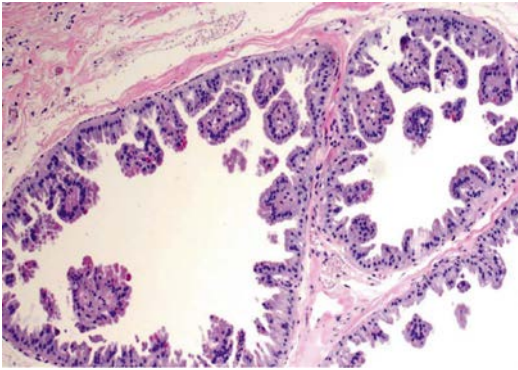


Fig. 18.9 Apocrine metaplasia

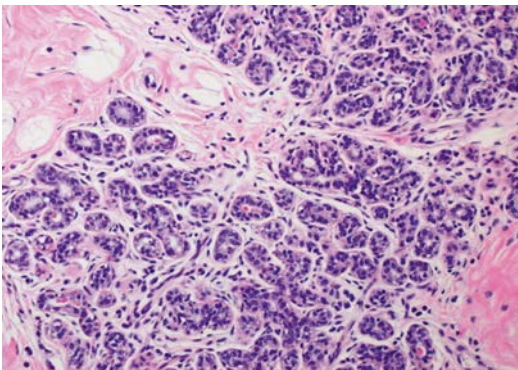


Fig. 18.10 Ductal adenosis

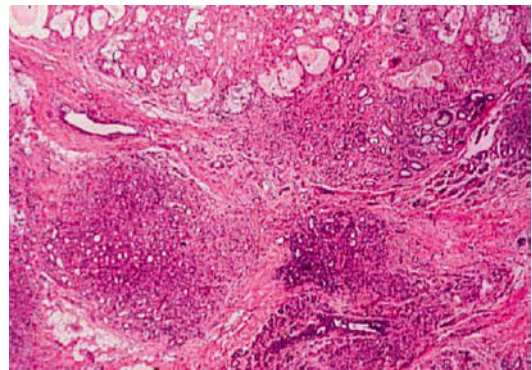


Fig. 18.11 Sclerosing adenosis

marker of benignity. Diagnostic features are presences of small, round tubular glands with wide lumens, distributed haphazardly in fibrous or adipose tissue. There is no stromal reaction or inflammation. Uniform tubules, often filled with dense eosinophilic secretions. Luminal cells are lined solely by a basement membrane. Cytoplasm may appear clear; apical snouts are absent. Differential diagnosis includes invasive tubular carcinoma (which shows desmoplasia and cytologic atypia) and sclerosing adenosis (which retains lobulocentric pattern and myoepithelial cells) [21]. Best confirmed with immunohistochemistry (loss of myoepithelial markers, but retention of basement membrane integrity via collagen IV or laminin staining) (Fig. 18.12). *Adenomyoepithelial (apocrine) adenosis* represents a form of microglandular adenosis with apocrine metaplasia, characterized by the presence of myoepithelial cells surrounding glandular structures. The presence of a myoepithelial layer or a continuous basement membrane rules out malignancy. Apart from the sclerosing subtype, adenoses are generally well-circumscribed [22–25].

- *Radial sclerosing lesion/complex sclerosing lesion*: According to the WHO classification, radial scars and complex sclerosing lesions represent a morphological continuum. Radial scar is ≤ 1 cm diameter, while complex sclerosing lesion is >1 cm.

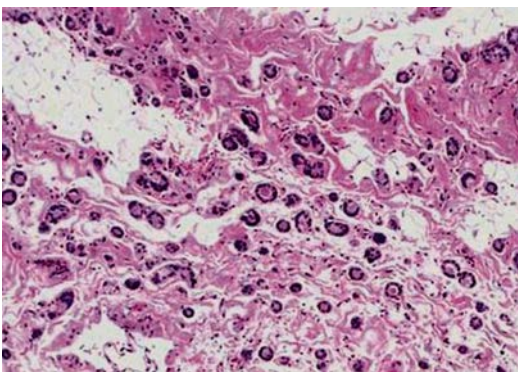


Fig. 18.12 Microglandular adenosis

Morphologically, there is a central fibroelastotic nidus with radiating entrapped ducts and lobules, forming a stellate pattern. These lesions may contain cysts, apocrine metaplasia, epithelial hyperplasia, and intraductal papillary structures. Despite their benign nature, their architectural complexity and radiologic features may mimic invasive carcinoma.

- *Small duct papillomas* arise in the TDLU and differ from large duct papillomas in etiology and clinical presentation. Microscopic features present fibrovascular cores lined by double-layered epithelium. They are located in small ducts deep in the breast. They are often associated with other proliferative lesions. Features suggestive of papillary carcinoma are monomorphic cell populations, absence of myoepithelial cells, presence of cribriform or micropapillary patterns, stromal hyalinization, and absence of apocrine differentiation (Fig. 18.12).
- *Proliferative breast disease without atypia* (1.5–2× increased risk) includes moderate to florid ductal hyperplasia, sclerosing adenosis, intraductal papilloma, complex sclerosing lesions (including radial scars), fibroadenomas with complex features such as apocrine cysts, sclerosing adenosis, and columnar cell changes (with or without flat epithelial atypia). Benign epithelial proliferative lesions of the breast include a spectrum of intraductal proliferations with varying degrees of cytological and architectural complexity [26]. These lesions primarily arise from the terminal duct lobular unit (TDLU) and are regarded as part of a morphologic continuum that ranges from benign hyperplasia to in situ carcinoma. Despite the WHO classification traditionally focusing on neoplasms, these lesions are discussed under epithelial tumors due to their recognized role as precursors to low-grade breast carcinomas, especially tubular carcinoma and low-grade ductal carcinoma in situ (DCIS).
- *Columnar cell lesions (CCLs)* represent clonal epithelial proliferations of the

TDLU, often identified in biopsies performed for suspicious calcifications on mammography. They include columnar cell change (CCC), columnar cell hyperplasia (CCH), and flat epithelial atypia (FEA). These entities may coexist within the same lobule or duct and should be considered part of a pathobiologic spectrum, rather than mutually exclusive diagnoses. In CCC, lining of one to two layers of tall columnar cells with oval, basally oriented nuclei are seen. Nucleoli are absent or inconspicuous. Apical cytoplasmic blebs and intraluminal secretions are frequently observed, and luminal calcifications are common. CCH has similar cytology to CCC but with >2 layers of cells. It shows nuclear crowding and stratification. Apical snouts and secretory debris are more prominent. Nuclei are still monomorphic without atypia. FEA is defined by low-grade cytologic atypia in one or more layers of flat epithelial cells (Fig. 18.13). Acini may appear round and expanded, lined by cuboidal or columnar cells. Nuclear polarity loss, hyperchromasia, increased N/C ratio, and prominent nucleoli are determined. Psammoma body-like calcifications may be seen. Considered the earliest form of low-grade

DCIS and a potential precursor to tubular carcinoma [27].

- *Usual ductal hyperplasia (UDH)* is a benign, non-clonal epithelial proliferation with heterogeneous architecture and cytology. Morphological features are bridging epithelial proliferations within ducts (micropapillary, fenestrated, or solid). There is peripheral streaming pattern where cells are parallel to bridges (in contrast to the perpendicular arrangement in DCIS). Tufts and fenestrations form secondary lumina. Cell borders are indistinct; nuclear size and shape are variable. No mitotic figures or necrosis are determined. UDH is classified by thickness. Mild form is constituted 2–4 cell layers. In moderate to severe UDH, there is nearly complete ductal filling without cytologic atypia. UDH is associated with a 1.5–2 $\times$ increased risk of subsequent breast carcinoma, although its predictive value is significantly lower than that of atypical hyperplasias or in situ carcinomas [28–30].
- *Atypical hyperplastic lesions* (4–5 $\times$ increased risk) include atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH). For example, atypical ductal hyperplasia (ADH) morphologically resembles

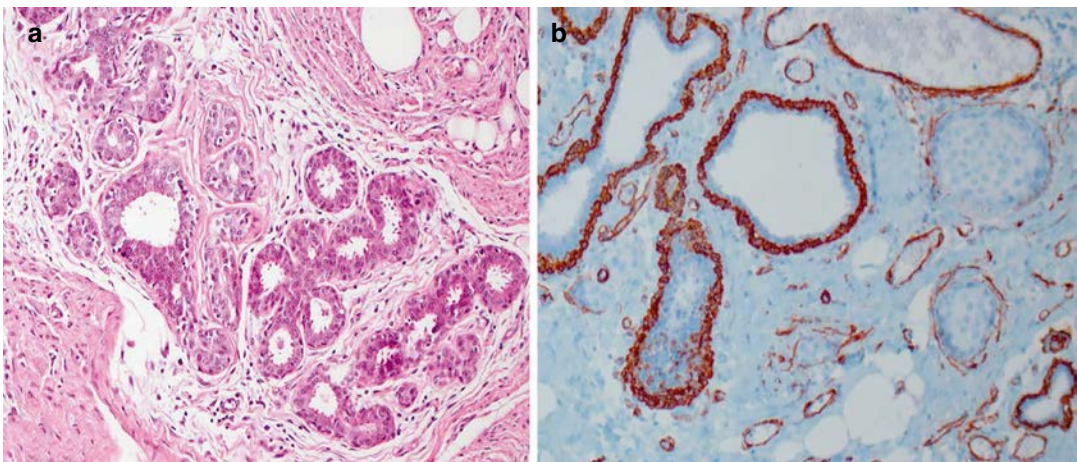


Fig. 18.13 (a) FEA. (b) Presence of myoepithelial cells with smooth muscle actin (SMA)

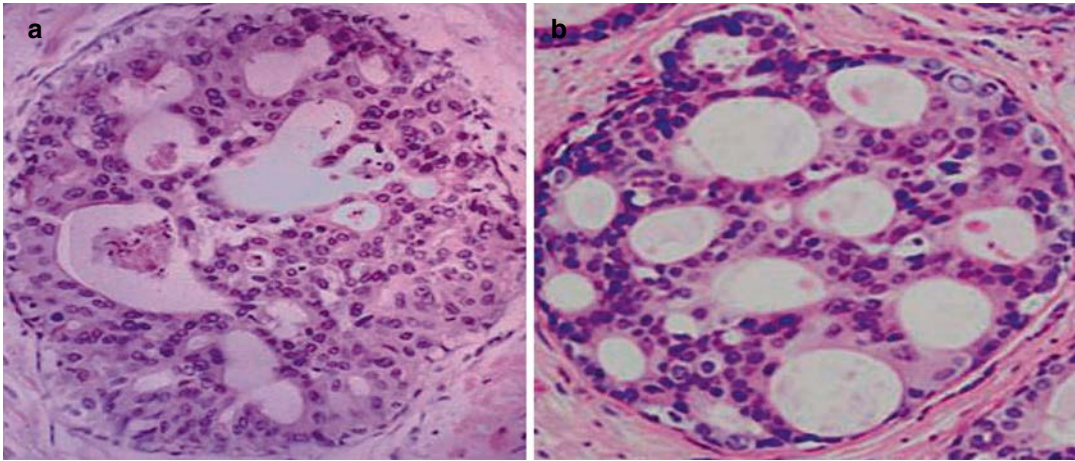


Fig. 18.14 (a) Streaming pattern in UDH. (b) Romen bridges in DCIS

low-grade ductal carcinoma in situ (DCIS) but lacks the full criteria for a definitive DCIS diagnosis. Diagnostic features are monotonous, low-grade epithelial cells forming radial, perpendicular arrangements around uniform luminal spaces; cribriform, micropapillary, or solid architectural patterns may be present; lesions partially fill the ductal lumen, unlike DCIS which usually involves the entire duct; and streaming pattern is absent (Fig. 18.14). These lesions will be discussed separately in the next chapter due to their neoplastic nature [31].

References

- Howard BA, Gusterson BA. Human breast development. *J Mammary Gland Biol Neoplasia*. 2020;25(1):3–17. <https://doi.org/10.1007/s10911-019-09442-3>.
- Dontu G, Ince TA. Intratumoral heterogeneity and its implications for cancer therapy. *J Pathol*. 2021;254(2):165–76. <https://doi.org/10.1002/path.5486>.
- Gatalica Z, Torlakovic EE. Pathology of the breast: recent advances and clinical implications. *Curr Oncol Rep*. 2020;22(5):49. <https://doi.org/10.1007/s11912-020-00910-0>.
- Bhargava R, Dabbs DJ. Immunohistology of the breast. In: Dabbs DJ, editor. *Diagnostic immunohistochemistry*. 5th ed. Elsevier; 2019. p. 563–617.
- Riera-Domingo C, Audigé A, Granja S, et al. Apocrine differentiation in breast cancer. *Breast Cancer Res Treat*. 2019;175(2):379–88. <https://doi.org/10.1007/s10549-019-05203-z>.
- Huo L, Zhang J, Gilcrease MZ, Gong Y, Wu Y, Zhang H, Resetskova E, Hunt KK, Deavers MT. Gross cystic disease fluid protein-15 and mammaglobin A expression determined by immunohistochemistry is of limited utility in triple-negative breast cancer. *Histopathology*. 2013;62(2):267–74. <https://doi.org/10.1111/j.1365-2559.2012.04344.x>.
- Cimino-Mathews A. Myoepithelial cells in breast cancer. *Adv Anat Pathol*. 2021;28(2):109–21. <https://doi.org/10.1097/PAP.0000000000000286>.
- Hassiotou F, Geddes DT. Anatomy of the human mammary gland: current status of knowledge. *Clin Anat*. 2019;32(2):250–66. <https://doi.org/10.1002/ca.23292>.
- Tiwari A, Srivastava G, Jain S. Accessory breast tissue: clinical presentation and diagnostic challenges. *Cureus*. 2021;13(4):e14419. <https://doi.org/10.7759/cureus.14419>.
- Pinder SE, Shaaban AM, Deb R. The terminal duct lobular unit: the anatomical and functional unit of the breast. *Histopathology*. 2021;79(6):904–15. <https://doi.org/10.1111/his.14397>.
- Secreto G, Zumoff B. Role of hormones in human breast cancer. *Endocrinol Metab Clin N Am*. 2022;51(1):107–26. <https://doi.org/10.1016/j.ecl.2021.09.006>.
- Sapino A, Marchiò C. Morphological and molecular features of pregnancy-like and clear cell changes in the breast. *Pathologica*. 2020;112(3):169–79. <https://doi.org/10.32074/1591-951X-42>.
- Schnitt SJ. Classification and prognosis of benign breast lesions: the impact of modern imaging and molecular biology. *Mod Pathol*. 2022;35(S1):44–54. <https://doi.org/10.1038/s41379-021-00945-4>.
- Lakhani SR, et al. *WHO classification of tumours of the breast*. 5th ed. IARC Press; 2019.

15. Rakha EA, Ellis IO. Diagnostic criteria and reproducibility of breast carcinoma classification. *Histopathology*. 2018;72(1):5–13. <https://doi.org/10.1111/his.13319>.
16. Badve S, Schnitt SJ, Baehner FL, et al. Interobserver variability in histologic evaluation of fibrocystic changes and atypical proliferative lesions. *Am J Surg Pathol*. 2019;43(10):1409–16. <https://doi.org/10.1097/PAS.0000000000001279>.
17. Schnitt SJ. Classification and histological risk stratification of benign breast lesions. *Mod Pathol*. 2022;35(S1):28–43. <https://doi.org/10.1038/s41379-021-00944-5>.
18. Guray M, Sahin AA. Benign breast diseases: classification, diagnosis, and management. *Oncologist*. 2020;25(4):e692–701. <https://doi.org/10.1634/theoncologist.2019-0674>.
19. Tan PH, Ellis IO, Allison KH, et al. The WHO classification of tumours of the breast. 5th ed. IARC; 2019.
20. Abdel-Fatah TMA, Powe DG, Hodi Z, et al. Morphologic and molecular characterization of apocrine-like lesions of the breast. *Histopathology*. 2018;73(3):397–407. <https://doi.org/10.1111/his.13662>.
21. Rakha EA, Ahmed MA, Ellis IO. Benign breast lesions: classification and diagnostic challenges. *Mod Pathol*. 2022;35(S1):6–27. <https://doi.org/10.1038/s41379-021-00941-8>.
22. Rosen PP, et al. Microglandular adenosis of the breast: a clinicopathologic study with long-term follow-up. *Am J Surg Pathol*. 2019;43(2):178–88. <https://doi.org/10.1097/PAS.0000000000001014>.
23. Varga Z, et al. Sclerosing adenosis of the breast: diagnostic pitfall. *Pathol Res Pract*. 2021;224:153561. <https://doi.org/10.1016/j.prp.2021.153561>.
24. Grabellus F, et al. Microglandular adenosis and its association with triple-negative breast carcinomas. *Pathol Int*. 2018;68(12):687–95. <https://doi.org/10.1111/pin.12764>.
25. Kwon J, et al. Radial scar of the breast: histological spectrum and diagnostic challenge. *J Pathol Transl Med*. 2021;55(2):122–9. <https://doi.org/10.4132/jptm.2020.08.04>.
26. Shaaban AM, et al. Risk stratification of proliferative breast lesions. *Histopathology*. 2017;70(4):548–65. <https://doi.org/10.1111/his.13127>.
27. Bleiweiss IJ. Columnar cell lesions and atypical hyperplasias: precursors or passengers? *Semin Diagn Pathol*. 2020;37(2):79–87. <https://doi.org/10.1053/j.semdp.2020.03.001>.
28. Allison KH, et al. WHO classification of breast epithelial lesions and their significance. *Mod Pathol*. 2022;35(S1):28–44. <https://doi.org/10.1038/s41379-021-00944-5>.
29. Schnitt SJ. Atypical ductal hyperplasia: current concepts and challenges. *Adv Anat Pathol*. 2019;26(4):255–63. <https://doi.org/10.1097/PAP.0000000000000235>.
30. Abdel-Fatah TMA, et al. Diagnostic reproducibility and clinical significance of atypical ductal hyperplasia. *Am J Surg Pathol*. 2018;42(9):1196–206. <https://doi.org/10.1097/PAS.0000000000001116>.
31. Murray M, et al. Atypical lobular hyperplasia and lobular carcinoma in situ: diagnostic criteria and clinical management. *Pathology*. 2021;53(4):421–30. <https://doi.org/10.1016/j.pathol.2021.03.003>.

19.1 Introduction

Breast neoplasms represent a highly heterogeneous group of lesions that encompass benign, atypical, and malignant proliferations originating from both epithelial and stromal components of the breast. These neoplasms range from common benign entities such as fibroadenomas and papillomas to a wide spectrum of in situ and invasive carcinomas, each with distinct histopathological, molecular, and clinical characteristics. The breast's unique composition of hormonally responsive epithelial and mesenchymal elements gives rise to several biphasic tumors as well, which are rarely encountered in other organs. Understanding the histogenetic origins, morphological diversity, and clinical behavior of breast tumors is essential for accurate diagnosis, prognostication, and therapeutic decision-making. With the advancement of immunohistochemistry and molecular profiling, the classification and risk stratification of breast neoplasms continue to evolve, enhancing personalized approaches in patient care. Breast neoplasms originate from

epithelial cells, epithelial-myoepithelial cells, and stromal cells [1–5].

19.2 Epithelial Tumors

Epithelial tumors of the breast are broadly categorized into benign and malignant groups. Benign epithelial tumors are characterized by the absence of stromal neoplastic components and include adenomas, intraductal papillomas, and nipple adenomas.

Adenomas of the breast are further subclassified into tubular adenoma, lactating adenoma, and apocrine adenoma. *Tubular adenoma* is typically observed in young adult women and presents as a solitary, firm, well-circumscribed, yellow-tan mass. Histologically, the stroma is sparse and disorganized, while the epithelial component comprises tightly packed ducts lined by both epithelial and myoepithelial cells. When all lining cells exhibit apocrine morphology, the lesion is termed an *apocrine adenoma*.

Lactating adenoma is a hyperplastic lesion seen during pregnancy and lactation. It is typically presented as a palpable, well-defined, solitary, or multiple nodule. Although most commonly arising in the breast, ectopic lactating adenomas can occur in the axilla, chest wall, or vulva. Microscopically, the lesion is composed of proliferative glandular elements lined by cuboidal epithelial cells with prominent vacuolization,

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indicative of active secretion. The glandular lumina are often distended, and foci of necrosis are frequently observed.

19.2.1 Large Duct Papilloma (Intraductal Papilloma)

Large duct papillomas, also known as *intraductal papillomas*, originate from the lactiferous ducts or sinuses. These lesions represent true neoplasms arising from a clonal proliferation of ductal epithelial cells. Unlike small duct papillomas, they are most often solitary and can form palpable masses, usually smaller than 3 cm. The average age at presentation is 48 years. In approximately 80% of patients, the lesion is associated with serous or bloody nipple discharge. Macroscopically, they appear as papillary structures within cystic spaces, typically less than 1 cm in diameter. Histologically, they are composed of fibrovascular cores lined by a double layer of epithelial and myoepithelial cells. Common features include apocrine metaplasia and infarction. Solitary intraductal papillomas are considered benign and are not regarded as precursors to papillary carcinoma. In contrast, small duct papillomas are associated with a higher risk of malignant transformation. Features favoring benignity include the presence of mature fibrous stroma, a double-layered epithelial covering (Fig. 19.1), absence of mitoses and necrosis, and lack of cribriform or trabecular architecture. Myoepithelial cells in the papillary projections can be highlighted using high molecular weight cytokeratin, p63, calponin, or S-100 protein immunostaining. Partial or complete hemorrhagic infarction can occasionally occur within a papilloma. This should not be mistaken for tumor necrosis or evidence of malignancy. Adjacent to infarcted areas, squamous metaplasia may be observed in the epithelial lining. However, the presence of an extensive squamous component within any breast lesion should always raise the suspicion of malignancy. When a papilloma develops within a large duct but lacks prominent, branching papillary projections, the lesion is classified as a *ductal adenoma*. In Carney com-

plex, ductal adenomas with prominent tubular differentiation have been reported.

Nipple adenoma is also known as florid papillomatosis of the nipple or erosive adenomatosis, nipple adenoma refers to a localized neoplastic proliferation involving the lactiferous ducts and the nipple epithelium. It is typically unilateral and most frequently observed between 30 and 50 years of age. Patients often present with nipple discharge, erosion, or crusting, which can mimic Paget's disease of the nipple. In approximately 16% of cases, an associated or subsequent carcinoma may be present. For this reason, distinguishing nipple adenoma from intraductal papilloma is critical. Histologically, the lesion is composed of papillary ductal structures often accompanied by dense, sometimes sclerotic stroma, a condition referred to as sclerosing papillomatosis. The presence of myoepithelial cells is an important feature that helps differentiate it from carcinoma. Immunohistochemical staining for p63, S-100, or calponin highlights the myoepithelial layer. In uncomplicated cases, simple local excision is usually curative. However, in lesions with extensive squamous metaplasia or atypical features, close histological evaluation is warranted due to the potential risk of malignancy.

19.3 Atypical Ductal Hyperplasia (ADH)

Atypical ductal hyperplasia (ADH) is a clonal intraductal epithelial proliferation characterized by architectural and cytologic features similar to low-grade DCIS but limited in extent and distribution. It falls under the category of high-risk breast lesions [1–5].

19.3.1 Pathogenesis

Clonal proliferation of ductal epithelial cells with partial architectural and cytologic atypia. Frequent loss of heterozygosity (LOH) at chromosome 16q and gain at 1q, which are also seen in DCIS and low-grade invasive ductal carci-

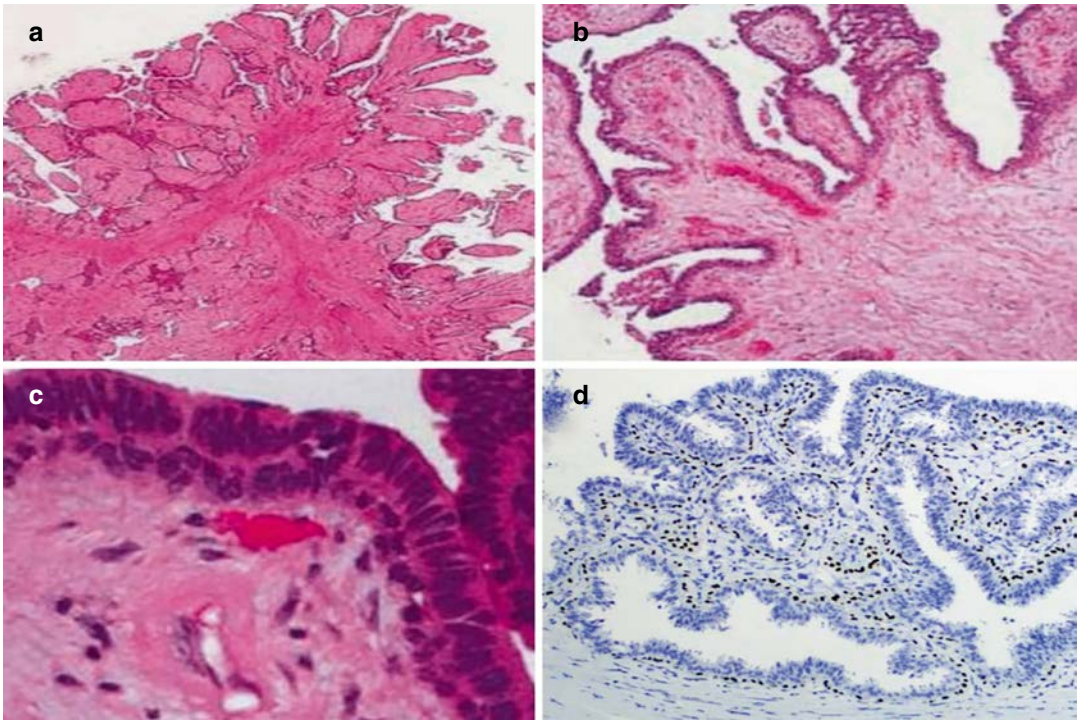


Fig. 19.1 (a) Intraductal papilloma. (b) Papillary projections with mature fibrous stroma. (c) Double-layered epithelial covering. (d) Presence of myoepithelial cells is highlighted by P63 immunohistochemistry

noma. Estrogen receptor (ER) positivity is common, indicating hormone-driven growth. Lack of high-level genomic instability; low proliferative index [1–5].

19.3.2 Histological Features

Composed of monomorphic epithelial cells with round to oval nuclei and small nucleoli. May exhibit cribriform, solid, or micropapillary architecture. Involves less than 2 mm of contiguous ductal space or fewer than two adjacent ducts. Shows partial loss of polarity and mild cytologic atypia [1].

19.3.3 Immunohistochemistry

Estrogen receptor (ER): positive in most cases. CK5/6: typically negative, indicating clonal proliferation (distinguishing from usual ductal

hyperplasia). Myoepithelial markers (p63, SMA): preserved around ducts, indicating noninvasive nature [1].

19.3.4 Clinical Significance

ADH is considered a risk factor for the development of breast cancer, with a four- to fivefold increased lifetime risk. Approximately 10–30% of ADH diagnosed on core needle biopsy may be upgraded to DCIS or invasive carcinoma upon surgical excision [1–5].

19.3.5 Management

Diagnosis is often made via core needle biopsy. Surgical excision is recommended to rule out co-existing higher-grade lesions. Patients are generally placed under increased surveillance and may be considered for chemoprevention [1–5].

19.4 Atypical Lobular Hyperplasia (ALH)

Atypical lobular hyperplasia is a clonal proliferation of discohesive epithelial cells partially filling the acini of a lobular unit. It shares cytologic features with LCIS but is limited in extent [1–5].

19.4.1 Pathogenesis

Characterized by clonal proliferation of small, discohesive epithelial cells within the terminal duct-lobular unit (TDLU). Loss of E-cadherin expression (CDH1 gene inactivation), a hallmark of lobular lesions, leading to cell discohesion. ER and progesterone receptor (PR) positivity is typical, supporting a hormone-responsive pathway. Alterations include 16q loss and 1q gain, similar to lobular carcinoma in situ and lobular carcinoma [1–5].

19.4.2 Histologic Features

Involves some but not all acini of a lobular unit. Small, uniform, discohesive cells with round nuclei and inconspicuous nucleoli. No significant nuclear pleomorphism or necrosis. Loss of normal acinar architecture is partial. E-cadherin negative (loss of membrane expression) [1–5].

19.4.3 Clinical Relevance

ALH is associated with a 1.5–2 fold increased risk of developing breast cancer in either breast. It is not an obligate precursor, but a risk indicator. Often discovered incidentally during biopsy for other findings [1–5].

19.4.4 Management

No surgery is required if ALH is the only finding on core biopsy and radiology is concordant. Patients require clinical and radiologic follow-up. Consider chemoprevention in selected high-risk patients.

19.5 Ductal Carcinoma In Situ (DCIS)

DCIS is a noninvasive breast carcinoma, defined as a proliferation of malignant epithelial cells confined to the ductal-lobular system without evidence of invasion beyond the basement membrane. It is considered a direct precursor to invasive ductal carcinoma [1–5].

19.5.1 Pathogenesis

Common molecular alterations: 16q loss, 1q gain (especially in low-grade DCIS), HER2 amplification, and TP53 mutations in high-grade DCIS. Subtype-specific differences: low-grade DCIS, ER-positive, HER2-negative, and low proliferation, and high-grade DCIS, ER-negative or variable, HER2-positive or TP53-mutated, high proliferation, and often with necrosis [6, 7].

19.5.2 Histological Subtypes

- *Cribriform*: Contains uniform punched-out spaces within neoplastic ducts (Fig. 19.2).
- *Solid*: Ducts filled entirely with neoplastic cells.
- *Micropapillary*: Delicate epithelial tufts protrude into the lumen without fibrovascular cores.

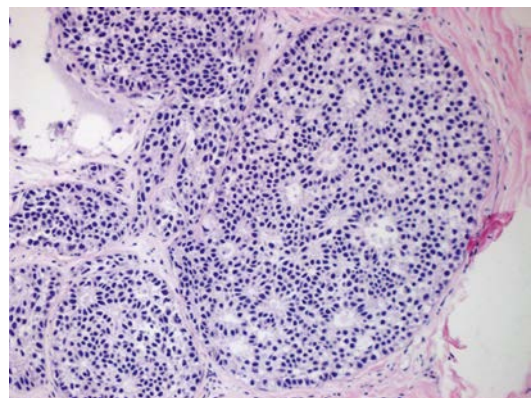


Fig. 19.2 Cribriform ductal carcinoma in situ composed of uniform punched-out spaces within neoplastic ducts

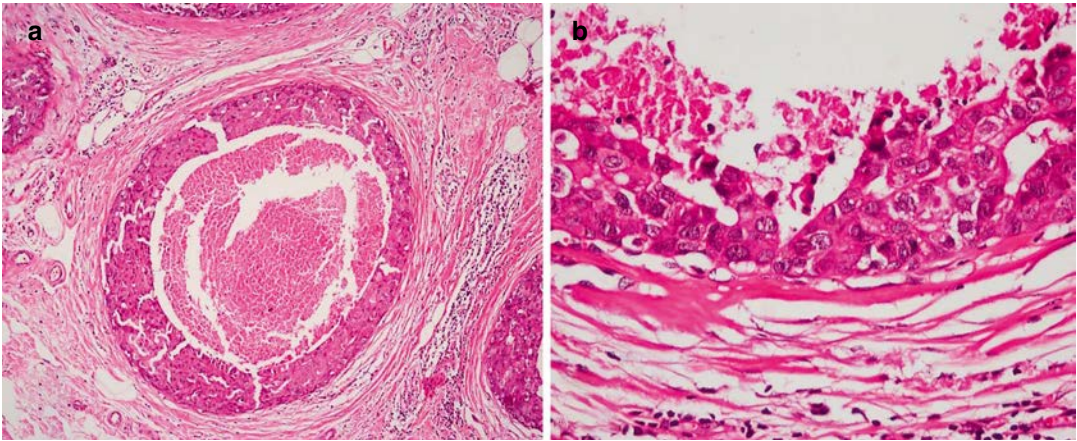


Fig. 19.3 Comedo type ductal carcinoma in situ characterized by central necrosis (a) and high-grade nuclei (b)

- *Papillary*: True fibrovascular cores lined by neoplastic epithelium.
- *Comedo*: Characterized by high-grade nuclei and central necrosis (“comedonecrosis”) (Fig. 19.3).

Nuclear Grading: Low-grade, small, uniform nuclei with rare mitoses. Intermediate-grade, moderate pleomorphism and mitotic activity. High-grade, large, pleomorphic nuclei, prominent nucleoli, frequent mitoses, and often with necrosis [1–6].

Immunohistochemical and Molecular Features: ER/PR, often positive in low-grade DCIS. HER2, frequently overexpressed in high-grade DCIS. Myoepithelial cell layer is intact (highlighted by p63, SMA), distinguishing DCIS from invasive carcinoma [1–5].

19.5.3 Clinical Presentation

It is often asymptomatic carcinoma, and standard cases are detected via screening mammography showing microcalcifications. It may present with nipple discharge or a palpable mass, especially in comedo-type [1].

19.5.4 Treatment

Surgical excision: Lumpectomy or mastectomy depending on lesion size, location, and patient

preference. **Radiotherapy**: Typically recommended after breast-conserving surgery. **Endocrine therapy**: tamoxifen or aromatase inhibitors for ER-positive lesions to reduce recurrence risk. **Sentinel lymph node biopsy**: considered in selected high-risk or large DCIS cases [6, 7].

19.6 Lobular Carcinoma In Situ (LCIS)

LCIS is a clonal proliferation of discohesive, neoplastic epithelial cells involving and expanding all acini of a lobular unit while remaining confined by the basement membrane [1–5].

19.6.1 Pathogenesis

CDH1 gene mutations leading to loss of E-cadherin, resulting in the hallmark discohesive cell morphology. Genomic alterations are similar to ALH: loss of 16q, gain of 1q, and chromosomal instability low in classic LCIS; it is more prominent in pleomorphic variants. ER and PR positivity supports hormonal sensitivity. Pleomorphic LCIS may have TP53 mutations, higher-grade features, and more aggressive behavior [1–5].

Histologic subtypes: *classic LCIS (cLCIS)*, small, uniform, discohesive cells that fill and distend lobules. Bland nuclei, with no necrosis or

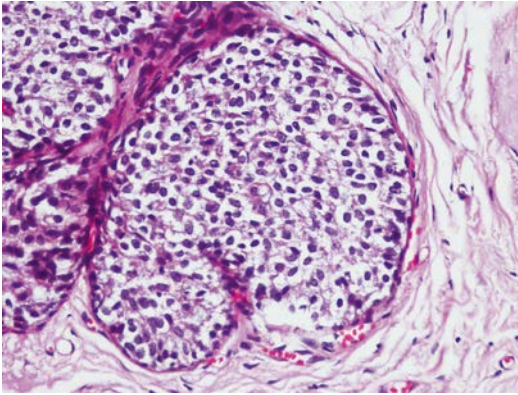


Fig. 19.4 Classic LCIS composed of small, uniform, discohesive cells fill and distend lobules

mitoses (Fig. 19.4). Loss of E-cadherin expression. Pleomorphic LCIS (pLCIS): larger cells with nuclear pleomorphism, prominent nucleoli, and necrosis; may mimic high-grade DCIS. It is considered more aggressive than cLCIS. Florid LCIS: extensive lobular involvement with massive expansion. Necrosis and calcification can be seen [1, 8].

19.6.2 Immunohistochemistry

E-cadherin: Negative (key feature distinguishing from ductal lesions). ER/PR: Usually positive in classic LCIS. HER2: Typically negative [1–5, 8].

19.6.3 Clinical Relevance

LCIS is both a risk marker and a non-obligate precursor for invasive carcinoma (ductal or lobular). Associated with a seven- to tenfold increased risk of breast cancer in both breasts. Risk persists for decades and is bilateral.

19.6.4 Detection

Often not palpable and not visible on imaging unless associated with calcifications (especially

in pleomorphic or florid types). Usually diagnosed incidentally on core biopsy.

19.6.5 Management

Classic LCIS: Surgical excision may not be needed if radiologic-pathologic concordance is achieved. *Close surveillance* and *chemoprevention* are considered. *Bilateral risk* requires comprehensive counseling.

Pleomorphic/Florid LCIS: Treated similarly to DCIS due to higher progression risk. Requires *surgical excision*, possibly followed by *radiation* or *endocrine therapy* [9].

19.7 Paget's Disease of the Nipple (Mammary Paget's Disease)

Paget's disease is a rare form of in situ breast carcinoma involving the epidermis of the nipple-areolar complex, almost always associated with underlying ductal carcinoma in situ (DCIS) or invasive ductal carcinoma (IDC) [1–5, 10]

19.7.1 Pathogenesis

Believed to arise from epidermotropic migration of malignant ductal epithelial cells (Paget cells) from underlying carcinoma through lactiferous ducts to the nipple epidermis. Less commonly, it may represent an intraepidermal carcinoma in situ arising independently [10].

19.7.2 Histopathology

Presence of Paget cells: large cells with abundant pale cytoplasm, pleomorphic nuclei, and prominent nucleoli within the epidermis. Often seen scattered singly or in small clusters in the basal or suprabasal layers of the epidermis (Fig. 19.5). Frequently associated with underlying high-grade DCIS or invasive carcinoma [1–5].

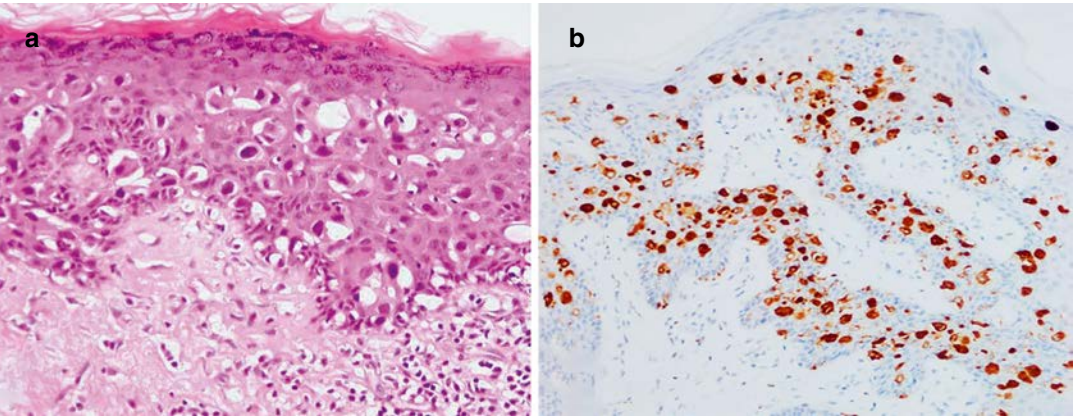


Fig. 19.5 (a) Paget cell are large cells with abundant pale cytoplasm, pleomorphic nuclei, and prominent nucleoli within the epidermis. (b) Cytokeratin 7 positivity in Paget cells

19.7.3 Immunohistochemistry [11]

Marker	Result
CK7	Positive (strong, diffuse)
HER2	Often <i>overexpressed/amplified</i>
CEA	Positive
EMA	Positive
S100/HMB-45	Negative (helps exclude melanoma)

Important: Differentiate from malignant melanoma or eczema clinically and histologically.

Clinical Features: Erythematous, scaly, crusted lesion of the nipple and areola, often resembling eczema. May be associated with itching, burning, or oozing. Often unilateral. Can precede, coincide with, or follow diagnosis of underlying carcinoma.

Diagnosis: Skin biopsy of the nipple lesion is diagnostic. Mammography and/or MRI are essential to assess for underlying malignancy.

Treatment: Depends on the presence and extent of underlying carcinoma—mastectomy (most common), breast-conserving surgery + radiation (in selected cases) HER2-targeted therapy if HER2-positive.

Prognosis: Determined by the nature of the underlying carcinoma. Paget’s disease without palpable mass or invasion has a relatively good prognosis [12].

19.8 Breast Carcinomas

Breast cancer is the most common type of cancer in women and represents a significant cause of cancer-related mortality. Although it can also occur in men, it is much more common in women. It is the most frequently diagnosed invasive cancer in women worldwide. The lifetime risk for a woman to develop breast cancer is approximately 12% (1 in 8). The incidence is higher in developed countries, but due to widespread screening programs and early detection, mortality rates have decreased over the years. Male breast cancer accounts for about 1% of all breast cancer cases.

Risk Factors: Risk factors are grouped into *non-modifiable* and *modifiable* categories.

1. *Non-modifiable Risk Factors*

- Female sex—the primary risk determinant
- Advancing age—risk increases with age

- Family history—especially breast or ovarian cancer in first-degree relatives
- Inherited mutations—particularly in BRCA1 and BRCA2 genes
- Personal history of breast cancer
- Dense breast tissue—higher proportion of fibroglandular tissue on imaging
- High-risk histologic lesions—such as atypical hyperplasia or lobular carcinoma in situ (LCIS) [4]

2. Modifiable Risk Factors

- Obesity, particularly in postmenopausal women
- Alcohol consumption
- Radiation exposure—especially therapeutic radiation to the chest during adolescence or early adulthood
- Physical inactivity
- Long-term hormone replacement therapy (HRT)
- Early menarche (before age 12)
- Late menopause (after age 55)
- Nulliparity (never having given birth) or late first childbirth [4]

19.8.1 Pathogenesis

Breast cancer develops through a multistep process in which normal epithelial cells acquire genetic and epigenetic alterations that lead to atypical hyperplasia, carcinoma in situ, and ultimately invasive carcinoma. This progression involves dysregulation in cellular proliferation, apoptosis, DNA repair, hormonal signaling, and tumor-stromal interactions [1–5, 13, 14].

1. Cellular Origin and Progression

- Most breast carcinomas arise from ductal or lobular epithelium.
- Cells of origin are believed to be luminal progenitor cells or basal epithelial cells.
- The histological progression is as follows:
Normal epithelium → hyperplasia → atypical hyperplasia → carcinoma in situ (DCIS/LCIS) → invasive carcinoma [1–5]

2. Molecular Pathways Involved [1–5, 14, 15]

Gene/pathway	Effect	Associated subtype
BRCA1/BRCA2	Impaired DNA repair via homologous recombination	Triple-negative, basal-like
TP53	Cell cycle arrest and apoptosis failure	HER2+ and basal-like tumors
PIK3CA	Activation of PI3K/AKT pathway → proliferation	Luminal A and B
HER2 (ERBB2)	RTK amplification → MAPK/PI3K pathway	HER2-enriched tumors
GATA3, FOXA1	Luminal cell differentiation	Luminal A/B
MYC, CCND1 (cyclin D1)	Increased cell cycle progression	ER-positive tumors

- ### 3. Epigenetic Mechanisms:
- DNA methylation, histone modifications, and microRNA alterations silence tumor suppressor genes (e.g., CDH1 → E-cadherin loss → lobular carcinoma invasion).

4. Hormonal Signaling

Estrogen receptor (ER) drives gene expression and cell proliferation. ER-positive tumors respond to anti-estrogen therapies (tamoxifen, aromatase inhibitors).

5. Tumor Microenvironment and EMT

Cancer-associated fibroblasts (CAFs), immune cells, and angiogenic signals (VEGF) contribute to tumor progression. Epithelial-mesenchymal transition (EMT): Loss of E-cadherin leads to increased invasiveness.

6. Immune Escape and Inflammation

Tumors express PD-L1 to evade immune response. Tumor-infiltrating lymphocytes (TILs) are abundant in triple-negative and HER2+ tumors, predicting better response to immunotherapy.

7. *Molecular Subtypes (Based on IHC Profiles)*
Estrogen receptor (ER), progesterone receptor (PR), HER2 status, and the Ki-67 proliferation index are the principal parameters used in the molecular subtyping of breast cancers based on immunohistochemical (IHC) profiles [14].

19.8.2 Estrogen Receptor (ER) and Progesterone Receptor (PR)

ER and PR are nuclear hormone receptors expressed in a subset of breast cancers. Their presence indicates hormone-responsive tumors, which generally have a better prognosis and respond well to endocrine therapy.

Interpretation of ER and PR status

Receptor status	Interpretation	Treatment implications
ER/PR positive	Hormone receptor-positive tumor	Eligible for hormone therapy (e.g., tamoxifen, aromatase inhibitors)
ER/PR negative	Hormone receptor-negative tumor	Not responsive to endocrine therapy; consider chemotherapy

19.8.3 Ki-67 Proliferation Index

Ki-67 is a nuclear protein expressed during active phases of the cell cycle but not in resting cells. It serves as a marker of tumor proliferation.

Interpretation of Ki-67 index

Ki-67 index (%)	Interpretation	Clinical implication
<10%	Low proliferation	Favorable prognosis; often luminal A subtype
10–20%	Intermediate proliferation	Variable prognosis; clinical context matters
>20%	High proliferation	More aggressive tumor; may benefit from chemotherapy

19.8.4 Human Epidermal Growth Factor Receptor 2 (HER2)

Her 2 is a trans membrane tyrosine kinase receptor involved in cell growth, proliferation, and survival. It is encoded by the ERBB2 gene on chromosome 17q12. While normally expressed in low amounts in epithelial cells, it is amplified or overexpressed in approximately 15–20% of invasive breast cancers. HER2-positive breast cancers tend to be more aggressive, have a higher proliferation rate, and are less responsive to hormone therapy if ER/PR negative. However, they respond well to HER2-targeted therapies such as trastuzumab. HER2 status is critical for prognosis and treatment planning.

19.8.5 Assessment of HER2 Status

HER2 evaluation is mandatory in all newly diagnosed invasive breast cancers. It is assessed via two primary methods.

1. *Immunohistochemistry (IHC)*

Detects HER2 protein expression on the cell membrane. Scoring system (Fig. 19.6)

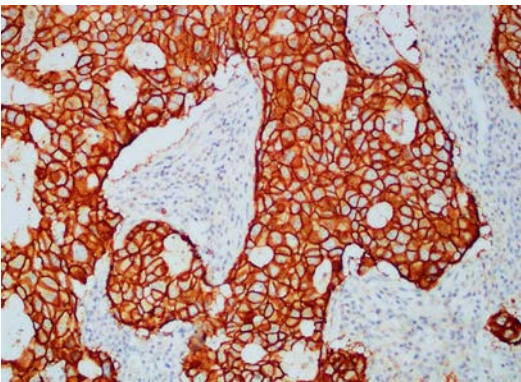


Fig. 19.6 Her2 status immunohistochemically which is strong membrane staining in >10% cells which is called HER 2 (3+)

Score	Interpretation	Action
0	Negative	No HER2 overexpression
1+	Negative	No HER2 overexpression
2+	Equivocal	Requires reflex testing with ISH
3+	Positive (strong membrane staining in >10% cells)	Eligible for HER2-targeted therapy

Subtype	ER	PR	HER2	Ki-67	Clinical notes
Luminal A	+	+	–	Low	Best prognosis, hormonal Rx
Luminal B	+	±	–/+	High	Intermediate prognosis
HER2-enriched	–	–	+	High	HER2-targeted therapy
Triple negative	–	–	–	High	Poor prognosis, basal-like

2. *In Situ Hybridization (ISH)*

Used when IHC score is 2+. It measures HER2 gene amplification by assessing the HER2/CEP17 ratio and gene copy number per cell.

Result	Interpretation
HER2/CEP17 ratio ≥ 2.0	HER2 amplified
HER2/CEP17 ratio < 2.0 and HER2 copies ≥ 6	HER2 amplified
HER2/CEP17 ratio < 2.0 and HER2 copies < 4	HER2 not amplified
Borderline results	Require expert review or repeat testing

19.8.6 Clinical Implications of HER2 Testing

HER2-positive cancers are treated with HER2-targeted agents such as:

- Trastuzumab (Herceptin)
- Pertuzumab
- T-DM1 (ado-trastuzumab emtansine)
- Lapatinib (for advanced/metastatic settings)

These therapies significantly improve survival outcomes.

- HER2 is both a prognostic and predictive marker. HER2 status must be reported along with ER and PR in all invasive breast cancer cases.—ASCO/CAP guidelines should be followed for HER2 testing and interpretation [16].

19.8.7 Familial Versus Sporadic Breast Cancer

Breast cancer can arise due to inherited (familial) or acquired (sporadic) genetic mutations. While they may present similarly, the underlying mechanisms, risk profiles, and clinical features differ significantly [17].

1. *Familial (Hereditary) Breast Cancer:* Cancers that arise due to inherited germline mutations, most often involving tumor suppressor genes

Molecular Pathogenesis:

- Germline mutations in high-penetrance genes: BRCA1 (chromosome 17q21), BRCA2 (chromosome 13q12), TP53 (Li-Fraumeni syndrome), PTEN (Cowden syndrome), PALB2, CHEK2, ATM (moderate-risk genes)
- Loss of heterozygosity leads to biallelic inactivation (Knudson’s two-hit hypothesis)
- DNA repair deficiency → genomic instability → malignant transformation.

2. *Sporadic Breast Cancer:* Cancers that occur due to somatic mutations acquired during life, unrelated to inherited gene defects.

Molecular Pathogenesis:

- Accumulated somatic mutations due to hormonal exposure, radiation, aging
- Common mutations: PIK3CA, TP53, HER2 amplification, CCND1, loss of RB, PTEN
- No inherited mutation; both hits are somatic

Comparison table: familial vs. sporadic breast cancer

Characteristic	Familial breast cancer	Sporadic breast cancer
Genetic basis	Germline mutation (inherited)	Somatic mutation (acquired)
Typical genes	BRCA1, BRCA2, TP53, PTEN	PIK3CA, TP53, HER2, CCND1
Age at diagnosis	Early (<50)	Usually >50
Bilateral tumors	More common	Rare
Associated syndromes	Yes (e.g. Li-Fraumeni)	No
Histologic subtypes	BRCA1: triple-negative	Luminal A/B, HER2+
Family history	Positive	Usually negative
Genetic testing	Recommended	Not routine

- BRCA1/2 mutations impair homologous recombination repair of DNA → sensitivity to PARP inhibitors.
- Triple-negative breast cancers (TNBC) are more frequent in BRCA1 mutation carriers.
- Even patients with “sporadic” cancers may harbor actionable mutations—so molecular profiling is often useful.

19.8.8 Histologic Types

Invasive Breast Carcinoma of No Special Type (NST) (Fig. 19.7)

(previously called invasive ductal carcinoma, not otherwise specified)

- Most common subtype (~70–80%).
- Irregular nests and cords of malignant epithelial cells infiltrating fibrous stroma.
- Desmoplastic reaction (dense fibrous tissue) is common.
- May show tubule formation, nuclear pleomorphism, and mitotic activity (used in grading).

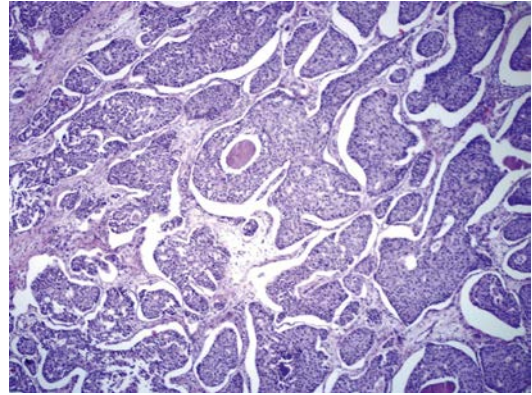


Fig. 19.7 Invasive breast carcinoma of no special type (NST), irregular nests and cords of malignant epithelial cells infiltrating fibrous stroma

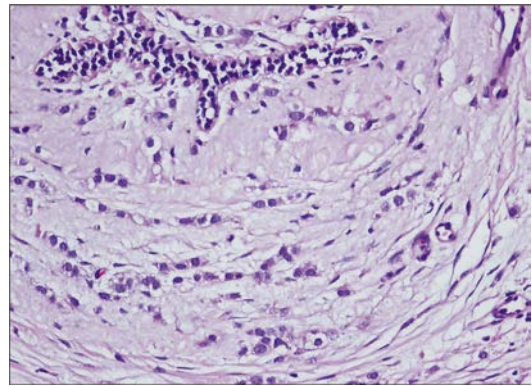


Fig. 19.8 Invasive lobular carcinoma is characterized by discohesive cells infiltrating in single-file lines or targetoid patterns

Invasive Lobular Carcinoma (ILC) (Fig. 19.8)

- Second most common (~10–15%).
- Characterized by discohesive cells infiltrating in single-file lines or targetoid patterns.
- Loss of E-cadherin expression (immunohistochemically negative).
- Often bilateral and multifocal.

Special Histological Types

(less common, but sometimes with prognostic significance)

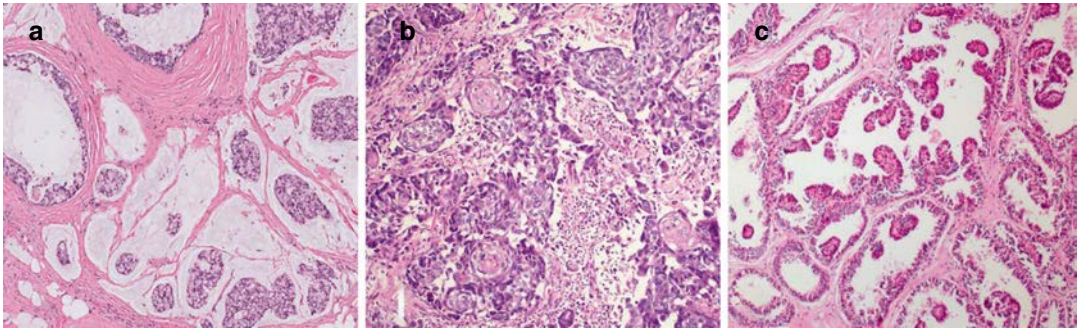


Fig. 19.9 (a) Mucinous (colloid) carcinoma. (b) Metaplastic carcinoma. (c) Papillary carcinoma

- *Tubular carcinoma*—well-differentiated, good prognosis.
- *Mucinous (colloid) carcinoma*—abundant mucin, better prognosis (Fig. 19.9a).
- *Metaplastic carcinoma*—aggressive, poor prognosis (Fig. 19.9b).
- Other special histological subtypes are *micro-papillary*, *papillary* (Fig. 19.9c), *secretory*, *apocrine*, *mucinous cystadenocarcinoma* NOS, *sebaceous carcinoma* types, etc. [1, 18].
- T1c: >10 mm but ≤20 mm
- T2: Tumor >2 cm but ≤5 cm
- T3: Tumor >5 cm
- T4: Tumor of any size with direct extension to chest wall and/or skin
 - T4a: Extension to chest wall
 - T4b: Ulceration and/or ipsilateral satellite skin nodules
 - T4c: Both T4a and T4b
 - T4d: Inflammatory carcinoma

19.8.9 Histological Grading

The Nottingham grading system is a semiquantitative method used to assess the degree of tumor differentiation in invasive breast carcinoma. It evaluates three morphological features, each scored from 1 to 3 (Table 19.1). The total score determines the tumor grade, which correlates with prognosis and sometimes with treatment decisions, based on three features (Table 19.2).

19.8.10 TNM Staging

T—Primary Tumor

TX: Primary tumor cannot be assessed

T0: No evidence of primary tumor

Tis: Carcinoma in situ (DCIS, LCIS, or Paget's disease without a tumor)

T1: Tumor ≤2 cm

- T1mi: Microinvasion ≤1 mm
- T1a: >1 mm but ≤5 mm
- T1b: >5 mm but ≤10 mm

N—Regional Lymph Nodes

NX: Regional lymph nodes cannot be assessed

N0: No regional lymph node metastasis

- N0(i+): Isolated tumor cells (≤0.2 mm) in lymph nodes
- N0(mol+): Molecularly detected metastases only

N1: Metastases to 1–3 axillary lymph nodes and/or internal mammary nodes

N2: Metastases to 4–9 axillary lymph nodes or clinically detected internal mammary nodes

N3:

- N3a: ≥10 axillary lymph nodes or infraclavicular nodes
- N3b: Internal mammary nodes + axillary nodes
- N3c: Supraclavicular lymph node involvement

M—Distant Metastasis

M0: No distant metastasis

- cM0(i+): Clinically no metastasis, but microscopic tumor cells found

M1: Distant metastasis present

Table 19.1 Nottingham histological grading criteria

Feature	Score 1	Score 2	Score 3
Tubule formation	>75% of tumor forms tubules (well-differentiated structure)	10–75% tubule formation (partially preserved ductal structure)	<10% tubule formation (mostly solid growth; poorly differentiated)
Nuclear pleomorphism	Small, uniform nuclei; minimal variation; resembles normal epithelial cells	Moderate nuclear enlargement and variation; slightly irregular nuclei	Marked pleomorphism; large, irregular nuclei; prominent nucleoli
Mitotic count	Low mitotic activity (e.g., 0–5 mitoses per 10 HPFs)	Intermediate mitotic activity (e.g., 6–10 mitoses per 10 HPFs)	High mitotic activity (>10 mitoses per 10 HPFs)

Table 19.2 Final grading based on total score

Total score	Grade	Interpretation
3–5 points	Grade 1—Well differentiated	Slow-growing tumor with favorable prognosis
6–7 points	Grade 2—Moderately differentiated	Intermediate aggressiveness and prognosis
8–9 points	Grade 3—Poorly differentiated	Aggressive tumor, higher risk of recurrence/metastasis

Stage Grouping (Anatomic Stage, Without Biomarkers)

Stage 0: Tis N0 M0

Stage I: T1 N0 M0

Stage II: T0–T2 N1 M0 or T2 N0 M0

Stage III: T3–T4 and/or N2–N3 M0

Stage IV: Any T, Any N, M1

cancer and guiding treatment. Prognostic factors tell us how aggressive a cancer is and help estimate the overall outcome or survival, regardless of treatment. Predictive factors tell us how likely a tumor will respond to a specific therapy (e.g., hormone therapy, chemotherapy, targeted therapy). Some factors can be both prognostic and predictive [4].

19.8.11 Lymph Node Involvement

Axillary lymph node metastasis is the most important prognostic factor at diagnosis. Sentinel lymph node biopsy is performed to assess metastasis [1].

19.8.12 Prognostic and Predictive Factors in Invasive Breast Carcinoma

Understanding prognostic and predictive factors is essential for assessing the behavior of breast

1. *Prognostic Factors* (Table 19.3)
2. *Predictive Factors* (Table 19.4)
3. *Combined Prognostic and Predictive Value*
Some markers serve dual roles:
 - Hormone receptor status (ER/PR): Good prognosis and predicts hormone therapy response.
 - HER2 status: HER2-positive tumors were once aggressive but now have improved prognosis with targeted therapy.
 - Gene expression profiles (like Oncotype DX): Estimate recurrence risk and predict chemotherapy benefit.

Table 19.3 Factors which are used to estimate the natural course and prognosis of the disease

Factor	Description	Impact
Tumor size	Measured in cm	Larger tumors (>2 cm) have worse prognosis
Lymph node involvement	Number and extent of metastatic nodes	Most important prognostic factor
Histological grade	Based on tubules, pleomorphism, mitoses (Nottingham system)	Higher grade → more aggressive behavior
Lymphovascular invasion	Presence of tumor cells in lymphatics or blood vessels	Associated with higher recurrence and spread
Histological type	E.g., tubular and mucinous types have better prognosis	Some special types behave less aggressively
Proliferation rate	Ki-67 index	High Ki-67 indicates rapid growth and worse prognosis

Table 19.4 Factors, which help choose the most effective targeted treatment

Factor	Description	Predicts response to
Estrogen receptor (ER)	Positive tumors grow with estrogen stimulation	Responds to hormone therapy (e.g., tamoxifen, aromatase inhibitors)
Progesterone receptor (PR)	Often coexpressed with ER	Supports hormone sensitivity
HER2 overexpression/amplification	Overactive HER2 pathway	Responds to anti-HER2 therapy (trastuzumab, pertuzumab)
PAM50 or oncotype DX gene signatures	Genomic profiling tests	Predict chemotherapy benefit and recurrence risk
Androgen receptor (AR) (<i>in some subtypes</i>)	Expressed in some triple-negative cancers	Emerging therapeutic target

Note: Triple-negative breast cancers lack ER, PR, and HER2 → no targeted therapy available → generally respond only to chemotherapy

19.8.13 Summary Table

Factor	Prognostic	Predictive	Notes
Tumor size	✓	✗	Larger tumors → worse prognosis
Lymph node status	✓	✗	Most powerful prognostic factor
Histological grade	✓	✗	High grade → aggressive tumor
ER/PR status	✓	✓	ER/PR+ tumors respond to endocrine therapy
HER2 status	✓	✓	Predicts response to HER2-targeted drugs
Ki-67 index	✓	—	High levels → more aggressive tumors
Gene expression tests	✓	✓	Used to personalize therapy decisions

Invasive breast carcinomas are a *heterogeneous group of tumors* with variable morphologies and clinical behaviors. Accurate classification and molecular characterization are essential for proper management. Pathology plays a central role in diagnosis, prognostication, and guiding therapy.

19.9 Male Breast Cancer

Male breast tissue is rudimentary but contains ductal structures, making it susceptible to tumor development. Male breast cancer accounts for approximately 1% of all breast cancers and 0.5% of all male cancers. The average age at diagnosis is 60–70 years, and it tends to be diagnosed at a more advanced stage than in females [2–5, 19].

19.9.1 Risk Factors

- Genetic: BRCA2 mutation (most common), also BRCA1, CHEK2
- Hormonal: Estrogen/androgen imbalance, Klinefelter syndrome (XXY), testicular diseases
- Radiation exposure
- Obesity
- Family history of breast cancer (especially in mother or sister)

19.9.2 Histologic Types

Tumor type	Description
Invasive ductal carcinoma (IDC)	Most common type (~85–90%), similar to IDC in women
Ductal carcinoma in situ (DCIS)	Less frequent than in females, but occurs
Lobular carcinoma	Very rare due to absence of lobules in male breast
Papillary carcinoma	More common in men than in women (~5%)
Mucinous, medullary carcinoma	Rare
Myoepithelial tumors	Extremely rare

19.9.3 Immunohistochemical (IHC) Profile

- ER (estrogen receptor): Positive in >90% of cases
- PR (progesterone receptor): Frequently positive
- HER2: Less frequently positive than in women
- Ki-67: Indicates proliferation rate (variable)

19.9.4 Clinical Presentation

Typically presents as a firm, unilateral subareolar mass. May also show nipple retraction, ulceration, or axillary lymphadenopathy. Diagnosis is often delayed compared to female breast cancer.

19.9.5 Diagnosis and Differential Diagnosis

- Imaging: Mammography and ultrasound
- Biopsy: Fine-needle aspiration (FNA) or core needle biopsy
- Differential diagnoses: Gynecomastia, metastatic tumors, dermatologic lesions

19.9.6 Treatment

- Surgery: Modified radical mastectomy is most common
- Adjuvant therapy:
 - Hormonal therapy (e.g., tamoxifen) for ER/PR positive cases
 - Chemotherapy
 - Radiotherapy

19.9.7 Prognosis

Prognosis is similar to that of female breast cancer, but often worse due to later stage at diagnosis. ER positivity is a favorable prognostic factor. Tumor size, grade, and lymph node involvement are important prognostic indicators.

19.10 Epithelial-Myoepithelial Tumors of the Breast

These are *rare biphasic tumors* of the breast that contain *both epithelial and myoepithelial cell components*. These two cell types grow together in a defined architectural pattern, and both may show benign or malignant features [1–5, 20].

19.10.1 Cellular Composition

Cell type	Function	Histological features
Epithelial cells	Line ducts and secrete milk/ luminal content	Cuboidal to columnar, form gland-like or ductal structures
Myoepithelial cells	Support, contractile function in ducts	Clear cytoplasm, elongated nuclei, often abluminally located

19.10.2 Major Tumors in This Category

1. *Adenomyoepithelioma*
Benign or borderline tumor composed of proliferating epithelial and myoepithelial cells. Usually well-circumscribed. May recur if incompletely excised. Rare cases may undergo malignant transformation (→ carcinoma).
2. *Myoepithelial Carcinoma (Malignant Myoepithelioma)*
Malignant counterpart of myoepithelial tumors. Highly atypical myoepithelial cells, often infiltrative growth. May arise de novo or from a preexisting benign lesion. Locally aggressive and potential for metastasis.
3. *Epithelial-Myoepithelial Carcinoma*
Rare, low-grade malignant tumor with dual-layered tubules: inner epithelial cells and outer myoepithelial cells.
Shares features with salivary gland-type tumors. May resemble adenoid cystic carcinoma in some aspects.

19.10.3 Immunohistochemistry (IHC) Markers

Cytokeratins (CK7, AE1/AE3) highlight epithelial cells, while SMA, p63, S100, calponin highlight myoepithelial cells. Ki-67 rate (proliferation index) is higher in malignant tumors.

19.10.4 Clinical Presentation

Usually presents as a palpable mass. May be detected incidentally on mammography. Typically affects middle-aged to older women.

19.10.5 Treatment and Prognosis

Benign lesions → local excision with clear margins.
Malignant tumors → wide excision or mastectomy ± radiation/chemotherapy depending on grade/stage.
Prognosis varies: Good for benign tumors. Guarded for malignant types due to recurrence/metastasis risk. Primary breast tumors can be broadly classified into two main groups: stromal tumors and epithelial tumors.

19.11 Stromal Tumors of the Breast

Stromal tumors originate from either interlobular or intralobular stroma. Intralobular stroma is the source of biphasic tumors unique to the breast, such as fibroadenoma and phyllodes tumor. This specialized stroma provides growth factors that stimulate the proliferation of the accompanying nonneoplastic epithelial component. Interlobular stromal tumors, in contrast, include lipomas and angiosarcomas, with angiosarcoma being among the most common malignant mesenchymal tumors in the breast [2].
Fibroadenoma is the most frequent benign tumor of the breast and represents a biphasic neoplasm composed of both stromal (monoclonal)

and epithelial (polyclonal) components. It often presents as a palpable, mobile, firm mass in young women aged 20–35 years, particularly during the reproductive years. In older women, it may be detected as a density on mammography. It occurs more commonly in the upper outer quadrant and typically measures 1–15 cm in diameter. Multiple and bilateral lesions may be seen in ~20% of cases. Increased incidence has been reported in renal transplant recipients receiving cyclosporine. The overall risk of malignancy is very low (~0.1%). When malignancy occurs, it most often arises in the epithelial component, typically as ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS)—both seen at similar frequencies. Risk increases if there is a family history of breast cancer or the presence of proliferative epithelial lesions. Grossly, fibroadenomas are seen as well-circumscribed, encapsulated, rubbery or elastic nodules. Cut surface shows solid, gray-white tissue with slit-like spaces. They are easily excisable from surrounding parenchyma. In histological examination, it separates from surrounding breast tissue by a fibrous capsule, composed of myxoid stroma with proliferative ductal elements. Although two subtypes of fibroadenoma have been described as pericanalicular and intracanalicular, the distinction has no clinical significance, because prognostically and therapeutically, the two subtypes are the same. Pericanalicular type retains round, open ducts surrounded by stroma, while intracanalicular type shows compressed, elongated ducts due to

stromal overgrowth (Fig. 19.10a). The stroma is rich in acid mucopolysaccharides and may become hyalinized with time. Elastic tissue is absent. Ductal epithelium is hormone-responsive, which explains lactational changes during pregnancy (increased cellularity, inflammation, and infarction) and hemosiderin-laden infarcted areas, visible as red foci macroscopically. These changes may mimic malignancy clinically and radiologically. Unusual variants may show lamellated cellular collagenous stroma. Postmenopausal regression is common due to hormonal withdrawal [21–23].

One of the hallmark mammographic findings is the presence of classic lobulated “popcorn” calcifications, particularly in older patients. In this demographic, calcification, ossification, and stromal hyalinization are more frequently observed. Histologically, reactive multinucleated giant cells, mononuclear inflammatory infiltrates, mature adipose tissue, smooth muscle bundles, and occasionally metaplastic cartilage can be seen within the stroma. Apocrine metaplasia is present in approximately 15% of cases and is typically positive for GCDFP-15. Stromal cells commonly express progesterone receptors (PR), whereas estrogen receptor (ER) expression is usually absent [21–23].

Giant fibroadenomas, including juvenile, fetal, or cellular subtypes, are characterized by lesions larger than 10 cm and predominantly occur in adolescents. These tumors exhibit prominent epithelial and/or stromal hypercellularity (Fig. 19.10b). They are more prevalent among

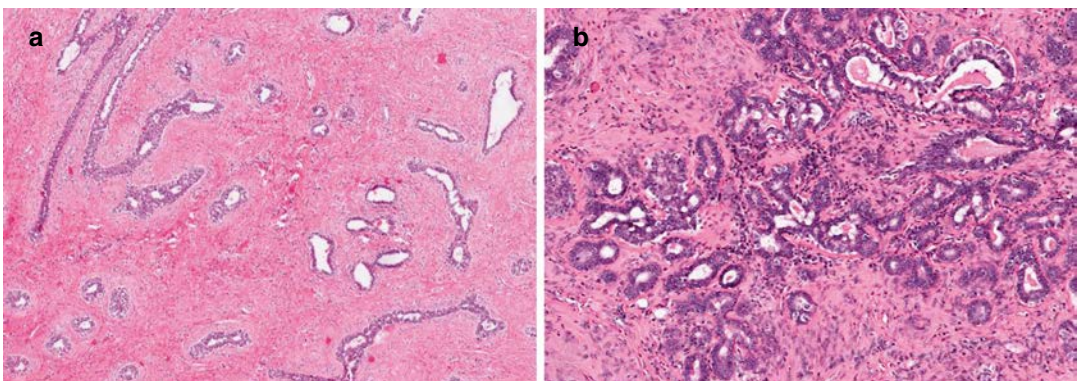


Fig. 19.10 (a) Pericanalicular type fibroadenoma. (b) Cellular giant fibroadenoma

individuals of African descent and may occur bilaterally. Some fibroadenomas display pronounced myxoid degeneration and may present either sporadically or as part of a genetic syndrome. For example, Carney complex is an autosomal dominant disorder involving mutations in the *PRKAR1A* gene on chromosome 17, which encodes the regulatory subunit of protein kinase A. Approximately half of the cases with Carney complex exhibit myxoid fibroadenomas. The syndrome is also characterized by cardiac and extracardiac myxomas, cutaneous hyperpigmentation, and endocrine hyperactivity [2, 24].

Phyllodes tumors are also biphasic neoplasms originating from intralobular stroma. While they may occur at any age, they are most frequently diagnosed in the fifth and sixth decades of life. These tumors are usually smaller than 5 cm and low-grade, although some may grow to a considerable size. Phyllodes tumors are graded as benign, borderline, or malignant, corresponding roughly to grades 1 through 3. Benign (grade 1) tumors exhibit pushing margins and fewer than five mitoses per 10 high-power fields (HPFs).

Malignant tumors show infiltrative margins and more than 10 mitoses per 10 HPFs and may recur or metastasize. High-grade tumors may behave aggressively, with hematogenous metastases occurring in approximately one-third of cases. Although historically referred to as *cystosarcoma phyllodes*, the majority are benign [25, 26].

Macroscopically, phyllodes tumors may resemble fibroadenomas. They typically demonstrate an intracanalicular growth pattern. In larger lesions, leaf-like projections of proliferative stroma extend into cleft-like spaces lined by epithelium—a feature known as *bulbous protrusions*. Necrosis, cystic changes, and hemorrhagic areas may also be seen. Key distinguishing features from fibroadenomas include increased stromal cellularity, higher mitotic activity, nuclear pleomorphism, presence of leaf-like architecture, infiltrative growth, older age at presentation, and more rapid growth kinetics. Microscopically, low-grade phyllodes tumors resemble fibroadenomas but are more cellular and show mitotic activity (Fig. 19.11). High-grade tumors can be difficult to distinguish from soft tissue sarcomas

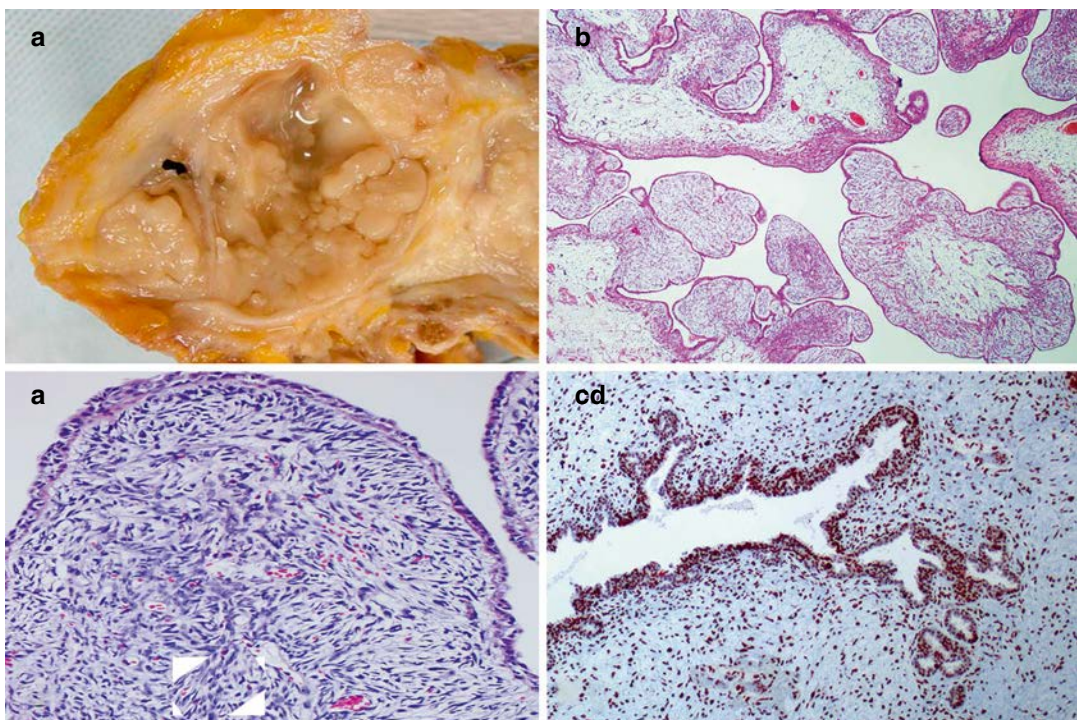


Fig. 19.11 Phyllodes tumor: (a) grossly leaf-like projections. (b) Bulbous protrusions. (c) Cellular stroma with increased mitotic activity. (d) PCNA expressions show proliferative activity of tumor

and may contain heterologous mesenchymal elements. The nature of the stroma determines whether a lesion is a fibroadenoma or a phyllodes tumor. Immunohistochemically, stromal cells usually express PR but not ER, similar to fibroadenomas. Presence of necrosis is associated with poor prognosis. The epithelial component is generally benign, though it may show proliferative activity. Malignant transformation of the epithelial component is rare. In contrast, high-grade stromal components can resemble sarcomas and metastasize to distant sites such as the lungs, bones, and central nervous system. Treatment varies by grade: low-grade tumors can be managed with wide local excision, while high-grade tumors may require simple mastectomy. If the fascia is involved, resection includes the underlying muscle. Axillary lymph node dissection is not typically performed as nodal metastasis is rare [25–27].

References

1. WHO Classification of Tumours Editorial Board. WHO classification of breast tumours, vol. 2. 5th ed. Lyon: IARC Press; 2019.
2. Hoda SA, Brogi E, Koerner FC, Rosen PP. Rosen's breast pathology. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2021.
3. Dabbs DJ. Breast pathology. 2nd ed. Philadelphia: Elsevier; 2017.
4. Kumar V, Abbash AK, Aster JC, editors. Robbins & Cotran pathologic basis of disease. 10th ed. Philadelphia: Elsevier; 2020.
5. Lester SC, Hicks DG. Diagnostic pathology breast. 3rd ed. Philadelphia: Elsevier; 2021.
6. Hophan SL, Odnokoz O, Liu H, Luo Y, Khan S. Ductal carcinoma in situ of breast: from molecular etiology to therapeutic management. *Endocrinology*. 2022;163(4):bqac027. <https://doi.org/10.1210/endo/bqac027>.
7. Gupta S, Deka L, Gupta R, Pant L, Singh S. Molecular phenotypes of ductal carcinoma-in-situ and invasive ductal carcinoma: a comparative study. *Indian J Pathol Microbiol*. 2012;55(1):43–6. <https://doi.org/10.4103/0377-4929.94854>.
8. Kuba MG, Brogi E. Update on lobular lesions of the breast. *Histopathology*. 2023;82(1):36–52. <https://doi.org/10.1111/his.14829>.
9. Cope W, Provenzano E. The diagnosis and management of lobular carcinoma in situ. *Diagn Histopathol*. 2023;29(3):153–61. <https://doi.org/10.1016/j.mpdhp.2022.12.004>.
10. Markarian S, Holmes DR. Mammary Paget's disease: an update. *Cancers*. 2022;14:2422. <https://doi.org/10.3390/cancers14102422>.
11. Lester T, Wang J, Bourne P, Yang Q, et al. Different panels of markers should be used to predict mammary Paget's disease associated with in situ or invasive ductal carcinoma of the breast. *Ann Clin Lab Sci*. 2009;39(1):17–24.
12. Kar H, Altındağ SD, Etit D, Yiğit S, Acar N, et al. Clinicopathological features of mammary Paget's disease: a single-center experience in Turkey. *Turk J Med Sci*. 2021;51(6):23. <https://doi.org/10.3906/sag-2103-148>.
13. Rakha EA, Tse GM, Quinn CM. An update on the pathological classification of breast cancer. *Histopathology*. 2023;82:5–16. <https://doi.org/10.1111/his.14786>.
14. Zhang X. Molecular classification of breast Cancer relevance and challenges. *Arch Pathol Lab Med*. 2023;147:46–51. <https://doi.org/10.5858/arpa.2022-0070-RA>.
15. Foulkes WD, Smith IE, Reis-Filho JS. Triple-negative breast cancer. *N Engl J Med*. 2010;363(20):1938–48. <https://doi.org/10.1056/NEJMra1001389>.
16. Wolff AC, Somerfield MR, Dowsett M, Hammond ME, Hayes DF, et al. Human epidermal growth factor receptor 2 testing in breast cancer: ASCO–College of American Pathologists Guideline Update. *J Clin Oncol*. 2023;41(22):3867–72. <https://doi.org/10.1200/JCO.22.02864>.
17. Turner N, Tutt A, Ashworth A. Hallmarks of 'BRCAness' in sporadic cancers. *Nat Rev Cancer*. 2004;4(10):814–9. <https://doi.org/10.1038/nrc1457>.
18. Zhang H, Yan PY. Unique molecular alteration of lobular breast cancer: association with pathological classification, tumor biology and behavior, and clinical management. *Cancers*. 2025;17:417. <https://doi.org/10.3390/cancers17030417>.
19. Yiğit S, Etit D, Kucukzeybek B, Yenipazar AE, Kucukzeybek Y, Sarı AA, Alacacioglu A. Male invasive breast carcinoma: nine years experience at a single center in Turkey. *West Indian Med J*. 2016. <https://doi.org/10.7727/wimj.2016.308>. e-published.
20. Foschini MP, Nishimura R, Fabbri VP, Varga Z, Kaya H, Cserni G. Breast lesions with myoepithelial phenotype. *Histopathology*. 2023;82(1):53–9. <https://doi.org/10.1111/his.14826>.
21. Badve S, Turbin D, Thorat MA. Fibroepithelial tumors of the breast: recent advances and diagnostic challenges. *Mod Pathol*. 2022;35(S1):75–90. <https://doi.org/10.1038/s41379-021-00943-6>.
22. Rakha EA, Ahmed MA, Ellis IO. Benign breast lesions: diagnostic criteria and clinical implications. *Pathology*. 2021;53(2):165–78. <https://doi.org/10.1016/j.pathol.2020.11.007>.
23. Seidman JD, Schnaper LA, Gown AM. Cytogenetic and molecular studies in fibroadenoma: evidence of monoclonality of stromal cells and polyclonality of epithelial components. *Hum Pathol*. 2020;102:35–41. <https://doi.org/10.1016/j.humpath.2020.06.00>.

24. Stratakis CA. Carney complex: a familial lentiginosis predisposing to a variety of tumors. *Rev Endocr Metab Disord.* 2016;17(4):419–39. <https://doi.org/10.1007/s11154-016-9385-9>.
25. Rakha EA, Elsayed ME, Eltobgy A, Bastati H, Green AR, Ellis IO. Fibroadenoma and phyllodes tumors: diagnostic challenges and potential diagnostic pitfalls. *Pathology.* 2020;52(1):45–52. <https://doi.org/10.1016/j.pathol.2019.08.007>.
26. Tan BY, Acs G, Apple SK, Badve S, Bleiweiss IJ, Brogi E, et al. Phyllodes tumours of the breast: a consensus review. *Histopathology.* 2016;68(1):5–21. <https://doi.org/10.1111/his.12876>.
27. Lim W, Park SY, Seo AN, Cho EY, Park IH, Song JY. Histologic features and molecular profiles of phyllodes tumors with recurrence and metastasis. *Virchows Arch.* 2020;477(1):55–65. <https://doi.org/10.1007/s00428-020-02784>.

Nonneoplastic Disorders of Lymph Nodes

20

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20.1 Structure of Lymph Nodes

Lymph nodes are encapsulated structures aligned along the lymphatic pathways, particularly concentrated in areas exposed to numerous antigens. Those located along mucosal surfaces are collectively referred to as mucosa-associated lymphoid tissue (MALT), which is further subclassified into GALT (gut-associated lymphoid tissue) and NALT (nasopharynx-associated lymphoid tissue, including tonsils). The fibrous capsule of a lymph node partitions its internal parenchyma into distinct compartments. Afferent lymphatic vessels open into the subcapsular sinus, which continues as cortical and trabecular sinuses. Upon entering the paracortex, the sinuses become more convoluted and form the medullary sinuses, which converge at the hilum to drain via efferent lymphatics. Arterial branches that supply follicles in the cortex transition into venules as they traverse the medullary area. The capillaries in the paracortex assume a specialized structure: the postcapillary high endothelial venules (HEVs), which permit lymphocyte trafficking from the bloodstream into the node [1].

Structurally and functionally, lymph nodes are divided into four major zones:

1. *Cortex*: rich in well-developed follicles; this is the site of B-lymphocyte proliferation.
2. *Medulla*: contains abundant plasma cells and medullary cords.
3. *Paracortex (deep cortex)*: a T-cell–dominant zone, dependent on the thymus for T-cell development and housing many T lymphocytes.
4. *Sinuses*: lined by phagocytic histiocytes that belong to the mononuclear phagocyte system.

Secondary follicles are more complex than primary ones: the germinal center comprises a heterogeneous mix of small and large cleaved cells (centrocytes), centroblasts (non-cleaved large cells), follicular dendritic cells (FDCs), and often tingible body macrophages. Centroblasts exhibit large vesicular nuclei and discernible nucleoli, whereas centrocytes tend to have more angular, condensed chromatin with inconspicuous nucleoli. Mitotic figures are readily observed due to the high proliferation rate. Occasional CD4⁺ T cells and plasma cells may intersperse within the germinal center. Tingible body macrophages, containing apoptotic debris, play a regulatory role in the germinal center reaction. Follicular dendritic reticulum cells are not well distinguished on H&E staining; they possess mildly indented nuclei and extend cytoplasmic

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processes that establish desmosomal contact with germinal center B cells. Surrounding the germinal center is the mantle zone, composed of small naive B lymphocytes, which express surface markers including CD19, CD20, CD22, IgM, and IgD. B cells within germinal centers, in addition to classical B-cell markers, often express IgG and IgA heavy chains (but usually not IgD). Follicular dendritic reticulum cells can be labeled by direct complement receptor reagents or by IgM immunostaining. Small helper T cells within the germinal center may be CD57⁺. In the sinuses, histiocytes can express CD68 and CD11b and demonstrate positivity for acid phosphatase. The paracortex, also termed the thymus-dependent area, houses the cellular immune response. Lymphocytes here are predominantly CD4⁺, small in size, with condensed chromatin and well-defined nuclei. Endothelial cells lining HEVs are characterized by large nuclei, small nucleoli, and columnar morphology [1] (Fig. 20.1).

In the paracortex, antigens are presented to T lymphocytes predominantly by dendritic cells (DCs) and other antigen-presenting cells (APCs). These bone marrow–derived cells display delicate chromatin with inconspicuous nucleoli and are ontogenetically related to cutaneous Langerhans cells. Plasmacytoid dendritic cells (pDCs)—which reside near high endothelial venules (HEVs)—constitute a specialized APC subset that produces large amounts of type I interferons and facilitates T-cell priming rather

than being T cells themselves. HEVs, formed by cuboidal endothelium, provide a gateway for lymphocyte trafficking from blood into the node. APCs are broadly divided into professional and nonprofessional presenters. Professional APCs (e.g., conventional DCs, macrophages, B cells) constitutively express MHC class II, whereas many non-professional cells upregulate MHC class II only upon activation—commonly under IFN- γ signaling. Naive T cells typically encounter antigen presented by dendritic cells in the paracortex, initiating clonal expansion and effector differentiation. “Reticular” or dendritic accessory cells form an intricate network in T-cell–dependent areas and across stromal niches. Although widely distributed in connective tissues, they are enriched in lymphoid organs. DCs arise from bone marrow progenitors; monocyte-derived DCs can be generated under GM-CSF with IL-4 (and/or TNF- α) in vitro, whereas circulating pDCs represent a distinct lineage defined by CD123, BDCA-2/CD303, and BDCA-4/CD304. After emigration, DCs further specialize in spleen, skin, and nodes. Conventional/myeloid DCs commonly show a CD11c⁺ phenotype, while they lack pan-T and pan-B markers [2]. Within lymph nodes, sinus histiocytes (monocyte/macrophage-derived) populate subcapsular and medullary sinuses and may diffusely infiltrate the paracortex. They are typically CD68⁺/CD163⁺ and often positive for lysosomal enzymes (e.g., acid phosphatase). Distinct tissue macrophage counterparts include microglia (CNS), mesangial cells (kidney), Kupffer cells (liver), and alveolar macrophages (lung). Functionally, macrophages are optimized for antigen processing, while DCs are optimized for antigen presentation to T and B cells. Major dendritic cell types in lymph nodes include follicular, interdigitating, plasmacytoid DCs, and Langerhans cells [1–3]:

- *Follicular dendritic cells (FDCs)* reside in germinal centers and extend processes among B cells. FDCs are non-hematopoietic stromal cells (CD45[−]) that retain native antigen as immune complexes for prolonged periods, thereby supporting affinity maturation and

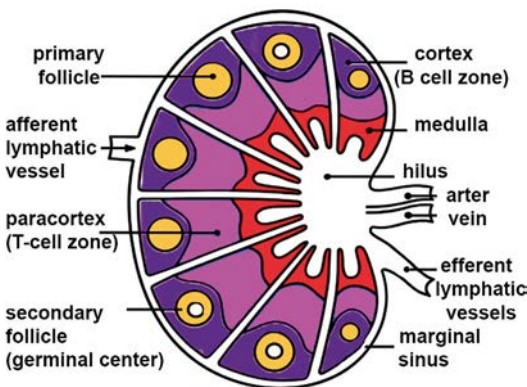


Fig. 20.1 Schematic structure of the lymph node

B-cell memory. They typically express complement receptors CD21 and CD35 (often CD23/clusterin) and lack classical MHC II-dependent antigen presentation to T cells.

- *Interdigitating dendritic cells (IDCs)* populate the paracortex and interact with T lymphocytes. They are HLA-DR/S100⁺, generally CD1a⁻, CD21⁻, and CD35⁻, and lack pan-B and pan-T antigens; they present processed peptide via MHC II to naïve T cells.
- *Langerhans cells (LCs)* are the epidermal DC subset that may traffic to nodes. They characteristically express CD1a and Langerin/CD207, are S100⁺, and contain Birbeck granules ultrastructurally—features that distinguish them from indeterminate cells and other DCs.
- *Plasmacytoid dendritic cells (pDCs)* are a type I interferon-producing DC subset, typically defined as Lin⁻ CD11c⁻/low CD123⁺ BDCA-2/CD303⁺ BDCA-4/CD304⁺; upon TLR7/9 stimulation, they orchestrate antiviral immunity and shape adaptive responses.

20.2 Reactive (Benign) Lesions of Lymph Nodes

Benign lymph node lesions typically consist of a polymorphous mixture of lymphoid cells displaying a polyclonal immunophenotype, with minimal cytologic atypia. Rather than obliterating the normal nodal architecture, they tend to cause architectural distortion. These lesions result in reactive hyperplasia, most frequently in response to antigenic stimulation. In clinical evaluation, cervical lymph nodes larger than 5 mm are generally considered abnormal in adults, whereas inguinal nodes up to 1 cm are often within normal limits in children, depending on the clinical context. Reactive lymphadenopathies can exhibit various histopathologic patterns [1] (Fig. 20.2):

- *Follicular patterns* include nonspecific follicular hyperplasia, progressive transformation of germinal centers, angiofollicular lymph node hyperplasia (Castleman disease), rheu-

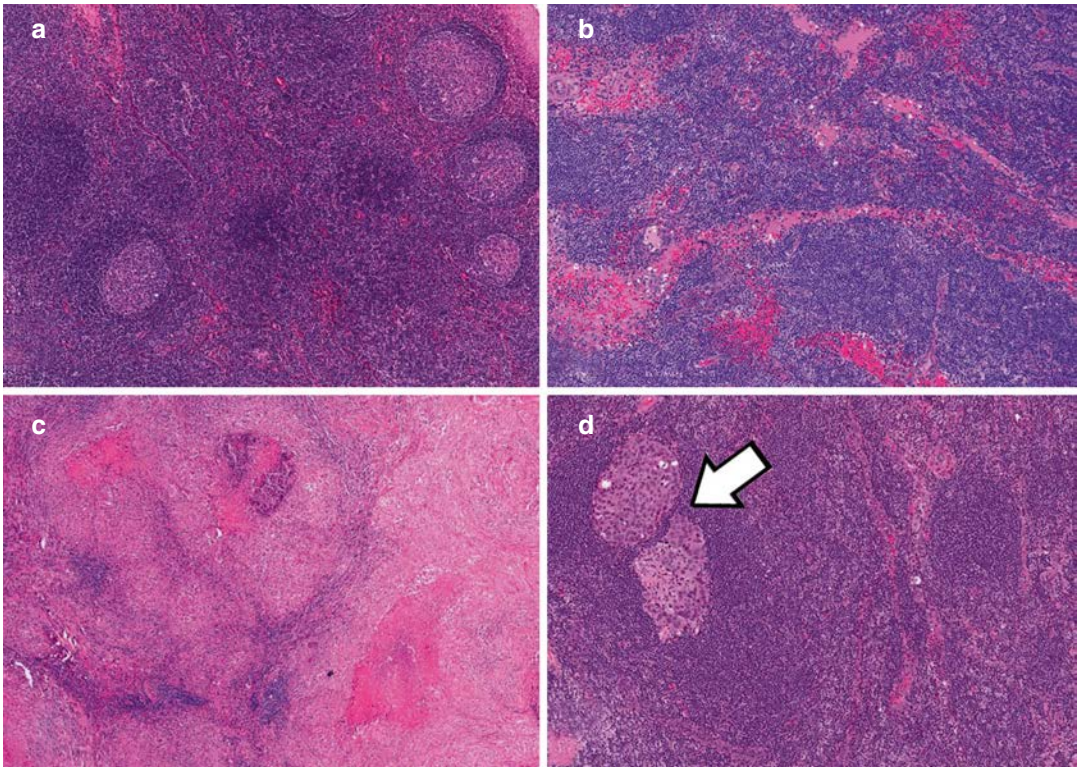


Fig. 20.2 (a) Reactive follicular hyperplasia. (b) Sinus histiocytosis. (c) Interfollicular hyperplasia with caseous granulomas. (d) Breast cancer metastasis (arrow) in a lymph node

matoid lymphadenopathy, and HIV/AIDS-related hyperplasia.

- *Interfollicular (paracortical) patterns* are common in conditions like dermatopathic lymphadenitis, Kikuchi-Fujimoto disease, and certain granulomatous reactions.
- *Sinusoidal patterns* are seen in sinus histiocytosis, Rosai-Dorfman disease, hemophagocytic syndrome, and monositoid B-cell hyperplasia.
- *Diffuse patterns* are observed in infections such as infectious mononucleosis and in drug-related or post-vaccine lymphadenitis.
- *Mixed patterns*, which overlap with follicular and paracortical changes, are seen in toxoplasmosis, cat scratch disease, and *Yersinia enterocolitica* lymphadenitis.

20.2.1 Nonspecific Follicular Hyperplasia

This is the most frequently encountered reactive pattern and is characterized by increased number and size of secondary follicles, resulting in expansion of the lymph node. Enlarged germinal centers may compress or obscure the mantle zones, though in some cases mantle zone hyperplasia coexists. Follicle shape is often irregular. In children, follicular hyperplasia frequently appears without identifiable etiology, while in adults, extensive follicular enlargement warrants investigation for underlying autoimmune or connective tissue disorders, such as systemic lupus erythematosus or rheumatoid arthritis [1, 4].

The most important differential diagnosis of follicular hyperplasia, especially florid hyperplasia,

is follicular lymphoma (FL), particularly the large-cell variants, which may mimic reactive patterns. Features favoring lymphoma include monomorphous populations, loss of follicular polarity, BCL2 expression within germinal centers, and loss of polarity or zonation (Table 20.1). The Ki-67 proliferation index is a valuable adjunct in distinguishing reactive follicular hyperplasia from lymphoid malignancies, especially FL (Fig. 20.3). In reactive lymph nodes, Ki-67 immunostaining typically demonstrates a polarized “zonal” pattern within germinal centers, where proliferation is confined predominantly to the dark zone, corresponding to actively dividing centroblasts. In contrast, FL shows a diffuse and non-polarized Ki-67 staining pattern throughout the follicle, reflecting the loss of follicular architecture and aberrant proliferation of neoplastic B cells. This distinction is especially useful when morphologic criteria are equivocal, and it complements BCL2, CD10, and BCL6 immunostains in the diagnostic algorithm. Importantly, Ki-67 staining should be interpreted in conjunction with histologic features, as high-grade FL variants may also show elevated but non-zonal Ki-67 expression [5–8].

Progressive transformation of germinal centers (PTGC) is a variant of follicular hyperplasia in which one or more enlarged germinal centers arise within a background of otherwise reactive follicles. These transformed centers typically occur in the mid-region of a node, surrounded by more conventional germinal centers. The enlarged follicles are irregular, densely infiltrated by small lymphocytes, and lose the sharp boundary between large and small cells; nevertheless, tingible body macrophages (the “starry sky” appear-

Table 20.1 Basic criteria for differentiating follicular hyperplasia and follicular lymphoma

Feature	Follicular hyperplasia	Follicular lymphoma
Nodal architecture	Preserved	Effaced or distorted
Follicle shape and size	Variable in shape and size	Uniform, monotonous follicles
Follicular density	Scattered, low density	Increased follicular density
Interfollicular areas	Rich in inflammatory cells	Infiltrated by neoplastic cells
Mantle zone	Well-preserved and prominent	Attenuated or absent
Germinal center polarity	Present (dark and light zones)	Absent (loss of polarization)
Mitotic activity	Moderate to high in reactive centers	Usually low in neoplastic follicles
Tingible body macrophages	Present	Typically absent

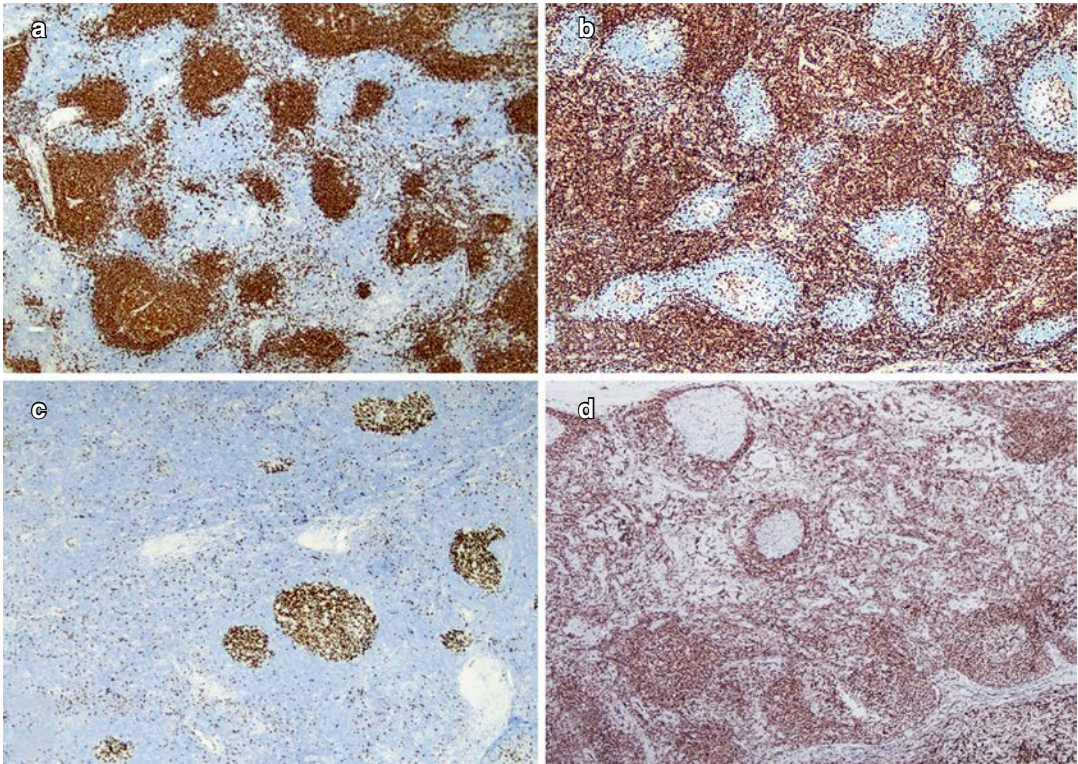


Fig. 20.3 (a) B lymphocytes expressing CD20 are located in the follicles. (b) Interfollicular areas filled with CD3-expressing T lymphocytes. (c) Normal zonal expres-

sion of Ki67 in reactive hyperplasia. (d) Loss of Bcl2 expression in germinal centers in reactive hyperplasia

ance) often persist. The follicular dendritic cell network may be expanded and increases in mantle zone cells and T lymphocytes are sometimes evident. PTGC is most frequently observed in the cervical region, especially in young males, and is considered a benign, self-limited process. At low magnification, PTGC foci may be 3–4 times larger than adjacent reactive follicles (Fig. 20.4). Mantle zone lymphocytes (IgM⁺/IgD⁺) and scattered CD4⁺/CD57⁺ T cells may intermix with residual germinal center and dendritic cells. The mantle zone may become obscured, and zones of transition between reactive follicles and transformed centers are often discernible (moth-eaten appearance). This appearance occurs due to infiltration of mantle zone B cells into the germinal center. Vascular penetration of small hyalinized vessels into germinal centers has been reported in PTGC, resembling features seen in hyaline-vascular Castleman disease; thus, Castleman dis-

ease should enter the differential diagnosis. Approximately 30–35% of reported PTGC cases are associated with nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL)—either concurrent, preceding, or following the lesion. The distinction between PTGC and NLPHL can be especially challenging because the so-called “popcorn” (LP) cells of NLPHL may mimic transformed germinal center large cells morphologically. Immunohistochemistry has limited utility in separating them: both LP cells and transformed germinal center B cells generally express B-cell markers and are negative for CD15/CD30. However, EMA positivity in LP cells and robust CD57⁺ T-cell rosettes encasing LP cells can aid in diagnosis. In PTGC, T cells are fewer and distributed singly or in small clusters; in NLPHL, LP cells are more crisply nodular and often surrounded by well-developed T-cell rosettes. Clinically, residual follicles containing

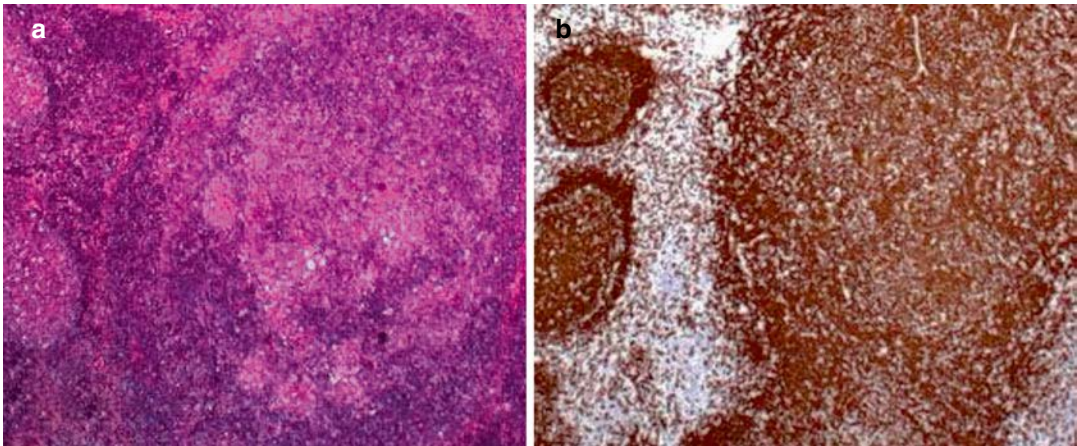


Fig. 20.4 (a) PTGC. (b) CD20 expressions in both normal follicles and in PTGC

PTGC features may persist in nodes affected by NLP HL—further complicating interpretation [9–11].

Castleman disease (angiofollicular lymph node hyperplasia) also presents follicular hyperplasia. There are hyaline-vascular and plasma cell subtypes. These two subgroups also differ clinically and histologically. The hyaline vascular type causes giant lymph node hyperplasia, which presents more with compression symptoms, while the plasma cell type presents with systemic findings. In solitary lesions, clinical findings may completely resolve with total excision. The hyaline vascular type is the most common form and usually presents with solitary involvement. It develops in younger patients and can cause a single mediastinal mass. It is asymptomatic outside of the mass. The hyaline-vascular type is characterized by an overgrowth of small vessels and abnormal follicles often surrounded by concentric mantle zone lymphocytes (onion-skin pattern or target follicle), sometimes with intervening capillaries that give a lollipop follicle appearance (Fig. 20.5). In plasma cell type, prominent interfollicular plasmacytosis, systemic symptoms, and elevated IL-6 may predominate; monoclonality in plasma cells (up to ~40%) has been reported, complicating the differential with plasmacytoma or plasma cell-rich processes [12, 13].

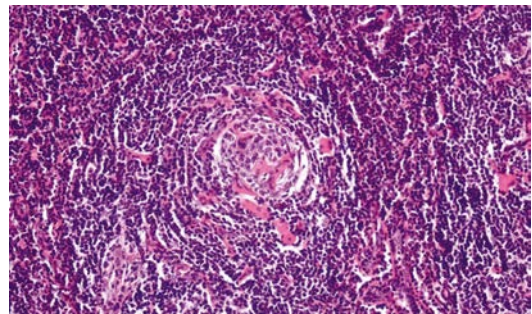


Fig. 20.5 Castleman disease

In patients with *rheumatoid arthritis*, generalized or localized lymphadenopathy may show both cortical and medullary follicular hyperplasia. Germinal centers may expand, compressing mantle zones, while mitoses, tingible body macrophages, and polarization remain present. Interfollicular plasma cell infiltrates, and capillary proliferation can also be seen, further overlapping with PTGC and Castleman features [14]. In secondary syphilis, lymph nodes often show follicular hyperplasia and plasmacytosis reminiscent of rheumatoid-associated changes; however, thickened capsules and trabeculae, perivenular plasma cell infiltrates, epithelioid histiocytes, and granulomas help distinguish it. If uncertain, Warthin–Starry silver stains, immunohistochemistry, or serology can identify spirochetes (*Treponema pallidum* within germinal centers or perivenular areas) [15].

In HIV infection, florid reactive follicular hyperplasia is the most frequent nodal finding. In AIDS-related lymphadenopathy, there may be a florid and explosive follicular hyperplasia with extremely enlarged follicles composed of a mixture of small and large centroblasts, plasma cells, and abundant tingible body macrophages, giving rise to the classic starry-sky pattern. Mitotic activity is usually elevated due to increased apoptosis and proliferation. Some germinal centers show clear light and dark zones, indicating antigen-driven germinal center reactions. The light zone contains centrocytes and dendritic cells, whereas the dark zone is rich in mitotic figures, apoptotic debris, and phagocytic macrophages. The mantle zone is often expanded but may become attenuated or lost as germinal centers enlarge. Large germinal centers may appear confluent (geographic pattern), compressing the interfollicular areas. Medullary cords may show increased plasma cells. Sinuses may show abundant monocytoid B cells and neutrophils, and mantle cells may encroach into germinal centers (moth-eaten follicles). Dendritic cells may form multinucleated polykaryocytes sometimes positive for HIV p24 antigen. While these changes are not unique to HIV, their presence should prompt correlation with clinical and virologic data. During the course of HIV disease, advanced immunologic collapse may present with secondary PTGC-like foci, and vascular proliferation reminiscent of Castleman disease may also appear in interfollicular zones; careful inspection of the subcapsular sinus and exclusion of Kaposi sarcoma are prudent in such cases [1, 9, 16].

20.2.2 Paracortical (Interfollicular) Hyperplasia

In unstimulated lymph nodes, paracortical (interfollicular) areas are subtle and encircle germinal centers. They contain small T lymphocytes, high endothelial venules, and circulating lymphocytes. Paracortical hyperplasia is not always apparent on low magnification and may be overlooked. The cellular makeup shifts depending on the intensity and duration of the stimulus: early

stages may be dominated by small T immunoblasts or activated high endothelial venule cells, while more chronic stimulation allows larger B immunoblasts of germinal center origin to predominate. Mixed transformations involving both T and B cells can be seen. The degree of interfollicular expansion varies between cases, and in severe forms, follicular structures may regress. Distinguishing such marked paracortical hyperplasia from Hodgkin lymphoma (HL) or non-Hodgkin lymphoma (NHL) can be challenging. The most common causes of paracortical hyperplasia include viral infections, drug hypersensitivity reactions, and post-vaccination lymphadenitis [1].

Infectious mononucleosis (IM) cannot be diagnosed by histopathological evaluation alone. Histology spans a spectrum between reactive follicular hyperplasia and overt lymphoma. Enlarged immunoblast proliferation in paracortical zones may produce a “speckled” or “moth-eaten” appearance at low power. The immunoblasts coexist with plasma cells, plasmacytoid lymphocytes, and proliferated venules, giving a polymorphic appearance. Occasionally, focal necrosis is seen. The proliferation may extend to the capsule and trabeculae. Sinuses generally remain intact, filled with monocytoid cells. Because immunoblast aggregates can appear in clusters or broad zones in IM, they may mimic large-cell (immunoblastic) lymphoma. If biopsy fragments or architectural context is insufficient, the distinction hinges on proving clonality (vs. polyclonality). In contrast, lymphomas often involve the entire node, lack architectural heterogeneity, and may obliterate follicles. In IM, B- and T-cell immunoblasts coexist, and B immunoblasts may even express CD43, further confounding interpretation. Due to atypical cytologic features of immunoblasts in IM, anaplastic large cell lymphoma (ALCL) may also enter the differential. However, ALCL cells are typically numerous, often EMA-positive, and of T- or null-cell phenotype. In IM, immunoblasts are usually B phenotype and CD15⁻. It should be noted, though, that CD15 negativity is not absolute in HL (15–40% of cases may lack CD15) [17–19].

Monocytoid B-cell (MBC) hyperplasia is primarily considered part of the interfollicular (paracortical) pattern of reactive lymph node changes, but it often shows features overlapping with the sinus pattern as well. Monocytoid B cells are typically located in the interfollicular areas, also known as the paracortex, often adjacent to or surrounding lymphoid follicles. These cells are found alongside reactive T cells, plasma cells, plasmacytoid lymphocytes, and proliferating venules, consistent with an interfollicular hyperplasia. Therefore, morphologically and immunologically, monocytoid B-cell hyperplasia is most often aligned with interfollicular reactive patterns. However, many histologic sections show that monocytoid B cells can extend into or partially fill subcapsular and medullary sinuses. These pale cytoplasmic, round to kidney-shaped cells may line or even dominate the sinuses, contributing to a sinusoidal component. MBC hyperplasia can be seen in conditions such as toxoplasmosis, infectious mononucleosis, cat-scratch disease, LGV, HIV, and CMV infections, as well as nonspecifically in reactive nodes. Some studies reported that ~15% of reactive hyperplasias showed monocytoid B-cell proliferation. Histologically, monocytoid B cells fill sinuses focal or diffuse, with pale cytoplasm, round or kidney-shaped nuclei, and inconspicuous nucleoli. Scattered polymorphonuclear leukocytes may be present. MBC hyperplasia often coexists with follicular hyperplasia. In low magnification, the node may appear lightly blue. The key diagnostic pitfall is differentiation from nodal marginal zone B-cell lymphoma (NMZL) or monocytoid B-cell lymphoma. Immunohistochemistry often offers limited discrimination: reactive cells tend to be bcl-2 negative, whereas neoplastic monocytoid B cells may be bcl-2 positive [20, 21].

Drug-associated lymphadenopathy: Certain antiepileptic drugs can provoke hypersensitivity reactions characterized by skin rash, systemic lymphadenopathy, and peripheral eosinophilia. The histologic spectrum in affected lymph nodes ranges from reactive hyperplasia to lesions mimicking lymphoma. In phenytoin-associated adenopathy, the normal nodal architecture may be

obliterated, replaced by a polymorphic infiltrate composed of histiocytes, immunoblasts, eosinophils, neutrophils, and plasma cells. Some immunoblasts with atypical nuclei may resemble Reed–Sternberg cells, and necrosis can be present. The critical distinguishing feature is that the atypical cells often exhibit a B-cell phenotype but remain polyclonal, which helps separate them from true lymphomas [22].

Vaccine-related lymphadenitis: Worldwide, true vaccine-induced lymphadenitis has become exceedingly rare since the cessation of routine smallpox vaccination. When it does occur, the lymph node histology mirrors that of viral infections. Differentiating from Hodgkin and non-Hodgkin lymphomas is essential, as misdiagnosis rates have been reported to be as high as 50% in some series. Consequently, vaccine history should always be elicited—especially in cases of axillary or lower cervical lymphadenopathy. The paracortex may show a speckled appearance due to immunoblasts, often accompanied by follicular or diffuse hyperplasia. A polymorphic infiltrate of immunoblasts, proliferated vessels, histiocytes, plasma cells, and mast cells may mimic the background of Hodgkin lymphoma. During COVID-19 pandemics, vaccine-related, especially mRNA vaccine-related, lymphadenopathies had occurred [23].

Toxoplasma lymphadenitis shows a mixed pattern, sometimes resembling infectious mononucleosis. Though it often involves postauricular or upper cervical nodes, generalized involvement can occur. Usually in immunocompetent individuals, it is self-resolving, while in immunodeficient patients, it may be more severe. Histologically, nodal architecture is preserved, and prominent follicular hyperplasia is seen. In the paracortex, small collections of epithelioid histiocytes may extend toward germinal centers, mimicking granulomas—but they never exceed ~20 cells and do not form true granulomas. There are no giant cells or necrosis foci. A characteristic accompanying finding is monocytoid B-cell proliferation in dilated sinuses and plasma cell infiltration in medullary cords. Genetic detection of *Toxoplasma* is uncommon, so serology should support histologic diagnosis. It is important to

remember that HIV infection sometimes shows overlapping features with toxoplasma lymphadenitis [24].

Dermatopathic lymphadenopathy may accompany skin lesions or occur without overt dermatologic signs. Its characteristic pattern is readily appreciated at low magnification: expanded paracortical areas with pale cells of varying size. Within these zones, macrophages laden with melanin and/or hemosiderin, reticular cells, plasma cells, and eosinophils are seen. The reticular cells and small irregular lymphocytes may mimic mycosis fungoides cells, but the key differentiators are that many cells are S-100, CD1a, and HLA-DR positive, which aids in distinction. Germinal centers may be compressed but still identifiable, and medullary sinuses likewise often contain histiocytes [25].

Kikuchi–Fujimoto disease (histiocytic necrotizing lymphadenitis) is more common in young women in Southeast Asia and often presents with cervical lymphadenopathy, fever, and spontaneous resolution. Misdiagnosis as Hodgkin or non-Hodgkin lymphoma is not uncommon. Histologically, there are patchy necroses with karyorrhectic debris in cortical and paracortical regions, with an absence of neutrophils in necrotic areas (Fig. 20.6). Around necrotic foci, large, atypical cells may appear, including immunoblasts and binucleate histiocytes, sometimes with plasmacytoid monocytes. True plasma cells are virtually absent. Foamy histiocytes often border necrosis. In more proliferative variants, a large-cell appearance may confound differentiation from lymphoma. The syncytial variant of nodular sclerosis Hodgkin lymphoma, with

widespread necrosis and lacunar Reed–Sternberg cells, can mimic Kikuchi disease. However, Hodgkin RS cells are typically CD30⁺, CD15⁺, and CD45⁺, whereas in Kikuchi disease, CD8⁺ T cells predominate, and RS phenotype is absent [26].

Sinus hyperplasia (sinus histiocytosis) may occur in isolation or coexist with follicular or paracortical hyperplasia. It typically develops in nodes draining neoplastic or infectious foci, though in most cases no clear etiologic agent is identified. Histologically, it is characterized by dilated sinuses filled with numerous macrophages, which appear benign and may contain ingested erythrocytes, hemosiderin granules, or carbon particles [27].

Rosai–Dorfman disease (sinus histiocytosis with massive lymphadenopathy): Rosai–Dorfman disease (RDD) is characterized by the accumulation of CD68-positive, S100-positive, and CD1a-negative histiocytes with frequent emperipolesis. It is an enigmatic entity with unclear etiology; some cases have been associated with HHV-6 infection. Clinically, it presents with massive, painless bilateral cervical lymphadenopathy, which can reach impressive sizes. Fever is common, but patients often otherwise remain well, and spontaneous regression may occur, though relapses are possible. Grossly, the lymph node is subdivided into nodules by fibrous bands, with a markedly thickened capsule. Perinodal fibrosis and a lymphoplasmacytic infiltrate are frequently evident. Expanded sinuses are packed with histiocytes—some with foamy cytoplasm—but mitoses are rare. Occasionally, large histiocytes with prominent nucleoli or “atypical” features may be seen, though the hallmark remains phagocytosis of hematopoietic cells (emperipolesis). Residual follicles are often scant, and medullary cords may show polyclonal plasma cells. Immunophenotypically, sinus histiocytes are S100⁺ and CD1a[−], distinguishing them from Langerhans cell histiocytosis. These histiocytes also express CD11, CD33, and CD68. If the histiocytes show pronounced atypia, one must exclude anaplastic large cell lymphoma or carcinoma metastasis; in ALCL, the neoplastic cells are typically CD30⁺ [28].



Fig. 20.6 Patch necrosis in Kikuchi–Fujimoto disease

Lymphoid hyperplasia associated with hemophagocytic syndrome (HLH) is a potentially fatal condition marked by fulminant systemic manifestations. Although initially described in viral settings, it is now understood that various infectious agents may trigger HLH in genetically or congenitally immunodeficient hosts. HLH may also occur in association with T-cell acute lymphoblastic leukemia, NK-cell lymphomas, or subcutaneous panniculitis-like T-cell lymphoma. Pathologically, sinuses (and often the entire node) are infiltrated by histiocytes that phagocytose hematopoietic elements, a signature finding. In imprint or frozen preparations, phagocytic cells are more conspicuous than in paraffin sections. The histologic features are commonly seen in spleen, bone marrow, liver, lymph nodes, and other organs. Near areas of necrosis, granulomas may appear. The hyperactivation of macrophages is thought to be driven by cytokines such as macrophage inflammatory protein-1 alpha and interferon gamma, though the precise mechanism remains obscure. A variant, EBV- or T-cell-associated HLH, is linked to perforin-1 gene mutations leading to defective cytolytic function in CD8⁺ T cells and NK cells. In up to 80% of fatal cases, EBV-related infectious mononucleosis is implicated. Within lymph nodes, infiltrates of atypical immunoblasts may extend into germinal centers; sinuses contain histiocytes with active phagocytosis. The resulting morphology can closely mimic large cell lymphoma, and the hemophagocytic features may be overlooked [29].

Kimura disease is a benign chronic inflammatory disorder of unknown etiology, endemic in Asian populations, and predominantly affecting young to middle-aged men. Patients typically present with deep subcutaneous masses in the head and neck region; involvement of the submandibular or parotid glands is common, and regional lymph nodes may also be affected. Lymphadenopathy may even be the sole manifestation in some cases. The nodal pattern is usually mixed. Peripheral eosinophilia and elevated serum IgE levels are characteristic. Pathologically, Kimura differs from eosinophilic angiolymphoid hyperplasia (Fig. 20.7). Even with conservative

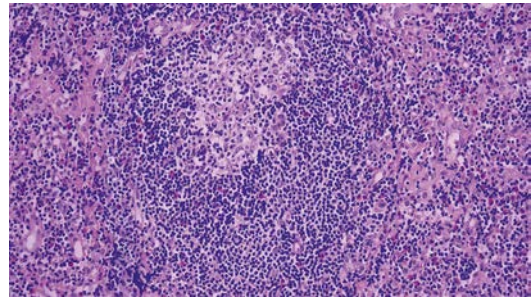


Fig. 20.7 Eosinophilic angiolymphoid hyperplasia

therapy, prognosis is excellent, though recurrence is frequent. Typical features include marked follicular hyperplasia, eosinophilic infiltration in the paracortex and sinuses, and increased numbers of postcapillary venules. These venules, together with eosinophils, can form small nodular aggregates within the paracortex. Other frequent findings include sclerosis obliterating sinuses and paracortex, Warthin–Finkeldey-type multinucleated giant cells (within germinal centers or sinuses), vascularization of germinal centers, proteinaceous deposits in germinal centers, and eosinophilic microabscesses in the paracortex. Focal necrosis of germinal centers may occur, and folliculolysis is commonly seen. IgE can be detected in germinal center cells, and surface IgE may be present on degranulated mast cells in the paracortex. The main differential diagnosis is Hodgkin lymphoma [30].

Granulomatous lymphadenitis: Many infectious and noninfectious entities can cause granulomatous lymphadenitis. Histologically, granulomas in lymph nodes resemble those in other tissues. They may show necrosis, suppuration, or caseation. Non-necrotizing epithelioid granulomas are characteristic of sarcoidosis, while necrotizing or caseating granulomas favor mycobacterial or fungal infection. Suppurative granulomas are typical of cat-scratch disease, LGV, tularemia, or *Yersinia* infections. To identify the causative agent, special stains (acid-fast, silver stains) should be employed, and culture of lymph node tissue may be diagnostic. *Sarcoidosis* is a systemic granulomatous disease with unknown cause or precise pathogenic mechanism. Clinically and histologically, it is well

characterized. Nodal lesions in sarcoidosis show non-necrotizing epithelioid granulomas. Granulomas may be circumscribed by sclerosis or evolve into hyaline structures. Langhans giant cells may be present. Within giant cells, there may be asteroid bodies, Schaumann bodies, calcium oxalate crystals, or Hamazaki–Wesenberg bodies (PAS-positive, acid-resistant inclusions). These inclusions are not specific to sarcoidosis and may appear in other conditions such as Hodgkin disease, non-Hodgkin lymphoma, Crohn disease (in mesenteric nodes), carcinoma-draining nodes, and berylliosis. In any granulomatous lymphadenitis, infectious etiologies must be excluded by special stains or culture. Fungal granulomas may also show necrosis. *Yersinia* lymphadenitis (mesenteric lymphadenitis) is most common in children and young adults, often mimicking appendicitis clinically. The appendix itself typically shows no infection, but the mesenteric lymph nodes are enlarged. Histology may demonstrate nonspecific follicular hyperplasia, collections of epithelioid cells, small necrotizing epithelioid cell clusters, or small necrotizing epithelioid granulomas. When granulomas are present, *Yersinia enterocolitica* (or more rarely *Y. pseudotuberculosis*) is the likely pathogen. Additional changes may include capsule thickening, follicular hyperplasia, widened lymphoid sinusoids filled with lymphocytes, and immunoblastic proliferation in the paracortex [1, 17, 24].

Whipple disease is a rare bacterial infection (*Tropheryma whipplei*) primarily affecting the small intestine, more common in middle-aged men. Clinical signs include weight loss, diarrhea, arthralgias; sometimes asymptomatic. Up to 50% of cases demonstrate peripheral lymphadenopathy, especially of abdominal nodes. Histologically, sinuses are dilated, with large histiocytes containing vacuoles from lipid digestion, and non-necrotizing granulomas may be present. A hallmark is PAS-positive, diastase-resistant, foamy organisms in histiocyte cytoplasm; on electron microscopy, these correspond to *T. whipplei* bacillary clusters. Previously, radiographic lymphangiography using lipid-based contrast (for Hodgkin staging) caused transient nodal changes; these are now rarely encountered. Post-

contrast residual empty spaces in sinuses, rimmed by foreign-body-type giant cells, may be seen. Eosinophils can also appear in sinuses and medullary cords [27].

20.2.3 Diffuse Pattern of Lymphoid Hyperplasia

The diffuse pattern is characterized by the loss or severe effacement of normal follicular architecture, with a uniform proliferation of reactive lymphoid cells throughout the lymph node. This pattern may involve small lymphocytes, immunoblasts, plasma cells, or histiocytes and is often associated with systemic immune responses or viral infections. Histologically, follicles are absent or obscured. The paracortex and medullary areas are expanded. Mixed inflammatory infiltrates are present, including immunoblasts, plasma cells, eosinophils, or monocytoid B cells. Necrosis or granulomas may occasionally be present depending on the underlying cause. Common causes of diffuse pattern of lymphoid hyperplasia are systemic viral infections such as infectious mononucleosis (EBV), CMV, HIV, and rubella, DRESS syndrome (drug-induced hypersensitivity), post-vaccination lymphadenitis, and autoimmune diseases. The main disorders to be considered in the differential diagnosis are diffuse large B-cell lymphoma (DLBCL), anaplastic large cell lymphoma (ALCL), and peripheral T-cell lymphoma. Immunophenotyping (e.g., CD20, CD3, CD30, ALK), clonality studies, and clinical correlation are essential [1, 27].

20.2.4 Mixed Pattern of Lymphoid Hyperplasia

The mixed pattern exhibits feature of both follicular and interfollicular (paracortical) hyperplasia, sometimes with involvement of sinuses. This heterogeneous appearance reflects a polyclonal immune reaction involving multiple components of the lymphoid architecture. Histologically, there are prominent secondary follicles with ger-

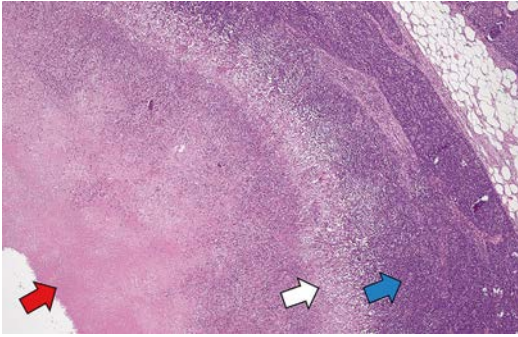


Fig. 20.8 Cat-scratch disease: Large necrotic area in the lower left (red arrow), normal reactive lymph node in the upper right (blue arrow) and surrounding fatty tissue, with a layer rich in pale-staining histiocytes (white arrow) in between (HE $\times 40$)

minimal center activity, expanded paracortex with immunoblasts, and reactive T cells. Sinuses may be dilated and filled with monocytoid B cells or histiocytes. There may be focal necrosis, eosinophils, or plasmacytoid cells. Common causes of mixed pattern are toxoplasma lymphadenitis, Kawasaki disease, infectious mononucleosis, cat-scratch disease (Fig. 20.8), Kimura disease, drug-induced hypersensitivity, and some forms of HIV-related lymphadenitis. Mixed patterns may mimic composite lymphoma or reactive lymphoproliferative disorders. Accurate diagnosis relies on architectural preservation, polytypic immunoglobulin expression, and supportive clinical data [1, 27–30].

References

- Willard-Mack CL. Normal structure, function, and histology of lymph nodes. *Toxicol Pathol.* 2006;34(5):409–24. <https://doi.org/10.1080/01926230600867727>.
- Ye Y, Gaugler B, Mohty M, Malard F. Plasmacytoid dendritic cell biology and its role in immune-mediated diseases. *Clin Transl Immunol.* 2020;9(5):e1139. <https://doi.org/10.1002/cti2.1139>.
- Neagu M, Constantin C, Jugulete G, Cauni V, Dubrac S, Szöllösi AG, Zurac S. Langerhans cells-revising their role in skin pathologies. *J Pers Med.* 2022;12(12):2072. <https://doi.org/10.3390/jpm12122072>.
- Gaddey HL, Riegel AM. Unexplained lymphadenopathy: evaluation and differential diagnosis. *Am Fam Physician.* 2016;94(11):896–903.
- Khanlari M, Chapman JR. Follicular lymphoma: updates for pathologists. *J Pathol Transl Med.* 2022;56(1):1–15. <https://doi.org/10.4132/jptm.2021.09.29>.
- Carbone A, Gloghini A. Diagnostic value of Ki-67 staining pattern in lymphoproliferative disorders. *Mod Pathol.* 2002;15(12):1274–80.
- Xue T, Yu BH, Yan WH, Jiang XN, Tian T, Zhou XY, Li XQ. Prognostic significance of histologic grade and Ki-67 proliferation index in follicular lymphoma. *Hematol Oncol.* 2020;38(5):665–72. <https://doi.org/10.1002/hon.2778>.
- WHO Classification of Tumours Editorial Board. WHO classification of haematolymphoid tumours. 5th ed. Lyon: IARC; 2022.
- Hwang ST, Sung DJ, Sim KC, Han NY, Park BJ, Kim MJ, Lee JH. Progressive transformation of germinal centers in presacral space: MRI findings and literature review. *Investig Magn Reson Imaging.* 2017;21(1):56–60. <https://doi.org/10.13104/imri.2017.21.1.56>.
- Hartmann S, Dojcinov S, Dotlic S, Gibson SE, Hsi ED, Klapper W, Klimkowska M, Pinilla SMR, Richter J, Sabattini E, Tousseyn T, de Jong D. The spectrum of nodular lymphocyte predominant Hodgkin lymphoma: a report of the lymphoma workshop of the 20th meeting of the European Association for Haematopathology. *Virchows Arch.* 2023;483(4):451–63. <https://doi.org/10.1007/s00428-023-03554-1>.
- Younes S, Rojansky RB, Menke JR, Gratzinger D, Natkunam Y. Pitfalls in the diagnosis of nodular lymphocyte predominant Hodgkin lymphoma: variant patterns, borderlines and mimics. *Cancers.* 2021;13(12):3021. <https://doi.org/10.3390/cancers13123021>.
- Hoffmann C, Oksenhendler E, Littler S, Grant L, Kanhai K, Fajgenbaum DC. The clinical picture of Castleman disease: a systematic review and meta-analysis. *Blood Adv.* 2024;8(18):4924–35. <https://doi.org/10.1182/bloodadvances.2024013548>.
- Yildiz J, Bağcı M, Sayın S, Kaya A, Yılmaz F, Ekinci O, Dal MS, Basturk A, Aydogdu I, Albayrak M, Dogan A, Erkurt MA, Korkmaz S, Ulas T, Eser B, Altuntas F. The clinicopathological features and survival of Castleman disease: a multicenter Turkish study. *Eur Rev Med Pharmacol Sci.* 2022;26(4):1131–7. https://doi.org/10.26355/eurrev_202202_28103.
- Ioachim HL, Medeiros LJ. Lymphadenopathy in rheumatoid arthritis. In: *Pathology of the immunologic system.* Springer; 2022.
- Gutierrez-Lanz E, Smith LB, Perry AM. Syphilis in hematopathology practice: a diagnostic challenge. *Arch Pathol Lab Med.* 2024;148(6):633–41. <https://doi.org/10.5858/arpa.2023-0078-RA>.

16. Nag D, Dey S, Nandi A, Bandyopadhyay R, Roychowdhury D, Roy R. Etiological study of lymphadenopathy in HIV-infected patients in a tertiary care hospital. *J Cytol*. 2016;33(2):66–70. <https://doi.org/10.4103/0970-9371.182518>.
17. Weiss LM, O'Malley D. Benign lymphadenopathies. *Mod Pathol*. 2013;26(Suppl 1):S88–96. <https://doi.org/10.1038/modpathol.2012.176>.
18. Pittaluga S. Viral-associated lymphoid proliferations. *Semin Diagn Pathol*. 2013;30(2):130–6. <https://doi.org/10.1053/j.semdp.2012.08.009>.
19. Nicolae A, Sabattini E, Ponzoni M, Paulli M, Lucioni M, Salviato T, Carbone A. Lymphadenitis/reactive-hyperplasia, mimickers of lymphomas, low-grade B-cell lymphomas, and Hodgkin lymphoma. *Hemato*. 2024;5(3):350–79. <https://doi.org/10.3390/hemato5030026>.
20. Kojima M, Motoori T, Iijima M, Ono T, Yoshizumi T, Matsumoto M, Masawa N, Nakamura S. Florid monocytoid B-cell hyperplasia resembling nodal marginal zone B-cell lymphoma of mucosa associated lymphoid tissue type. A histological and immunohistochemical study of four cases. *Pathol Res Pract*. 2006;202(12):877–82. <https://doi.org/10.1016/j.prp.2006.08.001>.
21. Yu SC, Chen KC, Huang RY. Nodal reactive proliferation of monocytoid B-cells may represent atypical memory B-cells. *J Microbiol Immunol Infect*. 2023;56(4):729–38. <https://doi.org/10.1016/j.jmii.2023.03.010>.
22. Chen HC, Wang RC, Tsai HP, Medeiros LJ, Chang KC. Morphologic spectrum of lymphadenopathy in drug reaction with eosinophilia and systemic symptoms syndrome. *Arch Pathol Lab Med*. 2022;146(9):1084–93. <https://doi.org/10.5858/arpa.2021-0087-OA>.
23. Ciliberti V, Maffei E, Giudice V, Ciancia G, Zeppa P, Caputo A. COVID-19 vaccine-associated lymphadenopathy: a review. *Infez Med*. 2024;32(2):119–30. <https://doi.org/10.53854/liim-3202-1>.
24. Faraz M, Rosado FGN. Reactive lymphadenopathies. *Clin Lab Med*. 2021;41(3):433–51. <https://doi.org/10.1016/j.cll.2021.04.001>.
25. Garces S, Yin CC, Miranda RN, Patel KP, Li S, Xu J, Thakral B, Poppiti RJ, Medina AM, Sriganeshan V, Castellano-Sánchez A, Khoury JD, Garces JC, Medeiros LJ. Clinical, histopathologic, and immunohistochemical features of dermatopathic lymphadenopathy: an update. *Mod Pathol*. 2020;33(6):1104–21. <https://doi.org/10.1038/s41379-019-0440-4>.
26. Mahajan VK, Sharma V, Sharma N, Rani R. Kikuchi-Fujimoto disease: a comprehensive review. *World J Clin Cases*. 2023;11(16):3664–79. <https://doi.org/10.12998/wjcc.v11.i16.3664>.
27. Egan C, Jaffe ES. Non-neoplastic histiocytic and dendritic cell disorders in lymph nodes. *Semin Diagn Pathol*. 2018;35(1):20–33. <https://doi.org/10.1053/j.semdp.2017.11.002>.
28. Goyal G, Ravindran A, Young JR, Shah MV, Bennani NN, Patnaik MM, Nowakowski GS, Thanarajasingam G, Habermann TM, Vassallo R, Sher T, Parikh SA, Rech KL, Go RS, Mayo Clinic Histiocytosis Working Group. Clinicopathological features, treatment approaches, and outcomes in Rosai-Dorfman disease. *Haematologica*. 2020;105(2):348–57. <https://doi.org/10.3324/haematol.2019.219626>.
29. Good SD, Wade SD, Kyttaris VC. The spectrum of hemophagocytic lymphohistiocytosis: a retrospective study comparing adult macrophage activation syndrome to malignancy-associated hemophagocytic lymphohistiocytosis. *Rheumatol Int*. 2022;42(7):1247–55. <https://doi.org/10.1007/s00296-021-05087-9>.
30. Parikh S, Sharma S, Shah JS. Kimura's disease: a confounding condition. *Indian J Otolaryngol Head Neck Surg*. 2022;74(Suppl 3):5342–6. <https://doi.org/10.1007/s12070-021-02511-1>.

21.1 Introduction

Leukemias and lymphomas are neoplasms arising from hematopoietic or immune system-derived cells at different stages of differentiation. While in principle neoplasms derived from all major and accessory immune cells (such as histiocytes, dendritic cells, and mast cells) could be considered within the same broad category, in practice, the term lymphoma is generally restricted to tumors originating from lymphocytes and their precursors. Historical entities such as histiocytic lymphoma or reticulum cell sarcoma are now recognized to be of lymphoid origin and have therefore been reclassified within the malignant lymphoma group. Clinically, diseases that form localized solid tumor masses are generally referred to as lymphomas, whereas those that disseminate in a diffuse and systemic fashion without forming mass lesions are called leukemias. In leukemias, not only lymphoid precursors but also progenitors of myeloid lineages (granulocytes, monocytes, megakaryocytes, and erythroid cells) may give rise to malignancies. For example, acute myeloblastic leukemia may

occasionally present as a solid mass, historically termed granulocytic sarcoma. The neoplasms of myeloid lineages are evaluated in Chap. 22. Overall, hematopoietic system neoplasms remain among the most conceptually and diagnostically challenging malignancies [1, 2].

In childhood, lymphomas rank as the third most common malignancy, following leukemias and central nervous system tumors. When considered together as hematopoietic malignancies, leukemias and lymphomas constitute the most frequent cancers of childhood. Among pediatric lymphomas, approximately 40% are Hodgkin lymphoma (HL) and 60% are non-Hodgkin lymphoma (NHL). Pediatric NHLs are typically of high grade and frequently present with extranodal involvement at diagnosis. Unlike leukemias, lymphomas are rarely observed in infancy; their incidence increases with age. For example, in the United States, the median age at diagnosis for pediatric NHL is approximately 10 years. Although case reports exist for nearly all lymphoma subtypes in the literature, most pediatric cases are restricted to HL and four main subtypes of NHL. The most common lymphomas in childhood can be summarized as follows: HL ($\approx 40\%$), Burkitt lymphoma ($\approx 25\%$), lymphoblastic lymphoma (15–20%), diffuse large B-cell lymphoma (DLBCL, 10–12%), and anaplastic large cell lymphoma (ALCL, 5–6%). In recent years, pediatric follicular lymphoma (PFL) has also been reported, but due to its rarity, it is not considered a major entity in this context. Contrarily, together

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with leukemias, lymphoid neoplasms account for approximately 4–5% of all cancers in adults worldwide. The overall annual incidence of lymphomas has increased steadily over the past decades, partly due to improved diagnostic techniques and aging populations. In adults, NHLs are significantly more frequent than HL. NHLs represent about 85–90% of all lymphomas, whereas HL constitutes the remaining 10–15%. The global age-adjusted incidence of NHL is estimated at ~19 cases per 100,000 persons per year, with higher prevalence in developed countries, while HL has a lower incidence of ~2–3 per 100,000 persons per year. The distribution of NHL subtypes in adults is also distinctive. The most common entities include DLBCL (~30–40%) and follicular lymphoma (FL; ~20%), followed by marginal zone lymphomas, mantle cell lymphoma, peripheral T-cell lymphomas, and Burkitt lymphoma. The relative frequency of subtypes varies geographically; for example, T-/NK-cell lymphomas are more prevalent in Asia and Latin America compared with Western countries. Adult lymphomas present with diverse clinical manifestations, ranging from localized nodal disease to aggressive systemic involvement with extranodal spread. Risk factors include age, immunosuppression (HIV, posttransplant, iatrogenic), chronic antigenic stimulation (e.g., *H. pylori* infection in gastric MALT lymphoma), autoimmune disorders, and specific genetic or chromosomal alterations. Advances in molecular diagnostics and immunophenotyping have significantly improved classification, prognostication, and therapeutic stratification [2–5].

The morphologic, immunophenotypic, and clinical features of leukemias and lymphomas reflect the lineage and maturation stage of the cell of origin. The major challenge in classification arises from the dynamic nature of hematopoietic cell differentiation. Unlike most somatic cells, which retain relatively stable antigenic and genetic identities, hematopoietic cells alter their antigenic profiles as they mature. For example, neutrophils express CD16, whereas their immediate precursors (metamyelocytes) do not. Similarly, both B and T lymphocytes undergo progressive shifts in their antigen expression pat-

terns during maturation, which pathologists use as diagnostic clues. Moreover, lymphoid cells undergo unique genetic rearrangements of immunoglobulin, B- and T-cell receptor genes during their development. These programmed alterations in gene expression create diagnostic challenges, but they also provide powerful tools for clonality assessment and molecular classification. Consequently, hematopathology often resembles detective work: assigning a definitive name to a suspected lymphoma can be compared to solving the identity of a well-constructed mystery novel [2].

21.2 Immunophenotypic Markers and Neoplastic Transformation

- *B-Cell Differentiation*: Immature B lymphocytes derived from bone marrow progenitor cells express surface IgM, which functions as the B-cell receptor (BCR). Early progenitors (pro-B cells) are characterized immunohistochemically by the expression of CD19, CD79a, CD34, CD10, and terminal deoxynucleotidyl transferase (TdT), while immunoglobulin genes have not yet undergone rearrangement (Fig. 21.1). Following rearrangement of the immunoglobulin heavy chain gene, these cells produce cytoplasmic μ chains and become pre-B cells. Neoplasms arising from this stage are classified as precursor B-lymphoblastic leukemia/lymphoma. With alternative splicing of Ig heavy chain mRNA, surface IgD is coexpressed alongside IgM. At this point, immunophenotypically, the cells express CD20 and CD22, but no longer express TdT or CD10. These antigen-naïve, mature B lymphocytes leave the bone marrow and migrate via the circulation to secondary lymphoid organs such as lymph nodes, spleen, mucosa-associated lymphoid tissues. Within the lymphoid follicles, they localize in the mantle zone of primary follicles and are referred to as mature B cells. Some mantle zone B cells express CD5, forming the putative cells of origin for mantle cell lymphoma

Fig. 21.1 Antigenic identity of B lymphocytes changing with maturation. (Courtesy: Prof. Dr. Gülden Diniz)

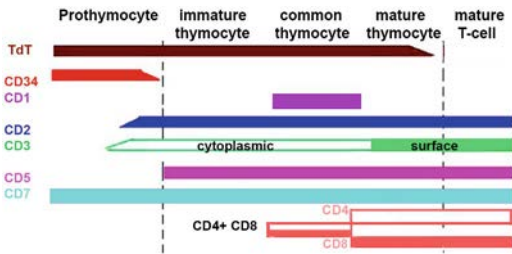
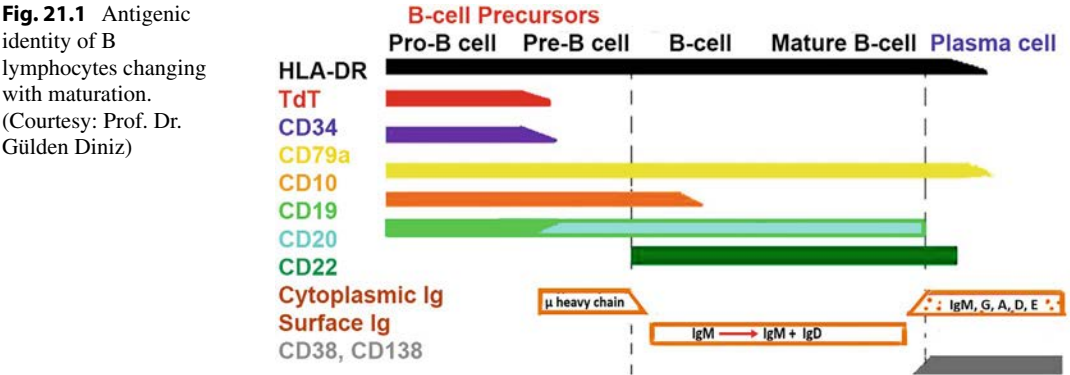


Fig. 21.2 Antigenic identity of T lymphocytes changing with maturation. (Courtesy: Prof. Dr. Gülden Diniz)

and subsets of small lymphocytic lymphoma. Upon antigen encounter, naïve B cells interact with T helper cell-derived IL-4 and migrate to germinal centers, where they differentiate into centroblasts with the help of follicular dendritic cells (FDCs). At the centroblast stage, surface immunoglobulin is downregulated, and BCL-2 expression is lost, allowing apoptosis of low-affinity clones. High-affinity clones survive despite lack of BCL-2 through survival signals from FDCs. Somatic hypermutation (SHM) occurs within variable regions of Ig genes, generating diverse clones with different antigen affinities. Centroblasts express the transcription factor BCL-6, and those with high-affinity BCRs differentiate into centrocytes. In centrocytes, BCL-2 is re-expressed while BCL-6 is downregulated by FDC and T-cell interactions through CD23 and CD40L signaling. Two key genomic alterations occur in germinal centers: class-switch recombination (CSR) and SHM, which refine antibody specificity and effector function. Centrocytes may differentiate into long-lived

memory B cells, which are residing in marginal zones of spleen and lymph nodes or plasma cells. Germinal center B cells typically express CD10 and BCL-6 in addition to pan-B markers. Neoplasms derived from this stage include Burkitt lymphoma, follicular lymphoma, diffuse large B-cell lymphoma (DLBCL), and Hodgkin lymphoma. Marginal zone memory B cells are precursors of marginal zone lymphomas and some small B-cell lymphomas [6, 7].

- **T-Cell Differentiation:** Immature T lymphocytes also express antigen-specific receptors known as T-cell receptors (TCRs), which mediate cellular immune responses or assist in humoral immunity. TCRs occur in two forms: $\gamma\delta$ TCR and $\alpha\beta$ TCR, the latter being predominant in lymph nodes and spleen. In the bone marrow, T-cell precursors are TCR-negative, carrying unrearranged germline TCR genes, and immunophenotypically express markers such as c-Kit (CD117) and CD44. These cells migrate to the thymus, where sequential gene rearrangements occur: β , then γ/δ , and finally α chains. Maturation proceeds from the thymic cortex to the medulla. At the cortical stage, thymocytes are CD4+CD8+ double-positive, and during selection in the medulla, they differentiate into either CD4+ helper T cells or CD8+ cytotoxic/suppressor T cells (Fig. 21.2) Neoplasms arising from immature thymic precursors are termed precursor T-lymphoblastic leukemia/lymphoma, whereas those derived from post-thymic mature T lymphocytes are classified as peripheral T-cell lymphomas [8, 9].

21.3 Molecular Pathogenesis and Diagnostic Tools

A critical event during both B- and T-cell development is V(D)J recombination mediated by recombination-activating genes (RAG1 and RAG2). DNA double-strand breaks during this process predispose to chromosomal translocations involving oncogenes, a hallmark of lymphoid malignancies. Today, modern diagnostics increasingly rely on molecular methods. Clonality assays of B- and T-cell receptor gene rearrangements (IgH, Igκ/Igλ on chromosomes 14, 2, and 22; TCR loci on chromosomes 14q11, 7q35, 7p13) are performed by polymerase chain reaction (PCR), which is sensitive and rapid technique. The most important advantage of PCR is applicable to paraffin tissue. These tests can be performed with the older Southern blotting technique, which is less sensitive and requires fresh tissue. Flow cytometry provides quantitative assessment of light chain restriction (κ/λ ratios), multiparametric immunophenotyping, DNA ploidy, and proliferative index (S-phase fraction). Non-Hodgkin lymphomas show aneuploidy in ~1/3 of cases, with proliferative rate correlating with histological grade [1, 2].

21.4 Classification

Hematopoietic progenitor cells are divided into two main lineages: lymphoid and myeloid progenitors. Lymphoid stem cells differentiate into B and T lymphocytes as their final products. Approximately 75% of lymphoid leukemias and nearly 90% of lymphomas are of B-cell origin. Leukemias and lymphomas exhibit distinct morphological, immunological, and clinical features depending on their cell of origin and stage of differentiation. However, it is important to note that the differentiation stage is not always predictive of disease behavior. For instance, Burkitt lymphoma, although derived from mature IgM-expressing follicular center B cells, demonstrates a more aggressive course and poorer treatment response than CD10-positive pre-B-cell acute lymphoblastic leukemia (ALL), which arises from a more immature stage (Fig. 21.3). The classification of lymphomas has undergone repeated revisions. Early systems included Rappaport (1966), Lukes–Collins (1974), Working Formulation (1982), and REAL (1994). The WHO classification (2001, revised 2008; 2017, and 2022 updates) integrates morphologic, immunophenotypic, clinical, and genetic data.

Fig. 21.3 Types of lymphoma according to the maturation stage of the lymphoid cell from which it originates. (Courtesy: Prof. Dr. Gülden Diniz)

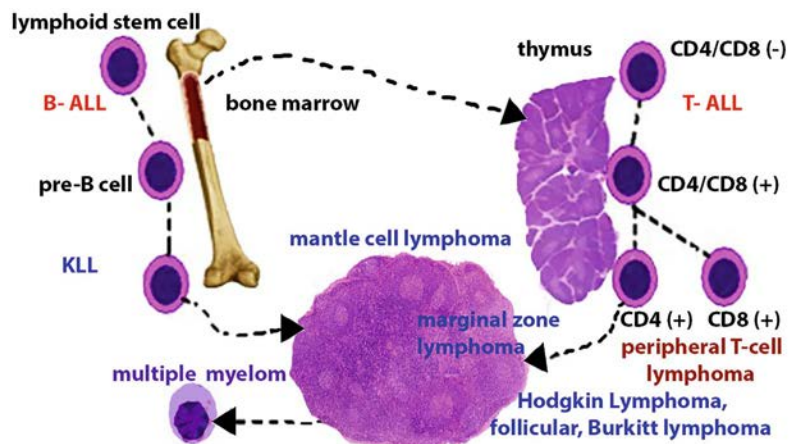


Table 21.1 Classification of lymphoid neoplasms (WHO 2022, simplified overview)

Category	Subtypes (examples)	Key features
B-cell neoplasms	Precursor B-lymphoblastic leukemia/lymphoma (B-ALL/LBL) Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) Follicular lymphoma Mantle cell lymphoma Marginal zone lymphoma (MALT, nodal, splenic) Burkitt lymphoma Diffuse large B-cell lymphoma (DLBCL) and variants High-grade B-cell lymphoma (double-/triple-hit) Plasma cell neoplasms (e.g., multiple myeloma)	CD19+, CD20+, PAX5+; most have recurrent cytogenetic abnormalities (e.g., t(14;18) BCL2 in follicular lymphoma; MYC translocation in Burkitt)
T- and NK-cell neoplasms	Precursor T-lymphoblastic leukemia/lymphoma (T-ALL/LBL) Peripheral T-cell lymphoma, NOS Angioimmunoblastic T-cell lymphoma (AITL) Anaplastic large cell lymphoma (ALK+/ALK−) Adult T-cell leukemia/lymphoma (HTLV-1 related) Extranodal NK/T-cell lymphoma, nasal type Hepatosplenic T-cell lymphoma	Often CD3+, CD2+, CD5+; variable CD4/CD8; cytotoxic markers in NK/T subtypes; common mutations: NOTCH1, TET2, RHOA, STAT3
Hodgkin lymphoma	Classical Hodgkin lymphoma (CHL): nodular sclerosis, mixed cellularity, lymphocyte-rich, Lymphocyte-depleted Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL)	CHL: CD30+, CD15+, weak PAX5+, CD45−. NLPHL: CD20+, BCL6+, CD30−, CD15−.
Immunodeficiency-associated lymphoproliferative disorders	EBV-positive DLBCL Posttransplantation lymphoproliferative disorders (PTLD) HHV8-associated lymphomas (e.g., primary effusion lymphoma)	Often arise in immunosuppressed settings (HIV, iatrogenic, posttransplant). EBV-driven in many cases

WHO divides non-Hodgkin lymphomas into four main categories: precursor B-cell neoplasms, mature B-cell neoplasms, precursor T-cell neoplasms, and mature T-cell/NK-cell neoplasms (Table 21.1). Precursor B- and T-cell groups also encompass acute lymphoblastic leukemia/lymphoma (ALL/LBL) [2].

21.5 Bone Marrow Infiltration in Lymphoproliferative Disorders

Bone marrow biopsy is an essential component in the diagnosis and staging of lymphoproliferative disorders, since bone marrow involvement frequently indicates advanced stage IV disease. At the time of initial evaluation, biopsy material

from the iliac crest provides important information not only about whether the marrow is infiltrated but also about the specific pattern of infiltration, which may carry diagnostic, prognostic, and therapeutic significance.

Aspirated material with anticoagulant allows for flow cytometric immunophenotyping, cytogenetic studies, and molecular analyses. Fluorescence in situ hybridization (FISH) can be performed on air-dried aspirate smears, imprint preparations, or cytospin slides and is particularly useful for identifying chromosomal alterations and fusion genes relevant to lymphoma classification. The trephine biopsy remains indispensable for histological evaluation, since infiltration patterns and stromal changes are best appreciated in sectioned material. Reticulin staining often highlights a mild increase in retic-

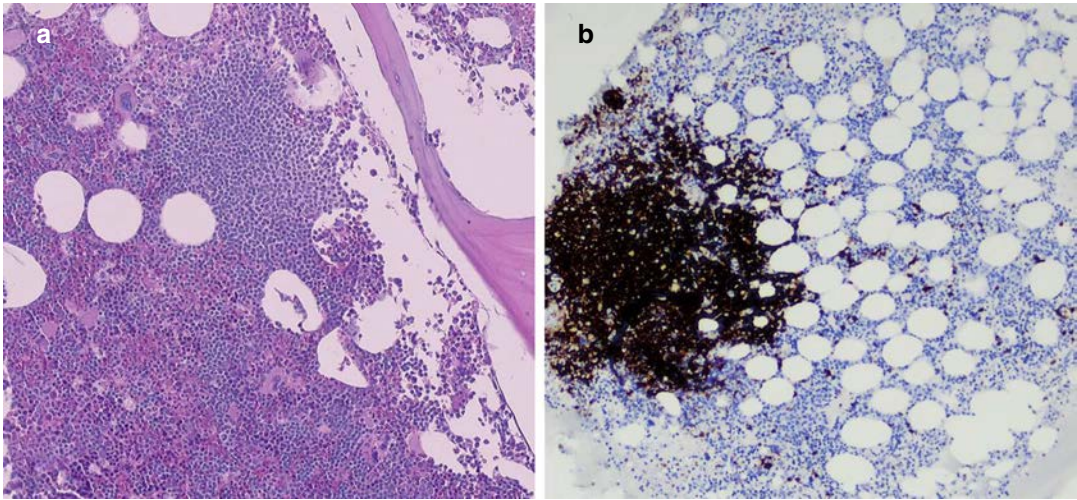


Fig. 21.4 Focal paratrabecular infiltration of a follicular lymphoma (a) is highlighted with immunohistochemical CD20 staining (b)

ular fibers, which helps to identify infiltrative foci, whereas over collagen fibrosis is much less common [10].

Histologically, lymphoma infiltration in bone marrow can be described in four major patterns. Interstitial infiltration consists of neoplastic cells scattered between hematopoietic and fat cells, usually preserving the marrow architecture. Focal or nodular infiltration is characterized by localized aggregates of tumor cells, which may be paratrabecular, adjacent to bony trabeculae (Fig. 21.4) or non-paratrabecular, forming random nodular or patchy clusters. This pattern nearly constitutes 70% of all infiltrations. Diffuse infiltration represents complete effacement of hematopoietic and adipose tissue by tumor cells (Fig. 21.5). Much less frequently, neoplastic cells may be restricted to endothelial-lined vascular spaces, producing a sinusoidal or intravascular pattern (<5%). In many cases, mixed patterns occur in the same biopsy. The frequency of bone marrow involvement varies with lymphoma subtype. Except for chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphomas, marrow infiltration is observed in approximately 30–50% of cases at diagnosis. B-cell lymphomas show marrow involvement more often than

T-cell neoplasms, and indolent B-cell tumors such as follicular lymphoma, small lymphocytic lymphoma, or marginal zone lymphoma typically present with focal and paratrabecular patterns. In contrast, aggressive lymphomas such as Burkitt lymphoma and lymphoblastic lymphoma usually display interstitial or diffuse patterns. Certain subtypes, including splenic marginal zone lymphoma, hepatosplenic T-cell lymphoma, and intravascular large B-cell lymphoma, are strongly associated with sinusoidal or intravascular marrow infiltration. Discordance between nodal or extranodal histology and bone marrow morphology is not uncommon, reported in 16–40% of cases. Often, the marrow shows a less aggressive histology compared with the primary tumor, but in some patients the opposite occurs, with more aggressive marrow involvement, which is associated with adverse prognosis. Because childhood NHL are generally high-grade, bone marrow infiltration is somewhat less common. In pediatric settings, bone marrow involvement is rare in Hodgkin lymphoma and tends to be focal when present, whereas in childhood non-Hodgkin lymphomas, diffuse infiltration is more frequently observed [10–13].

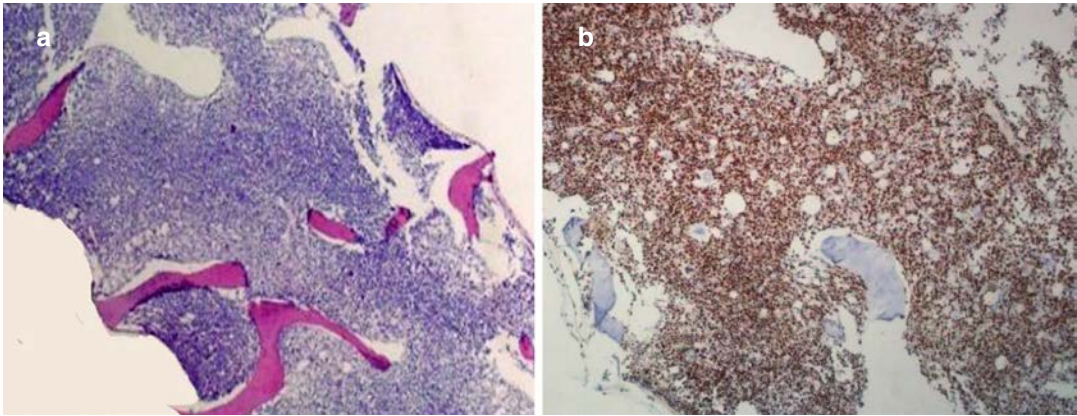


Fig. 21.5 (a) Diffuse bone marrow involvement in T-cell leukemia. (b) TdT positivity in cells

21.6 Hodgkin Lymphoma

Hodgkin lymphoma (HL) was first described by Thomas Hodgkin in 1832 and later termed Hodgkin's disease by Samuel Wilkins. Until the 1980s, there was considerable debate as to whether HL represented a true neoplasm or a reactive process secondary to infection. This controversy mainly arose because the neoplastic cells had lost most of their phenotypic features, making lineage determination difficult. With advances in immunologic and molecular studies over the past decades, it has been definitively established that the neoplastic cells of HL are derived from germinal center B cells. As a result, the designation lymphoma is now preferred. HL is divided into two main categories: classical HL (cHL) and nodular lymphocyte-predominant HL (NLP HL). Some features previously ascribed to the lymphocyte-rich subtype of cHL are now recognized as belonging to NLP HL. In NLP HL, the diagnostic hallmark cells are lymphocyte-predominant (LP) cells, also known as lymphocytic and histiocytic (LH) cells or popcorn cells, while in cHL they are Reed–Sternberg (RS) cells. Both cell types represent neoplastic proliferations of antigen-experienced germinal center B cells capable of interacting with T lymphocytes. A key feature of these neoplastic cells is somatic hypermutation of rearranged immunoglobulin variable (IgV) genes, which enhances antigen

affinity. LP cells often retain the expression of germinal center B-cell markers such as BCL6, HGAL, and centroblast-associated antigens. In contrast, RS cells usually lack these markers, making their cellular origin difficult to establish by immunohistochemistry. Nonetheless, clonal rearrangements and somatic mutations of immunoglobulin heavy and light chain genes are almost invariably detectable in HL, confirming their B-cell derivation. HL demonstrates a bimodal age distribution, with one incidence peak in adolescents and young adults (15–35 years) and a second peak in older adults (after 45–50 years). However, age distribution shows marked geographic variation. In less-developed countries and in socioeconomically disadvantaged groups within developed nations, the disease is more frequent in children and less common in young adults. Except for the nodular sclerosis (NS) subtype in young adults in the United States, HL overall is more common in males (male-to-female ratio approximately 1.3:1). Classical Hodgkin lymphoma (cHL) comprises four histologic subtypes. These are lymphocyte-rich (LR), mixed cellularity (MC), nodular sclerosis (NS), and lymphocyte-depleted (LD) HL [14–17].

In terms of histological subtypes, NS and LRHL are more prevalent among young adults, whereas MC and LDHL predominate in older patients. In less-developed regions, both pediatric

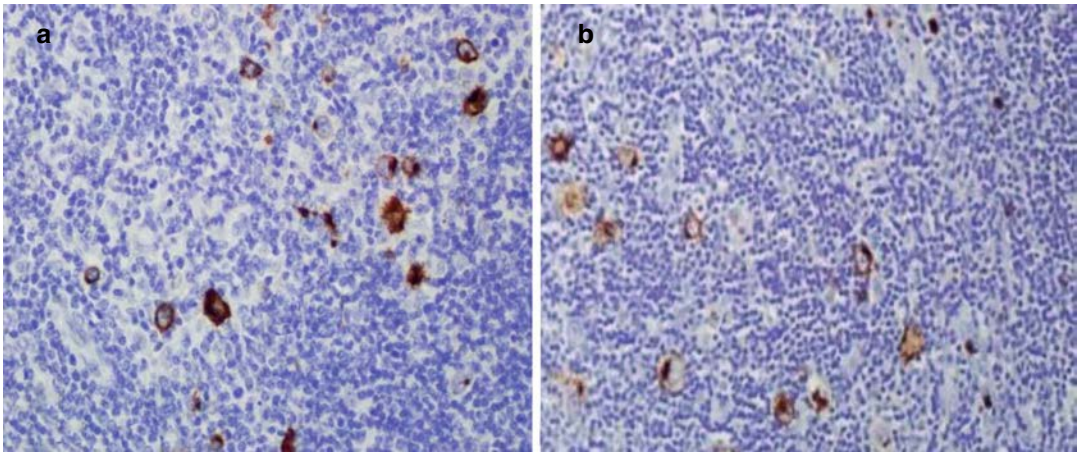


Fig. 21.6 (a) Strong cytoplasmic CD30 expression in RS cells. (b) CD15 expression not only in RS cells but also in small inflammatory cells

and adult cases are more often present with MC and LD subtypes. HL most commonly presents with painless peripheral lymphadenopathy. The disease usually involves a single lymph node or a small group of contiguous nodes; the involvement of multiple adjacent nodal regions typically reflects advanced disease. Systemic “B symptoms”—fever, night sweats, and weight loss—may also be observed. In contrast to NHL, extranodal involvement is relatively uncommon in HL. Among HL subtypes, the NS variant is the most frequent, accounting for approximately 60% of cases, followed by the mixed cellularity MC variant at ~30%. Other subtypes, including lymphocyte-rich classical HL (LRCHL) and LDHL, each constitute only about 3–5% of cases. NLPHL and LRCHL are associated with the most favorable prognosis, whereas MC and LD subtypes are more often linked to HIV infection, tend to present at advanced stages, and carry a poorer prognosis. Gross pathological appearance partly correlates with histological subtypes. Depending on the degree of fibrosis, lymph nodes may have a soft or firm consistency, with nodularity particularly common in the NS variant. Areas of necrosis may also be present. Except for NLPHL, the cut surface of affected lymph nodes generally appears more heterogeneous than that observed in NHL [14, 18].

In paraffin-embedded, formalin-fixed sections, RS cells and their variants (in all cHL sub-

types except NLPHL) typically express CD30 and CD15 (Fig. 21.6), but are negative for CD45RO, CD43, polyclonal CD3, and CD20. CD30 is a member of the tumor necrosis factor receptor (TNFR) superfamily, normally expressed on activated T and B lymphocytes. It is strongly and consistently expressed on RS cells in cHL and in anaplastic large cell lymphoma (ALCL), making it a hallmark diagnostic marker. Immunohistochemically, CD30 shows membranous and paranuclear (Golgi) staining in RS cells. Its restricted expression in normal tissues and strong presence in cHL have also made CD30 an important therapeutic target. The antibody–drug conjugate brentuximab vedotin, directed against CD30, is now widely used in relapsed or refractory HL. The small lymphocytes in the background are usually T cells, except in NSHL, where small B lymphocytes predominate. RS cell cytoplasm contains several proteins, including immunoglobulins, muramidase, and α 1-antitrypsin. PAX5, a transcription factor expressed during B-cell maturation, can be detected in most B-cell neoplasms, including those that lack other mature B-cell markers. In classical Hodgkin lymphoma, PAX5 shows a nuclear staining pattern in Reed–Sternberg (RS) cells. Importantly, the staining intensity in RS cells is typically weaker than in surrounding reactive B cells, a feature that facilitates their recognition in diagnostic practice. MUM1 (IRF4) is

Table 21.2 Immunohistochemical markers in Hodgkin lymphoma

Marker	Expression in RS cells	Pattern/notes	Diagnostic utility
CD30	Strongly positive	Membranous and paranuclear Golgi staining	Hallmark marker of RS cells; highly sensitive for classical HL
CD15	Positive in ~75–85% of cases	Membranous and cytoplasmic	Supports diagnosis of classical HL (less frequent in NLPHL)
PAX5	Weakly positive (nuclear)	Weaker than surrounding reactive B cells	Confirms B-cell lineage despite loss of other B-cell markers
MUM1 (IRF4)	Strongly positive	Nuclear	Indicates activated B-cell/plasmablastic phenotype
CD20	Usually negative (variable in NLPHL)	Membranous	Useful to distinguish NLPHL (strong CD20+) from cHL
CD45 (LCA)	Negative	–	Helps differentiate cHL (CD45–) from many NHLs (CD45+)
OCT2 and BOB.1	Usually negative in cHL; positive in NLPHL	Nuclear (when expressed)	Distinguishes NLPHL (OCT2/BOB.1+) from cHL
EBER (ISH)	Positive in ~40% overall, esp. MC and LD subtypes	Nuclear signal	Confirms EBV association, especially in HIV-related HL

a transcription factor associated with post-germinal center, plasmablastic differentiation. In Hodgkin lymphoma, RS cells are typically MUM1-positive, reflecting an activated B-cell/plasmablastic phenotype. This expression supports the concept that, despite their germinal center B-cell origin, RS cells have lost the program of mature B cells and adopted an aberrant transcriptional profile (Table 21.2). The heterogeneous inflammatory background is thought to represent an immunologic reaction driven by the neoplastic component. HL-derived cell lines produce multiple cytokines, including IL-1, TNF- α , TNF- β , G-CSF, M-CSF, and IL-4. RS cells secrete IL-6 and IL-9, which may act as autocrine growth factors; IL-6 is also implicated in the accumulation of plasma cells. In HL cases with eosinophilia, RS cells have been shown to express IL-5 mRNA, while NSHL frequently demonstrates TGF- β expression, thought to contribute to the characteristic fibrosis. Many clinicopathologic features of HL can thus be explained by cytokines produced by RS cells and surrounding reactive elements. The most important infectious agent implicated in the pathogenesis of Hodgkin lymphoma (HL) is the Epstein–Barr virus (EBV). Individuals with a history of infectious mononucleosis have an increased risk of developing HL, and the incidence of HL is three- to fourfold higher among EBV-seropositive persons compared to seronegative individuals. Patients with

HL typically demonstrate elevated antibody titers to viral capsid antigen, suggesting viral activation precedes the clinical diagnosis. In developing countries, particularly among children, the prevalence of EBV positivity is high, which may explain the increased frequency of the mixed cellularity (MC) subtype observed in these populations. Overall, approximately 40% of HL cases worldwide are associated with EBV infection. Using specific monoclonal antibodies, latent membrane protein-1 (LMP-1) has been demonstrated in RS cells and their variants, while in situ hybridization confirms the presence of EBV-encoded small RNAs (EBERs), providing strong evidence of infection. On the other hand, the types of HL whose association with EBV infection has not been proven are the NS subtype of cHL and NLPHL [2, 18].

- *Lymphocyte-rich Hodgkin lymphoma (LRHL)* is characterized by a background consisting predominantly of small lymphocytes, often mixed with numerous histiocytes, which can sometimes be dense. The diagnostic hallmark cells include variants of Reed–Sternberg cells known as lymphocytic and histiocytic (L&H) cells. These cells are characterized by large, frequently multilobated (“popcorn-like”) nuclei, a high nuclear-to-cytoplasmic ratio, finely dispersed chromatin, and inconspicuous nucleoli. In contrast to other subtypes of HL,

eosinophils, plasma cells, neutrophils, and classic RS cells are sparse in LRHL. Distinguishing LRHL from nodular lymphocyte-predominant HL (NLPHL) is critical: LRHL is rarer, tends to occur at an older age, and shows more frequent mediastinal involvement. In addition, the L&H cells are much fewer in number than seen in NLPHL. Even some cases that were previously described as a LRHL variant rich in L&H cells are now, in contemporary classification, interpreted as NLPHL.

- *Mixed cellularity Hodgkin lymphoma (MCHL)* is characterized by heterogeneous background infiltrate, composed of lymphocytes, histiocytes, eosinophils, and plasma cells. Within this milieu, numerous mononuclear Reed–Sternberg (RS) variants are observed; these resemble typical RS cells but have a single nucleus and can mimic immunoblasts. For diagnosis, it is essential to demonstrate the presence of the pathognomonic Reed–Sternberg (RS) cells. These are large cells with multiple nuclei or nuclear lobes, each containing prominent eosinophilic inclusion-like nucleoli and a perinuclear clear halo. The cytoplasm is moderate in amount and eosinophilic to amphophilic in staining. Typical binucleated RS cells—often referred to as “owl’s eye” cells—are not always easily identified (Fig. 21.7). Fibrosis is usually irregular

and necrosis is not a prominent feature. Among HL subtypes, MCHL is the one most frequently confused with peripheral T-cell lymphomas, particularly when a prominent component of epithelioid histiocytes is present.

- *Nodular sclerosis Hodgkin lymphoma (NSHL)* is the only subtype that occurs slightly more frequently in women. Its defining histologic feature is a thickened lymph node capsule with broad, birefringent collagen bands extending inward to divide the tumor into nodules. Within these nodules, the cellular composition varies and includes lymphocytes, histiocytes, eosinophils, plasma cells, and neutrophils, in addition to characteristic lacunar cells, a Reed–Sternberg (RS) cell variant (Fig. 21.8). Lacunar cells display multilobated nuclei with moderately prominent nucleoli and a clear perinuclear space produced by cytoplasmic retraction artifact. This artifact is most pronounced in formalin-fixed tissues, but less evident in samples fixed with Zenker or B5 solutions. Necrosis and microabscesses are often prominent in NSHL, and necrobiotic (“mummified”) cells with pyknotic nuclei and deeply eosinophilic cytoplasm are frequently observed. In some cases, fibrosis may be minimal; however, the presence of at least one well-developed birefringent collagen band arising from the capsule and extending into

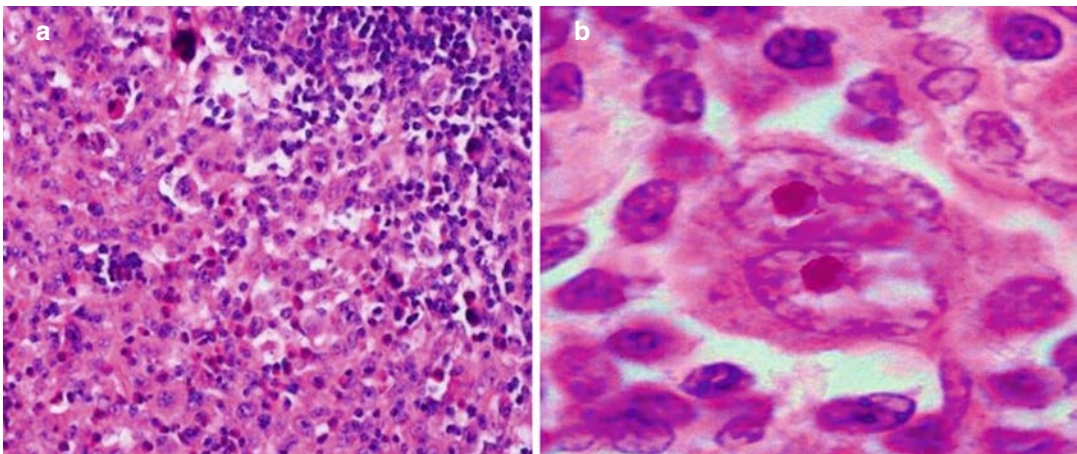


Fig. 21.7 (a) Mixed cellularity HL. (b) A Reed–Sternberg cell

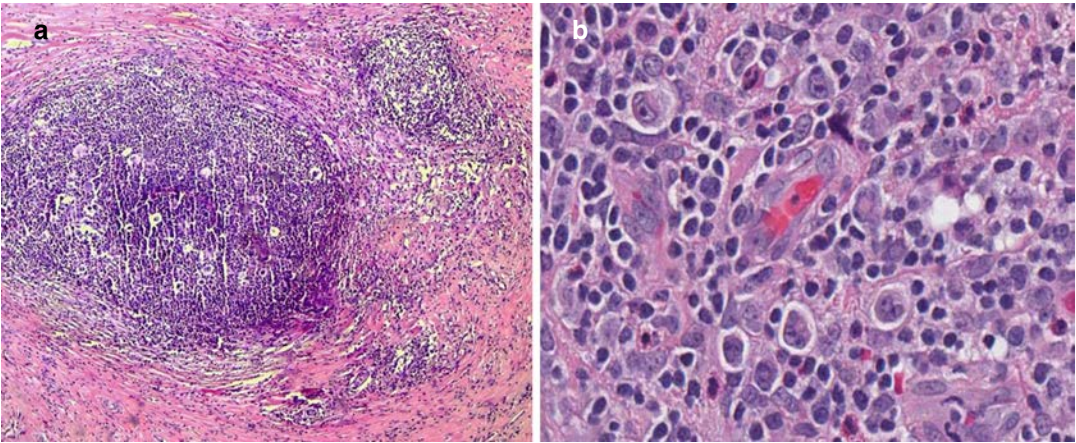


Fig. 21.8 (a) Nodular sclerosis HL. (b) Lacunar cells

Table 21.3 Ann Arbor staging system for HL (Cotswolds modification)

Stage	extent of disease
I	Involvement of a single lymph node region or a single lymphoid organ such as spleen, thymus, or Waldeyer's ring
II	Involvement of two or more lymph node regions on the same side of the diaphragm (mediastinal nodes count as a single region; hilar nodes are considered separately). The number of involved regions should be indicated as a suffix (e.g., stage II3 for three nodal regions involved)
III	Involvement of lymph node regions or lymphoid organs on both sides of the diaphragm <i>III1</i> : Involvement of spleen hilum, celiac, or portal lymph nodes, or liver <i>III2</i> : Involvement of para-aortic, iliac, or mesenteric lymph nodes
IV	Diffuse or disseminated involvement of one or more extranodal organs or tissues, with or without associated lymph node involvement

the node is required for classification as NSHL. Several variants of NSHL have been recognized. Cases with nodules containing numerous RS cell variants or pleomorphic forms, accompanied by reduced lymphocytes, tend to have a less favorable prognosis. When RS cells form cohesive clusters around necrotic foci, the so-called syncytial variant is diagnosed. These clustered cells lack the typical lacunar morphology. If a biopsy does not include typical NSHL areas, the syncytial variant may be easily mistaken for metastatic carcinoma or even a germ cell tumor.

- *Lymphocyte-depleted Hodgkin lymphoma (LDHL)* is rare, accounting for fewer than 5% of cases. It most often affects older patients and is associated with systemic symptoms, advanced-stage disease, and extensive supra-diaphragmatic involvement. Two morphologic patterns are recognized. These are diffuse

fibrosis type and reticular type. Diffuse fibrosis type is uncommon, characterized by replacement of nodal architecture with disorganized, non-birefringent fibrosis accompanied by marked depletion of lymphocytes. Large numbers of Reed–Sternberg (RS) cells are not necessarily required for diagnosis. Reticular type is characterized by marked proliferation of RS cells, which can be highly pleomorphic and bizarre. In extreme cases, these have historically been described as the sarcomatous type of HL. This variant may be confused with lymphocyte-depleted nodular sclerosis HL or with non-Hodgkin lymphomas containing numerous anaplastic tumor cells resembling RS cells (Table 21.3).

HL typically spreads from the initially involved lymph node to adjacent nodes through lymphatic channels. Retrograde lymphatic dis-

semination may also occur, and enlarging lymph nodes can directly invade adjacent organs. Hematogenous dissemination to distant organs is more frequent in the mixed cellularity (MC) and lymphocyte-depleted (LD) subtypes. Splenic involvement is almost always accompanied by hepatic infiltration. Although splenic disease is thought to facilitate hematogenous spread to distant sites, splenic infiltration alone does not necessarily indicate systemic dissemination. Abdominal disease commonly involves para-aortic and splenic lymph nodes, while mesenteric node involvement is rare. In nodular sclerosis HL (NSHL), mediastinal nodes are most frequently affected, with possible extension into the adjacent lung parenchyma. Extranodal disease originating primarily in non-lymphoid organs is rare; the most common extranodal sites are the liver (5–10%) and bone marrow (5–15%). Radiotherapy (RT) has been used in HL treatment since the 1920s. Extended-field RT was historically applied not only affected lymph nodes but also to adjacent nodal regions at risk of involvement. With the advent of modern approaches, combined modality therapy (chemotherapy plus RT) has become standard, particularly in patients with mediastinal masses and in pediatric cases, to reduce RT-related complications and avoid staging laparotomy. Today, the overall survival rate exceeds 90%. Prognosis is strongly influenced by disease stage and patient age at diagnosis. However, approximately 20% of patients fail to achieve complete remission or experience relapses after initial therapy; about half of these can achieve a second remission with salvage regimens. HL therapy is regarded as one of the greatest successes of modern oncology. The most serious late complication is the development of secondary malignancies. This includes an increased risk of NHLs (often of B-cell phenotype, especially following the lymphocyte-rich subtype), as well as carcinomas and sarcomas after long latency periods. The risk of solid tumors rises with time and is strongly associated with prior radiotherapy, as most secondary tumors arise in irradiated fields. MOPP chemotherapy has historically been linked with permanent sterility in men. Today, HL is considered one

of the most curable malignancies, with long-term survival rates exceeding 85–90% in early-stage disease under modern therapy. Prognosis depends on factors such as stage, presence of systemic “B” symptoms, bulky disease, and laboratory parameters (e.g., serum albumin, leukocytosis, lymphopenia). Standard treatment combines chemotherapy (ABVD or escalated BEACOPP regimens) with involved-site radiotherapy in selected cases. Immunotherapy is highly successful in refractory HL cases because HL is a neoplasm known for suppressing T-cell function. Therefore, novel targeted therapies, including brentuximab vedotin (anti-CD30 antibody–drug conjugate) and immune checkpoint inhibitors (e.g., PD-1 blockade), have significantly improved outcomes, particularly in relapsed or refractory HL [14, 15, 18, 19].

21.7 Nodular Lymphocyte-Predominant Hodgkin Lymphoma (NLPHL)

In NLPHL, the lymph node architecture is almost completely effaced by a nodular infiltrate, often leaving only a thin peripheral rim of residual tissue (Fig. 21.9). The nodular growth pattern can sometimes mimic follicular lymphoma. NLPHL nodules are primarily composed of small, round lymphocytes and variable numbers of epithelioid histiocytes, which may cluster. Eosinophils and neutrophils are rarely seen. Instead of classic Reed–Sternberg (RS) cells, NLPHL is characterized by lymphocytic and histiocytic (L&H) cells, also known as “popcorn cells.” These cells show folded, multilobulated nuclei with fine chromatin and small nucleoli, and are usually numerous within the nodules. NLPHL is believed to originate from B-cell areas of lymph nodes, particularly from progressively transformed germinal centers (PTGCs), although not all PTGCs evolve into HL. L&H cells express CD45, CD20, CD79a, BCL6, and PAX5 (the latter is often stronger than in classical HL). About 50% of cases express EMA, while EBER is negative. They do not express T-cell markers and, unlike classical RS cells, are usually negative for CD15

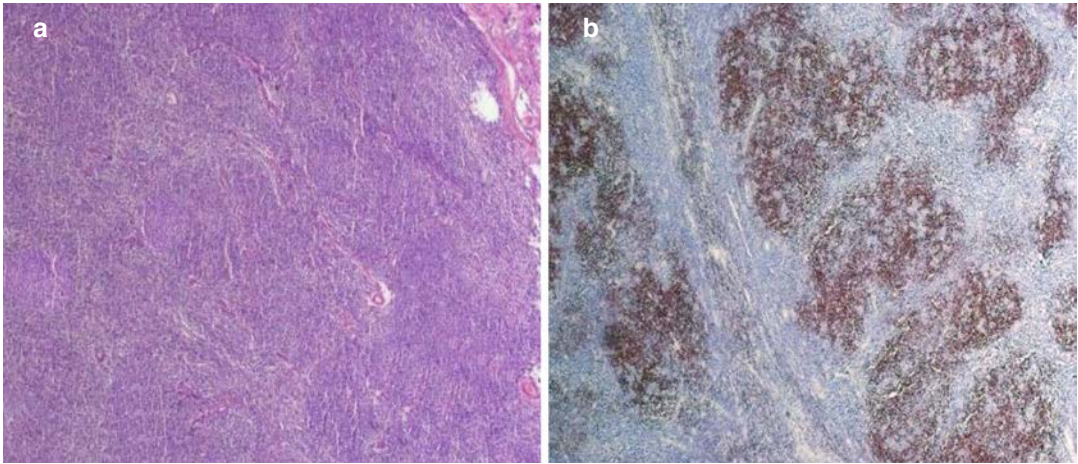


Fig. 21.9 (a) A lymph node with a vaguely nodular appearance in NLPHL, with its normal architecture erased. (b) T lymphocytes that create a mottled appearance in NLPHL with CD3

and CD30. The small lymphocytes surrounding the nodules are typically mantle zone B cells with a polytypic phenotype, although in some cases T cells predominate. L&H cells are frequently rosetted by CD57+ T cells. Nodules also contain a dense network of follicular dendritic cells (FDCs) and numerous small IgM+ and IgD+ B cells. On paraffin sections, popcorn cells react with CD45, CD20, CD74, and CDw75 antibodies. In most cases, multimeric immunoglobulin J chains and either κ or λ light chains (but not both) can be demonstrated. The presence of rearranged and somatically hypermutated Ig heavy chain genes in L&H cells confirms their germinal center B-cell origin. NLPHL typically presents with isolated cervical or axillary lymphadenopathy. The disease has an excellent prognosis, and in selected cases, watch-and-wait strategies have been recommended [16, 17].

21.8 Non-Hodgkin Lymphoma

- *Leukemias and their relationship with lymphomas:* When describing non-Hodgkin lymphomas (NHLs), it is important to also discuss leukemias, since in childhood the most frequent hematopoietic malignancy is lymphoblastic leukemia, which represents a clinical presentation of the same disease spectrum as lymphoblastic lymphoma. For this reason,

when bone marrow involvement is identified in a case, the diagnosis should specify the phenotype and indicate whether it represents leukemia and/or lymphoma infiltration. Acute leukemias are malignancies that arise from the neoplastic transformation and clonal proliferation of hematopoietic precursor cells. They may derive from progenitors with the potential for lymphoid, myeloid, or mixed differentiation. Historically, the French–American–British (FAB) classification of 1976 was widely used and provided a morphology-based framework. However, today the WHO classification (updated in 2022) is standard, as it integrates cytogenetic and molecular abnormalities. In this schema, acute myeloid leukemias (AMLs) are divided into five major categories. These are AML with recurrent genetic abnormalities, AML with myelodysplasia-related changes, therapy-related AML, myeloid proliferations associated with Down syndrome and AML, and not otherwise specified (NOS). The FAB system's M0–M7 subtypes are now largely encompassed within the NOS category. Similarly, acute lymphoblastic leukemias (ALLs) are classified as B-lymphoblastic, T-lymphoblastic, or those with recurrent genetic abnormalities. Diagnosis relies primarily on bone marrow aspiration smears, with evaluation of blast morphology and cytochemistry; biopsy is usually required

only in cases such as acute megakaryoblastic leukemia, where myelofibrosis obscures aspiration findings. AML originates from non-lymphoid precursors. The most immature forms may lack visible myeloperoxidase granules on light microscopy, detectable only by electron microscopy. AML is typically a disease of older adults (median age ~50), whereas ~80% of childhood leukemias are ALL. ALL blasts are higher nuclear-to-cytoplasmic ratio, scant cytoplasm, condensed chromatin, inconspicuous nucleoli (≤ 2), and basophilic cytoplasmic rim. AML blasts are more abundant gray-blue cytoplasm, frequent granules, 2–5 visible nucleoli, looser (“sieve-like”) chromatin. Auer rods, sometimes forming bundles (faggot cells), are diagnostic of AML, especially FAB M3 (acute promyelocytic leukemia). According to the FAB criteria, $\geq 20\%$ blasts in peripheral blood or marrow is required for diagnosis. One of the special variants of AML is AML-M6 (erythroleukemia, Di Guglielmo disease). It is characterized by cytoplasmic ferritin granules, mitochondrial iron deposits, and glycogen accumulation. Myeloid leukemias can involve lymph nodes, either in known leukemia patients or as the first manifestation of relapse or blastic transformation. These tumors are named as extramedullary myeloid tumors, granulocytic sarcoma, or chloroma for their yellowish color (myeloid neoplasms are discussed in detail in Chap. 22). Histologically, leukemic infiltrates can appear sinusoidal, interfollicular, or diffuse, often composed of uniform medium-sized cells with vesicular chromatin and prominent mitotic activity, sometimes producing a “starry sky” appearance (Fig. 21.5). Immunohistochemically, myeloblasts are positive for myeloperoxidase, CD43, and CD68, while they are weak positive or negative for leucocyte common antigen (LCA/CD45). Lymphoblasts are usually LCA (CD45) positive. Because of overlapping morphology, myeloid leukemias may be confused with NHLs (especially lymphoblastic or large-cell types), requiring immunophenotypic and cytochemical studies for accurate classification [2].

- *Chronic lymphoproliferative disorders (CLPDs)* are a heterogeneous group of indolent lymphoid neoplasms characterized by the clonal proliferation of mature B cells, T cells, or NK cells. Unlike acute leukemias, they usually present with a chronic clinical course, and patients may be asymptomatic at diagnosis. The spectrum includes B-cell disorders such as chronic lymphocytic leukemia (CLL), prolymphocytic leukemia (PLL), and hairy cell leukemia (HCL), T/NK-cell disorders such as T-prolymphocytic leukemia (T-PLL), large granular lymphocytic leukemia (T-LGL), Sézary syndrome, and adult T-cell leukemia/lymphoma (ATLL). These entities differ in morphology, immunophenotype, and clinical behavior, but they share the feature of being long-lasting clonal lymphoid proliferations, often involving the blood, bone marrow, lymph nodes, and spleen.
- *Hairy cell leukemia (HCL)* is a rare B-cell neoplasm, accounting for approximately 2% of adult leukemias. The name derives from its distinctive cytoplasmic projections—seen by electron microscopy as cylindrical microvilli or pseudopodia—that give the cells a “hairy” appearance. HCL shows a B-cell immunophenotype and occurs predominantly in middle-aged adults (median age ~ 50 years), with a marked male predominance (M:F $\approx$ 4:1). Splenomegaly is characteristic, whereas lymphadenopathy is typically absent. Patients usually present with pancytopenia, which often improves after splenectomy. Histochemically, hairy cells are positive for tartrate-resistant acid phosphatase (TRAP), showing activity around the nuclear membrane and Golgi zone. Bone marrow involvement is virtually pathognomonic, with diffuse infiltration and associated myelofibrosis. BRAF V600E is the genetic lesion underlying hairy-cell leukemia [2, 20].

Non-Hodgkin lymphoma (NHL) is the collective term for all lymphomas other than Hodgkin lymphoma (HL). Most NHLs are B-cell neoplasms, while a minority are of T- or NK-cell origin. Rare tumors lacking both B- and T-cell markers are sometimes referred to as “null-cell”

lymphomas. True histiocytic lymphomas are exceedingly rare.

In the United States, NHL accounts for approximately 3% of all malignancies. The male-to-female ratio is about 1.3:1, with a median age at diagnosis of ~55 years. However, NHL is also common in children, where it represents the third leading cause of cancer-related death, usually in the form of aggressive subtypes. Untreated pediatric NHLs may be rapidly fatal within weeks or months. NHL is more common in white populations. Follicular lymphomas occur less frequently in Europe than in North America, and overall, B-cell lymphomas are less frequent in Asia. NHL occurs with increased frequency in individuals with congenital or acquired immunodeficiencies (e.g., HIV infection, posttransplant immunosuppression). Since the 1970s, the global incidence of NHL has increased by ~3–4% per year, partly attributable to the HIV epidemic. Environmental risk factors such as hair dyes, pesticides, and organic chemicals have been implicated, although evidence is variable. Low-dose radiation does not appear to increase risk. Certain infectious agents play etiologic roles: HTLV-1 in adult T-cell leukemia/lymphoma (ATLL) and EBV in several NHL subtypes. Like HL, NHLs are staged using the Ann Arbor (Cotswolds-modified) system, but

staging is less prognostically useful since NHL spread is less predictable. Prognosis depends not only on stage and grade but also on patient age, tumor bulk, performance status, extranodal involvement, and CNS disease. Most NHLs arise in lymph nodes, but extranodal disease is much more frequent than in HL. Common sites include the gastrointestinal tract (e.g., small cell lymphomas), thymus (lymphoblastic lymphoma), and the Waldeyer's ring. The vast majority of NHLs are monoclonal B-cell tumors, with fewer of T-cell lineage. Accordingly, they often show clonal immunoglobulin heavy/light chain gene rearrangements or T-cell receptor gene rearrangements. Many NHLs are defined by characteristic chromosomal translocations, typically involving antigen receptor loci juxtaposed with oncogenes, leading to dysregulated gene expression. The most famous translocations are t(8;14)(q24.1;q32.3), MYC translocated to IgH locus in Burkitt lymphoma; t(3;14)(q27;q32.3), BCL6 translocated to IgH locus in diffuse large B-cell lymphoma (DLBCL); and t(2;5)(p23;q35), ALK–NPM fusion with aberrant tyrosine kinase activity in anaplastic large cell lymphoma (ALCL) (Table 21.4). Especially in pediatric cases, immunophenotyping is crucial for treatment decisions: whether the tumor arises from

Table 21.4 Immunohistochemical and cytogenetic features of selected lymphoid neoplasms

Lymphoma	Key immunophenotype	Cytogenetic/molecular features
Hodgkin lymphoma	<i>Classical HL (CHL)</i> : CD45–, CD30+, CD15+/, PAX5 weak+, CD20+/, EBV+/ <i>Nodular lymphocyte predominant HL (NLPHL)</i> : CD45+, CD20+, CD30–, CD15–, PAX5+, BCL6+, EMA+	CHL: No recurrent balanced translocations; frequent 9p24.1 (PD-L1/PD-L2) alterations NLPHL: Often lacks EBV; shares overlap with B-cell lymphomas
Burkitt lymphoma	CD20+, CD10+, BCL6+, sIg+, BCL2–, TdT–, Ki-67 >95%	t(8;14)(q24;q32) MYC-IGH (~80% cases); t(2;8)(p12;q24) or t(8;22)(q24;q11) in remaining cases
Diffuse large B-cell lymphoma (DLBCL)	CD19+, CD20+, CD22+, CD79a+, variable CD10, BCL6, MUM1; BCL2+/-; TdT–	Highly heterogeneous; includes rearrangements in BCL2, BCL6, and MYC; double-/triple-hit lymphomas defined by concurrent MYC + BCL2 and/or BCL6
ALK(+) anaplastic large cell lymphoma (ALCL)	CD30+, ALK+ (nuclear and/or cytoplasmic), CD45 variable, EMA+/-, cytotoxic markers (TIA1, granzyme B, perforin) often positive	t(2;5)(p23;q35) → NPM1:ALK fusion most common; variant ALK fusions also described
Lymphoblastic lymphoma (LBL)	<i>B-LBL</i> : CD19+, CD20–/+, CD22+, PAX5+, TdT+, CD34+/-, sIg– <i>T-LBL</i> : cytoplasmic CD3+, CD2+, CD5+, CD7+, TdT+, CD34+/-, CD99+	Various genetic lesions; B-LBL associated with translocations like t(9;22) BCR:ABL1, t(12;21) ETV6:RUNX1; T-LBL associated with NOTCH1 and CDKN2A alterations

precursor vs. mature lymphoid cells, B vs. T lineage, and whether it represents an anaplastic large cell lymphoma (ALK+ or CD30+).

21.9 Precursor Lymphoid Neoplasms

This group includes acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL), which represent different clinical presentations of the same disease spectrum. According to the former FAB classification, three subtypes of ALL were defined. According to this terminology, the L1 morphology is usually derived from precursor B-cells, showing blasts with coarse chromatin and inconspicuous nucleoli; this is the most frequent form (~85%). L3 morphology (Burkitt-type) is characterized by cytoplasmic lipid vacuoles and is typically TdT- and PAS-; this form is rare (<5%). Approximately 15% of ALLs are of T-cell lineage. Although FAB morphology was useful historically, the WHO classification now integrates immunophenotypic, cytogenetic, and molecular features, making it the current standard. ALL and LBL share nearly identical clinical, pathologic, immunologic, and genetic features. LBL represents the tissue-based equivalent of ALL and is considered a high-grade malignant lymphoma derived from lymphoblasts resembling immature thymocytes. When bone marrow blasts exceed 25%, the disease is classified as ALL; with lesser marrow involve-

ment and predominant tissue/lymph node disease, the term LBL is used. LBL is relatively rare overall but accounts for ~1/3 of pediatric NHL cases. Male predominance is noted (M:F ≈ 2:1). The classic presentation is a large mediastinal mass, often associated with pleural or pericardial effusions, leading to respiratory compromise. Less common sites include supradiaphragmatic nodes, Waldeyer's ring, gonads, skin, or bone.

The Phenotypic Distribution of ALL

B-ALL: 80–85% of ALLs; peaks in children <6 years.

T-ALL: 15–20% of ALLs; more frequent in adolescent males.

LBL cases: ~90% are T-cell, ~10% B-cell.

LBL effaces lymph node architecture diffusely and often extends into perinodal soft tissue. Tumors consist of monotonous populations of small- to medium-sized blasts with fine chromatin, inconspicuous nucleoli, high mitotic activity, frequent single-cell necrosis, and scant cytoplasm, which is often not visible on routine sections. “Crush artifacts” are common (Fig. 21.10). Tingible-body macrophages may produce a starry sky appearance. Minimal inflammatory background is typical. Immunohistochemically, LBL/ALL is cytoplasmic CD3+, nuclear TdT+, and CD43+; most cases are CD45+. Early immature forms may show only CD7 (pre-thymic phenotype). More

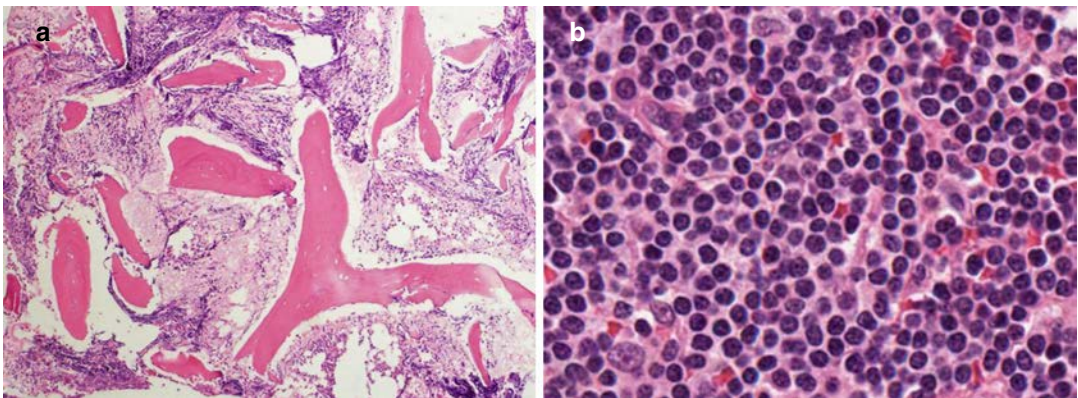


Fig. 21.10 (a) Bone marrow involvement of LBL with crushing artifact, (b) Neoplastic cells with very small nucleocytoplasmic ratio at high magnification

mature tumors express CD2, CD5, CD1, and CD4/CD8 combinations or cytotoxic/helper phenotypes. Some (~20%) show NK-associated markers (CD16, CD57). B-LBL/ALL is TdT+, CD19+, CD79a+, CD10+ (CALLA, often), CD34+ (~75%), and CD20 in ~50%. Surface Ig is typically absent; cytoplasmic Ig may be seen in pre-B stages. Rare TdT– B-LBL may mimic blastoid mantle cell lymphoma.

LBL is an aggressive neoplasm but responds well to multiagent chemotherapy regimens used for ALL, often achieving long-term remission. CNS is a common site of relapse; therefore, intrathecal chemotherapy or cranial irradiation is part of standard management. Prognostic factors include high-grade morphology, bone marrow or CNS involvement, elevated serum LDH, and advanced stage (most LBLs present at stage III/IV).

21.10 Mature B-Cell Neoplasms

A. Low-grade (indolent) B-cell lymphomas

- *Small lymphocytic lymphoma (SLL)/chronic lymphocytic leukemia (CLL)* is a low-grade diffuse B-cell lymphoma of small mature lymphocytes, representing the same disease with different clinical presentations. CLL is diagnosed when cir-

culating lymphocytes exceed 5000/ μ L and bone marrow infiltration surpasses 30%; otherwise, nodal or splenic disease is termed SLL. It constitutes about 5% of NHLs, usually affecting the elderly (mean age ~60). Patients often present with generalized lymphadenopathy (Fig. 21.11a), hepatosplenomegaly, and advanced-stage disease due to marrow involvement. The course is typically indolent, though Richter transformation to diffuse large B-cell lymphoma confers a poor prognosis. Tumor cells are CD45+, CD20+, usually CD23+, and weak CD5+ and show clonal immunoglobulin rearrangements; trisomy 12 and occasional TP53 mutations are detected. Median survival is ~6 years, and asymptomatic patients may be managed with watch-and-wait. Monoclonal B-cell lymphocytosis (MBL) represents an early precursor stage [2, 21, 22].

- *Lymphoplasmacytic lymphoma (LPL)* is a rare, indolent lymphoma composed of small lymphocytes, plasmacytoid lymphocytes, and plasma cells, accounting for ~5% of NHLs (more common in Europe). It typically affects older men and presents with widespread lymphadenopathy, splenomegaly, and bone marrow infiltration. Most cases are associated with IgM mono-

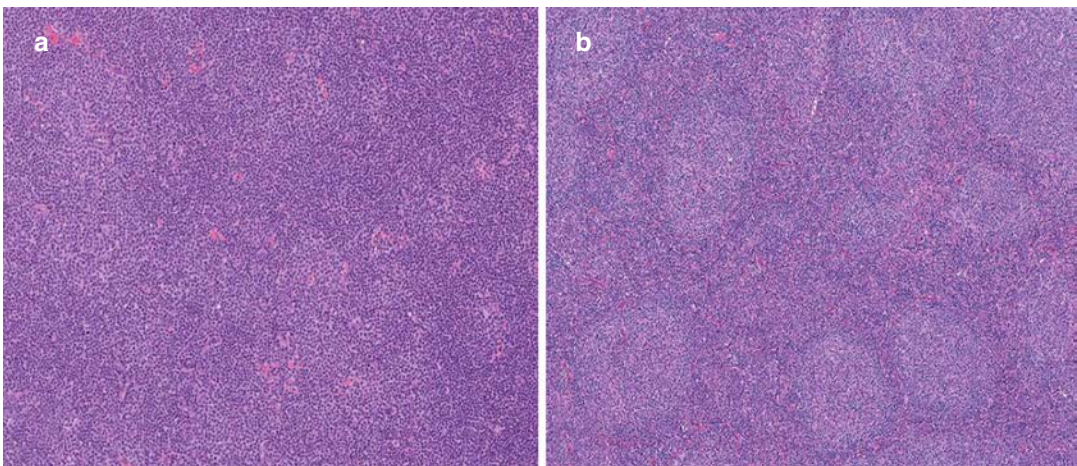


Fig. 21.11 (a) Lymph node is obliterated by diffuse monotonous cell infiltration in SLL. (b) Neoplastic cells show a nodular/follicular arrangement in FL

clonal gammopathy, and when serum IgM causes hyperviscosity, the disease is termed Waldenström macroglobulinemia. Histology shows diffuse effacement without proliferation centers, with Dutcher/Russell bodies, mast cells, and plasmacytoid cells. Tumor cells are CD45+, CD20+, and IgM+; negative for CD5, CD10, and CD23; and often positive for CD25, CD38, and CD71. Some cases carry a t(9;14)(p13;q32) translocation. Clinically, the course is indolent but not curable; plasmapheresis is required in hyperviscosity, and ~10% transform to aggressive lymphoma [2, 21, 22].

- *Nodal marginal zone lymphoma (NMZL)* accounts for about 5% of non-Hodgkin lymphomas and typically affects older adults, being very rare in children. The male-to-female ratio is roughly 1:2 in nodal cases and 1:1.3 in extranodal cases. It is a low-grade B-cell lymphoma derived from marginal zone cells that can differentiate toward monocytoid B cells or plasma cells. Primary nodal cases are sometimes called monocytoid B-cell lymphomas, while extranodal forms are usually classified as MALT lymphomas, particularly in the gastrointestinal tract, most often the stomach. Extranodal disease is frequently linked to autoimmune conditions, such as *H. pylori* infection in gastric cases or Sjögren syndrome in salivary gland cases. At diagnosis, bone marrow involvement occurs in ~40%, the spleen in 20%, the liver in 15%, and peripheral blood in ~5%. Early nodal disease shows tumor infiltration in the marginal zone around reactive follicles, sometimes colonizing germinal centers or spreading sinusoidally, with eventual effacement of nodal architecture. Neoplastic cells consistently express CD45 and CD20, along with CD19, CD20, CD22, and usually surface IgM. They are negative for CD5, CD10, CD23, and CD25. About 40% show monotypic light chain expression, but *bcl-1* and *bcl-2* rearrangements are absent. Some extranodal

cases demonstrate trisomy 23. Pathogenetically, *H. pylori* plays a central role in gastric marginal zone lymphoma by stimulating T-cell-mediated cytokine release and B-cell proliferation. Clinically, localized extranodal disease has an excellent prognosis, and gastric cases may regress with *H. pylori* eradication. However, both nodal and extranodal forms tend to become systemic over time, showing a chronic but indolent course. Bone marrow/peripheral blood involvement and transformation to diffuse large B-cell lymphoma are adverse prognostic indicators [2, 21].

B. Low to moderate grade B-cell lymphomas

- *Mantle cell lymphoma (MCL)* accounts for 5–10% of non-Hodgkin lymphomas (NHLs) in the United States, with higher frequency in Europe. It predominantly affects older adults, rarely children, and has a male predominance (~2:1). Most patients present with advanced (stage IV) disease and widespread lymphadenopathy. Bone marrow involvement occurs in about one-third of cases, with frequent infiltration of the spleen, Waldeyer's ring, peripheral blood, and gastrointestinal tract (lymphomatous polyposis). Two biologically distinct subtypes are recognized: the classical nodal form, SOX11-positive with little or no IGHV mutation and often aggressive (including blastoid variant), and the leukemic non-nodal form, SOX11-negative with IGHV mutations and frequent bone marrow, spleen, and blood involvement. Histologically, MCL is a low- to intermediate-grade lymphoma composed of small- to medium-sized lymphoid cells with mature chromatin and irregular nuclear contours. Growth patterns include diffuse effacement, nodular arrangements, or expanded mantle zones around germinal centers. Blastoid variants resemble lymphoblasts and carry a worse prognosis. Immunophenotypically, MCL cells express pan-B-cell markers (CD19, CD20, CD22), surface IgM ± IgD, and

frequently CD5 (aberrant coexpression) and CD43, but are typically CD23 negative, helping to distinguish them from CLL. They often show lambda light chain restriction. The hallmark genetic abnormality is t(11;14)(q13;q32), resulting in overexpression of cyclin D1 (CCND1/PRAD1), which drives uncontrolled cell cycle progression and proliferation. Clinically, MCL is considered an intermediate-grade lymphoma with a median survival of 4–5 years. Transformation to large cell lymphoma is relatively uncommon. A rare related entity, in situ mantle cell neoplasia, is characterized by cyclin D1-positive cells confined to mantle zones of reactive follicles and usually follows an indolent course [2, 23].

- *Follicular lymphoma (FL)*, historically called Brill–Symmers disease, is one of the most common non-Hodgkin lymphomas (NHL), representing ~40% of cases in the United States, 20% in Europe, and 10% in Asia. It typically affects middle-aged to older adults (median 55 years), while pediatric cases are extremely rare. The disease shows a slight male predominance (M:F $\approx$ 1.3:1). FL is a low- to

intermediate-grade B-cell lymphoma, corresponding to the neoplastic counterpart of germinal center B cells and maintaining a follicular architecture (Fig. 21.11b). While BCL2 expression is normally absent in reactive germinal centers, diffuse BCL2 expression is observed in follicular lymphoma, which mimics reactive hyperplasia with a follicular growth pattern (Fig. 21.12). FL has traditionally been graded by counting centroblasts in ten consecutive high-power fields within neoplastic follicles: grade 1 (0–5 centroblasts/HPF), grade 2 (6–15/HPF), grade 3a (>15/HPF with residual centrocytes), and grade 3b (sheets of centroblasts without centrocytes). Grades 1 and 2 have been regarded as indolent, grade 3a as intermediate, and grade 3b as aggressive, often managed similarly to diffuse large B-cell lymphoma (DLBCL). However, reproducibility issues in identifying and counting centroblasts, as well as clinical evidence showing little outcome difference between grades 1/2 and 3a under modern treatment regimens, have prompted revisions. In the fifth edition of the WHO classification (WHO-HAEM5 2022), grading of con-

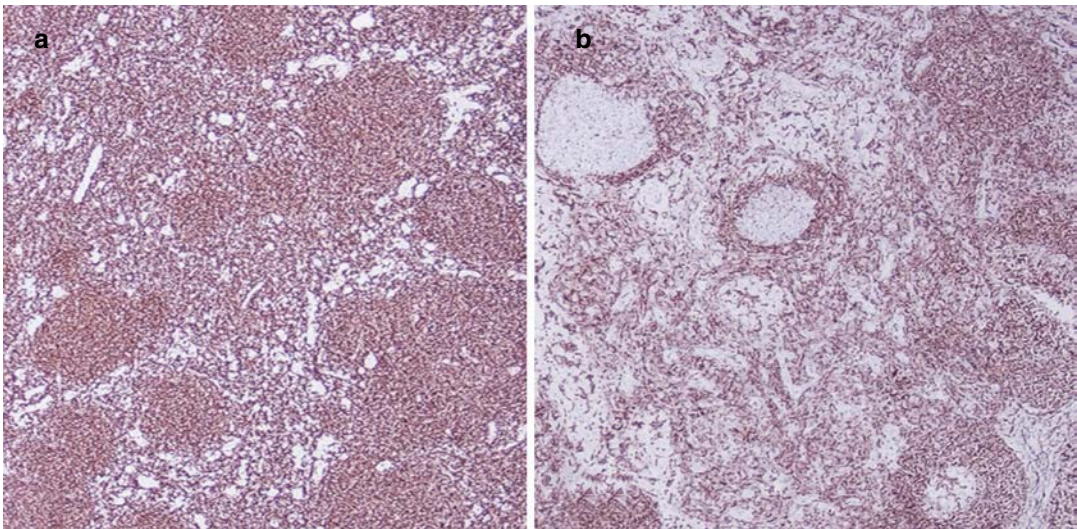


Fig. 21.12 (a) BCL2 expression is diffuse positive in FL. (b) BCL2-negative germinal centers in a reactive hyperplasia

ventional FL is now considered optional, with greater emphasis placed on molecular features and recognition of variant subtypes, such as blastoid or large centrocytic forms, which often lack the t(14;18) translocation and BCL2 expression but share other genetic alterations common to FL. Clinically, most patients present with lymphadenopathy, but two-thirds are diagnosed at stage IV, usually due to bone marrow infiltration. Liver and spleen are often involved. Despite advanced disease, the course is usually indolent, with occasional spontaneous regressions. However, 30–40% of cases transform into aggressive lymphomas, particularly DLBCL. Immunophenotypically, FL cells are B-cell lineage (surface/cytoplasmic Ig in >90%, usually IgM $\pm$ IgD), CD10 positive, CD5/CD43 negative, and BCL2 positive in ~80–90% of cases. They grow within a dendritic cell meshwork highlighted by CD21/CD35, with helper T cells often in interfollicular areas. Genetically, the hallmark t(14;18) (q32;q21) translocation is found in 80–90% of cases, leading to deregulated BCL2 expression and apoptosis inhibition. Breakpoints are clustered in the major (50–60%) or minor (10–20%) breakpoint regions. Secondary abnormalities (1p21–22, 6q23–26, 17p) contribute to aggressiveness and transformation, with TP53 and MYC mutations linked to progression. Prognosis is influenced by growth pattern and genetic complexity. Cases with preserved follicular growth and low-grade morphology have better survival, whereas diffuse areas (>25%) and complex cytogenetics predict poor outcome. Several variants of FL are now recognized as distinct entities. Predominantly diffuse FL shows a diffuse growth pattern with some genetic differences, such as CD23 expression, STAT6 mutations, or 1p36 deletion. FL with unusual cytological features includes blastoid or large centrocytic variants, which

cannot be graded by conventional criteria. Follicular large B-cell lymphoma (FLBCL) corresponds to the former grade 3B category, reclassified due to its distinct morphology and biology. In situ follicular neoplasia (ISFN) is retained as a precursor lesion by WHO-HAEM5. ISFN is defined by reactive follicles colonized by BCL2-positive and CD10-positive cells with IGH::BCL2 rearrangement. These lesions are usually incidental and rarely progress, but may coexist with overt FL. These changes emphasize a shift toward a biologically and clinically relevant classification. Optional grading reflects recognition that histological grade does not always guide therapy in the modern treatment era, whereas identification of biologically distinct variants and precursor lesions may have greater prognostic and therapeutic relevance [2, 24].

C. High-grade B-cell lymphomas

- *Diffuse large B-cell lymphoma (DLBCL)* is the most common NHL, accounting for about 35% of cases. It affects mainly adults (median age 55) but also occurs in children, where it represents 20–25% of pediatric lymphomas. Based on cell-of-origin, it is classified into germinal center B-cell-like (GCB) and activated B-cell-like (ABC) subtypes. GCB has a better prognosis, while ABC behaves more aggressively. In children, the GCB subtype predominates, partly explaining their more favorable outcome. DLBCL may arise de novo or evolve from other lymphomas (e.g., follicular lymphoma, CLL/SLL) and can also be associated with autoimmune diseases, immunodeficiency, or EBV infection. Patients usually present with a rapidly enlarging nodal or extranodal mass. About 40% are extranodal, commonly involving the gastrointestinal tract, skin, or Waldeyer's ring. Nodal disease often affects cervical, axillary, or mediastinal regions. B symptoms occur in ~25% of patients, and about half present with advanced stage (III–IV), often with liver

or spleen involvement. Bone marrow infiltration occurs in 10–15%, while blood involvement is rare. Histologically, lymph node architecture is effaced by large lymphoid cells with vesicular nuclei, prominent nucleoli, and moderate cytoplasm (Fig. 21.13a). Morphologic variants include centroblastic and immunoblastic forms. Necrosis and fibrosis are common. Immunophenotypically, nearly all cases are CD45+, CD20+, CD19+, and CD22+. CD10, BCL6, and BCL2 expression is variable. Ki-67 proliferation index is usually around 40% but can approach 100%. Aberrant CD5 or CD43 expression is rare. Genetically, BCL2, BCL6, and MYC alterations are frequent. “Double-hit” (MYC + BCL2) and “triple-hit” (MYC + BCL2 + BCL6) lymphomas define aggressive high-grade subgroups with poor prognosis. Treatment typically consists of R-CHOP chemotherapy, sometimes with radiotherapy. The remission rate is ~80%, and the 5-year overall survival is ~60%. Patients not achieving complete remission often relapse within a few years. Novel strategies such as CAR T-cell therapy, BTK inhibitors, and immunomodulatory drugs are expanding therapeutic options, especially in relapsed/refractory disease [25, 26].

- *Burkitt lymphoma (BL)* is an extremely aggressive B-cell lymphoma with the shortest known tumor cell cycle (24–48 hours). First described in Africa by Denis Burkitt, it was also the first human tumor linked to Epstein–Barr virus (EBV) and the first lymphoma associated with the c-MYC oncogene. Histologically, BL consists of uniform medium-sized B cells with basophilic cytoplasm and lipid vacuoles, round nuclei with multiple nucleoli, and frequent mitoses. Numerous tingible body macrophages among apoptotic debris create the classic “starry sky” pattern (Fig. 21.13b). The WHO classification recognizes three clinical variants:
 - *Endemic BL* (African children, often involving jaw/facial bones, strongly EBV-associated).
 - *Sporadic BL* (more frequent in Western countries, usually presenting with abdominal masses, especially ileocecal).
 - *Immunodeficiency-associated BL* (often HIV-related, with frequent nodal and marrow involvement).

Immunophenotypically, BL expresses surface IgM, CD19, CD20, CD22, CD79a, CD10, and BCL6, with a Ki-67 proliferation index close to 100%. It is negative for CD5, CD23, BCL2, CD138, and

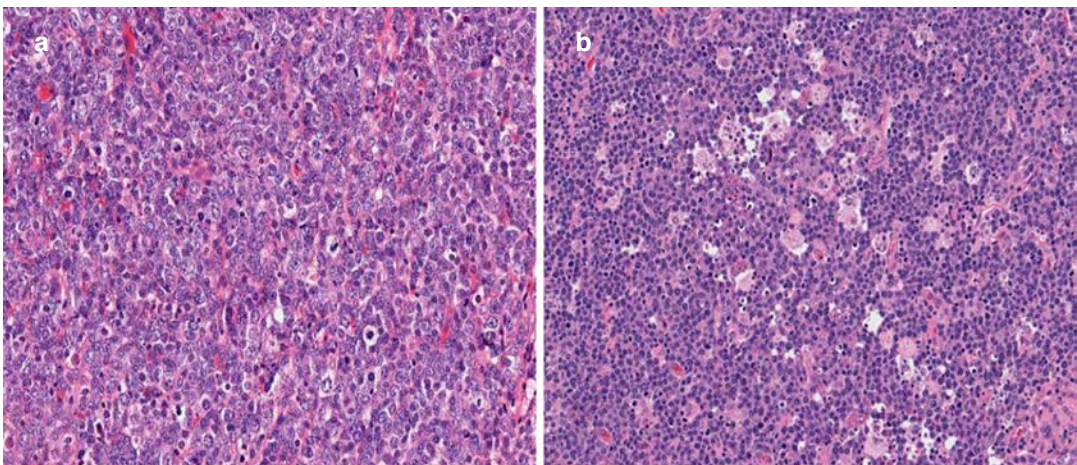


Fig. 21.13 (a) Large cell infiltration in DLBCL. (b) Starry sky appearance in BL

TdT. Cytogenetically, over 80% of cases harbor MYC translocations, most commonly t(8;14)(q24;q32) involving the Ig heavy chain locus. Clinically, about 70% of patients are present with advanced disease (stage III/IV), often with high LDH and risk of CNS involvement. Untreated, survival is limited to weeks or months, but with intensive multi-agent chemotherapy, 5-year survival reaches ~90% in children with localized disease and 60–70% in disseminated disease. Adult outcomes are less favorable, with survival around 50–70%. Relapses usually occur within the first year; absence of relapse after 2 years is considered curative [26, 27].

Mature T-cell neoplasms include nodal entities such as peripheral T-cell lymphoma (PTCL), angioimmunoblastic T-cell lymphoma (AITL), and follicular T-cell lymphoma. Most cases fall into intermediate- to high-grade categories [28].

- *Peripheral T-cell lymphoma (PTCL)* is a post-thymic T-cell lymphoma with morphology and immunophenotype resembling mature T cells. It is uncommon, accounting for 10–15% of diffuse lymphomas in the United States, more frequent in Asia, and predominantly affects older patients (male/female ratio ~3:2). HTLV-1 is the etiologic agent of adult T-cell leukemia/lymphoma, while EBV may be associated in a minority of PTCLs involving the upper aerodigestive tract. Patients often present generalized lymphadenopathy, skin involvement, and extranodal disease in bone marrow, liver, lung, or spleen (stage III/IV). B symptoms are common. Histology shows diffuse effacement without follicular architecture, with medium- to large-sized atypical lymphoid cells, irregular or multilobated nuclei, clear cytoplasm, abundant reactive background cells, and prominent high-endothelial venules. Immunophenotypically, most cases express CD45, CD2, CD3, CD5, and CD7, though aberrant loss of one or more T-cell antigens occurs in ~75% of cases, most often CD7. Most are CD4+CD8–, but other patterns exist. CD56 may be expressed in some, correlating with unusual extranodal sites. Clonal TCR gene rearrangements and cytogenetic abnormalities (6p, 1p, 1q) are frequent. Clinical stage is the main prognostic factor.
- *Angioimmunoblastic T-cell lymphoma (AITL)* is closely related to angioimmunoblastic lymphadenopathy and belongs to the T-follicular helper (TFH) cell-derived group. It shows diffuse nodal effacement, marked vascular proliferation, and absence of germinal centers and may contain EBV-positive B-cell blasts that mimic Reed–Sternberg cells. Genetically, AITL shares recurrent mutations with other TFH-derived lymphomas, supporting their biological relationship. Histologically, it may also appear as Lennert lymphoma, characterized by diffuse or clustered epithelioid histiocytes mixed with atypical T cells and inflammatory cells.
- *Adult T-cell leukemia/lymphoma (ATLL)* is a variant of PTCL associated with HTLV-1 infection, transmitted by blood transfusion, sexual contact, or breastfeeding. Patients usually have generalized lymphadenopathy, hepatosplenomegaly, skin and bone marrow involvement, hypercalcemia, and circulating multilobated “flower” cells. Immunophenotypically, ATLL is typically CD25 positive and CD7 negative. Prognosis is poor, with a median survival of less than 1 year.
- *Extranodal NK-/T-cell lymphoma, nasal type*, is also known as angiocentric T-cell lymphoma; this entity most often arises in the upper aerodigestive tract (especially nasal cavity) and skin. It shows a strong association with Epstein–Barr virus (EBV). Some patients develop hemophagocytic syndrome. The hallmark is vascular infiltration by atypical lymphoid cells, often leading to necrosis. Tumor cells typically lack most pan-T antigens but express CD2 and the NK marker CD56, suggesting derivation from NK cells, although they lack other NK markers (CD16, CD57).
- *Enteropathy-associated T-cell lymphoma (EATL)*: Two subtypes are recognized. Type I

is strongly associated with celiac disease and occurs mainly in Northern Europe, with pleomorphic intestinal infiltrates extending into the epithelium. Type II, also termed monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL), is not linked to celiac disease and is more frequent in Asian and Hispanic populations. Tumor cells infiltrate surface epithelium and adjacent mucosa, typically expressing CD8, CD56, MATK, and CD103. The jejunum is the most common site, but colon may also be involved.

- *Indolent gastrointestinal T-cell lymphoproliferative disorder* is derived from CD8+ (rarely CD4+) T cells; this disorder involves the GI tract, usually follows a benign course, and has an excellent prognosis.
- *Systemic EBV+ T-cell lymphoma of childhood* is a part of EBV-associated pediatric T-/NK-cell proliferations. Clinical spectrum ranges from localized cutaneous disease (e.g., hydroa vacciniforme-like disorder, mosquito-bite hypersensitivity) to fulminant systemic lymphoma with hepatosplenomegaly and hemophagocytic syndrome. The systemic form progresses rapidly and has poor prognosis.
- *Hepatosplenic T-cell lymphoma (HSTCL)* is a rare lymphoma involving hepatic sinusoids, splenic red pulp, and bone marrow. Tumor cells are usually negative for CD5 and CD7, with clonal rearrangements of TCR γ/δ or δ/α genes. Variants include hepatosplenic T-cell

lymphoma and erythrophagocytic $\gamma\delta$ T-cell lymphoma, historically confused with malignant histiocytosis. Clinically, patients present with hepatosplenomegaly, cytopenias, and hemophagocytic syndrome. Prognosis is poor, and the disease is highly aggressive.

- *Anaplastic large cell lymphoma (ALCL)* is a rare T-/null-cell lymphoma, accounting for ~5% of NHLs. It is defined by pleomorphic, large lymphoid cells with strong CD30 expressions that may mimic carcinoma or melanoma (Fig. 21.14). Tumor cells often have abundant cytoplasm and hallmark horseshoe- or doughnut-shaped nuclei with prominent nucleoli. Reed–Sternberg-like cells and a mixed reactive infiltrate with plasma cells, histiocytes, and eosinophils are common. Immunophenotypically, cells express CD30, CD45, EMA, CD25, and variably T-cell markers (CD3, CD43, CD45RO), with frequent aberrant loss of pan-T antigens. CD15 is negative. Some cases lack both B- and T-cell markers (null type). The major genetic hallmark is t(2;5) (p23;q35), producing the NPM–ALK fusion protein, which drives proliferation and blocks apoptosis. ALK is expressed in ~60–80% of ALCL, more often in children and young adults. Three clinical forms are recognized:
 - *ALK-positive systemic ALC* affects children and young adults, more common in males. Generally has a favorable prognosis, with 5-year survival ~80%.

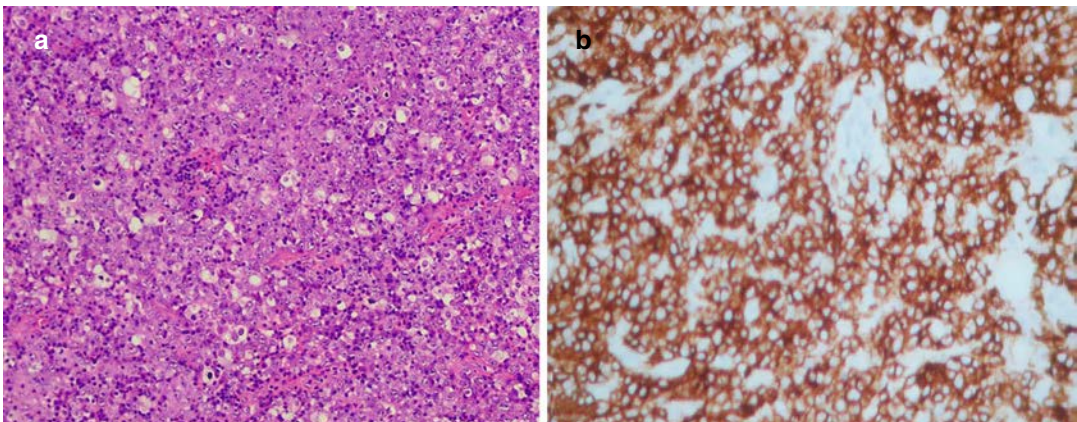


Fig. 21.14 (a) ALCL. (b) Diffuse CD30 expression in neoplastic cells

- *ALK-negative systemic ALCL* occurs in older adults, more aggressive, with ~40% 5-year survival.
- *Breast implant-associated ALCL* is ALK-negative; it arises ~10 years after implant surgery, usually confined to pericapsular effusion; prognosis is good if invasion is absent.
- *Cutaneous ALCL and lymphomatoid papulosis* represent indolent skin-limited forms, with high survival (>80%), though ~10% may progress to systemic disease.

Systemic disease is often advanced at presentation, with extranodal involvement (skin, bone, lung, soft tissue) in up to 60%. Prognosis is strongly determined by ALK status, age, stage, and presence of B symptoms. Standard therapy includes multi-agent chemotherapy (e.g., CHOP-based regimens), with radiotherapy or surgery for localized cutaneous disease. High-dose methotrexate or cytarabine may be used in pediatric cases. Relapses occur in ~30% but are often salvageable. Hematopoietic stem cell transplantation provides durable remission in selected patients. New targeted therapies, including ALK inhibitors and anti-CD30 agents (brentuximab vedotin), are promising, especially in relapsed/refractory disease.

- *Cutaneous lymphomas* are NHLs that originate primarily in the skin and are classified

into various subgroups based on clinical, histological, and immunophenotypic differences. The absence of extracutaneous involvement for at least 6 months after diagnosis is the key criterion distinguishing them from systemic lymphomas secondarily involving the skin. After gastrointestinal lymphomas, cutaneous lymphomas represent the second most common group of extranodal lymphomas. The majority have a T-cell phenotype (Fig. 21.15). Approximately half of the cases are composed of mycosis fungoides (MF), which derives from T cells. MF can occur at any age and in both sexes. Chronic antigenic stimulation, retroviral infections, and long-term exposure to carcinogenic substances have been implicated as possible etiologic factors. The classic form of MF is referred to as Alibert–Bazin-type classic MF, which progresses through three distinct clinical stages. The first stage, known as the premycotic stage, is characterized by erythematous, scaly patches resembling eczema, located on various areas of the trunk, often pruritic and most frequently found in sun-protected sites such as the gluteal region. The second stage, the infiltrated plaque stage (mycotic stage), also presents with intense pruritus, often leading to misdiagnosis as fungal infection. The third stage, the tumor stage, is defined by the development of nodular or tumoral lesions on preexisting patches or

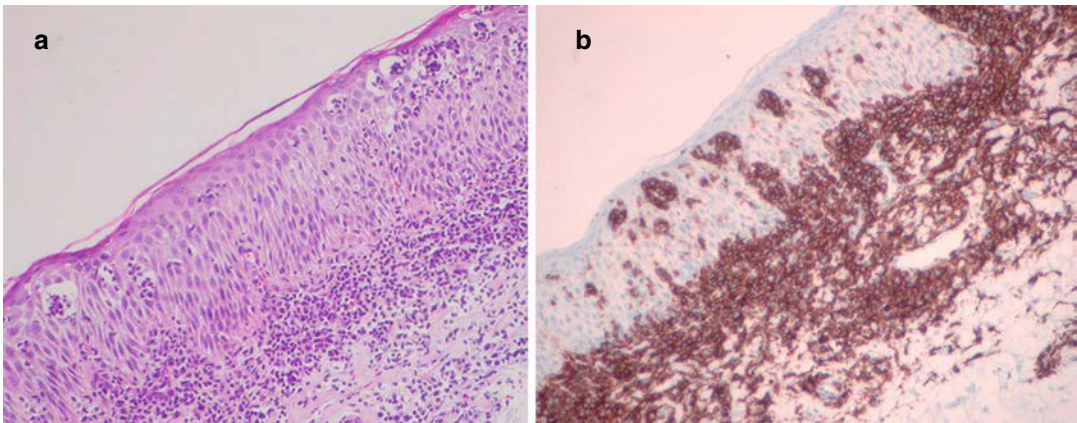


Fig. 21.15 (a) Notice the dense lymphoid infiltration with prominent epidermotropism and formation of Pautrier microabscesses. (b) The neoplastic cells are CD3-positive T lymphocytes

plaques or on clinically normal skin. During this stage, patches, plaques, and tumors often coexist. Extracutaneous involvement may occur, commonly affecting lymph nodes, bone marrow, spleen, liver, and lungs. Circulating neoplastic T cells, known as Sézary cells, are present in approximately 25% of cases, a condition termed Sézary syndrome. Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder is usually localized and managed with conservative therapy. Because it is rarely associated with systemic disease, it is thought to represent a clonal response to an unknown stimulus rather than a fully developed systemic lymphoma.

21.11 Other Neoplasms

- *True histiocytic lymphoma (malignant histiocytosis)* is a rare malignant neoplasm derived from monocytes or histiocytes, today recognized to account for only about 0.5% of large cell lymphomas. Many cases historically classified as such have been redefined through immunophenotyping as B-, T-, or null-cell lymphomas, often anaplastic large cell lymphoma. Documented cases are very few, typically in adult males, presenting with lymph node and skin involvement, sometimes also affecting the liver, spleen, or intestine. Bone marrow infiltration is frequent, and prognosis is poor, with most patients dying within 1 year despite multi-agent chemotherapy. Histologically, lymph node architecture is effaced by pleomorphic large cells with prominent nucleoli, requiring immunohistochemistry to confirm histiocytic differentiation (CD45, CD68, CD4, CD11c, lysozyme) and to exclude B- or T-cell markers.
- *Rare dendritic or reticulum cell sarcomas* include *follicular dendritic cell sarcoma* and *interdigitating dendritic cell sarcoma*. Follicular dendritic sarcoma usually arises in a single lymph node of adults and shows spindle cells in fascicular or storiform patterns, expressing CD21, CD35, and sometimes S-100 or CD68. It tends to recur locally but behaves as a low-grade sarcoma. Interdigitating dendritic cell sarcoma arises from paracortical dendritic cells, is also rare, and behaves more aggressively, with many patients dying within a year.
- *Langerhans cell histiocytosis (LCH)*, formerly called histiocytosis X, is a rare clonal proliferative disorder of dendritic cells with phenotypic and functional features similar to epidermal Langerhans cells. It often involves the skin, bone, or lung, though lymph nodes can also be affected. Most patients are children or young adults presenting with localized or generalized lymphadenopathy, sometimes with fever. It occurs in both children and adults but is more common in the pediatric population, particularly under the age of 15. The disease spectrum ranges from localized bone lesions (eosinophilic granuloma) to multisystem involvement with poor prognosis, such as Letterer–Siwe disease in infants. Histologically, LCH is characterized by infiltration of tissues with large mononuclear cells showing grooved, folded, or “coffee-bean” nuclei and abundant pale cytoplasm. Eosinophils, lymphocytes, plasma cells, and multinucleated giant cells are frequently admixed. Immunohistochemically, the lesional cells express CD1a, langerin (CD207), and S-100 protein (Fig. 21.16a). Ultrastructural hallmark is the presence of Birbeck granules, rod- or racket-shaped cytoplasmic organelles. Clinically, the most common sites are the bone (especially skull, ribs, pelvis), skin, and lymph nodes. In multisystem disease, the liver, spleen, bone marrow, and lungs may be affected. Prognosis depends on age at presentation, extent of organ involvement, and response to therapy. Localized disease often has an excellent outcome, while disseminated LCH with risk-organ involvement carries a poorer prognosis [29].
- *Plasma cell neoplasms* represent a spectrum of disorders characterized by the clonal proliferation of plasma cells, the most common of which is multiple myeloma (MM). When the disease is localized to a single site, it is referred to as plasmacytoma, whereas sys-

temic involvement of the bone marrow and multiple skeletal sites defines MM. Multiple myeloma is defined by the neoplastic expansion of monoclonal plasma cells within the bone marrow, usually associated with the production of a monoclonal immunoglobulin (M protein). The disease most frequently presents multifocal osteolytic lesions involving the vertebrae, ribs, skull, pelvis, femur, clavicle, and scapula. These lytic bone lesions result from increased osteoclast activation mediated by tumor cell–derived cytokines (e.g., RANKL, IL-6) and reduced osteoblast activity, producing the classic radiographic “punched-out” appearance. MM predominantly affects older adults, with a peak incidence between the ages of 50 and 80, and is more common in men. Clinical manifestations include bone pain, pathological fractures, anemia, hypercalcemia, renal impairment, and recurrent infections. The acronym CRAB (hypercalcemia, renal dysfunction, anemia, bone lesions) summarizes the main diagnostic features. Plasmacytoma may arise in the bone (solitary bone plasmacytoma) or soft tissues, most commonly in the upper aerodigestive tract (extramedullary plasmacytoma). Solitary plasmacytomas may remain localized but in a

significant proportion of cases progress to MM over time. Histologically, plasma cell neoplasms show sheets of mature and immature plasma cells with eccentric nuclei, clock-face chromatin, and perinuclear hof (Fig. 21.16b). Immunohistochemistry demonstrates monoclonal cytoplasmic immunoglobulin light chain restriction (κ or λ). Cytogenetically, MM is associated with recurrent abnormalities, including translocations involving the IgH locus at 14q32 (e.g., t[11;14], t[4;14], t[14;16]) and deletions at 17p13 (TP53), which have prognostic significance. Cyclin D1 antibody positivity, detected in approximately 25% of multiple myeloma cases, may be associated with the t(11;14) translocation. Treatment depends on the extent of disease. Solitary plasmacytomas are often managed with local radiotherapy or surgery, whereas MM requires systemic therapy, typically including proteasome inhibitors (e.g., bortezomib), immunomodulatory drugs (e.g., lenalidomide), corticosteroids, and autologous stem cell transplantation in eligible patients. Despite therapeutic advances, MM remains an incurable disease in most cases, although survival has significantly improved over the last two decades [30].

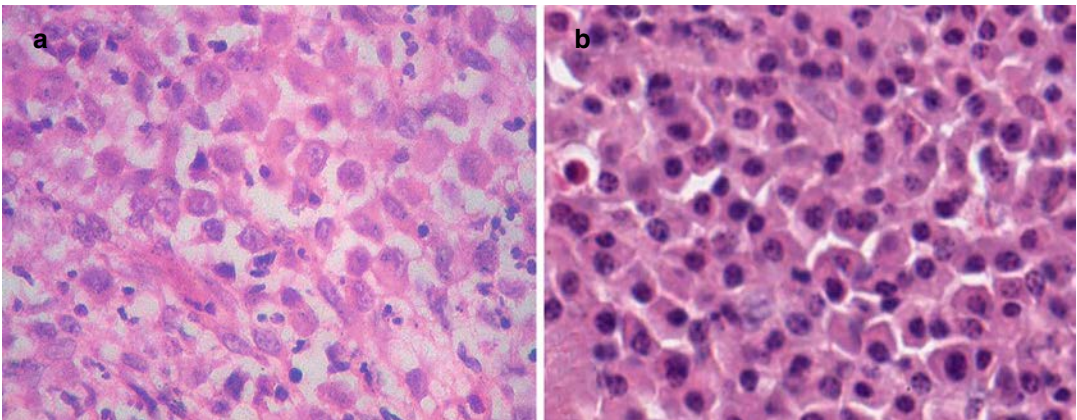


Fig. 21.16 (a) LCH in a 10-year-old girl with a persistent perianal ulcer and diabetes insipidus for 2 years. (b) Clock-face chromatin pattern in a plasmacytoma

References

1. Cairo MS, Pinkerton R. Childhood, adolescent and young adult non-Hodgkin lymphoma: state of the science. *Br J Haematol*. 2021;192(2):227–47.
2. WHO Classification of Tumours Editorial Board. WHO classification of haematolymphoid tumours. 5th ed. Lyon: IARC; 2022.
3. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin*. 2023;73(1):17–48. <https://doi.org/10.3322/caac.21763>.
4. Miranda-Filho A, Piñeros M, Znaor A, Marcos-Gragera R, Steliarova-Foucher E, Bray F. Global patterns and trends in the incidence of non-Hodgkin lymphoma. *Cancer Causes Control*. 2019;30(5):489–99. <https://doi.org/10.1007/s10552-019-01155-5>.
5. Mafra A, Laversanne M, Gospodarowicz M, Klinger P, De Paula SN, Piñeros M, Steliarova-Foucher E, Bray F, Znaor A. Global patterns of non-Hodgkin lymphoma in 2020. *Int J Cancer*. 2022;151(9):1474–81. <https://doi.org/10.1002/ijc.34163>.
6. Haberman AM, Gonzalez DG, Wong P, Zhang TT, Kerfoot SM. Germinal center B cell initiation, GC maturation, and the coevolution of its stromal cell niches. *Immunol Rev*. 2019;288(1):10–27. <https://doi.org/10.1111/imr.12731>.
7. Lee RD, Munro SA, Knutson TP, LaRue RS, Heltemes-Harris LM, Farrar MA. Single-cell analysis identifies dynamic gene expression networks that govern B cell development and transformation. *Nat Commun*. 2021;12(1):6843. <https://doi.org/10.1038/s41467-021-27232-5>.
8. Xing Y, Wang X, Jameson SC, Hogquist KA. Late stages of T cell maturation in the thymus involve NF- κ B and tonic type I interferon signaling. *Nat Immunol*. 2016;17(5):565–73. <https://doi.org/10.1038/ni.3419>.
9. Bao X, Qin Y, Lu L, Zheng M. Transcriptional regulation of early T-lymphocyte development in thymus. *Front Immunol*. 2022;13:884569. <https://doi.org/10.3389/fimmu.2022.884569>.
10. Martin-Moro F, Lopez-Jimenez J, Garcia-Marco JA, Garcia-Vela JA. Comparative review of the current and future strategies to evaluate bone marrow infiltration at diffuse large B-cell lymphoma diagnosis. *Diagnostics (Basel)*. 2024;14(6):658. <https://doi.org/10.3390/diagnostics14060658>.
11. Bonometti A, Tzankov A, Albrelli I, Russkamp NF, Dertinger S, Dimhofer S. Intrasinusoidal bone marrow involvement in mantle cell lymphoma: a case series with review of the main differential diagnoses. *Virchows Arch*. 2025;486(3):563–72. <https://doi.org/10.1007/s00428-024-03885-7>.
12. Khanlari M, Chapman JR. Follicular lymphoma: updates for pathologists. *J Pathol Transl Med*. 2022;56(1):1–15. <https://doi.org/10.4132/jptm.2021.09.29>.
13. Te Vrugt M, Newman H, Teachey DT, Burkhardt B. T-cell lymphoblastic lymphoma in children, adolescents and young adults. *Br J Haematol*. 2025;207:1213–21. <https://doi.org/10.1111/bjh.70053>.
14. Steidl C, Connors JM, Gascoyne RD. Molecular pathogenesis of Hodgkin's lymphoma: increasing evidence of the importance of microenvironment. *J Clin Oncol*. 2011;29(14):1812–26. <https://doi.org/10.1200/JCO.2010.32.8401>.
15. Mottok A, Steidl C. Biology of classical Hodgkin lymphoma: implications for prognosis and novel therapies. *Blood*. 2018;131(15):1654–65. <https://doi.org/10.1182/blood-2017-09-772632>.
16. Hartmann S, Döring C, Jakobus C, Rengstl B, Newrzela S, Tousseyn T, Sagaert X, Ponzoni M, Facchetti F, Steidl C, Gascoyne R, Küppers R, Hansmann L. Nodular lymphocyte predominant Hodgkin lymphoma and T Cell/histiocyte rich large B cell lymphoma – endpoints of a spectrum of one disease? *PLoS One*. 2013;8(11):e78812. <https://doi.org/10.1371/journal.pone.0078812>.
17. Younes S, Rojansky RB, Menke JR, Gratzinger D, Natkunam Y. Pitfalls in the diagnosis of nodular lymphocyte predominant Hodgkin lymphoma: variant patterns, borderlines and mimics. *Cancers (Basel)*. 2021;13(12):3021. <https://doi.org/10.3390/cancers13123021>.
18. Shanbhag S, Ambinder RF. Hodgkin lymphoma: a review and update on recent progress. *CA Cancer J Clin*. 2018;68(2):116–32. <https://doi.org/10.3322/caac.21438>.
19. Connors JM, Cozen W, Steidl C, Carbone A, Hoppe RT, Flechtner HH, Bartlett NL. Hodgkin lymphoma. *Nat Rev Dis Primers*. 2020;6(1):61. <https://doi.org/10.1038/s41572-020-0189-6>. Erratum in: *Nat Rev Dis Primers*. 2021;7(1):79. <https://doi.org/10.1038/s41572-021-00319-5>.
20. Tiaci E, Park JH, De Carolis L, Chung SS, Broccoli A, Scott S, Zaja F, Devlin S, Pulsoni A, Chung YR, Cimminiello M, Kim E, Rossi D, Stone RM, Motta G, Saven A, Varettoni M, Altman JK, Anastasia A, Grever MR, Ambrosetti A, Rai KR, Fraticelli V, Lacouture ME, Carella AM, Levine RL, Leoni P, Rambaldi A, Falzetti F, Ascani S, Capponi M, Martelli MP, Park CY, Pileri SA, Rosen N, Foà R, Berger MF, Zinzani PL, Abdel-Wahab O, Falini B, Tallman MS. Targeting mutant BRAF in relapsed or refractory hairy-cell leukemia. *N Engl J Med*. 2015;373(18):1733–47. <https://doi.org/10.1056/NEJMoa1506583>.
21. Yoshino T, Tanaka T, Sato Y. Differential diagnosis of chronic lymphocytic leukemia/small lymphocytic lymphoma and other indolent lymphomas, including mantle cell lymphoma. *J Clin Exp Hematop*. 2020;60(4):124–9. <https://doi.org/10.3960/jslrt.19041>.

22. Silkenstedt E, Salles G, Campo E, Dreyling M. B-cell non-Hodgkin lymphomas. *Lancet*. 2024;403(10438):1791–807. [https://doi.org/10.1016/S0140-6736\(23\)02705-8](https://doi.org/10.1016/S0140-6736(23)02705-8).
23. Wilson MR, Barrett A, Cheah CY, Eyre TA. How I manage mantle cell lymphoma: indolent versus aggressive disease. *Br J Haematol*. 2023;201(2):185–98. <https://doi.org/10.1111/bjh.18697>. Epub 2023 Feb 20. PMID: 36807902.
24. Kridel R. Follicular lymphoma: contemporary clinical management with a focus on recent therapeutic advances. *Korean J Intern Med*. 2025;40(3):371–93. <https://doi.org/10.3904/kjim.2024.279>.
25. Zamò A, Johnston P, Attygalle AD, Laurent C, Arber DA, Fend F. Aggressive B-cell lymphomas with a primary bone marrow presentation. *Histopathology*. 2020;77(3):369–79. <https://doi.org/10.1111/his.14124>.
26. Barracclough A, Hawkes E, Sehn LH, Smith SM. Diffuse large B-cell lymphoma. *Hematol Oncol*. 2024;42(6):e3202. <https://doi.org/10.1002/hon.3202>.
27. Moleti ML, Testi AM, Foà R. Treatment of relapsed/refractory paediatric aggressive B-cell non-Hodgkin lymphoma. *Br J Haematol*. 2020;189(5):826–43. <https://doi.org/10.1111/bjh.16461>.
28. de Leval L, Gaulard P, Dogan A. A practical approach to the modern diagnosis and classification of T- and NK-cell lymphomas. *Blood*. 2024;144(18):1855–72. <https://doi.org/10.1182/blood.2023021786>.
29. Rodriguez-Galindo C, Allen CE. Langerhans cell histiocytosis. *Blood*. 2020;135(16):1319–31. <https://doi.org/10.1182/blood.2019000934>.
30. Rajkumar SV. Multiple myeloma: 2024 update on diagnosis, risk-stratification, and management. *Am J Hematol*. 2024;99(9):1802–24. <https://doi.org/10.1002/ajh.27422>.

Myeloid Neoplasms and Myeloproliferative Disorders

22

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22.1 Introduction

Myeloid neoplasia, myeloproliferative disorders, and myeloproliferative neoplasms are terms used in hematology to describe a group of diseases characterized by the abnormal growth, proliferation, or development of blood cells. These disorders arise from genetic alterations in hematopoietic stem cells or progenitor cells in the bone marrow, which results in overproduction of certain types of blood cells (such as erythrocytes, white blood cells, and/or platelets) or dysregulated cell growth. These entities may present in acute or chronic forms, or chronic disease may progress into blastic (acute) phase.

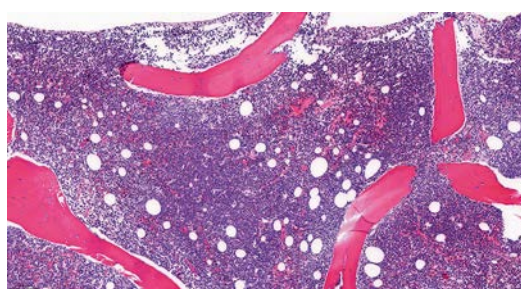


Fig. 22.1 Immature myeloid cells, “blasts” proliferate rapidly in AML, suppressing the production and growth of the normal bone marrow cells

22.2 Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is the clonal expansion of the myeloid cells in the bone marrow and, thus, in the peripheral blood. Rapidly proliferating immature myeloid cells (i.e., blasts)

suppresses the normal production and growth of the bone marrow cells (Fig. 22.1), resulting in acute bone marrow failure, and therefore, causing symptoms such as anemia, fatigue, shortness of breath, abnormal bleeding, and bruising.

Most AML cases are adults with a median age of 68 and with a slight male predominance [1]. History of chemotherapy and/or radiotherapy, exposure to radiation, smoking, exposure to benzene and similar chemicals, and history of blood disorders such as myelodysplastic syndrome are the known risk factors [2].

AML represents a heterogeneous group of disorders displaying different morphologic and molecular characteristics (Table 22.1). There used to be a cut-off of 20% blasts in the bone marrow for diagnosis; however, this cut-off has been eliminated in the current WHO classification, except AML with *BCR::ABL1* fusion and AML with *CEBPA* mutation which require $\geq 20\%$ blasts for diagnosis [3].

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Table 22.1 Classification of AML with defining genetic abnormalities per 2022 WHO classification [5]

Disorder	Key features	Bone marrow findings	Immunohistochemical features
Acute promyelocytic leukemia with <i>PML::RARA</i> fusion	Abnormal promyelocyte proliferation <i>PML::RARA</i> fusion (t(15;17)(q24;q21).) Previously called <i>acute promyelocytic leukemia</i> with t(15;17)(q24.1;q21.2); <i>acute promyelocytic leukemia</i> Often associated with coagulopathy Good prognosis	Hypercellular bone marrow Extensive blasts Hypergranular or microgranular blasts (abnormal promyelocytes) Auer rods may be seen in the cytoplasm of the blasts	CD34 negative CD13, CD33 and CD117 positive
AML with <i>RUNX1::RUNX1T1</i> fusion	<i>RUNX1::RUNX1T1</i> fusion May be called AML with t(8;21)(q22;q22.1) May present with myeloid sarcoma Presence of <i>KIT</i> mutations is associated with unfavorable prognosis	Hypercellular bone marrow Extensive blasts Blasts and myeloid precursors at various stages of maturation May show characteristics of AML without maturation Large blasts with basophilic cytoplasm and occasional Auer rods	CD34 positive CD13, MPO may be positive CD33 weak or negative
AML with <i>CBFB::MYH11</i> fusion	<i>CBFB::MYH11</i> fusion May be called AML with t(16;16)(p13.1;q22); AML with inv(16)(p13.1q22) Good prognosis	Hypercellular bone marrow Extensive blasts Myelomonocytic differentiation	Two sets of blasts: (1) CD34, MPO, CD117 positive, and (2) CD34 negative but other myeloid markers positive
AML with <i>DEK::NUP214</i> fusion	<i>DEK::NUP214</i> fusion Rare	Hypercellular bone marrow with increased blasts	CD13, CD33, CD34, CD38, KIT (CD117), CD123 and MPO positive CD34 may be negative
AML with <i>RBM15::MRTFA</i> fusion	<i>RBM15::MKL1</i> fusion Megakaryocytic differentiation Rare	Normocellular or hypercellular bone marrow Blasts may be <20% Myelofibrosis may be present	CD41, CD61, CD42b positive CD36 is positive CD13 and CD33 may be positive CD34, CD45, MPO, TdT are negative
AML with <i>BCR::ABL1</i> fusion	<i>BCR::ABL1</i> fusion Rare Poor prognosis	May show morphologic features of AML with minimal differentiation, without maturation, or with monocytic differentiation	CD34, CD13, CD33, and CD117 positive Lymphoid antigens such as CD7, CD19 and TdT may be expressed
AML with <i>KMT2A</i> rearrangement	<i>KMT2A</i> rearrangement	May show monocytic, monoblastic, or myelomonocytic features Large blasts with abundant basophilic cytoplasm	CD33, CD65, CD4, CD15, and lysozyme positive CD34 and CD117 variable
AML with <i>MECOM</i> rearrangement	<i>MECOM</i> rearrangement Poor prognosis	Variable cellularity Fibrosis may be seen Blasts show morphology of AML without maturation, acute myelomonocytic leukemia, or acute megakaryoblastic leukemia	CD34, CD33, CD13, CD117 positive CD38 positive CD7 expression may be seen

(continued)

Table 22.1 (continued)

Disorder	Key features	Bone marrow findings	Immunohistochemical features
AML with <i>NUP98</i> rearrangement	<i>NUP98</i> rearrangement Poor prognosis	High blast count Morphology of AML without maturation or AML with myelomonocytic or monocytic differentiation	CD34, CD117, CD13, CD33, and MPO positive
AML with <i>NPM1</i> mutation	<i>NPM1</i> mutation	Hypercellular bone marrow Myelomonocytic or monocytic differentiation common	CD34 usually negative CD33, CD117, CD123 positive
AML with <i>CEBPA</i> mutation	<i>CEBPA</i> mutation	Blasts with or without maturation	CD34, CD33, CD13, CD15, CD7 positive
AML, myelodysplasia-related	Exhibits specific cytogenetic and/or molecular abnormalities associated with myelodysplastic neoplasia Poor prognosis	Multilineage dysplasia	CD34, CD117, MPO positive
AML with other defined genetic alterations	AML with <i>CBFA2T3::GLIS2</i> fusion AML with <i>KAT6A::CREBBP</i> fusion AML with <i>FUS::ERG</i> fusion AML with <i>MNX1::ETV6</i> fusion AML with <i>NPM1::MLF1</i> fusion	Differs based on the molecular alteration	Differs based on the molecular alteration

Morphology of the blasts shows a wide spectrum based on the cell lineage and maturation level. Bone marrow is usually hypercellular with extensive blasts, but normocellular bone marrow with smaller counts of blasts may also be the case. *AML with minimal differentiation* is composed of poorly differentiated blasts which do not show evidence of myeloid differentiation. Blasts are medium-sized and have round nuclei with scattered chromatin and one or two nucleoli. The cytoplasm does not contain granules or Auer rods. The blasts in AML with minimal differentiation are usually positive for CD33, CD13, and CD117, with variable expression of CD34 (Fig. 22.2) and CD38. *AML without maturation* shows maturation arrest and myeloid differentiation. Blasts in AML without maturation may be medium to large; nucleus/cytoplasm ratio is increased with a round nuclei and one or two nucleoli. Granules or Auer rods may be seen in the blast cytoplasm. These blasts usually express myeloperoxidase (MPO), CD33, CD34, and CD117. *AML with*

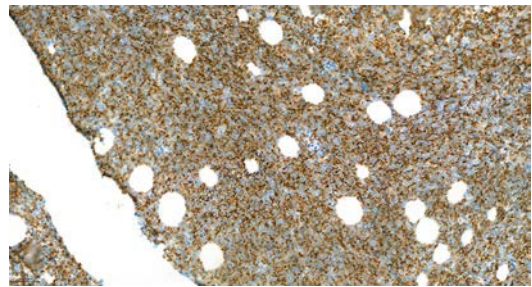


Fig. 22.2 Immunohistochemical CD34 expression is variable but seen in a substantial number of patients with AML

maturation has mature neutrophils in addition to immature/precursor myeloid cells. Blasts may have granules and/or Auer rods, and they are generally positive for MPO, CD33, CD117, and CD34. *Acute basophilic leukemia* is a leukemia that shows basophilic differentiation. Blasts are medium to large and show increased nucleus/cytoplasm ratio with oval/round nuclei, scattered chromatin, and several nucleoli. Basophilic gran-

ules in the cytoplasm is characteristic with lack of Auer rods. Blasts in acute basophilic leukemia express CD11b, CD113, CD33, and CD34. *Acute myelomonocytic leukemia* displays granulocytic and monocytic maturation. Blasts are medium to large sized, with abundant basophilic cytoplasm often containing vacuoles and nuclei with fine chromatin and one or two nucleoli. Starry sky pattern may sometimes be seen. Blasts frequently express CD13, CD15, CD33, CD117, and CD34. Expression of monocytic markers such as CD11c and CD163 may be seen. *Acute erythroid leukemia* is characterized by the proliferation of erythroblasts, with $\geq 30\%$ of the cells being immature erythroid cells that are medium to large, with a central nucleolus, fine chromatin, and cytoplasmic vacuoles, blebs, and/or granules. CD71 may be used to demonstrate immature erythroid cells. *Acute megakaryoblastic leukemia* contains blasts with megakaryocytic differentiation. In this entity, blasts vary from small to large in size, containing round or oval nuclei with fine chromatin and one to three nucleoli. Binucleated or multinucleated blasts may also be encountered. Blasts show expression of megakaryocytic markers such as CD41, CD36, and CD61 along with CD33 and CD34 [4].

In some cases, myeloid blasts constitute an extramedullary mass, known as *myeloid sarcoma*. While this entity shares common features with the bone marrow AML, its immunophenotypic profile varies depending on the maturation level/type of the blasts.

It should also be noted here that infrequently, acute leukemias may show mixed or ambiguous lineage. In such cases evidence of more than one lineage differentiation is present.

22.3 Myeloproliferative Neoplasms

The term “myeloproliferative disorder” was first introduced by William Dameshek in 1951 [6]. Dameshek included four main entities (*chronic myeloid leukemia, polycythemia vera, essential thrombocythemia, and primary myelofibrosis*) in his paper; however, currently, these disorders are mainly called myeloproliferative neoplasms

(MPNs) and classified by the World Health Organization (WHO), and according to the most recent WHO classification, there are eight disorders showing different and overlapping characteristics. Besides the four well-known classical MPNs, the last MPN category also includes chronic neutrophilic leukaemia (CNL), chronic eosinophilic leukemia, juvenile myelomonocytic leukaemia (JMML), and myeloproliferative neoplasm, unclassifiable (MPN-U) [7]. Here, the four main types of MPNs will be discussed.

For the diagnosis of MPN, clinical and molecular features should be evaluated along with histopathological features. A multidisciplinary approach is of utmost importance.

22.3.1 Chronic Myeloid Leukemia

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by neutrophilic leukocytosis and *BCR::ABL1* fusion in the majority of the cases. It is mostly diagnosed in the chronic phase. While generally asymptomatic, findings such as splenomegaly, fatigue, night sweats, and anemia may be encountered. Following the chronic phase, accelerated and blastic phases occur. CML is slightly more common among men.

More than 90% of the cases have the t(9;22) (q34;q11.2) translocation resulting in the Philadelphia (Ph) chromosome. While this translocation is not specific to CML, its presence provides a treatment advantage for the patients. It results in the formation of *BCR::ABL1* fusion gene, which gains continuous tyrosine kinase activity that is targeted by tyrosine kinase inhibitors. Other alterations involving the chromosomes 9 and/or 22 may be seen in the remainder of the cases. In transformation to the blastic phase, more alterations accumulate, and there is clonal evolution.

In the chronic phase, there is leukocytosis. No dysplasia is present in the peripheral blood or bone marrow. The bone marrow is hypercellular with the increase of granulocytic cells at different stages of growth. Megakaryocytes are also increased in number and with small size and hypolobulated nuclei (*dwarf megakaryocytes*). Eosinophils and basophils are also increased. A peritrabecular thick layer of immature granulocytes

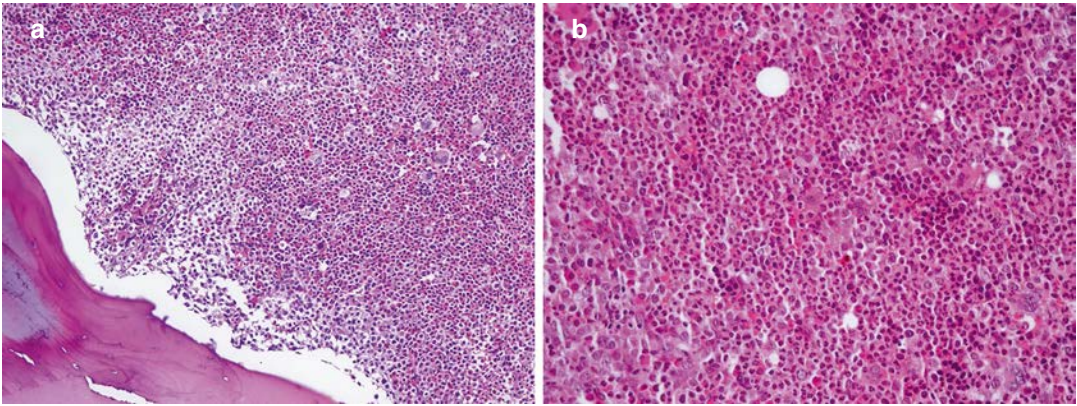


Fig. 22.3 CML is usually characterized by a peritrabecular thick layer of immature granulocytes (a), and the bone marrow is hypercellular with increase in granulocytic cells at different stages of growth (b)

cytes composed of 5–10 cells is usually striking (Fig. 22.3). Reticulin fibrosis may be seen in up to one third of the cases [8].

For the diagnosis of blastic phase, detection of $\geq 20\%$ myeloid blasts in the peripheral blood or bone marrow or formation of an extramedullary mass composed of blasts is required, or, in some cases, detection of lymphoblasts in the peripheral blood or bone marrow leads to the diagnosis of blastic phase [9].

The most important prognostic factor in CML patients is the response to tyrosine kinase inhibitors. They are used both in the chronic phase and blastic phase treatment.

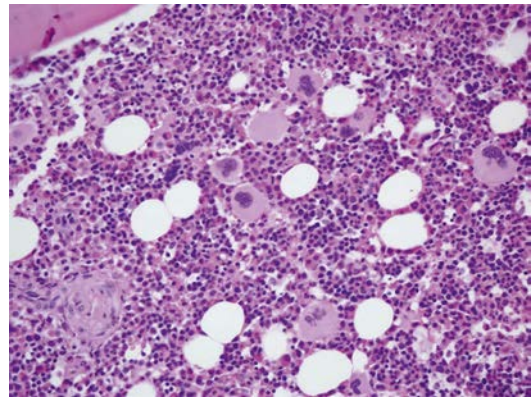


Fig. 22.4 In PV, erythroid islands may be striking, and megakaryocytes may form loose clusters, and they may show abnormal morphology and distribution

22.3.2 Polycythemia Vera

Polycythemia vera (PV) is a MPN characterized by erythrocytosis accompanied by leukocytosis and/or thrombocytosis, and it is usually associated with *JAK2* mutations. PV may be detected incidentally, or the diagnosis may follow the occurrence of vascular events. Also, symptoms such as fatigue, pruritus (worsened by bathing), night sweats, and/or headache occur in a notable number of patients.

The most common mutation seen in PV is *JAK2 p.V617F*, resulting in continuously active *JAK2* protein which activate the STAT, MAPK, and PI3K pathways, and therefore induce the proliferation of hematopoietic cells. It has been

claimed that *JAK2* variant allele frequency is critical for the risk of thrombotic events and progression to myelofibrosis [10, 11].

Bone marrow is usually hypercellular with proliferation of all three lineages. Erythroid islands are large and remarkable. Megakaryocytes may be increased in number forming loose clusters as well as abnormal distribution and abnormal morphology such as hypersegmented forms (Fig. 22.4) [12]. Blast-phase PV is characterized by myelodysplasia and myelofibrosis [13].

PV is generally an indolent disease; however, leukemic transformation and myelofibrosis may occur in the course of the disease.

22.3.3 Essential Thrombocythemia

Essential thrombocythemia (ET) is a MPN characterized by persistent thrombocytosis and increased numbers of large, mature megakaryocytes in the bone marrow. It is usually diagnosed in the chronic phase, but it may progress into accelerated and blast phases.

The clinical presentation of ET is variable. The patients may be asymptomatic or present with symptoms such as fatigue, vascular events (e.g., thrombosis).

While the peripheral blood smear shows thrombocytosis with a spectrum of platelets showing different morphology, bone marrow is normocellular. However, megakaryocytes are large with hyperlobulated (staghorn-like) nuclei and abundant cytoplasm (Fig. 22.5). No dysplasia is seen. In most cases, myelofibrosis is absent, and increase in reticular fibers should bring the suspicion of post-ET myelofibrosis [14].

The *JAK2 p.V617F* mutation may be detected in more than half of ET cases. Mutations in *CALR* and *MPL* genes are the other common mutations seen in patients with ET [15].

ET is generally an indolent disease with occasional thromboembolic events and rare progres-

sion into post ET myelofibrosis. Blast phase transformation is another rare occurrence.

22.3.4 Primary Myelofibrosis

Primary myelofibrosis (PMF) is characterized by abnormal proliferation of the megakaryocytic and granulocytic lineages in the bone marrow that is associated with progressive myelofibrosis. The patients may be asymptomatic or findings such as cytopenias, hepatosplenomegaly due to extramedullary hematopoiesis, weight loss, and night sweat may occur.

Mutations in *JAK2*, *CALR*, and *MPL* genes play a role in pathogenesis, similar to essential thrombocythemia [16].

In pre-PMF, bone marrow is hypercellular with minimal or absent reticulin fibrosis. Myeloid cells are predominant, and megakaryocytes are increased in number and form loose clusters. Megakaryocytic nuclei are often hyperchromatic and bulbous with cloud-like chromatin. Both hyperlobulated and hypolobulated forms may be seen.

In fibrotic PMF, atypical megakaryocyte proliferation is typical. Megakaryocytes show atypical localization and morphology. Erythroid cells are decreased in comparison with granulopoiesis.

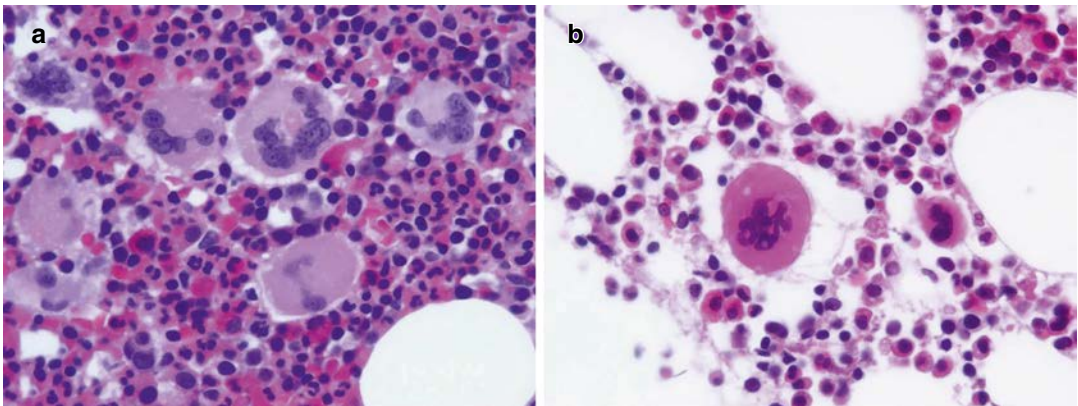


Fig. 22.5 (a, b) In ET, megakaryocytes are large with hyperlobulated (staghorn-like) nuclei and abundant cytoplasm. They may form loose clusters. No dysplasia is seen

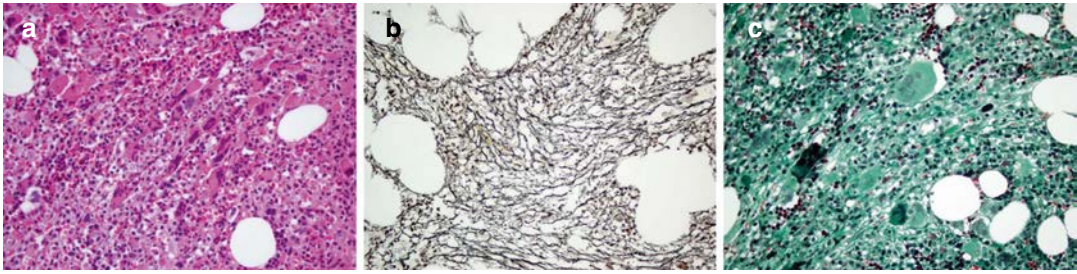


Fig. 22.6 In fibrotic PMF, atypical megakaryocyte proliferation is typical. Megakaryocytes exhibit atypical localization and morphology (a) and moderate or severe

myelofibrosis is present. (b) Reticulin stain showing grade 3 fibrosis. (c) Trichrome stain showing collagen fibrosis in the background

Moderate or severe myelofibrosis is present (Fig. 22.6) [17].

The prognosis varies depending on patient characteristics. Of note, transformation into blast phase may occur in some cases, and CD34 stain may help in demonstrating the blasts.

22.4 Myelodysplastic Neoplasm

Myelodysplastic neoplasm or myelodysplastic syndrome (MDN) is considered as a clonal hematopoietic neoplasm, characterized by cytopenia and dysplasia. It may progress into acute myeloid leukemia. For MDN diagnosis, histopathological findings should be evaluated with molecular, cytological, and laboratory findings.

Cytopenia in at least one lineage is required for diagnosis of MDN, and dysplasia in one or more lineages is typical. An increase in the blast count may occur; however, the number of the blasts is lower than 20%.

Dyserythropoiesis includes nuclear alterations such as budding, internuclear bridging, karyorrhexis, and multinuclearity and cytoplasmic alterations such as the formation of ring sideroblasts, vacuolization, and aberrant PAS positivity. Dysgranulopoiesis is characterized by nuclear hyposegmentation or hypersegmentation, cytoplasmic hypogranularity, pseudo-Chédiak-Higashi granules, and small size. Megakaryocyte dysplasia is characterized by micromegakaryocytes, non-lobated nuclei in megakaryocytes of all sizes, and multiple widely separated nuclei [18].

22.5 Myelodysplastic/Myeloproliferative Neoplasm

Myelodysplastic/myeloproliferative neoplasm (MDN/MPN) is a category used for neoplasms with overlapping features of myelodysplastic neoplasms (MDNs) and myeloproliferative neoplasms (MPNs).

The most common MDN/MPN is chronic myelomonocytic leukemia (CMML). CMML is defined by persistent peripheral blood monocytosis and somatic mutations in DNA methylation, histone modification, RNA splicing, and signal transduction. Prognosis is generally poor, and there is a risk of transformation to acute myeloid leukemia [19].

22.6 Mastocytosis

Mastocytosis is a rare, heterogenous disorder characterized by proliferation of the abnormal mast cells in different tissues. It may occur as cutaneous mastocytosis, systemic mastocytosis, or mast cell sarcoma. The clinical symptoms differ based on the involved tissue. In mastocytosis, atypical mast cells forms groups in a tissue, rarely presenting as a mass, and abnormal mast cells express CD117, CD25, and mast cell tryptase which may be demonstrated immunohistochemically in the tissue biopsies. The most common mutation associated with mastocytosis is *KIT* p.D816V, but

other mutations in the *KIT* gene may also be encountered [20].

In individuals with indolent systemic mastocytosis, life expectancy is high; however, in some cases, aggressive disease may be seen.

References

1. Vakiti A, Reynolds SB, Mewawalla P. Stat Pearls: acute myeloid leukemia. 2024. <https://www.ncbi.nlm.nih.gov/books/NBK507875/>. Last accessed on 1 June 2025.
2. Han X, Yun Z, Liu Z, Si Y, Tian S, Zhang Y, et al. Global, regional, and national burden of acute leukemia and its risk factors from 1990 to 2021 and predictions to 2040: findings from the global burden of disease study 2021. *Biomed Eng Online*. 2025;24(1):72.
3. Solary E, Gujral E. Acute myeloid leukaemia: introduction. In: WHO classification of haematolymphoid tumours. 5th ed. Lyon: IARC Press; 2022.
4. Chen W, Nejati R, Tembhare P, Marcogliese AN, Wang W, Loeb K. Acute myeloid leukaemia defined by differentiation. In: WHO classification of haematolymphoid tumours. Lyon: IARC Press; 2022.
5. Platzbecker U, Yeung CC, Fogelstrand L, Hu S, Khoury JD, Patkar N, Loghavi S, Haferlach T, Xiao W. Acute myeloid leukaemia with defining genetic abnormalities. In: WHO classification of tumours, haematolymphoid tumours. 5th ed. Lyon: IARC Press; 2022.
6. Dameshek W. Some speculations on the myeloproliferative syndromes. *Blood*. 1951;6:372–5.
7. Khoury JD. Myeloproliferative neoplasms: introduction. In: WHO classification of haematolymphoid tumours. Lyon: IARC Press; 2022.
8. Apperley JF, Godley LA, Radich J, Naresh KK, Cross NCP, Rousselot P, et al. Chronic myeloid leukaemia. In: WHO classification of tumours, haematolymphoid tumours. 5th ed. Lyon: IARC Press; 2022.
9. El Rassi F, Bergsagel JD, Arellano M, Gaddh M, Jillella A, Kota V, et al. Predicting early blast transformation in chronic-phase chronic myeloid leukemia: is immunophenotyping the missing link? *Cancer*. 2015;121(6):872–5.
10. Moliterno AR, Kaizer H, Reeves BN. JAK2 V617F allele burden in polycythemia vera: burden of proof. *Blood*. 2023;141(16):1934–42.
11. Chen CC, Chen JL, Lin AJ, Yu LH, Hou HA. Association of JAK2V617F allele burden and clinical correlates in polycythemia vera: a systematic review and meta-analysis. *Ann Hematol*. 2024;103(6):1947–65.
12. Harrison CN, Godley LA, Naresh KK, Dave SS, Mesa R, Giraudier S, et al. Polycythaemia vera. In: WHO classification of tumours, haematolymphoid tumours. 5th ed. Lyon: IARC Press; 2022.
13. Hidalgo López JE, Carballo-Zarate A, Verstovsek S, Wang SA, Hu S, Li S, et al. Bone marrow findings in blast phase of polycythemia vera. *Ann Hematol*. 2018;97(3):425–34.
14. Harrison CN, Godley LA, Naresh KK, Dave SS, Mesa R, Giraudier S. Essential thrombocythemia. In: WHO classification of hematolymphoid tumours. Lyon: IARC Press; 2022.
15. Tefferi A, Vannucchi AM, Barbui T. Essential thrombocythemia: 2024 update on diagnosis, risk stratification, and management. *Am J Hematol*. 2024;99(4):697–718.
16. Luque Paz D, Riou J, Verger E, Cassinat B, Chauveau A, Ianotto JC, et al. Genomic analysis of primary and secondary myelofibrosis redefines the prognostic impact of ASXL1 mutations: a FIM study. *Blood Adv*. 2021;5(5):1442–51.
17. Kanagal-Shamanna R, Naresh KK, Dave SS, Mesa R, Giraudier S, Harrison CN, et al. Primary myelofibrosis. In: WHO classification of hematolymphoid tumours. Lyon: IARC Press; 2022.
18. Khoury JD, Campbell P. Myelodysplastic neoplasms: introduction. In: WHO classification of hematolymphoid tumours. Lyon: IARC Press; 2022.
19. Elena C, Galli A, Such E, Meggendorfer M, Germing U, Rizzo E, et al. Integrating clinical features and genetic lesions in the risk assessment of patients with chronic myelomonocytic leukemia. *Blood*. 2016;128(10):1408–17.
20. Arock M, Sotlar K, Akin C, Broesby-Olsen S, Hoermann G, Escibano L, et al. KIT mutation analysis in mast cell neoplasms: recommendations of the European Competence Network on Mastocytosis. *Leukemia*. 2015;29(6):1223–32.

23.1 Bone Tissue and Structure

The human skeleton is composed of approximately 206 bones, which act like the structural framework of a building, supporting the body. Joints formed by the articulation of these bones, together with the attached muscles, tendons, and ligaments, provide mobility. In addition, bones protect vital organs such as the brain, lungs, heart, and liver by enclosing them, and they also host the hematopoietic system by housing the bone marrow [1, 2].

23.1.1 Types of Ossification

There are two principal pathways in the formation of bones that constitute the skeleton:

- *Intramembranous ossification*: Observed in flat bones such as those of the skull and face. Mesenchymal progenitor cells within vascularized connective tissue aggregate. These cells differentiate into osteoblasts under the influence of transcription factors *CBFA1/RUNX2* and *OSX* [1]. Osteoblasts produce the osteoid matrix composed of type I collagen

and chondroitin sulfate. The surrounding mesenchyme differentiates into the periosteum.

- *Endochondral ossification*: Responsible for the development of long bones of the extremities, short tubular bones of the hands and feet, and bones of the axial skeleton. Mesenchymal progenitor cells condense and differentiate into chondrocytes under the regulation of transcription factors *SOX9* [2], *SOX5*, and *SOX6*, forming a hyaline cartilage template. Chondrocytes in the center undergo hypertrophy, and the cartilaginous matrix they secrete becomes calcified. Osteoclasts resorb the calcified cartilage while blood vessels invade, bringing in osteoblasts, which then synthesize bone tissue. Eventually, the cartilage is completely replaced by the bone.

In some bones, such as the clavicle, both ossification types can occur together. The outer portion of long and flat bones is composed of dense, compact bone tissue known as the cortex. Inside the cortex lies the bone marrow, containing adipocytes and hematopoietic cells, along with cancellous (trabecular) bone made up of fine spicules. Bones are organized into cylindrical structures arranged longitudinally, called *osteons* or the *Haversian system*. At the center of each osteon is a *Haversian canal*, which is interconnected by transverse *Volkman's canals*. Vascular and neural networks within these canals provide the nourishment and innervation of the bone. Surrounding the canals are concentric lamellae,

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resembling growth rings of a tree trunk. Parallel to these lamellae are lacunae, each containing a stellate-shaped *osteocyte*. Osteocytes are not passive cells; they can modify the surrounding matrix and play a role in bone resorption [1, 2].

23.2 Bone Matrix

The main structural component of bone tissue is the mineralized matrix, composed of water, type I collagen fibers, and precipitated crystals of *calcium hydroxyapatite* and *calcium phosphate*. Within the matrix, type I collagen provides tensile strength, whereas calcium crystals confer resistance against compression.

In addition to type I collagen, *osteoblasts* synthesize calcium-binding proteins such as *osteonectin* and *osteocalcin*, as well as adhesion molecules including *osteopontin* and *fibronectin*. Over time, the matrix becomes mineralized; the unmineralized matrix is referred to as *osteoid*.

Bone is rich in minerals: besides calcium, it also contains phosphorus, magnesium, potassium, sodium, and iron.

23.2.1 Woven and Lamellar Bone

According to the arrangement of collagen fibers, two types of bone are defined:

Woven bone: Composed of randomly arranged collagen fibrils and produced rapidly within a short time. It is synthesized quickly during fractures or injuries to promote bone repair; however, it is not as strong as lamellar bone.

Lamellar bone: Composed of regularly and parallelly arranged collagen fibrils. It constitutes mature bone tissue. In healthy adults, lamellar bone is always present, whereas woven bone is observed only under pathological conditions [3, 4].

23.3 Bone Remodeling

Through the activity of the “small workers” within the bone, *osteoblasts* and *osteoclasts*, bone tissue is continuously renewed. Under

repetitive stress, bone thickens and strengthens, whereas with reduced stress, resorption predominates, and the bone becomes thinner. Bone modeling and remodeling are processes in which resorption and formation occur sequentially and simultaneously.

23.3.1 Factors Affecting Bone Metabolism [3, 4]

- Parathyroid Hormone (PTH)*: A polypeptide hormone secreted by the parathyroid glands. It increases serum calcium levels by mobilizing calcium from the bone, enhancing absorption in the small intestine, and promoting renal reabsorption. In addition, it regulates the body's acid–base balance through its effects on bicarbonate, ammonium, and phosphate. PTH receptors are present on preosteoblasts, osteoblasts, and chondrocytes, but interestingly not on osteoclasts. The net effect of PTH on the bone is *osteoclastic resorption*, mediated indirectly via osteoblasts. Osteoblasts secrete *osteoprotegerin (OPG)* and *RANK ligand (RANKL)*, which act on the RANK receptor of osteoclasts. Increased RANKL secretion promotes osteoclast differentiation and activation (bone resorption), whereas predominant OPG secretion suppresses these processes (Fig. 23.1). PTH also induces the release of mediators such as *IL-1*, *IL-6*, and *prostaglandin E* from osteoblasts, which further enhance RANKL secretion and bone resorption. However, when administered intermittently at low doses, PTH exerts an anabolic effect by stimulating bone formation (Table 23.1).
- Calcitonin*: A peptide hormone secreted by the parafollicular C cells of the thyroid gland. It acts to reduce serum calcium levels. Calcitonin receptors are located on preosteoclasts, osteoclasts, and monocytes. Its primary action is to inhibit osteoclastic bone resorption. It also increases renal calcium excretion. Its effect disappears within 1–2 days. The likely physiological role of calcitonin is to maintain serum calcium homeostasis following a calcium-rich diet.

Fig. 23.1 Osteoclastic differentiation

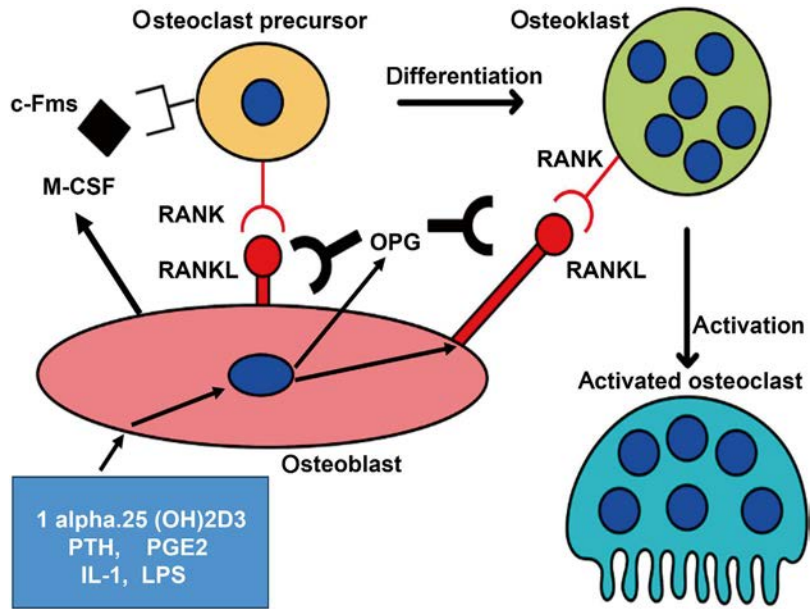
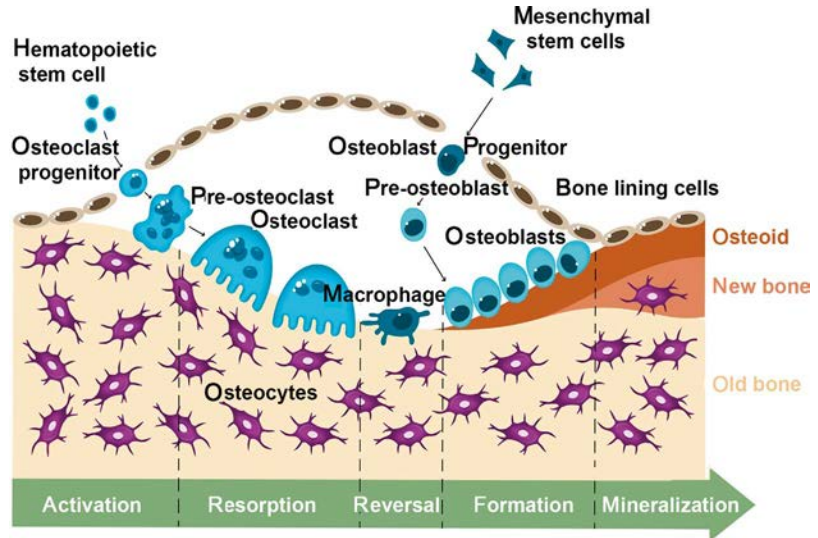


Table 23.1 Ingredient of normal bone

<i>Bone composition</i>		
Hydroxyapatite mineral crystals		~35–45%
Water		~15–25%
Collagens		~40%
Type I collagen	Woven and lamellar bone	
Type II collagen	Cartilage	
Type III collagen	Found in certain pathologic conditions	
<i>Noncollagenous proteins</i>		(Synthesized mainly from osteoblasts)
Osteonectin, bone sialoprotein	Calcium binding	
Osteopontin, fibronectin, thrombospondin	Adhesion proteins	
Osteocalcin	Mineralization proteins	
Collagenase, alkaline phosphatase, metalloproteinases	Enzymes	
PG, IL-1 and -6	Cytokines	
IGF-1, TGF- β , PDGF	Growth factors	
Glycosaminoglycans, (GAGs) (hyaluronic acid, chondroitin/heparan/keratan sulfate)	Hydrated polysaccharide gels	

- **Vitamin D:** Ergosterol and 7-dehydrocholesterol in the blood are converted in the skin under ultraviolet radiation to calciferol and cholecalciferol, respectively. These are hydroxylated in the liver to 25-hydroxy-vitamin D, and subsequently converted in the renal tubules to the active form, 1,25-dihydroxy-vitamin D. Low serum vitamin D and elevated PTH stimulate vitamin D synthesis. Vitamin D increases the synthesis of calcium-binding proteins (e.g., *osteocalcin*), promotes osteoclastic resorption, monocyte maturation, myelocyte differentiation, and insulin secretion. Deficiency disrupts mineralization of newly formed bone, leading to *rickets* in children and *osteomalacia* in adults. Excess vitamin D results in increased bone resorption and *hypercalcemia*.
- **Estrogens and Androgens:** Play an important role in the preservation of bone mass through their receptors on osteoblasts and osteoclasts.
- **Growth Hormone (GH):** Maintains bone mass by acting on osteoblasts and chondrocytes via their receptors.

Fig. 23.2 Bone remodeling



- **Proteolipids:** Involved in hydroxyapatite deposition.
- **Bone Morphogenetic Proteins (BMPs):** Essential for bone formation and repair.
- **Transforming Growth Factor-Beta (TGF- β):** Plays a critical role in bone formation, particularly during remodeling, in cooperation with BMPs.
- **Interleukin-6 (IL-6):** Secreted by osteoblasts and bone marrow mesenchymal cells in response to stimuli such as PTH, vitamin D, TNF, and IL-1. IL-6 activates RANKL on osteoclast precursors, thereby supporting osteoclast formation. It enhances osteoclast maturation, increases their number, and stimulates bone resorption. Estrogens and androgens inhibit IL-6 production in osteoblasts.
- **Mechanical Stress:** Disuse of an extremity for any reason leads to osteoporosis, whereas in weightlifters bones become thicker and shorter. In microgravity environments such as space, rapid bone loss occurs. Julius Wolff described this phenomenon in 1882 as: "Every change in form and function of bones is followed by changes in the internal architecture and external conformation, in strict accordance with mathematical laws." The most important determinant of bone structure, shape, and metabolic status is its adaptation to the loads and stresses applied to it (Fig. 23.2).

23.4 Non-neoplastic Diseases of the Bone

23.4.1 Bone Fracture and Healing

A fracture is the disruption of the anatomical integrity of bone resulting from reduced bone strength or mechanical overload.

23.4.1.1 Types of Fractures by Etiology

Traumatic fracture: Occurs when high-energy force is applied to healthy bone. **Pathologic fracture:** Develops when bone loses its strength due to pre-existing pathology such as tumor, osteomyelitis, or osteoporosis. **Stress fracture:** Occurs particularly in athletes as a result of repetitive trauma. **Insufficiency fracture:** Arises in osteoporotic and weakened bone under normal stress.

23.4.1.2 Classification of Fractures by Appearance and Morphology

Simple (closed) fracture: The skin remains intact. **Open (compound) fracture:** The fracture site communicates with the external environment. **Displaced fracture:** The fracture fragments are separated angularly or linearly. **Segmental fracture:** The bone is broken into multiple segments. **Compression fracture:** The bone is crushed (commonly seen in vertebrae). **Avulsion fracture:** A

bone fragment is pulled away at the site of tendon or ligament attachment (may also be referred to as an insufficiency fracture.)

23.4.1.3 Phases of Fracture Healing [5]

Stabilization of the fracture line is critical for proper healing. Once stabilized, healing proceeds in three major phases:

1. Hematoma and Inflammatory Phase

With fracture occurrence, adjacent blood vessels rupture, leading to hematoma formation around the fracture site. The hematoma clots, forming a fibrin-rich “repair/construction zone.” Pro-inflammatory mediators such as *tumor necrosis factor (TNF)* and *interleukin-1 (IL-1)* are released, and polymorphonuclear leukocytes and macrophages migrate to initiate the inflammatory response.

Growth factors including *PDGF*, *FGF*, *VEGF*, and *TGF- β* are secreted, activating fibroblasts, osteoprogenitor cells, and osteoclasts. *Endothelin* is also thought to play a key role in initiating osteoblastic and osteoclastic activity. This phase develops within the first 24–48 h.

2. Reparative Phase (Callus Formation)

Beginning from the second day, vascularization and fibroblastic proliferation increase along with collagen synthesis. By the end of the first week, the hematoma becomes organized, and differentiation into osteoblasts, osteoclasts, and chondroblasts increases.

Unmineralized collagen matrix (osteoid) and chondroid matrix become prominent at the fracture site. By the second to third week, this matrix connects the fracture ends, but since it is not yet mineralized, it lacks sufficient mechanical strength. This stage is referred to as *soft callus*.

From the second to third week, calcification and endochondral ossification occur within the collagen matrix, forming *hard callus*. At this stage, osteoid becomes mineralized, the fracture ends unite, and the bone can now bear weight.

3. Remodeling Phase

The fibrous bone and cartilage tissues formed during the soft callus phase are remodeled according to load-bearing dynamics: regions under mechanical stress are preserved, whereas unloaded areas undergo resorption. New bone is formed, and through this remodeling process, the bone gradually regains its original shape and mechanical strength over several months.

Clinical Significance: When evaluating a fracture, it is essential to determine whether it is *pathologic*. If there is no underlying bone pathology, the bone heals itself. However, if a primary or metastatic bone tumor is present, removal or treatment of the tumor becomes the priority. Similarly, if an underlying metabolic bone disease is present, correction of the metabolic disorder is crucial for bone healing. Histologically, callus tissue may mimic the appearance of osteosarcoma, an aggressive bone-forming tumor. Therefore, awareness of this possibility is important to avoid misdiagnosis [5, 6].

23.4.2 Osteoporosis/Osteopenia

A decrease in bone mass is called *osteopenia*. *Osteoporosis*, on the other hand, defines a much greater loss of the bone to a level that may cause fractures even without stress. Senile osteoporosis or postmenopausal osteoporosis is called *primary osteoporosis*, whereas if it develops in relation to another factor, it is called *secondary osteoporosis*, among endocrine diseases, hyperparathyroidism, hyperthyroidism, Cushing’s disease, and hypogonadism; among gastrointestinal problems, malnutrition, malabsorption, and inflammatory bowel disease; and among drugs, corticosteroids, proton pump inhibitors, anticoagulants, and anti-convulsants; and chronic kidney disease can be listed as causes of secondary osteoporosis. Bone mass increases from childhood to adulthood and reaches a maximum point. The size of this mass is directly related to the individual’s physical activity, nutritional characteristics, genetic factors, and hormonal status [7, 8].

23.4.2.1 Factors Involved in the Pathogenesis of Osteoporosis

Age-related changes: With aging, osteoblasts also age, and their synthetic capacity and responsiveness to growth factors decline. This reduces bone-forming capacity and constitutes the primary effect underlying senile osteoporosis.

Decreased physical activity: Mechanical forces stimulate bone remodeling in the direction of formation. The greater the load applied to the bone, the more it thickens to withstand that load. Low-intensity, repetitive exercise helps maintain bone thickness, but load-bearing exercise is more effective in increasing bone mass. In senile osteoporosis, decreased physical activity contributes to the development of bone loss. Marked bone loss is observed in paralyzed extremities or in cases of immobilization.

Calcium status: Low calcium intake limits bone mass. When hypocalcemia occurs (due to dietary deficiency or chronic renal failure), parathyroid hormone secretion increases, resulting in the mobilization of calcium from bone into the bloodstream; this reduces bone mass. If vitamin D deficiency is also present, the loss is even greater. This is a common feature in senile osteoporosis.

Hormonal effects: In women, following menopause, estrogen deficiency leads to rapid bone loss during the first 10 years. Annually, up to 2% of cortical bone and 9% of medullary bone may be lost. Reduced estrogen increases both resorption and formation, but resorption predominates over formation. The pathogenesis involves cytokines such as *IL-6*, *TNF- α* , and *IL-1*, secreted by monocytes, which increase RANKL expression and reduce OPG levels, thereby promoting osteoclast proliferation and preventing osteoclast apoptosis. As a result, osteoclast numbers increase and bone resorption is enhanced.

Genetic factors: Gene polymorphisms in the *Wnt signaling pathway* and single-gene mutations such as *LRP5* have been found to be associated with osteoporosis.

Clinical Findings: Clinically, patients present with kyphosis, lordosis, loss of height, and femoral neck fractures.

Microscopy: there is marked reduction in trabecular and cortical bone, thinning and focal interruptions of subchondral bone just beneath the articular cartilage—findings frequently observed in bone specimens removed during prosthesis surgery in patients with fractures.

Treatment

Exercise, adequate calcium and vitamin D intake, and drugs that reduce osteoclastic resorption are used in treatment. These include *bisphosphonates*, *denosumab* (an anti-RANKL antibody), and *hormone replacement therapy* [7, 8].

23.4.3 Rickets and Osteomalacia

Both conditions result from *vitamin D deficiency* or defects in its metabolism, leading to failure of calcium to be deposited onto newly formed osteoid.

In children: Seen at the epiphyseal growth plates, where active ossification occurs.

In adults: Appears as a defect of mineralization in areas undergoing bone remodeling. The thickness of unmineralized osteoid is increased; in some extreme cases, it may reach up to 35% of the entire bone [7, 8].

23.4.4 Hyperparathyroidism

Parathyroid hormone (PTH) primarily functions to increase serum calcium. It achieves this by

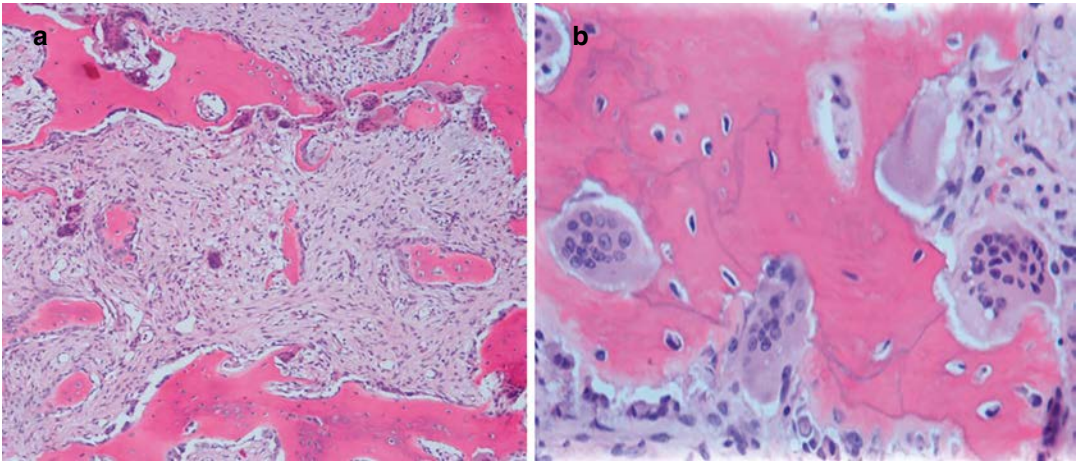


Fig. 23.3 Hyperparathyroidism: (a) Resorption tunnels formed by osteoclasts in cortical bone, fibrosis surrounding trabecular bone and in the bone marrow compartment. (b) Cement lines in the bone

mobilizing calcium from the bone and enhancing absorption from the kidney and intestine, thereby leading to *hypercalcemia*. The release of calcium from bone occurs through increased osteoclastic activity mediated by *upregulation of RANKL* and *downregulation of OPG*. This results in widespread osteoporosis.

Microscopy: Particularly in cortical bone, long resorption tunnels created by osteoclasts are observed, along with fibrosis around trabecular bone within the marrow space (*osteitis fibrosa cystica*) (Fig. 23.3).

Whether hyperparathyroidism is *primary* or *secondary* does not alter its appearance in the bone [9].

23.4.5 Avascular Necrosis

Osteonecrosis or avascular necrosis of the bone occurs when the blood supply to the bone is disrupted by any mechanism. It represents an ischemic necrosis. It is most commonly seen in the *femoral head* and is held responsible for approximately 10% of hip prosthesis surgeries. Etiologic factors include trauma or compression of vessels,

coagulation disorders, hematologic diseases, thrombosis due to vasculitis, corticosteroid use, sickle cell anemia, oral contraceptive use, Cushing's syndrome, gout, radiation, or idiopathic causes [10].

Clinical Features: In subchondral infarcts, pain initially occurs with activity, later progressing to persistent pain. Subchondral collapse may lead to separation of the articular cartilage from the underlying bone and the development of secondary osteoarthritis.

Microscopy: Lacunae that normally contain osteocytes appear empty. In fatty bone marrow regions, necrotic adipocytes are observed. If revascularization occurs after necrosis, necrotic trabeculae are resorbed, while some persist as a scaffold on which new viable bone is deposited (Fig. 23.4). This process is termed “creeping substitution.”

Treatment: Generally includes weight-bearing restriction, immobilization, and treatment of the underlying etiologic factor. In advanced cases, surgical intervention may be required.

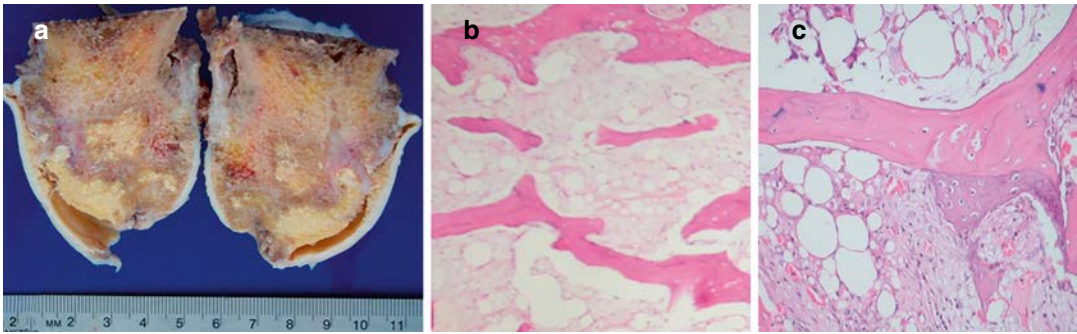


Fig. 23.4 (a) In the femoral head, the articular cartilage has detached from the subchondral bone as a consequence of subchondral bone necrosis. (b) Necrosis in the bone marrow without notable inflammatory cell infiltrates; osteocyte lacunae within the bone trabeculae appear

empty. (c) While necrotic bone trabeculae are being resorbed, some persist as a scaffold and serve as an architectonic framework upon which new viable bone is laid “creeping substitution”

23.5 Infectious Diseases of the Bone

23.5.1 Osteomyelitis

Osteomyelitis is an inflammatory condition of the bone caused by the invasion of microorganisms such as bacteria, fungi, parasites, or viruses. Microorganisms can reach the bone through three main pathways: hematogenous spread, direct inoculation, or contiguous extension. For example, infectious agents from another site in the body, such as urinary tract infections or pneumonia, may disseminate hematogenously and localize in the bone. This pathway is most commonly observed in children; in otherwise healthy adults, hematogenous osteomyelitis is uncommon. Soft tissue infections adjacent to the bone can also spread directly and lead to osteomyelitis, as seen in patients with diabetic foot infections. Post-traumatic or postoperative osteomyelitis develops when microorganisms are directly introduced into the affected area following severe trauma or surgery.

Radiologically, osteomyelitis is characterized by areas of bone erosion as well as lytic lesions in the cortex. When the infection extends beneath the periosteum, periosteal new bone formation may also be observed. This radiologic appear-

ance can mimic Ewing sarcoma or lymphoma. The *gold standard* in the diagnosis of osteomyelitis is the demonstration of the microorganism in *biopsy and culture* obtained from the suspected site [11–14].

23.5.1.1 Distribution of Causative Agents of Osteomyelitis by Age and Underlying Pathology

Neonatal period: The most common pathogens are *Staphylococcus aureus*, *Streptococcus agalactiae*, and *Escherichia coli*. The reason is that these three bacteria are frequently present in the vaginal flora and become pathogenic for the infant’s immature immune system during delivery.

Children older than 1 year: Most commonly caused by *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Haemophilus influenzae*. It usually affects the growing regions of the bone (metaphyseal–epiphyseal areas).

Children older than 4 years: *H. influenzae* is more commonly seen as the causative agent. It also involves the growing regions of the bone (metaphyseal–epiphyseal areas) and may extend into the joint, causing *septic arthritis*.

Adults: The most frequently isolated pathogen (80–90%) is *Staphylococcus aureus*, which expresses receptors for bone matrix. Genitourinary infections, intravenous drug users, *E. coli*, *Pseudomonas*, *Klebsiella*, mandibular infections, *Actinomyces*, sickle cell disease, *Salmonella*, bone trauma, and anaerobes are more commonly encountered.

In adults, the metaphysis is usually involved, but infection may extend to the diaphysis and epiphysis [11–14].

23.5.1.2 Classification of Osteomyelitis According to Clinical Features

Acute/Suppurative Osteomyelitis: Following the entry of the infectious agent into the bone, a

marked inflammatory response predominantly composed of polymorphonuclear leukocytes develops, accompanied by vascularized granulation tissue and edema. This process increases intramedullary pressure, compromises bone vascular supply, and leads to bone necrosis. Within the bone, areas of microabscess or abscess formation may be observed in association with intense polymorphonuclear inflammation. Necrotic bone surrounded by dense inflammatory infiltrates is referred to as “sequestrum.” The presence of sequestered bone tissue hampers healing and predisposes to progression into chronic recurrent osteomyelitis (Fig. 23.5). Treatment involves the administration of intensive intravenous and oral antibiotic therapy. However, when sequestered bone tissue is present, surgical debridement is required [11–14].

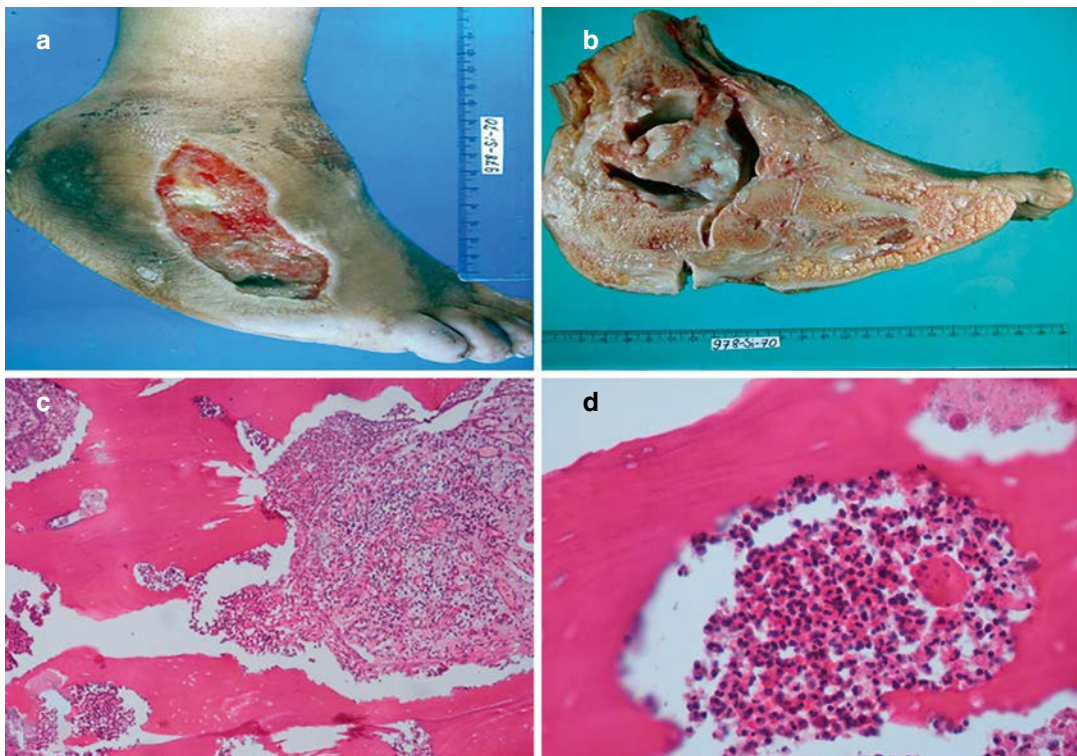


Fig. 23.5 (a) Patient with persistent osteomyelitis who underwent below-knee amputation. A fistula secondary to underlying osteomyelitis opens onto the skin with overlying ulceration. (b) On sagittal section of the foot, abscess formation is observed within the bone and in the joint

space. (c) Bone tissue necrosis (osteocyte lacunae empty). (d) Intense inflammation/abscess formation in the bone marrow characterized by abundant polymorphonuclear leukocytes and marked osteoclastic resorption

Subacute Osteomyelitis: Subacute osteomyelitis is more frequently observed in children and young adults. Patients typically present with pain lasting longer than 2 weeks, while systemic inflammatory symptoms are not prominent. Erythrocyte sedimentation rate (ESR) is mildly elevated, and C-reactive protein (CRP) levels are moderately increased. Fever rarely exceeds 38.5 °C. Radiological diagnosis is often challenging, and the condition may be mistaken for a bone tumor; therefore, biopsy may be required to exclude neoplasia. Diagnosis may be delayed for 3–5 months.

The underlying mechanisms include hematogenous spread of a bacterial agent that is partially contained by an active immune response, incomplete treatment due to prior antibiotic use before diagnosis, or colonization of the bone by a microorganism with low virulence. Metaphyseal involvement is usually observed first. Identification of the causative microorganism in the laboratory may be difficult; hence, polymerase chain reaction (PCR) performed on a sample obtained from the lesion site can be useful in detecting the infectious agent.

Histologically, areas of infiltration by polymorphonuclear leukocytes are present along with lymphoplasmacytic infiltrates and loose fibroblastic edematous tissue.

Chronic Osteomyelitis: Approximately 15–30% of acute osteomyelitis cases progress to chronic osteomyelitis. Chronic osteomyelitis may develop as a result of inadequate treatment of acute osteomyelitis, open fractures, the presence of foreign materials such as orthopedic implants or screw prostheses, peripheral arterial disease leading to impaired tissue perfusion, diabetes mellitus, immunosuppression causing insufficient host defense mechanisms, or defective tissue repair secondary to radiation-induced vascular injury. Clinically, patients may present with mild local pain, swelling, warmth, and tenderness. Non-healing wounds, pathological fractures at the site of chronic osteomyelitis, fistula formation into adjacent skin, and long-term bone deformities may also occur. Blood cultures are often negative, while ESR and CRP levels are mildly elevated. Histologically, lymphoplasma-

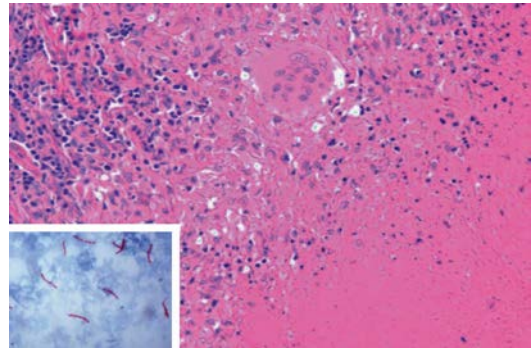


Fig. 23.6 Granuloma in tuberculous osteomyelitis: Central caseating necrosis surrounded by palisading histiocytes and multinucleated giant cells, with a chronic inflammatory infiltrate composed of lymphocytes. Ziehl–Neelsen acid-fast staining demonstrates red bacilli

cytic inflammation is observed along with foci of inflammatory infiltrates containing polymorphonuclear leukocytes. Treatment involves surgical removal of infected necrotic tissue (debridement). If a sinus tract is present, it should be excised. Bone grafting may be required to repair the defect. In addition to surgical intervention, intensive intravenous and oral antibiotic therapy is administered. The differential diagnosis is particularly important due to radiologic similarities with lymphoma, multiple myeloma, Ewing sarcoma, low-grade osteosarcoma, and Langerhans cell histiocytosis. Biopsy and pathological evaluation remain the gold standard for establishing a definitive diagnosis (Fig. 23.6).

Tuberculous Osteomyelitis: Tuberculosis remains an important public health problem in developing countries. Extrapulmonary involvement occurs in approximately 20% of tuberculosis cases, and 15–25% of these manifest as osteomyelitis. Tuberculous osteomyelitis most commonly involves the vertebrae, particularly the thoracic and lumbar regions. Progressive vertebral destruction may lead to long-term ankylosis of the spine, a condition known as *Pott's disease*. In addition to the spine, tuberculous osteomyelitis can also affect the knee, wrist, ankle, and elbow. Histopathological examination of biopsy specimens typically reveals caseous necrosis, palisading histiocytes, Langhans-type multinucleated giant cells, granulomas, and an inflamma-

tory infiltrate relatively poor in plasma cells. The presence of acid-fast bacilli on Ziehl–Neelsen staining is diagnostic. The gold standard for diagnosis is the demonstration of bacilli and their isolation in culture. However, in contemporary practice, polymerase chain reaction (PCR) techniques are increasingly important due to their higher sensitivity. In histological differential diagnosis, *rheumatoid nodules* may present a challenge. Rheumatoid nodules are characterized by a prominent plasma cell infiltrate, whereas in tuberculous osteomyelitis, plasma cell-rich inflammation is not observed, since the inflammatory response is primarily mediated by a type IV hypersensitivity reaction in which plasma cells do not play a major role [15].

Parasitic Osteomyelitis/Infestation (*Echinococcus*): *Echinococcus granulosus* is a cestode responsible for causing hydatid disease in humans. In its life cycle, carnivorous mammals such as dogs and cats serve as the definitive hosts, harboring the adult form of the parasite. Infection occurs when herbivores such as sheep, goats, or cattle—and occasionally humans as accidental intermediate hosts—ingest parasite eggs excreted in the feces of infected dogs. Once ingested by humans, the eggs hatch in the intestine, and the larvae disseminate hematogenously, most commonly localizing in the liver (60–70%) and lungs (23–30%), and more rarely in the bone (1–4%), where hydatid cysts subsequently develop. Skeletal involvement is characterized by expansile, lytic, multilocular cystic lesions. Macroscopically, a pearly white cuticular membrane is typically observed. Diagnosis can be established through serological tests and histopathological examination [16].

23.6 Congenital Diseases of the Bone

Numerous congenital/hereditary disorders primarily affect the skeletal system. The most common among these include achondroplasia, osteogenesis imperfecta, osteopetrosis, and Paget’s disease of the bone.

23.6.1 Achondroplasia

Achondroplasia is the most common cause of dwarfism. Approximately 80% of cases result from de novo mutations, while the remainder are transmitted in an autosomal dominant manner. The pathogenic mutation involves the fibroblast growth factor receptor-3 (FGFR3) gene, which encodes a transmembrane receptor regulating endochondral bone growth. Homozygous individuals usually die within the first few months of life, whereas heterozygotes generally have normal life expectancy except for short stature. Because endochondral ossification is impaired, long bones are predominantly affected, while flat bones remain largely normal. Consequently, achondroplasia is characterized by disproportionate limb shortening with a relatively normal head-to-trunk ratio, in contrast to the proportionate short stature caused by growth hormone deficiency [1, 2].

23.6.2 Osteogenesis Imperfecta (OI)

Osteogenesis imperfecta is the most common hereditary disease of connective tissue. It is characterized by a defect in the synthesis of type I collagen, a major structural component of the bone. Mutations in the genes encoding the $\alpha 1$ and $\alpha 2$ chains lead to autosomal dominant inheritance, resulting in misfolded collagen peptides. Consequently, collagen chains fail to assemble properly and lose their triple-helical structure. Type I collagen is not limited to the bone; it is also present in the skin, teeth, external ear, and sclera, and thus structural abnormalities develop in these organs as well. *Bone*: Due to the reduced or abnormal/irregular synthesis of osteoid tissue, bones are extremely fragile. *Teeth*: Defects in dentin structure cause small, misshapen, yellow–blue teeth (*dentinogenesis imperfecta*). *Eyes*: Reduced collagen content in the sclera allows the underlying choroid plexus to become visible, resulting in *blue sclera*. *Ear*: Structural abnormalities of the ossicles in the middle ear, together with neurosensory defects, cause hearing loss. The disease shows variable clinical and histological features depending on the nature of the mutation (*Types 1–8*).

Type 1 variant: Associated with a normal life span, but increased susceptibility to fractures, particularly during childhood.

Type 2 variant: Represents the most severe end of the spectrum and is lethal in the perinatal or intrauterine period.

Microscopy: Osteoid seams are thin, and bone trabeculae are decreased in thickness and number showing osteopenic appearance. Woven bone may be increased.

Treatment: Treatment is supportive and aims to reduce fracture risk. There is no definitive cure. The severe perinatal form is often lethal in utero, whereas mild forms are compatible with nearly normal life expectancy despite frequent fractures [6].

23.6.3 Osteopetrosis (Albers-Schönberg Disease, Marble Bone Disease)

Osteopetrosis is a hereditary disorder characterized by impaired osteoclastic bone resorption. The number of osteoclasts may be normal, increased, or decreased, but their resorptive function is defective. Two major inheritance patterns exist: autosomal recessive (infantile, malignant, severe form) and autosomal dominant (adult, benign form). Because osteoclastic activity is

essential for bone modeling and remodeling in response to stress, its reduction leads to excessively dense but fragile bones. Histologically, widened trabeculae containing increased numbers of nonfunctional osteoclasts are evident. The obliteration of the marrow cavity results in extramedullary hematopoiesis, producing hepatosplenomegaly and cytopenias. Cranial bone malformations may compress cranial nerves, leading to hearing and visual impairment. In some cases, deformities of the skull base cause hypopituitarism and diverse endocrine abnormalities. Radiographically, the disease shows several distinctive findings: a “goggle sign” reflecting excessive ossification of the skull, diffuse osteosclerosis with loss of the cortex–medulla distinction, calvarial thickening, the “sandwich vertebra” appearance, and “bone-within-bone” configurations in long bones. Microscopically, the bone exhibits a mosaic or Pagetoid pattern with marrow aplasia and clusters of inactive osteoclasts (Fig. 23.7). The most frequently involved genes include *TCIRG1*, *CLCN7*, *OSTM1*, *RANK*, and *RANKL*. Mutations in *TCIRG1*, *CLCN7*, or *OSTM1* are typically associated with nonfunctional osteoclasts, whereas mutations in *RANK* and *RANKL* cause an absence of osteoclasts. Importantly, *RANKL*-related forms do not respond to hematopoietic stem-cell transplantation (HSCT). Currently, early HSCT remains the only curative treatment, although emerging studies are exploring gene-therapy approaches and targeted molecular correction strategies [4].

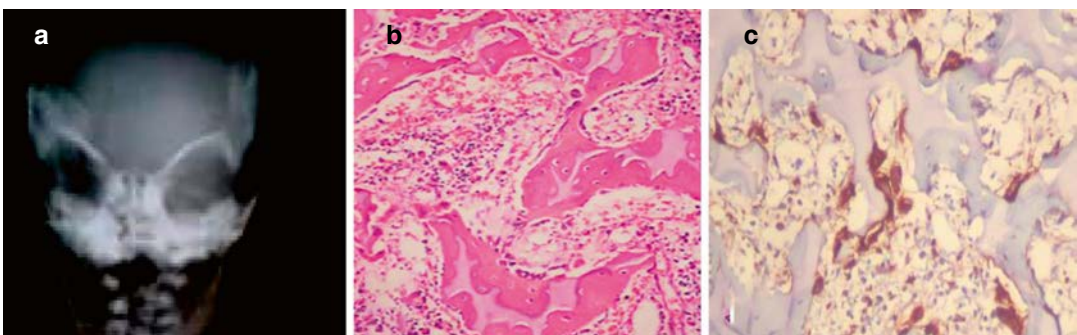


Fig. 23.7 Osteopetrosis: (a) Radiological Google sign. (b) Widened trabeculae containing increased numbers of non-functional osteoclasts. (c) TRAP expression in osteoclasts

23.6.4 Paget's Disease of the Bone

Paget's disease is a chronic skeletal disorder characterized by accelerated bone remodeling due to increased cellular activity of osteoclasts and osteoblasts. It was first described in 1876 by Sir James Paget under the term *osteitis deformans*. The prevalence increases after the age of 40, affecting about 1% of the population over 40 years. When a single bone is involved, the disease is referred to as the *monostotic form*, most frequently affecting the tibia, ilium, femur, and skull. When two or more bones are involved, it is termed the *polyostotic form*, with the spine, pelvis, and femur being the most common sites. The disease is often asymptomatic and is usually diagnosed incidentally by radiography. Serum alkaline phosphatase (ALP) levels are elevated. Enlargement of bone dimensions is a characteristic finding. Clinical manifestations arise mainly from compression of adjacent structures. Skull involvement may lead to cranial nerve compression, hearing loss, headaches, increased hat size, or *leontiasis ossea* (lion-like facial appearance) when the maxilla is affected. Although bones enlarge in size and diameter, their structural integrity is compromised, resulting in decreased load-bearing capacity and an increased risk of fractures [17].

23.6.5 Pathogenesis

Genetic factors: Mutations in the *SQSTM1* gene encoding p62 have been identified in about 50% of familial cases and 10% of sporadic cases, leading to enhanced osteoclastic activity. In juvenile Paget's disease, mutations causing RANK activation or OPG inactivation have been described.

Environmental factors: Viral involvement has been suggested, as viral particles have been detected in osteoclast nuclei. Measles virus, cytomegalovirus (CMV), and parvovirus have been implicated.

Histology

Osteolytic phase: Numerous multinucleated giant osteoclasts and broad resorption tunnels resembling those of hyperparathyroidism are seen.

Mixed phase: Simultaneous osteoclastic resorption and osteoblastic bone formation occur, leading to increased cellular turnover.

Osteosclerotic phase: Osteoclastic activity subsides, leaving immature bone trabeculae surrounded by cement lines that produce a "jigsaw" or mosaic pattern. Although bone thickening is evident, its structural quality is reduced, predisposing to deformities and fractures.

Complications: Secondary osteosarcoma (<1%) or tumor-like lesions may develop on the background of Paget's disease.

Treatment: Medical management includes bisphosphonates, calcitonin, and gallium nitrate. In cases with severe deformities, surgical interventions such as osteotomy or joint prosthesis replacement may be required [17].

23.7 Joint Structure and Pathology

A joint is the site where two or more bones meet. Joints allow bones to move, as in lifting the arm or bending the knee, but in some cases, such as the cranial bones, they primarily provide mechanical stability [18].

Joints can be classified according to their mobility and structural features into two main categories:

- **Synarthroses (immovable or slightly movable joints):** These joints lack a synovial lining and joint cavity. If the bones are connected by fibrous connective tissue, they are termed *fibrous synarthroses* (e.g., cranial sutures or the joints between teeth and the mandible). If the bones are united by cartilage, they are

called *cartilaginous synarthroses* (e.g., symphyses between pelvic bones or the joints between the sternum and ribs).

- *Diarthroses (synovial joints)*: These joints allow a wide range of motion. The articular surfaces of the bones are covered by hyaline cartilage. Both bones are enclosed within a joint capsule, the inner surface of which is lined by synovium. Synoviocytes within this layer secrete synovial fluid, which fills the joint cavity.

23.7.1 Fundamental Structures of Synovial (Diarthrodial) Joints

- *Joint Capsule/Ligaments*: The joint capsule is composed of dense connective tissue that continues with the periosteum, ensuring joint integrity and strength. It prevents leakage of synovial fluid. Ligaments and tendons may attach to its surface.
- *Synovial Membrane*: This vascular tissue lines the inner surface of the joint capsule. The synovial membrane secretes synovial fluid containing hyaluronic acid and plasma filtrate. Synoviocytes cover the inner surface but do not rest on a basement membrane. *Type A* synoviocytes resemble macrophages and remove debris through phagocytosis, while *Type B* synoviocytes resemble fibroblasts and produce synovial fluid.
- *Synovial Fluid*: Since articular cartilage is avascular, nutrients are provided by diffusion from synovial fluid, which contains plasma filtrate and hyaluronic acid. Synovial fluid also lubricates the joint, facilitating smooth movement and reducing friction.
- *Articular Cartilage*: This specialized connective tissue covers the articular surfaces, providing a smooth, wear-resistant, and shock-absorbing surface. It is composed of hyaline cartilage, 2–4 mm in thickness, and lacks blood vessels, lymphatics, and nerves. Nutrition is supplied by diffusion from synovial fluid. Articular cartilage is made up of chondrocytes (~5%) embedded in extracel-

lular matrix. The extracellular matrix consists of approximately 70% water, 10% type II collagen, and 15% proteoglycans, along with smaller amounts of collagen types I, IV, V, VI, IX, and XI. Proteoglycans provide resistance to compressive forces, while collagens counteract tensile stress and vertical loading [18].

23.7.2 Degenerative Joint Disease (Osteoarthritis)

Osteoarthritis (OA) is the most common disease of the joints. It is characterized by the degeneration of articular cartilage, which ultimately impairs the normal function of the joint. Although the term “osteoarthritis” may suggest an inflammatory disorder, OA primarily results from the inability of chondrocytes to adequately regulate the balance between synthesis and degradation in response to mechanical stress. Nevertheless, once cartilage damage occurs, the release of inflammatory mediators further exacerbates the process. In approximately 80% of patients with OA, no clear triggering factor can be identified. This group is classified as *primary (idiopathic) osteoarthritis*. Although a specific cause cannot be determined, aging, repetitive microtrauma, and obesity appear to contribute to disease development. The prevalence of OA increases after the age of 50, is more common in women, and affects nearly 40% of individuals in their 70s. When OA occurs in individuals younger than 50 years, an underlying predisposing factor should be suspected, and the disease is termed *secondary OA*. Causes of secondary OA include rheumatologic conditions, trauma affecting the joints, deposition of crystals such as urate or calcium pyrophosphate, accumulation of metabolic products such as homogenetic acid or amyloid, septic arthritis, intra-articular foreign bodies, and intra-articular injections. Additionally, diabetic neuropathy may result in impaired proprioception and pain sensation, predisposing to severe destructive changes in the joint, a condition referred to as a *Charcot joint* [19, 20].

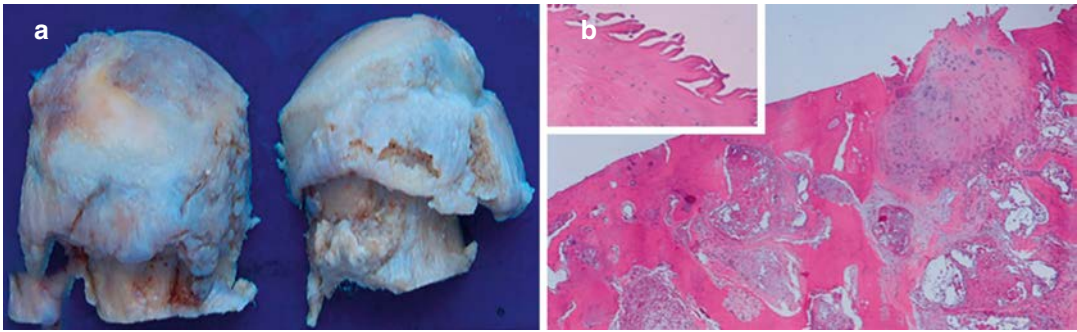


Fig. 23.8 (a) The femoral head has lost its normal contour due to degenerative joint disease, with surface cartilage loss, eburnation, and surrounding fibrillation. Osteophytic formation is notable at the load-bearing margin and around the head. (b) Histologically, low-power views show fibrillation characterized by fine clefts on the

articular cartilage surface; high-power views demonstrate loss of articular cartilage with an eburnated, sclerotic subchondral bone. To the right of the field, there is fibrohyaline reparative cartilage, and subjacent to this area, a subchondral cyst is present

Pathogenesis of OA: In the early stages of OA, chondrocytes proliferate and form clusters. While the water content of the cartilaginous matrix increases, the amount of proteoglycans decreases, thereby reducing the resistance of cartilage to mechanical stress. Type II collagen fibers begin to fragment, and fibrillation (fine surface irregularities) develops on the articular cartilage (Fig. 23.8). These changes progress to clefts extending deep into the cartilage, with eventual separation from the subchondral bone. Detached fragments of cartilage and bone fall into the joint space and are termed “*joint mice*.” With progressive loss of cartilage, the subchondral bone becomes exposed, a process known as *eburnation*. Eburnated bone is directly subjected to mechanical loading, prompting compensatory remodeling and thickening. However, focal areas of necrosis may develop within the subchondral bone. The exposed bone surface takes on a smooth, ivory-like, polished appearance. Moreover, synovial fluid penetrates the porous subchondral bone under pressure, leading to the formation of *subchondral cysts*. As part of an attempted repair response, growth factors stimulate new tissue formation, leading to the development of *osteophytes*, which are bony outgrowths covered by fibrocartilage or hyaline cartilage, typically located at the margins of the joint. The synovium plays a key role in maintaining and

nourishing articular cartilage. In primary OA, apart from a mild increase in chronic inflammatory cells, no major changes are observed in the synovium. In secondary OA, however, depending on the underlying etiology, lymphoplasmacytic inflammation or deposition of crystals and other substances may be seen [19, 20].

Clinical Features: Characteristic symptoms include pain that worsens with use, morning stiffness, crepitus (grating sound during movement), restricted range of motion, and muscle spasms or atrophy. Nerve compression by osteophytes may result in pain, numbness, or paresthesia in the innervated area. OA most commonly affects the hip and knee joints, followed by the lumbar and cervical spine, as well as the proximal and distal interphalangeal joints of the fingers, particularly the first carpometacarpal joint. Osteophytes of the distal interphalangeal joints, known as *Heberden’s nodes*, are more frequently observed in women. Importantly, the severity of radiological joint damage does not always correlate with the intensity of clinical symptoms. There is currently no curative treatment to halt or reverse the course of primary OA. Management includes activity modification, intra-articular corticosteroid injections, and platelet-rich plasma (PRP) injections, and stem cell therapies. In advanced arthritic cases, joint replacement surgery (arthro-

plasty) is recommended. PRP (platelet-rich plasma) is derived from the patient's own blood and is enriched with platelets, growth factors, and other bioactive substances that promote healing [19, 20].

23.7.3 Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic, nonsuppurative, systemic inflammatory disease that primarily affects the synovial membrane of the joints. In RA, besides the joints, other organ systems such as the skin, blood vessels, muscles, heart, lungs, kidneys, and eyes may also be affected. Its prevalence ranges between 0.1% and 5%. The age of onset is between 30 and 55 years. Women are affected 2–3 times more frequently than men. Approximately 5% of women over 65 years of age have RA [21, 22].

Symptoms: Morning stiffness, redness, pain, deformities, limited range of motion, subcutaneous nodules, fatigue, muscle weakness, and swelling.

Laboratory findings: In 50–70% of cases, rheumatoid factor, which has low specificity, is found, and autoantibodies against citrullinated peptides (ACPA), which are both sensitive and more than 90% specific, are detected.

Typically, symmetric peripheral polyarthritis; classically the metacarpophalangeal, metatarsophalangeal, and proximal interphalangeal joints of the hands and feet; also wrist, elbow, and knee; less commonly axial joints or rarely monoarticular involvement may be seen.

Pathogenesis of RA: It is an autoimmune process and is thought to be triggered in individuals with appropriate genetic predisposition (HLA-DRB1, HLA-DR4, changes in the *PTPN22* gene encoding protein tyrosine phosphatase associated with T-cell inhibition) by environmental factors (smoking, viral infections such as EBV, CMV, parvovirus). Especially autoantibodies (ACPA) against citrullinated proteins (citrullinated fibrinogen, type II collagen, α -enolase and vimentin,

etc.) are detected in 70% of patients. In approximately 80% of patients, serum IgM or IgA autoantibodies binding to the Fc portion of their own IgG are found. These autoantibodies are called rheumatoid factor. All these antibody complexes can deposit in joint tissues. CD4+ T helper (TH) cells may react with an arthritogen (possibly microbial or chemically modified autoantigen) in RA, initiating the autoimmune response. T cells produce cytokines that stimulate other inflammatory cells to cause tissue damage: IFN- γ from TH1 cells activates macrophages and synovial cells. IL-17 from TH17 cells attracts neutrophils and monocytes. TNF and IL-1 from macrophages stimulate resident synovial cells to secrete proteases that destroy hyaline cartilage. RANKL expressed on activated T cells stimulates osteoclasts and bone resorption (Fig. 23.9).

Morphology: ankylosis in joints, pannus tissue on articular cartilage, and “rice bodies” may be observed.

Microscopically: in hypertrophic and hyperplastic synovial tissue, lymphoid follicles with prominent germinal centers surrounded by abundant plasma cell population are seen. This finding is not specific to RA but is observed in almost all autoimmune-related arthritis. Hyperplasia of synovial cells may cause multinucleation; these cells are called Grimley–Sokoloff giant cells. Fibrinogen leaking from synovium into the joint cavity organizes to cover the articular cartilage, cutting off the connection between cartilage and synovial fluid, leading to necrosis of articular cartilage and development of empty chondrocyte

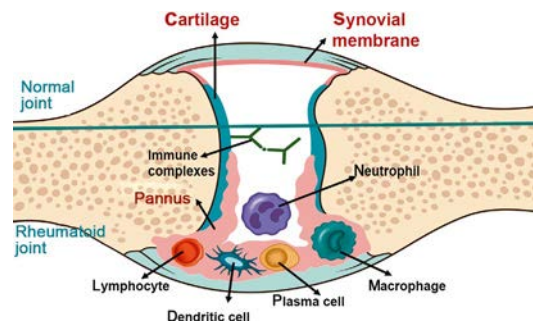


Fig. 23.9 Schematic appearance of rheumatoid arthritis

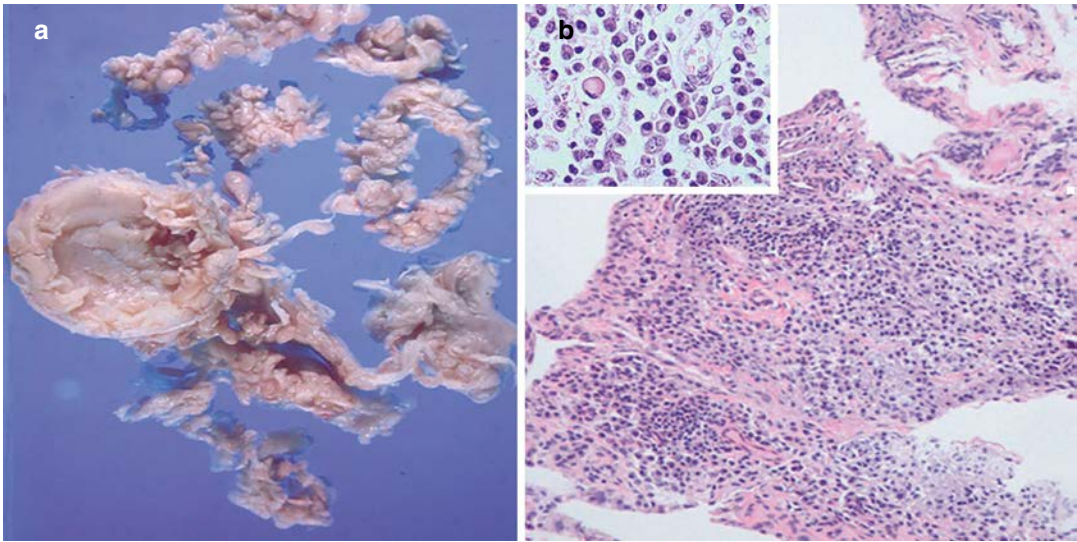


Fig. 23.10 (a) Synovectomy specimen from a patient with rheumatoid arthritis: synovial tissue demonstrates papillary synovial hyperplasia. (b) Histologic examina-

tion reveals dense lymphoplasmacytic inflammation, a characteristic finding in the synovial tissues of rheumatic diseases

lacunae (Weichselbaum lacunae). This fibrinoid exudate covering cartilage is called pannus. In addition, organized fibrinogen particles float in the joint cavity. Because they resemble rice, they are called rice bodies. In approximately 25% of cases, rheumatoid nodules may be seen, usually in the subcutaneous tissue along the extensor surfaces of the forearm, elbow, and tibia, and rarely in visceral organs. Histologically, granuloma consisting of central fibrinoid necrosis surrounded by palisading histiocytes and giant cells and lymphocytes and plasma cells around it are seen. The abundant presence of plasma cells is important in distinguishing them from tuberculous granulomas (Fig. 23.10).

Prognosis and Treatment: Most patients show periodic flares and remission periods, but structural damage is cumulative and irreversible over the years; if untreated, it may progress to destruction of articular cartilage and joint ankylosis. Nonsteroidal anti-inflammatory drugs (NSAIDs), immunosuppressive drugs, and anti-TNF medical therapies may be used. In advanced cases, surgical treatment and prosthesis may be applied [21, 22].

23.8 Crystal-Associated Arthritides

Crystal-associated arthritides are characterized by the accumulation of endogenous or exogenous crystals in the components of the joints and the resulting damage to the joint. Endogenous crystals include monosodium urate (MSU) (gout), calcium pyrophosphate dihydrate (pseudogout), basic calcium phosphate, and oxalate. With prostheses or applied medical treatments, exogenous crystals such as silicone, polyethylene, methyl methacrylate, and corticosteroid crystals may also trigger an inflammatory reaction that destructs cartilage [23–27].

23.8.1 Gout Disease

It is the acute inflammation of the joint caused by the accumulation of monosodium urate (MSU) crystals inside and around the joints. The increase of uric acid in the blood causes the accumulation of monosodium urate crystals as in the periarticular region, tendons, spinal ligaments, skin, and fibrous tissue. Only about 10% of hyperuricemic

patients develop clinical gout. Clinically, gout disease occurs after 20–30 years of hyperuricemia in individuals [23, 24].

Epidemiology: About 2–5% of chronic joint diseases are associated with gout disease. The classic site of involvement is the first metatarsophalangeal joint. In addition, ankle, heel, knee, wrist, finger, and elbow involvement may be observed.

Risk factors: Male sex over 40 years, hypertension, obesity, alcohol use, women over 70 years, chronic kidney disease, and drugs such as (thiazide) diuretics that reduce uric acid excretion. Congenital metabolic disorders; Lesch–Nyhan syndrome is caused by deficiency of hypoxanthine-guanine phosphoribosyltransferase (HGPRT), with hyperuricemia due to primary error in purine synthesis or excretion related to increased phosphoribosyl pyrophosphate synthetase activity.

Primary gout (~90%): In addition to hyperuricemia developing due to primary error in purine synthesis or excretion, idiopathic hyperuricemia develops in ~58% without metabolic disorder.

Secondary gout (~10%): Hyperuricemia developing due to myeloproliferative syndromes with high cell turnover (leukemia or other malignancies), hemolytic anemia, chronic kidney disease, or diuretic use.

Clinical course:

Asymptomatic Hyperuricemia: No clinical findings.

Acute Arthritis: Following hyperuricemia, sudden onset of severe joint pain, localized hyperemia, and warmth appear. Most initial attacks are monoarticular; 50% occur in the first metatarsophalangeal joint.

Asymptomatic Intercritical Period: Resolution of acute arthritis leads to a symptom-free interval. During this period, diagnosis is difficult. If appropriate treatment is not given, attacks recur at shorter intervals and often become polyarticular.

Chronic Tophaceous Gout: About 12 years after the first acute attack, untreated, related to the level and duration of hyperuricemia. Characteristically, juxta-articular bone and joint space loss is observed.

Pathogenesis: In gout disease, inflammation is triggered by the deposition of urate crystals in the joints, and macrophages and neutrophils phagocytose the crystals. Macrophages secrete IL-1 β , free radicals, and arachidonic acid metabolites such as LTB₄. These cytokines support more neutrophil and macrophage accumulation in the joint. In these cells, more cytokines are secreted, and in addition, phagocytosed crystals also damage the membranes of phagosomes, causing the leakage of free radicals and proteases. The crystals themselves can also activate complement through the alternative pathway, contributing to more leukocyte recruitment. The result is severe damage to articular cartilage, synovium, and periarticular tissue. The patient experiences severe pain with an acute arthritis picture. Recurrent acute arthritis attacks lead to the formation of tophi, which are clusters consisting of urate crystals and inflammatory tissue in the synovium and periarticular tissue (Fig. 23.11).

Morphology: Chalky-white tophi in joint and periarticular soft tissues, destruction in the bone and articular cartilage adjacent to the tophus.

Microscopy: In tophi and synovium, MSU crystals appear as feathery eosinophilic material accumulation, surrounded by macrophages, giant cells, and fibrosis (Fig. 23.12). MSU crystals dissolve with standard pathological tissue processing procedures; therefore, ethanol fixation or fresh tissue is recommended for preservation of crystals.

Cytological examination of synovial fluid in acute attack: Inflammatory exudate consisting of neutrophils and lymphocytes; in polarized light microscopy, MSU crystals are needle-shaped and show strong negative birefringence (bright).

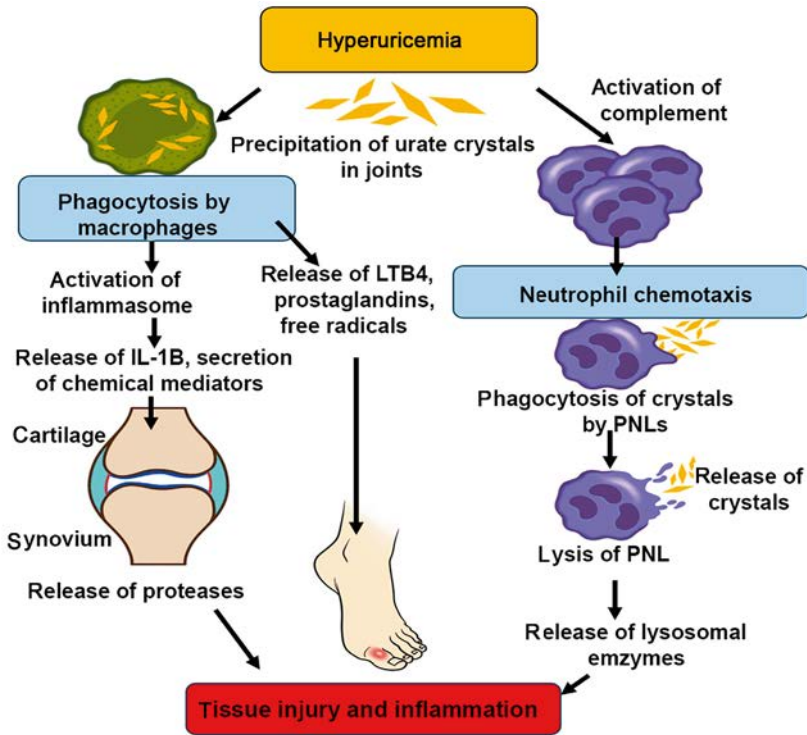


Fig. 23.11 Pathogenesis of gout disease

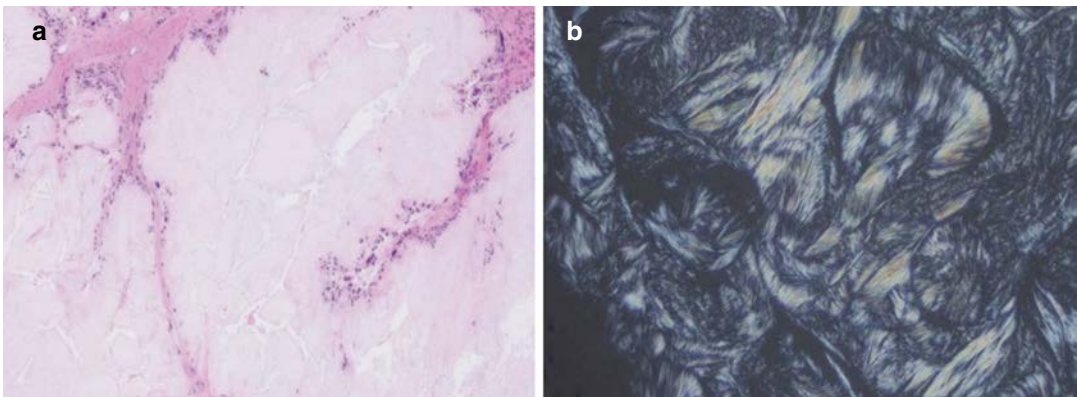


Fig. 23.12 (a) Gout tophi shows pale gray to brown accumulations, rarely giant cell reaction or fibrosis. (b) Under polarized light microscopy, they appear as straw-

chip or needle-shaped crystals. In tissues that enter aqueous fixatives (such as formalin) urate crystals dissolve and a pale pink to white nodule like residue may remain

Treatment: The aim of gout treatment is to reduce symptoms with NSAIDs, colchicine in acute attacks, and to lower urate levels with xanthine oxidase inhibitors [23, 24].

23.8.2 Calcium Pyrophosphate Crystal Deposition Disease (CPPD, Pseudogout)

CPPD is the second most common crystal-associated joint disease. Both sexes are equally affected. The incidence is 0.9/1000. About 25% of cases present with an acutely swollen joint clinically mimicking gout, hence the name pseudogout. The most common presentation resembles osteoarthritis; in ~50% of patients, progressive arthritis develops, usually polyarticular, with onset typically in the fourth decade. The joints most frequently affected are, in order, the knee, ankle, wrist, elbow, hip, and shoulder; metacarpal and metatarsal involvement is rare. Forms include sporadic (idiopathic), hereditary, and secondary. Mutations in the *ANKH* gene, which encodes a protein involved in pyrophosphate transport, and in *TNFRSF11B* (encoding osteoprotegerin) have been associated with the disease. Secondary causes include hyperparathyroidism, hemochromatosis, and diabetes mellitus [25–27].

Pathogenesis: With degradation of cartilage proteoglycans, crystal deposition occurs around chondrocytes. Inflammation is triggered by macrophage activation, similar to gout, but is less severe.

Morphology: Chalky-white deposits in articular cartilage, menisci, and intervertebral discs.

Microscopy: Basophilic aggregates on H&E staining; under polarized light, crystals are rhomboid/ellipsoid and show positive birefringence (Fig. 23.13).

Treatment: Supportive only; no curative therapy is currently available.

23.8.3 Arthropathies Associated with Hydroxyapatite Deposition

Hydroxyapatite, octacalcium phosphate, and tricalcium phosphate crystals may deposit in periarthritic tissues outside the synovium. These deposits may be associated with trauma, renal failure, hyperparathyroidism, sarcoidosis, malignancy, or hypermetabolic states. They are surrounded by mild chronic inflammation containing macrophages and, frequently, multinucleated

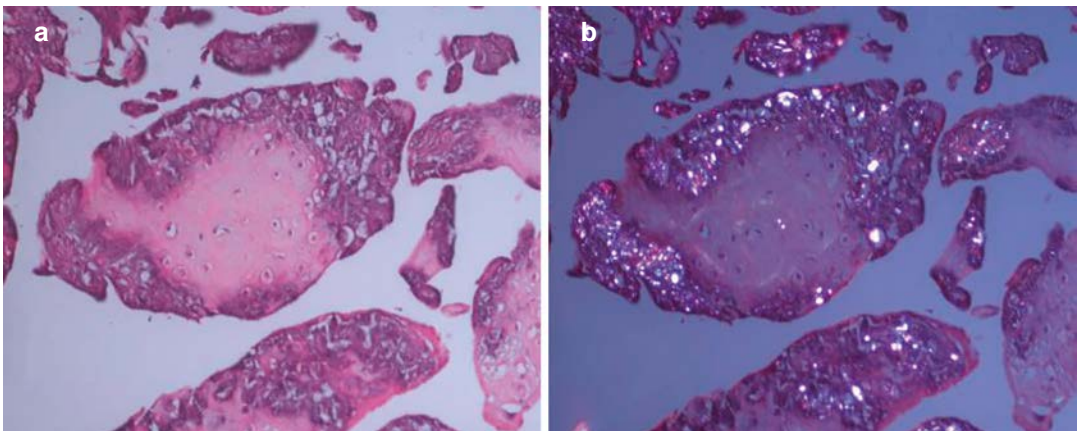


Fig. 23.13 (a) Synovial tissue shows blue–violet aggregates. (b) Under polarized light microscopy, crystals show positive birefringence

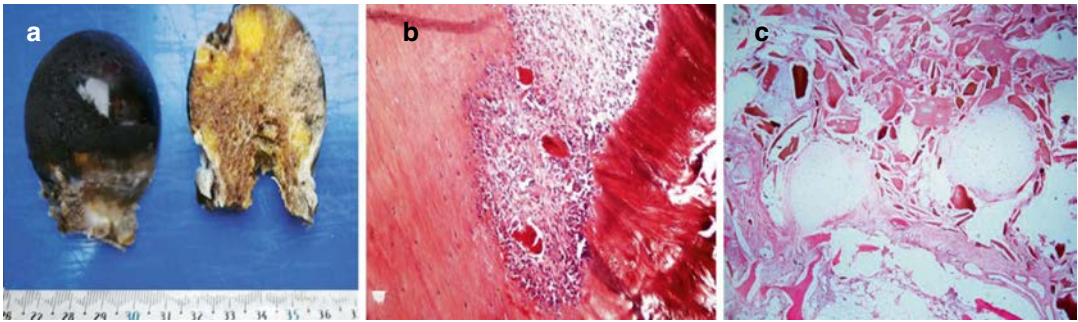


Fig. 23.14 (a) A 45-year-old patient with alkaptonuria underwent excision of the femoral head for degenerative joint disease. Articular cartilage is extensively lost in most areas. Homogentisic acid deposition in the subchondral bone has produced a striking glossy black, marble-like

appearance. On section, the subchondral bone (appearing yellow shows necrosis) and residual articular cartilage is black. (b, c) Histologically, dark brown HGA pigment deposition is seen in periarticular regions, within entheses of ligaments, and in cartilage chips within the synovium

giant cells. Unlike urate or pyrophosphate crystals, they do not exhibit birefringence under polarized light [28–31].

23.8.4 Ochronosis (Alkaptonuria)

Ochronosis results from the hereditary deficiency of the enzyme *homogentisic acid oxidase*, leading to accumulation of homogentisic acid (HGA) in soft tissues and joints. It is inherited in an autosomal recessive manner and involves impaired tyrosine/phenylalanine metabolism. HGA accumulates in collagen-rich tissues and undergoes oxidation, forming dark pigments. Clinically, early findings may include darkening of urine upon exposure to air. Progressive deposition of blue–black pigment occurs in cartilage, auricular structures, sclera, skin, tendons, and connective tissue, leading to joint pain, stiffness, restricted movement, and progressive arthropathy. The weakening of collagen results in reduced resistance, predisposing tendons, ligaments, and articular cartilage to rupture and fragmentation. Symptoms typically become prominent in the third to fourth decades of life. Macroscopically, pigmentation is visible in joint structures. Histologically, brown–black pigment deposits are evident within macrophages, collagen, and cartilage (Fig. 23.14). Diagnosis is established by demonstrating elevated urinary HGA and con-

firmed by genetic testing. Although dietary restriction of phenylalanine and tyrosine has been suggested, its effectiveness is limited. There is currently no curative treatment [29].

23.9 Hemophilic/Hemorrhagic Arthropathy

This condition arises from recurrent intra-articular hemorrhages (hemarthroses), leading to chronic synovitis and joint destruction. It is most often associated with hemophilia A (factor VIII deficiency) and hemophilia B (factor IX deficiency), but may also occur in von Willebrand disease or during anticoagulant therapy. Weight-bearing joints such as the knees, hips, and elbows are most frequently affected. Recurrent intra-articular hemorrhages induce inflammation, synovial hypertrophy, and proliferation. Hemoglobin degradation products accumulate as hemosiderin within intra-articular tissues, damaging chondrocyte matrix and accelerating cartilage degeneration (Fig. 23.15).

Morphology: Synovial hypertrophy and villous proliferation, hemosiderin deposition within macrophages, fibrosis, pannus-like tissue formation, cartilage erosion, and subchondral bone changes eventually result in degenerative joint disease.

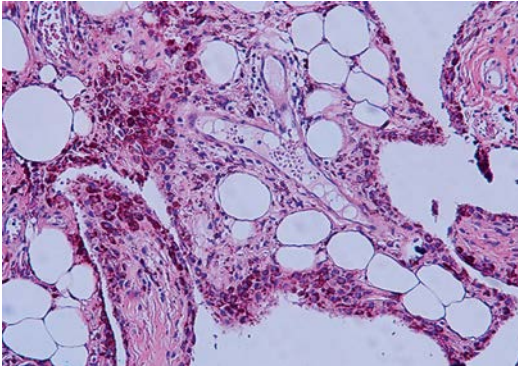


Fig. 23.15 Hemorrhagic arthropathy: synovial membrane shows hyperplasia and proliferation; hemosiderin is observed within synoviocytes secondary to hemoglobin breakdown

Treatment: Replacement of the deficient coagulation factor to prevent bleeding episodes and minimize joint damage [30].

23.10 Metallosis

Metal prostheses are frequently used in degenerative joint disease or after tumor resections. Metallosis is a chronic inflammatory reaction and tissue-damaging process caused by the accumulation of metallic debris around a prosthesis due to metal-on-metal friction, wear, or corrosion. Metal ions and particles are phagocytosed by synovial cells and macrophages, leading to cytokine release, osteolysis, tissue destruction, and fibrosis.

Morphology: Macrophages and multinucleated giant cells surrounding metal particles; intracellular brown/gray metallic granules; chronic mononuclear inflammation; and proliferation of fibrous tissue [31].

References

1. Wysokinski D, Pawlowska E, Blasiak J. RUNX2: a master bone growth regulator that may be involved in the DNA damage response. *DNA Cell Biol.* 2015;34(5):305–15.
2. Wright E, Hargrave MR, Christiansen J, Cooper L, Kun J, Evans T, Gangadharan U, Greenfield A,

- Koopman P. The Sry-related gene Sox9 is expressed during chondrogenesis in mouse embryos. *Nat Genet.* 1995;9(1):15–20.
3. Boskey AL, Robey PG. The composition of bone. In: Bilezikian JP, editor. *Primer on the metabolic bone diseases and disorders of mineral metabolism.* Hoboken: Wiley-Blackwell; 2018. p. 84–92.
4. Feng W, Liu H, Luo T, Liu D, Du J, Sun J, Wang W, Han X, Yang K, Guo J, Amizuka N, Li M. Combination of IL-6 and sIL-6R differentially regulate varying levels of RANKL-induced osteoclastogenesis through NF- κ B, ERK and JNK signaling pathways. *Sci Rep.* 2017;7:41411. <https://doi.org/10.1038/srep41411>. Erratum in: *Sci Rep.* 2022;12(1):3746. doi: 10.1038/s41598-022-07357-3. PMID: 28128332; PMCID: PMC5269740.
5. Beeharry MW, Ahmad B. Principles of fracture healing and fixation: a literature review. *Cureus.* 2024;16(12):e76250. <https://doi.org/10.7759/cureus.76250>. PMID: 39717521; PMCID: PMC11665253.
6. Yu H, Li C, Wu H, Xia W, Wang Y, Zhao J, Xu C. Pathogenic mechanisms of osteogenesis imperfecta, evidence for classification. *Orphanet J Rare Dis.* 2023;18:234.
7. Porter JL, Varacallo MA. Osteoporosis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023.
8. Hatano M, et al. Diaphyseal femoral fracture due to severe vitamin D3 deficiency. *J Bone Miner Res.* 2020;35(5):926–33.
9. Roumpou A, Palermo A, Tournis S, Hasenmajer V, Pasieka JL, Kaltsas G, Isidori A, Kassi E. Bone in parathyroid diseases revisited: evidence from epidemiological, surgical and new drug outcomes. *Endocr Rev.* 2025;46(4):576–620.
10. Chen L, Hong G, Fang B, Zhou G, Han X, Guan T, He W. Predicting the collapse of the femoral head due to osteonecrosis: from basic methods to application prospects. *J Orthop Translat.* 2017;11:62–72. <https://doi.org/10.1016/j.jot.2016.11.002>.
11. Dartnell J, Ramachandran M, Katchburian M. Haematogenous acute and subacute paediatric osteomyelitis: a systematic review of the literature. *J Bone Joint Surg Br.* 2019;101-B(5):e99.
12. Hatzenbuehler J, Pulling TJ. Diagnosis and management of osteomyelitis. *Am Fam Physician.* 2017;96(2):102–9.
13. Pineda C, Espinosa R, Pena A. Radiographic imaging in osteomyelitis: the role of plain radiography, CT, MRI, and scintigraphy. *Semin Plast Surg.* 2019;33(1):13–21.
14. Lew DP, Waldvogel FA. Osteomyelitis. *Lancet.* 2020;396(10267):397–409.
15. Held M, Laubscher M, Zar HJ, Dunn RN. GeneXpert polymerase chain reaction for spinal tuberculosis in children: a prospective study. *Bone Joint J.* 2016;98-B(6):852–6.
16. Moro P, Schantz PM. Echinococcosis: a review. *Int J Infect Dis.* 2019;88:127–33.

17. Ralston SH, Layfield R. Pathogenesis of Paget disease of bone. *Calcif Tissue Int.* 2022;110(5):575–83.
18. Sophia Fox AJ, Bedi A, Rodeo SA. The basic science of articular cartilage: structure, composition, and function. *Sports Health.* 2016;8(4):267–77.
19. Jevotovsky DS, Alfonso AR, Einhorn TA, Chiu ES. Osteoarthritis and stem cell therapy in humans: a systematic review. *Osteoarthr Cartil.* 2018;26(6):711–29.
20. Li G, Yin J, Gao J, Cheng TS, Pavlos NJ, Zhang C, et al. Subchondral bone in osteoarthritis: insight into risk factors and microstructural changes. *Arthritis Res Ther.* 2013;15(6):223.
21. Firestein GS, McInnes IB. Immunopathogenesis of rheumatoid arthritis. *Immunity.* 2017;46(2):183–96.
22. Bugatti S, Caporali R, Manzo A, Montecucco C. The lymphoid microenvironment in rheumatoid synovitis. *Autoimmun Rev.* 2018;17(9):895–902.
23. Kuo CF, Grainge MJ, Zhang W, Doherty M. Global epidemiology of gout: prevalence, incidence and risk factors. *Nat Rev Rheumatol.* 2015;11(11):649–62.
24. Ragab G, Elshahaly M, Bardin T. Gout: an old disease in new perspective – a review. *J Adv Res.* 2017;8(5):495–511.
25. Abhishek A, Doherty M. Calcium pyrophosphate deposition disease: state of the art and future directions. *Ann Rheum Dis.* 2016;75(6):1039–45.
26. Ryu JH, Kim HA. Clinical manifestations and risk factors of calcium pyrophosphate deposition disease. *Korean J Intern Med.* 2017;32(2):419–28.
27. Rosenthal AK, Gohr CM, Mitton-Fitzgerald E, Gohr CM. Calcium crystal deposition diseases — update on pathogenesis and management. *Curr Opin Rheumatol.* 2022;34(2):144–51.
28. Kumar V, Abbas AK, Aster JC. Robbins and Cotran pathologic basis of disease. 10th ed. Philadelphia: Elsevier; 2021.
29. Davison AS, Milan AM, Hughes AT, Dutton JJ, Ranganath LR. Alkaptonuria, ochronosis, and ochronotic arthropathy. *Rheumatology (Oxford).* 2020;59(12):3899–901.
30. Melchiorre D, Linari S, Manetti M, Romano E, Innocenti M, Matucci-Cerinic M, et al. Clinical and morphologic characteristics of hemophilic arthropathy: an ultrasound study. *Semin Thromb Hemost.* 2016;42(5):541–9.
31. Gibon E, Amanatullah DF, Loi F, Pajarinen J, Nabeshima A, Yao Z, et al. The biological response to orthopaedic implants for joint replacement: part I. Metals. *J Biomed Mater Res B Appl Biomater.* 2017;105(7):2162–73.

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24.1 Welcome Aboard to Bone Tumor Pathology

This chapter is dedicated to pathological aspects of bone tumors; however, special care has been taken to avoid overly detailed histologic descriptions that is often challenging even among experienced pathologists. Only a brief overview of the known etiopathogenetic mechanisms or cytogenetic findings is provided, focusing on a few tumor groups where these pathways have been reasonably well established. The section you are about to read is designed to provide a general overview of bone tumors for medical students at different levels and for general practitioners, offering a foundation for understanding and keeping up with current developments in this field. For this reason, the emphasis is placed on highlights and key points, rather than exhaustive microscopic or molecular detail. References for further reading—covering the classification, pathogenesis, and clinicopathologic management of bone tumors—are listed at the end of the chapter [1–5]. Although not covered in the

context of this chapter before hitting on the road, readers are encouraged to review the mechanisms of bone formation and resorption, bone histology (including the matrix composition and the structure and function of osteoblasts, osteoclasts, and osteocytes), and the process of fracture healing, which can histologically mimic many bone tumors and is essential for a deeper understanding of the subject [1–3].

24.2 An Overview of Bone Tumors: A “Hard” Topic!

The first and best news about bone tumors is that they are very rare. They account for only about 0.2% of all human tumors. They are less common than soft tissue tumors, and there are fewer tumor types than soft tissue counterparts [2]. But here is the first bit of bad news: bone tumor pathology is one of the “hardest” subjects of pathology. What makes it “hard” starts with the fact that bone itself is a “hard” organ (remember, this hardness is due to the calcium stored in the bone matrix). The most important effect of this hardness is the difficulty in obtaining biopsies and the challenges encountered in processing bone tissues in pathology laboratories. Orthopedic surgeons cannot simply remove a tumor as easily as they would take out a skin nevus. Pathologists cannot cut bone tissue for examination as easily as they would slice through an uterine leiomyoma. Preparation of tissues for histopathological

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examination is also more laborious than other organs. Cutting large bones may require the use of a handsaw or electric saw. For all the samples (biopsies, curettage materials, excisional biopsies, or resections), then, to preserve the bone cells, the tissue must be fixed in formaldehyde. To prepare slides thin enough (about 3–4 μm) for microscopic examination, this fixed tissue must be softened as well, meaning the calcium in the bone must be removed. This is achieved by placing the tissue in decalcifying solutions as acids (usually formic acid) or chelating agents as EDTA. Decalcification process may be extremely time-consuming, depending on the part of the bone. The use of stronger acids reduces the time but negatively affects further examinations by damaging the properties of the tissue. All these steps as processing the tissue, reaching a diagnosis, and performing cell- and molecular-level studies—essential for understanding the etiopathogenesis of bone tumors—are challenging [4]. Yet, amid all these bones, saws, and acids, bone tumors remain a mysterious and fascinating topic, containing molecular pathways that also regulate normal bone growth. (As for how such a topic could be “fascinating or cool,” you have probably already answered that question for yourself the day you decided to study medicine!)

24.3 Classification and Etiopathogenesis Bone Tumors

Like other tumors, bone tumors are classified based on their cellular origin and structural organization. However, unlike most neoplasms, their classification also considers matrix production (osteoid or chondroid), a unique feature of bone pathology. Behaviorally, bone tumors are grouped as benign, intermediate, or malignant. The intermediate category represents lesions with behavior between benign and malignant, capable of local aggressiveness, cortical breach, soft tissue extension, or rare metastasis. The WHO classifi-

cations of bone tumors remains relatively stable compared to classifications for hematopathologic or head and neck tumors (Table 24.1). Interestingly, some “intermediate” tumors, such as giant cell tumor of bone and occasionally chondroblastoma, may metastasize to the lungs without being classified as “malignant”. These pulmonary metastases are thought to result from tumor cells entering the venous system and settling in the lungs, which somehow tolerate their presence. This process is like the growth of a seed that finds suitable soil and, in essence, represents a kind of a “nonaggression pact.” Factors associated with such behavior include multiple recurrences, patient age, surgical type, and elevated cytokines (RANKL, IL-6, TNF) and chemokines (SDF-1, MCP-1) that promote monocyte recruitment. Despite these insights, many aspects of bone tumor biology remain unresolved [1–3].

Returning to classification, the largest groups of bone tumors are osteogenic (bone cell-derived) and chondrogenic (cartilage cell-derived) tumors. Both produce their respective extracellular matrices—osteoid and cartilage—which are crucial for skeletal strength. However, bone is a heterogeneous tissue, containing not only bone and cartilage cells but also marrow-derived cells, fat, blood vessels, nerves, lymphatics, and fibrous tissue, all of which can give rise to tumors. For diagnosis, cellular features, growth pattern, and the presence of osteoid or cartilage matrix are essential. Distinguishing benign from malignant tumors relies on whether the tumor invades existing trabeculae, breaches the cortex into soft tissue, exhibits cellular atypia, or shows abnormal mitoses. The degree of malignancy is generally inherent to the tumor type. Unlike soft tissue tumors, criteria such as cellularity or mitotic rate are less important for grading bone tumors. The question of why bone tumors develop has no single answer, as there is no single type of bone tumor. Like other tumors, some genetic predispositions have been identified—for example, hereditary retinoblastoma or Li-Fraumeni syndrome in osteosarcoma. Similarly, environmental factors such as radiation exposure, or underlying chronic

Table 24.1 WHO Classification of Bone Tumors (2020)

Tumor group	Behavior	Examples/subtypes
Chondrogenic tumors	Benign	Enchondroma; osteochondroma; subungual exostosis; bizarre parosteal osteochondromatous proliferation; periosteal chondroma; chondroblastoma NOS; chondromyxoid fibroma; osteochondromyxoma
	Intermediate (locally aggressive)	Chondromatosis NOS; atypical cartilaginous tumor
	Malignant	Chondrosarcoma (grades 1–3); periosteal chondrosarcoma; clear cell chondrosarcoma; mesenchymal chondrosarcoma; dedifferentiated chondrosarcoma
Osteogenic tumors	Benign	Osteoma NOS; osteoid osteoma NOS
	Intermediate	Osteoblastoma NOS
	Malignant	Low-grade central osteosarcoma; osteosarcoma NOS (conventional, telangiectatic, small cell); parosteal; periosteal; high-grade surface; secondary osteosarcoma. Less aggressive types: parosteal OS and low-grade intramedullary OS. Secondary OS: on the background of fibrous dysplasia, osteomyelitis, or Paget’s disease
Fibrogenic tumors	Intermediate	Desmoplastic fibroma
	Malignant	Fibrosarcoma NOS
Vascular tumors	Benign	Hemangioma NOS
	Intermediate	Epithelioid hemangioma
	Malignant	Epithelioid hemangioendothelioma NOS; angiosarcoma
Osteoclastic giant cell–rich tumors	Benign	Aneurysmal bone cyst; non-ossifying fibroma
	Intermediate	Giant cell tumor of bone NOS
	Malignant	Giant cell tumor of bone, malignant
Notochordal tumors	Benign	Benign notochordal tumor
	Malignant	Chordoma NOS; chondroid chordoma; poorly differentiated chordoma; dedifferentiated chordoma
Other mesenchymal tumors of bone	Benign	Fibrous dysplasia; simple bone cyst; chondromesenchymal hamartoma of chest wall; osteofibrous dysplasia; lipoma NOS; hibernoma
	Intermediate	Osteofibrous dysplasia–like adamantinoma; mesenchymoma NOS
	Malignant	Adamantinoma of long bones; dedifferentiated adamantinoma; leiomyosarcoma NOS; pleomorphic sarcoma undifferentiated
Hematopoietic neoplasms of bone	Malignant	Plasmacytoma of bone; malignant lymphoma (non-Hodgkin NOS); Hodgkin disease NOS; diffuse large B-cell lymphoma NOS; follicular lymphoma NOS; marginal zone B-cell lymphoma NOS; T-cell lymphoma NOS; anaplastic large cell lymphoma NOS; Burkitt lymphoma NOS; Langerhans cell histiocytosis (NOS or disseminated); Erdheim–Chester disease; Rosai–Dorfman disease

conditions like osteomyelitis, Paget disease, or benign lesions such as fibrous dysplasia, can create a setting for secondary bone tumors, including osteosarcoma (discussed in detail below). In general, conditions that increase bone turnover, regions of the skeleton that are prone to growth, and periods of skeletal development may increase susceptibility, particularly for osteosarcoma, though each tumor subtype has its own unique developmental pathway [1].

24.4 Clinical Approach to Bone Tumors

One of the most important aspects of bone tumors is that most bone tumors occur within specific age groups and tend to involve a particular skeletal region depending on the tumor type (Fig. 24.1). Orthopedic surgeons, radiologists, and pathologists all rely on this information, using it to guide their differential diagnosis. Therefore, anyone

Fig. 24.1 Distribution of bone tumors by age

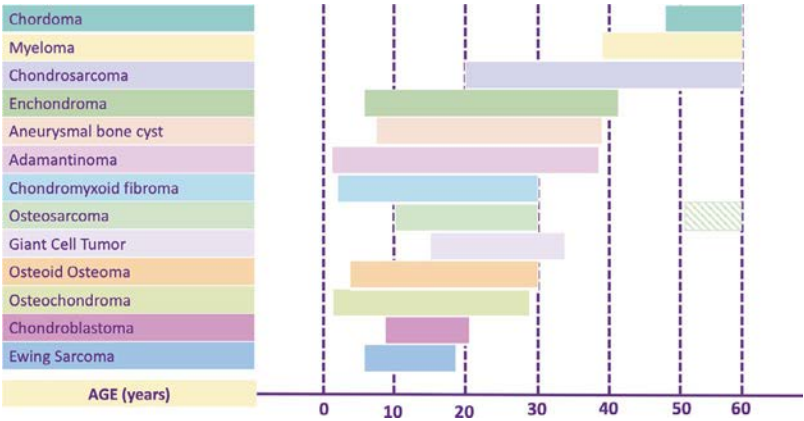
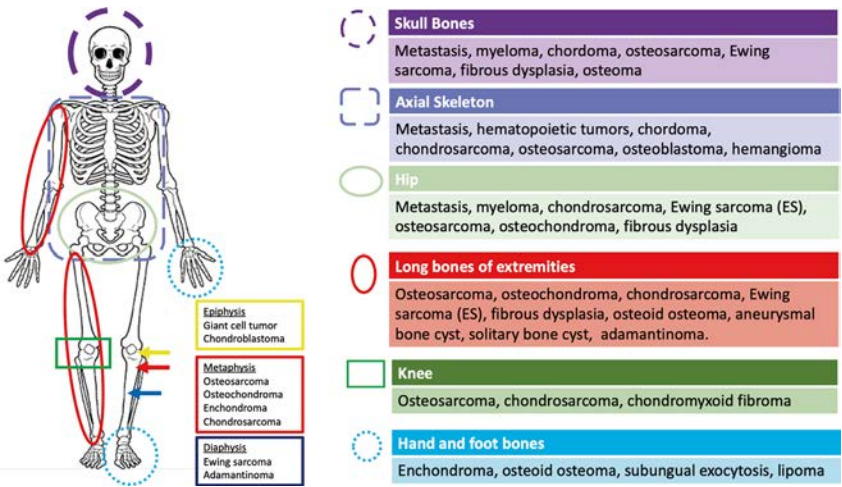


Fig. 24.2 Skeletal distribution of bone tumors



who wants to have general information about bone tumors should know where the common tumors are located (whether in the axial skeleton or in the appendicular skeleton) (Fig. 24.2) and, if located in the appendicular skeleton, which part of the long bones they affect (Fig. 24.3) (Table 24.2). Most common benign bone tumors are osteochondroma, enchondroma, osteoid osteoma, and non-ossifying fibroma (Table 24.3). Most common malignant bone tumors include osteosarcoma, chondrosarcoma, Ewing’s sarcoma, myeloma, and metastasis (Table 24.4).

Other common tumors include simple bone cyst, fibrous dysplasia, osteofibrous dysplasia, aneurysmal bone cyst, and Langerhans cell histiocytosis. The absence of the word “tumor” in the name of these tumors and tumor-like lesions should not be misleading. Please also note that some tumors, despite being very common, don’t cause many symptoms and aren’t surgically treated unless they pose a risk (i.e., fracture) to the patient, so they aren’t examined pathologically. Non-ossifying fibroma is a prime example of these so-called don’t-touch-me lesions.

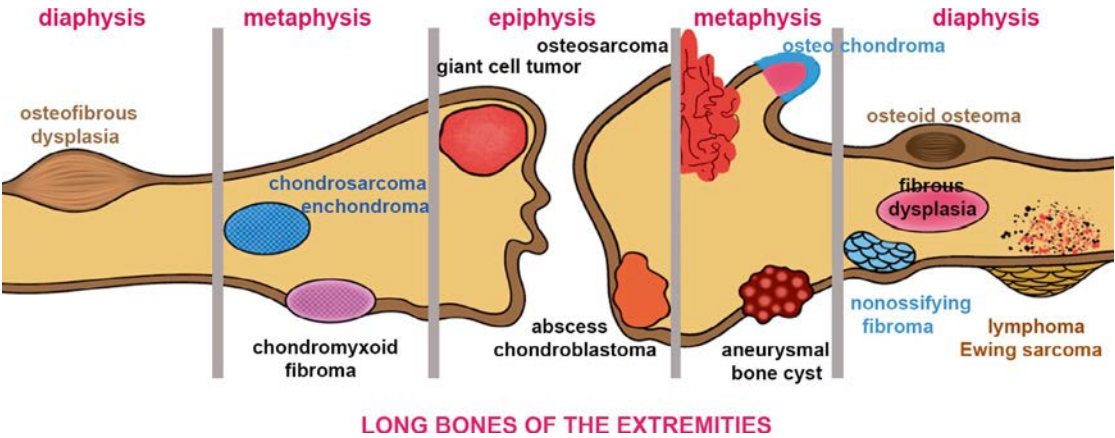


Fig. 24.3 Preferred anatomical localization of bone tumors and tumor-like lesions in extremity long bones

Table 24.2 Localization of bone tumors: Key Site-Specific Features

Localization	Tumors
Typical localization of selected tumors	Adamantinoma, OFD: middle third of tibia Simple bone cyst: Proximal humerus or femoral neck CRMO (chronic recurrent multifocal osteomyelitis): medial third of clavicle Enchondroma: phalanges and metaphyses of long bones Chordoma: clivus and sacrum Chondrosarcoma: pelvis and scapula Parosteal osteosarcoma: distal femoral metaphysis, posterior aspect Subungual exostosis: distal phalanx of the big toe Osteoma: facial bones
Epiphyseal tumors	Giant cell tumor, chondroblastoma, clear cell chondrosarcoma, telangiectatic osteosarcoma
Metaphyseal tumors	Osteosarcoma, chondromyxoid fibroma, aneurysmal bone cyst
Diaphyseal tumors	Ewing sarcoma, adamantinoma, fibrous dysplasia, simple bone cyst
Cortical lesions	Fibrosarcoma, osteoid osteoma, metastasis, osteomyelitis, stress fracture
Juxtacortical lesions	Osteochondroma, bizarre parosteal osteochondromatous proliferation (BPOP), parosteal osteosarcoma, periosteal osteosarcoma
Central tumors	Simple bone cyst, aneurysmal bone cyst, Langerhans cell histiocytosis, fibrous dysplasia, enchondroma
Eccentric tumors	Osteosarcoma, non-ossifying fibroma (NOF), chondroblastoma, chondromyxoid fibroma, giant cell tumor, osteoblastoma
Multifocal bone lesions	Vascular tumors, Langerhans cell histiocytosis, leukemia/lymphoma, Ewing sarcoma, fibrous dysplasia, osteomyelitis, hyperparathyroidism, enchondromatosis, osteochondromatosis

Table 24.3 Common Benign bone tumors with Key Clinical and Histopathological Findings

Tumor	Keywords
Osteoma	Compact lesion, facial bones, accompany Gardner syndrome. “Ivory or trabecular” type
Osteoid osteoma	<25 years, diaphysis, nocturnal pain relieved by NSAIDs, radiolucent nidus in cortex.
Osteoblastoma	Similar histology with osteoid osteoma. Medullary localization.
Osteochondroma	Adolescents/young adults, metaphysis near knee, cartilage-capped bony projection, continuous with cortex/medulla.
Enchondroma	20–40 years, small bones of hand/feet, well-circumscribed lytic lesion, cartilage matrix calcification, multiple → Ollier disease
Chondroblastoma	Epiphyseal localization. <20 years (epiphyses are open). Rich reticular network. Chicken-wire calcification.
Fibrous dysplasia	Childhood, monostotic > polyostotic, café-au-lait spots on skin, ground-glass appearance in radiology, <i>Pathology</i> : Chinese characters trabeculae, metaplastic bone, fibroblastic background proliferation
Simple/solitary (unicameral) bone cyst (UBC)	Children/adolescents, proximal humerus/femur, metaphysis, fluid-filled cavity, pathologic fracture, radiological “fallen leaf sign”
Aneurysmal bone cyst (ABC)	<20 years, metaphysis, eccentric, expansile lytic lesion, blood-filled spaces, septations. Rule-out telangiectatic osteosarcoma
Giant cell tumor	20–40 years, epiphysis, around knee, soap-bubble lesion, multinucleated giant cells (<i>borderline; locally aggressive</i>) <i>Pathology</i> : mononuclear neoplastic cells, giant cells with dozens of nuclei, nuclear similarity, H3G3A (HGW34), SATB2
Non-ossifying fibroma (NOF)	Children/adolescents, metaphysis, incidental finding, fibrous stroma, self-limited. “Do not touch unless fracture risk.”
Hemangioma of bone	Adults, vertebra (most common), asymptomatic, “corduroy” or “polka-dot” radiographic pattern

Table 24.4 Common Malignant bone tumors With Key Clinical and Histopathological Findings

Tumor	Keywords
Osteosarcoma	Most common malignant primary bone tumor. 10–20 years, knee region, pain/swelling, sunburst periosteal reaction, Codman triangle, lung metastasis. Osteoblastic-chondroblastic-fibroblastic conventional ones. Malignant osteoid (osteoid produced by malignant cells), lace-like osteoid. Low-grade OS types: intramedullary OS, parosteal OS. Secondary OS: (due to) radiation, osteomyelitis, fibrous dysplasia. More aggressive variants: Telangiectatic OS, small cell OS, secondary OS. Differential diagnosis with all bone lesions! (especially rule-out fracture healing)
Ewing sarcoma	Children/adolescents, diaphysis, onion-skin periosteal reaction, small round blue cells, t(11;22), molecular analysis may be required
Chondrosarcoma	Adults >40, pelvis/ribs, cartilage matrix calcification, lobulated masses. Binucleation, increased cellularity, “entrapped bone”
Chordoma	Adults, midline (sacrum, clivus), lobulated destructive mass, physaliphorous cells, chords, immunohistochemical positivity with epithelial and mesenchymal markers. Brachyuria is specific!
Multiple myeloma	>50 years, multiple lytic lesions, skull/pelvis/spine, Bence-Jones proteinuria. Plasma cells (immunohistochemistry Kappa-Lambda)
Lymphoma	Differential diagnosis with Ewing sarcoma (small blue round cell tumors!)
Metastatic bone tumors	Adults, most common malignant bone tumors, axial skeleton, lytic or blastic (prostate → blastic; kidney/lung/thyroid → lytic)

24.5 Osteogenic Tumors

24.5.1 Osteoma

Osteoma is a benign bone tumor usually seen in middle-aged women. It often arise in the skull and facial bones and are usually single, but multiple lesions can suggest Gardner syndrome [3]. Grossly, they form hard, round, or oval, sessile masses made of compact bone. Microscopically, two patterns are seen: a *compact* (“ivory”) *osteoma*, composed of dense lamellar bone with Haversian systems and no fibrous stroma, and a *trabecular osteoma*, which contains marrow tissue surrounded by cortical bone (Fig. 24.4).

24.5.2 Osteoid Osteoma and Osteoblastoma

These two benign (OO) and intermediate (OB) bone tumors look similar under the microscope but behave differently in patients. Osteoid osteoma usually affects people in their teens or 20s, is less than 2 cm in size, and favors the appendicular skeleton—especially the femur and tibia, in the diaphysis or metaphysis, most often in the cortex. It causes intense night pain due to prostaglandin E2 production, which improves with aspirin or other NSAIDs. Osteoblastoma, on the other hand, typically occurs in patients over 20 years old, is larger than 2 cm, and often arises

in the spine, involving the medulla and cortex. The pain is mild and dull and does not respond well to aspirin. Histologically, both lesions contain interlacing trabecular bone lined by plump osteoblasts and vascularized stroma. FOSB gene locus rearrangements are noted in OO. The differential diagnosis of OB from osteosarcoma may require demonstration of permeative growth to neighboring bone by radiological workup (Figs. 24.5, 24.6, and 24.7).

24.5.3 Osteosarcoma

Osteosarcoma is the most common malignant bone tumor, and it stands out in the field of bone tumors for several reasons. It affects two distinct age groups, shows considerable histological diversity, and can mimic many other bone lesions and tumors, including fracture healing. Currently, there is no immunohistochemical marker to facilitate tissue diagnosis, no clear molecular signature, and no targeted therapy beyond standard surgical resection and chemotherapy. All of these features make osteosarcoma the “diva” of bone tumors, the most recognized and extensively studied member of this tumor family. Osteosarcoma is an aggressive tumor, with 10–20% of patients presenting with lung metastases at the time of diagnosis. It usually presents with localized pain, swelling, or a palpable soft tissue mass, and in some cases, as noted above, a pathologic fracture may be the first sign. Most patients are adolescents, with about three-quarters of cases occurring in the second decade of life (Fig. 24.8). A smaller second peak is seen in older adults, often in association with secondary osteosarcoma (see below). There is a slight male predominance and importantly; please note that in young patients, early symptoms such as pain or swelling are sometimes dismissed as minor sports injuries (“he fell, he bumped, he probably injured something”), delaying recognition. Persistent pain, especially at rest or at night, or unexplained, painful or painless swelling should always raise concern for a possible bone tumor. The tumor typically arises in the metaphysis of

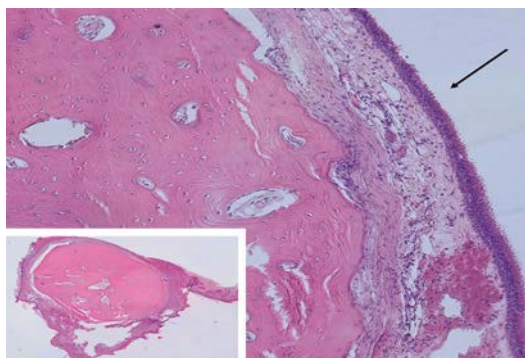


Fig. 24.4 Osteoma: note the relationship of tumor with sinus mucosa (arrow) and compact bony nature of the lesion (inset)

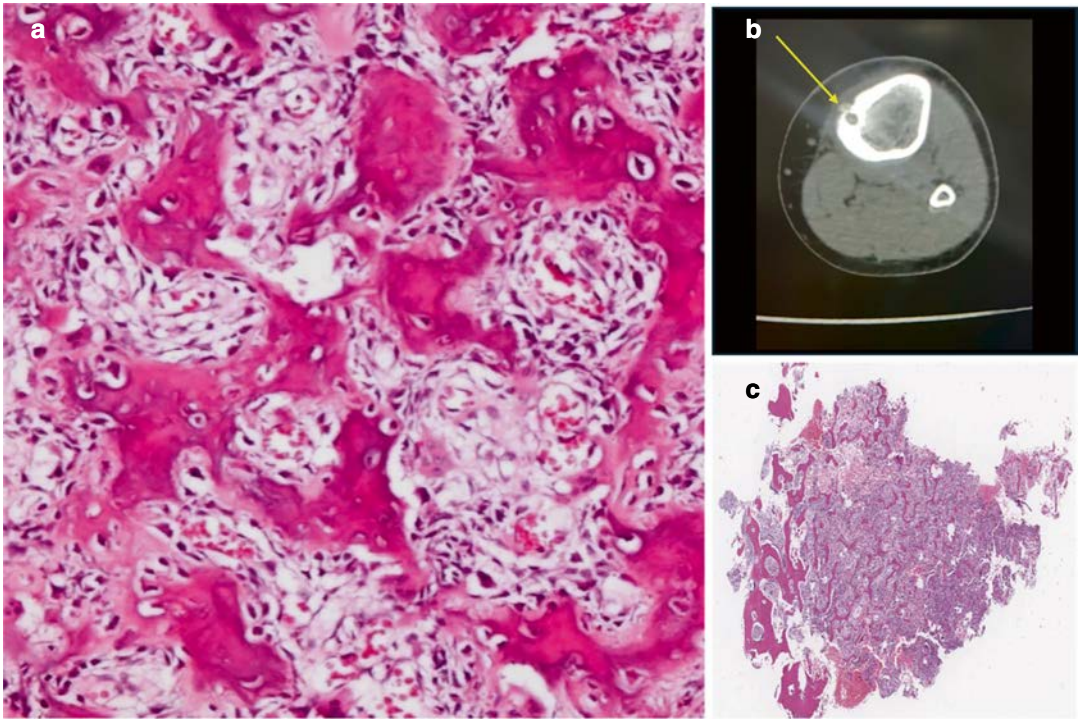


Fig. 24.5 (a) Osteoid osteoma-osteoblastoma histology with anastomosing osteoid trabeculae and plump epithelioid-looking osteoblasts, (b) computed tomography

view of intracortical lytic “nidus” of osteoid osteoma (arrow). (Courtesy of Ipek Tamsel, MD), (c) histopathology of nidus

long bones, most commonly the distal femur and proximal tibia (around knee, close to the largest growth plates!), but may also involve the proximal humerus, proximal femur, pelvis, and jaw! Radiologically, it shows mixed lytic and sclerotic areas, with a characteristic Codman triangle (periosteal lifting) and sunburst pattern of periosteal reaction (Fig. 24.9). Less aggressive forms include parosteal osteosarcoma, which typically occurs in middle-aged women on the posterior femur, and low-grade intramedullary osteosarcoma. Secondary osteosarcomas may arise on the background of preexisting bone disorders, such as fibrous dysplasia, chronic osteomyelitis, or Paget disease. Histologically, the classic (conventional) types include osteoblastic, chondroblastic, and fibroblastic variants. (See Table 24.1 and 24.4 for osteosarcoma types) Osteosarcoma is the only primary malignant osteogenic tumor, and in theory, its histo-

logical definition is straightforward: it is characterized by malignant cells producing osteoid (immature bone matrix), which often has a delicate, lace-like appearance surrounding the tumor cells. However in practice, distinguishing osteoid can be challenging, as it may also appear coarser or more trabecular and the bone is a complex organ with continuous formation and resorption involving multiple cell types. Determining which cells are malignant can therefore be difficult. Osteosarcomas have been described that mimic other tumors, including giant cell tumor-like, osteoblastoma-like, and chondroblastoma-like variants, highlighting its role as a “great imitator.” Unfortunately there is no reliable tissue marker for diagnosis of osteosarcoma, and SATB2 is regarded as a very sensitive marker for osteoblastic differentiation but lacks specificity. MDM2 amplification is noted in low-grade osteosarcomas.

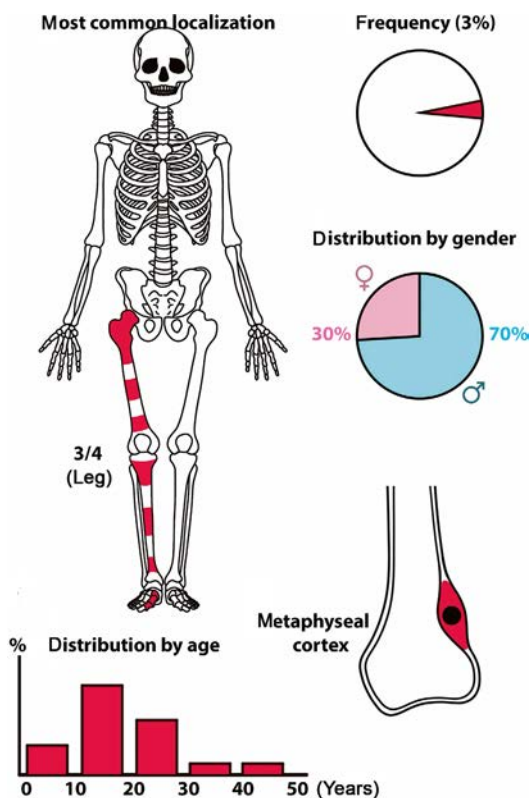


Fig. 24.6 Features of osteoid osteoma

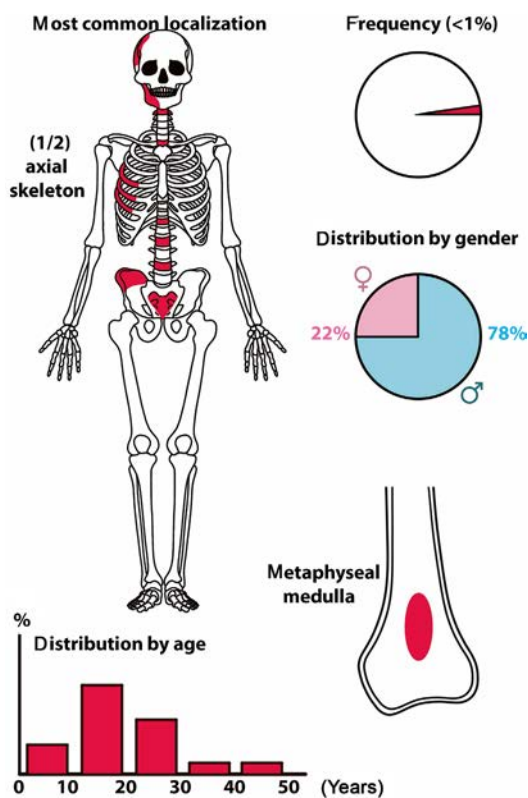


Fig. 24.7 Features of osteoblastoma

Osteosarcoma develops when genetic and environmental factors disrupt normal bone growth. It can arise in inherited cancer syndromes, such as hereditary retinoblastoma (RB1 mutations), Li-Fraumeni syndrome (TP53 inactivation), or Rothmund-Thomson syndrome (RECQL4 inactivation), as well as through alterations in p16 or overexpression of MDM2, which inactivates p53. Secondary osteosarcomas occur on preexisting bone problems or after insults like prior radiation exposure (often with a latency of ~10 years), Paget disease, fibrous dysplasia, or chronic osteomyelitis. At the molecular level, dysregulation of key signaling pathways—including WNT, TGF- β /BMP, FGF, and Indian hedgehog—and transcription factors like RUNX2 and SATB2 drive abnormal osteo-

blast proliferation and osteoid production. Growth factors such as TGF- β , BMPs, and IGFs further promote malignant transformation. Together, these genetic and molecular changes create an environment that allows bone cells to become cancerous, explaining the etiology and pathogenesis of osteosarcoma in a concise, integrated view. By the time a medical student graduates, it is important to understand that osteosarcoma is a malignant tumor with frequent lung metastases and must be considered in the differential diagnosis of virtually all bone lesions. It is also reassuring to know that with modern limb-sparing surgical techniques and chemotherapy, the 5-year survival rate can reach approximately 75%, allowing many patients to achieve successful outcomes.

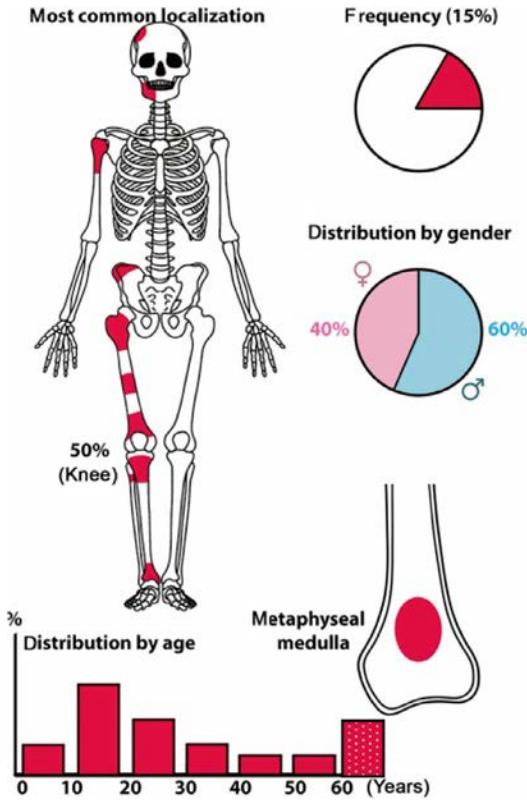


Fig. 24.8 Features of conventional osteosarcoma

24.6 Chondrogenic Tumors

They account for approximately one-fifth of all bone tumors. Although they have more subtypes than osteogenic tumors, fortunately, more than half of them are benign in nature [3]. These tumors are of chondrogenic origin, but it should be remembered that in some entities such as chondroblastoma and chondromyxoid fibroma, the amount of hyaline cartilage matrix may be minimal.

24.6.1 Osteochondroma

Osteochondroma is the most common, mostly asymptomatic benign bone tumor in adolescents and young adults, with a slight male predominance (Fig. 24.10). It typically arises from the metaphysis of long bones, most commonly around the knee (~40% of cases). Morphologically, osteochondromas appear as mushroom- or broccoli-shaped projections (1–20 cm) with a cartilage cap. A key feature is that the medullary cavity of the stalk is continu-

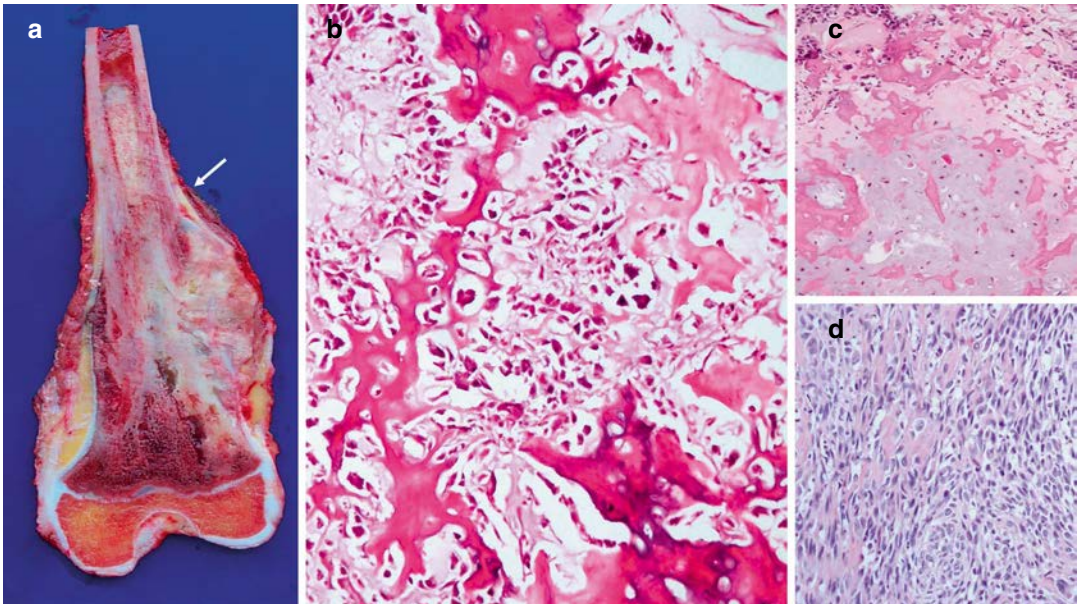


Fig. 24.9 Osteosarcoma: (a) Metaphyseal tumor with both osteoid and chondroid producing areas. Note the Codman triangle (arrow), sign of extracortical extension and aggressive periosteal reaction. (b) Typical conventional osteoblastic osteosarcoma with atypical cells pro-

ducing lace-like osteoid. (c) Chondroblastic areas of conventional osteosarcoma. (d) Fibroblastic areas of conventional osteosarcoma with neoplastic osteoid production, critical for tissue diagnosis

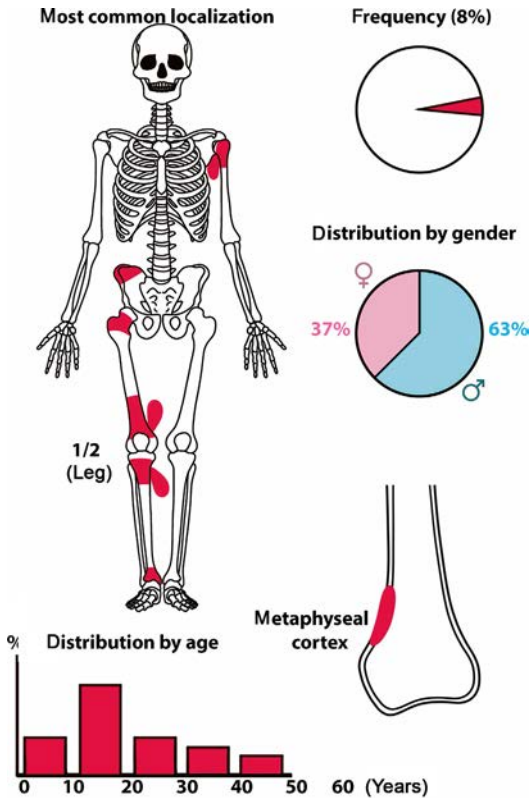


Fig. 24.10 Features of osteochondroma

ous with the underlying bone, which helps distinguish it from other bone lesions. Microscopically, the lesion consists of mature bone covered by a hyaline cartilage cap (Fig. 24.11). Pathogenesis can be developmental or neoplastic. Hereditary osteochondromas are caused by germline loss-of-function mutations in *EXT1* or *EXT2*, while sporadic lesions usually result from *EXT1* inactivation, affecting heparan sulfate proteoglycan synthesis and disrupting normal endochondral ossification. Please note that in hereditary multiple exostoses, lesions are often multiple and may appear in atypical locations. Malignant transformation can also occur in these hereditary cases. In adults, the cartilage cap of an osteochondroma is usually less than 0.5–1 cm. A thicker cap (>2–3 cm) or the presence of pain may raise concern for malignant transformation to chondrosarcoma (Fig. 24.11).

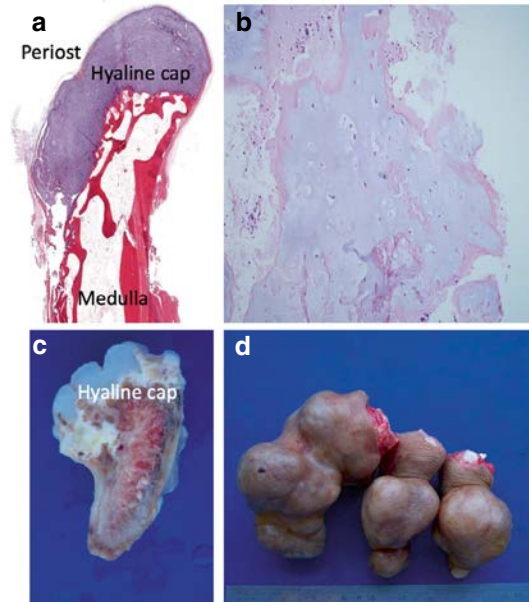


Fig. 24.11 (a) Osteochondroma, a mushroom or broccoli-like chondroid lesion with a hyaline cartilaginous cap. The thickness of the cartilaginous cap is important for the risk of malignant transformation. (b) Enchondroma, characterized by hypocellular cartilaginous lobules encased by bone (c) Subungual exostosis, a lesion similar to osteochondroma but capped by fibrocartilaginous tissue, rather than hyaline cartilage. (d) Amputated fingers of a patient with multiple enchondromas (“Ollier’s disease”)

24.6.2 Subungual Exostosis

A benign painful, firm subungual lesion that typically arises beneath the nail bed of the distal phalanx, most often affecting the great toe, causing nail elevation or deformity. Despite general resemblance with osteochondroma, it is characterized by a bony outgrowth capped by fibrocartilaginous tissue, rather than hyaline cartilage as seen in osteochondroma. The lesion is thought to be related to trauma or chronic irritation.

24.6.3 Enchondroma

Enchondromas are benign cartilage tumors typically seen in the small bones of the hands and feet in patients aged 20–40. Radiologically, they appear as well-circumscribed, lytic lesions with *chondroid matrix calcifications*. Multiple lesions

suggest Ollier disease (Fig. 24.1). Microscopically, it is characterized by hyaline cartilage with low cellularity and minimal atypia. Distinguishing enchondroma from grade 1 chondrosarcoma is one of the most challenging subjects in bone pathology. Heterozygous somatic mutations are described in the IDH1 and IDH2 genes in both tumors.

24.6.4 Chondroblastoma

Chondroblastoma is a rare, benign cartilage-producing tumor that usually affects adolescents and young adults (second decade of life). It arises in the epiphysis of long bones, most commonly the proximal humerus, proximal tibia, and proximal femur (Fig. 24.12). Patients usually present

with localized pain and sometimes joint swelling or limited motion, because the tumor grows close to the joint surface. Radiology typically appears as a well-defined, lytic lesion in the epiphysis, sometimes with thin sclerotic borders and spotty calcifications. Microscopically, it is composed of chondroblasts (immature cartilage cells) arranged in sheets, with a characteristic “chicken-wire” calcification surrounding individual cells. Osteoclast-like giant cells are often scattered throughout the lesion. K36M mutations are commonly identified in chondroblastoma.

24.6.5 Chondromyxoid Fibroma

Chondromyxoid fibroma (CMF) is a rare, benign tumor of cartilaginous and myxoid differentia-

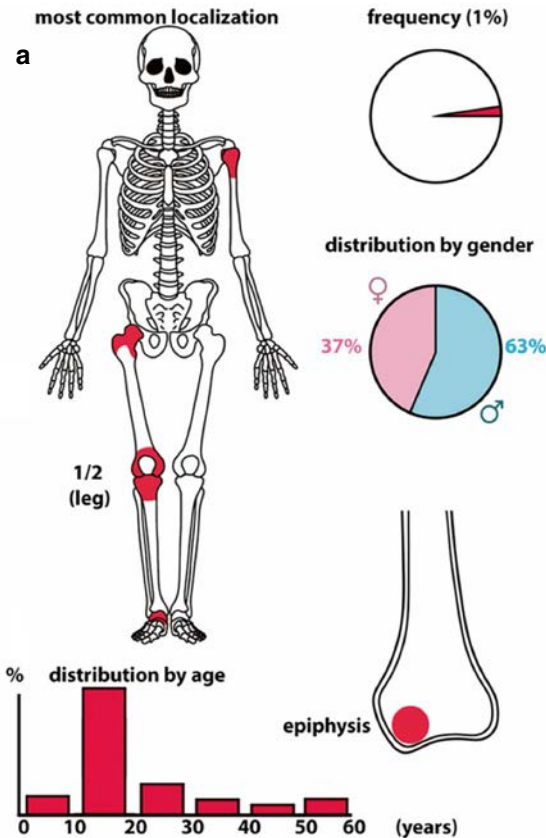


Fig. 24.12 (a) Features of chondroblastoma. (b) A faint chondroid matrix is present in the background, showing delicate “chicken wire”-type calcification surrounding

individual cells. (c) Cells with moderate to narrow eosinophilic cytoplasm, well-defined cell borders and a mildly plasmacytoid appearance

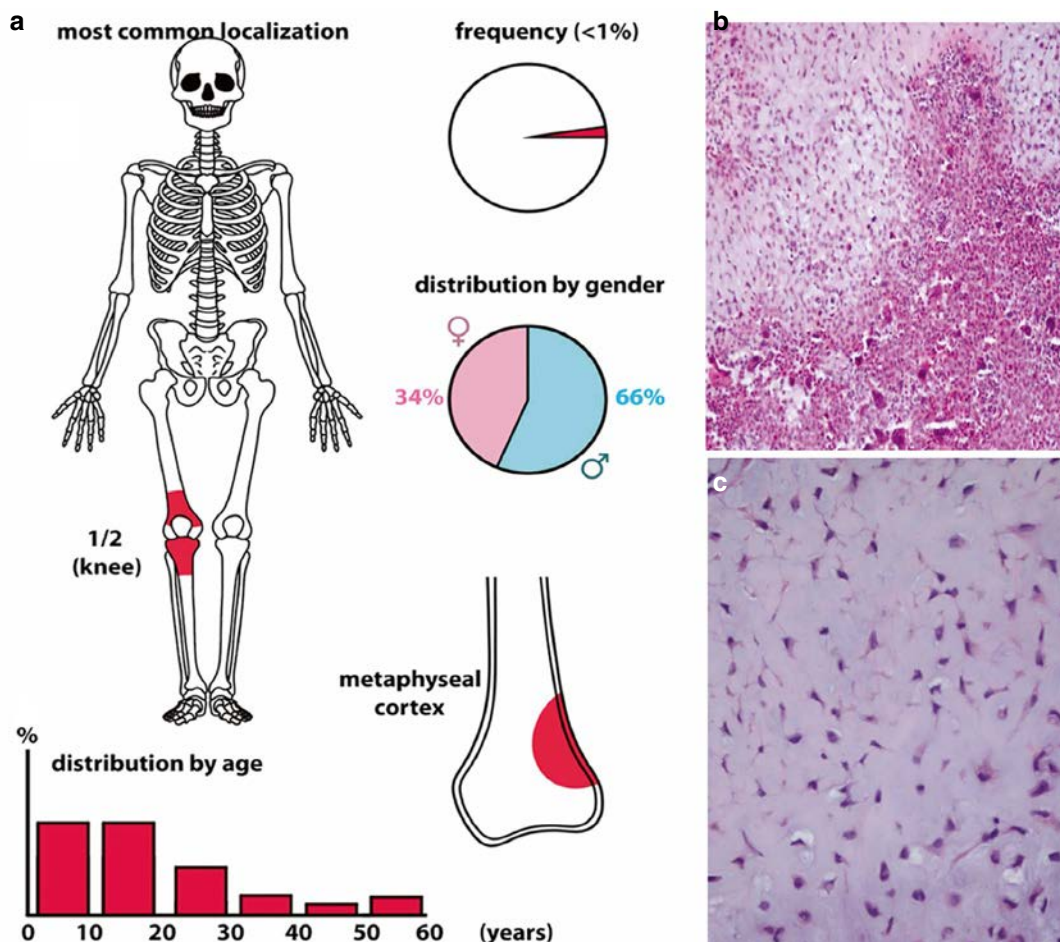


Fig. 24.13 (a) Features of chondromyxoid fibroma (b) Lobules separated by spindle cells and multinucleated

giant cells. (c) The center of the lobules shows angular to stellate cells embedded in a chondroid–myxoid stroma

tion. It typically occurs in adolescents and young adults, usually in the metaphysis of long bones (often the tibia or femur). Patients present with pain and sometimes swelling at the affected site (Fig. 24.13). Radiologically it shows a well-circumscribed, eccentric, lytic lesion, often with scalloped or lobulated borders, sometimes causing cortical expansion or thinning. Histologically, the tumor has a lobular architecture, with alternating areas of chondroid, myxoid, and fibrous tissue. The cellular areas often contain spindle-shaped or stellate cells in a myxoid background, sometimes with giant cells at the periphery of the lobules. CMF can penetrate soft tissue (penetrate the cortex) and invade adjacent bones. This

locally aggressive behavior can lead to these rare tumors being confused with malignancy.

24.6.6 Chondrosarcoma

Chondrosarcoma is a malignant cartilage-producing tumor, typically seen in *adults over 40*. It often involves the *pelvis, shoulder, and ribs*. Patients usually present with *slow-growing masses and pain*. Radiologically, it appears as *lytic lesions with rings and arcs or popcorn calcifications* within the medullary cavity. Microscopically, there are *malignant chondrocytes* within a hyaline cartilage matrix, showing

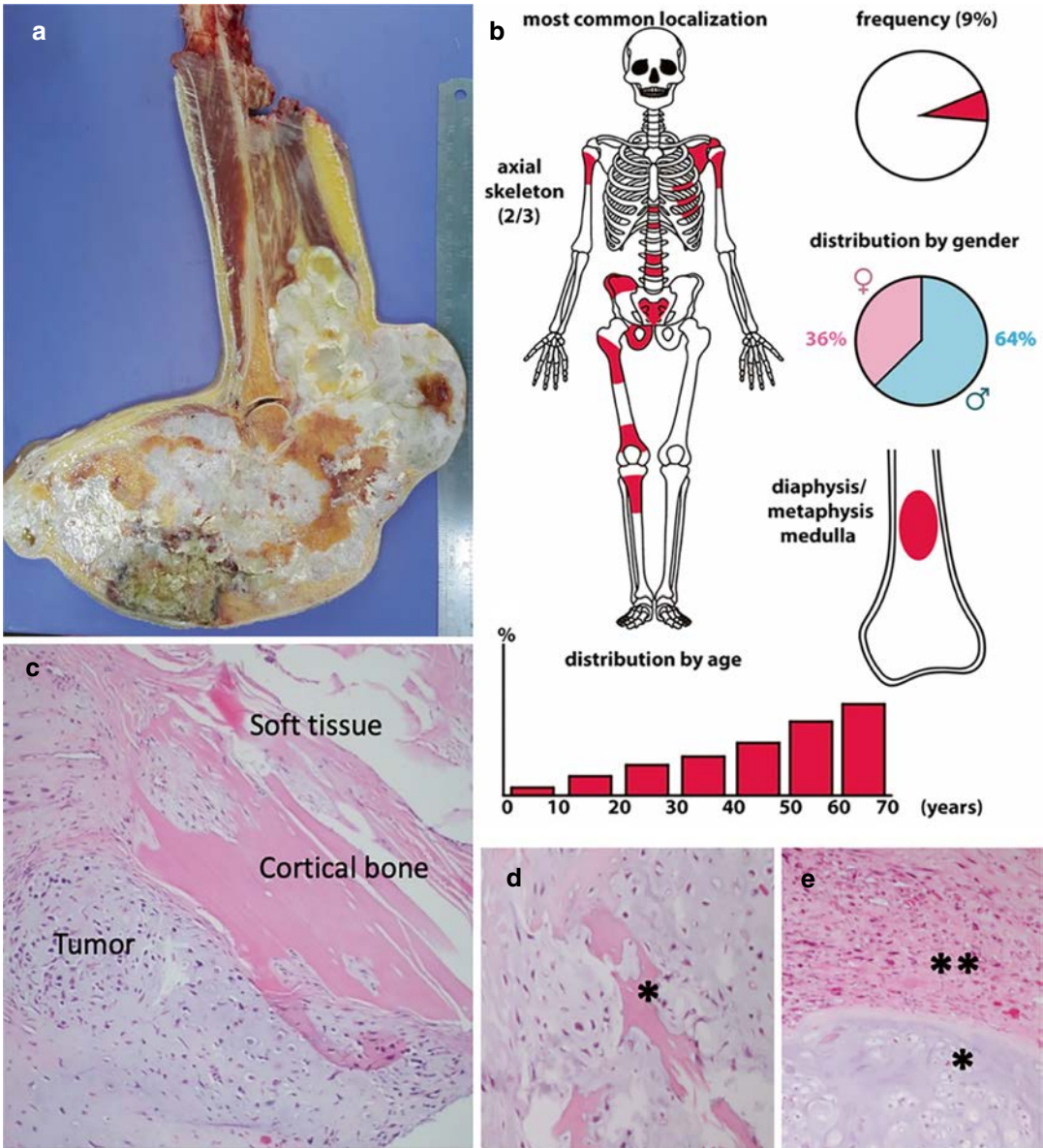


Fig. 24.14 (a) Cut surface of chondrosarcoma with lobularly arranged glistening chondroid matrix. (b) Features of conventional chondrosarcoma. (c) Cellular tumor with atypical chondrocytes embedded in cartilaginous matrix. Note the cortical invasion of tumor. (d) Lamellar bone (*)

“entrapped” and infiltrated by tumor showing aggressive tumor behavior invading the host bone. (e) Dedifferentiated chondrosarcoma. Dedifferentiated pleomorphic spindle cell sarcoma area (**), showing sharp demarcation with chondrosarcoma component (*)

increased cellularity and atypia. Chondrosarcoma is graded according to its cellularity, loss of lobularity, and presence nuclear atypia or binuclear chondrocytes grades 1–3. Dedifferentiation may occur in chondrosarcomas. (Fig. 24.14)

Atypical cartilaginous tumor (ACT) and *grade 1 chondrosarcoma* represent the same low-grade malignant cartilage-forming neoplasm within the WHO 2020 classification, with terminology depending on the anatomic site. Lesions occur-

ring in the appendicular skeleton (long bones) are termed *ACT*, reflecting their locally aggressive but non-metastatic behavior, whereas those in the axial skeleton (pelvis, ribs, shoulder girdle) are referred to as *grade 1 chondrosarcoma* due to their relatively higher risk of recurrence and metastasis.

Histologically, these tumors display lobulated growth, hyaline cartilage matrix, slight cellular atypia, and lack of permeative invasion seen in higher-grade chondrosarcomas. IDH1 and IDH2 mutations are common molecular alterations in both chondrosarcoma and ACT. Treatment is typically intralesional curettage for ACT in long bones, while wide excision may be required for axial or recurrent lesions while conventional chondrosarcoma are usually treated with wide resection or even amputation (Fig. 24.14).

24.7 Vascular Tumors of Bone

24.7.1 Hemangioma

Histologically similar to soft tissue counterpart. Most commonly occur in the vertebral bodies of the spine, particularly thoracic and lumbar vertebrae. Two main subtypes are recognized histologically: cavernous (large vascular spaces) and capillary (small vascular channels). Often, trabecular bone is interspersed between vascular channels, giving a “honeycomb” or “soap-bubble” appearance. Risk of pathological fracture should be considered.

24.7.2 Angiosarcoma

Angiosarcoma also has the same features with its soft tissue counterpart; it is a highly malignant vascular tumor of bone, characterized by rapidly proliferating, atypical endothelial cells

forming irregular, blood-filled vascular channels. Histologically, it demonstrates marked cellular atypia, frequent mitoses, and areas of necrosis, distinguishing it from benign vascular lesions such as bone hemangioma. It can arise *de novo* or, less commonly, secondary to radiation exposure or chronic lymphedema. The tumor most often affects the long bones of the extremities, particularly the femur, tibia, and humerus but can also involve flat bones. Clinically, patients present with pain, swelling, or pathological fractures, and lesions are typically aggressive with a high risk of local recurrence and distant metastasis, commonly to the lungs. Angiosarcoma predominantly occurs in adults between 50 and 70 years, with a slight male predominance. Early diagnosis relies on histopathology supported by immunohistochemistry (CD31, CD34, ERG positivity) and imaging studies, although differentiation from other high-grade sarcomas, can be challenging.

24.8 Osteoclastic Giant Cell Rich Tumors of Bone

24.8.1 Giant Cell Tumor (GCT)

GCT is a locally aggressive, benign tumor usually affecting adults aged 20–40, often at the epiphysis around the knee (Fig. 24.15). Radiologically, it appears as a *soap-bubble lesion*, similar to *chondroblastoma* in epiphyseal location, however it occurs after epiphyseal closure. Microscopically, it consists of numerous multinucleated osteoclast-like giant cells in the background of “neoplastic” mononuclear stromal cells. H3F3A mutations and histone H3.3 G34W immunostaining enhance the diagnosis of GCT (Fig. 24.15) and enables targeted therapy for GCT with denosumab. Rare pulmonary metastases may be seen in GCT.

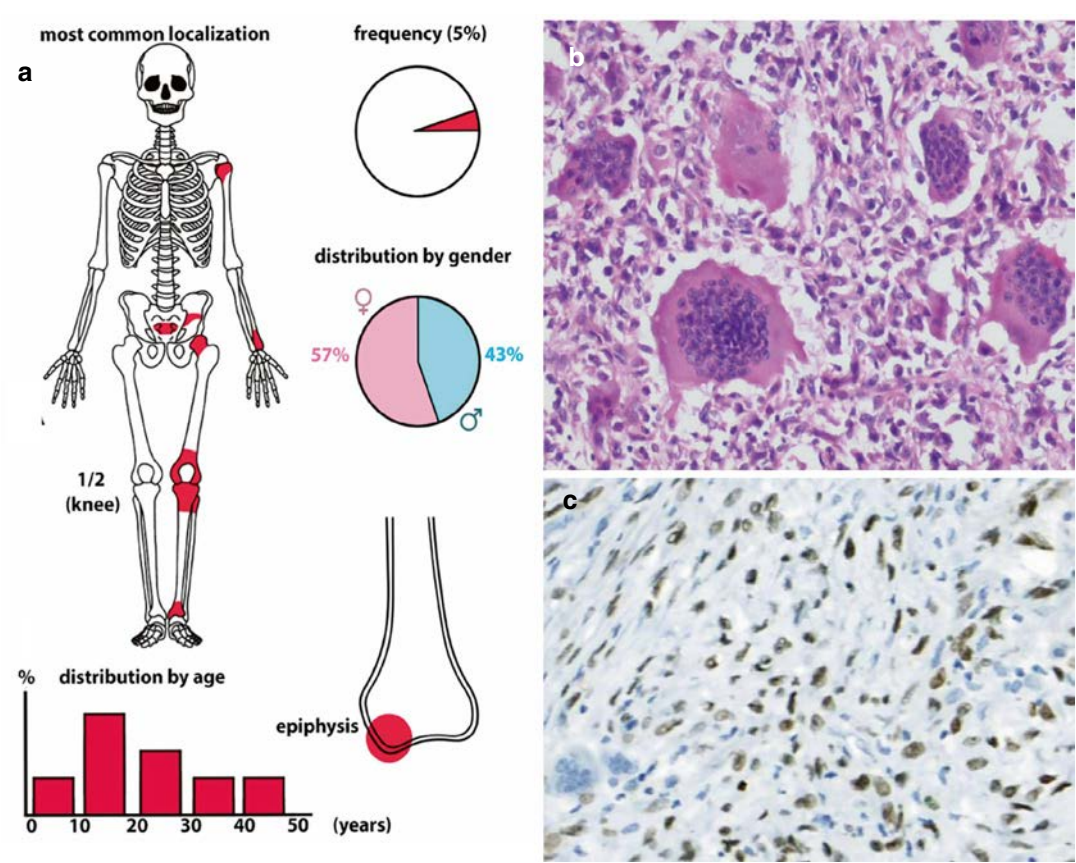


Fig. 24.15 (a) Features of giant cell tumor. (b) Numerous multinucleated osteoclast-like giant cells in the background of mononuclear stromal cells. (c) Immunohistological nuclear H3.3 G34W (H3F3A) positivity

24.9 Aneurysmal Bone Cyst (ABC)

ABC is an expansile, lytic lesion that usually occurs in children and young adults. It commonly affects the metaphysis of long bones. Radiologically, it shows a *multiloculated, blood-*

filled cavity with thin septations. Microscopically, it consists of blood-filled spaces separated by fibrous septa containing osteoclast-like giant cells, fibroblasts, and reactive woven bone (Fig. 24.16). ABC may also arise as a secondary lesion. Primary ABC's show rearrangement of USP6 gene.

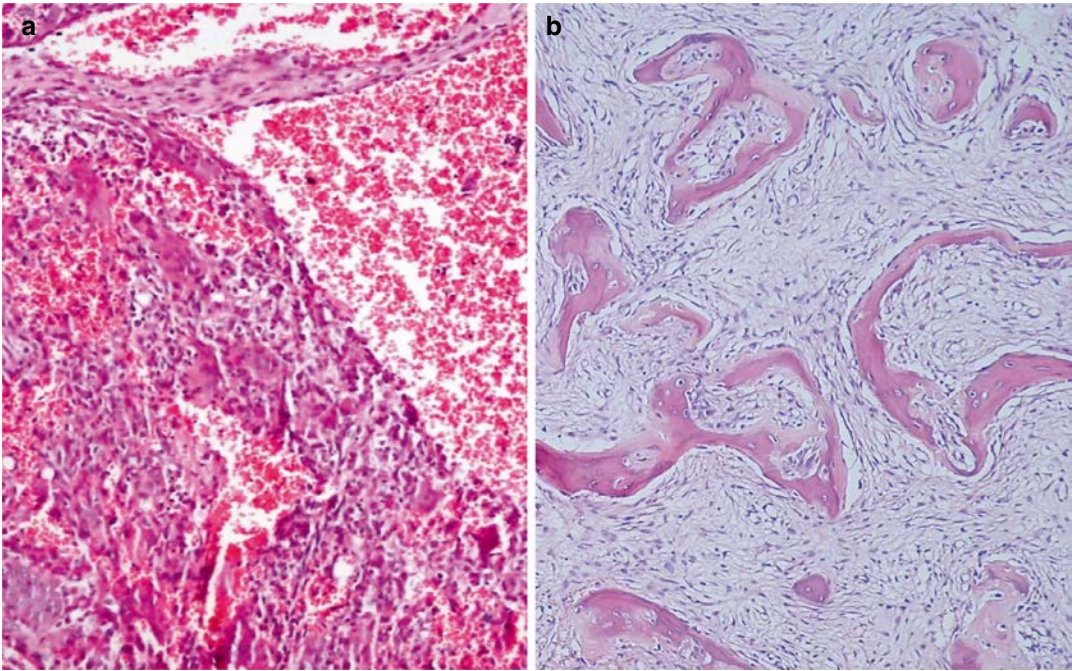


Fig. 24.16 (a) Aneurysmal bone cyst with blood filled spaces. (b) Fibrous dysplasia with curvilinear C-, X-, O-, 8-shaped-metaplastic bone trabeculae “alphabet soup”

24.10 Non-ossifying Fibroma (NOF)

Non-ossifying fibroma is the most common benign bone lesion in children and adolescents. It usually occurs in the *metaphysis of long bones*, most often the distal femur or tibia, and is often discovered incidentally on X-rays. Radiologically, it appears as a *well-defined,*

eccentric, lytic lesion with a sclerotic margin. Microscopically, the lesion consists of *spindle-shaped fibroblasts arranged in a storiform (whorled) pattern*, intermixed with scattered histiocytes and occasional giant cells. NOFs are usually asymptomatic and *self-resolved by adulthood*, making them clinically insignificant in most cases.

24.11 Notochordal Cell Tumors

24.11.1 Chordoma

Chordoma is a rare, malignant bone tumor that develops from embryonic notochordal remnants. It mainly involves the bones of the body's midline, especially the *sacrum* and the base of the skull (*clivus*). Patients usually have *slowly worsening pain*, sometimes with *nerve problems* or symptoms caused by pressure on nearby structures. On imaging, chordomas appear as *destructive bone lesions* located along the midline. Under the microscope, they contain special tumor cells called *physaliphorous* (“bubble-bearing”) cells lying in a *gel-like (myxoid) tissue background*. Chordomas are tricky tumors which can immunohistochemically express both epithelial and mesenchymal tissue markers which cause differential diagnosis of them with both sarcomas and carcinomas, but thanks to brachyury which is a specific biomarker for chordoma, this problem is almost solved.

24.12 Other Mesenchymal Tumors of Bone

24.12.1 Fibrous Dysplasia

Fibrous dysplasia is a benign developmental bone disorder where normal bone is replaced by fibrous tissue and irregular woven bone. It can be monostotic (single bone, most common) or polyostotic (multiple bones), sometimes associated with café-au-lait spots and endocrine abnormalities in McCune-Albright syndrome. Radiologically, lesions have a characteristic ground-glass appearance. Microscopically, thin, irregular trabeculae of woven bone (“Chinese characters”) are embedded in fibrous stroma (Fig. 24.16).

Other mesenchymal tumors can occasionally involve bone, either as primary bone lesions or more commonly as soft tissue tumors invading the bone. The detailed histologic characteristics of these tumors are covered extensively in the soft tissue tumor section, so only general principles

are highlighted here. Distinguishing a soft tissue tumor invading bone from a primary bone tumor relies largely on radiologic features, as imaging can reveal the tumor's origin, pattern of bone destruction, and relationship to surrounding structures. Recognizing this distinction is important for diagnosis, treatment planning, and prognosis, even though histology alone may not always provide a definitive answer.

24.13 Hematopoietic Neoplasms of Bone

24.13.1 Plasmacytoma

Plasmacytoma of bone is a rare, *localized* neoplasm of plasma cells arising within the medullary cavity of a single bone, most *commonly the vertebrae, pelvis, and long bones*. It primarily affects *middle-aged and older adults* and is slightly more common in men. Clinically, patients may present with *localized bone pain* or, occasionally, pathologic fractures, well-defined lytic bone lesions. Histologically, the tumor consists of *sheets of monoclonal plasma cells* with characteristic eccentric nuclei, abundant cytoplasm, and a “clock-face” chromatin pattern; immunohistochemistry is necessary to confirm *monoclonality* with expression of either *kappa or lambda light chains*. Distinguishing a solitary plasmacytoma from multiple myeloma requires *absence of systemic involvement*; therefore next step following a diagnosis of plasmacytoma should be a thorough hematological survey as treatment of myeloma requires systemic treatment while plasmacytoma is typically treated with localized radiotherapy.

24.14 Langerhans Cell Histiocytosis

Langerhans cell histiocytosis is a rare disorder characterized by the clonal proliferation of Langerhans-type dendritic cells, which can affect bones, skin, lymph nodes, and other organs. It primarily affects children and young adults,

though it can occur at any age. Bone lesions usually present with localized pain, swelling, or tenderness, most commonly involving the skull, mandible, ribs, spine, and long bones. Lesions may be solitary or multifocal, and systemic symptoms such as fever, weight loss, or fatigue can occur in more extensive disease. Imaging typically shows lytic lesions with well-defined edges, and spinal involvement may lead to vertebral plana. Histologically, LCH lesions contain Langerhans cells with characteristic coffee-bean like nuclei intermixed with eosinophils, lymphocytes, and macrophages. The density of eosinophils may vary among cases. Immunohistochemistry is positive for CD1a, langerin (CD207), and S100, confirming the diagnosis. Recently, BRAF V600E mutation was shown in more than half of LCH cases. Prognosis depends on disease extent; solitary bone lesions often respond well to surgical curettage or limited radiotherapy, while multisystem disease may require systemic chemotherapy.

24.15 Primary Bone Lymphoma

Primary bone lymphoma is a rare form of extranodal non-Hodgkin lymphoma that arises within bone, most commonly in adults over 40 years of age, with a slight male predominance. The majority of cases are diffuse large B-cell lymphoma (DLBCL) which may have originated from centrocytes. Patients usually present with progressive localized bone pain that is unrelieved by rest and occasionally swelling, soft tissue mass, or pathologic fracture. Systemic “B” symptoms such as fever, night sweats, or weight loss are less common than in nodal lymphoma. Radiologically, typically appears as a lytic lesion with variable cortical destruction and sometimes an associated soft tissue mass which can mimic other aggressive bone tumors. Histologically, the bone marrow is replaced by sheets of malignant lymphoid cells expressing B-cell markers such as CD20 and CD79a, making immunohistochemistry crucial for diagnosis. The disease usually responds well to combined chemotherapy and radiotherapy, and localized diseases carry a favorable

prognosis compared to other primary bone malignancies. Accurate treatment requires distinguishing bone lymphoma from other small round cell tumors of bone.

24.16 Metastasis

Bone metastases are the most common malignant bone lesions in adults, far more frequent than primary bone tumors. They typically arise from breast, prostate, lung, kidney, and thyroid cancers, with the spine, pelvis, ribs, and proximal long bones being the most commonly affected sites. Clinically, patients may present with bone pain, pathological fractures, or hypercalcemia, though lesions are sometimes found incidentally on imaging. Radiologically, metastases can be lytic, sclerotic, or mixed, depending on the primary tumor type. Histopathologically, bone metastases are generally straightforward to identify, as the tumor cells resemble the primary malignancy, making differentiation from primary bone tumors relatively easier. Recognizing bone metastases is crucial for staging, prognosis, and guiding systemic therapy.

24.17 Undifferentiated Round Cell Sarcomas of Bone and Soft Tissue

Undifferentiated round cell sarcomas of both bone and soft tissue are a group of malignant tumors composed of small, uniform, primitive-appearing round cells with high nuclear-to-cytoplasmic ratios. They typically arise in the diaphysis or metaphysis of long bones such as the femur, tibia, and humerus but can also occur in the pelvis, ribs, and soft tissues of the trunk and extremities. These tumors often present with pain, swelling, and sometimes pathologic fractures. Radiologically, they appear as destructive, permeative lytic lesions with onion-skin type periosteal reaction, particularly in Ewing sarcoma. The differential diagnosis from other small round cell tumors as lymphoma, neuroblastoma, and rhabdomyosarcoma is utmost important as

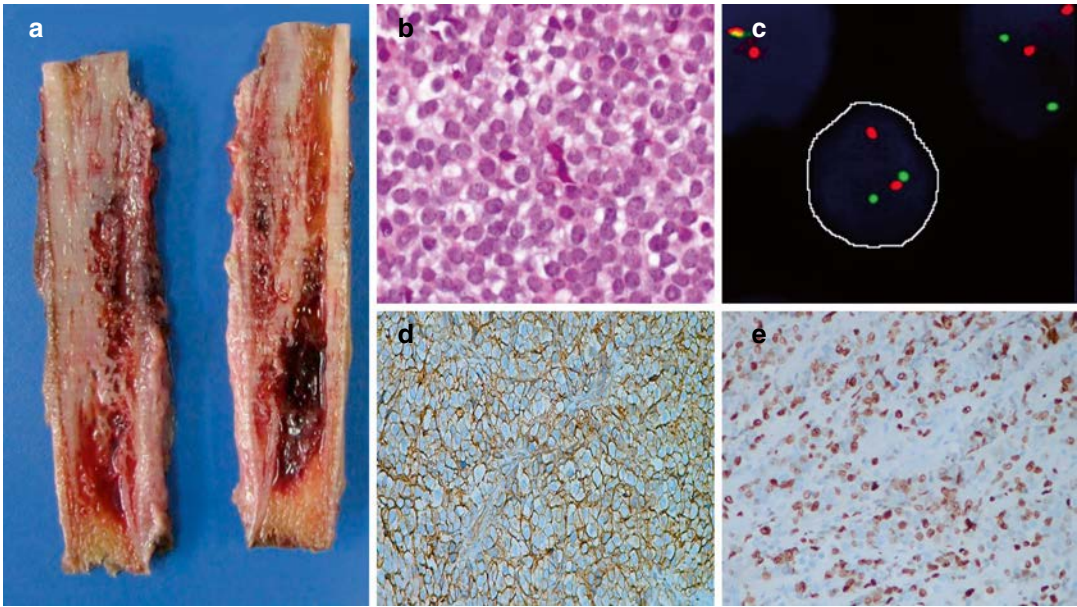


Fig. 24.17 (a) Macroscopic view of Ewing sarcoma. (b) Small round cell tumor with salt-pepper chromatin and inconspicuous nuclei. (c) Fluorescence in situ hybridization (FISH) demonstrating EWSR1–FLI1 gene rearrange-

ment (break-apart signals indicate the presence of the translocation). (d) Membranous CD99 positivity. (e) Nuclear NKX2.2 positivity

the treatment of all these tumors is completely different than each other. These tumors are among the most frequent entities for which bone pathologists rely on immunohistochemical and molecular analyses (Fig. 24.17).

Histologically, **Ewing sarcoma** shows sheets of uniform round cells with scant cytoplasm and fine chromatin, often expressing CD99 (MIC2), NKX2.2, and FLI1 on immunohistochemistry. **CIC-rearranged sarcomas** may show slightly larger cells with more pleomorphism and express WT1 and ETV4, while **BCOR-altered sarcomas** display a more myxoid stroma and nuclear BCOR positivity. Diagnosis is confirmed by molecular tests demonstrating characteristic gene

fusions, such as EWSR1–FLI1 in Ewing sarcoma, CIC–DUX4 in CIC-rearranged sarcoma, and BCOR–CCNB3 in BCOR-altered sarcoma or other fusion partners in **EWSR1 non-ETS fusion sarcomas**. Despite overlapping morphology, identifying the exact genetic alteration is crucial for prognosis and therapeutic planning.

To summarize, bone tumors are rare but intriguing lesions whose etiopathogenesis is still under investigation and are often closely related to the pathways involved in skeletal growth or fracture healing. For an overview of the key pathological concepts and diagnostic clues relevant to bone tumors, a brief summary is provided in Table 24.5.

Table 24.5 Quick review-key facts: what a medical student needs to know about bone tumor pathology

General	Bone tumors are very rare (0.2% of all human tumors). Malignant ones are even rarer. Can be seen in all age groups, but some tumors prefer certain age groups
Etiopathogenesis	Etiology is obscure in most of them
Clinical management	►Multidisciplinary approach (especially orthopedics, radiology, pathology correlation) is utmost important ►Age + Location → Key to Bone Tumor Diagnosis (all specialities use these patterns for differential diagnosis) ►Direct X-Ray is not out fashioned it is the initial and most crucial step for diagnostic workup. MRI is important to evaluate the extent of the disease ►Most bone tumors are osteolytic. Lesions borders are important. Radiomorphological classification of bone tumors as “well-defined osteolytic,” “ill-defined osteolytic,” or “sclerotic” help to classify many bone tumors

References

1. Kumar V, Abbas AK, Aster JC, editors. Robbins & Cotran pathologic basis of disease. 10th ed. Philadelphia: Elsevier; 2020.
2. Vigorita VJ, Ghelman B, Mintz D. Orthopaedic pathology. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2016.
3. WHO Classification of Tumours Editorial Board. WHO classification of tumours of soft tissue and bone, vol. 3. 5th ed. Lyon: IARC Press; 2020.
4. Rekhi B, Uppin S, Kattoor J, Jambhekar NA, Singh P, Pant V, Rao S, Afroz N. Grossing and reporting of bone tumor specimens in surgical oncology: rationale with current evidence and recent updates. Indian J Cancer. 2021;58(3):326–35. https://doi.org/10.4103/ijc.IJC_59_21.
5. Pattamapaspong N, Peh WCG. Benign incidental do-not-touch bone lesions. Br J Radiol. 2022;96(1142):20211334. <https://doi.org/10.1259/bjr.20211334>.

Summary and Key Points

Soft tissue tumors represent a diverse group of neoplasms with varying origins, behaviors, and clinical implications. Understanding their classification, histological features, and diagnostic tools is essential for accurate diagnosis and effective management.

- Soft tissue tumors arise from connective tissues such as fat, muscle, vessels, and nerves.
- WHO classification organizes tumors by lineage and behavior (benign vs malignant).
- Histological evaluation focuses on cell morphology, stroma, vascular patterns, mitotic activity, and necrosis.
- Immunohistochemistry and molecular diagnostics are critical for confirming tumor type.
- Common tumors include lipoma, liposarcoma, rhabdomyosarcoma, and angiosarcoma.
- Grading (FNCLCC) and staging (AJCC) systems guide prognosis and treatment planning.
- Clinical management varies from observation to multimodal therapy depending on tumor type and grade.

25.1 Introduction

Soft tissue tumors represent a heterogeneous group of neoplasms originating from non-epithelial, extraskeletal mesenchymal tissues, including adipose tissue, skeletal and smooth muscle, fibrous connective tissue, vascular structures, and peripheral nerves [1, 2]. Although soft tissue tumors are relatively rare, they encompass a wide spectrum of benign and malignant entities. Benign tumors, such as lipomas, are common and typically innocuous, whereas malignant counterparts, known as soft tissue sarcomas, are often aggressive and may pose significant diagnostic and therapeutic challenges [2, 3]. Importantly, their histological appearance doesn't always reflect their clinical behavior—some may look harmless but act malignantly and vice versa. Consequently, prognostic assessments made without a definitive diagnosis may be inaccurate and clinically misleading [4, 5].

Understanding the pathology of soft tissue tumors is essential, as these tumors often present with subtle clinical signs and require careful histological and immunohistochemical evaluation for accurate diagnosis. This chapter provides a foundational overview of soft tissue tumor classification, histological features, diagnostic tools, and clinical relevance, aiming to simplify complex concepts for students at the beginning of their pathology journey.

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25.2 Classification of Soft Tissue Tumors

Soft tissue tumors are categorized based on their tissue of origin, following the World Health Organization (WHO) classification [1]. The main groups include adipocytic, fibroblastic/myofibroblastic, vascular, muscle-derived, peripheral nerve sheath tumors, and tumors of uncertain differentiation. Each category contains both benign and malignant entities, with distinct histological and clinical features [6–8]. This classification system provides a framework for diagnosis, guiding further histopathological and molecular evaluation. Undifferentiated small round cell sarcoma of bone and soft tissue, including Ewing sarcoma, round cell sarcoma with EWSR1-nonETS fusions, and other rare small round cell sarcomas with CIC or BCOR gene rearrangements, are classified in a separate tumor section of the WHO classification [1, 9].

25.3 Histological Features of Soft Tissue Tumors

Histological examination is the cornerstone of soft tissue tumor diagnosis. It involves the microscopic evaluation of tissue architecture, cellular morphology, and stromal characteristics. Histological features must be interpreted in conjunction with immunohistochemical and molecular findings to reach a definitive diagnosis. These tools help distinguish between benign and malignant lesions, identify the tumor lineage, and detect specific genetic alterations that guide prognosis and therapy [7, 8, 10].

25.3.1 Key Histological Parameters

Cell Morphology (Fig. 25.1)

- *Spindle cells*: Elongated, cigar-shaped nuclei; common in fibrosarcoma, leiomyosarcoma.

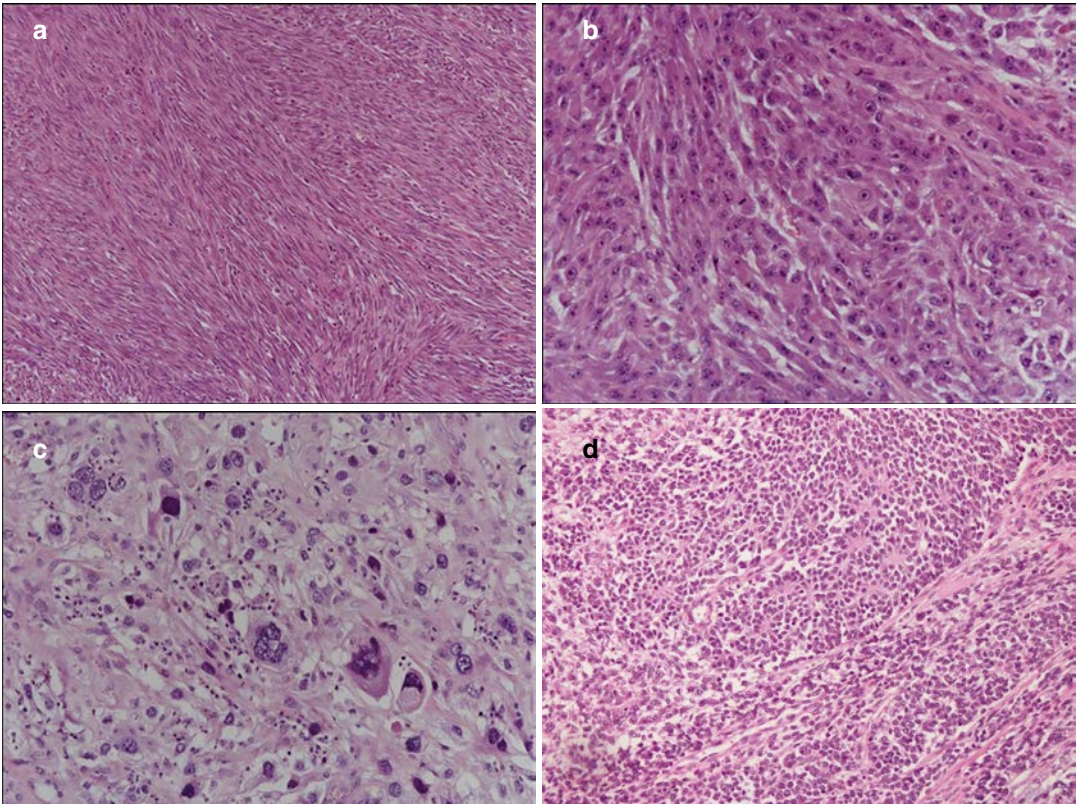


Fig. 25.1 Representative cell morphologies at various soft tissue tumors. Spindle (a), epithelioid (b), pleomorphic (c), small round cells (d)

- *Epithelioid cells*: Round or polygonal with abundant cytoplasm; seen in epithelioid sarcoma.
- *Pleomorphic cells*: Marked variation in size and shape; typical of undifferentiated sarcoma.
- *Small round cells*: Uniform, hyperchromatic nuclei; found in rhabdomyosarcoma and Ewing sarcoma.

Stroma

- *Myxoid stroma*: Gelatinous matrix with scattered cells; seen in intramuscular myxoma, myxoid liposarcoma, and myxofibrosarcoma.
- *Collagenous stroma*: Dense fibrous background; common in desmoid-type fibromatosis.
- *Vascular stroma*: Prominent blood vessels; characteristic of hemangioma and angiosarcoma.

Vascular Patterns

- *Slit-like spaces*: Seen in Kaposi sarcoma.
- *Curvilinear capillaries*: Found in myxoid liposarcoma.
- *Hobnail endothelial cells*: Typical of angiosarcoma.

Mitotic Activity: High mitotic rate suggests malignancy; atypical mitoses are a hallmark of aggressive tumors [10].

Necrosis: Tumor necrosis is often associated with high-grade sarcomas. Geographic necrosis may be seen in undifferentiated pleomorphic sarcoma [11].

Immunohistochemistry (IHC): Uses antibodies to detect specific proteins expressed by tumor cells. Helps confirm lineage and differentiate between morphologically similar tumors [10, 12] (Table 25.1).

Molecular pathology has become an essential tool in the diagnosis and classification of soft tissue tumors. Many of these tumors harbor specific genetic alterations that not only aid in diagnosis but also have prognostic and therapeutic implications. Molecular diagnostics (fluorescence in situ hybridization-FISH, RT-PCR, next-generating sequencing-NGS, etc.) detects genetic mutations, translocations, as well as fusion genes. They help distinguish morphologically similar tumors, especially when histology and IHC are inconclusive. Some mutations guide the use of targeted therapies, improving patient outcomes [10, 12] (Table 25.2).

Table 25.1 Some immunohistochemical markers associated with soft tissue tumors

Marker	Associated tumor type
S100	Schwannoma, liposarcoma
Desmin	Leiomyoma, rhabdomyosarcoma
SMA (smooth muscle actin)	Leiomyosarcoma, myofibroblastic tumors
Myogenin, MyoD1	Rhabdomyosarcoma
CD31, CD34, ERG	Vascular tumors (e.g., angiosarcoma)
Cytokeratins (AE1/AE3)	Synovial sarcoma, epithelioid sarcoma

Table 25.2 Certain soft tissue neoplasms are characterized by specific gene fusions, while others are driven by activating mutations that may serve as potential targets for molecular therapies

Tumor type	Molecular alteration	Diagnostic utility/therapeutic target
Atypical lipomatous tumor/well-differentiated liposarcoma	<i>HMGA(2)</i> , <i>MDM2</i> and <i>CDK4</i> amplification	Confirms diagnosis
Myxoid liposarcoma	<i>DDIT3::FUS/ESR1</i> fusions	Confirms diagnosis
Alveolar rhabdomyosarcoma	<i>FOXO1A::PAX3/7</i> fusion	Indicates aggressive subtype
Synovial sarcoma	<i>SS18::SSX1/2</i> fusion	Highly specific marker
Ewing sarcoma	<i>ESR1::FLI1/ERG/ETV1</i> fusions	Diagnostic and prognostic significance
Clear cell sarcoma	<i>ESR1::ATF1/CREB1</i> fusions	Helps differentiate from melanoma
Desmoplastic small round cell tumor	<i>ESR1::WT1</i> fusion	Confirms diagnosis
Infantile fibrosarcoma	<i>ETV6::NTRK3</i> fusion	Confirms diagnosis
Dermatofibrosarcoma Protuberans (DFSP)	<i>COL1A1::PDGFB</i> fusion	Imatinib in advanced cases

25.4 Common Soft Tissue Tumor Types

Soft tissue tumors represent a diverse group of lesions, each characterized by unique histological, immunohistochemical, and molecular profiles. Each of these tumors presents unique diagnostic challenges and clinical implications. Recognizing their key features is essential for accurate classification and effective treatment planning. Below is an overview of some of the most encountered benign and malignant soft tissue tumors (Table 25.3).

25.4.1 Adipocytic Tumors

- *Lipoma*: Soft, mobile, and slow-growing benign well-circumscribed tumor composed of mature adipocytes. Representing the most prevalent soft tissue tumor, it predominantly arises in the subcutaneous compartment, particularly in areas including the dorsal trunk, shoulder girdle, and gluteal region. The tumor size can vary significantly, but it is generally encapsulated. Grossly, it appears as soft, yellow masses resembling normal fat tissue. Several histologic variants of lipoma may be encountered, although they do not carry clinical significance (Fig. 25.2) [1, 13].
 - *Osteolipoma*: contains areas of bone formation.

- *Chondrolipoma*: features cartilaginous nodules.
- *Fibrolipoma*: includes dense fibrous tissue.
- *Myxolipoma*: exhibits prominent myxoid changes.
- *Myolipoma*: contains smooth muscle elements.
- *Intramuscular lipoma*: Infiltrative subtype, may recur locally if not completely excised.
- *Spindle cell lipoma*: predominantly affects males over the age of 40 and is most located in the posterior neck and shoulder region. Histologically, it consists of mature adipocytes interspersed with uniform, bland spindle cells.
- *Angiolipoma*: typically presents in young adults and is most frequently found in the forearm. It is characterized morphologically by a prominent capillary network, frequently accompanied by fibrin thrombi within the vascular lumina.
- *Hibernoma*: A rare, benign tumor derived from brown adipose tissue. It most commonly affects young adults and is typically located in the scapular region. Brown fat, which plays a role in thermogenesis, is physiologically abundant in hibernating animals and is present in humans primarily during the neonatal period, especially in the gluteal region. Gross examination reveals a lobulated, brown-colored mass. On microscopic examination,

Table 25.3 Major categories of soft tissue tumors

Tumor category	Origin	Examples	Benign/malignant
Adipocytic tumors	Fat tissue	Lipoma, liposarcoma	Benign/malignant
Fibroblastic/myofibroblastic tumors	Fibroblasts, myofibroblasts	Nodular fasciitis, myxofibrosarcoma	Benign/malignant
Vascular tumors	Blood or lymphatic vessels	Hemangioma, angiosarcoma	Benign/malignant
Muscle tumors	Smooth or skeletal muscle	Leiomyoma, rhabdomyosarcoma	Benign/malignant
Peripheral nerve sheath tumors	Schwann cells, nerve sheath	Schwannoma, MPNST	Benign/malignant
Tumors of uncertain differentiation	Undefined lineage	Synovial sarcoma, epithelioid sarcoma, undifferentiated sarcoma	Malignant

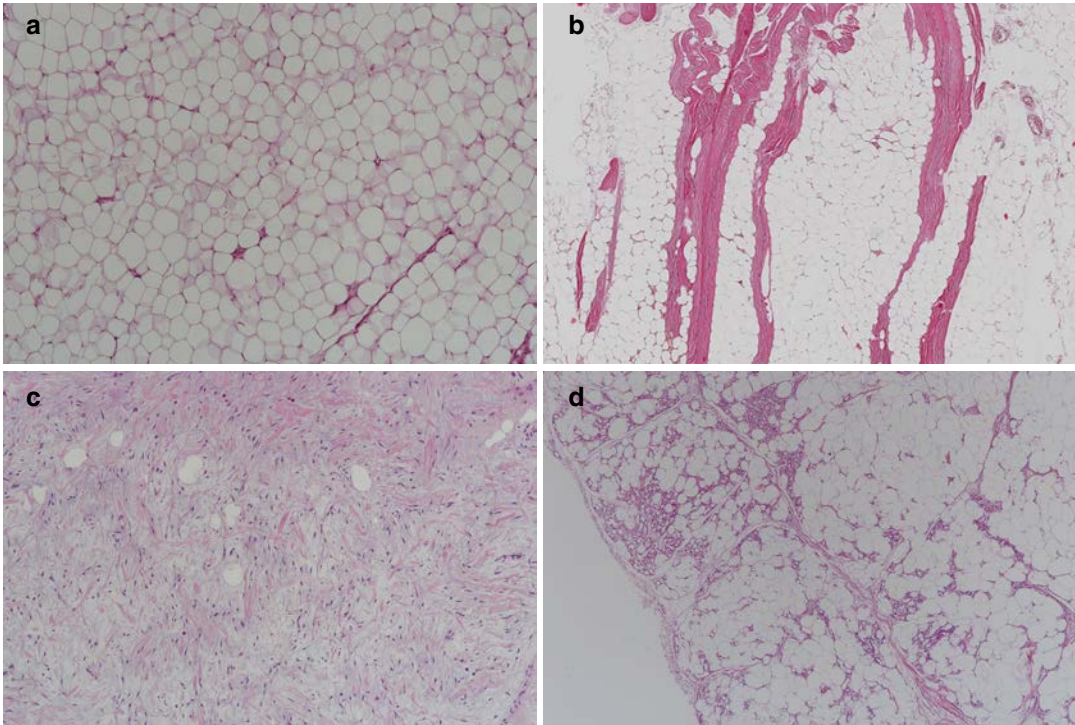


Fig. 25.2 (a) Benign lipoma is composed of uniform mature adipocytes. (b) Intramuscular lipoma. Prominent adipocytic component between striated muscle cells. (c) Spindle cell lipoma. Mature adipocytes interspersed with

uniform, bland spindle cells. (d) Angiolipoma. Mature adipocytic lesion with a capillary sized vascular component and fibrin microthrombi at the vascular lumens

hibernoma is characterized by sheets of large polygonal adipocytes exhibiting abundant granular eosinophilic cytoplasm and centrally positioned nuclei. The lesion is highly vascularized, featuring a dense network of branching capillaries.

- **Liposarcoma:** Malignant adipocytic tumor (Fig. 25.3). Subtypes include:
 - *Atypical Lipomatous Tumor/Well-Differentiated Liposarcoma (ATL/WDLS):* Resembles lipoma but contains atypical cells. Histopathologically, it is composed of mature adipocytes interspersed with scattered atypical stromal cells/lipoblasts which exhibit hyperchromatic nuclei. It commonly arises in the extremities and retroperitoneum. Although locally aggressive, this tumor does not metastasize [14].
 - *Dedifferentiated Liposarcoma:* More aggressive subtype of liposarcoma with

metastatic potential. Morphologically, it consists of areas of well-differentiated liposarcoma adjacent to regions of high-grade non-lipomatous sarcoma. It often exhibits MDM2 and CDK4 amplification, similar to ATL/WDLS [15–18].

- *Myxoid Liposarcoma:* Histologically, it is defined by a prominent myxoid extracellular matrix interlaced with a fine arborizing capillary network, often described as “chicken-wire” vasculature. The presence of lipoblasts is a key diagnostic feature. At the molecular level, it typically harbors FUS::DDIT3 gene fusion. The tumor is considered as intermediate malignancy, with a capacity of metastasis, particularly in cases that exhibit a round cell component, which is associated with more aggressive behavior. Tumors with round cell component [19].

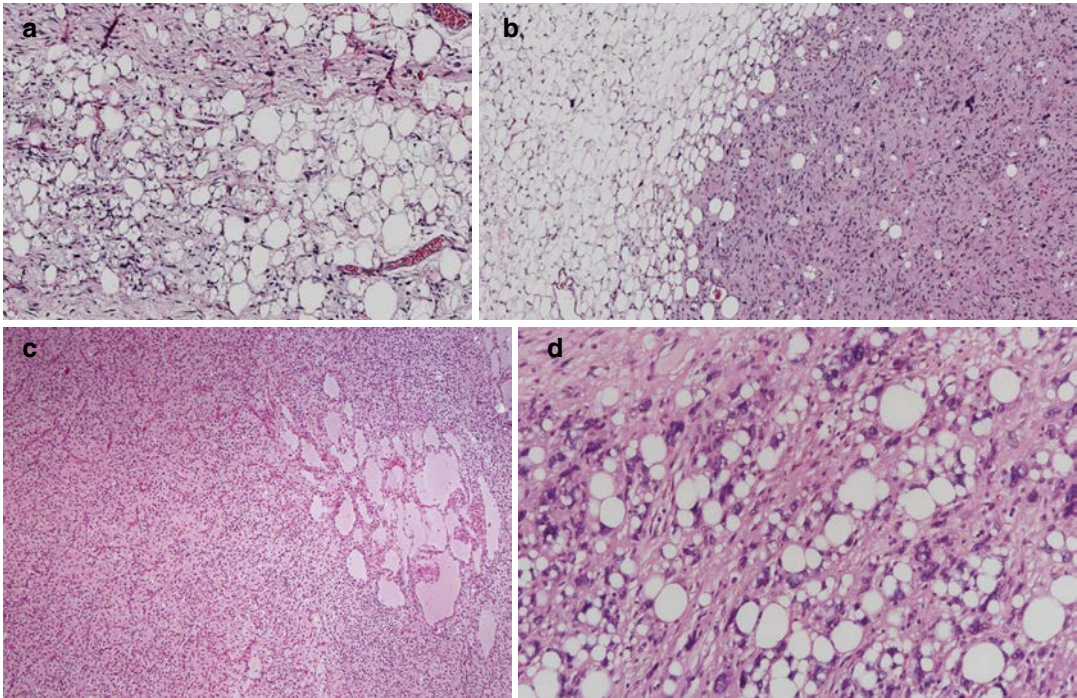


Fig. 25.3 (a) Atypical lipomatous tumor/well-differentiated liposarcoma (ATL/WDLS) consists of mature adipocytes and scattered atypical stromal cells with hyperchromatic cells and/or lipoblasts lodged in fibrous band. (b) Dedifferentiated liposarcoma. The left side of the figure has the appearance of well-differentiated

liposarcoma, whereas the right side of the tumor has a nonspecific spindle cell sarcoma appearance. (c) Myxoid liposarcoma with prominent myxoid background and capillary network contains immature adipocytes. (d) Pleomorphic liposarcoma composed of pleomorphic lipoblasts with lipid droplets at cytoplasm

- *Pleomorphic Liposarcoma*: Least common subtype, aggressive behavior. Microscopically highly atypical/pleomorphic cells, bizarre multinucleated giant cells, and lipoblasts [20].

25.4.2 Fibroblastic and Myofibroblastic Tumors

- *Nodular Fasciitis*: Benign lesion characterized by the proliferation of fibroblasts and myofibroblasts. Although it grows rapidly, it is self-limited and nonaggressive and may regress spontaneously. Morphologically it presents as a cellular lesion with loosely arranged spindled cells in a myxoid stroma, often resembling a tissue culture-like appearance. Generally, contains extravasated red blood cells and inflammatory cells (Fig. 25.4).

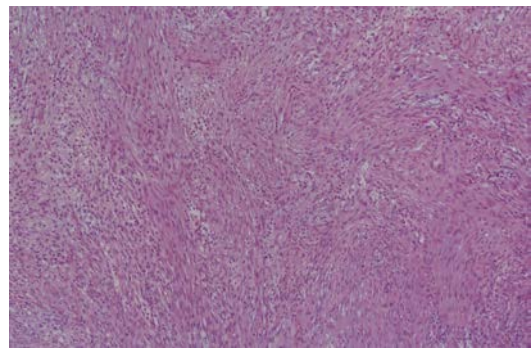


Fig. 25.4 Nodular fasciitis with haphazard oriented plump spindled cells in a myxoid stroma background and extravasated erythrocytes

Frequently associated with FOSB gene rearrangement, supporting its neoplastic but non-malignant nature [1, 21, 22].

- *Desmoid fibromatosis*: Locally aggressive spindle cell neoplasm composed of uniform

cells arranged in fascicles within a collagen-rich stroma, exhibiting low mitotic activity (Fig. 25.5). It infiltrates surrounding muscle, fat, or soft tissue but does not metastasize. Nuclear β -catenin positivity is a key diagnostic feature in most cases, and the tumor may also express smooth muscle actin. It is associated with mutations in CTNNB1 gene or familial adenomatous polyposis (FAP) [1, 23, 24].

- *Dermatofibrosarcoma protuberans*: Dermal or subcutaneous low-grade malignant neoplasm exhibits indolent growth yet demonstrates locally infiltrative behavior. Histologically, it is composed of uniform spindle-shaped cells arranged in a storiform architecture, with minimal mitotic activity. Honeycomb pattern if infiltrate the subcutaneous tissue (Fig. 25.6).

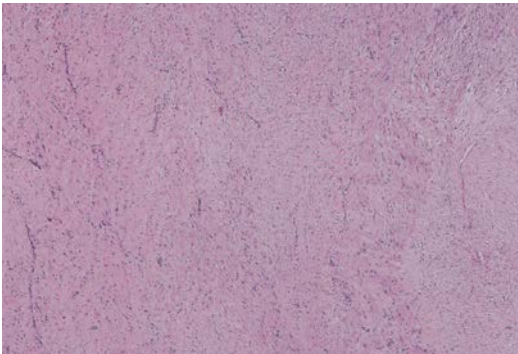


Fig. 25.5 Desmoid fibromatosis is composed of long fascicles of spindled myofibroblasts with fibrillary cytoplasm and bland nuclei admixed with collagenous stroma

The tumor is strongly positive for CD34 and is associated with COL1A1::PDGFB gene fusion [1, 25–27].

- *Myxofibrosarcoma*: Malignant fibroblastic tumor, commonly seen in older adults. Abundant myxoid stroma with spindle and pleomorphic cells varying degrees of nuclear atypia [1].
- *Fibrosarcoma*: Rare and aggressive, occurs in both infants and adults. Malignant spindle cell tumor with histopathologically classic “herringbone” pattern (intersecting bundles). Moderate to high cellular atypia depending on tumor grade (Fig. 25.7). Infantile fibrosarcoma is often associated with ETV6::NTRK3 gene fusion and has a better prognosis [1, 28].

25.4.3 Vascular Tumors

- *Hemangioma*: Benign vascular tumor, often seen in infants. Composed of capillary or cavernous vessels (Fig. 25.8). Usually regress over time.
- *Kaposi sarcoma*: Intermediate malignancy, associated with HHV-8 infection. Seen in immunocompromised patients (e.g., HIV/AIDS). Clinically presenting as purple-red cutaneous nodules, the lesion demonstrates a proliferation of bland spindle-shaped cells forming slit-like vascular spaces. Histological features include extravasated erythrocytes accompanied by a polymorphic inflammatory

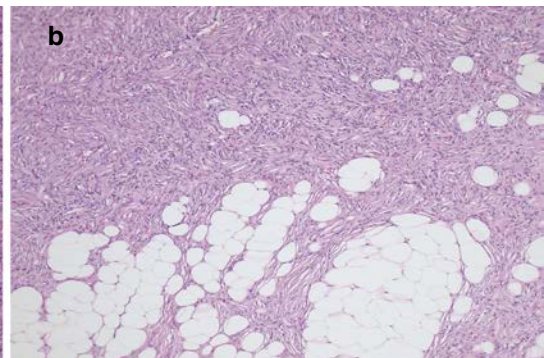
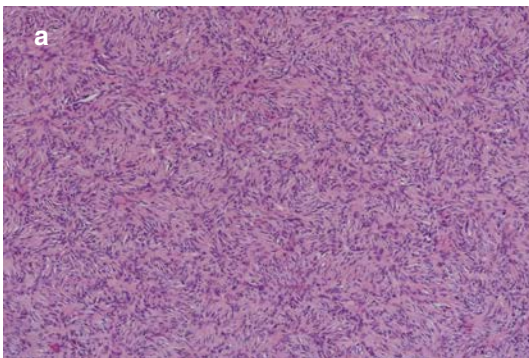


Fig. 25.6 Dermatofibrosarcoma protuberans. Tumor with storiform pattern and monotonous uniform spindled cells (a). The tumor infiltrates the subcutaneous fat in a honeycomb appearance (b)

infiltrate, predominantly comprising lymphocytes and plasma cells (Fig. 25.9). Positive with CD31/CD34 and HHV8 (LANA-1) [1, 29, 30].

- *Angiosarcoma*: Malignant endothelial tumor. Can arise in skin, breast, liver, or deep soft tissues. Histopathologically irregular vascular channels with atypical/pleomorphic cells (Fig. 25.10). ERG/CD31/CD34-positive [1].

25.4.4 Smooth Muscle Tumors

- *Leiomyoma*: Benign smooth muscle tumor. Common in uterus, skin, and gastrointestinal tract. Morphologically well-circumscribed lesion characterized by intersecting fascicles of uniform spindle cells, exhibiting blunt-

ended (cigar-shaped) nuclei and eosinophilic cytoplasm, with minimal cytologic atypia (Fig. 25.11) [31].

- *Leiomyosarcoma*: Malignant counterpart with local recurrence and distant metastasis risk. Can arise in uterus, retroperitoneum, and deep soft tissues. Histopathologically, it shows atypical spindle cells with cigar-shaped nuclei, high mitotic activity. Tumor necrosis and infiltrative growth are common. May show pleomorphic cells and bizarre nuclei (Fig. 25.12). Both leiomyoma and leiomyosarcoma are positive with desmin, h-caldesmon, and smooth muscle actin (SMA) immunohistochemically [1, 32].

25.4.5 Skeletal Muscle Tumors

- *Rhabdomyoma*: A rare benign tumor of skeletal muscle origin, characterized histologically by large polygonal cells with abundant eosinophilic cytoplasm and distinct cross-striations. Most commonly observed in children, particularly in the head and neck region. Cardiac rhabdomyomas are frequently associated with tuberous sclerosis [1, 33].
- *Rhabdomyosarcoma*: Malignant counterpart with four subtypes. Histological section showing primitive round to spindle-shaped malignant cells, many with eosinophilic cytoplasm. Occasional cross-striations are observed, supporting skeletal muscle differentiation.

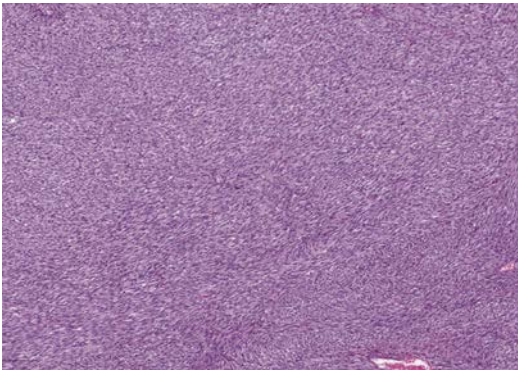


Fig. 25.7 Fibrosarcoma is organized in long intersecting fascicles in a “herringbone” growth pattern

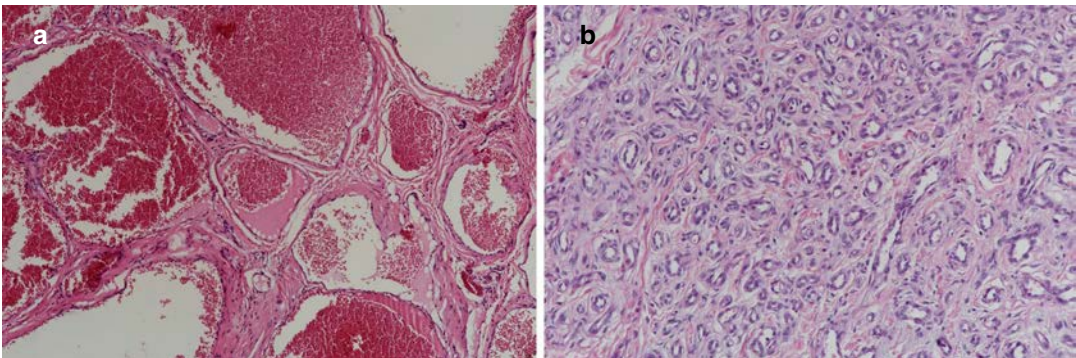


Fig. 25.8 Hemangioma is composed of thin-walled vascular vessels with large lumen at cavernous hemangioma (a) and small, well-formed vascular spaces lined by one-layer endothelial cells at capillary hemangioma (b)

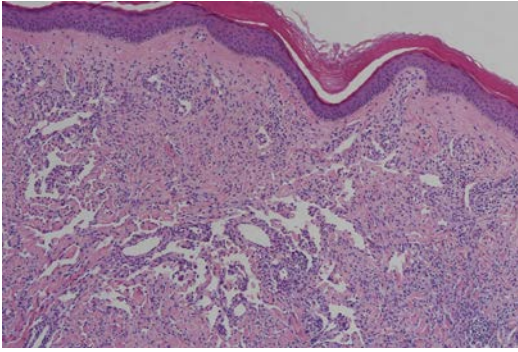


Fig. 25.9 Kaposi sarcoma is composed of uniformly atypical, spindled cells with slit like vascular spaces and extravasated erythrocytes

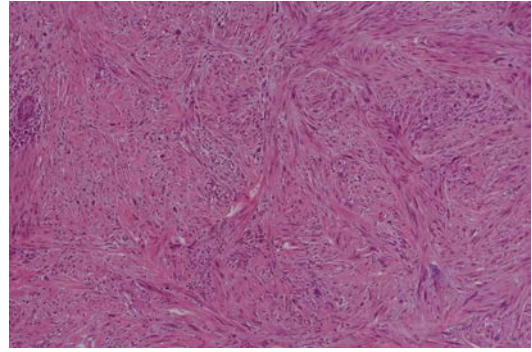


Fig. 25.12 Leiomyosarcoma is typically composed of intersecting fascicles of spindle cells with blunt-ended (cigar-shaped nuclei) and eosinophilic cytoplasm. Multiple mitoses are seen

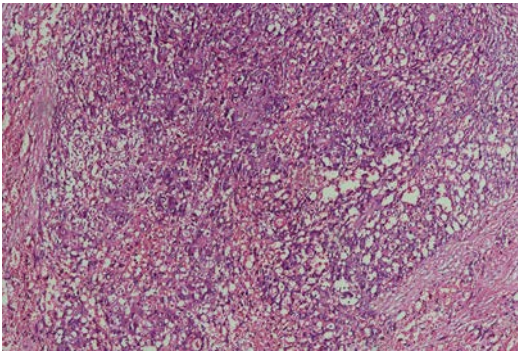


Fig. 25.10 Angiosarcoma showing irregular branched blood vessels composed of atypical endothelial cells

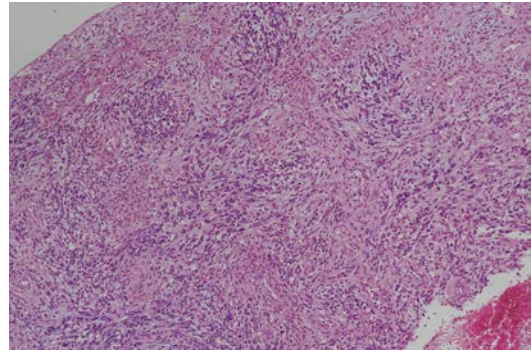


Fig. 25.13 Embryonal rhabdomyosarcoma. Malignant cells ranging from primitive/round to abundant eosinophilic cells with focal cytoplasmic striations (skeletal muscle differentiation)

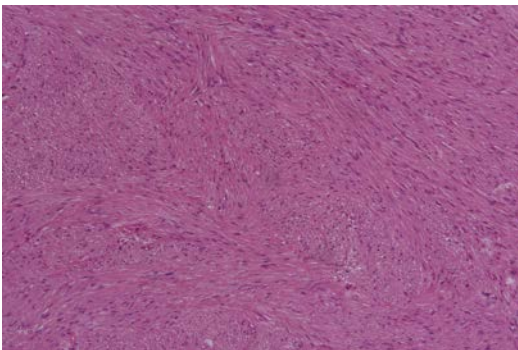


Fig. 25.11 Leiomyoma is showing cytologically bland spindle cells with eosinophilic fibrillary cytoplasm and blunt-ended nuclei

- *Embryonal*: Most common in children, generally has a better prognosis, tends to arise at head and neck and genital region. It has a loose myxoid stroma and small round or spindle cells especially under the epithelium (cambium layer) (Fig. 25.13).
- *Alveolar*: More aggressive, associated with FOXO1::PAX3/7 gene fusions. It shows nests of discohesive cells separated by fibrous septa, forming an alveolar like pattern (Fig. 25.14).
- *Pleomorphic*: Usually seen in adults, poor prognosis, contains highly atypical and pleomorphic cells.
- *Spindle cell/Sclerosing*: This tumor can occur in both children and adults, with common sites including the head and neck, paratesticular area, and extremities. The spindle cell variant is typified of elongated

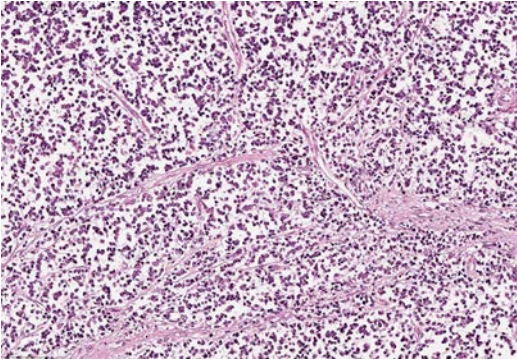


Fig. 25.14 Alveolar rhabdomyosarcoma characterized by discohesive round malignant tumor cells arranged in a pattern that creates pseudoalveolar spaces

tumor cells arranged in fascicles, histologically mimicking smooth muscle tumors. The sclerosing variant features dense, hyalinized stroma with pseudovascular pattern, and tumor cells forming nests or cords, sometimes mimicking other sarcomas. Molecular studies have identified three subgroups: congenital fusion-positive tumors, MYOD1-mutant tumors, and intraosseous variants with EWSR1 or FUS fusions. The MYOD1-mutant subtype is particularly aggressive and associated with poor prognosis. In contrast, congenital fusion-positive cases tend to have a more favorable outcome.

Immunohistochemically both benign and malignant skeletal tumor is positive with desmin, myogenin, and myoD1. These markers confirm skeletal muscle origin and aid in diagnosis [1, 34, 35].

25.4.6 Peripheral Nerve Sheath Tumors

- *Schwannoma*: Benign nerve sheath tumor, usually well circumscribed and encapsulated. Histologically it shows two distinct areas: Antoni A and Antoni B. Antoni A areas are characterized by high cellularity, with spindle cells arranged in palisading patterns and form-

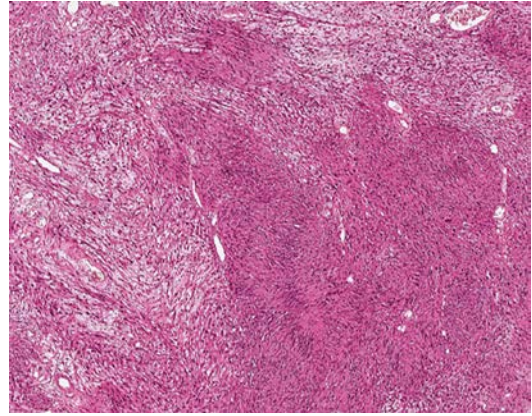


Fig. 25.15 Schwannoma demonstrates cellularly Antoni A and myxoid Antoni B areas

ing Verocay bodies. In contrast, Antoni B areas exhibit lower cellularity and a loosely textured myxoid stroma (Fig. 25.15). It is strongly positive with S-100 and SOX10; does not show significant atypia or mitotic activity [36–38].

- *Neurofibroma*: Benign, nonencapsulated peripheral nerve sheath tumor composed of a mixture of Schwann cells, fibroblasts, and perineurial-like cells. Histologically, it displays a loosely arranged proliferation of spindle-shaped cells with wavy or comma-shaped nuclei embedded in a collagenous or myxoid stroma. Unlike schwannoma, neurofibroma lacks Antoni A/B areas and Verocay bodies. Mast cells are commonly scattered throughout the tumor (Fig. 25.16). Immunohistochemically, it is positive for S100 protein but usually less intensely than schwannoma. It may be solitary or multiple, and multiple lesions are often associated with neurofibromatosis type 1 (NF1) [39, 40].
- *Malignant Peripheral Nerve Sheath Tumor (MPNST)*: Aggressive malignant tumor, with a high risk of local recurrence and distant metastasis. It arises from peripheral nerves or preexisting neurofibromas. It is often associated with neurofibromatosis type 1. Histologically, the tumor is composed of spindle-shaped cells arranged in fascicles with hyperchromatic, wavy nuclei. Marked nuclear atypia, high mitotic activity, and areas of

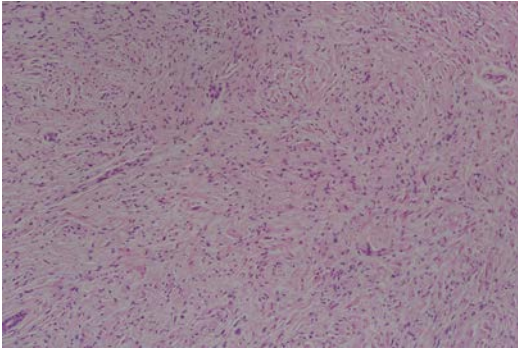


Fig. 25.16 Neurofibroma shows wavy or comma-shaped nuclei in a collagenous background

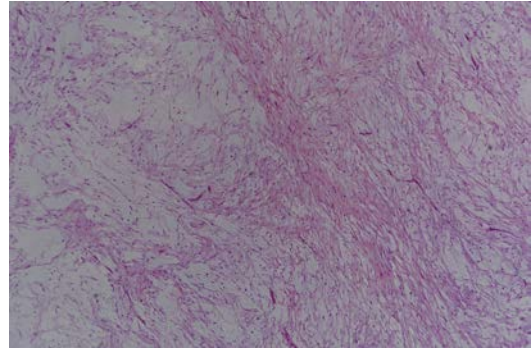


Fig. 25.18 Intramuscular myxoma. Cellularity is very low in a quite myxoid background

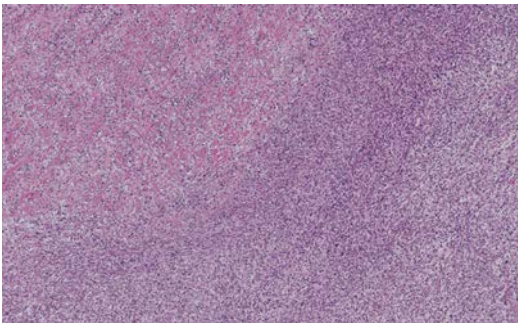


Fig. 25.17 Malignant peripheral nerve sheath tumor. Transition from hypocellular to hypercellular areas composed of spindle cells organized in long fascicles with some wavy and hyperchromatic nuclei

necrosis are commonly observed. The tumor may show heterologous differentiation, such as rhabdomyoblastic or cartilaginous elements (Fig. 25.17). Immunohistochemically, MPNST is variably positive for S-100 protein (usually focal) and may express SOX10. Loss of H3K27me3 expression is a helpful diagnostic marker in many cases. MPNST is aggressive, with a high risk of local recurrence and distant metastasis [39–41].

25.4.7 Tumors of Uncertain Differentiation

- *Intramuscular myxoma*: Benign gelatinous tumor within muscle tissue. Histologically, the tumor shows low cellularity; it is com-

posed of scattered spindle-shaped cells embedded in hypocellular abundant myxoid stroma (Fig. 25.18) [1].

- *Atypical Fibroxanthoma (AFX)*: Low-grade dermal tumor, often in sun-exposed areas of elderly patients. Histologically, it is composed of pleomorphic spindle and epithelioid cells, often mimicking melanoma or sarcoma. Nuclear atypia, frequent mitoses, and sometimes atypical mitotic figures can be seen but lacks deep tissue invasion. Despite its alarming histology, AFX behaves in a clinically indolent manner and has an excellent prognosis after complete excision [1, 42, 43].
- *Synovial Sarcoma*: Malignant soft tissue tumor that typically affects adolescents and young adults. Although its name suggests an origin from synovial tissue, it actually arises from mesenchymal stem cells and can occur in various locations, most commonly near large joints of the extremities. Synovial sarcoma is molecularly defined by the characteristic chromosomal translocation t(X;18)(p11;q11), which leads to the fusion of the SS18 gene with either SSX1 or SSX2. This genetic alteration plays a central role in tumorigenesis and serves as a key diagnostic marker. Histologically, the tumor is classified into monophasic, biphasic, and poorly differentiated subtypes. The tumor shows high cellularity, hyperchromatic nuclei, and frequent mitotic figures. Necrosis is common in high-grade tumors (Fig. 25.19).

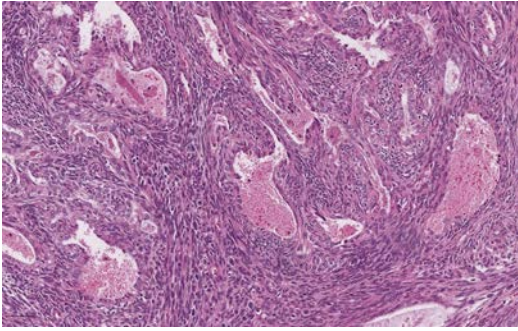


Fig. 25.19 Synovial sarcoma showing biphasic atypical spindle cells and epithelial component with glandular structures

- Biphasic: Contains both spindle cells and epithelial-like glandular structures.
- Monophasic: Consists mainly of spindle cells arranged in fascicles.
- Poorly differentiated: Composed of small round cells with high mitotic activity and areas of necrosis.

Immunohistochemically cytokeratin and epithelial membrane antigen (EMA) are typically positive in epithelial areas. TLE1 is a sensitive marker for synovial sarcoma. CD99 and BCL2 are also frequently positive. A fusion-specific antibody for SS18-SSX is highly specific. Prognosis is influenced by multiple factors, including tumor size, anatomical location, histologic subtype, and the presence or absence of metastatic disease. It has a high potential for metastasis, especially to the lungs, even in early stages [1, 44, 45].

- *Epithelioid Sarcoma*: Rare soft tissue sarcoma that typically affects young adults. It has a high rate of local recurrence and distant metastasis, particularly to the lungs and lymph nodes. The tumor most commonly arises in the distal extremities. Clinically it can mimic other tumors and may be mistaken for a benign lesion. Histologically, it is characterized by nodular aggregates of epithelioid cells with central necrosis, often mimicking granulomatous inflammation. The tumor cells demonstrate abundant eosinophilic cytoplasm, vesicular nuclei, and conspicuous nucleoli (Fig. 25.20). Immunohistochemically, it typi-

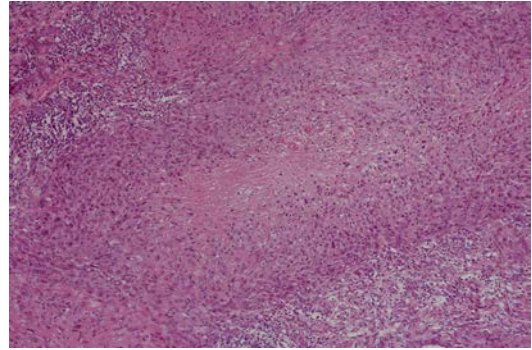


Fig. 25.20 Epithelioid sarcoma. Malignant epithelioid cells with eosinophilic cytoplasm and vesicular chromatin surrounding a necrosis zone

cally expresses cytokeratins, EMA, and vimentin, reflecting both epithelial and mesenchymal differentiation. CD34 is positive in approximately half of cases. A key diagnostic feature is the loss of INI1 (SMARCB1) expression [46–48].

- *Clear Cell Sarcoma of Soft Tissue*: Rare, aggressive soft tissue sarcoma with melanocytic differentiation. Typically affects young adults and adolescents. It most commonly arises in the deep soft tissues of the distal extremities, particularly around tendons and aponeuroses. Due to its indolent growth and superficial location, it may be mistaken for a benign lesion, which can delay diagnosis. Clear cell sarcoma is associated with a significant risk of both local recurrence and distant metastasis, particularly involving the lungs and regional lymph nodes. Histologically, it comprises uniform polygonal to spindle-shaped cells with clear to pale eosinophilic cytoplasm, vesicular nuclei, and conspicuous nucleoli. These neoplastic cells are typically organized in nests or fascicular arrangements, separated by fibrous septa (Fig. 25.21). Melanin pigment may be present in some cases. Immunohistochemically, the tumor expresses S100 protein, HMB-45, and Melan-A, reflecting its melanocytic differentiation. These features can lead to confusion with malignant melanoma. It involves

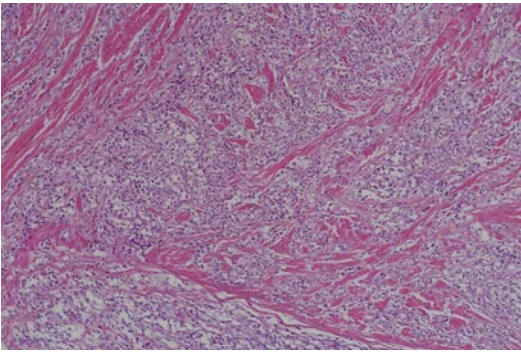


Fig. 25.21 Clear cell sarcoma showing nests and short fascicles of spindle/polygonal cells with eosinophilic cytoplasm, vesicular nuclei, and prominent nucleoli, separated by fibrous septa

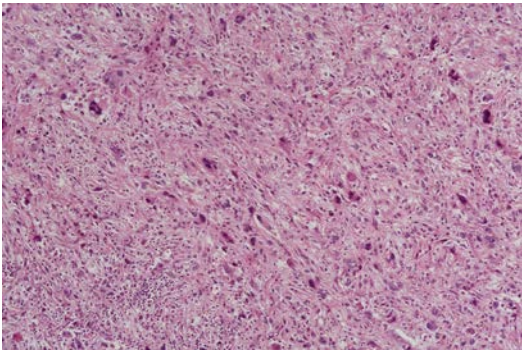


Fig. 25.22 Undifferentiated sarcoma composed of spindle–polygonal anaplastic cells

Table 25.4 Commonly used immunohistochemical (IHC) markers for diagnosing various types of soft tissue tumors [12, 52]

Tumor type	Common IHC markers	Diagnostic notes
Liposarcoma	S100, MDM2, CDK4	S100 for adipocytic differentiation; MDM2/CDK4 in well-differentiated types
Rhabdomyosarcoma	Desmin, myogenin, MyoD1	Markers of skeletal muscle differentiation
Leiomyosarcoma	SMA, desmin, H-caldesmon	Smooth muscle markers; H-caldesmon is specific
Angiosarcoma	CD31, CD34, ERG	Endothelial markers; ERG is highly specific
Schwannoma	S100, SOX10	Strong S100 positivity; SOX10 supports neural origin
Synovial sarcoma	Cytokeratins, EMA, TLE1	Epithelial markers; TLE1 is sensitive
MPNST	S100 (variable), SOX10, H3K27me3	Loss of H3K27me3 supports diagnosis

These markers help pathologists determine the lineage and nature of the tumor cells. Grading and staging are essential components of soft tissue tumor evaluation. They help determine the tumor’s aggressiveness, guide treatment decisions, and predict patient outcomes.

EWSR1::ATF1 gene fusion, which is critical for confirming the diagnosis and distinguishing it from melanoma and other soft tissue tumors [1, 49–51].

- *Undifferentiated Sarcoma*: High-grade sarcoma with no clear origin and lack identifiable differentiation under current histopathological and molecular techniques. This tumor can arise at any age and in any anatomical location, with no significant sex predilection. It is highly aggressive and poses significant challenges in treatment. Histopathologically, it often shows high-grade morphology with frequent necrosis and hemorrhage (Fig. 25.22). Genomic studies reveal complex karyotypic abnormalities [11, 52] (Table 25.4).

25.5 Histologic Grading (FNCLCC System)

The French Federation of Cancer Centers Sarcoma Group (FNCLCC) grading system is one of the most widely adopted histological grading schemes for soft tissue sarcomas [1]. It assesses three key parameters—tumor differentiation, mitotic count, and extent of necrosis. Higher histological grades correlate with an increased risk of local recurrence and distant metastasis (Table 25.5).

Total Score (Sum of the three parameters):

- *Grade 1*: 2–3 points (low grade)
- *Grade 2*: 4–5 points (intermediate grade)
- *Grade 3*: 6–8 points (high grade)

Table 25.5 The French Federation of Cancer Centers Sarcoma Group (FNCLCC) grading system for soft tissue sarcomas [1]

Parameter	Score range	Description
Tumor Differentiation	1–3	How closely the tumor resembles normal tissue
Mitotic Count	1–3	Number of mitoses per 10 high-power fields (HPF)
Tumor Necrosis	0–2	Percentage of tumor area showing necrosis

25.5.1 Tumor Staging (AJCC System)

The *American Joint Committee on Cancer (AJCC)* staging system uses the TNM format:

- *T (Tumor size and depth)*:
 - T1: ≤ 5 cm
 - T2: >5 cm
 - Superficial vs deep location
- *N (Lymph Node Involvement)*:
 - N0: No regional lymph node metastasis
 - N1: Regional lymph node metastasis
- *M (Distant Metastasis)*:
 - M0: No distant metastasis
 - M1: Distant metastasis present
- *Stage Grouping*: Combines T, N, and M to assign an overall stage (I–IV)

Grading reflects the tumor’s biological behavior, while staging describes its anatomical extent. Together, they provide a comprehensive picture of disease severity and help guide prognosis and treatment planning.

25.6 Clinical Relevance of Soft Tissue Tumors

Soft tissue tumors present a wide range of clinical behaviors, from harmless benign masses to aggressive malignancies with metastatic potential. Understanding their clinical relevance is essential for early recognition, appropriate referral, and effective management.

25.7 Presentation and Symptoms

- *Benign tumors*: Often asymptomatic, slow-growing, and discovered incidentally.
- *Malignant tumors*: May present with pain, rapid growth, deep location, or functional impairment.
- *Mass effect*: Tumors may compress adjacent structures, causing neurological or vascular symptoms.

25.8 Prognostic Factors (Table 25.6)

Table 25.6 Several factors influence prognosis in soft tissue sarcomas

Factor	Impact on prognosis
Tumor size	Larger tumors have worse outcomes
Depth of invasion	Deep-seated tumors are more aggressive
Histologic grade	High-grade tumors have higher recurrence
Surgical margins	Positive margins increase recurrence risk
Metastasis	Lung is the most common site

25.9 Treatment Overview

- *Benign tumors*: Often managed with observation or simple excision.
- *Malignant tumors*: Require a multidisciplinary approach
 - *Surgery*: Mainstay of treatment; goal is complete excision with clear margins.
 - *Radiation therapy*: Used pre- or postoperatively to reduce recurrence.
 - *Chemotherapy*: Reserved for high-grade or metastatic sarcomas.
 - *Targeted therapy*: Especially relevant for GIST (e.g., imatinib for KIT mutations).

25.10 Follow-Up and Surveillance

- Regular imaging and clinical exams are essential for detecting recurrence.
- Surveillance protocols vary based on tumor type, grade, and stage.

Soft tissue tumors, though rare, require careful clinical attention due to their potential for significant morbidity and mortality. Early recognition and accurate diagnosis are key to improving patient outcomes.

References

1. WHO Classification of Tumours Editorial Board, editor. WHO Classification of Tumours Editorial Board. Soft tissue and bone tumours [Internet]. 5th ed. Lyon: International Agency for Research on Cancer; 2020. Available from: <https://publications.iarc.fr/588>.
2. Trojani M, Contesso G, Coindre JM, Rouesse J, Bui NB, de Mascarel A, et al. Soft-tissue sarcomas of adults; study of pathological prognostic variables and definition of a histopathological grading system. *Int J Cancer*. 1984;33(1):37–42.
3. Coindre JM, Terrier P, Guillou L, Le Doussal V, Collin F, Ranchère D, et al. Predictive value of grade for metastasis development in the main histologic types of adult soft tissue sarcomas: a study of 1240 patients from the French Federation of Cancer Centers Sarcoma Group. *Cancer*. 2001;91(10):1914–26.
4. Toro JR, Travis LB, Wu HJ, Zhu K, Fletcher CDM, Devesa SS. Incidence patterns of soft tissue sarcomas, regardless of primary site, in the surveillance, epidemiology and end results program, 1978–2001: an analysis of 26,758 cases. *Int J Cancer*. 2006;119(12):2922–30.
5. Merry E, Thway K, Jones RL, Huang PH. Predictive and prognostic transcriptomic biomarkers in soft tissue sarcomas. *NPJ Precis Oncol*. 2021;5(1):17.
6. Papke DJ, Hornick JL. Recent advances in the diagnosis, classification and molecular pathogenesis of cutaneous mesenchymal neoplasms. *Histopathology*. 2022;80(1):216–32.
7. Choi JH, Ro JY. The 2020 WHO classification of tumors of soft tissue: selected changes and new entities. *Adv Anat Pathol*. 2021;28(1):44–58.
8. Sbaraglia M, Dei Tos AP. The pathology of soft tissue sarcomas. *Radiol Med*. 2019;124(4):266–81.
9. Kallen ME, Hornick JL. The 2020 WHO classification: what's new in soft tissue tumor pathology? *Am J Surg Pathol*. 2021;45(1):e1–23.
10. Hornick JL, editor. Pattern recognition, practical soft tissue pathology: a diagnostic approach. 2nd ed. Elsevier; 2019.
11. Fletcher CDM. Undifferentiated sarcomas: what to do? And does it matter? A surgical pathology perspective. *Ultrastruct Pathol*. 2008;32(2):31–6.
12. Hornick JL. Limited biopsies of soft tissue tumors: the contemporary role of immunohistochemistry and molecular diagnostics. *Mod Pathol*. 2019;32(Suppl 1):27–37.
13. Kindblom LG, Angervall L, Stener B, Wickbom I. Intermuscular and intramuscular lipomas and hibernomas. A clinical, roentgenologic, histologic, and prognostic study of 46 cases. *Cancer*. 1974;33(3):754–62.
14. Evans HL. Atypical lipomatous tumor, its variants, and its combined forms: a study of 61 cases, with a minimum follow-up of 10 years. *Am J Surg Pathol*. 2007;31(1):1–14.
15. Singer S, Succi ND, Ambrosini G, Sambol E, Decarolis P, Wu Y, et al. Gene expression profiling of liposarcoma identifies distinct biological types/subtypes and potential therapeutic targets in well-differentiated and dedifferentiated liposarcoma. *Cancer Res*. 2007;67(14):6626–36.

16. Aleixo PB, Hartmann AA, Menezes IC, Meurer RT, Oliveira AM. Can MDM2 and CDK4 make the diagnosis of well differentiated/dedifferentiated liposarcoma? An immunohistochemical study on 129 soft tissue tumours. *J Clin Pathol*. 2009;62:1127–35.
17. Kammerer-Jacquet SF, Thierry S, Cabillic F, Lannes M, Burtin F, Henno S, et al. Differential diagnosis of atypical lipomatous tumor/well-differentiated liposarcoma and dedifferentiated liposarcoma: utility of p16 in combination with MDM2 and CDK4 immunohistochemistry. *Hum Pathol*. 2017;59:34–40.
18. Choi KY, Mack L, Caragea M, Monument M, Puloski S, Bouchard-Fortier A. MDM2 analysis in the management of benign lipomas versus atypical lipomatous tumors/well-differentiated liposarcomas: a useful prognostication tool? *Am J Surg* [Internet]. 2022;224(2):747–50. Available from: <https://doi.org/10.1016/j.amjsurg.2022.03.052>.
19. Narendra S, Valente A, Tull J, Zhang S. DDIT3 gene break-apart as a molecular marker for diagnosis of myxoid liposarcoma—assay validation and clinical experience. *Diagn Mol Pathol*. 2011;20(4):218–24.
20. Hornick JL, Bosenberg MW, Mentzel T, McMenamin ME, Oliveira AM, Fletcher CDM. Pleomorphic liposarcoma: clinicopathologic analysis of 57 cases. *Am J Surg Pathol*. 2004;28(10):1257–67.
21. Montgomery EA, Meis JM. Nodular fasciitis. Its morphologic spectrum and immunohistochemical profile. *Am J Surg Pathol*. 1991;15(10):942–8.
22. Shin C, Low I, Ng D, Oei P, Miles C, Symmans P. USP6 gene rearrangement in nodular fasciitis and histological mimics. *Histopathology*. 2016;69(5):784–91.
23. De Wever I, Dal Cin P, Fletcher CD, Mandahl N, Mertens F, Mitelman F, et al. Cytogenetic, clinical, and morphologic correlations in 78 cases of fibromatosis: a report from the CHAMP Study Group. *CHromosomes And Morphology*. *Mod Pathol*. 2000;13(10):1080–5.
24. Le Guellec S, Soubeyran I, Rochaix P, Filleron T, Neuville A, Hostein I, et al. CTNNB1 mutation analysis is a useful tool for the diagnosis of desmoid tumors: a study of 260 desmoid tumors and 191 potential morphologic mimics. *Mod Pathol*. 2012;25(12):1551–8.
25. Fletcher CD, Evans BJ, MacArtney JC, Smith N, Wilson Jones E, McKee PH. Dermatofibrosarcoma protuberans: a clinicopathological and immunohistochemical study with a review of the literature. *Histopathology*. 1985;9(9):921–38.
26. Takahira T, Oda Y, Tamiya S, Higaki K, Yamamoto H, Kobayashi C, et al. Detection of COL1A1-PDGFB fusion transcripts and PDGFB/PDGFRB mRNA expression in dermatofibrosarcoma protuberans. *Mod Pathol*. 2007;20(6):668–75.
27. Sigel JE, Bergfeld WF, Goldblum JR. A morphologic study of dermatofibrosarcoma protuberans: expansion of a histologic profile. *J Cutan Pathol*. 2000;27(4):159–63.
28. Yamazaki F, Nakatani F, Asano N, Wakai S, Sekimizu M, Mitani S, et al. Novel NTRK3 fusions in fibrosarcomas of adults. *Am J Surg Pathol*. 2019;43(4):523–30.
29. Chor PJ, Santa Cruz DJ. Kaposi's sarcoma. A clinicopathologic review and differential diagnosis. *J Cutan Pathol*. 1992;19(1):6–20.
30. Hammock L, Reisenauer A, Wang W, Cohen C, Birdsong G, Folpe AL. Latency-associated nuclear antigen expression and human herpesvirus-8 polymerase chain reaction in the evaluation of Kaposi sarcoma and other vascular tumors in HIV-positive patients. *Mod Pathol*. 2005;18(4):463–8.
31. Miettinen M, Fetsch JF. Evaluation of biological potential of smooth muscle tumours. *Histopathology*. 2006;48(1):97–105.
32. Lee CH, Turbin DA, Sung YCV, Espinosa I, Montgomery K, van de Rijn M, et al. A panel of antibodies to determine site of origin and malignancy in smooth muscle tumors. *Mod Pathol*. 2009;22(12):1519–31.
33. Kapadia SB, Meis JM, Frisman DM, Ellis GL, Heffner DK. Fetal rhabdomyoma of the head and neck: a clinicopathologic and immunophenotypic study of 24 cases. *Hum Pathol*. 1993;24(7):754–65.
34. Agaram NP. Evolving classification of rhabdomyosarcoma. *Histopathology*. 2022;80(1):98–108.
35. Dehner CA, Rudzinski ER, Davis JL. Rhabdomyosarcoma: updates on classification and the necessity of molecular testing beyond immunohistochemistry. *Hum Pathol*. 2024;147:72–81.
36. Hilton DA, Hanemann CO. Schwannomas and their pathogenesis. *Brain Pathol*. 2014;24(3):205–20.
37. Kocharyan AH, Briggs S, Cosetti MK, Heman-Ackah SM, Golfinos JG, Roland JTJ. Atypical Schwannoma: a 10-year experience. *Am J Otolaryngol*. 2020;41(1):102309.
38. Helbing DL, Schulz A, Morrison H. Pathomechanisms in schwannoma development and progression. *Oncogene*. 2020;39(32):5421–9.
39. Belakhova SM, Rodriguez FJ. Diagnostic pathology of tumors of peripheral nerve. *Neurosurgery*. 2021;88(3):443–56.
40. Miettinen MM, Antonescu CR, Fletcher CDM, Kim A, Lazar AJ, Quezado MM, et al. Histopathologic evaluation of atypical neurofibromatous tumors and their transformation into malignant peripheral nerve sheath tumor in patients with neurofibromatosis 1—a consensus overview. *Hum Pathol*. 2017;67:1–10.
41. Schaefer IM, Fletcher CD, Hornick JL. Loss of H3K27 trimethylation distinguishes malignant peripheral nerve sheath tumors from histologic mimics. *Mod Pathol*. 2016;29(1):4–13.
42. Mentzel T, Requena L, Brenn T. Atypical fibroxanthoma revisited. *Surg Pathol Clin*. 2017;10(2):319–35.
43. Koelsche C, Stichel D, Griewank KG, Schrimpf D, Reuss DE, Bewerunge-Hudler M, et al. Genome-wide methylation profiling and copy number analysis in atypical fibroxanthomas and pleomorphic dermal sarcomas indicate a similar molecular phenotype. *Clin Sarcoma Res*. 2019;9:2.
44. El Beaino M, Rassy E, Hadid B, Araujo DM, Pavlidis N, Lin PP. Synovial sarcoma: a complex disease with

- multifaceted signaling and epigenetic landscapes. *Curr Oncol Rep*. 2020;22(12):124.
45. Thway K, Fisher C. Synovial sarcoma: defining features and diagnostic evolution. *Ann Diagn Pathol*. 2014;18(6):369–80.
46. Thway K, Jones RL, Noujaim J, Fisher C. Epithelioid sarcoma: diagnostic features and genetics. *Adv Anat Pathol* [Internet]. 2016 [cited 2021 Nov 9];23(1):41–9. Available from: <https://pubmed.ncbi.nlm.nih.gov/26645461/>.
47. Elsamna ST, Amer K, Elkattawy O, Beebe KS. Epithelioid sarcoma: half a century later. *Acta Oncol* [Internet]. 2020 [cited 2021 Nov 9];59(1):48–54. Available from: <https://pubmed.ncbi.nlm.nih.gov/31478778/>.
48. Dey B, Srinivas BH, Badhe B, Nachiappa Ganesh R, Gochhait D, Toi PC, et al. Malignant epithelioid soft tissue tumours – a pathologist’s perspective with review of literature. *Cureus* [Internet]. 2020 [cited 2021 Nov 9];12(12). Available from: <https://pubmed.ncbi.nlm.nih.gov/33520482/>.
49. Hisaoka M, Ishida T, Kuo TT, Matsuyama A, Imamura T, Nishida K, et al. Clear cell sarcoma of soft tissue: a clinicopathologic, immunohistochemical, and molecular analysis of 33 cases. *Am J Surg Pathol*. 2008;32(3):452–60.
50. Hocar O, Le Cesne A, Berissi S, Terrier P, Bonvalot S, Vanel D, et al. Clear cell sarcoma (malignant melanoma) of soft parts: a clinicopathologic study of 52 cases. *Dermatol Res Pract*. 2012;2012:984096.
51. Yang L, Chen Y, Cui T, Knösel T, Zhang Q, Geier C, et al. Identification of biomarkers to distinguish clear cell sarcoma from malignant melanoma. *Hum Pathol*. 2012;43(9):1463–70.
52. Thway K, Fisher C. Undifferentiated and dedifferentiated soft tissue neoplasms: immunohistochemical surrogates for differential diagnosis. *Semin Diagn Pathol*. 2021;38(6):170–86.

Genodermatoses and Infectious Diseases of Skin

26

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26.1 Genodermatoses

26.1.1 Introduction

Genodermatoses are a diverse group of hereditary skin disorders that arise due to genetic defects, independent of environmental influences. These conditions result from mutations that alter the structure or function of the epidermis, dermal connective tissue, or skin appendages such as hair, nails, and sweat glands. The clinical manifestations range from localized cutaneous lesions to multisystem syndromes involving the nervous system, eyes, or internal organs. Advances in molecular genetics and next-generation sequencing have provided valuable insights into the pathogenesis of genodermatoses, allowing for more accurate diagnosis, genetic counseling, and the development of targeted therapeutic strategies. Understanding the genetic and molecular basis of these disorders not only aids in clinical management but also sheds light on fundamental

mechanisms governing skin development, differentiation, and homeostasis. The most frequently encountered genodermatoses (Table 26.1), along with their characteristic clinical manifestations, genetic basis, and histopathological findings, are outlined in the following section [1, 2].

Ichthyoses are a group of cornification disorders characterized by a defective skin barrier due to abnormal epidermal differentiation and desquamation. Clinically and etiologically heterogeneous, they represent a broad spectrum of diseases marked by generalized scaling. They may be non-syndromic, syndromic, or acquired. Selected non-syndromic ichthyoses are summarized below [3].

- *Ichthyosis vulgaris* is the most common cornification disorder, estimated to affect between 1 in 100 and 1 in 250 individuals. It results from loss-of-function mutations in the filaggrin gene, inherited in an autosomal semi-dominant manner. Profilaggrin, a key component of keratohyalin granules in the granular layer, is cleaved during keratinocyte differentiation into filaggrin peptides that aggregate keratin intermediate filaments. Filaggrin deficiency leads to an impaired cornified envelope, increased transepidermal water loss, and enhanced penetration of allergens and irritants. In heterozygotes, the disease is often not apparent at birth. Infancy or early childhood shows xerosis and mild-to-moderate desquamation. Scaling typically involves the

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Table 26.1 Common genodermatoses and their key features

Disease	Inheritance pattern/gene defect	Main clinical features	Histopathological features
Ichthyosis vulgaris	Autosomal semidominant; <i>FLG</i> gene (filaggrin) mutation	Dry, scaly skin, accentuated in extensor areas; often associated with atopy	Compact orthokeratosis, reduced granular layer, normal epidermal thickness
X-linked ichthyosis	X-linked recessive; <i>STS</i> gene deletion	Generalized scaling, darker polygonal scales, sparing of flexural areas	Lamellar hyperkeratosis with retained nuclei; thickened stratum corneum
Xeroderma pigmentosum (XP)	Autosomal recessive; DNA repair gene defects (<i>XPA–XPG</i>)	Extreme UV sensitivity, freckling, early-onset skin cancers	Epidermal atrophy, keratinocyte atypia, solar elastosis, early malignant transformation
Neurofibromatosis type 1 (NF1)	Autosomal dominant; <i>NF1</i> gene mutation on chromosome 17	Café-au-lait macules, axillary freckling, multiple neurofibromas, Lisch nodules	Spindle cell proliferation with wavy nuclei in myxoid stroma; diffuse neurofibroma may involve dermis
Tuberous sclerosis complex (TSC)	Autosomal dominant; <i>TSC1</i> (<i>hamartin</i>) or <i>TSC2</i> (<i>tuberin</i>) mutation	Facial angiofibromas, shagreen patches, periungual fibromas, CNS and renal involvement	Dermal fibrosis with enlarged vessels; angiofibroma with vascular and fibrous components
Albinism (oculocutaneous)	Autosomal recessive; <i>TYR</i> , <i>OCA2</i> , <i>SLC45A2</i> mutations	Generalized hypopigmentation of skin, hair, eyes; photophobia	Markedly decreased or absent melanin pigment in basal keratinocytes and melanocytes
Incontinentia pigmenti	X-linked dominant (lethal in males); <i>IKBK</i> G/ <i>NEMO</i> gene mutation	Vesiculobullous lesions → verrucous stage → hyperpigmented whorls → hypopigmented atrophy	Eosinophilic spongiosis (early), melanin incontinence with dermal melanophages (late stage)
Darier disease (keratosis follicularis)	Autosomal dominant; <i>ATP2A2</i> gene mutation	Greasy, crusted papules in seborrheic areas, nail changes	Suprabasal acantholysis, dyskeratosis with corps ronds and grains
Hailey–Hailey disease (familial benign pemphigus)	Autosomal dominant; <i>ATP2C1</i> gene mutation	Recurrent erosions and vesicles in intertriginous areas	Widespread suprabasal acantholysis forming “dilapidated brick wall” pattern
Epidermolysis bullosa (EB)	Autosomal dominant or recessive; mutations in <i>COL7A1</i> , <i>KRT5</i> , <i>KRT14</i> , <i>LAMB3</i> , <i>ITGB4</i>	Skin fragility, blister formation after minor trauma, mucosal involvement in severe types	Subepidermal or intraepidermal blistering depending on subtype; reduced or absent anchoring fibrils

extensor surfaces of the extremities; flexures are spared. Palmoplantar hyperlinearity is common. Although worsening in childhood, ichthyosis vulgaris frequently improves with age. It commonly coexists with keratosis pilaris and atopic traits such as asthma, hay fever, and atopic dermatitis. Histopathology reveals

mild orthokeratotic hyperkeratosis, acanthosis, a frequently diminished granular layer, and follicular plugging. On electron microscopy, 30%–50% of affected individuals lack a granular layer and keratohyalin granules, whereas others show structural abnormalities of these granules. Immunohistochemistry demonstrates

reduced or absent filaggrin staining in most patients [3].

- *X-linked recessive ichthyosis* is also known as steroid sulfatase (STS) deficiency; X-linked recessive ichthyosis is due to deletions or inactivating mutations of the STS gene on Xp22.31 and occurs exclusively in males. Impaired hydrolysis of cholesterol sulfate and dehydroepiandrosterone sulfate leads to accumulation of cholesterol 3-sulfate in the epidermis. Most patients show mild erythroderma with generalized exfoliation in the neonatal period. Subsequently, polygonal, dark-brown, adherent scales develop symmetrically on the extremities, trunk, and neck; the characteristic involvement of the neck is termed the “dirty neck disease.” Other body folds, the palms/soles, and most of the face (except preauricular skin) are typically spared. Cryptorchidism is ~20-fold more frequent than in the general population. Histology shows hyperkeratosis or parakeratosis over a normal or mildly thickened granular layer; follicular hyperkeratosis may be present. Electron microscopy reveals increased size and number of keratohyalin granules [3].
- *Epidermolytic ichthyosis* is formerly known as bullous congenital ichthyosiform erythroderma, epidermolytic ichthyosis arises from heterozygous autosomal dominant mutations in keratin 1 (KRT1) and KRT10. KRT1 variants are often associated with potentially severe palmoplantar keratoderma. Mutations disrupt keratin pairing, oligomerization, and filament formation, weakening the cytoskeleton and compromising epidermal integrity, which results in cytolysis and blistering. At birth, patients show erythroderma, denudation, and widespread erosions. Over time, fragility and blistering wane, while severe hyperkeratosis develops. Periodic shedding of large superficial epidermal sheets may reveal tender erythematous skin. Flexural thickening along skin lines is typical; extensor hyperkeratosis often appears “cobblestoned.” The hallmark “epidermolytic hyperkeratosis” (keratinocyte degeneration with a “blown out by a shotgun” look) distinguishes this entity.

Histology shows dense orthokeratotic hyperkeratosis, prominent acanthosis and hypergranulosis, suprabasal/granular cell cytolysis, and small intraepidermal blisters. Superficial intraepidermal clefts and conspicuous keratinocyte vacuolization occur, with a mild superficial perivascular lymphohistiocytic infiltrate [1–3].

- *Lamellar ichthyosis*: Classic lamellar ichthyosis (non-erythrodermic autosomal recessive lamellar ichthyosis) is most commonly linked to mutations in TGM1, ABCA12, or CYP4F22. It usually presents at birth and persists lifelong. Most neonates are encased in a collodion membrane that transitions over weeks to large brown, plate-like scales forming mosaic or tree-bark patterns; erythroderma is not expected. Scales are centrally adherent with raised borders and superficial fissuring. “Bathing suit ichthyosis,” due to temperature-sensitive TGM1 mutations, predominantly affects the trunk and scalp. Facial skin tightness commonly causes ectropion, eclabium, and hypoplasia of nasal and auricular cartilages. A substantial proportion develops palmoplantar keratoderma, ranging from accentuation of dermatoglyphics to fissuring. Histology is not diagnostic: massive orthokeratotic hyperkeratosis with an acanthotic epidermis, sometimes psoriasiform or papillomatous [1–3].
- *Congenital ichthyosiform erythroderma (CIE)* is also called non-bullous congenital ichthyosiform erythroderma; CIE results from autosomal recessive mutations in TGM1, ALOXE3, ALOX12B, or ABCA12. It typically presents at birth with erythroderma or a collodion membrane, followed by lifelong generalized erythroderma and scaling of variable intensity—often milder than classic lamellar ichthyosis. Severe cases may display ectropion, diffuse scaling, and cicatricial alopecia; palmoplantar keratoderma may occur. Occlusion of sweat ducts commonly causes hypohidrosis and heat intolerance; secondary nail dystrophy may be seen. Adults carry a risk of cutaneous SCC (squamous cell carcinoma) and BCC (basal cell carcinoma).

Histology is not specific but shows more focal or widespread parakeratosis, more pronounced acanthosis, and hypergranulosis than in lamellar ichthyosis [1, 2].

- *Collodion baby*: Mechanisms underlying the collodion membrane are not fully understood. Common etiologies include deficiencies in TGM1 and various lipid-processing enzymes/transporters (e.g., ALOX12B > ALOXE3, CERS3, PNPLA1, SULT2B1). Less frequent causes include fatty aldehyde dehydrogenase deficiency (Sjögren–Larsson syndrome), impaired activation of adipose triglyceride lipase (neutral lipid storage disease), and β -glucocerebrosidase deficiency (Gaucher disease). Collodion infants are often premature and small for gestational age and have high perinatal morbidity/mortality. At birth, the skin is encased in a taut, shiny, transparent film resembling plastic wrap, causing ectropion, eclabium, and hypoplastic nasal/auricular cartilage. As the parchment-like membrane dries, fissures, and detaches, barrier dysfunction produces water loss, microbial ingress, and fluid/electrolyte imbalance. Peeling over 2–4 weeks reveals the underlying phenotype—most commonly CIE or lamellar ichthyosis. Histology is nonspecific, usually showing an excessively thick orthokeratotic stratum corneum; immu-

nostaining may demonstrate presence/absence of TGM1 in the upper epidermis [1, 2].

- *Harlequin ichthyosis* is the most severe end of autosomal recessive congenital ichthyoses due to ABCA12 mutations. Improved neonatal intensive care and systemic retinoid therapy have increased survival. Affected neonates—often premature—may die within days to weeks from respiratory failure or sepsis. They are covered by a rigid, armor-like, massively thickened stratum corneum that restricts movement and ventilation. Soon after birth, large, adherent yellow plates separated by deep, bright-red fissures appear. Excessive transepidermal water and heat loss cause dehydration and electrolyte imbalance. Ectropion, eclabium, rudimentary auricular/nasal cartilage, and microcephaly can occur. Distal extremities are edematous and encased in glove-like keratotic sheaths; constricting bands can lead to auto-amputation. Survivors develop severe exfoliative ichthyosiform erythroderma and painful palmoplantar fissures in ~50%. Dystrophic nails and poor hair growth are common. Histology shows an excessively thick, compact orthokeratotic stratum corneum (occasionally with parakeratosis) and prominent keratotic plugs in follicles and sweat ducts (Fig. 26.1) [1–3].

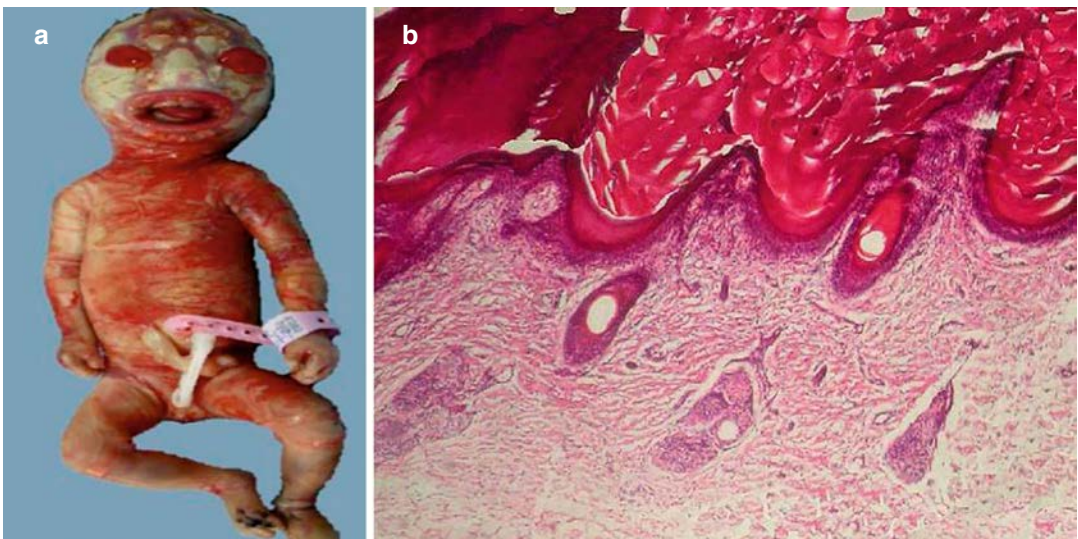


Fig. 26.1 (a) Harlequin baby. (b) Compact orthokeratosis

Hereditary palmoplantar keratoderms (PPKs) may be hereditary or acquired and are classified as diffuse, localized, or punctate by pattern of involvement; hands and feet may differ clinically. Distinguishing features include erythematous margins, transgredient spread beyond palmoplantar skin, and pseudoainhum. Hyperhidrosis, maceration, blisters, fungal superinfection, malodor, and pain may occur. Associated findings to assess include nail dystrophy, hypotrichosis, oral lesions, hyperkeratosis on non-volar skin, hearing deficits, ocular signs, cardiomyopathy, and woolly hair. Selected hereditary PPKs [4–7]:

- *Vörner–Unna–Thost (diffuse epidermolytic PPK)*: Autosomal dominant KRT1/KRT9 mutations. Early childhood thick yellow keratosis; in adults, sharply demarcated, smooth, waxy plaques with erythema. Histology: epidermolytic hyperkeratosis, papillomatosis, intracellular vacuolization, conspicuous cytoplasmic inclusions; intraepidermal blistering from keratinocyte cytolysis with a mild superficial dermal infiltrate. Lesional changes may be subtle/patchy and require careful sampling.
- *Mal de Meleda (diffuse non-epidermolytic PPK)*: Autosomal recessive SLURP1 mutations. Progressive transgredient keratosis from early infancy; severe cases lead to contractures, pseudoainhum, and frequent fungal superinfection. Histology: orthohyperkeratosis, hypo-normogranulosis, acanthosis, characteristic papillomatosis; PAS staining helps exclude dermatophytes.
- *Vohwinkel syndrome*: Autosomal dominant GJB2 (connexin-26 protein) gene mutations. Honeycomb-like diffuse PPK with starfish-shaped keratoses over joints and pseudoainhum; nonprogressive high-tone sensorineural hearing loss. Histology nonspecific: papillomatosis and marked orthohyperkeratosis.
- *Huriez syndrome*: Autosomal dominant SMARCAD1 mutations. Infant-onset dorsal hand scleroatrophy → sclerodactyly and loss of dermatoglyphics; parchment-like mild palmar/plantar keratosis and later focal pressure-related plaques; nail hypoplasia; increased SCC risk in atrophic areas. Histology: ortho-hyperkeratosis, acanthosis, hypergranulosis; absence of Langerhans cells.
- *Olmsted syndrome*: Usually autosomal dominant (rare recessive) TRPV3 gain-of-function mutations. Sharply demarcated diffuse PPK with progressive flexion contractures, constriction, auto-amputation; painful/pruritic warty hyperkeratosis periorificially/intertriginously. SCC and melanoma have been reported in keratotic areas. Histology: ortho-/parakeratosis, papillomatosis, acanthosis with perivascular inflammation and increased mast cells [7].
- *Papillon–Lefèvre syndrome*: Autosomal recessive disorder caused by mutations in the gene encoding cathepsin C, a lysosomal cysteine protease that activates serine proteases in the skin and inflammatory cells. Clinically, it is characterized by diffuse, transgredient palmoplantar keratoderma with associated erythema, psoriasiform plaques over the knees and elbows, and pseudoainhum formation. Additional features include severe periodontitis leading to premature loss of teeth and increased susceptibility to pyogenic infections of internal organs.
- *Howel–Evans syndrome*: Autosomal dominant RHBDF2 missense mutations. Focal PPK over pressure points of toes; often with keratosis pilaris, xerosis, and oral leukokeratosis; increased esophageal carcinoma risk.
- *Isolated punctate PPK*: Autosomal dominant; heterozygous AAGAB mutations (α/γ -adaplin binding protein p34). Numerous small keratotic papules beginning in adolescence/early adulthood; histology shows a shallow epidermal depression topped by compact orthohyperkeratosis, with hypogranulosis, parakeratosis, and elongated curved rete ridges.
- *PPK with woolly hair*:
- *Naxos disease*: Homozygous mutations in plakoglobin (a hemidesmosomal component in epidermis, hair follicles, and heart). Non-epidermolytic diffuse PPK presenting in the first year; woolly hair at birth; arrhythmogenic

right-ventricular cardiomyopathy in adolescence.

- Carvajal syndrome: Pathogenic variants in desmoplakin (biallelic or heterozygous). Striate PPK, woolly hair (often at birth), and cardiomyopathy (predominantly left-sided, but either ventricle may be involved). Histology shows widened intercellular spaces and partial separation of suprabasal keratinocytes with dense eosinophilic cytoplasm around a pyknotic nucleus.

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder caused by mutations in the *NF1* gene, which encodes neurofibromin. These mutations exhibit variable expressivity. In large series, approximately half of affected individuals have no family history, suggesting that many cases arise from new spontaneous mutations. *Café-au-lait macules (CALMs)* are uniformly pigmented patches or macules ranging in color from light to dark brown, found anywhere on the body except the scalp and palmoplantar regions. They may not be evident at birth but typically become more prominent during the first year of life, often fading in adulthood. *Crowe's sign* refers to freckling in intertriginous regions, particularly the axillae, groin, and neck, consisting of numerous 1–3 mm brown macules. Multiple variants of neurofibromas occur in NF1. The most common form is the *cutaneous neurofibroma*, a soft to slightly rubbery papule or nodule ranging from a few millimeters to several centimeters in diameter, with colors from skin-toned to pink or brown. They characteristically invaginate under light pressure, producing the pathognomonic “buttonhole” sign. *Subcutaneous neurofibromas* are located deeper in the dermis or subcutis, are firmer, and tend to be less conspicuous. *Plexiform neurofibromas* extend along nerves, forming tender, firm nodules or masses in the subcutaneous tissue with a “bag of worms” texture on palpation. Unlike other types, plexiform neurofibromas are almost always congenital [8, 9]. According to the 2021 revised diagnostic criteria, NF1 is diagnosed in an individual *without* an affected parent if two or more of the fol-

lowing are present and in an individual *with* an affected parent if one or more are present:

- Six or more café-au-lait macules >5 mm in diameter in prepubertal individuals or > 15 mm post pubertally
- Freckling in the axillary or inguinal region
- Two or more neurofibromas of any type, or one plexiform neurofibroma
- Optic pathway glioma
- Two or more Lisch nodules (iris hamartomas) or two or more choroidal abnormalities
- A distinctive osseous lesion, such as sphenoid dysplasia, anterolateral bowing of the tibia, or pseudarthrosis of a long bone
- A heterozygous pathogenic *NF1* variant with a variant allele fraction of 50% in normal tissue

Histopathology

- *CALMs*: Increased epidermal melanin, giant melanosomes, and a higher number of melanocytes compared to surrounding skin.
- *Cutaneous neurofibromas*: Well-circumscribed but unencapsulated dermal proliferations of small nerve fibers, composed of loosely arranged spindle cells with pale cytoplasm and long, wavy nuclei. These are intermixed with fibroblasts, Schwann cells, and perineurial cells within a collagenous stroma containing variable mucin and scattered mast cells.
- *Plexiform neurofibromas*: Hypertrophic nerves surrounded by spindle fibroblasts and Schwann cells, growing in a plexiform pattern within a myxoid matrix.
- *Malignant peripheral nerve sheath tumor (MPNST)*: Intersecting fascicles of tightly packed spindle cells with wavy, hyperchromatic, and pleomorphic nuclei. The cells stain positively for S100, exhibit increased mitotic activity, and frequently form perivascular whorls.

Tuberous sclerosis complex (TSC) is a neurocutaneous developmental disorder with multisystem involvement, transmitted in an autosomal dominant pattern. Transmission across more than

two generations is uncommon, and 50%–70% of cases result from new spontaneous mutations. The defective gene is located on the long arm of chromosome 9, with mutations identified in TSC1, encoding hamartin, and TSC2, encoding tuberin. The cutaneous signs of TSC fall into four main categories [8–10]:

1. *Hypopigmented macules*—Often the earliest sign, sometimes present at birth. They are usually oval or “ash leaf” shaped, measuring 1–3 cm in length, though smaller polygonal or “fingerprint” macules are most common. Multiple guttate (“confetti”) macules, ~2 mm in size, may appear on the extremities. Lesions can occur singly or in multiples on the trunk and limbs, with hypopigmentation more evident under Wood’s lamp examination. Presence of three or more hypomelanotic macules ≥ 5 mm in diameter constitutes a major diagnostic criterion.
2. *Angiofibromas*—Formerly referred to as “sebaceous adenomas,” these are hamartomas of blood vessels and connective tissue, unrelated to sebaceous glands. They typically develop between ages 3–10, presenting as multiple, symmetrical, 2 mm, yellowish-pink or red, smooth papules on the malar regions, chin, and forehead. At least three lesions are required for diagnosis, as one or two angiofibromas may be seen in the general population.
3. *Shagreen patch*—A type of collagenoma, most often located in the lumbosacral region but also occurring on the trunk.
4. *Periungual/subungual fibromas (Koenen tumors)*—Firm, flesh-colored, slow-growing tumors 5–10 mm in diameter, usually appearing during adolescence. Often multiple, they can distort the nail bed if large. Fibromas may also occur on the gingiva or oral mucosa. Additional cutaneous findings include fibrous cephalic plaques, which are larger angiofibroma variants on the face or scalp, and molluscum pendulum-like lesions resembling large acrochordons, often in flexural regions such as the neck, axillae, and groin. Hamartomas may occur in various organs,

including the eyes, brain, kidneys, heart, and lungs. Neurological manifestations are common and include seizures, intellectual disability, and neuropsychiatric disorders.

Histopathology

- *Hypopigmented macules*: Reduced epidermal melanin with a normal number of melanocytes.
- *Angiofibromas*: Irregular proliferation of fibrous tissue and blood vessels; adnexal structures may be compressed by hamartomatous expansion. Characteristic concentric perifollicular fibrosis is present.
- *Fibrous cephalic plaques*: Similar histological pattern to angiofibromas.
- *Shagreen patches and ungual fibromas*: Collagenomas characterized by thick collagen bundles replacing the dermis, with loss of elastic fibers. Fibroblasts may be large and morphologically atypical.
- It is thought that the various fibrous lesions of TSC represent a spectrum of the same histopathological process, with perifollicular fibrosis being a distinctive hallmark.

Xeroderma pigmentosum (XP) is a rare autosomal recessive disorder characterized by extreme cutaneous sensitivity to ultraviolet (UV) radiation, early-onset skin malignancies of ectodermal or mesodermal origin, and various ophthalmologic abnormalities. The underlying defect is the inability to repair DNA damage induced by UV light. UV exposure causes thymine dimer formation in DNA, which, under normal circumstances, is corrected via nucleotide excision repair through a series of enzymatic reactions that resynthesize the affected short single-stranded DNA segment. In XP, the failure of this repair process disrupts vital cellular functions, leading to cell degeneration and the development of skin cancers. This repair defect occurs not only in skin cells but also in immune system cells, particularly lymphocytes, which contributes to an increased risk of extracutaneous malignancies. The hereditary defect involves mutations in multiple possible genes, resulting in distinct clinical subtypes. At birth, the skin appears normal. The

disease typically manifests within the first year of life with photosensitivity in sun-exposed areas. The earliest sign is often a severe sunburn-like reaction. Freckle-like hyperpigmented macules, skin thickening, and hyperkeratosis develop, with occasional vesiculobullous lesions. Over time, atrophic patches and telangiectasias appear, producing a poikiloderma pattern. Atrophy and contractures, especially around the nose and mouth, may cause a characteristic “bird-like” facies. Actinic keratoses are common. Cutaneous malignancies include BCC, SCC, and, less frequently, melanoma. SCC may also develop on the distal lips and tongue. Ocular involvement is frequent and includes severe photophobia, keratitis, corneal opacification, and neovascularization. Loss of eyelashes, ectropion, and malignancies such as squamous cell carcinoma and melanoma in UV-exposed ocular regions have also been reported. Neurological manifestations may include intellectual disability, microcephaly, epilepsy, cerebellar ataxia, and sensorineural hearing loss. Short stature and gonadal dysfunction may also occur. Patients with XP have a markedly elevated risk (approximately 10–20 times higher than the general population) for internal malignancies, including tumors of the brain, lung, oral cavity, gastrointestinal tract, kidney, and hematopoietic system [10, 11].

Incontinentia pigmenti (IP) is a rare X-linked dominant disorder that predominantly affects female infants and is typically lethal in males. It is associated with mutations in the *IKBKG* gene (inhibitor of kappa-B kinase gamma), which encodes a component of the NEMO (NF-kappa-B

essential modulator) complex. The first stage of skin lesions most often presents as linear vesicles, typically observed on the extremities. In otherwise healthy female infants, the condition usually appears within the first few weeks to months of life as linear erythema and vesicles (stage 1). Vesiculobullous lesions are most frequently found on the extremities and scalp and occasionally on the trunk. These lesions resolve within days to weeks, giving way to verrucous linear plaques affecting the extremities (stage 2). Subsequently, reticular, gray-brown hyperpigmented streaks and whorls develop (stage 3). These hyperpigmented lines tend to fade by adolescence. From adolescence onward, linear hypopigmented bands lacking hair follicles and sweat glands appear on the posterior aspects of the extremities (stage 4), and in adulthood, this may be the only clinical manifestation of the disease (Fig. 26.2). Skeletal and dental abnormalities, ocular disorders, and central nervous system involvement (including seizures and intellectual disability) may be associated. Histopathology in the first stage shows eosinophilic spongiosis, intraepidermal vesicles containing eosinophils, dyskeratotic keratinocytes, and perivascular infiltrates of lymphocytes and eosinophils. In the second stage, papillomatosis, hyperkeratosis, and acanthosis are present, with keratinocytes typically showing dyskeratosis and forming squamous whorls. In the third stage, melanin incontinence and basal cell hyperpigmentation are seen, sometimes accompanied by basal cell degeneration. In the fourth stage, the epidermis is thinned, and adnexal structures in the dermis are absent [12, 13].

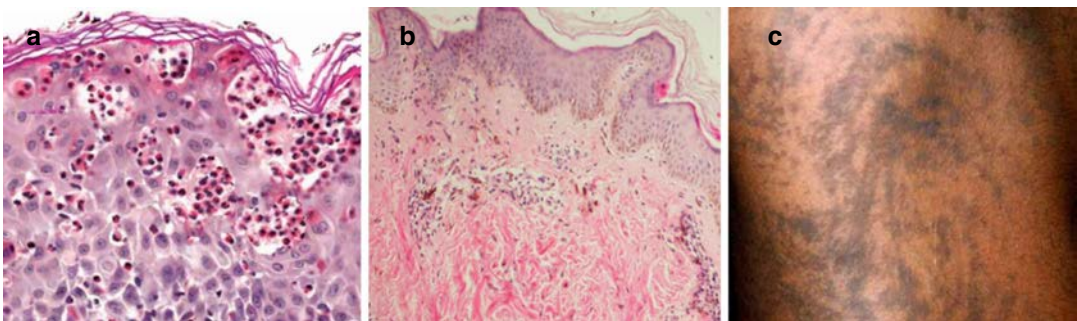


Fig. 26.2 (a) Eosinophilic spongiosis in the first stage. (b) Melanin incontinence and basal cell hyperpigmentation in the third stage. (c) Gray-brown hyperpigmented streaks on the skin

Ectodermal Dysplasias These genetic disorders comprise a group of conditions characterized by abnormalities in at least two primary ectodermal-derived structures—hair, teeth, nails, and sweat glands. Other ectodermal structures, such as mucous membranes and sebaceous glands, as well as non-ectodermal structures, may also be affected. Different forms of ectodermal dysplasia are distinguished based on the type of ectodermal abnormalities present, associated non-ectodermal anomalies, mode of inheritance, and underlying genetic defect. The ectodysplasin, WNT, and p63 signaling pathways play a role in the pathogenesis of ectodermal dysplasias [12, 13].

- *Hypohidrotic ectodermal dysplasia* encompasses a group of conditions characterized by sparse or absent scalp hair, missing or peg-shaped teeth, and reduced sweating. The most common form is X-linked, although clinically similar autosomal dominant and autosomal recessive forms exist. A collodion membrane may be present in affected newborns. When hair is present, it is usually lightly pigmented and may darken during adolescence. Secondary sexual hair is generally normal, but body hair is often sparse or absent. Most patients are unable to sweat to a noticeable degree, which can lead to elevated body temperature in hot environments or during exertion, resulting in symptomatic hyperthermia. The skin is smooth, and dermatoglyphics may be absent due to a lack of eccrine openings. Nails are usually normal. Both primary and secondary dentitions are affected; teeth may be missing or reduced in number and may have abnormal shapes. Affected individuals typically have a characteristic facial appearance with a saddle nose, prominent everted lips, and frontal bossing. Skin biopsy is generally not required.
- *Hidrotic ectodermal dysplasia* is an autosomal dominant condition caused by missense mutations in the GJB6 gene, which encodes connexin 30 and is thought to be regulated by the p63 transcription factor. It is characterized by the triad of hypotrichosis, nail dystrophy, and

palmoplantar keratoderma. Teeth and sweating are normal. Hair is brittle and pale, and both hair loss and nail changes may progress over time. In affected infants, nails are typically milky white and smaller than normal, gradually thickening throughout childhood. On the palmoplantar surfaces, papules arranged in a cobblestone-like pattern may extend dorsally and distally. Oral leukoplakia has been reported, and sparse eyelashes may predispose patients to conjunctivitis and blepharitis. Histologically, the palmoplantar skin shows orthokeratosis with a normal granular layer. In papular lesions, eccrine syringofibroadenomatosis may be present, characterized by proliferation of ductal structures within a fibrovascular stroma [12, 13].

Epidermolysis bullosa (EB) is a group of inherited disorders characterized by increased mechanical fragility of the skin and blister formation. EB may be hereditary or acquired; the following discussion focuses on selected hereditary subtypes. Mutations in the COL7A1 gene, which encodes type VII collagen, cause both dominant and recessive forms of dystrophic EB. Type VII collagen is a key component of anchoring fibrils; thus, tissue separation occurs just below the lamina densa. The resulting blisters tend to heal with scarring. In severe recessive dystrophic EB, mutations introduce premature stop codons, leading to complete absence of type VII collagen and anchoring fibrils. Milder forms are associated with missense mutations in one or both COL7A1 alleles, resulting in anchoring fibril dysfunction rather than absence. Mutations in COL17A1, which encodes the $\alpha 1$ chain of type XVII collagen—a homotrimeric transmembrane collagen located within the hemidesmosome-anchoring filament complex of basal keratinocytes—can cause junctional EB. This recessive EB subtype is characterized by separation within the lamina lucida of the basement membrane. Patients with two null COL17A1 alleles typically present with widespread blistering, whereas those with missense mutations that partially preserve type XVII collagen function exhibit milder clinical pheno-

types. Laminin 332, a major structural component of the lamina densa, mediates epidermal adhesion by linking $\alpha 6 \beta 4$ integrin at the cell surface to anchoring fibrils composed of type VII collagen. Mutations in any of the genes encoding its three polypeptide chains can also cause junctional EB. The most severe form results from complete absence of laminin 332 in the skin [1, 2, 13].

26.2 Infectious Diseases of Skin

26.2.1 Introduction

The skin, as the body's largest organ and primary physical barrier, is constantly exposed to a wide range of microorganisms including bacteria, viruses, fungi, and parasites. Most of these organisms are harmless commensals; however, under certain conditions, they can cause infection. Cutaneous infections may be limited to epidermis or dermis, or they may extend into deeper tissues and systemic circulation. Clinical and histopathological spectrum of infectious skin diseases is broad, ranging from superficial bacterial impetigo to chronic granulomatous infections such as cutaneous tuberculosis or leprosy. Viral infections like molluscum contagiosum and verruca vulgaris, fungal infections including dermatophytosis and candidiasis, and parasitic infestations such as leishmaniasis represent other major categories.

Understanding the etiologic agents, mechanisms of transmission, and characteristic microscopic features is essential for accurate diagnosis and appropriate treatment. Recognition of specific histopathologic patterns—such as necrosis, granulomatous inflammation, viral cytopathic changes, or fungal hyphae—plays a critical role in the differential diagnosis of skin infections.

Staphylococcal scalded skin syndrome (SSSS) is most seen in children under 5 years of age and is caused by exfoliative toxins of *Staphylococcus aureus* phage group II, types 55 and 71, which target desmoglein 1. Clinically, there is usually an extracutaneous infectious focus such as the nose, nasopharynx, or conjunctiva. Following prodromal symptoms—fever, malaise, and irritability lasting several days—cutaneous tenderness and erythema develop. The erythema typically begins on the head and neck and in flexural areas, spreading over the entire body within 48 hours. Loose, superficial epidermal bullae that are Nikolsky sign—positive are followed by wrinkling of the skin and desquamation. Characteristic findings include periorificial radial fissuring and crusting (Fig. 26.3). Histopathology shows no bacteria in the skin; instead, there is separation within the epidermis at the level of the granular layer (subcorneal cleavage), with sparse neutrophils, a few acantholytic keratinocytes, and a sparse mixed-cell infiltrate in the dermis [14, 15].

Ecthyma gangrenosum is infectious vasculitis that causes cutaneous necrosis. It most com-



Fig. 26.3 Bullae residues in the neck, desquamation and perioral linear fissuration in staphylococcal scalded skin syndrome

monly occurs in the setting of *Pseudomonas* bacteremia, typically in neutropenic patients. However, it may also result from other bacterial pathogens such as *Escherichia coli* and *Klebsiella pneumoniae*, or from fungal organisms including *Candida*, *Mucor*, and *Fusarium*. Clinically, it usually begins as a small number of erythematous or purpuric macules, most often located in the anogenital region or on the lower extremities. These lesions subsequently evolve into hemorrhagic vesicles or bullae, which rupture to form necrotic ulcers with a central black eschar. When the diagnosis is suspected, a skin lesion biopsy and tissue culture—along with blood and urine cultures—should be obtained. Histopathologic examination shows epidermal and dermal necrosis, a mixed inflammatory cell infiltrate, and necrotizing hemorrhagic vasculitis. Gram-negative bacilli or other causative organisms can be seen within the media and adventitia of deeper vessel walls, while the intima is characteristically spared [14, 15].

Necrotizing fasciitis is a life-threatening infection, most often affecting the extremities, characterized by rapidly progressive necrosis of the subcutaneous fat and fascia. Without prompt diagnosis, aggressive surgical intervention, and immediate antibiotic therapy, the condition can be fatal. It is divided into two main subtypes: Type 1, a polymicrobial form involving at least one anaerobic organism (e.g., *Bacteroides*, *Peptostreptococcus*) in addition to facultative anaerobes such as streptococci and *Enterobacteriaceae*; and Type 2, a monomicrobial form most commonly caused by group A streptococci. The skin over the affected area appears shiny and tense, with severe pain, tenderness, erythema, warmth, and swelling. Early in the course, the pain may be disproportionately severe relative to cutaneous findings. The disease progresses rapidly, with the skin changing from red and purple to a characteristic gray-blue discoloration. Hemorrhagic bullae may develop. Superficial fascial and fat necrosis can produce a foul-smelling discharge. Involvement of nerves may lead to anesthesia in the affected area. Subcutaneous tissues may feel firm and “woody” on palpation. Patients often present with fever,

chills, malaise, leukocytosis, tachycardia, and may progress to shock. When it involves the perineal and genital regions, the condition is referred to as Fournier’s gangrene. Histopathology shows vasculitis with inflammation of vessel walls, thrombosis, a mixed inflammatory infiltrate composed of neutrophils and lymphocytes, and necrosis involving the epidermis, dermis, and upper subcutaneous tissue [14, 15].

Cutaneous Anthrax The causative agent is *Bacillus anthracis*, an aerobic, spore-forming, Gram-positive bacterium, which can be transmitted to humans through contact with infected animals or their wool, hides, or carcasses. Cutaneous anthrax is the mildest form of the disease, accounting for approximately 95% of all anthrax infections. The average incubation period is about 7 days. It typically begins on an exposed site, such as the forearm or fingers, as a purpuric macule or papule. Within 48 h, a 1–3 mm vesicle surrounded by non-pitting edema develops. The vesicle ulcerates, becomes hemorrhagic, and progresses to a painless, black necrotic eschar accompanied by increasing surrounding erythema and edema. The eschar heals within 1–2 weeks without leaving a permanent scar. Pain is generally absent in this clinical presentation. Histopathology reveals spongiosis, papillary dermal edema, erythrocyte extravasation, and a superficial and deep dermal inflammatory infiltrate rich in neutrophils. The infiltrate may involve nerve structures. Advanced lesions may show extensive ulceration and coagulative necrosis. Small clusters of Gram-positive bacilli are typically present [14, 15].

Syphilis is a chronic infection primarily transmitted through sexual contact, caused by *Treponema pallidum*, and is characterized by a variety of clinical manifestations and involvement of multiple organ systems. Prenatal transmission can result in congenital syphilis. The disease is classified into primary, secondary, latent (early and late), and tertiary syphilis according to its stage. Mucocutaneous manifestations range from genital ulcers to widespread papulosquamous eruptions and granulomatous nodules [14, 16].

- *Primary syphilis* develops, on average, 21 days (range 10–90 days) after exposure, usually at the site of inoculation, most often the anogenital area, as a solitary, sharply demarcated, oval or round, painless chancre with a firm, clean base. Painless regional lymphadenopathy may be present. Even without treatment, it heals spontaneously within a few weeks without scarring. Histopathologically, the chancre shows epidermal ulceration, peripheral acanthosis, a diffuse dermal infiltrate composed of plasma cells, lymphocytes, and histiocytes, endothelial swelling and proliferation of vessels, and perivascular spirochetes, which can be demonstrated by Warthin–Starry or immunohistochemical staining.
 - *Secondary syphilis* appears 3–10 weeks after chancre onset as a result of hematogenous dissemination, with prodromal symptoms including fever, malaise, headache, sore throat, conjunctivitis, arthralgia, hepatosplenomegaly, and generalized lymphadenopathy. In addition to systemic findings, recurrent episodes of mucocutaneous disease occur. The most common clinical finding is a generalized, non-pruritic papulosquamous eruption, with lesions varying from a few millimeters to several centimeters and ranging in color from pink to violaceous or reddish-brown. Mucosal involvement is common and may present as superficial aphthous-like ulcers or large gray mucous patches. Condylomata lata, resulting from local spread of the organism, are most often seen in the anogenital region and other moist areas. Lymphadenopathy frequently accompanies the lesions. Other cutaneous findings include annular or figurate plaques with central hyperpigmentation (often on the face), moth-eaten alopecia, angular cheilitis, papules at the oral commissures, granulomatous nodules, and plaques. Malignant syphilis (lues maligna) is rare and is characterized by disseminated ulcerative lesions resembling the primary chancre. Histopathology of secondary syphilis is variable, as in its clinical presentation. The epidermis may be normal, psoriasiform, necrotic, or ulcerated. The dermis contains a perivascular, lichenoid, nodular, or diffuse infiltrate composed of plasma cells, lymphocytes, and histiocytes; advanced lesions may be granulomatous and resemble sarcoidosis or other granulomatous dermatoses. Endothelial swelling and vascular proliferation may be seen, and spirochetes can be demonstrated. Vasculitis is present in lues maligna. In syphilitic alopecia, there is a peribulbar inflammatory infiltrate rich in plasma cells, resembling alopecia areata. After a period of 3–12 weeks, untreated secondary syphilis usually resolves spontaneously, and the patient becomes asymptomatic. The diagnosis of *latent syphilis* is made when serologic tests for syphilis are positive in the absence of clinical evidence of treponemal infection. The early latent stage, defined (according to the CDC's temporal definition) as within 1 year from the onset of latency, carries a risk of recurrence; approximately 90% of secondary relapses occur within the first year. The late latent stage refers to latency beyond 1 year, during which relapses are uncommon. This stage may last for months or years.
 - *Tertiary syphilis*, now rare, develops months or even years after the initial infection and is characterized by variable manifestations involving the skin, bones, central nervous system, heart, and large vessels. Approximately half of patients with tertiary syphilis develop “benign” late syphilis with gumma formation; about one-quarter develop cardiovascular symptoms, and one-quarter develop neurological symptoms. In tertiary syphilis, non-treponemal serologic tests are generally positive at high titers. Patients with tertiary syphilis should undergo lumbar puncture and cerebrospinal fluid analysis to determine the presence of neurosyphilis before initiating treatment. Histopathology shows tuberculoid granulomas with or without caseation, accompanied by plasma cell infiltrates; endothelial swelling may be present, but spirochetes are generally not seen.
- Molluscum contagiosum* is the most common poxvirus infection in humans. In children, it is a

self-limiting condition, whereas in adults it can present as a sexually transmitted disease. Transmission occurs primarily through direct skin-to-skin contact, although, rarely, fomites may serve as a vehicle. Clinically, lesions can develop anywhere on the skin but are most commonly found in intertriginous areas such as the axillae and neck folds, as well as on the lateral trunk, thighs, buttocks, and genital region. They present as umbilicated papules with a waxy surface. Widespread, large, and sometimes disfiguring lesions may occur in immunocompromised individuals, particularly those with AIDS. In children with atopic dermatitis, an associated molluscum dermatitis is common. When lesions display a pustular or furuncle-like inflammatory appearance, this is indicative of a developing host immune response. Histopathology shows a crateriform architecture filled with squamous epithelium. Above the basal layer, keratinocytes contain large intracytoplasmic inclusion bodies—known as molluscum bodies or Henderson–Patterson bodies—which displace the nucleus and cytoplasmic granules to the periphery (Fig. 26.4). A dermal inflammatory infiltrate of variable density, sometimes with pseudolymphomatous features, may also be observed [17].

Verruca vulgaris (common wart) is a common benign skin lesion caused by the human papillomavirus (HPV), most frequently types 1, 2, 4, or 7. The virus infects the basal layer of the epidermis and induces proliferation of keratinocytes. These lesions are more frequent in children and

young adults and are transmitted by direct skin contact or through contaminated objects. Clinically, common warts appear as firm, rough, hyperkeratotic papules or nodules. They are usually located on hands, fingers, or knees. On histopathology, there is epidermal hyperplasia, papillomatosis, hyperkeratosis, and koilocytosis in the upper layers (Fig. 26.5). Diagnosis is clinical in most cases, and spontaneous regression can occur. Treatment options include topical salicylic acid, cryotherapy, or immunomodulators such as imiquimod [17].

Cutaneous leishmaniasis is a parasitic skin disease caused by an obligate intracellular protozoan transmitted by the bite of an infected female sandfly. The organisms reside within the phagolysosomes of mononuclear phagocytes and produce a chronic clinical course. The disease is distributed worldwide but is endemic in Latin America, the Mediterranean basin, and parts of Asia and Africa. Most individuals remain asymptomatic and develop lasting immunity. The clinical manifestations of the cutaneous form depend on the host's cell-mediated immune response and the infecting *Leishmania* species. Clinical variants include cutaneous, disseminated cutaneous, diffuse cutaneous, mucocutaneous/mucosal, and visceral leishmaniasis. The most common cutaneous presentation is the classic ulcer, which develops after an incubation period of 2–8 months, beginning as an acneiform papule at the site of the bite—usually located on exposed, visible skin areas—and gradually evolving into a typically painless ulcer with a firmly adherent crust. Removal of the crust reveals the “nail sign.” The most frequent cutaneous type is the dry or anthroponotic form. In the zoonotic form of cutaneous leishmaniasis, a shorter incubation period is followed by rapid ulceration with marked inflammation (Fig. 26.6). Another cutaneous variant, leishmaniasis recidivans, is characterized by new papulonodular lesions arising around the scar 6–18 months after apparent healing. Histopathology shows a massive dermal granulomatous infiltrate composed of lymphocytes, histiocytes, multinucleated giant cells, plasma cells, and neutrophils;

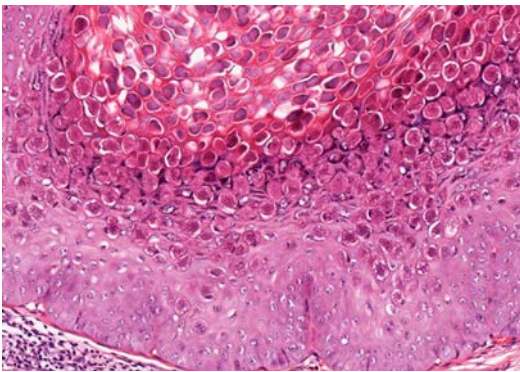


Fig. 26.4 Molluscum or Henderson–Patterson bodies in molluscum contagiosum

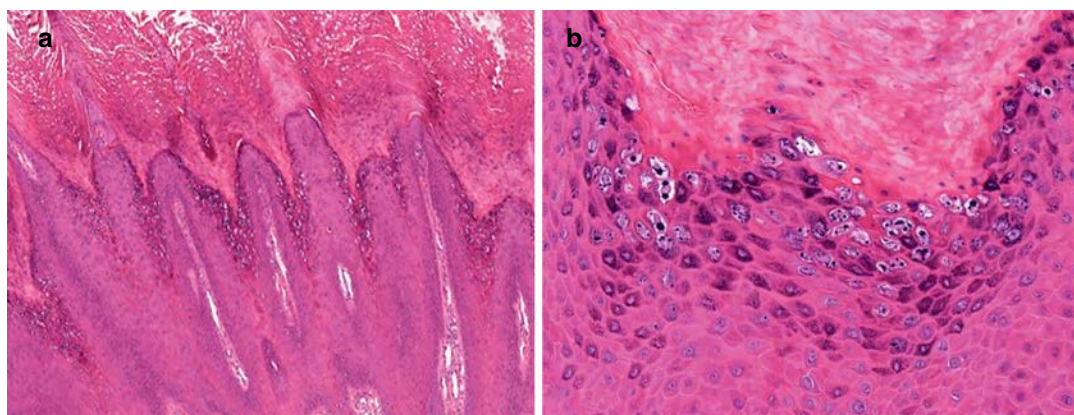


Fig. 26.5 (a) Typical papillomatosis and hyperkeratosis in a wart. (b) Koilocytosis in the upper layers

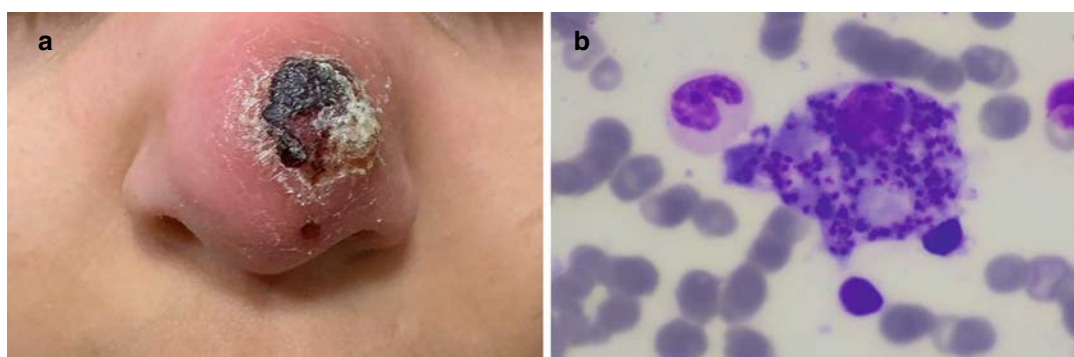


Fig. 26.6 (a) Ulcer with thick crust observed on erythematous inflammatory base on the dorsum of the nose in zoonotic leishmaniasis. (b) Numerous amastigotes are

visualized within histiocytes in blood smear of a patient with visceral leishmaniasis

pseudoepitheliomatous hyperplasia; and small tuberculoid granulomas. Amastigotes with kinetoplasts appear as intracellular bodies within dermal macrophages. The kinetoplast is seen as an oval body near the nucleus, functioning as a mitochondrial structure with its own DNA. The amastigotes are usually found within histiocytes and can be visualized on H&E stains but are best demonstrated with Giemsa staining. Peripheral localization of the organisms within macrophages produces the so-called marquee sign. Over time, the lesions show an increasing number of giant cells and fewer parasites; in long-standing cutaneous leishmaniasis, tuberculoid granulomas with caseous necrosis may be observed. In the cicatricial stage, the epidermis becomes flattened, and the dermis develops fibrotic areas with hyperpigmentation [18].

Cutaneous tuberculosis is a rare form of extrapulmonary tuberculosis caused by *Mycobacterium tuberculosis* or occasionally *Mycobacterium bovis*. Infection may result from direct inoculation, spread from an underlying focus, or hematogenous dissemination. It occurs more frequently in individuals with prior sensitization to tuberculosis or immunosuppression. Diagnosis is based on skin biopsy, showing granulomatous inflammation with epithelioid histiocytes, Langhans-type giant cells, and caseous necrosis (Fig. 26.7a). Mycobacteria can be demonstrated by Ziehl–Neelsen stain or PCR. Treatment follows standard antituberculous regimens (isoniazid, rifampicin, ethambutol, pyrazinamide). Clinical forms include lupus vulgaris, tuberculosis verrucosa cutis, and scrofuloderma [19].

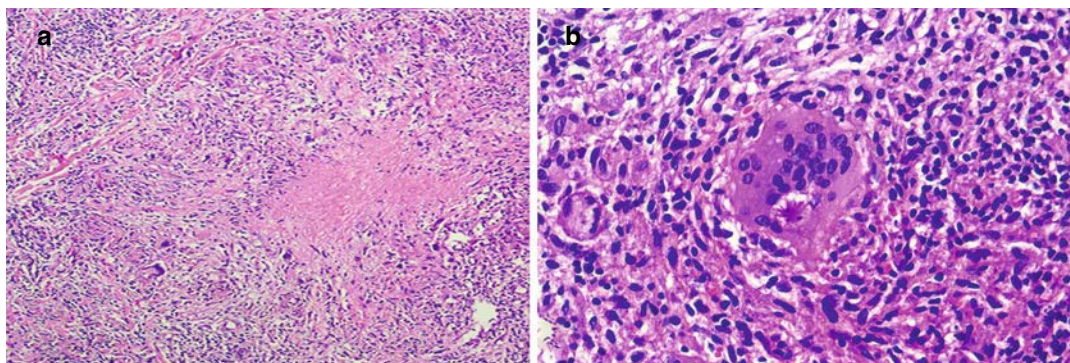


Fig. 26.7 (a) Irregular granulomas with giant cells and caseous necrosis in a patient with lupus vulgaris. (b) Foreign-body type giant cell with Schaumann body in a patient with cutaneous sarcoidosis

- *Lupus vulgaris* presents as slowly enlarging reddish-brown plaques, often on the head and neck.
- *Tuberculosis verrucosa cutis* develops in previously sensitized individuals after inoculation, leading to warty plaques on the hands or feet.
- *Scrofuloderma* occurs when tuberculosis spreads from deeper structures such as lymph nodes to the skin, forming ulcerated nodules and sinus tracts.

Cutaneous sarcoidosis is also characterized by presences of granulomas similar cutaneous tuberculosis. Both are granulomatous diseases characterized by collections of epithelioid histiocytes and giant cells. However, there are several histopathological differences between tuberculosis and sarcoidosis granulomas (Table 26.2). In summary, while both diseases present with epithelioid granulomas, the presence of caseous necrosis and acid-fast bacilli are diagnostic clues for tuberculosis. Sarcoid granulomas, on the other hand, are noncaseating and well-formed and often show characteristic inclusions in the Langhans or foreign-body type giant cells (Fig. 26.7b). Correlation with clinical, radiological, and microbiological findings is essential for definitive diagnosis [20].

Table 26.2 Differential histopathological features of tuberculosis and sarcoidosis

Feature	Tuberculosis	Sarcoidosis
Etiology	<i>Mycobacterium tuberculosis</i> infection	Unknown, likely immune-mediated
Necrosis	Present (caseating)	Absent (noncaseating)
Granuloma structure	Irregular, with necrotic center	Compact, well-formed, sharply demarcated
Giant cells	Langhans type, bacilli may be present	Langhans or foreign-body type, with Schaumann/asteroid bodies
Lymphocytic rim	Prominent, often mixed with plasma cells	Sparse, peripheral
Special stains	Positive for AFB (Ziehl–Neelsen, auramine)	Negative for AFB
Fibrosis	May accompany healing or fibrosis after necrosis	Often develops in chronic lesions

References

1. Johnston RB. Disorders of epidermal maturation and keratinization. In: Johnston RB, editor. *Weedon's skin pathology essentials*. 2nd ed. China: Elsevier; 2017. p. 196–221.
2. Rapini RP. Some genodermatoses. In: Rapini RP, editor. *Practical dermatopathology*. 2nd ed. Beijing: Elsevier; 2012. p. 159–66.
3. Richard G. Ichtyoses, erythrokeratodermas, and related disorders. In: Bologna JL, Schaffer JV, Cerroni L, editors. *Dermatology*. 5th ed. Philadelphia: Elsevier; 2022. p. 894–930.
4. Metze D, Sübmuth K, Oji V. Palmoplantar keratodermas. In: Bologna JL, Schaffer JV, Cerroni L, editors. *Dermatology*. 5th ed. Philadelphia: Elsevier; 2022. p. 931–50.
5. Mozzillo N, Nunziata CA, Caraco C, et al. Malignant melanoma developing in an area of hereditary palmoplantar keratoderma (Mal de Meleda). *J Surg Oncol*. 2003;84:229–33.
6. Hamm H, Traupe H, Bocker EB, et al. The scleroderma-like syndrome of Huriez: a cancer-prone genodermatosis. *Br J Dermatol*. 1996;134:512–8.
7. Dessureault J, Poulin Y, Bourcier M, et al. Olmsted syndrome-palmoplantar and periorificial keratodermas: association with malignant melanoma. *J Cutan Med Surg*. 2003;7:236–42.
8. Tsao H, Luo S. Neurofibromatosis and tuberous sclerosis complex. In: Bologna JL, Schaffer JV, Cerroni L, editors. *Dermatology*. 5th ed. Philadelphia: Elsevier; 2022. p. 992–1011.
9. Legius E, Messiaen L, Wolkenstein P, et al. Revised diagnostic criteria for neurofibromatosis type 1 and Legius syndrome: an international consensus recommendation. *Genet Med*. 2021;23:1506–13.
10. Bayliss SJ, Kumar MG, Hernández-Martín Á, Cohen BA, Martínez-Menchón T, Guillén-Navarro E, Sybert VP. Other genodermatoses. In: Bologna JL, Schaffer JV, Cerroni L, editors. *Dermatology*. 5th ed. Philadelphia: Elsevier; 2022. p. 1035–66.
11. Lim HW, Rosen CF. Photodermatological disorders. In: Bologna JL, Schaffer JV, Cerroni L, editors. *Dermatology*. 5th ed. Philadelphia: Elsevier; 2022. p. 1564–84.
12. Kittler NW, Howard RM, Frieden IJ. Vesiculopustular and erosive disorders in newborns and infants. In: Bologna JL, Schaffer JV, Cerroni L, editors. *Dermatology*. 5th ed. Philadelphia: Elsevier; 2022. p. 568–685.
13. Nyström A, Bruckner-Tuderman L. Biology of the extracellular matrix. In: Bologna JL, Schaffer JV, Cerroni L, editors. *Dermatology*. 5th ed. Philadelphia: Elsevier; 2022. p. 1692–706.
14. Johnston RB. Bacterial and rickettsial infections. In: Johnston RB, editor. *Weedon's skin pathology essentials*. 2nd ed. Beijing: Elsevier; 2017. p. 404–31.
15. Rapini RP. Bacterial diseases. In: Rapini RP, editor. *Practical dermatopathology*. 2nd ed. Beijing: Elsevier; 2012. p. 167–86.
16. Johnston RB. Spirochetal infections. In: Johnston RB, editor. *Weedon's skin pathology essentials*. 2nd ed. Beijing: Elsevier; 2017. p. 433–7.
17. Rapini RP. Viral, rickettsial, and chlamydial diseases. In: Rapini RP, editor. *Practical dermatopathology*. 2nd ed. Beijing: Elsevier; 2012. p. 207–17.
18. Rapini RP. Parasitic diseases. In: Rapini RP, editor. *Practical dermatopathology*. 2nd ed. Beijing: Elsevier; 2012. p. 219–29.
19. Nguyen KH, Alcantara CA, Glassman I, May N, Mundra A, Mukundan A, Urness B, Yoon S, Sakaki R, Dayal S, et al. Cutaneous manifestations of *Mycobacterium tuberculosis*: a literature review. *Pathogens*. 2023;12(7):920. <https://doi.org/10.3390/pathogens12070920>.
20. Judson MA. The clinical features of sarcoidosis: a comprehensive review. *Clin Rev Allergy Immunol*. 2015;49(1):63–78. <https://doi.org/10.1007/s12016-014-8450-y>.

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27.1 Introduction

Noninflammatory dermatoses encompass a broad spectrum of diseases that affect the skin, its appendages, and the mucocutaneous interface. The skin, as the largest organ of the body, exhibits a limited number of morphological reaction patterns to various internal and external stimuli. Therefore, diverse etiologic factors—such as genetic defects, immune-mediated processes, infections, metabolic alterations, or environmental exposures—may produce overlapping clinical and histopathologic manifestations. Understanding the basic structural organization of the epidermis, dermoepidermal junction, and dermis is crucial for interpreting these patterns. Dermatoses are classified according to the predominant tissue response or the elementary lesion that reflects the underlying pathogenic mechanism. For example, acanthosis and hyperkeratosis indicate epidermal proliferation; vacuolar alteration and necrotic keratinocytes reflect

interface injury; and spongiosis signifies intercellular edema within the epidermis. Similarly, dermal and subepidermal changes such as fibrosis, granulomatous inflammation, or vascular injury contribute to the overall diagnostic pattern. Accurate interpretation of these reaction patterns requires clinicopathologic correlation, as many dermatoses share similar microscopic appearances. Ancillary diagnostic tools—including special stains, immunofluorescence, and molecular analyses—have refined classification and differential diagnosis. This chapter aims to outline the fundamental pathological principles, structural alterations, and diagnostic approach to dermatoses, serving as a bridge between clinical dermatology and histopathologic interpretation [1–3].

27.2 Dermatoses with Epidermal Hyperplasia (Psoriasiform Hyperplasia)

Psoriasis is the prototype of disorders characterized by epidermal hyperplasia, also known as acanthosis, and is among the most common dermatoses. The epidermal changes seen in hyperplastic disorders are, in fact, referred to as *psoriasiform hyperplasia*. This type of hyperplasia describes lesions in which elongation of the rete ridges is observed [2, 3].

1. *Psoriasis* affects approximately 2% of the global population and can occur at any age,

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with peaks in incidence during the third decade (20–30 years) and the fifth to sixth decades (50–60 years) of life. Up to 20%–30% of patients develop psoriatic arthritis. Moreover, patients with moderate-to-severe psoriasis are at relatively increased risk for metabolic syndrome, atherosclerotic cardiovascular disease, and depression. Familial aggregation is common, with 30%–40% of patients having a first-degree relative affected by psoriasis. More than 50 genetic loci have been identified that confer susceptibility to psoriasis, most of which are involved in immune response regulation, while some affect keratinocyte proliferation and differentiation (psoriasis susceptibility genes PSORS1–12). The most significant of these is HLA-Cw*0602, located within the major histocompatibility complex (MHC) region on chromosome 6p21.3. Although psoriasis was once considered a primary keratinization disorder, it is now recognized as an immune-mediated disease, driven particularly by dysregulation of the Th17/IL-23 axis. A substantial proportion of immune-activating mediators are produced by keratinocytes and dendritic cells (DCs), highlighting the dynamic cross talk between the skin and the immune system in disease pathogenesis. In genetically predisposed individuals, triggers such as trauma, infections, or drugs can damage keratinocytes, leading to the release of autoantigens such as LL37. LL37, one of the best-characterized autoantigens, forms complexes with pathogen-derived DNA or self-DNA from damaged keratinocytes, which activate TLR9 on plasmacytoid DCs. This activation results in the production of IFN- α , which, together with TNF- α , IL-6, and IL-1 β , promotes activation of myeloid DCs (mDCs). Activated mDCs produce IL-12, TNF- α , and IL-23, which drive the differentiation of Th17 cells and amplify their secretion of IL-17. Effector Th17 cells subsequently release IL-17, IL-22, and IL-36, which stimulate keratinocytes to produce antimicrobial peptides (AMPs) and chemokines, perpetuating inflammation and promoting keratinocyte hyperproliferation [2–5].

- *Chronic plaque psoriasis* is characterized by sharply demarcated, erythematous, scaly plaques, typically located symmetrically on the knees, elbows, scalp, lumbosacral region, and extensor surfaces of the extremities. Genital involvement is also common. The “wax spot phenomenon” refers to the appearance of silvery-white scales that detach in fragments when a psoriatic plaque is gently scraped with a blunt scalpel. The “last cuticle phenomenon” describes the presence of an adherent scale at the base of the lesion after removal of superficial scales. The Auspitz sign is characterized by pinpoint bleeding upon scraping a psoriatic plaque, caused by transection of dilated capillaries in the tips of dermal papillae. However, this sign is not specific and may also be positive in other papillary dermatoses with papillomatosis. Additionally, the Koebner phenomenon, in which new typical psoriatic lesions develop at sites of trauma on uninvolved skin, is frequently observed [2–5].
- *Guttate psoriasis* usually develops in children and adolescents following an upper respiratory tract infection, most often streptococcal. It is characterized by numerous, monomorphic, droplet-shaped papules, 1–10 mm in diameter, salmon-pink to erythematous in color, with fine overlying scaling, distributed on the trunk and extremities.
- *Erythrodermic psoriasis* is a relatively rare but severe form, presenting with erythema, scaling, exudation, and exfoliation involving more than 90% of the body surface area. Palmoplantar keratoderma and nail involvement may be present.
- *Generalized pustular psoriasis* is characterized by the acute onset of fever and the appearance of numerous, sterile, 2–3 mm pustules on an erythematous base, predominantly on the trunk and proximal extremities. The pustules are superficial and may coalesce to form “lakes of pus.” They resolve rapidly, leaving annular scaly patches. When occurring during pregnancy, this condition is termed *impetigo herpetiformis*.
- *Palmoplantar pustular psoriasis* is restricted to the palms and soles and presents with ster-

ile pustules intermingled with yellow-brown macules, as well as erythematous, scaly plaques. Psoriasis can also involve the scalp, retroauricular folds, intergluteal cleft, inguinal folds, axillae, inframammary areas, as well as the genital region and nails. Nail disease may affect the matrix, nail bed, or hyponychium. Small parakeratotic foci in the proximal matrix lead to pitting. Involvement of the mid-matrix results in leukonychia. When the entire matrix is affected, the nail becomes white, friable, and crumbling. Nail bed involvement produces oil-drop (salmon patch) discoloration, reflecting leukocyte exocytosis beneath the nail plate. Other nail findings include splinter hemorrhages, subungual hyperkeratosis, and distal onycholysis (Fig. 27.1).

In a newly developed psoriatic lesion, the histopathological features are not yet diagnostic. The dermis shows papillary edema and dilated capillaries, accompanied by a superficial perivascular lymphohistiocytic infiltrate. In acute eruptive guttate lesions, there is mild epidermal acanthosis without parakeratosis, along with keratinocyte swelling and evidence of mast cell

degranulation. In a fully developed guttate lesion or in a biopsy taken from the active marginal zone of an enlarging psoriatic plaque, diagnostic findings become evident. These include increased and dilated, tortuous capillaries in the papillary dermis that extend close to the epidermal surface, edema in the dermal papillae, and a mixed perivascular infiltrate composed of lymphocytes, histiocytes, and neutrophils. Over these foci, the granular layer is absent and parakeratosis is present. There is marked acanthosis with elongation of the rete ridges. Accumulation of neutrophils within an intraepidermal spongiotic pustule is termed Kogoj's spongiform pustule, while the presence of neutrophils and/or neutrophil remnants within the parakeratotic stratum corneum is referred to as a Munro microabscess (Fig. 27.2). Spongiosis may be observed in early-stage lesions, guttate psoriasis, erythrodermic psoriasis, inverse psoriasis, and palmoplantar psoriasis. However, this finding can complicate the differential diagnosis with other dermatoses that display a similar histopathological pattern. Histopathological features that favor a diagnosis of psoriasis include the pattern of capillaries in the papillary dermis, the presence of neutrophil

Fig. 27.1 Examples of chronic plaque psoriasis accompanied by nail involvement



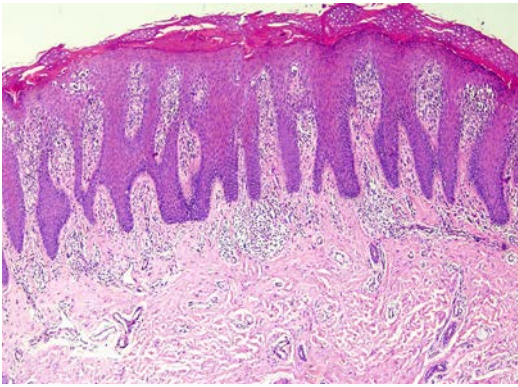


Fig. 27.2 Diffuse parakeratosis, regular acanthosis, elongation of dermal papillae, tortuous capillaries in the papillary dermis, and perivascular lymphocytic infiltration

aggregates in the epidermis, and club-shaped rete ridges with thinning of the suprapapillary plates. In pustular psoriasis, neutrophil accumulation is the predominant feature, whereas acanthosis and hyperkeratosis are less pronounced [2–5].

2. *Pityriasis rosea*

Pityriasis rosea is a papulosquamous eruption that typically occurs in adolescents and young adults, with a higher incidence during the spring season. It may occasionally be accompanied by pruritus and resolves spontaneously within 6–8 weeks. Although the exact etiology of pityriasis rosea remains unclear, human herpesvirus 7 (HHV-7) and, to a lesser extent, HHV-6 have been implicated. In more than half of classic cases, the disease begins with a solitary herald lesion, referred to as a herald patch or medallion lesion, which is usually located on the trunk. This lesion appears as a salmon-colored, pink-brown patch or plaque with a slightly elevated border. Fine scales are present in the center, whereas the periphery exhibits collarette-type scaling. Within days, numerous smaller papules and plaques resembling the herald lesion develop on the trunk and proximal extremities. These lesions are generally round or oval in shape, with their long axes aligned along the Langer lines. On the back, this distribution pattern creates the so-called “Christmas tree” appearance (Fig. 27.3). Histopathological examination reveals spongi-



Fig. 27.3 Salmon pink papules parallel to Langer’s lines, some with annular scales

otic dermatitis, elongation of the rete ridges, focal parakeratosis, mild acanthosis, and widening of the dermal papillae. Perivascular lymphocytes are observed, and eosinophils are occasionally present. In some cases, focal extravasation of erythrocytes may be seen [6, 7].

3. *Pityriasis lichenoides*

Pityriasis lichenoides is a rare disorder comprising two subtypes: *pityriasis lichenoides et varioliformis acuta* (PLEVA) and *pityriasis lichenoides chronica* (PLC). Although its etiology remains unknown, it is thought to represent a response to foreign antigens such as infectious agents and drugs. In both subtypes, T-cell infiltrates with demonstrable clonality may be observed. The consideration of pityriasis lichenoides as a T-cell lymphoproliferative disorder may help explain its relationship to other lymphoproliferative diseases such as mycosis fungoides. Because differentiation from T-cell lymphomas can sometimes be challenging, patients with pityriasis lichenoides and an abnormal T-cell phenotype should be followed long term. Clinically, pityriasis lichenoides is charac-

terized by recurrent, erythematous, purpuric papules that may spontaneously regress. In many patients, acute and chronic manifestations may occur sequentially or simultaneously. PLEVA lesions are typically ulcerated, sometimes accompanied by vesicles or pustules, and crusting. Systemic findings such as malaise, fever, lymphadenopathy, and arthritis may occur. The term *febrile ulceronecrotic Mucha–Habermann disease* has been used to describe severe variants with large, confluent necrotic skin lesions and possible mucosal, gastrointestinal, and pulmonary involvement. PLC presents with erythematous, red-brown, scaly papules. Postinflammatory hypopigmented macules may develop. The disease tends to regress more slowly over weeks to months and may follow a recurrent course with prolonged remission periods. Histopathologically, superficial, perivascular interface dermatitis is observed. In PLEVA, there is a dense, wedge-shaped lymphocytic infiltrate, often involving both follicular and eccrine adnexal epithelium. Neutrophils may also be present. The epidermis shows parakeratosis and, in well-developed lesions, damage ranging from edema to widespread epidermal necrosis. Extravasation of erythrocytes is a common finding. While a perivascular lymphocytic infiltrate is a consistent feature, true lymphocytic vasculitis with fibrinoid necrosis of the vessel walls is rare and only occasionally seen in PLEVA. In PLC, histology reveals a milder lymphocytic interface dermatitis with parakeratosis, focal keratinocyte necrosis, and mild erythrocyte extravasation [6, 7].

4. Parapsoriasis

Parapsoriasis encompasses two entities: small-plaque and large-plaque parapsoriasis. However, the exact nosology of large-plaque parapsoriasis remains controversial. Some authors consider it a distinct entity or a potential precursor of mycosis fungoides (MF), whereas many authorities in the field of cutaneous lymphomas regard it as an early stage of MF. Clinical morphology and lesion distribution are similar to early MF, and the histopathological features of untreated lesions may be indistinguishable from

those of MF. Small-plaque parapsoriasis, despite the use of the term “plaque” in its nomenclature, is clinically characterized by chronic, usually asymptomatic, thin scaly patches. Although the course may initially fluctuate, it often becomes chronic and progressive over time. Lesions may be presented diffusely on the trunk and extremities or in a more localized distribution on sun-protected areas. Small-plaque parapsoriasis typically manifests as thin, scaly, round-to-oval patches less than 5 cm in diameter with variable degrees of erythema. When accompanied by long, finger-like patches symmetrically distributed on the lateral trunk, the clinical presentation is referred to as “digitate dermatosis.” Histopathological features include focal parakeratosis, occasional epidermal atrophy, acanthosis, spongiosis, focal basal layer liquefaction, perivascular lymphocytic infiltrates, and erythrocyte extravasation [6, 7].

5. Pityriasis rubra pilaris

Pityriasis rubra pilaris (PRP) may be hereditary due to CARD14 mutations, but infections, UV exposure, minor cutaneous trauma, autoimmunity, or abnormal immunologic responses to specific antigens may also play a role in its etiology. The classic clinical features of PRP are papules on an erythematous background, accompanied by follicular hyperkeratosis. These papules may coalesce on the trunk and extremities to form plaques ranging in color from salmon to orange-red. Between plaques, areas of normal skin may be seen as “islands of sparing.” Erythroderma can develop. Palmoplantar involvement may present as orange-red, waxy keratoderma. On the scalp, fine scaly erythema may mimic seborrheic dermatitis. Nail changes include subungual hyperkeratosis and yellow-brown discoloration. PRP is classified according to age of onset, disease duration, and extent of skin involvement [6, 7]:

- Type I (classic adult) is the most common form, typically self-limited within 3 years.
- Type II (atypical adult) is characterized by a prolonged clinical course, often with thick

ichthyosiform scaly plaques predominantly on the lower extremities.

- Type III (classic juvenile) resembles the classic adult form.
- Type IV (circumscribed juvenile) is the most common juvenile form, presenting with focal lesions.
- Type V (atypical juvenile) is frequently associated with CARD14 mutations; resembles the atypical adult type, but with more prominent ichthyosiform desquamation.
- Type VI is associated with HIV infection, often accompanied by nodulocystic lesions of acne conglobata and hidradenitis suppurativa.

Histopathology shows alternating vertical and horizontal ortho- and parakeratosis, producing a characteristic “checkerboard pattern,” along with a psoriasiform dermatitis. There is irregular hyperkeratosis. Hair follicles appear dilated and filled with a keratinous plug, with shoulder parakeratosis surrounding the follicular ostia. The dermis shows a sparse perivascular lymphohistiocytic infiltrate, occasionally admixed with eosinophils and plasma cells. Important histopathological clues that distinguish pityriasis rubra pilaris (PRP) from psoriasis include the presence of short and broad-based rete ridges and thickening of the suprapapillary plates. Acantholysis and focal acantholytic dyskeratosis in the epidermis have also been described and may aid in distinguishing PRP from psoriasis [6, 7].

6. *Chronic allergic dermatitis* and *contact dermatitis* share overlapping clinical and histopathologic features, yet they differ in pathogenesis and primary mechanisms. Chronic allergic dermatitis is an immune-mediated condition that develops as a delayed-type (type IV) hypersensitivity reaction following prolonged or repeated exposure to allergens such as metals, plants, or cosmetics. Contact dermatitis may arise through similar allergic mechanisms or as an irritant reaction caused by direct toxic injury

to keratinocytes. In both, acute lesions show spongiosis, epidermal edema, and a perivascular lymphocytic infiltrate, while chronic lesions evolve toward epidermal hyperplasia, hyperkeratosis, parakeratosis, and dermal fibrosis, often accompanied by persistent pruritus (Fig. 27.4a), especially chronic lesions histopathologically similar to psoriasis vulgaris. In contrast, lichen simplex chronicus is not primarily an inflammatory or allergic disease but a reactive epidermal hyperplasia secondary to chronic scratching or rubbing. Thus, while chronic allergic and contact dermatitis are primary inflammatory dermatoses driven by immune or irritant mechanisms, lichen simplex chronicus reflects a secondary morphological response to mechanical injury. Recognizing this distinction is essential for accurate histopathologic interpretation and targeted management [6, 7].

7. *Lichen simplex chronicus (LCS)* is a chronic condition, typically seen in adults, characterized by epidermal hypertrophy and lichenification that gives the skin a leathery appearance, resulting from habitual rubbing or scratching. Clinically, it presents plaques, coalescing papules, hyperpigmentation, and varying degrees of erythema. Lesions may be solitary or multiple and are most frequently located on the posterolateral neck, nape, anogenital region, shins, ankles, and the dorsal aspects of the hands, feet, and forearms. Predisposing factors include xerosis, atopy, psoriasis, stasis dermatitis, anxiety, obsessive-compulsive disorder, localized neuropathic pruritus, and pruritus associated with systemic diseases. Histopathological features of LSC include compact hyperkeratosis, irregular acanthosis with elongation of the rete ridges, hypergranulosis, and vertically oriented collagen bundles in the papillary dermis (Fig. 27.4b). A perivascular lymphocytic infiltrate is observed, and, occasionally, multinucleated fibroblasts known as Montgomery giant cells may be present [6, 7].

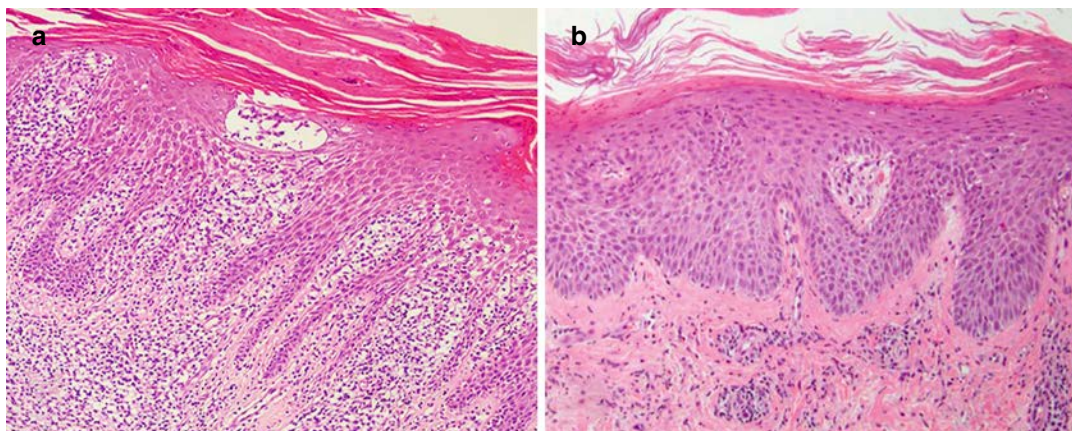


Fig. 27.4 (a) Chronic allergic dermatitis. (b) Lichen simplex chronicus

27.3 Interface Dermatitis

Interface dermatitis generally represents a group of disorders characterized by vacuolar changes in basal keratinocytes and associated band-like mononuclear cell infiltration in the upper and middle dermis. Some entities characterized by interphase dermatitis are discussed here.

1. *Lichen planus*

The prevalence of lichen planus (LP) varies across geographic regions, but it is estimated to affect approximately 1% of the general population. Most cases occur between 30 and 60 years of age. Oral mucosal involvement is observed in nearly three-quarters of patients with cutaneous LP and may occasionally represent the sole manifestation. LP is primarily a T cell-mediated immunological disorder. In this process, keratinocytes display antigens that are perceived as foreign or abnormal (e.g., drug metabolites, viral proteins, autoantigens). Among potential exogenous antigens, viruses—particularly hepatitis C virus—have received considerable attention for their possible role. Although numerous case reports have described patients with both LP and autoimmune diseases, larger cohort studies have not demonstrated an increased incidence of auto-

immunity in LP patients. Certain HLA antigens (e.g., HLA-DR1, -DR6, -DR9) have been reported to show significant associations with LP. There are conflicting data regarding the phenotype of the inflammatory infiltrate in LP lesions. Early immunohistochemical studies suggested an increased CD4+/CD8+ T-cell ratio, whereas more recent studies—especially in older lesions—have shown CD8+ T cells to be predominant. CD8+ T cells isolated from lesional skin were found to exhibit specific cytotoxic activity against both lesional and normal keratinocytes. The characteristic primary lesion of LP is an intensely pruritic, small, polygonal, violaceous, flat-topped papule, most frequently localized on the flexor wrists, forearms, dorsum of the hands, tibia, and lumbosacral region (Fig. 27.5). Papules often appear shiny or translucent, and Wickham's striae—a fine network of white lines—can be observed on their surface, corresponding histologically to focal thickening of the granular layer. LP papules may be widely distributed or coalesce into larger plaques. Koebner phenomenon is typically positive. Numerous clinical variants exist, including acute exanthematous LP, actinic LP, annular LP, atrophic LP, bullous LP, linear LP, hypertrophic LP, inverse LP, pigmented LP, nail LP, oral LP, vulvovaginal LP, ulcerative LP, LP pemphigoides, and lichen planopilaris.

Despite its diverse clinical presentations, the histopathology of LP is relatively uniform. The hallmark features include compact hyperkeratosis, wedge-shaped hypergranulosis, irregular “saw-tooth” acanthosis, vacuolar degeneration of the basal layer, and a band-like lymphocytic infiltrate at the dermoepidermal junction (Fig. 27.6a). Apoptotic or dyskeratotic keratinocytes, termed colloid bodies (also known as Civatte, hyaline, or cytoid bodies), are usually found in the lower epidermis and superficial dermis. Basal cell vacuolar changes may coalesce, leading to small clefts

between the epidermis and dermis, known as Max-Joseph spaces. Pigment incontinence with dermal melanophages is commonly observed. Active lesions often show an increased number of epidermal Langerhans cells. Plasma cells, macrophages, eosinophils, and mast cells may also be present in the dermis, though less frequently. Distinguishing features from other interface dermatitis include wedge-shaped hypergranulosis and the infiltrate being located close to the epidermis. Oral LP lesions generally exhibit parakeratosis rather than hyperkeratosis, and in late stages the epithelium may become atrophic. They are more likely to present as erosive or ulcerative, and the characteristic band-like lymphocytic infiltrate is less prominent compared to cutaneous LP. Actinic LP resembles lichen planus but demonstrates more pronounced melanin incontinence and focal parakeratosis. In hypertrophic LP, epithelial hyperplasia is more prominent and may range up to pseudoepitheliomatous hyperplasia. Features of both LP and lichen simplex chronicus are present: marked hyperplasia with overlying orthokeratosis, vertically oriented collagen bundles in the papillary dermis, and basal cell damage confined to the tips of rete ridges. Atrophic LP is characterized by epidermal atrophy rather than acanthosis. Lichen planopilaris lesions in the early stage are characterized by a dense inflammatory cell infiltrate composed of lymphocytes and macrophages involving the infundibulum and isthmus of the hair follicles. In



Fig. 27.5 Purple colored, polygonal shaped papules with thin scales on the ankle and dorsum of the foot

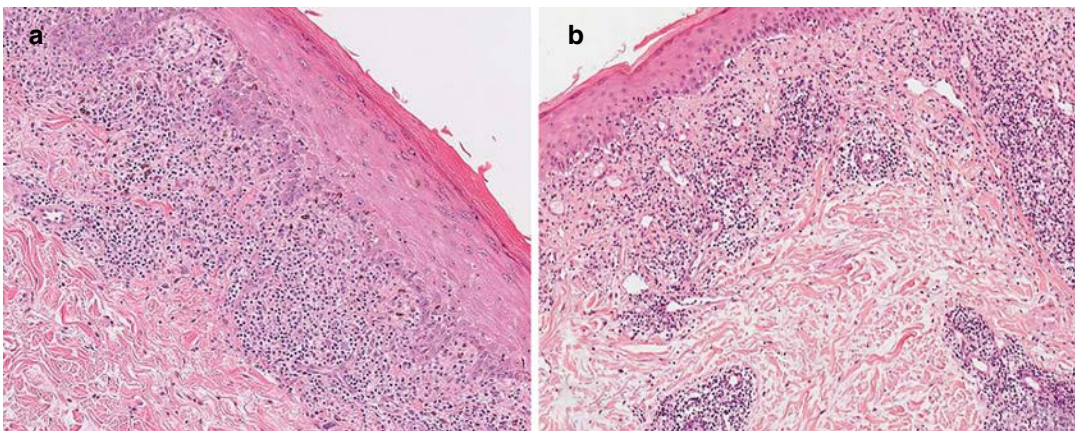


Fig. 27.6 (a) Lichen planus. (b) Discoid lupus erythematosus

later stages, fibrosis and follicular destruction occur, while the epidermis is usually preserved. In LP pemphigoides, bullous lesions demonstrate subepidermal clefting containing eosinophils and occasionally neutrophils. At the blister margins, Civatte bodies may sometimes be present in the basal layer, accompanied by a mild perivascular infiltrate composed of lymphocytes, neutrophils, and eosinophils [8–11].

2. *Lupus erythematosus*

The major clinical variants of lupus erythematosus (LE) include chronic discoid LE (DLE), subacute cutaneous LE (SCLE), and systemic LE (SLE). DLE is typically characterized by well-demarcated, erythematous plaques with scales and follicular plugging, most commonly affecting the face, neck, and scalp, but sometimes also involving the lips, oral mucosa, and hands. Atrophy and scarring are common. Histopathology shows marked vacuolar alteration, numerous dyskeratotic keratinocytes, and interface dermatitis, along with an inflammatory infiltrate involving the superficial and deep dermis, including perifollicular areas (Fig. 27.6b). Epidermal hyperkeratosis and follicular plugging are observed. In advanced lesions, basement membrane thickening may be present. SCLE is a form of lupus that develops on photosensitive areas such as the face, neck, upper trunk, and extensor surfaces of the extremities. It is characterized by recurrent, non-scarring annular or papulosquamous lesions. Histopathologically, vacuolar degeneration of the basal layer is prominent. Epidermal atrophy, dermal edema, and superficial mucin deposition are seen. In contrast to DLE, hyperkeratosis, follicular plugging, basement membrane thickening, and lymphocytic infiltration are less pronounced. SLE presents with the characteristic acute cutaneous eruption—an erythematous, slightly indurated, and mildly scaly plaque with a malar “butterfly” distribution on the face. Histopathological findings include prominent vacuolar changes, edema, foci of hemorrhage, a mild lymphocytic infiltrate in the upper dermis, and deposition of fibrinoid material around capillaries and within connective

tissue. The basement membrane is usually of normal thickness. Direct immunofluorescence of lesional skin can be used as a supportive diagnostic tool, especially when routine histopathology is inconclusive. The most characteristic DIF finding in cutaneous LE is granular deposition of IgG and IgM along the dermoepidermal junction and around hair follicles. In SCLE, these deposits are reported to occur primarily within the epidermis.

3. *Lichen nitidus*

Lichen nitidus is a condition more frequently observed in children and young adults. It commonly involves the flexor surfaces of the upper extremities, as well as the chest, abdomen, dorsum of the hands, and genital region. Less commonly, oral mucosa and nails may also be affected. The Koebner phenomenon is typically positive. Clinically, the lesions consist of numerous, discrete, skin-colored, uniform, pinpoint-sized papules (Fig. 27.7). Histopathologically, there is an infiltrate composed of lymphocytes, epithelioid cells, and occasionally Langhans giant cells. This infiltrate is characteristically surrounded by hyperplastic rete ridges, producing the typical “ball and claw” appearance. Additional features include epidermal atrophy, parakeratosis, hypogranulosis, vacuolar degeneration of the



Fig. 27.7 Multiple discrete, skin-colored, smooth-surfaced papules located in the abdomen

basal layer, and melanin incontinence, sometimes accompanied by Civatte bodies. The lichenoid infiltrate is situated in close proximity to the epidermis.

27.4 Vesiculobullous Diseases

The vesiculobullous reaction pattern can be classified according to the level at which the blister forms and the nature of the accompanying inflammatory infiltrate (Fig. 27.8).

- *Intraepidermal bullae* occur in friction blisters, contact dermatitis, eczema, and epidermolysis bullosa simplex, localized type.
- Intraepidermal blister formation with *supra-basal acantholysis* is a hallmark of some viral diseases (HSV, VZV), pemphigus vulgaris, pemphigus vegetans, Hailey–Hailey disease, Darier’s disease, Grover’s disease, and paraneoplastic pemphigus.
- *Subepidermal bullae* may be associated with minimal inflammation or with infiltrates rich in lymphocytes, neutrophils, or eosinophils:
 - **Minimal infiltrates:** *toxic epidermal necrolysis, epidermolysis bullosa, porphyria cutanea tarda.*
 - **Lymphocytic infiltrates:** *erythema multiforme, fixed drug eruption, lichen sclerosus et atrophicus, lichen planus pemphigoides, bullous mycosis fungoides.*
 - **Eosinophilic infiltrates:** *bullous pemphigoid (prototype), drug reaction, pemphigoid gestationis, arthropod bite.*
- *Intracorneal and subcorneal bullae* are observed in conditions such as impetigo, infantile acropustulosis, transient neonatal pustular melanosis, erythema toxicum neonatorum, staphylococcal scalded skin syndrome, miliaria crystallina, acute generalized exanthematous pustulosis, subcorneal pustular dermatosis (Sneddon–Wilkinson disease), pemphigus foliaceus, and IgA pemphigus.

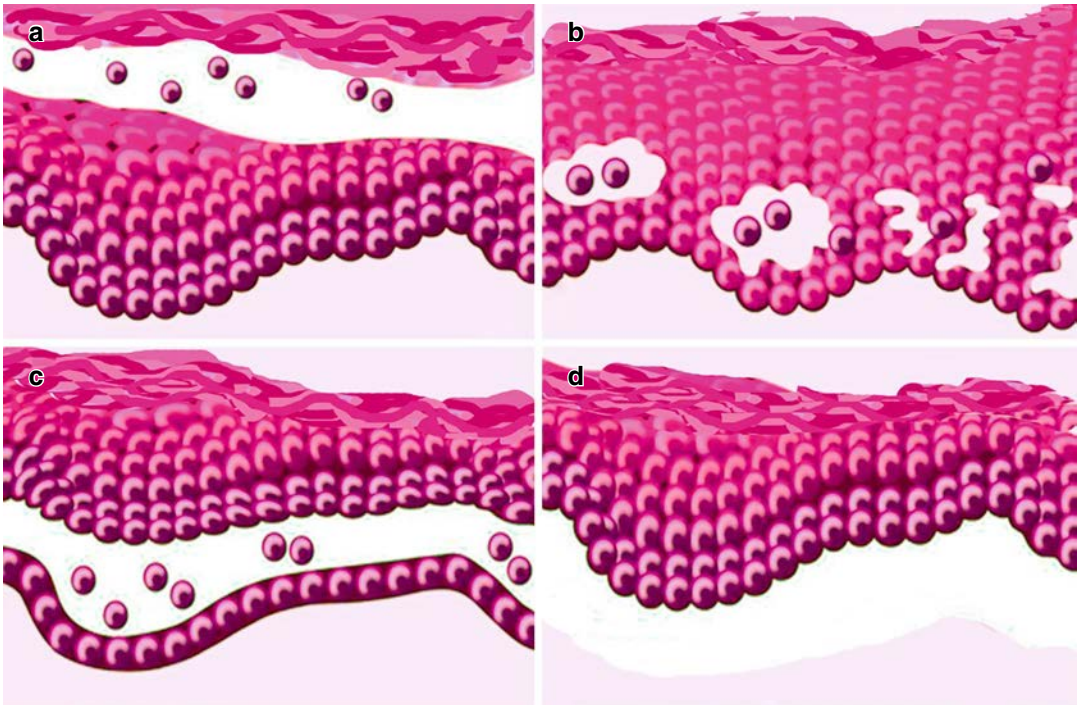


Fig. 27.8 (a) Subcorneal, (b) intraepidermal, (c) suprabasal, and (d) subepidermal acantholysis

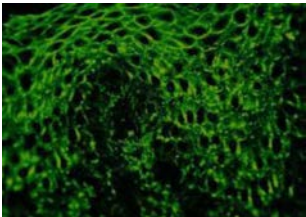
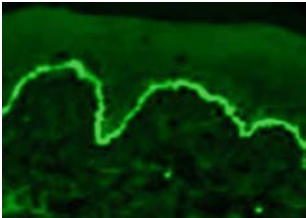
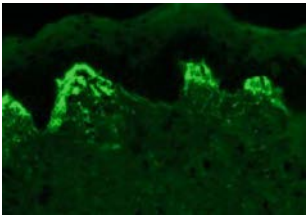
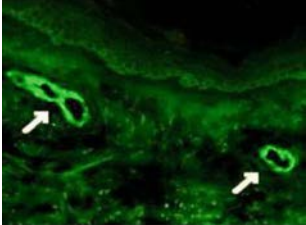
- **Neutrophilic infiltrates:** *linear IgA bullous dermatosis, mucous membrane pemphigoid, dermatitis herpetiformis, epidermolysis bullosa acquisita (EBA).*

Direct immunofluorescence (DIF) analysis plays a crucial role in the differential diagnosis of vesiculobullous dermatoses. The diag-

nosis is reached based on the type and location of the immune deposit (Table 27.1). Some selected vesiculobullous disorders will be discussed here based on the above classification [12–15].

1. *Steven Johnson syndrome/(SJS)/toxic epidermal necrolysis (TEN)*

Table 27.1 Guide for direct immunofluorescence (DIF) examination

DIF image	Characteristic appearance	Main protein/antibody	Disease
	Between squamous cells, net-like (fish-net pattern)	IgG, IgA (all forms of pemphigus)	Pemphigus (IgA pemphigus and all variants)
	Intercellular, lace-like	IgG	Paraneoplastic pemphigus
	Linear at the basement membrane zone	C3, IgG	Bullous pemphigoid and cicatricial pemphigoid
	Linear at the basement membrane zone	C3	Herpes gestationis
	Linear at the basement membrane zone	C3, IgG	Epidermolysis bullosa acquisita
	Granular at the basement membrane zone and tip of dermal papillae	IgA	Dermatitis herpetiformis
	Perivascular	IgA, C3	Henoch–Schönlein vasculitis
	Granular at basement membrane zone, vessel wall	C3, IgM	Erythema multiforme
	Linear or granular at basement membrane zone	IgA	Linear IgA dermatosis
	Linear at basement membrane zone	C3, IgG	Bullous systemic lupus erythematosus (SLE)

SJS/TEN is severe cutaneous adverse drug reactions that typically develop 7–21 days after exposure to the offending drug (most commonly allopurinol, aminopenicillins, antiretroviral agents, barbiturates, carbamazepine, phenytoin, lamotrigine, phenylbutazone, piroxicam, sulfadiazine, sulfasalazine, and trimethoprim-sulfamethoxazole). The clinical course begins with upper respiratory tract infection–like prodromal symptoms, followed by mucocutaneous tenderness, pain, erythema, erosions, dark red to violaceous macules, atypical target lesions, Nikolsky-positive bullous lesions, and variable degrees of epidermal detachment. Based on the extent of epidermal detachment, the disease is classified as SJS: <10% of body surface area; SJS–TEN overlap: 10%–30%; TEN: >30%. The pathogenesis involves widespread keratinocyte apoptosis mediated by Fas–Fas ligand interaction, perforin, granzyme B, and granulysin. Lesions predominantly affect the face, neck, and trunk, with involvement of at least two mucosal sites. Systemic manifestations such as fever, lymphadenopathy, cytopenia, and hepatitis are frequently observed. Histopathological examination reveals, in early lesions, scattered apoptotic keratinocytes within the basal and immediate suprabasal layers of the epidermis. In advanced lesions, there is confluent necrosis involving the entire epidermis, accompanied by subepidermal blister formation and a sparse perivascular infiltrate predominantly composed of lymphocytes.

2. *Pemphigus foliaceus*

Pemphigus foliaceus (PF) is an autoimmune bullous disease characterized by IgG autoantibodies directed against desmoglein 1, a desmosomal component expressed more abundantly in the upper epidermal layers compared to the basal layer. Clinically, it presents with erythematous, scaly, crusted, eroded skin lesions often described as resembling “cornflakes,” typically without significant mucosal involvement. Lesions most commonly affect the face, scalp, and upper trunk. Vesicles and bullae are fragile, Nikolsky sign positive, and may rupture easily. The disease can remain localized or progress to erythroderma. The histopathological features of pemphigus foliaceus, pemphigus erythematosus, and fogo selvagem are similar. Blisters are located subcorneally, within or adjacent to the granular layer of the epidermis, with acantholysis in the upper epidermis (Fig. 27.9a). Because the bullae are very superficial and fragile, it is often difficult to obtain intact specimens for histological examination. These superficial blisters may be histologically indistinguishable from those seen in staphylococcal scalded skin syndrome or bullous impetigo. A supportive diagnostic feature is the presence of a dense eosinophilic infiltrate within the epidermis and upper dermis. Rarely, neutrophilic spongiosis, similar to that observed in IgA pemphigus, may be seen. Direct immunofluorescence (DIF) demonstrates a fish-net or chicken-wire pattern

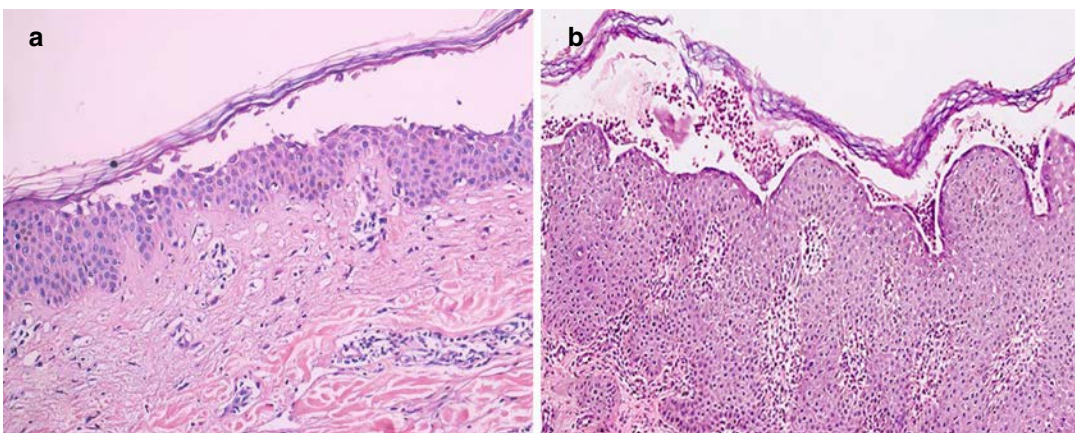


Fig. 27.9 (a) Subcorneal acantholysis in PF. (b) Subcorneal pustules in SPD

of intercellular IgG deposition, most prominent in the upper epidermis, and usually accompanied by C3 deposition [12–15].

3. Subcorneal pustular dermatosis

Subcorneal pustular dermatosis (SPD), also known as Sneddon–Wilkinson disease, is characterized by very superficial, subcorneal, sterile pustules, typically presenting as annular or polycyclic lesions that often begin in the flexural areas. In some vesiculopustules, gravitational separation may produce a clear fluid layer above and pus below. The disease follows a cyclical course, in which healing lesions resolve with desquamation, while new pustules simultaneously appear. Histopathology typically demonstrates subcorneal pustules filled with neutrophils (Fig. 27.9b). Minimal spongiosis may be present, and there is usually a mild superficial perivascular infiltrate in the dermis. DIF is negative, with no immune deposits observed [12–15].

4. Pemphigus vulgaris

Pemphigus vulgaris (PV) is an autoimmune blistering disorder caused by autoantibodies directed against desmoglein 3 (which is expressed more strongly throughout the mucosal epithelium and in the lower layers of the epidermis) and desmoglein 1, both components of desmosomes mediating keratinocyte adhesion. In some

patients, autoantibodies are directed only against desmoglein 3. Clinically, painful erosions of the oral mucosa are present in all patients, whereas a subset also develops flaccid blisters, positive Nikolsky sign, and widespread cutaneous erosions. Based on these clinical features, pemphigus vulgaris is classified into two subtypes: the mucosal-dominant type, characterized by minimal cutaneous involvement, and the mucocutaneous type, in which widespread cutaneous bullae and erosions accompany mucosal involvement. Mucosal blisters are rarely observed intact. The buccal and palatal mucosa are most frequently affected, but lesions may also occur on the pharynx, larynx, esophagus, conjunctiva, nasal mucosa, vagina, labia, penis, and anus. The characteristic histopathological feature is acantholysis with intraepidermal blister formation, without keratinocyte necrosis. Acantholysis typically occurs immediately above the basal cell layer, i.e., suprabasal level. Basal cells remain attached to the basement membrane through hemidesmosomes but lose adhesion to adjacent keratinocytes, producing the classic “row of tombstones” appearance (Fig. 27.10). Some acantholytic keratinocytes are observed free within the blister cavity. The intraepidermal blister cavity may also contain inflammatory cells, particularly eosinophils. In the dermis, a moderate mononuclear infiltrate with eosinophils is present. Early lesions may demonstrate eosinophilic spongiosis without acantholysis. The acantholytic process may

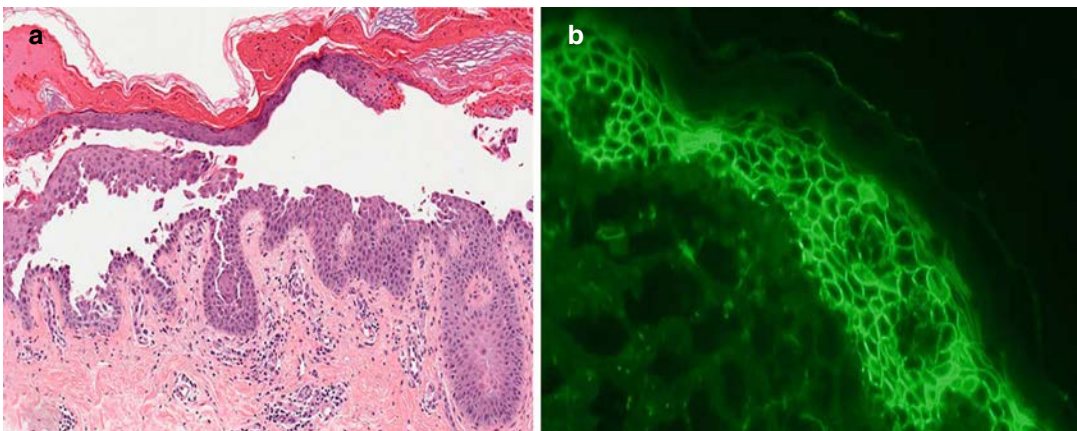


Fig. 27.10 (a) Suprabasal acantholysis (b) chicken-wire pattern IgG depositions in pemphigus vulgaris

also involve hair follicles. The dermal papillary architecture is usually preserved, and dermal papillae frequently project upward into the blister cavity. DIF shows intercellular deposition of IgG and C3 throughout the epidermis, more prominent in the lower layers, producing the characteristic fish-net or chicken-wire pattern [12–15].

5. Darier disease

Mutations in the ATP2A2 gene, inherited in an autosomal dominant manner, result in dysfunction of the endoplasmic reticulum Ca^{2+} ATPase (SERCA2), leading to impaired intracellular Ca^{2+} signaling. The primary lesions are red to brown keratotic papules, often with crusts, distributed in a seborrheic pattern involving the trunk, scalp, face, and lateral neck. Lesions tend to coalesce and may form papillomatous masses. Occasionally, sterile vesicles or bullae may be observed. In most patients, lesions also occur in intertriginous areas. Approximately half of the patients present with flat wart-like papules typically located on the dorsum of the hands and feet. Palmoplantar papules and keratin-filled depressions are common. Nail changes include longitudinal red and/or white streaks, fissures, wedge-shaped subungual hyperkeratosis, and V-shaped distal notching. In the oral mucosa, whitish papules or plaques may be seen. The most important histopathological findings of Darier disease are acantholysis and dyskeratosis. Acantholysis is associated with suprabasal cleft formation. Dyskeratosis results from keratinocyte apoptosis. Two types of dyskeratotic cells are typically seen:

- **Corps ronds:** Rounded keratinocytes with eosinophilic cytoplasm, surrounded by a halo-like structure, with a small, dark, pyknotic nucleus. They are usually located in the upper epidermis or at the stratum spinosum–granulosa junction and exhibit discohesion/dyskeratosis.
- **Grains:** Small, oval keratinocytes located in the stratum corneum, characterized by a cigar-shaped pyknotic nucleus and intensely eosino-

philic cytoplasm composed of collapsed keratin bundles with remnants of parakeratotic nuclei.

The epidermis overlying acantholytic and dyskeratotic foci is thickened, papillomatous, and hyperkeratotic. The superficial dermis shows a mild to moderate perivascular inflammatory infiltrate [16].

6. Hailey–Hailey disease

Mutations in the ATP2C1 gene, inherited in an autosomal dominant manner, lead to dysfunction of the Golgi-associated Ca^{2+} ATPase, thereby impairing intracellular calcium signaling. Clinically, the disease most frequently involves intertriginous areas such as the axillae, groin, lateral neck, and perianal region, but it may also affect the scalp, antecubital and popliteal fossae, and trunk. In women, isolated vulvar involvement may occasionally be observed. The lesions initially present as flaccid vesicles on erythematous or normal-appearing skin, which spread peripherally to form an annular border, while simultaneously evolving into macerated and crusted erosions. Histopathology shows suprabasal clefts at various levels of the epidermis, accompanied by focal acantholysis, producing the classic “dilapidated brick wall” appearance. Acantholytic keratinocytes are present above these clefts. Broad areas of discohesion consisting of single or clustered acantholytic cells are observed. Necrotic keratinocytes are rare, and acantholytic dyskeratotic cells may occasionally be seen. In more chronic lesions, features include epidermal hyperplasia, parakeratosis, and focal crusting. The superficial dermis demonstrates a moderate perivascular lymphocytic infiltrate [16].

7. Erythema multiforme

Erythema multiforme (EM) is a self-limited, recurrent hypersensitivity reaction that is classified into two subtypes: erythema multiforme minor and erythema multiforme major. In EM

minor, typical papular target lesions predominate, with fewer atypical target lesions, and mucosal involvement is absent or very mild. In contrast, EM major is characterized by moderate to severe mucosal involvement accompanied by systemic symptoms such as fever, malaise, and arthralgia. The initial lesions are well-demarcated, round, pink to red macules, which evolve into typical targetoid papules and, with enlargement, into plaques. The center of the papule/plaque appears darker in color. Epidermal changes such as bullae or crusts may be observed. The typical target lesion consists of a dark erythematous, purpuric, or vesicular/bullous center, a surrounding pale (edematous) halo, and an outermost bright erythematous halo. EM most commonly develops following herpes simplex virus (HSV) infection, although it may occasionally occur after drug exposure (Fig. 27.11). The earliest pathological feature is apoptosis of individual or clustered keratinocytes. As the process advances, a mild to moderate lymphocytic infiltrate involving the dermoepidermal junction becomes evident. Basal vacuolar alteration and spongiosis may be present, and eosinophils can be seen within the dermal infiltrate. Compared with Stevens–Johnson syndrome (SJS), the dermal inflammatory component is more pronounced in EM [12–15].

8. Bullous pemphigoid

Bullous pemphigoid (BP) is an autoimmune blistering disorder characterized by autoantibodies directed against the hemidesmosomal components BP180 (collagen XVII) and BP230, in which both humoral and cellular immune responses play pivotal roles. The hallmark of BP is the detection of circulating autoantibodies against structural components of the basement membrane zone (BMZ), together with their linear deposition along the BMZ in perilesional skin, accompanied by complement activation. BP180 is a transmembrane protein composed of a globular cytoplasmic domain and a large extracellular region containing 15 collagenous segments. In the majority of patients, the antibody response targets the membrane-proximal non-collagenous 16A (NC16A) domain of BP180. BP230, on the other hand, is a cytoplasmic protein belonging to the plakin family. Cytokine profiling studies have shown that the Th1 response, mediated by IFN- γ , promotes IgG1 and IgG2 secretion, whereas the Th2 response, mediated by IL-4, IL-5, and IL-13, induces the production of IgG4 and IgE. Accordingly, the presence of IgG1, IgG4, and IgE autoantibodies against BP180 and BP230 strongly suggests that both Th1- and Th2-driven pathways contribute to the immunopathogenesis of BP. Bullous pemphigoid (BP) is classically characterized by tense bullae measuring 1–3 cm in diameter, which may be serous or hemorrhagic in content, negative Nikolsky sign, and intense

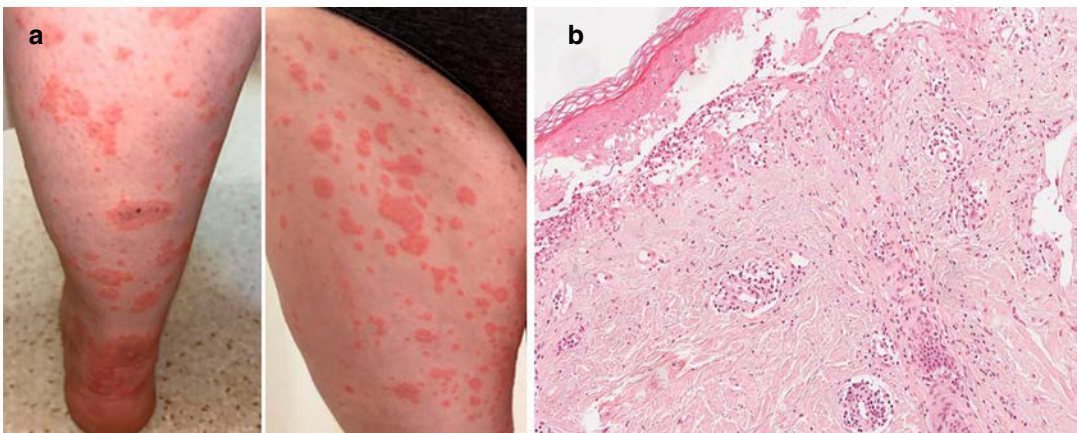


Fig. 27.11 (a) Typical complete and incomplete target lesions on the posterior tibia and anterior thigh. (b) Epidermal necrosis and dermal inflammation in EM

pruritus. Vesicles and bullae typically arise on either normal-appearing or erythematous skin, frequently accompanied by urticarial, infiltrated plaques or eczematous lesions, occasionally forming annular or figurate patterns. Lesions predominantly affect the trunk, lower abdomen, proximal extremities, inner thighs, flexor surfaces of the forearms, and inguinal and axillary regions. Mucosal involvement is uncommon. A non-bullous prodromal phase may precede the bullous stage, presenting as severe pruritus alone or in association with excoriated, eczematous, papular, or urticarial lesions. Several clinical variants have been described, including dyshidrosiform BP, prurigo nodularis-like BP, vesicular BP, annular BP, erythema multiforme-like BP, urticarial BP, erythrodermic BP, lichen planus pemphigoides, pemphigoid vegetans, and localized forms.

Histopathologically, BP is characterized by subepidermal blister formation without acantholysis, with numerous eosinophils within the dermis, epidermis, and blister cavity (Fig. 27.12). Even in the non-bullous phase, abundant eosinophils are observed in perivascular and interstitial areas of the upper and mid-dermis, occasionally accompanied by neutrophils and lymphocytes. Eosinophilic spongiosis or eosinophilic infiltration at the dermoepidermal junction may also be observed in some biopsies. Pemphigoid gestationis (PG), an entity occurring during pregnancy, demonstrates histopathological features identical

to those of BP. DIF of perilesional skin typically shows linear, continuous deposition of IgG and C3 along the dermoepidermal junction. In some cases, IgA or IgE deposition may also be present. Indirect immunofluorescence (IIF) on salt-split normal human skin reveals epidermal-side binding of circulating antibodies [12–15].

9. *Dermatitis herpetiformis*

Dermatitis herpetiformis (DH) is an autoimmune blistering disorder observed in approximately one-quarter of patients with gluten sensitivity, in which gluten-induced IgA–epidermal transglutaminase 3 (TG3) immune complexes play a central role. A strong association of gluten sensitivity and DH with HLA-DQ2 or HLA-DQ8 haplotypes is well established. The relevant antigenic component is gliadin. Following ingestion of gluten-containing foods, gliadin-derived glutamine residues are absorbed through the lamina propria and undergo deamidation by tissue transglutaminase (TG2). Deamidated gliadin peptides bind to HLA-DQ2 molecules on dendritic antigen-presenting cells and are presented to T helper cells. Activated T cells subsequently stimulate B cells, which differentiate into plasma cells producing IgA antibodies directed against multiple antigens, including gliadin, gliadin–TG2 complexes, TG2 itself, and epidermal transglutaminase (TG3). Circulating anti-TG3 IgA antibodies form

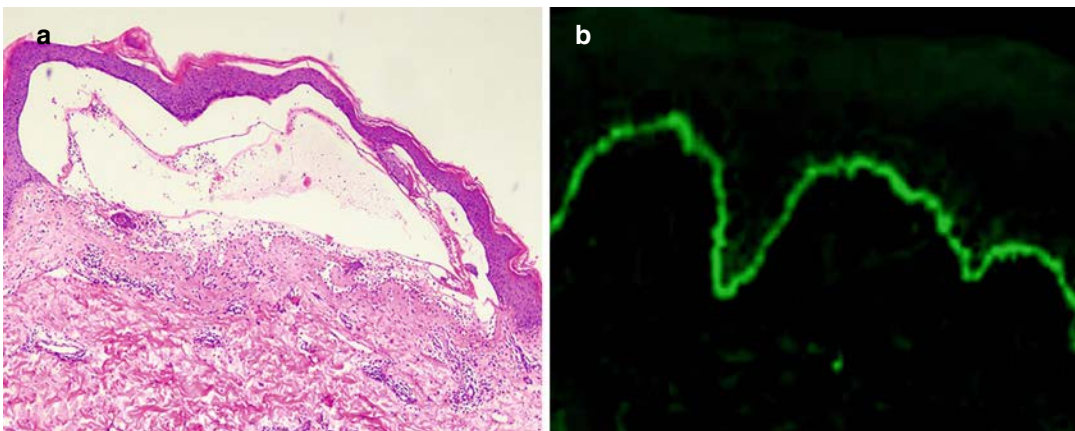


Fig. 27.12 (a) Subepidermal acantholysis. (b) Linear IgG deposition in bullous pemphigoid

immune complexes with TG3 that deposit within the dermal papillae, leading to recruitment of neutrophils, inflammation, and the formation of neutrophilic microabscesses characteristic of DH. Clinically, DH presents with symmetrically distributed, grouped vesicles on erythematous and papular bases, most commonly involving the extensor surfaces of the elbows, knees, buttocks, and scalp. Lesions are accompanied by burning and intense pruritus, often leading to excoriated papules and erosions due to scratching. Mucosal involvement is rare.

Histopathologically, biopsies from vesicular lesions reveal a subepidermal blister with a predominantly neutrophilic infiltrate. Biopsies from erythematous but non-vesicular sites show collections of neutrophils within the dermal papillae and dermal edema due to superficial perivascular lymphocytic infiltrate. DIF demonstrates granular IgA deposition within the dermal papillae, a diagnostic hallmark of DH [17] (Fig. 27.13).

10. Linear IgA bullous dermatosis

Linear IgA bullous dermatosis (LABD) is an autoimmune subepidermal blistering disorder characterized by the linear deposition of IgA along the basement membrane zone (BMZ). Based on the ultrastructural localization of IgA deposits determined by immunoelectron microscopy, two subtypes are recognized: the lamina lucida type and the sublamina densa type. In the

lamina lucida variant, the most common antigenic targets are thought to be the proteolytic fragments of BP180, namely, the 97 kDa protein (LAD-97) and the 120 kDa protein (LAD-1). Other reported autoantigens include BP230, laminin 332, and type VII collagen. LABD may occur in both childhood and adulthood and has been associated with systemic diseases, drug exposure, and malignancies. Clinical manifestations are typically more characteristic in children, whereas in adults, the disease may mimic dermatitis herpetiformis or bullous pemphigoid. Clinically, LABD is characterized by grouped vesicles and bullae, papules, and urticarial plaques, which often display an annular or polycyclic configuration. Lesions predominantly involve the extensor surfaces of the extremities (such as the knees, elbows, and buttocks) and the trunk. The development of new vesicles at the periphery of older lesions results in the classic appearance described as “string of pearls” or “cluster of jewels.” Mucosal involvement may also occur. Histopathologically, LABD shows a subepidermal blister often accompanied by interface dermatitis. A characteristic finding is the presence of neutrophils along the dermoepidermal junction and within the papillary dermis, where microabscesses may form. The inflammatory infiltrate typically consists predominantly of neutrophils, often accompanied by eosinophils—the latter being particularly prominent in drug-induced cases. Additional findings may include

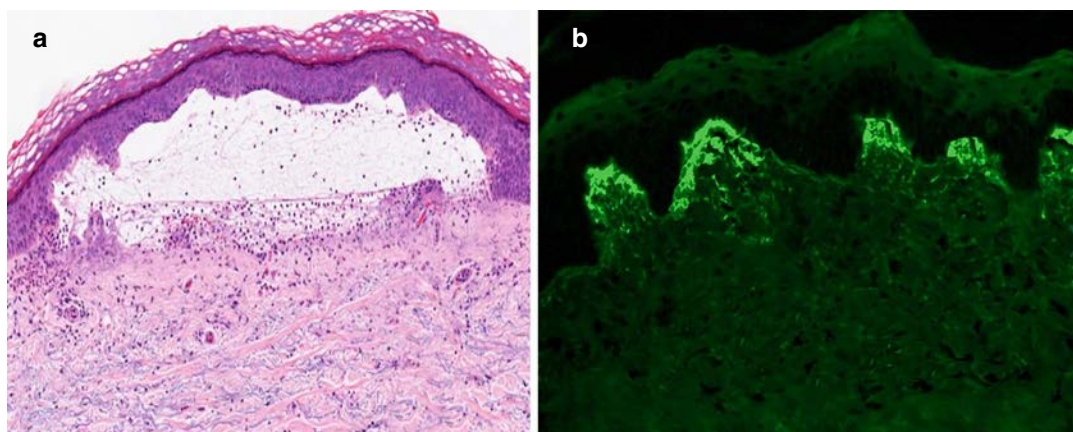


Fig. 27.13 (a) Subepidermal blister. (b) Granular IgA deposits on tip of dermal papillae

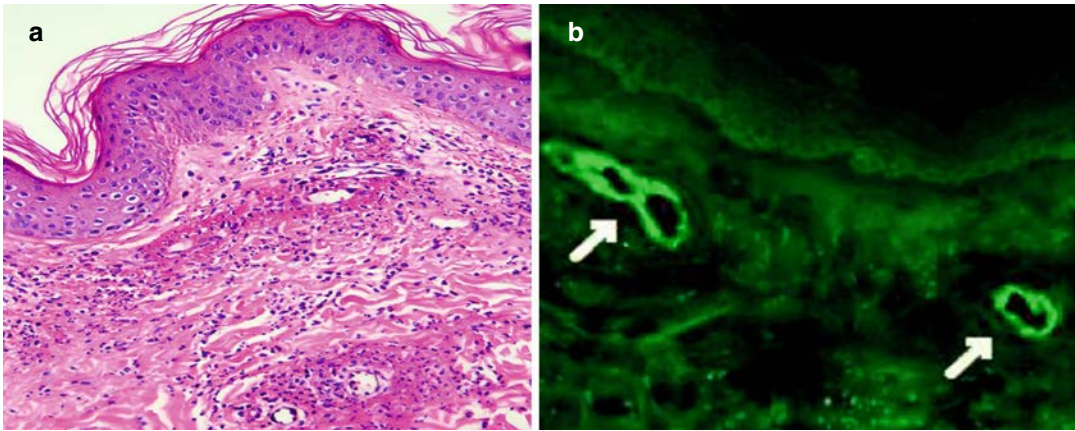


Fig. 27.14 (a) Neutrophilic infiltration, fibrinoid necrosis, and nuclear debris. (b) Perivascular C3 deposits in LCV

epidermal exocytosis and neutrophil-rich inflammation involving the dermoepidermal junction. On DIF, LABD demonstrates a linear, continuous deposition of IgA along the BMZ, sometimes accompanied by C3, whereas IgG and IgM are typically absent. IIF using salt-split skin most commonly shows IgA autoantibodies binding to the epidermal side (lamina lucida type LABD), while in rarer cases, antibodies bind to the dermal side (sublamina densa type LABD) [17].

27.5 Leukocytoclastic Vasculitis

Leukocytoclastic vasculitis (LCV) is a small-vessel vasculitis characterized histologically by neutrophilic infiltration, fibrinoid necrosis of vessel walls, and nuclear debris (leukocytoclasia). It predominantly involves postcapillary venules in the dermis and clinically presents as palpable purpura, especially on the lower extremities.

Although LCV is not primary dermatosis, its cutaneous manifestations frequently mimic or coexist with true dermatoses, making it an important consideration in the differential diagnosis of skin diseases with vascular or purpuric features. In direct immunofluorescence (DIF) studies, immune complex deposition is observed around small dermal vessels. The pattern depends on the underlying cause IgA and C3 deposition is typical of *Henoch–Schönlein purpura* (IgA vasculitis), whereas other cases may reveal IgM, IgG, or

C3. These findings support an immune complex-mediated pathogenesis and help differentiate LCV from nonimmune vasculopathic lesions (Fig. 27.14) [18].

References

1. Ständer S, Pereira MP, Weisshaar E, Bernhard JD. Pruritus and dysesthesia. In: Bologna JL, Schaffer JV, Cerroni L, editors. *Dermatology*. 5th ed. Philadelphia: Elsevier; 2022. p. 110–27.
2. Johnston RB. Psoriasiform reaction pattern. In: Johnston RB, editor. *Weedon's skin pathology essentials*. 2nd ed. Beijing: Elsevier; 2017. p. 54–67.
3. Sezer E. Psoriasis and psoriasiform dermatitis. *Türk Klinikleri J Dermatol-Spec Top*. 2012;5(1):5–9.
4. Ergun T. Psoriasis Etiyopatogenezinde Güncel Bilgiler. In: Alpsoy E, Ergun T, Şendır N, editors. *Tüm Yönleriyle psoriasis*. Galenos; 2020. p. 19–29.
5. Van de Kerkhof PCM, Iversen L. Psoriasis. In: Bologna JL, Schaffer JV, Cerroni L, editors. *Dermatology*. 5th ed. Philadelphia: Elsevier; 2022. p. 139–65.
6. Rapini RP. Eczematous and papulosquamous diseases. In: Rapini RP, editor. *Practical dermatopathology*. 2nd ed. Beijing: Elsevier; 2012. p. 45–59.
7. Cribier B, Wood GS, Reizner GT. Other papulosquamous disorders. In: Bologna JL, Schaffer JV, Cerroni L, editors. *Dermatology*. 5th ed. Philadelphia: Elsevier; 2022. p. 164–76.
8. Shiohara T, Mizukawa Y. Lichen planus and lichenoid dermatoses. In: Bologna JL, Schaffer JV, Cerroni L, editors. *Dermatology*. 5th ed. Philadelphia: Elsevier; 2022. p. 189–209.
9. Barajas L, Steuer M, Amerson E. Variable clinical course of lichen planus following hepatitis C cure

- with directacting antivirals: a case series and literature review. *J Am Acad Dermatol.* 2021;84:1142–6.
10. Gürer MA, Adışen E. Interface dermatitis. *Türk Klin J Dermatol-Spec Top.* 2012;5(1):10–8.
 11. Johnston RB. Lichenoid reaction pattern. In: Johnston RB, editor. *Weedon's skin pathology essentials.* 2nd ed. Beijing: Elsevier; 2017. p. 54–67.
 12. Johnston RB. Vesiculobullous reaction pattern. In: Johnston RB, editor. *Weedon's skin pathology essentials.* 2nd ed. Beijing: Elsevier; 2017. p. 91–133.
 13. Rapini RP. Intraepidermal vesicular and pustular diseases. In: Rapini RP, editor. *Practical dermatopathology.* 2nd ed. Beijing: Elsevier; 2012. p. 87–91.
 14. Özaygen Erkin G. Otoimmün Büllöz Hastalıklarda Histopatolojik Bulgular. In: Uzun S, Durdu M, Kaya Tİ, Aktan Ş, editors. *Otoimmün Büllöz Hastalıklar.* Galenos; 2017. p. 44–50.
 15. Rapini RP. Subepidermal vesicular diseases. In: Rapini RP, editor. *Practical dermatopathology.* 2nd ed. Beijing: Elsevier; 2012. p. 93–100.
 16. Hohl MH. Darier disease and Hailey–Hailey disease. In: Bologna JL, Schaffer JV, Cerroni L, editors. *Dermatology.* 5th ed. Philadelphia: Elsevier; 2022.
 17. Aktan Ş, Durdu M. Otoimmün Büllöz Hastalıkların Etiyopatogenezi. In: Uzun S, Durdu M, Kaya Tİ, Aktan Ş, editors. *Otoimmün Büllöz Hastalıklar.* Galenos; 2017. p. 16–28.
 18. Micheletti RG, Werth VP. Small vessel vasculitis of the skin. *Rheum Dis Clin N Am.* 2015;41(1):21–32, vii. <https://doi.org/10.1016/j.rdc.2014.09.006>.

Neoplasms of Skin and Skin Appendages

28

Neşe Çallı Demirkan and Erdem Çomut

28.1 Keratinocytic Tumors

Keratinocytic tumors are composed of lesions derived from keratinocytes of the epidermis and adnexal structures. Among cystic lesions, epidermoid cysts are lined by stratified squamous epithelium with a preserved granular layer, and their lumen contains lamellar keratin. In contrast, pilar (tricholemmal) cysts, often found on the scalp, are lined by pale squamous epithelium lacking a granular layer, and the lumen is filled with compact, eosinophilic keratin. Dermoid cysts, typically congenital and located along embryonic fusion lines (e.g., lateral brow, midline forehead or neck), resemble epidermoid cysts histologically but can be distinguished by the presence of adnexal glands and terminal hair follicle remnants in their walls. Additionally, benign keratinocytic proliferations include entities such as warts, acanthomas, and seborrheic keratosis. Actinic, arsenic, and PUVA keratoses are premalignant lesions with the potential to develop into squamous cell carcinoma. Keratinocytic malignancies (basal cell carcinomas and squamous cell carcinomas) are the most common malignancies. Merkel cell carcinoma is much less common but is considered a malignancy of neuroendocrine cells originating from the skin and is therefore

described in the keratinocytic/epidermal tumors section [1].

Exposure to radiation is an important risk factor for keratinocytic cancers. UVB (290–320 nm wavelength), UVA (320–400 nm wavelength) and artificial UV are estimated to cause 95% of keratinocytic cancers. Other etiologic factors include immunosuppression, arsenic exposure, HPV infection, and smoking. In genetic disorders such as xeroderma pigmentosum—a nucleotide excision repair defect—hypersensitivity to sunlight occurs, and the risk of skin cancer rises from childhood.

Seborrheic keratosis (SK) is the most common cutaneous benign neoplasm. Although it can occur on any part of the body, the face and upper trunk are the preferred sites, and it is more common in men. It is hypothesized that advancing age, genetic predisposition, and exposure to environmental factors (e.g., sunlight) contribute to the development of these lesions. Various oncogenic mutations involving *FGFR3* and *FOXN1* have been implicated in the pathogenesis. Additionally, Merkel cell polyomavirus nucleic acid has recently been detected in SK [2].

SK is characterized by well-circumscribed, endophytic, exophytic, or flat keratinocyte proliferation. Morphologically, acanthotic, hyperkeratotic, reticulate/adenoïd variant, clonal type, irritated type, melanoacanthoma, and adamantinoid type have been described. The most common acanthotic type is characterized by thick layers/columns of proliferating basaloid and

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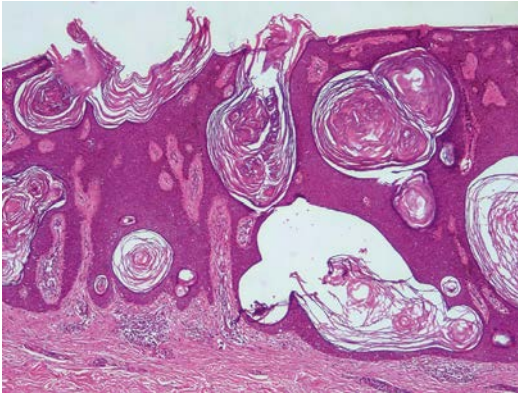


Fig. 28.1 Seborrheic keratosis showing thickened epidermis composed of proliferating basaloid and squamoid cells with multiple keratin-filled cysts. (H&E, $\times 40$ magnification)

squamoid cells, along with keratin cysts (Fig. 28.1). Hyperkeratosis, papillomatosis, and acanthosis may be observed to varying degrees across different histopathologic types.

SK is a benign epidermal tumor with no malignant potential. Despite their benign nature, SK lesions may cause significant cosmetic concerns and negatively impact quality of life. Most cases can be easily diagnosed clinically. Differentiation from melanocytic tumors may be required when melanin pigment is observed within keratinocytes. Clinically, it may also be confusing with verruca vulgaris, actinic keratosis, and pigmented basal cell carcinoma. A thorough clinical evaluation combined with histopathological examination is essential for accurate differential diagnosis and determining optimal therapeutic strategies. Dermoscopy is increasingly used for clinical follow-up of SK [3]. Treatment typically consists of lesion removal for cosmetic reasons or symptomatic relief. Lesions may also be treated with cryotherapy, shave excision, or electrodesiccation and curettage.

28.1.1 Keratoacanthoma (KA)

KA is a distinctive, self-limiting, low-grade squamous neoplasm characterized by rapid growth, stabilization, and spontaneous regression. It is

largely confined to the hair-bearing skin. The etiological factors are similar to SCC, but KA is suggested to develop as a result of low or intermittent UV-damaged skin proliferations.

It appears as a dome-like lesion, typically solitary and 1–2 cm in diameter, with a central keratin plug. Histopathologically, both exophytic and endophytic keratinocytic proliferations are observed. Fully developed lesions exhibit a crater-like architecture with a central keratin plug. Squamous epithelium extends into the dermis, forming an irregular lower border. Basaloid cells are located at the periphery of squamous epithelial islets. During maturation, they differentiate into large squamous cells exhibiting pale eosinophilic cytoplasm. A mixed inflammatory infiltrate is often present in the stroma. Neutrophils may infiltrate epithelial islands, occasionally forming microabscesses. While mitotic figures may be present, atypical mitoses with stromal invasion strongly suggest squamous cell carcinoma. A subset of well-differentiated squamous cell carcinomas may be classified as the keratoacanthoma variant. Immunohistochemical evaluation of Ki-67 proliferative index and p53 expression patterns can assist in differential diagnosis. Squamous cell carcinoma typically demonstrates either null (complete loss) or diffuse strong p53 expression, along with irregular Ki-67 proliferation extending beyond the basal layer. In contrast, KA shows Ki-67 and p53 expression restricted to the proliferative zone. For diagnostically challenging lesions, the term “squamoproliferative tumor of uncertain malignant potential or keratoacanthoma-like proliferation” may be applied [1].

Verrucas and condylomas are common, contagious epithelial tumors caused by human papilloma virus (HPV). Although most are benign, warts caused by HPV 16 and 18 are the most important risk factor for anogenital malignancy and intraepithelial lesions. They can affect all skin and mucous membranes. Clinical manifestations vary according to HPV type, location, and host immune response. *Verruca vulgaris* is the common form. Marked hyperkeratosis, acanthosis, papillary projec-

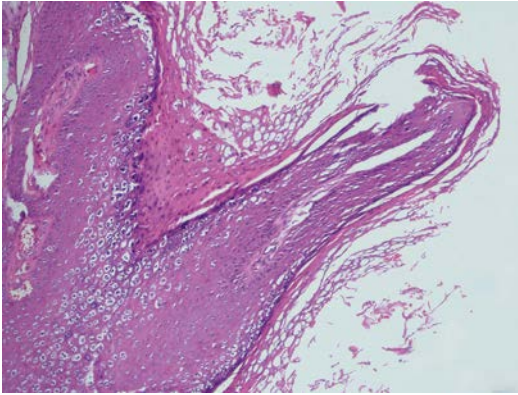


Fig. 28.2 Hyperkeratosis, acanthosis, papillary projections, and parakeratosis with koilocytotic changes in the upper epidermis. (H&E, $\times 100$ magnification)

tions, and parakeratosis are observed. Koilocytes, characterized by perinuclear vacuolization and pyknotic nuclei, are observed in the malpighian and granular layers (Fig. 28.2). *Verruca plantaris* is a thick, hyperkeratotic lesion typically seen on the sole of the foot, characterized by loosely arranged hyperkeratosis in a basket-weave pattern and the presence of koilocytes near the surface.

Acanthomas represent benign epidermal keratinocytic proliferations that may exhibit normal or extensive aberrant keratinization. *Clear cell acanthomas* are well-demarcated lesions characterized by psoriasiform epidermal hyperplasia with fused rete ridges. They are composed of keratinocytes exhibiting pale-to-clear glycogen-rich cytoplasm, showing an abrupt peripheral transition to surrounding normal epidermis. Pale keratinocytes contain PAS-positive glycogen. Overlying parakeratosis is present, with neutrophils in both the epidermis and stratum corneum. There is still controversy over whether clear cell acanthoma is an inflammatory dermatosis or reactive process.

Actinic keratosis (AK), also known as solar keratosis, is a very common neoplastic intraepidermal squamous proliferative lesion. Dermoscopic features include a red pseudonetwork in barely visible lesions and a reddish background with prominent follicles or rosettes—also referred to as the “strawberry pattern”—in visible, easily palpable, keratotic lesions. Thick

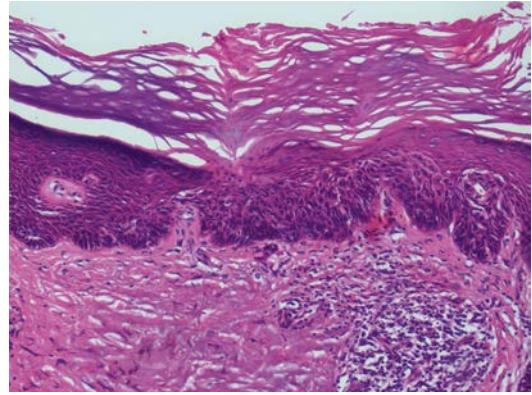


Fig. 28.3 Actinic keratosis characterized by basal and mid-spinous layer squamous dysplasia, overlying parakeratosis, and prominent solar elastosis in the dermis. (H&E, $\times 100$ magnification)

lesions with severe hyperkeratosis, well-defined borders, and compact keratin masses appear as white/yellowish structureless areas under dermoscopy. AK occurs on sun-exposed skin of the face, lips (actinic cheilitis), ears, scalp, neck, forearms, and dorsum of the hand. Like squamous cell carcinoma, AKs exhibit a UV signature, a high mutation load, and alterations in somatic copy number. Commonly mutated genes include *TP53*, *CDKN2A*, *CDKN2B*, *NOTCH1*, *NOTCH2*, and *FAT1* [4].

AK is characterized by squamous dysplasia involving the basal to middle spinous layer keratinocytes. By definition, squamous dysplasia does not extend through the full thickness of the epidermis (Fig. 28.3). Dysplastic keratinocytes show enlarged and irregular hyperchromatic or vesicular nuclei. Mitotic figures including atypical forms are common. The granular cell layer is typically absent and overlain by parakeratosis. Acrosyringeal units and follicular openings are preserved, but dysplastic keratinocytes may extend along preexisting adnexal structures. Dermal changes include solar elastosis, increased vascularity with lymphocyte and plasma cell infiltration. *Arsenical keratosis* is a precancerous lesion that typically develops within 2–30 years in individuals exposed to arsenic. PUVA is a form of treatment for diseases such as psoriasis in which epidermal keratinocytes are exposed to high doses of UVA radiation. Long-term PUVA

therapy increases the risk of developing AK and squamous cell carcinoma. *PUVA keratosis*, the associated lesion, typically exhibits less keratinocytic atypia compared to lesions induced by chronic sun exposure.

AK is considered a precancerous lesion resulting from cumulative sun exposure and carries a risk of progression to squamous cell carcinoma. AK may remain stable, regress, or progress to invasive squamous cell carcinoma. Therefore, treatment strategies for AK focus on removal of the lesion to prevent malignancy. In addition to surgical excision, other treatment modalities include cryotherapy, topical chemotherapeutic agents such as 5-fluorouracil or imiquimod, photodynamic therapies.

Bowen's disease is a form of in situ squamous cell carcinoma characterized by full-thickness involvement of the epidermis by dysplastic squamous cells. Dermoscopic features include scaling, glomerular punctiform vessels, yellow crust, hemorrhage, hypopigmentation, and linear irregular vessels. Although the etiology is not clear, sun damage, UVB/PUVA treatment, arsenic exposure, and HPV in genital lesions are seen as the main factors. The risk of invasion is higher in organ transplant recipients on immunosuppressive regimens and in populations with prolonged exposure to arsenic. The average age of onset is >60 years, and sun-exposed and nonexposed areas are equally affected. In young people, Bowen's disease is more commonly associated with exposure to ultraviolet (UV) radiation from tanning beds and arsenic exposure. Typical sites of involvement include the lower extremities, head, neck, and hands. Less commonly affected areas include the periungual, genital, and perianal regions. Classic cutaneous Bowen's disease presents as a single or multiple, erythematous, irregularly circumscribed, keratotic, scaly, crusted patch or plaque. *Queyrat's erythroplasia* is a form of Bowen's disease localized to the glans penis, presenting as bright red, sharply circumscribed plaques at the mucocutaneous junction. These lesions carry a higher risk of progression to invasive carcinoma compared to those at other anatomical sites. The cure is achievable through complete surgical excision.

Typical features of Bowen's disease are hyperkeratosis, parakeratosis, hypo- or hypergranulosis, and plaque-like acanthosis. The epidermis exhibits loss of normal polarity and keratinocytic maturation. Atypical keratinocytes involving the full-thickness epidermis appear pale or vacuolated and may be multinucleated with hyperchromatic nuclei. Single-cell keratinization and abnormal mitosis may be observed. These changes are limited to an intact dermoepidermal basement membrane. The upper parts of the dermis may contain inflammatory infiltrates; sweat glands may sometimes be involved.

Bowenoid papulosis is characterized by solitary or multiple verruca-like papules or plaques in the genital area. Partial or complete epidermal dysplasia similar to Bowen's disease is observed. Typical koilocytes are not seen. It often contains small inclusion-like basophilic bodies in the stratum corneum, or granular layer, and this feature is helpful in differentiation from Bowen's disease.

28.1.2 Squamous Cell Carcinoma (SCC)

SCC is a malignant neoplasm arising from epidermal and mucosal keratinocytes. It is the second most common skin cancer (after basal cell carcinoma) and accounts for 20%–25% of all skin cancers [5]. Its incidence increases with advancing age and increased sunlight exposure. Light-skinned individuals are more commonly affected, and the disease shows a higher prevalence in males. SCC is most common on the chronically sun-exposed head and neck, back of the hand, and lower lip, followed by the trunk and legs (especially in women). *Onycholemmal carcinomas* are a subtype of SCC originating from the nail bed. *Verrucous SCC* is almost always found on the genitals, hands, and feet. SCC may develop at sites of chronic trauma or inflammation, such as chronic ulcers, burn scars, commonly described as Marjolin ulcer. Other risk factors include radiation therapy, arsenic, industrial carcinogen exposure, immunosuppression, and HPV infection.

Cutaneous SCCs likely originate from epidermal or follicular stem cells. Prolonged exposure to UV radiation is a major cause of cutaneous SCC. Epigenetic alterations, advanced age, immunosuppression, and environmentally induced defects appear to contribute to impaired elimination of precursors to malignant transformation. UV-induced *TP53* mutations are early events; other mutations include tumor suppressor genes such as *NOTCH1* and *NOTCH2*. Activating mutations in oncogenes such as *HRAS* and *KRAS* are also frequently involved. SCC exhibits the highest mutation burden of all solid tumors. The accumulation of mutations ultimately affects the PI3K/AKT/mTOR signaling pathways mediated by NF- κ B, activation of MAPK and epidermal growth factor receptor (EGFR) [6]. The hypermethylation of certain 5' cytosine-phosphate-guanine 3' (CpG) islands, especially due to UV radiation, increases the expression of dimethyltransferase 1, leading to changes in proteins involved in keratinocyte homeostasis. These changes are linked to aggressive behavior and metastasis [1, 7].

SCC usually presents as a solitary plaque that progresses to a hyperkeratotic or ulcerated nodule. In well-to-moderately differentiated SCC, keratin-associated dermoscopic criteria are predominant, while in poorly differentiated SCC, a polymorphous vascular pattern predominates. Classic SCC in situ shows complete loss of maturation with the presence of atypical keratinocytes, mitosis, and dyskeratotic cells at all levels of the epidermis. Some SCCs can develop invasively de novo, without an identifiable in situ component. The differentiation of these tumors ranges from well to poor; however, most cases are categorized as well to moderately differentiated. Invasion is characterized by atypical squamous cells arranged in nests, sheets, and arrays extending from the epidermis into the dermis and subcutaneous adipose tissue (Fig. 28.4). The cells have abundant eosinophilic cytoplasm and often large, vesicular nuclei. There are prominent intercellular bridges. The periphery of the tumor may show a moderate to severe chronic inflammatory infiltrate. Most SCCs develop on a background of AK, with histologic evidence often present at the

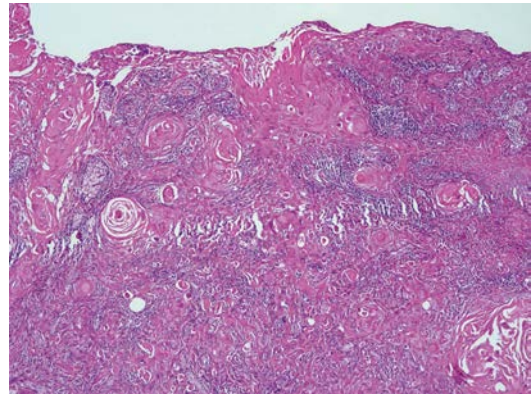


Fig. 28.4 Squamous cell carcinoma composed of atypical squamous cells arranged in nests, sheets, and arrays infiltrating the dermis. (H&E, $\times 40$ magnification)

tumor margins. Tumor cells may infiltrate between nerve bundles, adventitia of vessels, lymphatics, and deep fascial planes. The presence of perineural lymphocytes may be a clue to perineural invasion in deep sections. Central keratinization and keratin pearls are seen depending on the degree of differentiation. Grading is based on the degree of anaplasia in cell groups. In well-differentiated SCC; pleomorphism is mild, the squamous nature of the cells is clear, and intercellular bridges are prominent. In moderately differentiated SCC, pleomorphism is moderate, keratinization is reduced, and mitotic activity is increased. Most cells have smaller, basophilic cytoplasm. Poorly differentiated SCC is composed of undifferentiated pleomorphic cells with little or no keratinization. The World Health Organization has categorized these histopathological types of SCC into six forms: verrucous SCC, acantholytic SCC, lymphoepithelial SCC, clear cell SCC, spindle cell SCC, and SCC with sarcomatoid differentiation [8]. Acantholytic SCC is a histologic variant in which acantholysis develops as a result of loosening of intercellular bridges, clinical presentation is similar to classic SCC [7].

The typical lesion is a nonhealing, keratotic, erythematous, ulcerated papule or nodule. Patients may present with pain, bleeding, or itching. Most of these types of SCC are locally aggressive tumors, and the risk of distant metas-

tasis to organs like the lung, liver, and brain is between 2% and 5%. SCC arising in organ transplant patients is often multiple and aggressive. The most risky tumors are those that develop after Bowen's disease or those located in areas such as lips, perineum, vulva, penis, Marjolin's ulcer developing in large burn areas, radiation scar, and thermal burns. Tumors with desmoplastic or adenosquamous histology are generally considered to be more aggressive and have a worse prognosis. High-risk histological prognostic features include tumor thickness >2 mm, Clark level IV or V invasion, and poor differentiation. Perineural invasion of nerves >0.1 mm in diameter is associated with higher disease-specific mortality rates. Metastasis is rare in tumors <2 mm thick, with the risk increasing to 5% for 2–5 mm and 20% for >5 mm lesions. The 5-year survival rate for lymph node metastasis is 25%–35%. Surgery is the cornerstone of SCC treatment and radiotherapy is sometimes necessary. Metastatic cutaneous SCC (CSCC) remains a challenge to treat, but new drugs targeting various signaling pathways, particularly immunotherapies, offer hope for improving treatment outcomes. EGFR inhibitors have shown promise as potential treatments for CSCC, with several studies highlighting the importance of this pathway. Recently, the high mutational burden of CSCC and the increased risk in immunosuppressed patients have led to the exploration of immunotherapy as a treatment option. Patients receiving medications that increase CSCC risk should be closely monitored dermatologically, especially upon the emergence of suspicious skin lesions [5–8].

28.1.3 Basal Cell Carcinoma (BCC)

BCC is the most common malignancy among fair-skinned populations worldwide. It is a slow-growing tumor that rarely metastasizes. Individuals with nevoid BCC syndrome (typically caused by the *PTCH1* mutation) develop multiple BCCs starting in childhood or adolescence. Due to the histopathological diversity of BCC, the classification system recognizing sub-

types is based on risk level: low-risk subtypes are nodular (pigmented and keratotic), superficial (multifocal), fibroepithelial, and infundibulocystic (adnexal). High-risk subtypes are especially micronodular, infiltrating, sclerosing/morpheic, and sarcomatoid differentiation types [8]. Basosquamous carcinoma, a controversial entity with a higher risk of recurrence compared to other types, is defined as a malignancy with features of both BCC and SCC.

Although the “cell of origin” of BCCs has not been precisely defined, primitive hair follicle cells, which have many morphological and common features with the epidermis, have been implicated. The pathogenesis of BCC involves a combination of genetic susceptibility and UV-induced mutations. Inactivating alterations in the *TP53* gene are found in 40%–65% of sporadic cases, and the loss of heterozygosity of this gene is mutually exclusive with *PTCH1* mutations. Activation of the Sonic hedgehog (SHH) pathway, often due to mutated *PTCH1* receptors, is key in BCC development. When *PTCH1* is mutated, it causes an increased release of the transmembrane protein smoothened (SMO), which in turn activates the downstream *GLI1* transcriptional pathway. This pathway plays a key role in cell renewal, fate determination, while also making keratinocytes resistant to apoptosis [8]. In approximately 10% of sporadic BCCs, an activating mutation in *SMO* is found, while the remaining 90% are caused by an inactivating mutation in *PTCH1* [9].

The tumor consists of nodular islands of basaloid cells, typically arising from the epidermis and extending into the dermis. Palisading basaloid cells around the tumor islands are characteristic (Fig. 28.5a, b). The stroma shows fibromyxoid changes, retraction of tumor nests from the stroma (retraction artifact), calcification, and amyloid deposition. Apoptotic cells are common among basaloid tumor cells with hyperchromatic nuclei and narrow cytoplasm. Tumor nests may be colonized by melanocytes and may contain melanin pigment. Mature keratinization is most commonly seen in the nodular type. It may be ulcerated or cystic. Perineural invasion is not expected in low-risk subtypes. Perineural

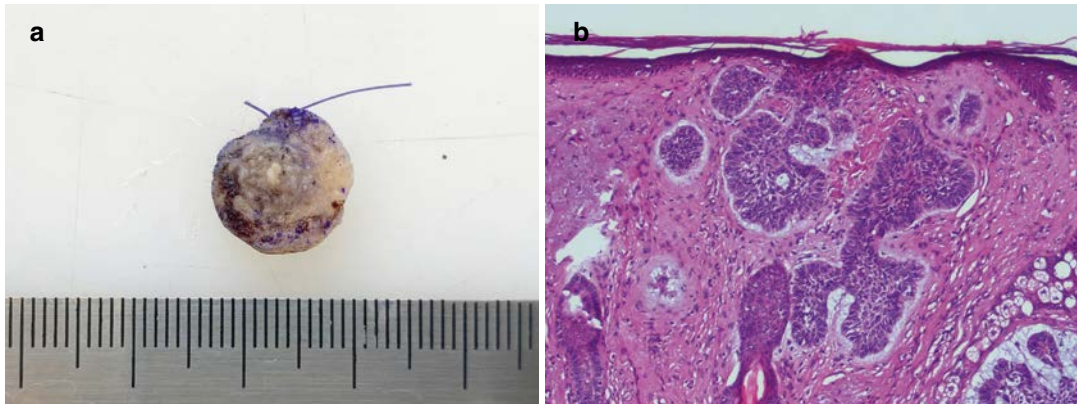


Fig. 28.5 Gross appearance of a basal cell carcinoma, showing a firm, tan-white cut surface with central ulceration and peripheral hemorrhagic areas. A suture marker is visible for orientation (a). Basal cell carcinoma arising

from the epidermis and extending into the dermis, with peripheral palisading of basaloid tumor cells (b). (H&E, ×40 magnification)

invasion involving nerves ≥ 0.1 mm in diameter is linked to higher disease-specific mortality. Micronodular BCC is characterized by small nests of neoplastic cells infiltrating the dermis, often posing challenges in achieving clear surgical margins and carrying a higher risk of recurrence. In the superficial subtype, basaloid lobules adhere broadly to the epidermis and exhibit limited downward extensions into the dermis. The surrounding stroma is typically loose and myxoid. Multifocal tumor foci, several millimeters in diameter, may be present at considerable distances from one another. Basosquamous (metatypical) carcinoma is usually larger and more poorly circumscribed. It is characterized by nested basaloid tumor zones alongside a squamoid component exhibiting typical keratinization. This variant tends to behave more aggressively than other types and is associated with both regional and distant metastases. Keratotic BCC is characterized by prominent keratin production in the centers of tumor islands. Rare subtypes, such as BCC with adnexal or sarcomatoid differentiation, can be challenging to distinguish from adnexal neoplasms.

BCC is common in the head and neck, followed by the trunk and extremities. BCC has also been reported in the perianal and genital areas, nail unit, palms, and soles. All patients with Gorlin (nevroid BCC) syndrome develop BCC;

patients with xeroderma pigmentosum and patients with Bazex-Dupre-Christol and Rombo syndrome are also at risk.

The nodular type is the most common type of BCC (60%–80%), usually located on the head. It often takes the form of a pearly ulceronodule with telangiectasia. Superficial type accounts for 30% of BCCs. It is most commonly found on the trunk, often in the form of multiple, erythematous patches. Fibroepithelial BCC, also known as Pinkus tumor, is a rare variant with a different clinical presentation and a slow course. It presents as a flesh-colored or erythematous nodule. Sclerosing morphea-form tumors have a whitish, atrophic appearance. Excision is sufficient in the low-risk group. Molecular tests are not required for diagnosis and treatment. Locally advanced BCC has a 0.3% chance of invading the skull, dura, and brain. In such rare metastatic cases, identification of mutations in the Hedgehog pathway in combination with a high tumor mutation burden may be helpful. Inhibition of the Hedgehog pathway is pharmacologically effective with vismodegib. SMO mutations can confer resistance to vismodegib. The presence of BCC usually increases the risk of developing other epithelial malignancies. Therefore, patients with BCC require a full-body skin examination, including the scalp.

28.1.4 Merkel Cell Carcinoma (MCC)

MCC is a rare and highly aggressive neuroendocrine carcinoma that originates in the skin [8]. MCC is more frequently observed in males and primarily impacts fair-skinned individuals who experience prolonged sun exposure. Factors such as immunosuppression (e.g., from chronic lymphocytic leukemia or organ transplantation) and advanced age (over 75 years) are recognized as predisposing conditions [10, 11].

Merkel cells are large, clear, oval-shaped cells found in the skin, where they serve as mechanoreceptors by directly interacting with nerve endings, primarily in the fingertips, lips, and glabrous skin [12]. Due to their structural and immunohistochemical similarities to Merkel cells, these tumors were named MCC. However, the exact cellular origin remains uncertain, with B-cell precursors, fibroblasts, and epidermal precursor cells being the most widely suggested origins [13]. The pathogenesis of MCC is primarily driven by two key factors: Merkel cell polyomavirus (MCPyV) and ultraviolet (UV) radiation. MCPyV drives oncogenesis by integrating into the host cell DNA and inactivating the *RB1* tumor suppressor gene, while virus-negative MCC is driven by UV-induced DNA damage, leading to a higher mutation burden [14, 15].

The tumor is typically localized in the dermis and/or subcutaneous adipose tissue, presenting

either as a well-circumscribed nodule or with an infiltrative growth pattern. Involvement of the epidermis is uncommon. The cells are small round, hyperchromatic, and demonstrate high mitotic activity (Fig. 28.6a, b). As observed in other neuroendocrine tumors, the nuclei exhibit a characteristic “salt-and-pepper” chromatin pattern. Lymphovascular invasion is frequently present. The tumor typically presents as pure MCC; however, in some cases, it can appear as a combined tumor, most commonly with squamous cell carcinoma. The differential diagnosis includes small round cell tumors such as small cell lung carcinoma, lymphoma, and Ewing sarcoma, as well as cutaneous tumors like BCC, basaloid squamous cell carcinoma, and small cell melanoma, with immunohistochemistry playing a crucial role alongside morphology in accurate diagnosis. Immunohistochemically, perinuclear dot-like staining with CK20 is a hallmark feature. The tumor expresses epithelial markers such as AE1/AE3 and EMA, as well as neuroendocrine markers including CD56, chromogranin, synaptophysin, and INSM-1. Immunohistochemistry targeting the MCPyV large T-antigen contributes to the diagnosis of virus-associated MCC [10].

MCC typically presents as a rapidly growing, red to purple, painless nodule. The tumor exhibits a strong propensity for regional lymph node involvement and has a high potential for distant metastasis [11]. Patients with MCPyV-positive

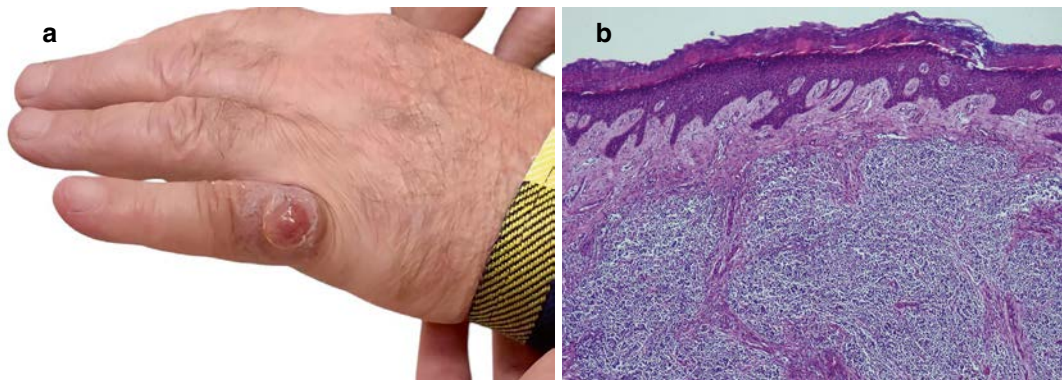


Fig. 28.6 Gross appearance of Merkel cell carcinoma presenting as a dome-shaped, erythematous nodule with overlying scale on the dorsal hand (**a**). Merkel cell carcinoma

composed of small, round, hyperchromatic cells infiltrating the dermis (**b**). (H&E, ×40 magnification)

MCC have a better prognosis than patients with virus-negative tumors. In locoregional disease, radiation therapy plays an important role in disease control. Immunomodulatory therapy in advanced disease has improved patient survival rates in recent years.

28.2 Cutaneous Adnexal Tumors

Cutaneous adnexal tumors include hamartomatous lesions and tumors that differentiate into one or more of the skin appendages (follicular, eccrine, apocrine, sebaceous gland). They are rarer than keratinocytic tumors and mostly benign; however, the incidence of malignant

forms is increasing with an aging population. Carcinomas often present de novo, but some have a preexisting benign component. Adnexal tumors that mimic BCC or SCC may show a wide variety of shapes and colors under dermoscopy but lack the typical dermoscopic features of these cancers [16]. Adnexal neoplasms can be cutaneous markers of a wide variety of inherited syndromes; therefore, accurate diagnosis is important to alert the clinician (Table 28.1). Along with multiple lesions, a family history of cancer and potential mutations through genetic screening should be evaluated to assess for a syndromic condition. Apart from syndromic cases, genetic alterations have recently been identified in sporadic lesions; however, the etiology and pathogenesis of

Table 28.1 Genetic syndromes linked to cutaneous adnexal tumors

Follicular tumors	Genetic syndrome	Genetic alteration
Trichilemmoma	Nevus sebaceous	<i>HRAS</i> mutation
	Cowden	<i>PTEN</i> mutation
Trichoblastoma	Brooke-Spiegler ^a	<i>CYLD</i> mutation
Cribriform trichoblastomas (trichoepithelioma)	Multiple familial trichoepithelioma 1 ^a	<i>CTNNB1</i> , <i>HRAS</i> , and <i>PTCH1</i> mutations
Trichogermminoma		<i>GRHL</i> fusion
Pilomatricoma and pilomatrical carcinoma	Gardner	<i>CTNNB1</i> mutation
Sweat gland tumors	Genetic syndrome	Genetic syndromes
Hidradenoma		<i>CRTC1/3::MAML2</i> fusion
Cylindroma	Familial cylindromatosis ^a	<i>CYLD</i> mutation
Spiradenoma	Brooke-Spiegler ^a	<i>CYLD</i> and <i>ALPK1</i> mutations
Syringocystadenoma papilliferum		<i>BRAF</i> p.V600E mutation
Hidradenoma papilliferum		<i>PIK3CA</i> or <i>AKT</i> mutation
Cutaneous mixed tumor		<i>PLAG1</i> fusions
Poroma and porocarcinoma		<i>YAP::MAML2</i> <i>YAP1::NUTM1</i> fusions
NUT adnexal carcinoma		<i>BRD3::NUTM1</i> , <i>NSD3::NUTM1</i> , <i>BRD3::NUTM2B</i> fusions
Secretory carcinoma		<i>ETV6::NTRK3</i> fusion
Digital papillary adenocarcinoma		HPV42 virus integration
Adenoid cystic carcinoma		<i>MYB::NFIB</i> fusion
Sebaceous tumors	Genetic syndrome	Genetic alteration
Nevus sebaceous		<i>HRAS</i> , <i>KRAS</i> and <i>NRAS</i> mutations
Sebaceoma and sebaceous adenoma	Muir Torre	<i>HRAS</i> , <i>KRAS</i> , <i>TP53</i> , <i>CDKN2A</i> , <i>EGFR</i> mutations DNA MMR gene-deficient
Sebaceous carcinoma Extraocular Periocular	Muir Torre	<i>TP53</i> , <i>PIK3CA</i> , <i>NOTCH1</i> , <i>ZNF750</i> , <i>RB1</i> , <i>FAT3</i> , <i>KMT2D</i> , <i>PCDH15</i> , <i>HRAS</i> , <i>KRAS</i> mutations <i>TP53</i> , <i>RB1</i> , <i>ZNF750</i> , mutations

^aCYLD-related syndrome family [17–20]

adnexal tumors remain largely unclear. The oncogenesis of these tumors is associated with a wide range of genetic mechanisms (e.g., point mutation, fusion genes, viral integration, etc.).

28.2.1 Follicular Tumors

Trichofolliculoma and *trichoepithelioma* (cribriform *trichoblastoma*) are hamartomatous lesions and hair follicle nevi that show differentiation toward the hair follicle. *Trichoblastoma* is another tumor that differentiates into a specific segment of the follicle and is composed of follicular germinative epithelial cells (Fig. 28.7). Mesenchymal cells surrounded by islands of cells form a cellular stroma and have the appearance of dermal tissue similar to the papillae of the hair follicle. *Trichogerminoma* is a rare follicular tumor in which fusions involving the *GRHL1*, *GRHL2*, or *GRHL3* genes have recently been identified. *Trichoadenoma* and *trichilemmoma* differentiate toward the outer root sheath. *Pilomatricoma*, also known as *pilomatrixoma* or *Malherbe's calcified epithelioma*, is a tumor originating from the hair matrix (Fig. 28.8). It is most commonly seen in the head, neck, and upper extremities, typically presenting before the age of 20. The malignant form, *pilomatrical carcinoma*, is rare. These tumors may occur sporadically or in the setting of Gardner syndrome. Mutations in *CTNBN1*, the gene encoding β -catenin, are particularly common in sporadic matrix tumors, whereas mutations in the *APC* gene are typically found in tumors associated with Gardner syndrome. The microscopic structure consists of basaloid cell islands, ghost cells, and calcification foci. Immunohistochemical detection of nuclear β -catenin expression is a strong indicator of matrical differentiation.

28.2.2 Sweat Gland Tumors

Syringomas are benign tumors with eccrine sweat gland differentiation. They are often multiple and commonly occur around the eyes, typically appearing during puberty or in adult women. The

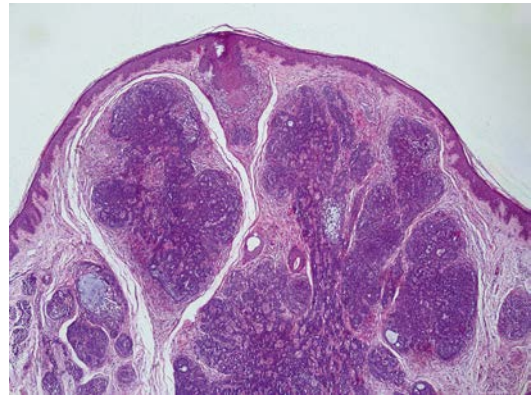


Fig. 28.7 Trichoblastoma showing well-circumscribed dermal lobules composed of basaloid follicular germinative epithelial cells embedded in a fibrotic stroma. (H&E, ×40 magnification)

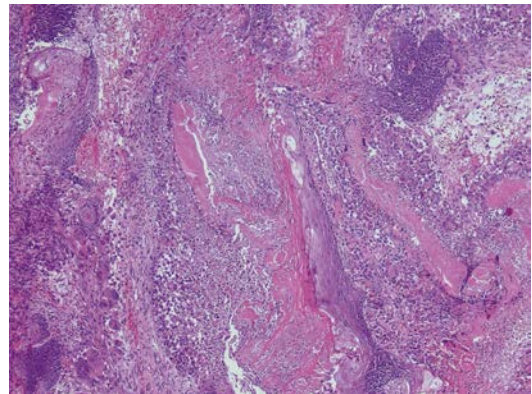


Fig. 28.8 Pilomatricoma composed of basaloid cell islands, eosinophilic ghost cells, and multinucleated giant cells within the dermis. (H&E, ×100 magnification)

lesions are well circumscribed. Ductal structures are seen in the fibrous stroma of the superficial dermis. Comma-shaped extensions of these ductal structures create a tadpole-like appearance. *Chondroid syringoma*, also known as a mixed tumor of the skin, is most commonly localized to the head and neck region. *Eccrine poroma* typically presents as a solitary mass on the plantar surface. Basaloid or keratinized tumor cells are small and uniform. The most important feature is the presence of sharply defined, broad, anastomosing tumor bands that extend continuously from the epidermis. *Clear cell hidradenoma* is a tumor typically located on the face or trunk, char-

acterized by solid islands, ductal structures, cystic cavities, and two distinct cell types. *Cylindromas* are among the most common adnexal skin tumors, though their histogenetic origin remains controversial. Ultrastructurally, it resembles the intradermal coiled duct of the eccrine sweat gland; however, it has also been observed in tumors exhibiting apocrine differentiation. It is most commonly localized in the head and neck region. Multiple lesions may be seen in patients with a family history of CYLD-related syndromes [17]. Islands with palisading basaloid cells are surrounded by a thick or cylinder-like hyaline membrane. *Spiradenomas* are extremely rare benign tumors that occur in young adults, with no predilection for gender or race. Multiple spiradenomas are inherited in an autosomal dominant pattern and often occur together with trichoepitheliomas, cylindromas, and parotid gland tumors. This combination is known as Brooke-Spiegler syndrome. Cylindromas and spiradenomas share a similar homogeneous nodular morphology. *Syringocystadenoma papilliferum* is a skin adnexal tumor with apocrine differentiation. It typically presents at birth or in early childhood, most commonly on the head and scalp. It may arise in association with nevus sebaceous. The lesions consist of epidermal invaginations and papillary extensions. The lining epithelium includes cuboidal cells in the lower layers and columnar cells in the upper layers, showing decapitation secretion. Although *adnexal carcinomas with NUT gene alterations* have metastatic potential, they tend to behave less aggressively than classic NUT carcinomas and typically harbor *BRD4:NUTM1* fusions.

28.2.3 Sebaceous Tumors

Sebaceous tumors represent a spectrum ranging from hyperplasia that mimics normal sebaceous glands to anaplastic or basaloid sebaceous carcinoma. *Nevus sebaceous* is a hamartoma of pilosebaceous-apocrine units and is typically located on the scalp. Approximately 30%–60% of sebaceous neoplasms exhibit a dMMR phenotype, although only about half of these carry a

germline mutation. Germline mutations are more frequently found in sebaceous adenomas and extraocular tumors. *Sebaceoma* is a benign adnexal neoplasm with sebaceous differentiation. It is composed of rounded cellular lobules and microcystic spaces, predominantly consisting of immature basaloid cells with scattered mature sebocytes. In sebaceoma, basaloid cells comprise more than 50% of the tumor. When mature sebaceous cells with cytoplasmic vacuoles predominate, it is classified as a *sebaceous adenoma*. The presence of multiple sebaceous adenomas should prompt consideration of *Muir-Torre syndrome*.

Sebaceous carcinoma (SC) is a malignant epithelial tumor of the sebaceous glands. They are classified into extraocular and periocular (eyelid) types depending on their anatomical location. The risk increases among individuals in their 60s and 70s, as well as in organ transplant recipients. Periocular involvement is found in 75% of both Caucasian and Asian patients, while extraocular involvement is less common and occurs only in Caucasians [18]. It is usually located in the head and neck region. Extraocular SCs can be divided into three molecular-genetic classes: ultraviolet (UV), microsatellite instability (MSI), and paucimutational signatures. SCs with UV signature carry the highest frequency of mutations, including *TP53*, *RREB1*, and the Notch family. MSI-associated SCs more commonly carry *HRAS* and *KRAS* mutations along with *TP53*, *RBI*, *RREB1*, and Notch family members. Finally, paucimutational SCs show fewer mutations such as *HRAS* and *NOTCH1*. Periocular SCs frequently harbor mutations in *TP53*, *RBI*, the Notch family, and *ZNF750* and exhibit *MYC* locus acquisition. A small subset is associated with high-risk HPV (types 16 and 18), occurs in younger patients, and has a lower relapse rate. Well-differentiated tumors consist of lobules of polygonal tumor cells with atypical, oval vesicular nuclei and abundant intracytoplasmic vacuoles giving a foamy appearance. Central comedo-type necrosis may be seen. Less differentiated tumors show a higher nucleus/cytoplasm ratio, nuclear pleomorphism, prominent nucleoli, basophilic cytoplasm with fewer intracellular vacuoles, and marked mitotic activity. Although immunohistochemistry

plays a limited role in the diagnosis of adnexal tumors, androgen receptor (AR) staining can be useful for identifying sebaceous differentiation, while EMA and CEA may assist in highlighting ductal structures.

Cutaneous adnexal tumors may present as solitary lesions or as multiple papules, nodules, or plaques. Syndromic cases are typically multiple. The head and neck are the most commonly affected areas. Some lesions have distinctive clinical features. Syringomas appear as skin-colored or slightly yellow, smooth papules. The eruptive variant presents as scattered, small papules—mostly on the anterior chest wall and flexural areas of the limbs—that may coalesce into plaques and show a linear or unilateral distribution. Sebaceoma and sebaceous adenoma usually present as well-circumscribed, yellow-tan nodules. Symptoms may range from completely asymptomatic to painful. Features such as irregular borders, discoloration, firmness, and ulceration may suggest malignancy; however, diagnosis most often relies on histopathological examination. Surgical excision remains the mainstay of treatment for adnexal tumors. Mohs micrographic surgery is increasingly favored for its efficacy. Simple excision is curative for sebaceomas and sebaceous adenomas. However, in patients with Muir-Torre syndrome, these tumors may signal an increased risk of visceral malignancies, contributing to morbidity and mortality. Currently, there is no established treatment algorithm for invasive cutaneous adnexal carcinomas.

28.3 Melanocyte and Melanocytic Lesions

Melanocytes are cells of neural crest origin and are found in the skin, eyes, brain membranes, mucous membranes, and digestive tract. They produce the pigment melanin, which makes an important contribution to the formation of skin color, and mainly has a protective function against UV radiation. The basal layer of the skin typically contains one melanocyte per ten keratinocytes. The cells have small, dark nuclei on

H&E staining, typically appear round, and show clear cytoplasm due to processing artifact. Their dendritic processes can be highlighted with special stains. In melanocytes, melanogenic tyrosinase is synthesized in the endoplasmic reticulum associated with the Golgi apparatus. This enzyme is utilized within melanosomes to produce pigment through four sequential stages. Once matured, the melanin pigment is rapidly transferred to neighboring keratinocytes via dendritic processes. Under normal conditions, mature melanin pigment is not visible within melanocytes.

Melanocytic lesions include benign, intermediate (melanocytoma), and malignant lesions (melanoma) (Fig. 28.9) [8]. The term *melanocytoma* refers to genetically intermediate lesions, whereas *nevi* are limited to benign lesions carrying only the initiating mutation without any additional pathogenic alterations.

Benign melanocytic lesions of the skin are categorized into three groups: those without cellular proliferation (reflecting disorders of melanin production and/or transfer) and those involving proliferation of dermal dendritic cells or epidermal melanocytes. *Freckles (ephelides)*, *melasma*, *melanocytic macules (as seen in Albright syndrome)*, *mucosal melanocytic macules*, and *Becker's melanosis* are lesions without cellular proliferation. However, melanocytic proliferation may be observed in the latter two. *Mongolian spot*, *nevus of Ota*, *nevus Ito*, and *blue nevus* are dermal dendritic cell proliferations. Epidermal melanocyte proliferations are divided into two groups: *lentiginous hyperplasia* and *melanocytic nevus*. Lentiginous hyperplasias are solar (actinic) *lentigo* and *lentigo simplex*.

28.3.1 Melanocytic Nevus

Nevi are benign lesions, either congenital or acquired, that arise from melanocytes. Giant congenital melanocytic nevi represent more complex lesions and carry a very low risk of developing melanoma. Nevus are more commonly observed in individuals with lighter skin tones, particularly within white populations. Palmar, plantar, subungual, and conjunctival nevi are more common in

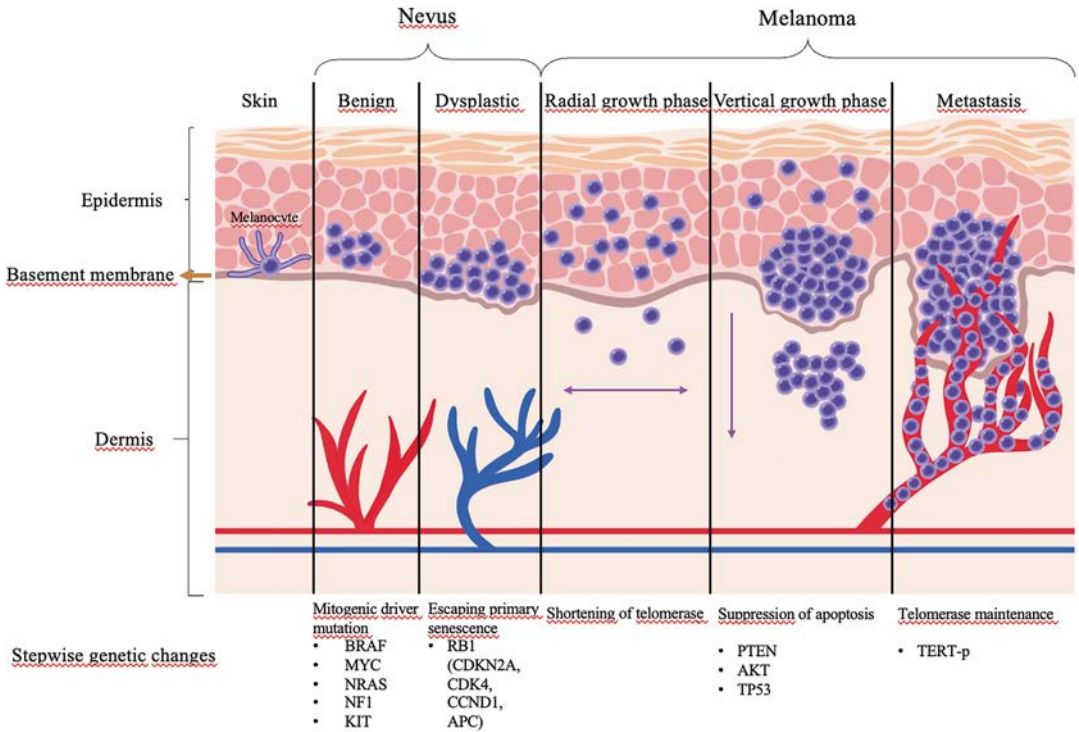


Fig. 28.9 Histologic and genetic features across the spectrum from benign nevus to melanoma

those with darker skin tones. Nevi are rare in early childhood but increase in number, peaking in the third decade of life, and then gradually decrease with age. The most rapid development occurs during puberty. In contrast to melanomas, nevi stop growing after reaching a certain size and gradually involute.

Common acquired nevi are typically brown, evenly pigmented, less than 6 mm in diameter, well-circumscribed, and may appear as either flat macules or slightly raised papules. Surface nevus cells are larger, tend to produce melanin, and grow in nests (Type A). Deeper nevus cells are smaller, produce little or no pigment, and grow in cords, being more mature (Type B). The most mature nevus cells are found in the deepest parts of the lesions, where they take a spindle shape, resemble neural tissue, and grow in fascicles (Type C). These cells can sometimes form neuroid structures. This maturation is associated with enzymatic changes, such as a progressive loss of tyrosinase activity and a gain in cholinesterase activity in deeper, pigmentless, nerve-like

nevus cells. This pattern helps distinguish benign nevi from melanomas, which show little to no maturation.

Nevi are formed by clonal proliferation of partially transformed melanocytes, which are controlled through intact tumor-suppressive mechanisms, such as oncogene-driven replication and aging. Benign nevi typically harbor a single MAPK pathway mutation, like the BRAF p.V600E mutation (in acquired nevi). Other mutations include *NRAS* (in congenital and some acquired nevi), *HRAS*, or kinase fusions involving *ALK*, *BRAF*, *ROS1*, *NTRK1*, *NTRK3*, *MET*, *MAP 3 K8*, or *RET* (in Spitz nevi), or RAS factor fusion mutations (*RASGRF1* and *RASGRF2*). In addition, blue nevi are characterized by mutations in the $G\alpha q$ pathway, with no accompanying genetic alterations.

Common acquired nevi vary from small, pigmented macules to raised, flesh-colored lesions. The surface may be dome-shaped, polypoid, or papillomatous. Melanocytic nevi are typically symmetric and well-defined (Fig. 28.10a–d).

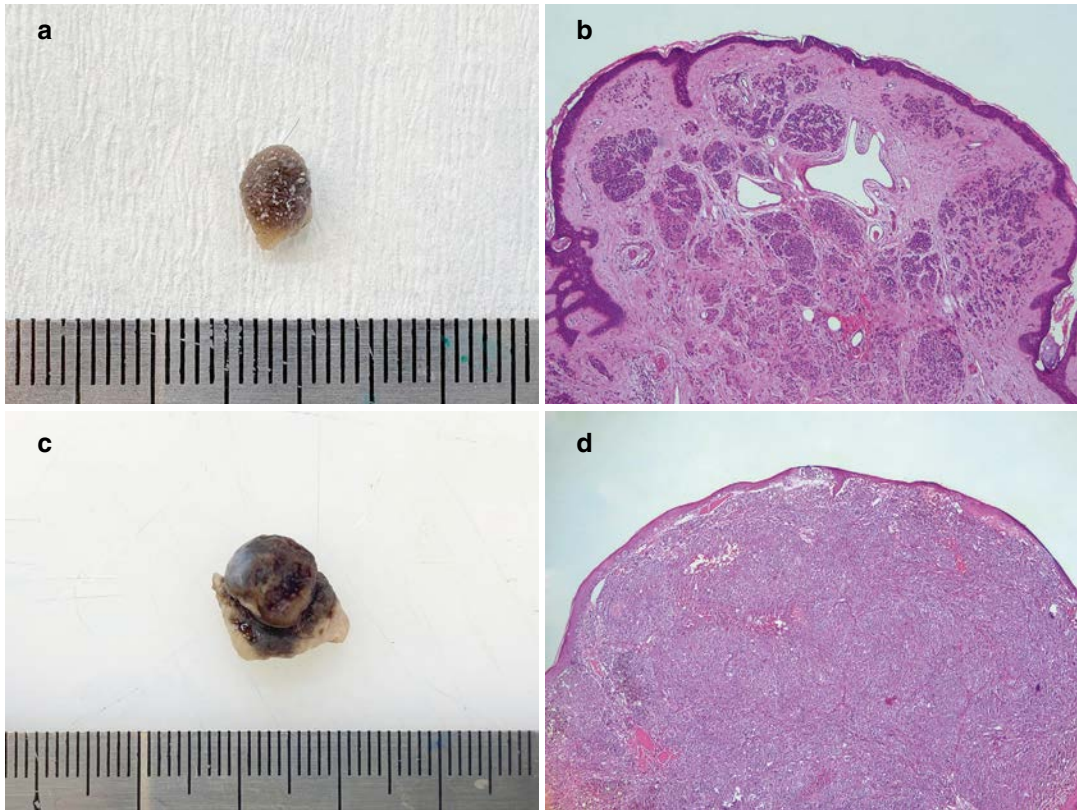


Fig. 28.10 Gross image of an intradermal nevus showing a small, well-circumscribed, pigmented lesion (a). Histologic section of the same intradermal nevus, demonstrating nests of benign melanocytes confined to the dermis (b). (H&E, $\times 40$ magnification) Gross image of a

melanoma, presenting as an asymmetrical, irregularly pigmented nodule (c). Histologic section of the melanoma showing a nodular morphology composed of a highly cellular dermal proliferation with partial pigmentation and marked cytologic atypia. (H&E, $\times 40$ magnification) (d)

They are classified based on the location of nevus cell aggregates: junctional nevi are located in the epidermis, dermal nevi in the dermis, and compound nevi in both. Junctional nevi, believed to represent the early developmental stage of nevi, are associated with the epidermis and consist of cell nests that extend from the rete ridges into the dermis. Histopathologically, these nevi consist of cell nests with round nuclei and no nucleoli. They show minimal or no mitotic activity.

Ordinary melanocytic nevi are not considered to have clinically significant premalignant potential. However, because they can appear in various shapes and colors, surgical excision is recommended either to differentiate them from malignant lesions or for cosmetic reasons.

28.3.2 Intermediate Melanocytic Lesions

This group includes Wnt-activated deep penetrating (plexiform) melanocytoma, pigmented epithelioid melanocytoma (also known as PRKAR1A-inactivated melanocytoma), BAP1-inactivated melanocytoma, and melanocytic tumors driven by microphthalmia-associated transcription factor (MITF) activation.

Intermediate melanocytic tumors often present with features such as older patient age, lesions larger than 1 cm, asymmetry, ulceration, and abnormal nodular growth. Morphologic features include severe cytologic atypia, necrosis, mitotic rates of at least 3–6 per mm^2 (depending on the

age of the patient), loss of p16 expression, widespread (i.e., >75% nuclear, grade 4+) expression of PRAME, and Ki-67 proliferation index greater than 10%. However, detailed clinical studies will be needed to specifically define this group. Histopathologic features and genetic or morphologic characteristics are important in determining the risk of progression to melanoma.

28.3.3 Dysplastic Nevi (DN)

DN were first described in hereditary melanoma families, but they can also be seen in individuals without a history of melanoma. In families with a history of melanoma, the disease risk does not follow Mendelian inheritance and is considered multifactorial. UV exposure is an important factor in their etiology, though DN can also be found in sun-protected areas. DN is a risk factor for melanoma, and the risk increases with the size of the lesion, the number of nevi, and the degree of dysplasia. DN and melanomas have overlapping dermoscopic features. Regular dermoscopic monitoring and total body photography can improve the detection of early-stage melanomas and help avoid unnecessary biopsies [21]. In familial dysplastic syndrome, the risk can rise up to 100%, and melanoma often develops de novo in these patients. DN rarely transform into melanoma, and it should be assessed in the context of other risk factors, such as skin color, cumulative sun damage (e.g., solar lentigines or “freckles”), genetic predisposition, and findings from family genomic studies. DN have been analyzed for allelic imbalance and found to have recurring losses of heterozygosity of the *CDKN2A* and *TP53* loci and *BRAF* V600E mutations [22].

DN are typically composed of both dermal and/or junctional components. Morphological changes are described in two categories: architectural and cytological. Architectural abnormalities include the presence of junctional shoulders adjacent to a dermal component (or the lesion being entirely junctional), bridging of melanocytic nests across between adjacent rete ridges, and the

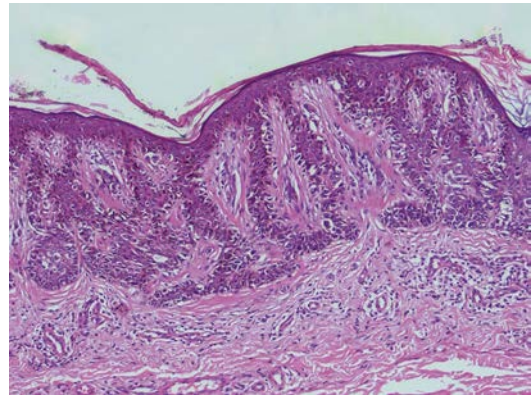


Fig. 28.11 Dysplastic nevus characterized by low-grade cytologic atypia in melanocytes and eosinophilic fibroplasia surrounding the rete ridges, with bridging of melanocytic nests and lentiginous spread in the lower epidermis. (H&E, $\times 100$ magnification)

presence of scattered melanocytic cells in a lentiginous pattern within the lower epidermal layers (Fig. 28.11). Dermal responses to the lesion may include mild, patchy lymphocytic infiltrates in the superficial dermis, melanin incontinence, and lamellar fibroplasia surrounding nests of epidermal melanocytes. Cytonuclear changes are characterized by enlarged nuclei, chromatin clumping, hyperchromasia, and variably prominent nucleoli. Atypical mitosis is not expected; however, their presence should prompt thorough evaluation to rule out melanoma. Cytonuclear atypia is graded as either low- or high-grade dysplasia.

The lesions are usually larger than 5 mm in diameter and can be either solitary or multiple. DN are commonly seen in adolescents, but they can appear at any age and may undergo regression. Clinical signs of dysplasia include the presence of macular lesions that are entirely macular or centrally papular, lesions exceeding 5 mm in diameter, variable pigmentation within the lesion, and irregular or indistinct lesion borders. High-grade DN that have not been completely excised should be re-excised due to the potential for histological overlap with melanoma or the possibility of malignant progression. In patients with risk factors, frequent dermoscopic monitoring is recommended.

Clinical Spitz tumors represent a broad spectrum of lesions. At one end of the spectrum, *Spitz nevi* are well-circumscribed and symmetrical lesions that often arise on the faces or extremities of children and less commonly in young adults. Typically, they develop as well-circumscribed pink to reddish, smooth-surfaced plaques, papules, or nodules, usually measuring less than 6 mm in diameter.

Atypical Spitz tumor (Spitz melanocytoma) was derived to describe spitzoid tumors that exhibit atypical features such as increased cellularity, asymmetry, decreased maturation, deep invasion, and cytological atypia. Despite atypical features, these lesions do not fully meet the morphologic criteria to be definitively classified as melanoma. At the opposite end of the spectrum lies *Spitz melanoma*, which is characterized by a higher mutational burden compared to Spitz melanocytoma and Spitz nevi, and may occasionally display a UV-induced mutation signature [23].

Microscopically, Spitz nevus is symmetrical and mostly compound type. The overlying epidermis is typically hyperplastic. Maturation is maintained in the epithelioid or spindle cell islands extending vertically into the dermis from the dermoepidermal junction. Cytologic atypia is mild, and mitotic activity is low. Solitary or clustered eosinophilic globules (Kamino bodies) may be present. In contrast, atypical Spitz tumors may demonstrate architectural asymmetry and lack the typical zonation pattern. They often contain irregular, densely cellular nests or nodules, composed of large spindle-shaped or epithelioid melanocytes.

Spitz nevi are often hypopigmented and may clinically resemble pyogenic granulomas or hemangiomas. *Atypical Spitz Tumors* can occur across a wide age range but are most commonly observed in individuals between 10 and 40 years of age. These lesions typically present as mottled-colored plaques or nodules with irregular borders and surfaces, measuring 7–10 mm in diameter, and are usually larger than conventional Spitz nevi.

Despite significant genomic insights into Spitz lesions, the clinical classification of diagnosti-

cally challenging spitzoid tumors remains difficult. Looking ahead, advancements in artificial intelligence and deep learning offer promise for the development of clinically useful tools, although substantial progress is still required.

28.3.4 Melanoma

Melanoma is an aggressive malignancy of pigment-producing cells called melanocytes. Although cutaneous melanoma is relatively rare, it is considerably more aggressive than other skin tumors. Its incidence has been increasing in recent years. Environmental factors such as ultraviolet (UV) radiation, as well as host-related factors such as fair skin, increased number of nevi, and family history, play a role in its etiology. The clinical diagnosis of melanoma is based on the analysis of morphological criteria, which makes the process subjective and often challenging, particularly for dermatologists and general practitioners. It is performed through visual inspection supported by dermoscopy. There are multiple clinical and architectural subtypes, including superficial spreading melanoma (SSM), acral lentiginous melanoma (ALM), lentigo malign melanoma (LMM), nodular melanoma (NM), desmoplastic melanoma, and amelanotic melanoma. Superficial spreading melanomas account for approximately 70% of all melanoma cases. Acral lentiginous melanomas are more common in patients with dark skin pigmentation and typically affect the palms, soles, and subungual regions. Lentigo maligna is more common in older age groups and presents as a slow-growing lesion in sun-exposed areas such as the face and scalp. Nodular melanomas are characterized by the absence of a radial growth phase, prominent vertical invasion and variable clinical appearance. Desmoplastic melanomas are sporadic and usually occur in elderly patients. Amelanotic melanomas, characterized by absence of pigmentation, pose a diagnostic challenge and are considered rare [24, 25].

Recent genetic and environmental studies, along with clinical variables such as age at onset, tumor location, and histopathologic features,

have enabled the identification of nine distinct melanoma subtypes [8]. The complexity of this classification arises from the molecular heterogeneity underlying melanoma pathogenesis. The first three subtypes occur in sun-exposed skin with marked solar elastosis due to cumulative sun damage: low cumulative sun damage (CSD), high CSD damage, and desmoplastic melanoma. These subtypes typically exhibit a UV-related mutational signature, characterized by multiple point mutations—most commonly cytosine to thymidine (C > T) transitions at dipyrimidine sites. This common pathway likely accounts for 80–85% of melanocytic tumors in the white population. The remaining six melanoma types arising from sun-protected skin are acral melanoma, mucosal melanoma, uveal melanoma, melanoma associated with congenital nevus or blue nevus, and Spitz melanoma. They generally display low mutational burden but are marked by extensive copy number alterations, often involving multiple genomic amplifications [8].

Melanomas are in the radial growth phase (RGP) when they are confined to the epidermis, and they generally have a good prognosis. However, once they penetrate the dermis beyond the basement membrane, they enter the vertical growth phase (VGP) and acquire the potential to metastasize. This transition is clinically significant. With the exception of nodular melanoma, which directly enters the VGP, a preceding RGP is observed in most other melanoma subtypes.

Somatic mutations in G1/S checkpoint genes (particularly loss of *CDKN2A*) are detected in 70% of melanomas. Tumor suppressor mechanisms are disrupted through deletion or mutation of *CDKN2A* (encoding p16), amplification or mutation of *CDK4* (the target kinase of p16), and loss of *RB1*. Germline mutations in *CDKN2A* and *CDK4* are also associated with a high-penetrance familial risk of melanoma. In low CSD melanomas, *BRAF* p.V600E mutation is the predominant driver event activating the MAPK pathway [26]. In contrast, high CSD melanomas rarely harbor *BRAF* p.V600E mutations. Instead, they typically contain other *BRAF* mutations or, more commonly, loss-of-function mutations in *NF1*, activating mutations in *NRAS*, or sometimes in

KIT. Similar genetic alterations (e.g., *GNAQ* and *GNA11* mutations) observed in uveal melanomas, blue nevus-associated melanomas, and leptomeningeal melanomas suggest a shared developmental origin from a distinct melanocyte lineage, one that does not reside within epithelial structures. Additional molecular events in melanoma pathogenesis include alterations in the p53 pathway, epigenetic and chromatin remodeling abnormalities (such as *SWI/SNF* complex or *BAP1* alterations), and telomerase activation via *TERT* promoter mutations or gene amplification [27, 28] (Table 28.2).

In melanoma in the RGP, large, pleomorphic melanocytic cells are present either as isolated units or in the form of nests confined to the epidermis, demonstrating pagetoid spread throughout all levels. These cells exhibit hyperchromatic nuclei with prominent nucleoli and show marked variation in size and shape. Atypical mitotic figures are frequently observed. In early invasive, microinvasive, and in situ melanomas, a characteristic dense, band-like infiltration of mononuclear inflammatory cells is observed at the base of the lesion, often accompanied by melanophages. In the tumorigenic VGP, atypical melanocytic cells disrupt the basement membrane and directly invade the dermis. Within the dermis, a solid tumor mass of neoplastic melanocytes is typically present, exceeding in diameter the largest intraepidermal nest. Cytologic and architectural asymmetry is common, including variability in cell shape, size, pigmentation, and host inflammatory response. The tumor frequently fills and expands the papillary dermis, or it may infiltrate between thick collagen bundles of the reticular dermis. The overlying epidermis may be ulcerated; when intact, it often appears atrophic and compressed. The intensity of dermal inflammatory infiltrate in nodular melanoma is highly variable. Lymphocytes interspersed among tumor cells, known as tumor-infiltrating lymphocytes (TILs), are considered morphologic evidence of host immune-mediated apoptosis. Cytologically, tumor cells in the dermis demonstrate marked pleomorphism, typically falling into two principal categories: epithelioid and spindle-shaped cells. While both may be present in a given tumor,

Table 28.2 Immunohistochemical markers associated with genetic alterations in melanocytic tumors

IHC markers ^a	Genetic alterations	Type of melanocytic tumors
BRAFV600E	<i>BRAFV600E</i> activating point mutation	Acquired nevus Small congenital nevus Melanoma BAP1-inactivated melanocytic tumor Deep penetrating nevus
NRAS Q61R	<i>NRAS</i> Q61R activating point mutation	Large congenital nevus Melanoma
ALK	<i>ALK</i> translocation	Spitz nevus Atypical Spitz tumor Spitz melanoma
ROS1	<i>ROS1</i> translocation	Spitz nevus Atypical Spitz tumor
Pan-TRK	<i>NTRK1</i> or <i>NTRK3</i> translocation	Spitz nevus Atypical Spitz tumor Pigmented spindle cell nevus
β-Catenin/LEF1	<i>CTNNB1</i> activating mutation	Deep penetrating nevus (DPN) DPN-like melanoma
BAP1	Loss of function mutation and loss of heterozygosity in <i>BAP1</i>	BAP1-inactivated melanocytic tumor
PRKR1A1	Loss of function mutation and loss of heterozygosity in <i>PRKR1A1</i>	Pigmented epithelioid melanocytoma (PEM)
c-KIT (CD117)	<i>KIT</i> mutations	Mucosal and acral melanomas
N/A ^b	<i>GNAQ/GNA11</i> mutations	Uveal melanomas Blue nevus-associated melanomas

N/A not available, IHC immunohistochemistry [27, 28]

^aIHC markers associated with genetic alterations

^bNo IHC marker is available for detecting GNAQ/GNA11 mutations to date

one phenotype often predominates. In general, lentiginous melanomas such as ALM and LMM possess a dermal invasive component composed primarily of spindle-shaped cells. Conversely, in SSM and NM, the tumor is predominantly made up of epithelioid cells. Epithelioid cells commonly form alveolar or nest-like structures, whereas spindle cells display irregular branching arrangements. Melanin pigment within tumor cells often aids in the diagnosis. Immunohistochemical markers of melanocytic lineage, such as Sox10, S100, HMB45, and Melan-A, are valuable in the differential diagnosis, particularly since metastatic melanoma cells can exhibit a wide range of morphologies. Diffuse PRAME immunoreactivity provides additional support for a diagnosis of melanoma, but it is not definitive and should never replace expert histopathologic assessment [29].

They usually arise de novo, but to a lesser extent, they also develop on the background of a preexisting nevus. The ABCDE criteria are key

clinical features for the recognition of melanocytic lesions undergoing change: A-asymmetry, B-border irregularities, C-color variation, D-diameter greater than 6 mm, and E-evolution (such as ulceration, bleeding or changes in pain, itching, or other symptoms). They are usually larger than benign nevi and exhibit irregular borders and heterogenous pigmentation (Fig. 28.10a–d). Macular areas correspond to the early superficial growth phase (RGP), whereas raised nodular areas usually indicate dermal invasion (VGP). The prognosis of melanoma is closely linked to early detection. When melanoma is confined to the epidermis (melanoma in situ, or Stage 0), the risk of metastatic spread is negligible. Although Breslow tumor thickness is the most important prognostic factor, histopathological parameters such as ulceration, atypical mitotic figure count, presence of regression, Clark level, lymphovascular invasion, TILs, perineural invasion, and microsatellitosis are also considered important prognostic markers.

The Melanocytic Pathology Assessment Tool and Diagnostic Hierarchy (MPATH-Dx V2.0) defines four proposed classes aimed at providing a management-based classification system for melanocytic lesions and facilitating clearer communication between pathologists and clinicians [30]. Class I lesions carry a very low risk of progression to melanoma and include common acquired and congenital nevi without atypia, dysplastic nevi with low-grade atypia, and common blue nevi. Class II lesions are associated with a low risk of progression but require further evaluation; this category encompasses dysplastic nevi with high-grade atypia, Spitz nevi, melanocytomas and their atypical variants (including cellular blue nevus/melanocytoma, plexiform, or deep penetrating nevus/melanocytoma), as well as lentigo maligna and melanoma in situ. Class III corresponds to AJCC stage pT1a melanoma, which carries a low risk of local and regional metastasis. Class IV includes melanomas at AJCC stage pT1b or higher, characterized by a moderate to high risk of regional and/or distant metastatic spread. While surgical excision is the cornerstone of treatment in early-stage melanoma, increasingly effective therapies are available for advanced disease, including BRAF inhibitors, immune checkpoint inhibitors targeting PD-1 and CTLA-4, combination regimens with targeted therapy, and experimental approaches such as cancer vaccines. Nevertheless, prevention and early detection remain fundamental in reducing melanoma-associated morbidity and mortality.

References

- Fortarezza F, Cazzato G, Ingravallo G, Dei Tos AP. The 2023 WHO updates on skin tumors: advances since the 2018 edition. *Pathologica*. 2024;116(4):193–206.
- Gorai S, Ahmad S, Raza SSM, Khan HD, Raza MA, Etaee F, Cockerell CJ, Apalla Z, Goldust M. Update of pathophysiology and treatment options of seborrheic keratosis. *Dermatol Ther*. 2022;35(12):e15934.
- Álvarez-Salafranca M, Zaballos P. [Translated article] Dermoscopy of squamous cell carcinoma: from actinic keratosis to invasive forms. *Actas Dermosifiliogr*. 2024;115(9):T883–95. English, Spanish.
- Lee YB, Kim JI. Genetic studies of actinic keratosis development: where are we now? *Ann Dermatol*. 2023;35(6):389–99.
- Queirolo P, Cinquini M, Argenziano G, Bassetto F, Bossi P, Boutros A, Clemente C, de Giorgi V, Del Vecchio M, Patuzzo R, Pennachiole E, Peris K, Quaglino P, Reali A, Zalaudek I, Spagnolo F. Guidelines for the diagnosis and treatment of cutaneous squamous cell carcinoma: a GRADE approach for evidence evaluation and recommendations by the Italian Association of Medical Oncology. *ESMO Open*. 2024;9(5):103005.
- Corchado-Cobos R, García-Sancha N, González-Sarmiento R, Pérez-Losada J, Cañueto J. Cutaneous squamous cell carcinoma: from biology to therapy. *Int J Mol Sci*. 2020;21(8):2956.
- Cozma EC, Banciu LM, Soare C, Cretoiu SM. Update on the molecular pathology of cutaneous squamous cell carcinoma. *Int J Mol Sci*. 2023;24(7):6646.
- International Agency for Research on Cancer. WHO Classification of Tumour. Available online: <https://tumourclassification.iarc.who.int/welcome/#preview>. Accessed on 13 Jan 2023.
- Lang BM, Balermipas P, Bauer A, Blum A, Dirschka T, Follmann M, Frank J, Frerich B, Fritz K, Hauschild A, Heindl LM, Howaldt HP, Ihrler S, Kakkassery V, Klumpp B, Krause-Bergmann A, Löser C, Meissner M, Sachse MM, Schlaak M, Schön MP, Tischendorf L, Tronnier M, Vordermark D, Welzel J, Weichenthal M, Wiegand S, Kaufmann R, Grabbe S. S2k guideline basal cell carcinoma of the skin (update 2023). *J Dtsch Dermatol Ges*. 2024;22(12):1697–714.
- Comut E, Karstarli Bakay OS, Demirkan NC. What is the predominant etiological factor for Merkel cell carcinoma in Turkey: viral infection or sun exposure? *BMC Cancer*. 2025;25(1):336.
- Walsh NM, Cerroni L. Merkel cell carcinoma: a review. *J Cutan Pathol*. 2021;48:411–21.
- Halata Z, Grim M, Bauman KI. Friedrich Sigmund Merkel and his “Merkel cell”, morphology, development, and physiology: review and new results. *Anat Rec A Discov Mol Cell Evol Biol*. 2003;271:225–39.
- Akaike T, Nghiem P. Scientific and clinical developments in Merkel cell carcinoma: a polyomavirus-driven, often-lethal skin cancer. *J Dermatol Sci*. 2022;105:2–10.
- Tanda ET, d’Amato AL, Rossi G, Croce E, Boutros A, Cecchi F, et al. Merkel cell carcinoma: an immunotherapy fairy-tale? *Front Oncol*. 2021;11:739006.
- Feng H, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human Merkel cell carcinoma. *Science* (1979). 2008;319(5866):1096–100.
- Lai M, Muscianese M, Piana S, Chester J, Borsari S, Paolino G, Pellacani G, Longo C, Pampena R. Dermoscopy of cutaneous adnexal tumours: a systematic review of the literature. *J Eur Acad Dermatol Venereol*. 2022;36(9):1524–40.
- Nagy N, Dubois A, Szell M, Rajan N. Genetic testing in CYLD cutaneous syndrome: an update. *Appl Clin Genet*. 2021;14:427–44.

18. Seger EW, Neill BC, Tolkachjov SN. Adnexal and sebaceous carcinomas. *Dermatol Clin.* 2023;41(1):117–32.
19. Kervarrec T, Sohier P, Pissaloux D, de la Fouchardiere A, Cribier B, Battistella M, Macagno N. Genetics of adnexal tumors: an update. *Ann Dermatol Venereol.* 2023;150(3):202–7.
20. Cazzato G, Daruishi M, Fortarezza F, Colagrande A, Marzullo A, Ingravallo G, Dei Tos AP, Yang RK, Cho WC. Gene fusion-driven cutaneous adnexal neoplasms: an updated review emphasizing molecular characteristics. *Am J Dermatopathol.* 2025;47(6):453–61.
21. Drozdowski R, Spaccarelli N, Peters MS, Grant-Kels JM. Dysplastic nevus part I: historical perspective, classification, and epidemiology. *J Am Acad Dermatol.* 2023;88(1):1–10.
22. Spaccarelli N, Drozdowski R, Peters MS, Grant-Kels JM. Dysplastic nevus part II: dysplastic nevi: molecular/genetic profiles and management. *J Am Acad Dermatol.* 2023;88(1):13–20.
23. Chatzopoulos K, Syrnioti A, Linos K. Spitz melanocytic tumors: a fascinating 75-year journey. *Genes (Basel).* 2024;15(2):195.
24. Naik PP. Cutaneous malignant melanoma: a review of early diagnosis and management. *World J Oncol.* 2021;12(1):7–19.
25. Bastian BC. The molecular pathology of melanoma: an integrated taxonomy of melanocytic neoplasia. *Annu Rev Pathol.* 2014;9:239–71.
26. Shain AH, Yeh I, Kovalyshyn I, Sriharan A, Talevich E, Gagnon A, Dummer R, North J, Pincus L, Ruben B, Rickaby W, D'Arrigo C, Robson A, Bastian BC. The genetic evolution of melanoma from precursor lesions. *N Engl J Med.* 2015;373(20):1926–36.
27. Huang C, Lau TW, Smoller BR. Diagnosing cutaneous melanocytic tumors in the molecular era: updates and review of literature. *Dermatopathology (Basel).* 2024;11(1):26–51.
28. Andea AA. Molecular testing in melanoma for the surgical pathologist. *Pathology.* 2023;55(2):245–57.
29. Lezcano C, Jungbluth AA, Busam KJ. Immunohistochemistry for PRAME in dermatopathology. *Am J Dermatopathol.* 2023;45(11):733–47.
30. Barnhill RL, Elder DE, Piepkorn MW, Knezevich SR, Reisch LM, Eguchi MM, Bastian BC, Blokx W, Bosenberg M, Busam KJ, Carr R, Cochran A, Cook MG, Duncan LM, Elenitsas R, de la Fouchardière A, Gerami P, Johansson I, Ko J, Landman G, Lazar AJ, Lowe L, Massi D, Messina J, Mihic-Probst D, Parker DC, Schmidt B, Shea CR, Scolyer RA, Tetzlaff M, Xu X, Yeh I, Zembowicz A, Elmore JG. Revision of the melanocytic pathology assessment tool and hierarchy for diagnosis classification schema for melanocytic lesions: a consensus statement. *JAMA Netw Open.* 2023;6(1):e2250613.

Nonneoplastic Central Nervous System Diseases

29

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29.1 Introduction

Nonneoplastic central nervous system (CNS) pathologies involve wide-ranging etiologies such as hemorrhage, ischemia, vascular lesions, infections, autoimmune, degenerative, developmental, and metabolic disorders. This broad etiological repertoire is associated with diverse diseases showing specific clinical, laboratory, and radiological signs. Even further, modern molecular and radiological methods enable scientists to understand that some clinical presentations previously considered as a single disease are, in fact, different pathologies and disorders. Hence, it would not be false to claim that an in-depth overview of nonneoplastic CNS diseases deserves an encyclopedia series. However, this chapter, with a highly summarized style, aims to provide a bird's-eye view by giving introductory information for those interested in understanding nonneoplastic CNS diseases. Also, despite these diseases having widely divergent etiologies, they often harbor greatly converging injury pathways, including, but not limited to, excitotoxicity due to

glutamate excess, reperfusion and oxidative stress, mitochondrial damage, lipid peroxidation, inflammatory mediators, and perturbations of mechanisms controlling cell death (i.e., apoptosis, autophagy). Therefore, this chapter does not repeat shared pathogenesis pathways if the considered disease has a unique etiology and minimal causal similarities with other nonneoplastic CNS diseases.

29.2 Cellular Principles of Neuropathogenesis

29.2.1 Neural Injury Responses

Acute CNS injury causes adaptive responses or the death of neurons, depending on the insult severity. Surviving neurons undergo initial cytoplasmic swelling and dissolution of Nissl substances. If neurons can repair the damaged cellular material, Nissl bodies reappear, accompanied by increases in heat shock proteins and neurotrophic factors such as NGF and BDNF, which provide adaptive plasticity and foster survival. Following damage, astrocytes undergo gliosis, characterized by marked glial hypertrophy and proliferation around the damaged area, as well as an increase in type III intermediate filament proteins, including GFAP and vimentin. While astrocytic responses may limit damage by restoring the blood-brain barrier (BBB), reducing vasogenic edema and glutamate excess, their for-

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mation of a glial scar that limits axonal regeneration acts detrimental [1]. Microgliosis is the phenomenon where resting microglia get activated by retracting processes, undergo amoeboid morphology, proliferate, and are recruited to damaged sites within hours after CNS injury. Similar to astrocytes, microglial responses may both reduce and exacerbate damage, with the former involving M2-like microglia that secrete anti-inflammatory mediators, phagocytose debris, and stimulate regeneration, and the latter involving M1-like microglia that secrete pro-inflammatory cytokines, proteases, and reactive oxygen species (ROS) [2].

29.2.2 Cerebral Edema, Herniation, and Intracranial Pressure

Cerebral edema occurs due to excess water retention in the neural parenchyma, classified into several types based on its principal cause. Yet, different edema types may co-occur, especially when the damage is severe or ongoing. Cytotoxic edema begins with an intracellular metabolic perturbation, where a diminished ATP supply hampers the Na^+/K^+ -ATPase activity, leading to intracytoplasmic sodium retention and the flow of excess water from outside to inside the cells. This phenomenon is mainly associated with ischemia and insults causing mitochondrial injury, but trauma may also cause cytotoxic edema at late phases. Vasogenic edema mainly involves the dysfunction of the BBB, leading to leakage of blood plasma fluid and proteins to the extracellular compartments, prevalent in hemorrhagic, inflammatory, and malignant CNS diseases. Osmotic, or alternatively called ionic edema, occurs as a result of hypoosmolar states, such as those that happen during hyponatremia and syndrome of inappropriate antidiuretic hormone secretion (SIADH). In osmotic edema, water flows into the extracellular CNS compartments without BBB disruption. As the cranial vault is mostly a closed space, water retention in the CNS enhances the intracranial pressure (ICP), which normally ranges between 7 and 15 mmHg in supine adults, and values exceeding 20–22 mmHg are considered the treatment threshold [3]. If the

ICP increases prominently and timely treatment is lacking, brain tissues traverse the skull's rigid boundaries, called cerebral herniation, leading to focal CNS lesions or death. Cerebral herniations may be subfalcine, uncal, central, or upward transtentorial or tonsillar, where the latter may cause rapid cardiac and respiratory arrest due to the medullary compression elicited by descending cerebellar tonsils. Currently, several preclinical and clinical studies are testing new treatments for CNS edema, targeting various molecules and pathways, including the SUR1-TRPM4 cation channel, aquaporin-4, the $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransporter NKCC1, and vasopressin receptors. While these approaches have yielded promising results in preclinical experiments, their translation to the clinic requires time and optimization.

29.3 Hemorrhagic Stroke

About 10%–15% of strokes happen due to intracerebral hemorrhage (ICH), with mortality rates reaching up to 65% at 1 year, and only ~20% of survivors can live independently at 6 months after the event. The principal risk factor is chronic hypertension, damaging vessels by lipohyalinosis, and leading to the development of microaneurysms such as Charcot-Bouchard lesions, all associated with vessel rupture. Other causal components include cerebral amyloid angiopathy among the elderly population, anticoagulant use or coagulopathies, vascular malformations, illicit drugs, and chronic alcohol intake. After the bleeding, central cascades of CNS injury involve the fast expansion of intracranial volume, leading to a mass effect, perihematoma edema, widespread intracranial vasoconstriction, toxicity of extracellular hemoglobin and its iron component, oxidative stress, and inflammation accompanied by significant leukocytic infiltration [4].

29.4 Ischemic Neuropathologies

29.4.1 Ischemic Stroke

Ischemic stroke is the most common stroke type caused by a cerebral artery occlusion, leading to

rapid declines in cerebral blood flow and oxygen supply. Atherosclerosis, atrial fibrillation, and procoagulant status are among the major risk factors. The clinical severity and constellation of symptoms depend on the involved vascular territory and the extent of collateral circulation, which typically manifests as sudden focal neurological deficits, such as aphasia, hemisensory loss, hemiparesis, and hemianopia [5]. The infarct core develops within minutes after vessel occlusion, when blood flow critically falls, precluding the survival of neural cells. The hypoperfused yet still viable tissue, surrounding the infarct core and known as the ischemic penumbra, can be salvaged with timely treatment, enabling reperfusion. The pathogenic events of cerebral ischemia involve impairments of ATP-dependent ion pumps, subsequent depolarizations, overstimulation of NMDA and AMPA receptors, and activation of proteases, lipases, and endonucleases. Spreading depolarization waves in the penumbra increase the metabolic demand of neurons, accelerating infarct expansion if not countered promptly. The dying neural cells release excessive glutamate, triggering a vicious cycle of excitotoxicity. Reperfusion paradoxically amplifies oxidative damage, as the injured mitochondria are unable to metabolize the resupplied oxygen adequately. ROS also activate matrix metalloproteinases (MMPs) that disrupt the BBB, enhance edema, and increase the risk of hemorrhagic transformation, especially in association with thrombolytic treatment [5, 6].

29.4.2 Hypoxic-Ischemic Encephalopathy

Hypoxic-ischemic encephalopathy (HIE) affects about 1–3 neonates per 1000 live births in developed countries, and up to 8 per 1000 in developing countries, which accounts for the main reason for neonatal mortality and prolonged disability. Protracted labor, maternal hypotension, cord accidents, and severe fetal acidemia constitute antepartum and intrapartum risk factors, and HIE itself is the most common etiology of neonatal seizures and among the major causes of cerebral palsy, characterized by posture, tone,

and movement abnormalities [7]. HIE generally manifests with infants' weak reflexes, hypotonia, feeding difficulty, inadequate consciousness, seizures, and respiratory abnormalities. The pathogenesis involves mechanisms highly similar to ischemic stroke, including ATP depletion, impairment of ionic channels, cellular swelling, excitotoxicity, apoptosis, and necrosis, which occur in phases comprising acute, latent (<6 h), secondary injury (6–72 h), and lastly the tertiary one, where the neural plasticity is diminished. Therapeutic hypothermia (TH) is the single clinically approved treatment for HIE. However, there is still debate about its potency to reduce mortality rates and its significant side effects, including bradycardia, hypotension, hypoglycemia, and sepsis, underline the necessity for discovering novel treatments. One approach would be to combine TH with erythropoietin treatment, which, according to recent meta-analyses, could improve clinical outcomes, including reductions in acute cerebral injury, mortality, and the risks of intellectual and motor developmental impairment [7].

29.5 Traumatic Neuropathologies

29.5.1 Traumatic Brain and Spinal Cord Injury

About 69 million people per year undergo traumatic brain injury (TBI) due to falls, accidents, sports activities, and assaults. TBI is a non-focal injury that involves multiple pathologies and symptoms simultaneously. TBI damages the CNS by blast overpressure causing contusions, ischemia, and hemorrhages due to vascular disruption, rotational, and shear forces leading to diffuse axonal injury, which progresses to Wallerian degeneration. Within minutes after the insult, vasoconstriction leads to cerebral hypoperfusion, harming CNS autoregulation and BBB and causing excitotoxicity, mitochondrial damage, cell death, and secondary edema [8]. Neuroinflammation may act partially beneficially by clearing cellular debris through the actions of microglia and astrocytes, but it is mainly associated with detrimental pathways. The glymphatic

system and inflammasome activation, triggered by the hemoglobin degradation product heme, are emerging concepts that may serve as novel therapeutic targets in addition to current treatments, which are limited to craniotomy, osmotic agents for edema, and supportive care. Traumatic spinal cord injury (TSCI) has a lower global incidence, but it still constitutes a significant population health problem. The cellular pathogenesis of posttraumatic spine injury is similar to that of the brain, but here the glial scar formation is more critical as it limits axonal reconnection, remyelination, and ultimately the functional spinal cord recovery. Several preclinical and clinical trials investigate versatile modalities with potential therapeutic activity for TBI and TSCI, including neurotrophic factors, Nogo receptor and aquaporin-4 antagonists, anti-RGMA antibodies, riluzole, stem cell therapy, and neuromodulation. Comprehensive physical therapies utilizing integrated systems and virtual reality could also alleviate the impairments in gait, balance, and dual-task abilities among TBI and TSCI survivors [8].

29.5.2 Chronic Traumatic Encephalopathy

Chronic traumatic encephalopathy (CTE) is the result of repeated head traumas that mainly occur due to sportive activities such as boxing and hockey and also due to blast injuries among the military personnel. The pathology involves the neuronal and astrocytic accumulation of hyperphosphorylated tau (p-tau), especially in perivascular areas at the profundity of cortical sulci and in superficial laminae, regions that are influenced less in other tauopathies. Besides the pathogenesis mechanisms such as inflammation, microgliosis, and ROS injury shared by other CNS lesions, changes relatively more specific to CTE also exist, including white matter degeneration with axonal varicosities and occasional inclusions of β -amyloid and TDP-43 [9]. Traumatic encephalopathy syndrome (TES) manifests with persistent changes in mood, behavior, and cognition, which begin years after cranial trauma, and its definitive diagnosis can only be made postmor-

tem. Exposure to repetitive trauma at an early age, ApoE genotype, and old age constitute TES risk factors [10].

29.6 Hypertensive Encephalopathy and Cerebral Small Vessel Disease

A fast and sharp rise in blood pressure impairs cerebral autoregulation, damaging arterioles, breaching the BBB, and causing vasogenic edema, which particularly affects the cortex and posterior brain regions. Visual symptoms, including cortical blindness, commonly occur due to a tendency to affect posterior brain regions. Other symptoms include intense headache, nausea and vomiting, confusion or decreased consciousness, and seizures. The abruptness of blood pressure elevation is the leading factor causing endothelial dysfunction and edema, which occurs not necessarily with absolute values. Early interventions to reduce blood pressure can achieve rapid symptom relief and full recovery within days. As explained below, uncontrolled high blood pressure, if it progresses to a chronic course, causes constant damage to small vessels [11]. Over 50% of persons aged 65 years or older are affected by cerebral small vessel disease (CSVD), which is a major cause of vascular dementia and lacunar infarcts, where the latter accounts for about one-third of all strokes, collectively with hypertensive intracerebral hemorrhages. While chronic hypertension is one of the primary drivers of pathogenesis, blood pressure variability independently associates with a greater CSVD burden, causing microbleeds as evidenced by white matter hyperintensities (WMH), regardless of mean blood pressure [11]. Sustained exposure to high blood pressure leads to concentric fibrotic thickening of the penetrating arterioles, known as arteriosclerosis. The accompanying lipohyalinosis and fibrinoid necrosis further narrow and enhance the fragility of cerebral vessels. Dysfunction of endothelial cells, BBB injury, inflammation, and extracellular matrix remodeling potentiate the pathogenesis. Ongoing microvascular ischemic infarcts and inflammation constitute principal

factors mediating hypertension-induced acceleration of WMH accumulation, memory deficits, and executive dysfunction [11]. CSVD-induced vascular dementia can also enhance Alzheimer's pathology, reducing the age threshold when signs and symptoms manifest. The therapeutic approach directly targets the etiology through maintaining blood pressure levels within normal limits with proper antihypertensive medications and attentive follow-ups, which slows WMH accumulation and cognitive impairment.

29.7 Vascular Malformations

29.7.1 Cavernous and Arteriovenous Malformations

Cerebral vascular malformations include arteriovenous malformations (AVM), cerebral cavernous malformations (CCM), and venous angiomas (VA). AVMs and CCMs are associated with abnormal vascular maturation and reactivation of angiogenic and possibly embryonic pathways. VAs possess structural proteins typical of a normal, mature vascular wall and no innate angiogenic potential. AVMs are solitary and more often single lesions compared to CCMs, which can be multiple in approximately 13%–33% of cases. Cerebral parenchyma is present among the vascular structures in AVMs, as well as microbleeding, calcification, thrombotic and malformed vessels, fibrosis, and gliosis, which constitute secondary changes. AVMs have a nidus formed by dysplastic vessels that connect feeding arteries and draining veins without a capillary bed, resulting in high-flow shunts and cerebral hemodynamic perturbations. AVMs occur with a prevalence of ~0.02% clinically and mostly remain undetected as indicated by autopsy studies. AVM etiology is complex, including both genetic predisposition and congenital existence, such as seen in hereditary hemorrhagic telangiectasia, and also post-injury angiogenic stimuli. The Spetzler-Martin grading of AVMs, which considers their size, venous drainage, and location in eloquent cortex, aids in treatment decisions that may include neurosurgical, radiosurgical, and multimodal approaches. CCMs are

relatively well-demarcated lesions, lacking large feeding arteries and draining veins, and having thin-walled, irregular, dilated sinusoidal channels that resemble capillaries. CCMs are devoid of subendothelial sustenance due to an abnormal basal lamina, in contrast to AVMs, which have intact pericytes and cellular connections. The lack of subendothelial structural support may be associated with a higher frequency of microbleeds encountered in CCMs, as indicated by their higher hemosiderin content and gliosis. An embryonic character is relevant to both AVMs and CCMs, where the latter lesions are considered more immature. The immaturity of these lesions may stem from a defect in embryogenesis and also likely from the reactivation of embryonic proteins in adult cells with abnormal intracellular or extracellular composition. CCMs affect about 0.1%–0.5% of the population, including sporadic cases and familial clusters. Familial CCMs follow an autosomal dominant inheritance caused by loss-of-function mutations in the *CCM1* (KRIT1), *CCM2*, or *CCM3* (PDCD10) genes, where a second hit somatic mutation may be involved in lesion formation. While most CCMs are diagnosed incidentally, they may manifest with seizures, neurologic deficits, and hemorrhagic stroke. Differing percentages are reported for their hemorrhagic risks, which increase with previous bleeding and specific locations, such as the brainstem [12, 13].

29.7.2 AVMs and CCMs Differ in Degree of Vascular Maturation

Insufficient maturation of capillaries during the approximately third gestational week of humans is considered the beginning of AVM development. The angiogenic nature of AVMs stems from their expression of angiogenic growth factor receptors (i.e., Flk-1), as well as their extracellular matrix proteins (i.e., higher fibronectin and collagen III levels), and MMPs (i.e., higher MMP-2 and MMP-9 levels). All features of this protein expression composition resemble fetal rather than adult cerebral vessels, which enable parenchymal penetration by newly forming

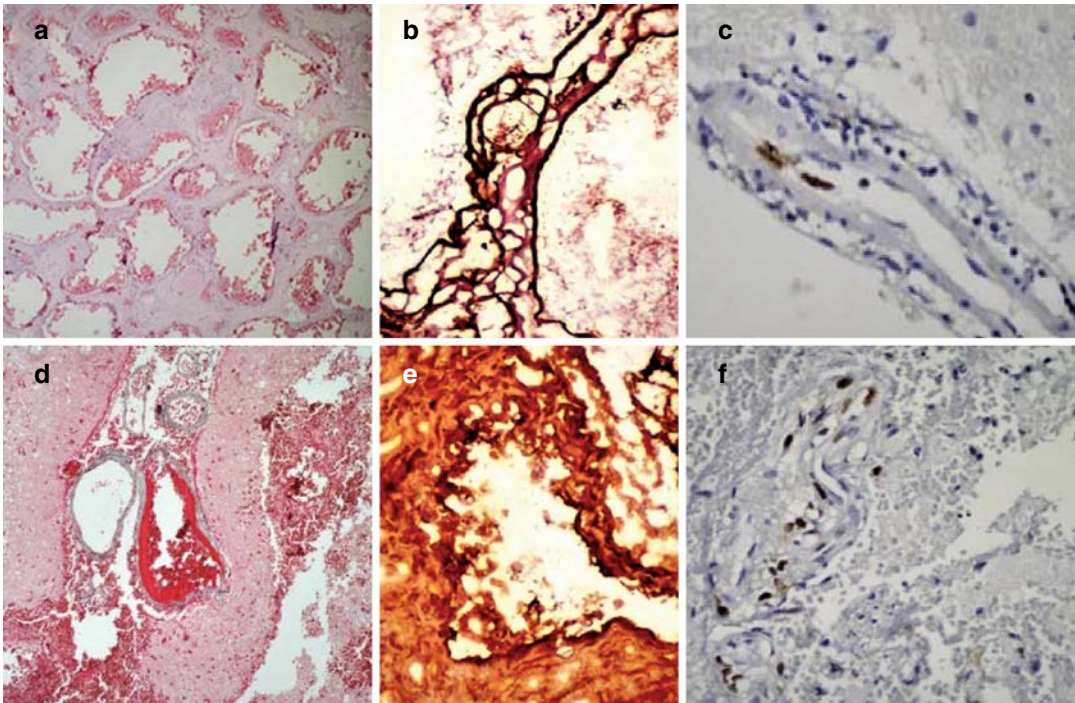


Fig. 29.1 (a), (b), and (c) depict CCMs and (d), (e), and (f) demonstrate AVMs. (a) H&E staining, $\times 40$. (b) $\alpha 5\beta 1$ Integrin-stained CCM, $\times 200$. (c) Low Ki67 staining in

CCM endothelia, $\times 40$. (d) Trichrome staining, $\times 40$. (e) $\alpha 5\beta 1$ Integrin-stained AVM, $\times 200$. (f) AVM endothelia with abundant Ki67 labeling, $\times 40$

microvessels. The molecular content of AVMs also significantly differs from that of CCMs. AVMs express higher Integrin $\alpha 5\beta 1$ and lower Integrin $\alpha 5\beta 3$ and a lower ratio of fibronectin-to-laminin than CCMs, which also express smooth muscle actin, all of which indicate higher immaturity of CCMs. However, some studies have shown that AVMs exert higher neovascularization in cornea implant experiments and higher Ki67 cell proliferation indices in human paraffin specimens than CCMs, which seems antithetical, as tissues with higher immaturity generally proliferate and grow faster [12, 13] (Fig. 29.1).

29.8 Infectious CNS Diseases

29.8.1 Bacterial CNS Infections

Bacterial CNS infections in immunologically intact adults generally occur during high-grade bacteremia, where bacteria cross the BBB via the

choroid plexus and meningeal vessels. The pathology, referred to as leptomeningitis or more commonly meningitis, describes infections of the leptomeningeal and subarachnoid spaces, while the phrase cerebritis designates cerebral parenchymal infections. Among infants and immunocompromised adults, CNS infections can develop with a lesser microbial load and atypical pathogens. Virulence factors, such as pneumococcal adhesins, bind to endothelial receptors, activate leukocyte adhesion, and disrupt the BBB's tight junctions, leading to neutrophil infiltration into cerebral parenchyma, which is amplified with inflammatory cytokines, MMPs, ROS, and excess nitric oxide (NO), leading to the development of vasogenic edema. Dense polymorphonuclear leukocyte (MPN) infiltration in subarachnoid spaces, particularly among basal cisterns, meningeal vessel vasculitis, microvascular thrombosis, cerebral micro-or macroinfarcts, and vasogenic and cytotoxic edema, contribute to neural injury and constitute features of acute purulent leptomeningeal

inflammation. When not countered in a timely or efficient manner, the infection progresses to early and late cerebritis, which occur on days 1–3 and 4–9 after bacterial propagation, respectively. While perivascular neutrophilic cuffing, focal necrosis, and endothelial proliferation constitute the hallmarks of early cerebritis, late cerebritis is typified by expanding necrosis, mixed inflammatory invasion including macrophages, and fibroblast activation leading to capsule formation. Granulation tissue development, collagen deposition, and neovascularization occur during the early stages of capsule formation, between the 10th and 13th days. Abscess formation, characterized by distinct necrotic, inflammatory cell layer, fibrous capsule, neovascular granulation, and outer gliosis zones, accompanied by edema, constitutes the features of late capsule completion on day 14 and later. *Streptococcus* and *Staphylococcus* species are the most common causes of cerebral abscesses. A brain abscess can be polymicrobial, particularly when the infectious origin is otogenic or nasal sinus, or during a hematogenous dissemination, as seen in pulmonary infections and endocarditis. Mixed bacterial sources complicate the diagnosis by causing histological heterogeneity and necessitate the use of broad-spectrum antibiotics for treatment. The headache, fever, and focal neurologic deficit triad are present in only about 20% of patients, so the diagnosis relies more on microbiological tests and neuroimaging. Approximately 70% of patients recover fully with timely drainage and antibacterial therapy that covers both aerobic and anaerobic bacteria [9]. Among the bacterial CNS infections, those caused by *Mycobacterium tuberculosis* (MT) warrant discussion due to their unique features. Tuberculous meningitis (TM) is the most common form of MT infection in the CNS, caused by bacteremia during the primary infection or late reactivation of the latent infection. As the extrapulmonary MT infections present with atypical signs and symptoms, the diagnosis of TM may be difficult. Radiological findings showing a predilection for involvement of basal brain regions and the patient's history may be indicative. Thick, gray-greenish exudate covering the basal cisterns, pons, Sylvian fissure,

and cisterna magna is characteristic, which may convert to a fibrous character among patients who live relatively longer. Lesions of CNS tuberculosis characteristically consist of a central area of caseous necrosis surrounded by epithelioid cells and a peripheral ring of lymphocytes, which may contain small numbers of Langhans giant cells, in contrast to pulmonary tuberculosis lesions that include these cells in abundance. Acid-resistant bacilli exist in varying numbers, and meningeal vascular inflammation may extend into the brain parenchyma, causing vasculitis, thrombosis, infarcts, and fibrinoid necrosis. Outer cerebral cortex lamina and the cerebellar superficial follicles may show signs of perivenous lymphocytic infiltration and microglial proliferation. TM may rarely follow an acute fulminant course with a polymorph-rich exudate leading to acute tuberculous encephalopathy manifested with cerebral swelling, patchy or diffuse demyelination, white matter hemorrhagic areas, neuronal loss, and gliosis. This pathology may develop due to an antigenic similarity between MT and myelin components. Tuberculomas, which are generally multiple oval to round lesions measuring 2–12 mm in diameter, may cause intracranial masses in endemic areas of tuberculosis and reside in the cerebellum, pontine tegmentum, and paracentral lobule. Tuberculomas are distinguished from pseudoabscesses, which are formed by the liquefaction of caseous material and lack a surrounding granulomatous reaction. Tuberculosis abscesses in the subdural and epidural spaces are very rare, where the latter often develop as complications of spinal tuberculosis or Pott's abscess. Unlike other types of MT infections of the CNS, tuberculous brain abscesses contain numerous MT bacilli in their necrotic center, surrounded by pus, which has become more common due to the AIDS epidemic [9].

29.8.2 Viral CNS Infections

Viral CNS infections present with signs differing by the viral type and load and the intensity of inflammatory responses, but they mostly mani-

fest acutely with fever, variable changes in consciousness (from confusion and lethargy to coma), focal or generalized seizures, and focal neurological signs. Specific treatments for viral CNS infections are still lacking, except for the herpes simplex virus (HSV) encephalitis treated with acyclovir and CMV encephalitis treated with either acyclovir, cidofovir, foscarnet, ganciclovir, and valganciclovir. Viruses that mainly cause gray matter infections of the brain and spinal medulla, so-called polioencephalitis and poliomyelitis, are caused by poliovirus, Coxsackievirus A4, A7, and B3, echovirus 2 or 9, enterovirus 70 or 71, and rabies, which is a lyssavirus. Arbovirus infections also predominantly involve the gray matter, yet the CNS white matter may be influenced at varying rates. Rabies CNS infection is accompanied by mild to moderate inflammation, including minimal perivascular lymphocytes, microglial nodules, and relatively well-preserved neuronal morphology except for the hallmark eosinophilic Negri bodies in hippocampal pyramidal and cerebellar Purkinje neurons. Viral infections, mostly limited to the white matter of the CNS, so-called leukoencephalitis or leukoencephalopathy, are caused by human immunodeficiency virus (HIV) or JC virus, a papovavirus responsible for progressive multifocal leukoencephalopathy. Viral CNS infections involving both the gray and white matter of the brain and spinal medulla are referred to as panencephalitis and panmyelitis, respectively. These conditions are primarily caused by HSV-1 or HSV-2, cytomegalovirus (CMV), and varicella zoster virus (VZV). HSV-1 constitutes the leading viral pathogen of necrotizing viral panencephalitis among immunocompromised patients, and HSV-2 can cause necrotizing panmyelitis. Other necrotizing viral CNS infections caused by CMV or VZV also develop more often among the immunosuppressed population, where CMV may infect the ependymal CNS layer, called ependymitis. HIV can cause different types of CNS infections, including aseptic meningitis, HIV encephalitis, HIV leukoencephalopathy, and vacuolar myelopathy. HIV encephalitis is also known as subacute or microglial nodule encephalitis, characterized by the presence of abundant

microglial nodules, particularly in the cerebral white matter, thalamus, basal ganglia, and cerebellum, as well as by reactive gliosis, relative paleness of myelin structures, and multinuclear giant cells. HIV leukoencephalopathy manifests with diffuse myelin paleness, which is peculiarly not a real myelin loss as shown by myelin-specific stains and which may contain sparse macrophages. Vacuolar myelopathy is characterized by the vacuolization of the spinal medulla's white matter in the posterior and lateral columns. Microscopic findings include mild gliosis and the dispersed presence of lipid-laden macrophages, with no lymphocytic infiltration. With the progression of disease, vacuolization leads to myelin degradation and secondary axonal injury, conditions that mimic subacute combined degeneration of the spinal medulla [14] (Fig. 29.2).

29.8.3 John Cunningham Virus and Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a rare, fatal demyelinating disease caused by reactivation of John Cunningham virus (JCV) in immunocompromised patients. The virus is present in up to 85% of healthy adults, remaining latent in the lymphoid tissues, kidneys, and likely the brain until the cellular immunity remains intact. Cellular entry of JCV involves 5-HT_{2A} serotonin receptors and sialic acid moieties. Multifocal confluent white matter lesions, often sparing the cortex but occasionally extending into subcortical grey matter, are encountered in gross pathology. Histopathologically, extensive depletion of oligodendrocytes due to lytic intracellular viral replication, enlarged nuclei containing viral inclusions, and astrocytes with bizarre morphology are remarkable. While myelin and axonal loss occur significantly, PML lesions differ from MS with their irregular borders, lack of periventricular Dawson's fingers and central vein sign, and their general involvement of U-fibers and cortical regions. Following an antiretroviral regimen or withdrawal of the etiological immunosuppressive monoclonal anti-

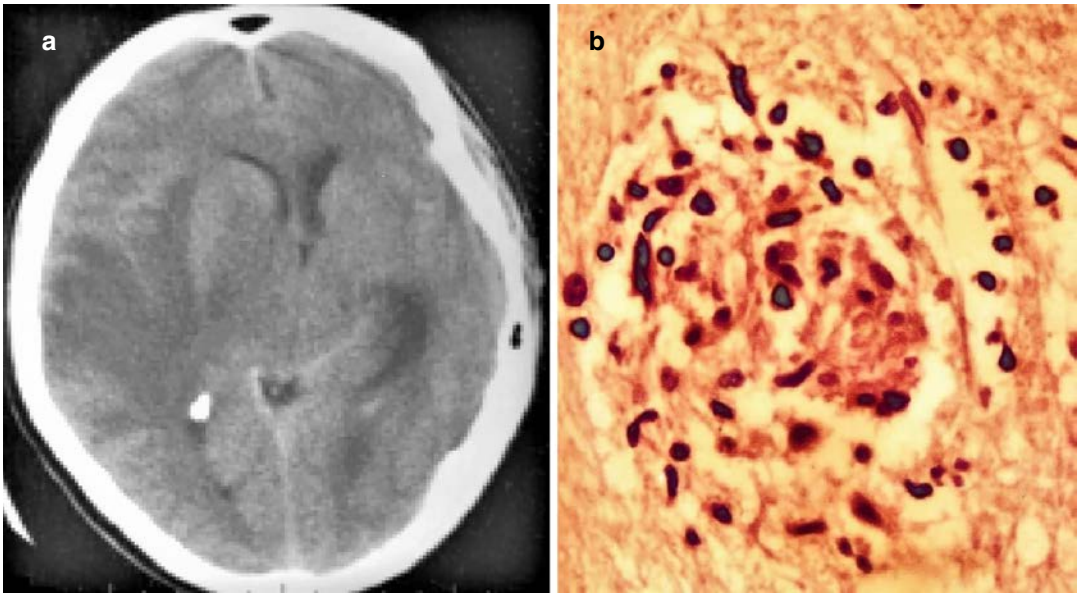


Fig. 29.2 (a) Herpes simplex encephalitis. Large low-density region in the right temporal lobe, severe midline shift, compression of the right lateral ventricle and the

brain stem on non-enhanced cranial CT. (b) HIV encephalitis. Microglial nodule formation, H&E $\times 400$ m

body treatment, immune reconstitution inflammatory syndrome (IRIS) may develop, characterized by paradoxical lesion expansion and contrast enhancement, which complicates recovery [15].

29.8.4 Fungal CNS Infections

Intracranial fungal infections (ICFIs) are most frequently caused by *Cryptococcus neoformans* (CN), followed by *Candida* and *Aspergillus* species in developing countries. However, less-known fungal species can also cause CNS infections in low-income countries and among immunosuppressed individuals. Diagnosis of ICFIs increasingly involves serological, immunofluorescent, and molecular tools. Still, biopsies of the brain, meninges, and CSF are not rare for the differential diagnoses of invasive mycosis, followed by culture and staining methods such as methenamine-silver, India ink, and acid-fast stainings. With their capsules mediating immune evasion, CN fungal yeasts disperse via the bloodstream and settle in gelatinous pseudocysts

around Virchow-Robin spaces and meninges, causing meningoencephalitis with occasional granulomas, despite inducing generally minimal inflammation in the CNS. *Candida* species cause opportunistic CNS fungemia characterized by microabscesses with hyphae and pseudohyphae, a neutrophil-rich inflammation, occasional vasculitis and hemorrhage, and tissue necrosis. *Aspergillus* and *Zygomycota* induce angioinvasive CNS infections among the severely immunosuppressed, which invade through sinuses or hematogenous seeding. Their neuropathology is characterized by extensive vascular invasion and thrombosis, causing infarction and hemorrhagic necrotic areas. Histopathologically, *Aspergillus* species appear with their branching septate hyphae, while the broad, nonseptate ribbon-like hyphae constitute the trademark of *Mucor* species of *Zygomycota* [16] (Fig. 29.3).

29.8.5 Parasitic CNS Infections

Many parasites, ranging from single-cellular parasites to the cyclophyllid cestode worm *Taenia*,

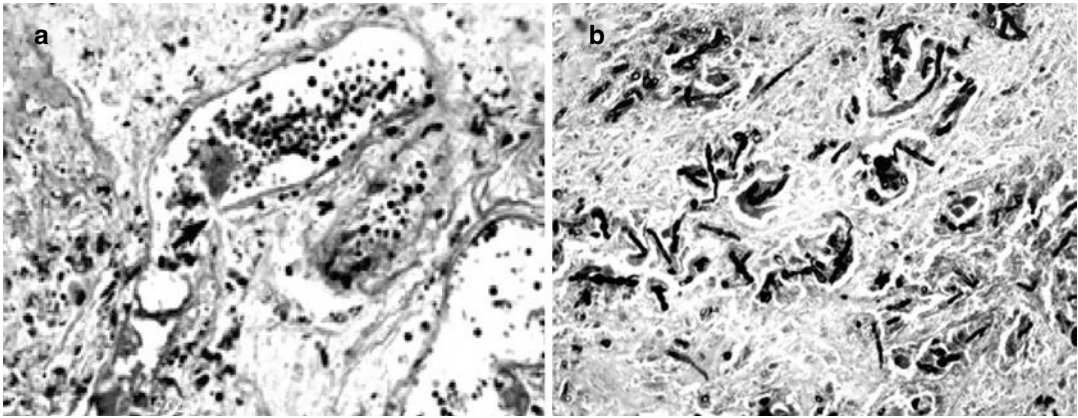


Fig. 29.3 Cerebral fungal infection with *Xylohypha bantiana*. (a) Fungal vascular invasion accompanied by thrombosis, H&E $\times 250$. (b) Fungal elements on methenamine silver stain, $\times 400$

may cause CNS infections. *Toxoplasma gondii* tachyzoites invade the brain and form cystic bradyzoites in neurons and glia by using a Trojan horse tactic, where the infected immune cells transport these parasites through the BBB. Tachyzoites and bradyzoite cysts lodge inside the multiple necrotizing abscesses, accompanied by marked inflammation composed of macrophages, mononuclear microglia, and lymphocytes, with cyst walls histopathologically visible in chronic lesions. The CNS pathogenesis of malaria caused by *Plasmodium* species occurs due to the sequestration of parasitized erythrocytes in the cerebral microvasculature, which obliterates microcapillaries and venules, resulting in ring hemorrhages around microvessels, BBB disruption, and subsequent perivascular edema, axonal and myelin damage, and microglial activation. Neurocysticercosis is a tapeworm infection of the CNS, where the ingested *Taenia solium* eggs could form larval cysts inside the brain parenchyma, subarachnoid space, and ventricles. Inflammatory responses of the host vary depending on the cyst stage, classified as viable $\rightarrow$ colloid $\rightarrow$ granular $\rightarrow$ calcified. Minimal inflammation exists at the viable cyst stage. Infiltration and edema accompany the colloid stage, and the granular and calcified stages exhibit gliosis, calcifications around the inflammatory scars, which may be associated with arachnoiditis and obstructive hydrocephalus [17].

29.8.6 Prion Diseases

Prion diseases are spongiform encephalopathies that share a common feature associated with their pathogenesis, which involves the sequential misfolding of a normal protein, PrPC, into pathogenic, β -sheet-rich PrP^{Sc}, which aggregates and propagates. PrP^{Sc} uniquely replicates by autocatalysis, a process that continues unless the depletion of PrPC occurs, which is a prion glycoprotein widely expressed in all cell types of the CNS and encoded by the *PRNP* gene in humans. Prion proteins in prefibrillary oligomer or mature amyloid fiber structures act neurotoxically by extracellular and intracellular injury, the latter of which involves mitochondrial damage and oxidative stress. The infectious prion diseases include kuru, dietary transmission of bovine spongiform encephalopathy (BSE), and the iatrogenic variant of Creutzfeldt-Jakob disease (CJD). Prion diseases may arise in sporadic, genetic, and acquired forms, including sporadic, variant, and familial CJD, Gerstmann-Sträussler-Scheinker syndrome (GSS), and fatal familial insomnia (FFI). Their classic micromorphological triad comprises spongiform vacuolation, neuronal loss, and gliosis, with variable accompaniment by PrP^{Sc} deposits. An intense deposition of PrP^{Sc} is a hallmark of dietary BSE transmission. While specific GSS variants harbor PrP amyloid plaques with minimal spongiosis, sporadic CJD (sCJD) is charac-

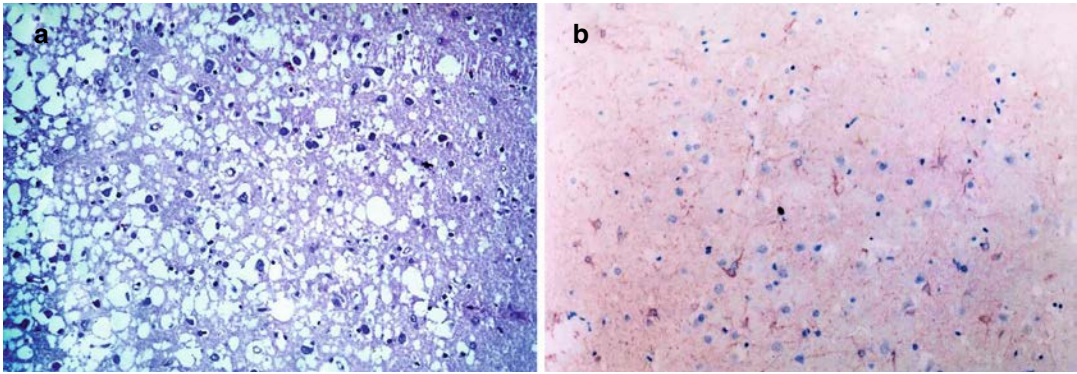


Fig. 29.4 (a) Widespread spongiform changes in Creutzfeldt-Jakob disease, H&E $\times 200$. (b) PrP^{Sc} immunopositivity in Creutzfeldt-Jakob disease, $\times 200$

terized by widespread spongiosis, with prominent neural loss involving the cortex, thalamus, and basal ganglia. Florid amyloid plaques, which are especially prevalent in the cerebral and cerebellar cortex, accompanied by severe thalamic neuronal loss, characterize variant CJD (vCJD). GSS and FFI, both caused by PRNP mutations, induce degeneration in diverse cerebral areas. While FFI is associated with the intensive degeneration of the thalamic anterior and mediodorsal nuclei, in correlation with an insomnia phenotype, GSS manifests more prominently with amyloid PrP plaques accumulating in the cerebral cortex and cerebellum [14] (Fig. 29.4).

29.9 Autoimmune CNS Diseases

29.9.1 Multiple Sclerosis

Multiple sclerosis (MS) is an autoimmune CNS disease, where immune cells mount immunity mainly against myelin components, and its histopathological classification is based on the existence of complement, oligodendrocyte apoptosis, and plaque borders. Well before radiologically detectable overt lesions appear, normal-appearing white matter contains subtle oligodendrocyte injury, phosphorylation of axonal neurofilaments, and perfusion abnormalities. Acute, active lesions are infiltrated by macrophages phagocytosing myelin debris, as well as T and B lymphocytes,

exhibiting a perivascular cuffing pattern, and show oligodendrocyte loss and reactive gliosis. The MS hallmark, an oligoclonal band comprising immunoglobulins, is produced by plasma cells infiltrating the perivascular spaces and meninges. In slowly expanding lesions, active microglia at lesion rims contribute to ongoing demyelination beyond the early inflammatory phase, while chronic, inactive lesions exhibit sharply demarcated plaque borders, sparse macrophages, and minimal inflammation [18] (Fig. 29.5).

29.9.2 Acute Disseminated Encephalomyelitis

Acute disseminated encephalomyelitis (ADEM) is commonly triggered by an infectious event or, rarely, vaccinations against viral or bacterial pathogens, where up to 85% of cases have a previous immunologic trigger. The pathogenesis likely involves molecular mimicry, where autoreactive T cells targeting MOG, myelin basic protein (MBP), and proteolipid protein (PLP) develop an immune response leading to multifocal demyelination. ADEM mainly affects children 5–8 years old, where adults comprise about 25% but have a poorer prognosis. Typical signs and symptoms include fever, seizures, polyfocal neurological deficits, encephalopathy, and coma in severe cases. Histopathological features that

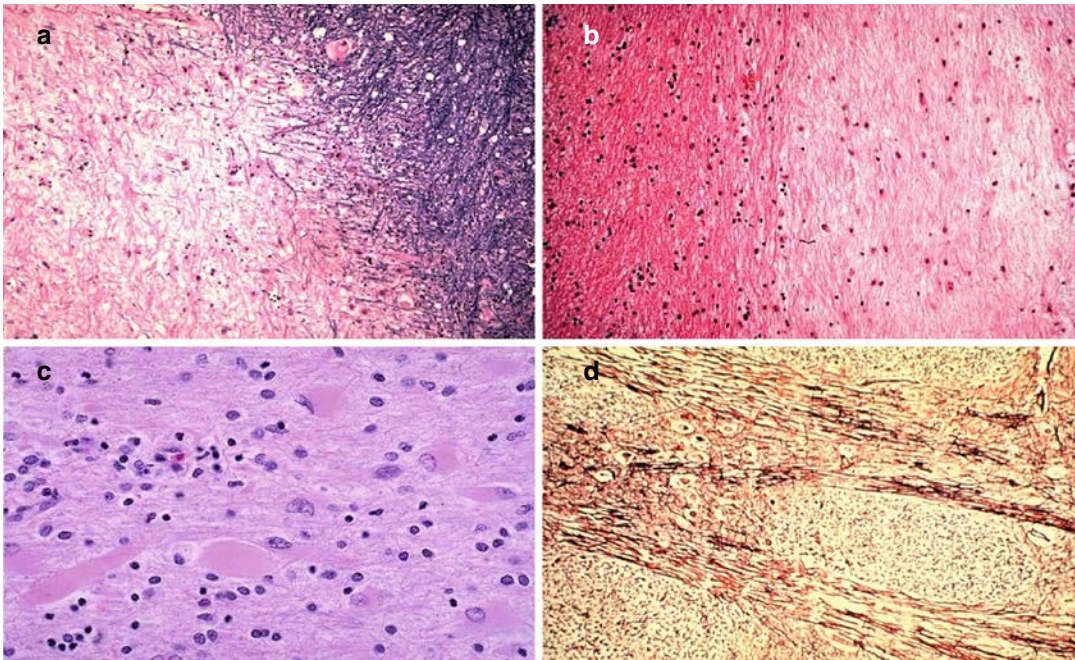


Fig. 29.5 MS histopathology. (a) A chronic plaque sharply demarcated from surrounding neural tissue, Luxol Fast Blue/Periodic Acid Schiff, $\times 100$. (b) Cellular rarefaction inside a chronic plaque, H&E $\times 40$. (c) Lymphocytic

infiltration and reactive astrocytes within the cerebral parenchyma and perivascular areas, H&E $\times 200$. (d) Axonal depletion in silver staining, Bielschowsky, $\times 100$

differentiate ADEM from MS include ADEM presenting as inflammatory demyelination mainly around small veins, with relatively better axonal preservation. Anti-MOG antibodies are present in a considerable percentage, particularly in recurrent or multiphasic cases, now recognized as a distinct entity, called MOG ADEM [19].

29.9.3 Neuromyelitis Optica Spectrum Disorders

Neuromyelitis optica spectrum disorders (NMOSD) are chronic autoimmune demyelinating diseases of the CNS that primarily affect the optic nerves and spinal cord, with possible involvement of the brainstem, diencephalon, and cerebrum. About 70%–80% of NMOSD patients develop IgG antibodies against the water channel aquaporin 4 (AQP4) expressed by the BBB astrocytes, which cause secondary oligodendrocyte and neuronal injury by activating complement

and damaging the astrocytic foot processes. IgG-negative NMOSD patients have anti MOG IgG antibodies and show distinct clinical features. Immunohistopathologically, perivascular deposition of activated complement (C9neo), granulocytic infiltration atypical for MS, macrophages with myelin debris, and necrosis are common. Besides the optic nerves, NMOSD may involve the area postrema leading to intractable hiccups, nausea, and vomiting periependymal brain regions, and the spinal medulla causing longitudinally extensive transverse myelitis. Disability accrues mainly from relapses rather than the progression of disease [20].

29.9.4 Autoimmune Encephalitides

Autoimmune encephalitides can arise due to antibodies such as anti-GABA-R, anti-AMPA-R, anti-NMDA-R, LGI-1, and CASPR2 targeting the neural cell surface and synapses.

Antibodies such as Hu, Yo, Ma2, and CRMP5 targeting intracellular antigens can trigger similar neuropathologies, which are more closely related to paraneoplastic syndromes. Cell-surface and synaptic antibody-mediated encephalitides exhibit less inflammation, lower synaptic dysfunction, and a better response to immunotherapy than encephalitides caused by antibodies specific to intracellular antigens. Relating to the fact that GABA is a foremost inhibitory neurotransmitter, anti-GABA-R encephalitis presents with seizures and status epilepticus, which may accompany cognitive dysfunction, psychosis, ataxia, and opsoclonus-myoclonus. About 50%–70% of anti-GABA-R encephalitis relates to small-cell lung cancer among middle-aged and elderly males, characterized by abnormal temporal metabolism in PET and medial temporal lobe and hippocampal hyperintensities in MR images. Anti-AMPA-R encephalitis is a limbic encephalitis, and MRI signs of damage in mesiotemporal areas and basal ganglia mirror AMPA-R expression patterns in the brain. Anti-AMPA-R encephalitis is commonly associated with thymoma, breast, ovarian, and lung tumors, which manifests with memory loss, psychosis, seizures, and movement or sleep disturbances. The encephalitides triggered by Hu, Yo, Ma2, and CRMP5 antibodies are caused by direct T-lymphocytic destruction of neurons. For example, encephalitis caused by the onconeural Hu antibody exhibits significant neuronal loss, microglial nodules, and gliosis, which has a poor prognosis [21].

29.10 Neurodegenerative Disorders

29.10.1 Alzheimer's Disease

Alzheimer's disease (AD), well-known as a leading cause of dementia, is pathologically defined by extracellular amyloid- β (A β) plaques, intracellular neurofibrillary tangles of tau aggregates, and cerebral amyloid angiopathy (CAA). Macroscopically, cerebral cortical atrophy, hippocampal shrinkage, widening of sulci, and ven-

tricular enlargement are characteristic and reflect neuronal loss. Sequential cleavage of amyloid precursor protein (APP) by β - and γ -secretase enzymes produces A β peptides, which aggregate into oligomers and fibrils to form amyloid plaques. A β oligomers are neurotoxic, disrupt synaptic function, and initiate downstream tauopathies through the hyperphosphorylated tau. Hyperphosphorylated tau (h-tau) forms paired helical filaments (PHFs) and neurofibrillary tangles (NFTs), which correlate significantly more closely with cognitive decline and AD progression than A β plaques. Tau pathology typically spreads stereotypically, following the synaptic networks. The pathogenesis involves a range of mechanisms, in addition to the direct neurotoxicity of protein accumulation, including microglial activation and clustering around A β plaques and NFTs, the release of inflammatory mediators, mitochondrial and metabolic perturbations, oxidative stress, and DNA double-strand breaks. *APOE* ϵ 4 allele enhances AD risk by accelerating A β deposition and tau pathology. Rare autosomal-dominant *APP*, *PSEN1*, and *PSEN2* mutations are responsible for early-onset familial AD via increased A β 42 production. Commonly accompanying pathologies, such as argyrophilic grain disease, vascular lesions, and Lewy bodies, influence clinical phenotype and disease progression [22].

29.10.2 Parkinson's Disease and Lewy Body Spectrum Disorders

Parkinson's disease (PD), PD with dementia (PDD), and dementia with Lewy bodies (DLB) constitute the Lewy body spectrum disorders (LBSDs). Loss of dopaminergic neurons in the substantia nigra, especially the ventrolateral group projecting to the posterolateral putamen, is typical for PD, in addition to phosphorylated α -synuclein aggregates, which compose Lewy bodies and Lewy neurites. While PD is primarily associated with nigrostriatal degeneration, PDD and DLB exhibit neuronal depletion in cortical and limbic systems and are distinguished by the

first onset of cognitive versus motor symptoms. Histopathologically, CNS tissues in PDD and DLB commonly harbor A β plaques and tau deposits, similar to those in AD, and their intensities correlate with accelerations in cognitive decline, as well as TDP-43 pathology or vascular lesions in lesser percentages. This feature concurs with the feature that a considerable percentage of PD patients develop cognitive decline or frank dementia with progressing disease. The intensity of AD pathology is highest in DLB, lower in PDD, and lowest in PD without dementia. In LBSDs, α -synuclein pathology spreads through synaptically connected networks, where α -synuclein aggregates cause neural damage through mechanisms shared by many nonneoplastic CNS disorders, such as oxidative stress and BBB injury. Additionally, they disrupt molecular pathways regulating autophagic cell death. Mutations in the *Parkin*, *PINK1*, *SNCA*, *LRKK2*, *GBA*, and *DJ-1* genes are involved in both familial and sporadic disease forms. Lastly, variants in *APOE* ϵ 4, *SNCA*, and *GBA* genes are implicated in LBSD susceptibility and associated cognitive decline [23].

29.10.3 Frontotemporal Lobar Degeneration

Frontotemporal lobar degeneration (FTLD) is characterized by early-onset deficits in behavior or a progressive decline in language skills and comprises different clinical variants, including semantic dementia (SD), behavioral FTD (bvFTD), and progressive nonfluent aphasia (PNFA). FTLD may overlap with other symptoms such as FTLD-ALS spectrum diseases, corticobasal degeneration (CBD), and progressive supranuclear palsy (PSP). C9orf72 repeat expansions, *TARDBP* mutations, haploinsufficiency of *GRN* (progranulin), and neuronal and glial TDP-43 inclusions are among the pathomolecular hallmarks of FTLD. TDP-43 and FUS are RNA-binding proteins prone to misfolding in prion-like domains, which cause disruptions of RNA splicing, dysfunction of stress granules and

autophagy, and abnormal liquid-liquid phase separation. About 5%–10% of FTLD patients are negative for tau and TDP-43 but harbor FUS-positive inclusions, which generally present with psychiatric symptoms. In all types of FTLD, corpora amylacea, currently referred to as wasteosomes, accumulate in varying percentages, which may serve as future CSF biomarkers [24].

29.10.4 Huntington's Disease

Huntington's Disease (HD) arises due to CAG trinucleotide repeat mutations in the *HTT* gene, resulting in the formation of an aberrant huntingtin protein with a polyglutamine tract. Mutant huntingtin protein misfolds, forming nuclear and cytoplasmic deposits, which disrupt nuclear trafficking, transcription, proteostasis, mitochondrial function, and cell survival. Mutant huntingtin aggregates exist within the nuclear and neuritic p62-positive neuronal inclusions in the striatal areas, which atrophy correlates with the development of chorea. Over 35 repeats of CAG trinucleotides cause the disease, where the repeat length inversely correlates with the age of onset and severity. Perturbed DNA repair mechanisms may be associated with earlier disease onset and progression by promoting somatic expansion of CAG repeats. The disease generally starts in mid-adult life with psychiatric symptoms, chorea, and progressive dementia. In the later stages of HD, extensive neuronal loss occurs in neocortical areas, such as the frontal, cingulate, and motor cortices, which correlates with personality changes and a decline in executive functions [25].

29.10.5 Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a fatal CNS disorder, whose etiology involves a progressive loss of upper and lower motor neurons, causing muscle weakness, atrophy, and subsequent respiratory failure. About half of

ALS patients exhibit behavioral changes or cognitive problems, and 10%–15% evolve to frontotemporal dementia. Prominent motor neuron loss, corticospinal tract degeneration with a lateral sclerosis pattern, eosinophilic Bunina bodies, and neuronal and glial TDP-43-positive inclusions, which are present in ~95% of cases, are the pathological hallmarks of ALS. TDP-43 proteinopathy is a key component of both classical and familial ALS, as its aggregation causes loss of nuclear function and a gain-of-toxic cytoplasmic effect, which is exacerbated by the aggregation of another protein, superoxide dismutase-1 (SOD1), a crucial enzyme in the antioxidant defense. A variant ALS type, spinal and bulbar muscular atrophy (SBMA), also known as Kennedy's disease, is caused by CAG expansions in the gene encoding the androgen receptor [26].

29.10.6 Spinocerebellar Ataxias

Spinocerebellar ataxias (SCAs) are autosomal dominant disorders associated with degeneration of cerebellar dentate nuclei, Purkinje cells, and inferior olivary neurons. Their pathogenesis resembles that of HD and SBMA, since the causative factor is the CAG repeat expansions in the *ATXN1* gene, leading to a mutant Ataxin-1 protein with an elongated polyglutamine tract. Through aberrant interactions with Capicua and other regulatory proteins, Ataxin-1 protein acts as a toxin to Purkinje cells and other cerebellar neurons. Other SCA types developing due to similar polyglutamine-mediated toxicity include SCA2, SCA3/MJD, SCA6, SCA7, and SCA17. SCAs, which do not involve polyglutamine toxicity, comprise SCA19/22, SCA21, and SCA31, where the latter is associated with penta nucleotide repeat insertions leading to abnormal protein deposition in Purkinje cells. The remaining SCAs, unrelated to aberrant nucleotide repeats, arise from point mutations in genes encoding potassium channels or proteins regulating synaptic function [27].

29.11 Developmental CNS Diseases

29.11.1 Neural Tube Defects

In mammals, neural tube closure begins at multiple sites, fusing sequentially. Defects at any closure point are associated with divergent types of neural tube defects (NTDs), such as spina bifida or anencephaly. While a mother's obesity, diabetes, and hyperthermia exposure during gestation increases the risk of NTDs, a foremost factor of neonates born with NTDs involves inadequate blood folic acid levels of their mothers during gestation, a feature known for decades. A plethora of changes in molecular cascades occurs due to suboptimal folic acid, including the blockage of thymidylate synthesis, leading to uracil insertion into DNA; defective DNA repair, causing DNA breaks and replication stress; and ultimately, the apoptotic death of embryonic neuroepithelial cells around the neural tube. Research in recent years, focusing on the residual NTD risk of approximately 30% after folate supplementation, has revealed divergent factors that can be classified into two groups. The first group includes variants of the *MTHFR*, *MTRR*, and *FOLR1* genes, which are involved in folate metabolism. The second group comprises mutations in genes such as *VANGL1* or *VANGL2*, which regulate planar cell polarity and disrupt neural tube closure mechanics [28] (Fig. 29.6).

29.11.2 Cerebral Cortex Anomalies

Brain cortex development in humans is a highly complex process that involves the timely proliferation and migration of neurons and requires the proper and flawless progression of folding and lamination stages. Disruptions in any of these events at distinct developmental steps cause different cortical anomalies. Versatile genes with similar functions, such as those involved in stabilizing microtubules necessary for radial neuronal migration and regulating dynein-mediated

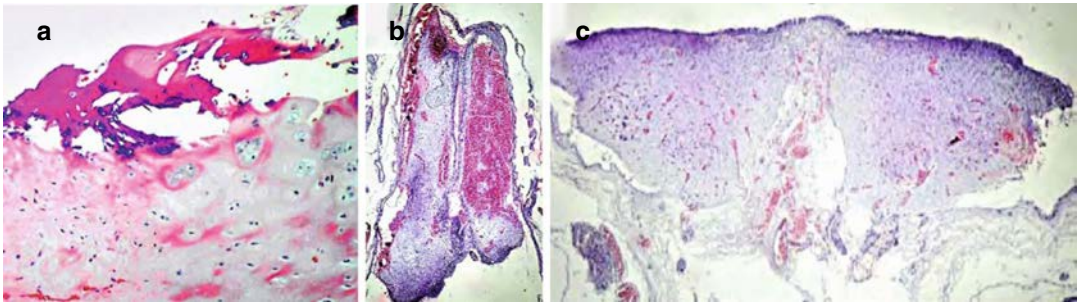


Fig. 29.6 Histopathological features of spina bifida. (a) Split cord malformation Type I (diastematomyelia) with formation of bony spur by mature cartilage and ossification foci, H&E $\times 100$. (b) Split cord malformation Type II

with asymmetrical split hemicords wrapped by a common arachnoidal membrane, H&E $\times 40$. (c) Dorsal myeloschisis with fibro-neurovascular stalk including glia, neurons, and peripheral nerves, H&E $\times 40$

nuclear translocation along microtubules, cause neuronal migration failure and the subsequent development of classical (Type I) lissencephaly. On the contrary, neurons can develop an overmigratory type and traverse the pial basement due to an abnormally glycosylated dystroglycan, leading to the development of cobblestone (Type II) lissencephaly, as seen in muscle-eye-brain, Fukuyama, and Walker-Warburg syndromes. Inordinately small gyri separated by shallow sulci and aberrant cortical lamination are characteristic features of polymicrogyria. Differing from other cortical anomalies, polymicrogyria has a much diverse etiological repertoire. These etiologies comprise abnormal leptomeningeal development, inadequacy of extracellular matrix substrates that direct cell migration, and fusion of adjacent gyri due to intrauterine ischemia or infections. However, a specific type of polymicrogyria, defined as bilateral frontoparietal polymicrogyria, has a single etiology associated with mutations in the GPR56 gene. GPR56 gene defects disrupt the radial glial endfeet, the pial basement membrane, and the positioning of Cajal-Retzius cells [29].

29.11.3 Hydrocephalus

Hydrocephalus arises from derangements of cerebrospinal fluid (CSF) dynamics due to divergent mechanisms, including enhanced CSF

secretion, flow blockage, or defective absorption, which dilate cerebral ventricles and cause flow or pressure-related neural tissue damage. Hydrocephalus is classified as congenital, acquired or secondary, and idiopathic normal pressure hydrocephalus (iNPH). Several genes are responsible for congenital hydrocephalus, which mediate the formation of midline structures, regulate ciliary functions that control CSF flow, and maintain ependymal cell integrity. Dysfunctioning and peeling of the ependymal cell layer hinder CSF flow and impair glymphatic clearance. Acquired or secondary hydrocephalus involves blockage of arachnoid granulations due to inflammatory fibrosis, blood, or both, which develops after subarachnoid or intraventricular hemorrhage or infections. Inflammation and subsequent arachnoid fibrosis and blockage are promoted by NF κ B activation, increased tenascin C, and upregulated TGF β /SMAD signaling. These pathways also trigger secondary pathogenesis mechanisms, such as CSF hypersecretion resulting from the improper expression of aquaporins 1 and 4, NKCC transporters, VEGF, and components of the Wnt pathway. Idiopathic normal pressure hydrocephalus (iNPH) is a unique pathology explicating ventriculomegaly but surprisingly without overt intracranial hypertension and manifests with gait disturbance, urinary incontinence, and cognitive impairments. While its responsible mechanisms are not entirely illuminated, glymphatic impairments reducing inter-

stitial fluid and CSF exchange, ciliary motility defects in ependymal lining, and lastly, genetic predisposition due to familial iNPH cases are blamed [30].

29.12 Metabolic CNS Diseases

29.12.1 Hypoglycemic Encephalopathy

As neurons are responsible for producing uninterrupted electrical signals, they have a high demand for a constant energy supply. This particular need is reflected in the fact that the human brain receives 20% of the cardiac output and consumes 20% of the body's oxygen, despite constituting only about 2% of the total body weight. Glucose is the prominent cerebral energy source that relates to the development of hypoglycemic encephalopathy during severe hypoglycemic attacks or prolonged hypoglycemia. Specific brain regions are especially vulnerable to hypoglycemia, including the hippocampal CA1 and dentate gyrus, subiculum, basal ganglia, and cortical layers II and III. In parallel, neuroimaging features of hypoglycemic encephalopathy primarily consist of injury to the white matter and grey nuclei, and widespread involvement indicates poor prognosis. Neuronal depolarization due to energy failure triggers neuronal depolarization and the release of excess glutamate and aspartate, leading to excitotoxicity promoted by the overactivation of Poly(ADP-ribose) Polymerase-1 (PARP1) and zinc efflux. Hypoglycemia alone may not always cause prominent brain damage. Still, when simultaneous respiratory depression with hypoxia or hypercapnia occurs, selective neuronal and laminar cortical necrosis and microglial activation strongly accelerate neuropathogenesis. When the hypoglycemic stage is prolonged, cytotoxic edema develops due to ion channel dysfunction secondary to ATP depletion, which exacerbates neural damage and leads to coma, persistent neural deficits, and death [31].

29.12.2 Hepatic Encephalopathy

Severe hepatic dysfunction in diseases like cirrhosis hinders the urea cycle continuity, which subsequently hampers detoxification and increases circulating levels of ammonia that readily cross the BBB. Astrocytes metabolize high amounts of ammonia via glutamine synthetase, leading to glutamine accumulation, cytotoxic glial edema, impaired osmotic regulation, and abnormal neurotransmitter cycling. Hyperammonemia also induces oxidative and nitrosative stress, mitochondrial damage, manganese toxicity, impeded autophagy, and glial senescence. Accompanying lowerings in cerebral glucose uptake, osmolytes, and GABA and an increase in lactate happen particularly in the hippocampus and cerebellum. Neuronal dendritic spine loss and diminished cortical synaptic plasticity arise due to both metabolic damage and inflammation, the latter involving inflammatory mediators, gut dysbiosis, and endotoxemia [32].

29.12.3 Uremic Encephalopathy

Uremic encephalopathy, which typically occurs during severe renal failure, develops due to neural injury caused by multiple toxins, including uremic solutes such as urea, indolic compounds, and guanidines, some of which act as NMDA receptor agonists. The damage elicited by these toxins is augmented by coexisting acid-base and electrolyte imbalances, vascular and BBB dysregulation, and inflammation. Overt stimulation of NMDA receptors leads to seizures, myoclonus, and cognitive slowing. The neural activities further deteriorate due to GABAergic dysfunction and the accumulation of aromatic and branched-chain amino acids, which may act as false neurotransmitters. Reactive oxygen radicals and secondary hyperparathyroidism, which elevate cortical calcium, synergistically accelerate neuronal damage, and parathormone is among the leading factors associated with the clinical presentation. Basal ganglia findings such as the

lentiform fork sign on MRI constitute hallmark features of uremic encephalopathy, especially encountered among patients who also have diabetes [33].

29.12.4 Wernicke Encephalopathy and Korsakoff Syndrome

Wernicke encephalopathy (WE) is primarily encountered in patients with alcoholism compounded by inadequate nutrition, depleting thiamine, a cofactor of pyruvate dehydrogenase and α -ketoglutarate dehydrogenase enzymes, which are essential in energy metabolism. Independent of WE, alcohol per se is also responsible for frontal cortical shrinkage, white matter loss, neurotoxic hippocampal impairment, and cerebellar degeneration. Thiamine deficiency cause diminished cerebral ATP production, lactate accumulation, and mitochondrial injury, to which astrocytes are particularly vulnerable. Thiamine depletion also perturbs transport proteins of glutamate (EAAT1/EAAT2), GABA (GAT3), as well aquaporin 4, which synergistically enhance neural damage. Hallmark signs of WE include confusion, gait ataxia, nystagmus, and ophthalmoplegia. Characteristic neuropathologic lesions include symmetric petechial hemorrhages in mammillary bodies, medial thalami, periaqueductal region, and dorsal brainstem, accompanied by neuronal loss and gliosis. Acute WE may be reversed with timely thiamine replacement, but if left untreated, the disease progresses to Korsakoff syndrome (KS). KS manifests with severe anterograde amnesia, retrograde memory loss, confabulation, and executive dysfunction [34].

29.12.5 Storage Diseases

Storage diseases in humans relate to defects in lysosomal functioning, dysfunctional, or absent enzymes responsible for degrading specific substrates, or both. Failure to catabolize or degrade any substrate in human metabolism leads to its abnormal accumulation in various organs, including the brain, resulting in divergent neuropathol-

ogies dependent on the type and amount of substrate accumulation. Metachromatic leukodystrophy is an autosomal recessive lysosomal disorder caused by biallelic mutations in genes encoding arylsulfatase-A or saposin-B enzymes. The dysfunction of these enzymes causes sulfatide deposition, particularly cerebroside 3-sulfate, which has an excessive presence in Schwann cells and oligodendrocytes, leading to myelinolysis, inflammation, and gliosis. Severe demyelination is accompanied by the abundance of hallmark globoid cells, multinucleated macrophages with PAS-positive myelin debris inclusions, as well as gliosis. GM2 gangliosidosis or Tay-Sachs disease is the result of autosomal recessive HEXA mutations encoding β -hexosaminidase-A enzyme. Deficient β -hexosaminidase-A causes lysosomal accumulation of excess GM2 ganglioside in neurons, which leads to progressive neuronal distention, microglial activation, and cortical degeneration starting from infancy. Niemann-Pick disease is, in fact, not a single disease as thought previously, which is now classified into different subtypes, A, B and C. Subtypes A and B result from acid sphingomyelinase deficiency due to autosomal recessive SMPD1 mutations. Subtype C arises from NPC1 or NPC2 gene mutations, impairing the trafficking and leading lysosomal accumulation of cholesterol and glycosphingolipids. In subtype A, sphingomyelin deposits in macrophages and microglia are often associated with early neurodegeneration. In subtype C, abnormal substrate accumulation occurs in both neurons and glia, leading to degeneration of the cortex, basal ganglia, and cerebellum. Gaucher disease arises due to autosomal recessive GBA1 mutations, causing glucocerebrosidase deficiency and subsequent deposition of glucocerebroside and glucosylsphingosine in macrophages and microglia. Glucocerebroside-laden microglia, altered levels of sphingolipids, and disrupted membrane lipid homeostasis resulting from dysfunctional lysosomes lead to endoplasmic reticulum stress, neuroinflammation, and neurotoxicity, with the latter primarily occurring in individuals with homozygous GBA mutations and associated with Parkinson's disease signs [35].

29.13 Pathology of Neurotoxic Conditions

29.13.1 Heavy Metal Neurotoxicity

Several metal compounds, including heavy metals, can accumulate in the brain and cause neuropathological changes, primarily in vulnerability-prone nuclei of the CNS. Without exception, all heavy metals cause significant oxidative and mitochondrial damage, central to their neurotoxic actions. Metals' traversal through the BBB and entry into the brain initiate a vicious cycle, where the integrity of the BBB diminishes in correlation with the level of penetrated metal and neuronal damage, particularly in the locus coeruleus. All these harmful events culminate in neurodegenerative disorders and cognitive decline, supported by epidemiological studies showing increased risk of AD with chronic exposure to lead, cadmium, and manganese. Lead causes neurodevelopmental delay and enhances dementia risk in adults by perturbing neurogenesis, synaptic signaling, and calcium regulation. Mercury accumulation occurs in neuromelanin-rich neurons (e.g., in the locus coeruleus), compromising BBB integrity and causing a spreading toxicity to astrocytes, oligodendrocytes, and neurons. Minamata disease is an extreme form of mercury poisoning, manifested with ataxia, numbness in extremities, peripheral vision loss, and hearing and speech damage—symptoms of its congenital form, including extensive brain damage and microcephaly, mimic cerebral palsy. Cadmium enters the brain via calcium transporters, impairing astrocyte glycogen metabolism, vesicular neurotransmitter release, and synaptic function. Arsenic affects neuronal proliferation and epigenetic regulation, features associated with neurodevelopmental delays of infants exposed to arsenic during the prenatal period. Although manganese is classifiable as a heavy metal, it is also an essential element and a cofactor of crucial enzymes, such as Mn-superoxide dismutase-2 (SOD2), which resides in mitochondria and is involved in antioxidant defense. Nonetheless, sustained exposure to manganese may lead to its supraphysiological deposition in

the basal ganglia, particularly in the globus pallidus, where it activates microglia, resulting in dopaminergic dysfunction and motor deficits similar to those observed in Parkinson's disease [36].

29.13.2 Chemotherapy Neurotoxicity

Classical chemotherapeutics, which target cell division steps of rapidly proliferating cancer cells, could cause diverse neurotoxicities. Recently employed targeted cancer treatment agents could also lead to neural injury, which will not be dealt with here, as there are insufficient studies monitoring their long-term effects. As microtubules are essential for organelle and macromolecular transport along axons, anticancer agents that act via microtubular damage, such as vinca alkaloids and taxanes like vincristine and paclitaxel, cause distal axonal degeneration and neuropathy, respectively. Platinum chemotherapeutics such as cisplatin and oxaliplatin cause sensory axonal neuropathy, which is often persistent or irreversible. The pathogenesis of this axonal neuropathy involves the formation of DNA adducts in dorsal root ganglionic neurons and ion channel dysfunction. Taxanes may also induce similar neuropathic changes through mitochondrial damage and neuroinflammation [37].

29.13.3 Methanol Neurotoxicity

Methanol neurotoxicity generally develops with ingestion, which is rarely accidental, sometimes suicidal, and, unwittingly, by consuming methanol used in illegal alcoholic beverages. Methanol neurotoxicity manifests with headache, changes in consciousness and coordination, abdominal pain, vomiting, and a specific breath smell. Vision impairment due to optic nerve injury starts quickly, and survivors of methanol poisoning would live with permanent blindness and renal failure. Methanol primarily affects the basal ganglia, particularly the putamen, exhibiting hemorrhagic and nonhemorrhagic lesions, which could be bilateral and cystic. Petechial cortical

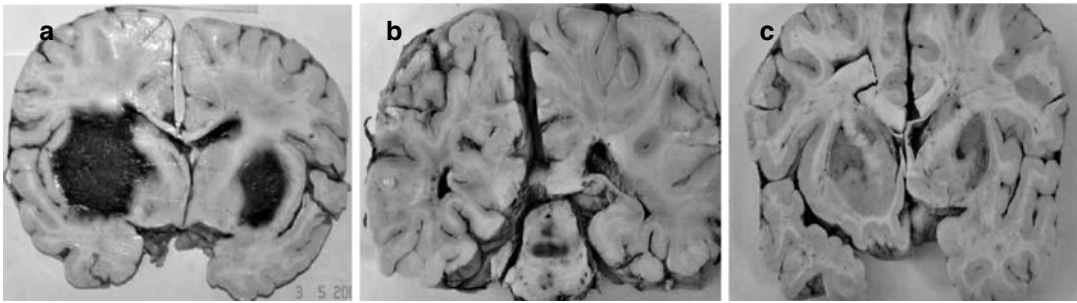


Fig. 29.7 Brain autopsy material showing hemorrhagic necrosis in thalamus, hypothalamus, and ventricular tamponade (a), petechial hemorrhages in pons (b), bilateral putaminal and pallidal necrosis and petechial hemorrhages (c)

bleedings and cerebral edema also commonly accompany. Long-term survivors may also develop hippocampal ischemic changes, as well as laminar and cystic necrosis of the cerebral cortex and white matter, respectively. Biochemical pathogenesis involves the stepwise conversion of methanol through alcohol and aldehyde dehydrogenases to formic acid, which inhibits the mitochondrial cytochrome C oxidase enzyme and subsequently leads to oxidative respiration inhibition, resulting in cytotoxicity. Formic acid also induces metabolic acidosis and a variety of other metabolic disturbances, further precipitating the neurotoxicity [38] (Fig. 29.7).

References

1. Sofroniew MV, Vinters HV. Astrocytes: biology and pathology. *Acta Neuropathol.* 2010;119(1):7–35.
2. DiSabato DJ, Quan N, Godbout JP. Neuroinflammation: the devil is in the details. *J Neurochem.* 2016;139(Suppl 2):136–53.
3. Koenig MA. Cerebral edema and elevated intracranial pressure. *Continuum (Minneapolis Minn).* 2018;24(6):1588–602.
4. Magid-Bernstein J, Girard R, Polster S, Srinath A, Romanos S, Awad IA, Sansing LH. Cerebral hemorrhage: pathophysiology, treatment, and future directions. *Circ Res.* 2022;130(8):1204–29.
5. Hankey GJ. Stroke. *Lancet.* 2017;389(10069):641–54.
6. Guo P, Li H, Zhang X, Liu Y, Xue S, Yong VW, Xue M. Matrix metalloproteinase-9 in hemorrhagic transformation after acute ischemic stroke. *Mol Med Rep.* 2025;32(2):225.
7. He M, Zhao Y, Jiang J, Mo W, Yao Q. Efficacy and safety of high-dose erythropoietin combined with hypothermia therapy in neonatal hypoxic-ischemic encephalopathy: a systematic review and meta-analysis. *Mol Biotechnol.* 2025. <https://doi.org/10.1007/s12033-025-01419-3>.
8. Yang Z, Li P, Wei J. Perceiving traumatic brain injury from lymphatic system. *Mol Psychiatry.* 2025;30:5546–62. <https://doi.org/10.1038/s41380-025-03126-6>.
9. Fukushima S, Fujimori T, Iio K, Hagiya H. Severe intracranial infection. *J Am Coll Emerg Physicians Open.* 2025;6(1):100026. <https://doi.org/10.1016/j.acepo.2024.100026>.
10. Babcock KJ, Abdolmohammadi B, McKee AC. Recent advances in chronic traumatic encephalopathy. *Am J Pathol.* 2025;195:S0002-9440(25)00295-0.
11. Hainsworth AH, Markus HS, Schneider JA. Cerebral small vessel disease, hypertension, and vascular contributions to cognitive impairment and dementia. *Hypertension.* 2024;81(1):75–86.
12. Malinverno M, Maderna C, Abu Taha A, Corada M, Orsenigo F, Valentino M, Pisati F, Fusco C, Graziano P, Giannotta M, Yu QC, Zeng YA, Lampugnani MG, Magnusson PU, Dejana E. Endothelial cell clonal expansion in the development of cerebral cavernous malformations. *Nat Commun.* 2019;10(1):2761. <https://doi.org/10.1038/s41467-019-10707-x>.
13. Ota T. An updated review on the pathogenesis of brain arteriovenous malformations and its therapeutic targets. *J Neuroendovasc Ther.* 2025;19(1):2024–0008.
14. Sousa IP Jr, Dos Santos FB, de Paula VS, Vieira TCRG, Dias HG, Barros CA, da Silva EE. Viral and prion infections associated with central nervous system syndromes in Brazil. *Viruses.* 2021;13(7):1370. <https://doi.org/10.3390/v13071370>.
15. Eis PS, Smith EB 3rd, Jalilzadeh S, Hatchwell E. Genetics of progressive multifocal leukoencephalopathy: update on case reports with an inborn error of immunity and risk variants found in drug-linked cases. *Front Neurol.* 2025;16:1629581. <https://doi.org/10.3389/fneur.2025.1629581>.
16. Takoutsing BD, Ooi SZY, Egu C, Gillespie CS, Dalle DU, Erhabor J, Ciuculete AC, Kesici Ö, Awad AK, Dokponou YCH, Khan M, Ikwegbuanyi CA, Dada OE, Bandyopadhyay S, Bankole NDA. Management and outcome of intracranial fungal infections in children and adults in Africa: a scoping review. *BMC*

- Infect Dis. 2024;24(1):789. <https://doi.org/10.1186/s12879-024-09694-2>.
17. Shahrivar F, Moghimi A, Hosseinzadeh R, Kohansal MH, Mortazavi A, Galeh TM, Ahmadpour E. A comprehensive review on the neurological impact of parasitic infections. *Microb Pathog*. 2025;206:107762. <https://doi.org/10.1016/j.micpath.2025.107762>.
 18. Rida Zainab S, Zeb Khan J, Khalid Tipu M, Jahan F, Irshad N. A review on multiple sclerosis: unravelling the complexities of pathogenesis, progression, mechanisms and therapeutic innovations. *Neuroscience*. 2025;567:133–49.
 19. Çiçek A, De Temmerman L, De Weweire M, De Backer H, Buyle M, Clement F. Thunderclap headache as a first manifestation of acute disseminated encephalomyelitis: case report and literature review. *BMC Neurol*. 2024;24(1):315. <https://doi.org/10.1186/s12883-024-03803-z>.
 20. Leitner U, Chew SH, Blanch J, Viswanathan M, Patil S, Ward K, Bhuta S, Zhang P, Sun J, Broadley SA. Characteristics of MRI lesions in AQP4 antibody-positive NMOSD, MOGAD, and multiple sclerosis: a systematic review and meta-analysis. *J Neurol*. 2025;272(9):560. <https://doi.org/10.1007/s00415-025-13303-w>.
 21. Campetella L, Smolik K, Farina A, Joubert B, Muñiz-Castrillo S, Desestret V, Honnorat J. Neurodegeneration and the immune system: lessons from autoimmune encephalitis. *J Neurol*. 2025;272(5):359. <https://doi.org/10.1007/s00415-025-13094-0>.
 22. Jin Z, Lu Y, Tang H, Cui H. Integrating neuroinflammation biomarkers into the ATN(X) framework: advances in Alzheimer's pathogenesis, diagnosis, and insights from non-human primate models. *Alzheimers Dement*. 2025;21(8):e70472. <https://doi.org/10.1002/alz.70472>.
 23. Tanaka M. Parkinson's disease: bridging gaps, building biomarkers, and reimagining clinical translation. *Cells*. 2025;14(15):1161. <https://doi.org/10.3390/cells1415116>.
 24. Ravasia K, Hirsch-Reinshagen V. Selective cellular and regional vulnerability in frontotemporal lobar degeneration: a scoping review. *Free Neuropathol*. 2025;6:11. <https://doi.org/10.17879/freeneuropathology-2025-5812>.
 25. Blusch A, Björkqvist M. Neuroinflammation in Huntington's disease: causes, consequences, and treatment strategies. *J Huntingtons Dis*. 2025;14(3):258–69.
 26. Chaouch A, Crook A, Douglas AGL, McDermott CJ, Al-Chalabi A, McNeill A, Bedford J, Howard J, MacLeod R. The use of genetic testing in amyotrophic lateral sclerosis (ALS): a practical approach. *Amyotroph Lateral Scler Frontotemporal Degener*. 2026;27:28–34.
 27. Klockgether T, Grobe-Einsler M, Faber J. Biomarkers in spinocerebellar ataxias. *Cerebellum*. 2025;24(4):104. <https://doi.org/10.1007/s12311-025-01856-5>.
 28. Rai S, Leydier L, Sharma S, Katwala J, Sahu A. A quest for genetic causes underlying signaling pathways associated with neural tube defects. *Front Pediatr*. 2023;11:1126209. <https://doi.org/10.3389/fped.2023.1126209>.
 29. Russ JB, Agarwal S, Venkatesan C, Scelsa B, Vollmer B, Tarui T, Pardo AC, Lemmon ME, Mulkey SB, Hart AR, Nagaraj UD, Kuller JA, Whitehead MT, Cohen JL, Gebb JS, Glenn OA, Norton ME, Gano D. Fetal malformations of cortical development: review and clinical guidance. *Brain*. 2025;148(6):1888–903.
 30. Deng X, Chen Y, Duan Q, Ding J, Wang Z, Wang J, Chen X, Zhou L, Zhao L. Genetic and molecular mechanisms of hydrocephalus. *Front Mol Neurosci*. 2025;17:1512455. <https://doi.org/10.3389/fnmol.2024.1512455>.
 31. Witsch J, Neugebauer H, Flechsenhar J, Jüttler E. Hypoglycemic encephalopathy: a case series and literature review on outcome determination. *J Neurol*. 2012;259(10):2172–81.
 32. Gallego JJ, Ballester MP, Fiorillo A, Casanova-Ferrer F, López-Gramaje A, Urios A, Arenas YM, Ríos MP, Durbán L, Megías J, San-Miguel T, Benlloch S, Lluch P, Jalan R, Montoliu C. Ammonia and beyond—biomarkers of hepatic encephalopathy. *Metab Brain Dis*. 2025;40(1):100. <https://doi.org/10.1007/s11011-024-01512-7>.
 33. Greco F, Buoso A, Cea L, D'Andrea V, Bernetti C, Beomonte Zobel B, Mallio CA. Magnetic resonance imaging in uremic encephalopathy: identifying key imaging patterns and clinical correlations. *J Clin Med*. 2024;13(14):4092. <https://doi.org/10.3390/jcm13144092>.
 34. Eva L, Brehar FM, Florian IA, Covache-Busuioc RA, Costin HP, Dumitrascu DI, Bratu BG, Glavan LA, Ciurea AV. Neuropsychiatric and neuropsychological aspects of alcohol-related cognitive disorders: an in-depth review of Wernicke's encephalopathy and Korsakoff's syndrome. *J Clin Med*. 2023;12(18):6101. <https://doi.org/10.3390/jcm12186101>.
 35. Elendu C, Babawale EA, Babarinde FO, Babatunde OD, Chukwu C, Chiegboka SF, Shode OP, Ngozi-Ibeh JK, Njoku A, Ikokwu MN, Kaka GU, Hassan JI, Fatungase OO, Osifodunrin T, Udoeze CA, Ikeji VI. Neurological manifestations of lysosomal storage diseases. *Ann Med Surg (Lond)*. 2024;86(11):6619–35.
 36. Pamphlett R, Bishop DP. The toxic metal hypothesis for neurological disorders. *Front Neurol*. 2023;14:1173779. <https://doi.org/10.3389/fneur.2023.1173779>.
 37. Kuil LE, Nicola C, Dietrich J, Castel H. Neurotoxicity of chemotherapy and brain-radiotherapy in cancer: overlapping mechanisms underlying cognitive impairment. *J Clin Exp Neuropsychol*. 2025;47:1–41.
 38. Karayel F, Turan AA, Sav A, Pakis I, Akyildiz EU, Ersoy G. Methanol intoxication: pathological changes of central nervous system (17 cases). *Am J Forensic Med Pathol*. 2010;31(1):34–6.

30.1 Incidence of Brain Tumors

Tumors of the central nervous system (CNS) represent around 3% of all malignancies, but are the second most common type of tumor in children and young adults. Population-based studies indicate an overall incidence of intracranial tumors of approximately 21/100,000 per year [1]. Of all intracranial tumors, roughly 40% originate from neuroepithelium, 35% from meningotheelial cells, 14.4% from oral ectoderm (pituitary adenomas and craniopharyngiomas), and 7.5% from peripheral nerve sheath elements. Lymphomas and germ cell tumors account for 2.3% and 0.5%, respectively [2].

30.2 History of WHO Classifications

For the last 45 years, various classifications have been proposed in the history of CNS tumors. The first classification by Bailey and Cushing was established and published in 1926. Since then, a series of classifications have been proposed, including those by Kernohan et al. (1949),

Russell and Rubinstein (1959), and Zülch (1965). The existence of multiple classifications has created confusion, as the same tumor could be referred to by different names depending on the system used [3]. The WHO published a series of classifications in 1979, 1993, 2000, 2007, 2016, and most recently in 2021 [3–7]. As of today, there are a wide variety of types and subtypes—nearly 120 different primary brain tumors, each presenting with unique clinical characteristics and distinct histologic features.

Starting with the fourth edition published in 2007, molecular features became increasingly significant for predicting patient prognosis and outcomes. In the updated fourth edition released in 2016, these molecular characteristics were incorporated alongside histology. This represented a pivotal shift in restructuring the diagnoses of CNS tumors in the molecular era, leading to the definition of new entities or variants based on a combination of histological features and molecular alterations. Furthermore, a new synoptic format for pathology reporting was proposed to enhance clarity and consistency in reporting [8].

The fifth edition, released in 2021, builds on the numerous developments in the field that emerged after the 2016 fourth edition. It also incorporates recommendations from the Consortium to Inform Molecular and Practical Approaches to Central Nervous System Tumor Taxonomy (cIMPACT-NOW), which is not an official WHO initiative. The fifth edition places a

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greater emphasis on molecular and genetic/epigenetic features for both classification and grading, while still maintaining the histopathologic foundations established in cIMPACT 6 [9].

The main changes proposed by the 2021 WHO classification can be summarized as follows:

1. Integrated and layered diagnosis
2. Grading of tumor types
3. Removal of “anaplastic” as a prefix
4. Integrated grading criteria
5. Upgraded entities
6. Defined cut-off and measurement values for mitotic count
7. Consideration of the impact of novel molecular techniques on the diagnosis and treatment of tumors

Recent classification recommendations include a diverse range of additions, such as integrated diagnosis for diffuse astrocytoma and MYB-altered cancers in other organ systems. It is also advised to use the grade designation “CNS WHO” [10–17].

30.3 Major Changes in the Recent WHO Classification [16, 17]

30.3.1 Integrated Diagnosis

Recent edition recommends the layered reporting structure introduced in the 2016 edition. It proposes an integrated diagnosis that considers histological features, grading, and molecular information. It is advised to use the grade designation as “CNS WHO” (e.g., pilocytic astrocytoma, CNS WHO grade 1).

30.3.2 Grading

In earlier editions, central nervous system tumors were assigned a malignancy scale for each tumor type, and these grades were compared across different types. Recently, this approach has largely been substituted by grading tumors within each

specific type. Therefore, while grades still reflect the natural history of the tumors, there is not always a direct correlation between the same numerical grade for different tumor types.

30.3.3 Omitted Prefix

The term “anaplastic” has been replaced with “grade 3,” and its use is no longer recommended. Currently, this diagnosis is referred to as “CNS WHO grade 3.” Similarly, the highest grade of oligodendroglioma is ideally labeled as “oligodendroglioma,” IDH-mutant and 1p/19q codeleted, CNS WHO grade 3.

30.3.4 Integrated Grading Criteria

For the first time, molecular features have been integrated into the grading schema of tumors, potentially taking priority over traditional histological characteristics. For example, adult diffuse astrocytomas might be classified as IDH-wildtype glioblastoma (CNS WHO grade 4), if they meet the histological criteria for grades 2 or 3 and also display specific markers such as EGFR amplification, TERT promoter mutation, or the combined gain of chromosome 7 alongside loss of chromosome 10 (+7/–10). This innovative approach offers great promise for improving diagnostic accuracy.

30.3.5 Upgrading Entities

Based upon the collected data, myxopapillary ependymoma was upgraded to CNS WHO grade 2.

30.3.6 Proliferative Index (Mitotic Index)

It is recommended that mitotic activity should be reported as the number of mitoses per square millimeter. As a common method, most grading cri-

teria depend on high-power fields (HPFs). Therefore, continuation of counting mitotic activity is a prerequisite in an area of 10 HPFs. The equation of 10 HPFs is nearly 2 square millimeters.

30.3.7 Novel Diagnostic Technologies

Recent advancements in molecular techniques, such as next-generation sequencing (NGS) and DNA methylation profiling, have significantly improved the use of biodata assets in clinical neurooncology. Inductive data from NGS and methylome profiling are now being used to identify DNA methylation patterns through arrays, which is an effective method for recognizing tumors with unusual histomorphology. Today, a wide range of user-friendly applications is avail-

able to address various characteristics of numerous central nervous system neoplasms [16, 17].

30.4 Major Tumor Groups

30.4.1 Glial, Glioneuronal, and Neuronal Tumors

30.4.1.1 Adult-Type Diffuse Gliomas (Table 30.1)

(i) *Glioblastoma, IDH-Wildtype*

Glioblastoma is the most common type of glioma in the brain, accounting for nearly 50% of all gliomas and 14% of all intracranial tumors. Its peak incidence occurs in individuals during their fifth and sixth decades of life. The sex distribution for this condition is approximately 3:2, with males being more affected than females (Table 30.2).

Table 30.1 Classification of adult-type gliomas, and special notes (WHO CNS 5) [16, 18]

Type	Grade	Notes
Astrocytoma, IDH-mutant	2/3/4	1. Revised nomenclature—The term diffuse and anaplastic no longer used 2. Combined histological and molecular grading introduced 3. The term “Astrocytoma, IDH wildtype” eliminated
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	2/3	1. Current grading approach remains unchanged (similar to WHO 2016) 2. Term “Oligoastrocytoma” deleted
Glioblastoma, IDH-wildtype	4	1. Term “Glioblastoma, IDH-mutant” eliminated 2. Term “multiforme” removed 3. Combined histological and molecular grading introduced 4. Three subtypes, i.e., giant cell GB, gliosarcoma, and epithelioid GB no longer included in the main classification but described in text section

Table 30.2 Major histopathologic, immunohistochemical, and molecular features of glioblastoma IDH wildtype [16, 19]

Tumor type	Histopathologic features	Immunohistochemical features	Molecular genetics
Glioblastoma IDH wildtype	Geographic necrosis with perinecrotic pseudopalisading by tumor cells, prominent cellularity and nuclear pleomorphism, brisk mitotic figures, microvascular “endothelial” proliferation, capillary and glomeruloid appearances (Fig. 30.1a)	GFAP+, Olig2+, S-100+, SOX10+; EMA–, HMB45–, Melan-A–, CD45–	IDH- and H3-wildtype; TERT promoter mutation; EGFR gene amplification; Polysomy 7 and monosomy 10 (+7/–10)

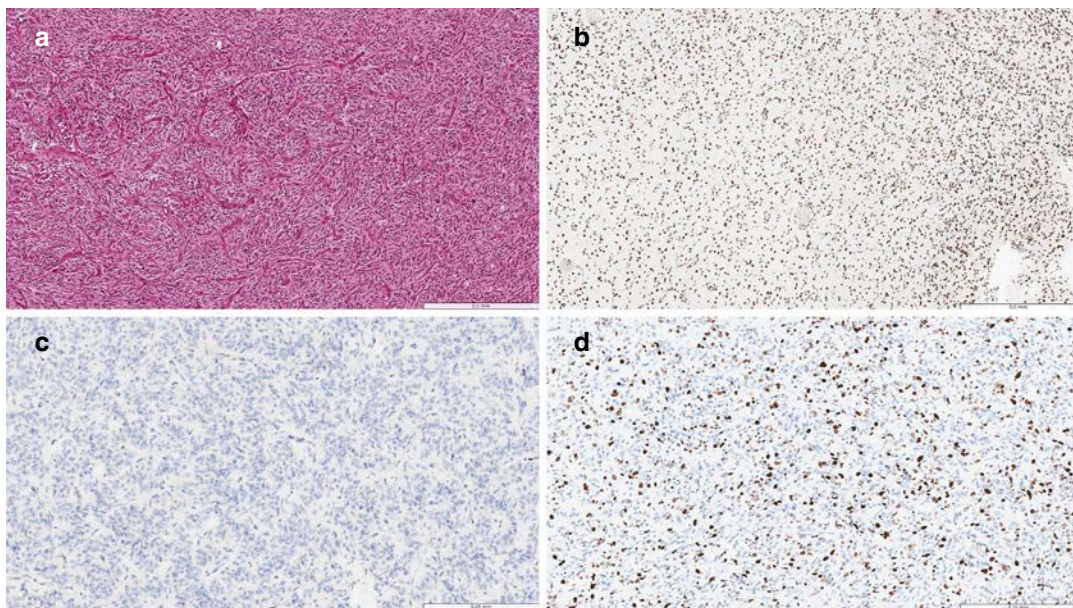


Fig. 30.1 GBM wildtype. (a) Atypical cells forming fascicles with prominent microvascular proliferation. (b) Loss of nuclear ATRX expressivity. (c) Loss of IDH1 expression in tumor cells. (d) Ki67 index reveals a high proliferation (30%)

Table 30.3 Major grading, histopathological, and molecular criteria [16, 18]

Subtypes	Histopathology	Mitotic index	Molecules
Astrocytoma, grade 2	Hypercellularity, MVP–, necrosis–	Low or lack mitotic activity	CDKN2A/B homozygous deletion; IDH1/2 intact, 1p19q intact, TP53, ATRX mutations
Astrocytoma, grade 3	Necrosis+, MVP+	Elevated mitotic activity	CDKN2A/B homozygous deletion; IDH1/2 intact, 1p19q intact, TP53, ATRX mutations
Astrocytoma, grade 4	Necrosis+, MVP+ (Fig. 30.2a–d)	Elevated mitotic activity	CDKN2A/B homozygous deletion; IDH1/2 intact, 1p19q intact, TP53, ATRX mutations

MVP microvascular proliferation

Table 30.4 Major features of oligodendroglioma: histopathological, molecular, and grading [16, 18]

Subtypes	Histopathologic features	Immunohistochemistry	Molecules	Mitotic index	WHO grade
Oligodendroglioma	Round cells, chickenwire pattern vasculature, calcospherites, GFOC, minigemistocytes	GFAP+ Olig2+	IDH1 or IDH2 mutation, P53 (wildtype), ATRX (wildtype) 1p9q codeletion	Low mitosis without necrosis	2
Oligodendroglioma	Round cells, chickenwire pattern, calcospherites, GFOC, minigemistocytes	GFAP+ Olig2+	IDH1 or IDH2 mutations, P53 (wildtype), ATRX (wildtype) 1p9q codeletion	>6/HPF, microvascular proliferation, necrosis	3

GFOC glial fibrillary oligodendroglia

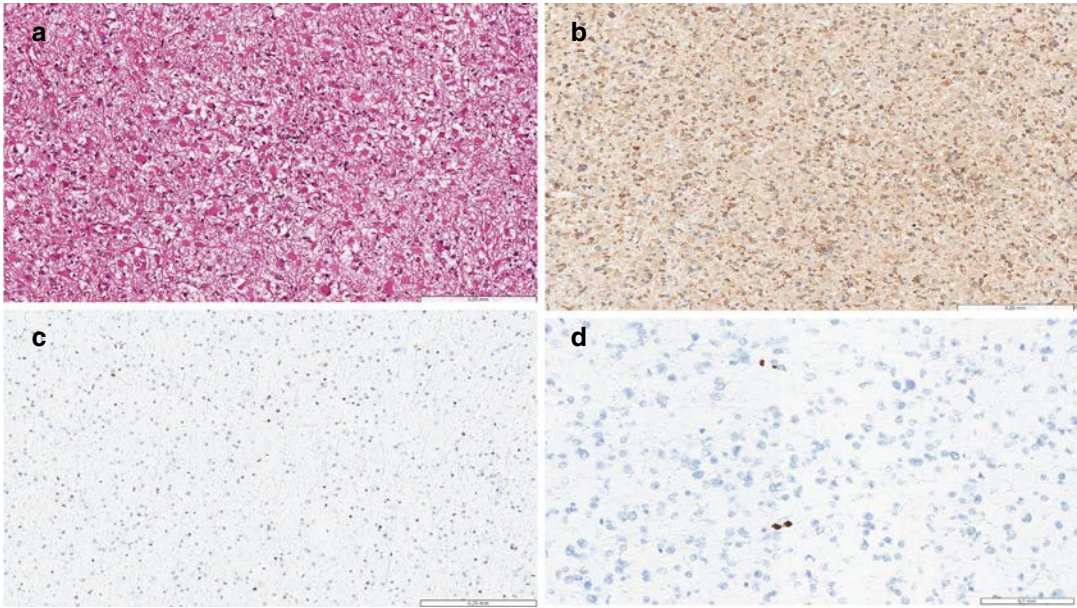


Fig. 30.2 Astrocytoma IDH-mutant, grade 2. (a) Gemistocytes with abundant cytoplasm are randomly distributed in a background. (b) Diffuse cytoplasmic IDH1

expression is noted. (c) There is faint reactivity with ATRX. (d) The Ki67 index reveals a low proliferation rate of 1%

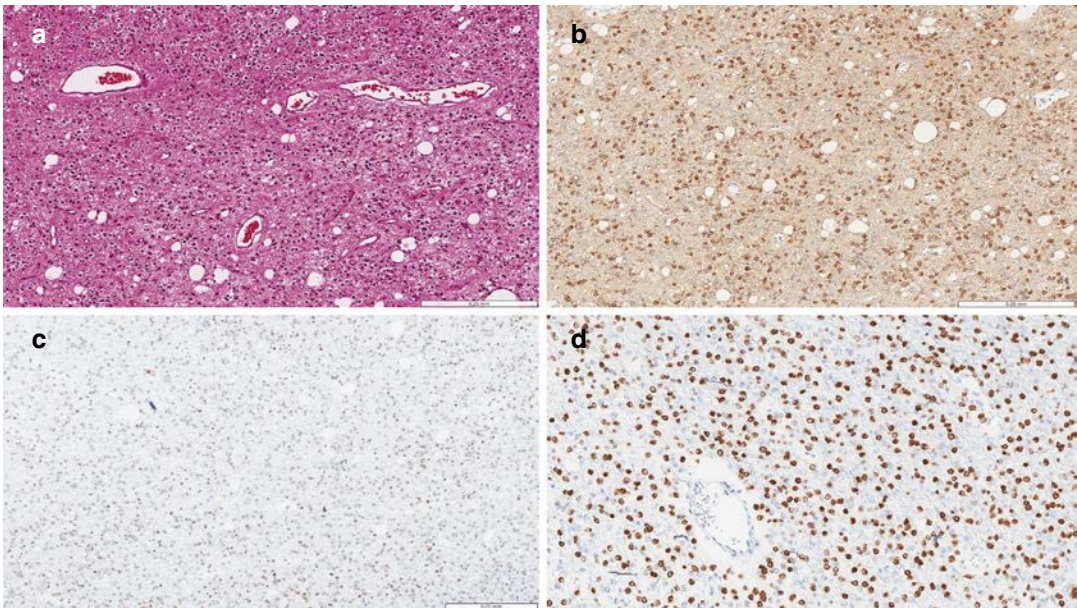


Fig. 30.3 Oligodendroglioma, grade 2. (a) Oligodendroglioma consists of cells with rounded nuclei and areas of perinuclear clearing, resulting in a poached-

egg appearance. (b) Diffuse cytoplasmic IDH1 expression is observed. (c) There is strong reactivity with ATRX. (d) Diffuse Olig2 expression is noted

- (ii) *Astrocytoma, IDH-Mutant* (Table 30.3)
- (iii) *Oligodendroglioma, IDH-Mutant and 1p/19q Codeleted* (Table 30.4; Fig. 30.3)

30.4.1.2 Pediatric-Type Diffuse Low-Grade Gliomas (Table 30.5; Fig. 30.4)

Table 30.5 WHO CNS 5 classification of pediatric-type diffuse low-grade gliomas [16, 20]

Category	Subcategory	WHO grade
Pediatric-type diffuse low-grade gliomas	Diffuse astrocytoma, <i>MYB</i> or <i>MYBL1</i> altered	1
	Angiocentric glioma	1
	Polymorphous low-grade neuroepithelial tumor of the young (PLNTY)	1
	Diffuse low-grade glioma, MAPK pathway-altered	Grade not yet assigned

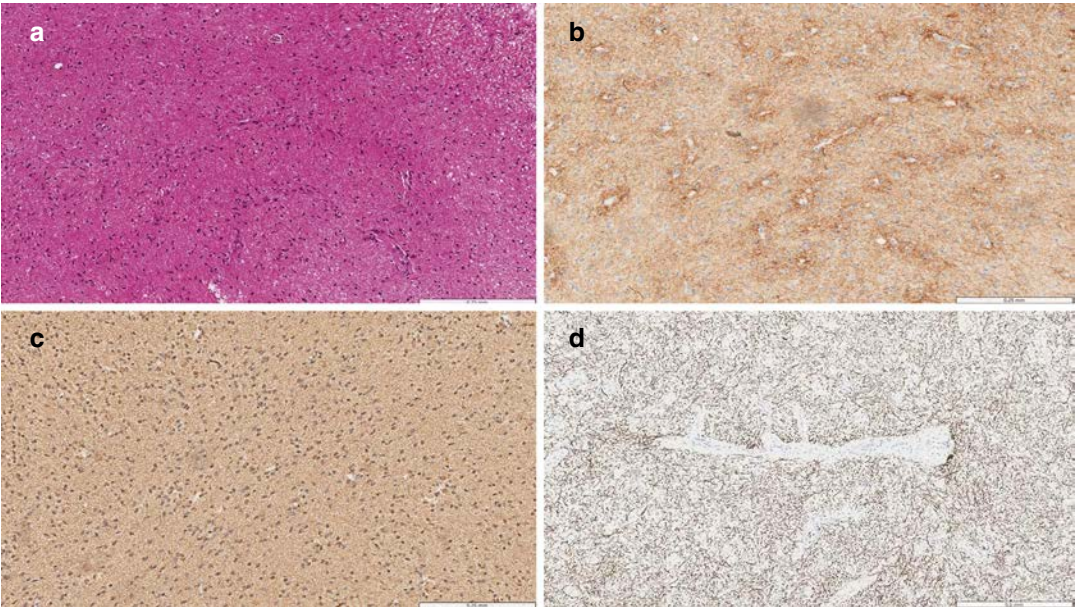


Fig. 30.4 Angiocentric glioma. (a) In solid areas of angiocentric glioma, elongated cells with bipolar cytoplasmic processes are the predominant feature. (b) Angiocentric tumor cells are best visualized using EMA. (c) There is diffuse background reactivity with GFAP. (d) NFP identifies a distinct angiocentric pattern

30.4.1.3 Pediatric-Type Diffuse High-Grade Gliomas
(Table 30.6; Fig. 30.5)

Table 30.6 Major immunohistochemical and molecular features of pediatric high-grade gliomas [16, 21]

Type	Immunohistochemistry	Molecular biology
Diffuse midline glioma, H3 K27-altered	H3K27M, H3K27me3*, Olig+, S100+, GFAP+	<i>H3.3</i> and <i>H3.1</i> , <i>EGFR</i> , <i>EZH1P</i>
Diffuse hemispheric glioma, H3G34-mutant	H3G34, H3K36me3*, p53, ATRX	<i>H3.3</i> and <i>H3.1</i> , <i>TP53</i> , <i>ATRX</i>
Diffuse pediatric type high-grade glioma, H3-wild type and IDH-wild type	IDH1R132H, H3K27me3*, H3K36me3*	<i>IDH1</i> , <i>IDH2</i> , <i>H3.3</i> and <i>H3.1</i> , <i>PDGFRA</i> , <i>MYCN</i> , <i>EGFR</i>
Infant type hemispheric glioma	ALK, ROS1, c-MET	<i>ALK</i> , <i>ROS1</i> , <i>MET</i>

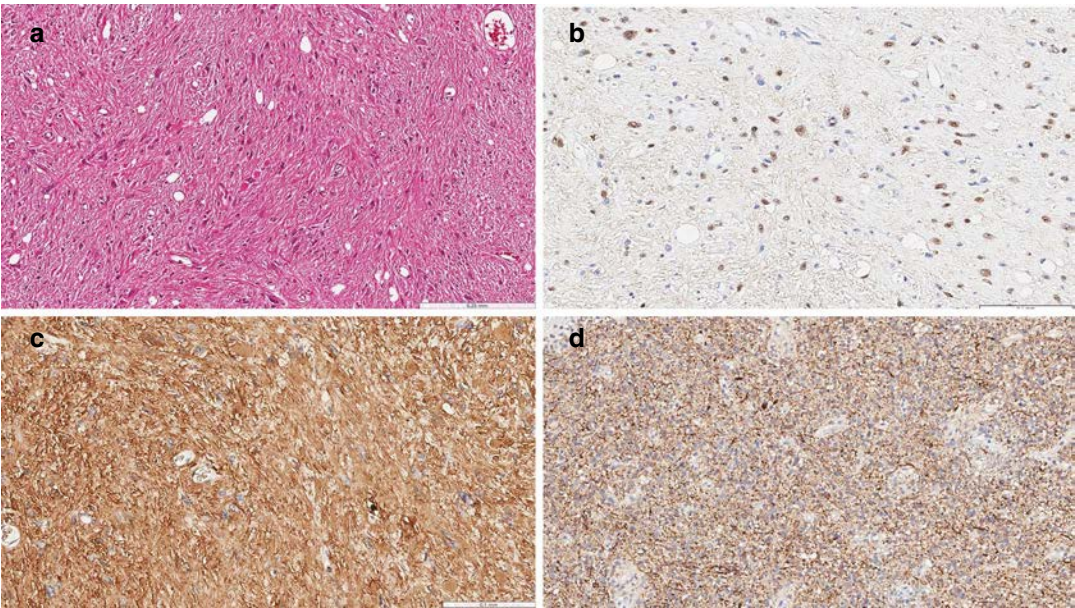


Fig. 30.5 Diffuse midline glioma, H3 K27-altered. **(a)** Infiltrative neoplastic cells are observed in a disarrayed pattern. **(b)** Nuclear H3K27m reactivity is a characteristic feature of the tumor. **(c)** Tumor cells exhibit diffuse GFAP expression. **(d)** The neurofilament stain emphasizes the diffusely infiltrative growth

30.4.1.4 Circumscribed Gliomas (Table 30.7; Figs. 30.6 and 30.7)

Table 30.7 Major immunohistochemical and molecular features of circumscribed glial tumors [16, 22]

Tumor type	Immunohistochemical features	Typical molecular alteration	WHO grade
Pilocytic astrocytoma (PA)	GFAP+, S100+, OLIG2+, synaptophysin+, SOX10+, p16+ NFP–, NeuN–, chromogranin–, CD34–	Solitary MAPK alteration <i>BRAF</i> fusions, <i>BRAF</i> V600E mutation, <i>FGFR1</i> mutation <i>NF1</i> mutation, <i>KRAS</i> mutation	1
Pilomyxoid astrocytoma (PMA)	Similar to pilocytic astrocytomas	Solitary MAPK alteration <i>BRAF</i> fusions, <i>BRAF</i> V600E mutation, <i>NF1</i> mutation, others	Grade not yet assigned
Pleomorphic xanthoastrocytoma (PXA)	GFAP+, S100+, <i>BRAF</i> V600E+; focal synaptophysin+, neurofilament+, class III+, β -tubulin+, MAP2+	<i>BRAF</i> V600E mutation and <i>CDKN2A/B</i> homozygous loss	2/3
Subependymal giant cell astrocytoma (SEGA)	GFAP+, Olig2+, EMA+, Syn+, NeuN+, neuropeptides+; SOX10+, nestin+; TTF1+	<i>TSC1</i> or <i>TSC2</i> mutation	1
Chordoid glioma (CG)	GFAP+, nuclear TTF1+, CD34+; EMA+, S100+ Syn–, chromogranin–, NFP–	<i>PRKCA</i> p.D463H mutation	2
Astroblastoma <i>MNI</i> altered	GFAP+, Olig2+, D2–40+, EMA+; LCAM1–	<i>MNI</i> fusions	Grade not yet assigned
High-grade astrocytoma with piloid features	Loss of nuclear ATRX expression, IDH1 p.R132H–; rare H3 p.K28M (K27M)-mutant protein	Unknown	Grade not yet assigned

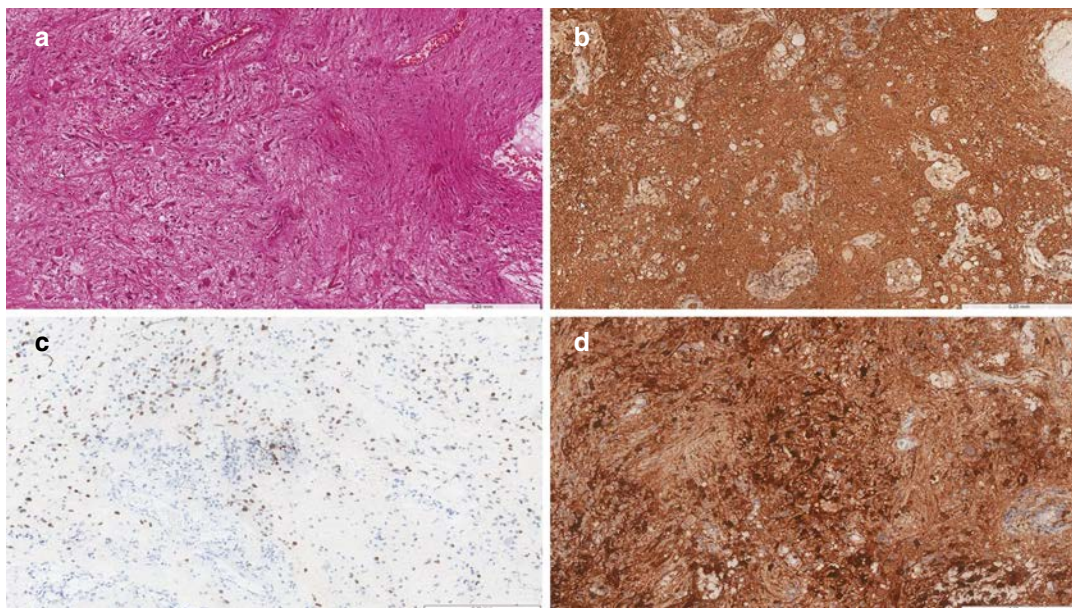


Fig. 30.6 Pilocytic astrocytoma. (a) Characteristic biphasic appearance of pilocytic astrocytoma. (b) Diffuse and strong GFAP expression amid hyalinized blood ves-

sels. (c) Sparse reactivity with Olig2. (d) Diffuse and strong P16 expression

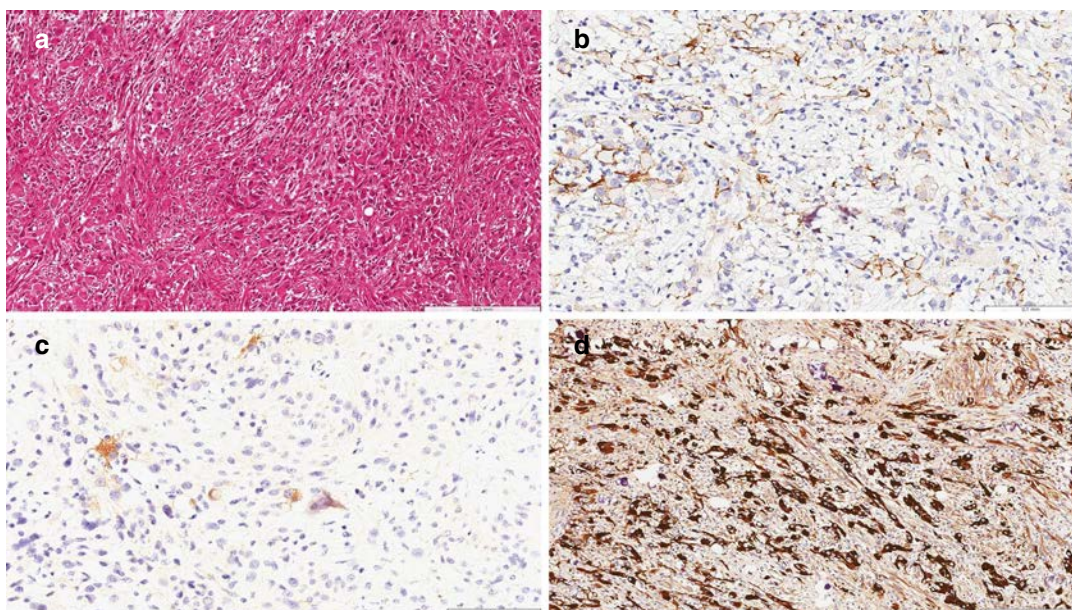


Fig. 30.7 Pleomorphic xanthoastrocytoma (PXA). (a) Low power field magnification reveals fascicles formed by pleomorphic cells. (b) BRAF stainings are particularly

striking. (c) Single ganglioid cells can be identified using synaptophysin. (d) The reticulin framework is another hallmark characteristic of the tumor

30.4.1.5 Glioneuronal and Neuronal Tumors (Table 30.8; Fig. 30.8; Table 30.9; Figs. 30.9 and 30.10)

Table 30.8 Glioneuronal and neuronal tumors and histologic features [16, 23]

	Histologic findings	WHO grade
<i>Mainly composed of ganglion and ganglioid cells</i>		
Ganglioglioma	Atypical ganglionic (neuronal-like) cell component and glioma component, atypical neurons may be binucleated and/or abnormally clustered (“kissing neurons”), calcifications, eosinophilic granular bodies	1
Gangliocytoma	Similar to ganglioglioma but composed entirely of dysplastic, mature-appearing ganglioid tumor cells	1
Desmoplastic infantile ganglioglioma (DIG)/astrocytoma (DIA)	Desmoplasia with spindled cells arranged in storiform or fascicular architecture; ganglionic or neuronal cells intermixed in the ganglioglioma type	1
Multinodular and vacuolating neuronal tumor (MVNT)	Nodules of monomorphic neurocytic cells with vacuolar change	1
Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)	Hamartomatous lesion of ganglion cells	1
<i>Mainly composed of neurocytes</i>		
Central neurocytoma/extraventricular neurocytoma/cerebellar liponeurocytoma	Uniform, round nuclei with speckled chromatin (“oligo-like”), fibrillary background	2
Papillary glioneuronal tumor (PGNT)	Ganglioid cells between the papillary structures	1
Rosette-forming glioneuronal tumor (RGNT)	Neurocytic component with rosettes and areas resembling pilocytic astrocytoma	1
Diffuse leptomeningeal glioneuronal tumor (DLGNT)	Monomorphic oligodendrocyte-like tumor cells, diffusely or in small nests in the leptomeninges, with desmoplastic and myxoid changes	Grade not yet assigned
<i>Mainly composed of oligodendroglia-like cells</i>		
Dysembryoplastic neuroepithelial tumor (DNT)	Small, monomorphic tumor cells with perinuclear clearing (“oligo-like”), specific glioneuronal elements—“oligo-like” tumor cells lining bundles of axons, “floating neurons”	1
Myxoid glioneuronal tumor (MGNT)	“Oligo-like” cells in prominent myxoid background	1
Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters (DGONC)*	“Oligo-like” tumor cells, multinucleated cells, nuclear clusters	Grade not yet assigned

*the provisional tumor type by WHO CNS5

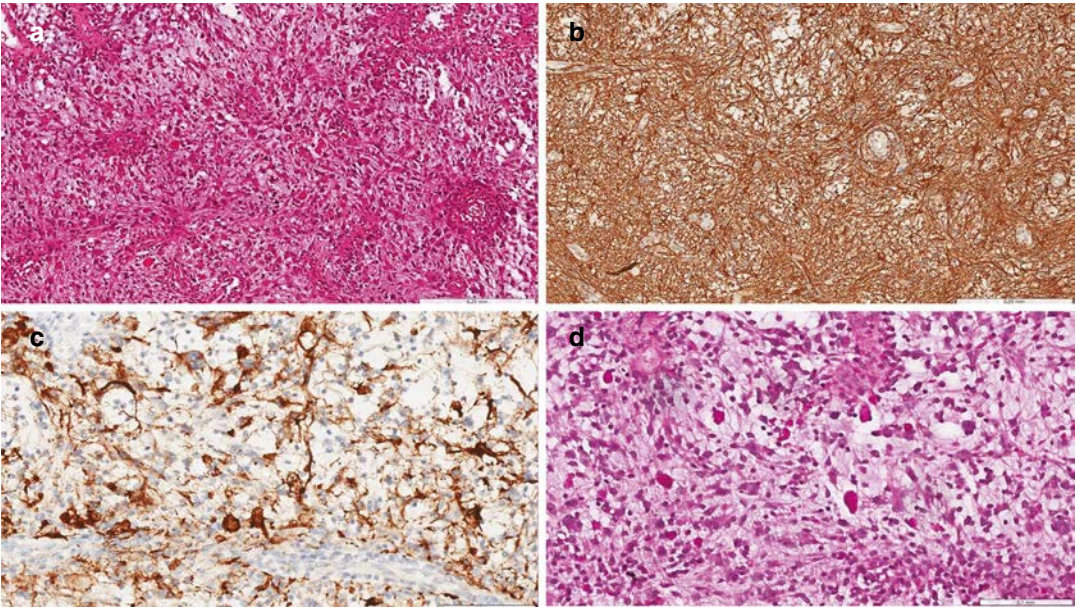


Fig. 30.8 Ganglioglioma. (a) Ganglioglioma consists of neoplastic ganglion and glial cells. (b) The glial component primarily expresses GFAP. (c) Scattered synaptophysin-reactive cells are easily identifiable. (d) PAS stains Rosenthal fibers specifically

Table 30.9 Glioneuronal and neuronal tumors: immunohistochemical and molecular features [16, 23]

	IHC findings
<i>Mainly composed of ganglion and ganglioid cells</i>	
Ganglioglioma, gangliocytoma	BRAF V600E or other MAPK activating alterations
Desmoplastic infantile ganglioglioma (DIG)/astrocytoma (DIA)	SYN+, NFP+, NeuN+, GFAP+ in glioma component
Multinodular and vacuolating neuronal tumor (MVNT)	Olig2+, Syn+, NeuN–
Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)	Syn+, CD3+ (LEU4), PCP2+, PCP4+ (Purkinje cells), calbindin+
<i>Mainly composed of neurocytes</i>	
Central neurocytoma/extraventricular neurocytoma/cerebellar liponeurocytoma	GFAP–, Syn+; NeuN+, TTF-1+; FGFR1-TACC1 gene fusion
Papillary glioneuronal tumor (PGNT)	GFAP+; PRKCA gene fusion, usually SLC44A1-PRKCA
Rosette-forming glioneuronal tumor (RGNT)	FGFR1 hotspot mutation with co-occurring PIK3CA and/or NF1 mutation
Diffuse leptomeningeal glioneuronal tumor (DLGNT)	Frequent chromosome 1p deletion (19q intact); KIAA1549-BRAF fusion or other MAPK activating alteration
<i>Mainly composed of oligodendroglia-like cells</i>	
Dysembryoplastic neuroepithelial tumor (DNT)	FGFR1 alterations
Myxoid glioneuronal tumor (MGNT)	PDGFRA K385 mutations
Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters (DGONC)*	Olig2+, synaptophysin+, NeuN–

*: is the provisional tumor type by WHO CNS5

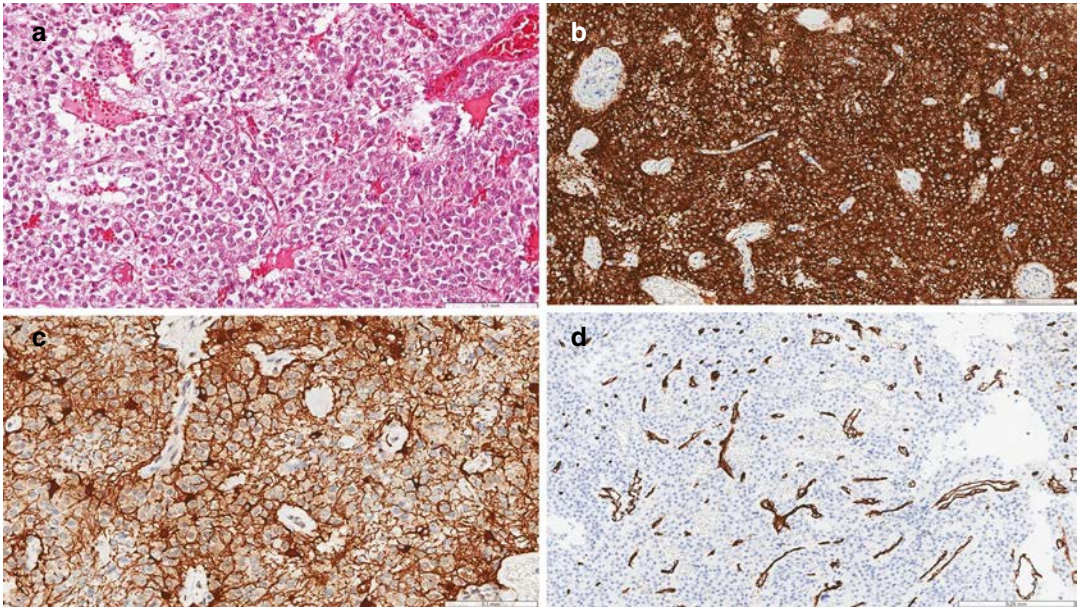


Fig. 30.9 Central neurocytoma. (a) Monotonous cells exhibit round nuclei with salt-and-pepper chromatin patterns. (b) Diffuse staining is observed with synaptophysin.

(c) A GFAP-reactive intervening tumor component is another feature. (d) The prolific vasculature is stained by CD34, revealing a dense vascular framework

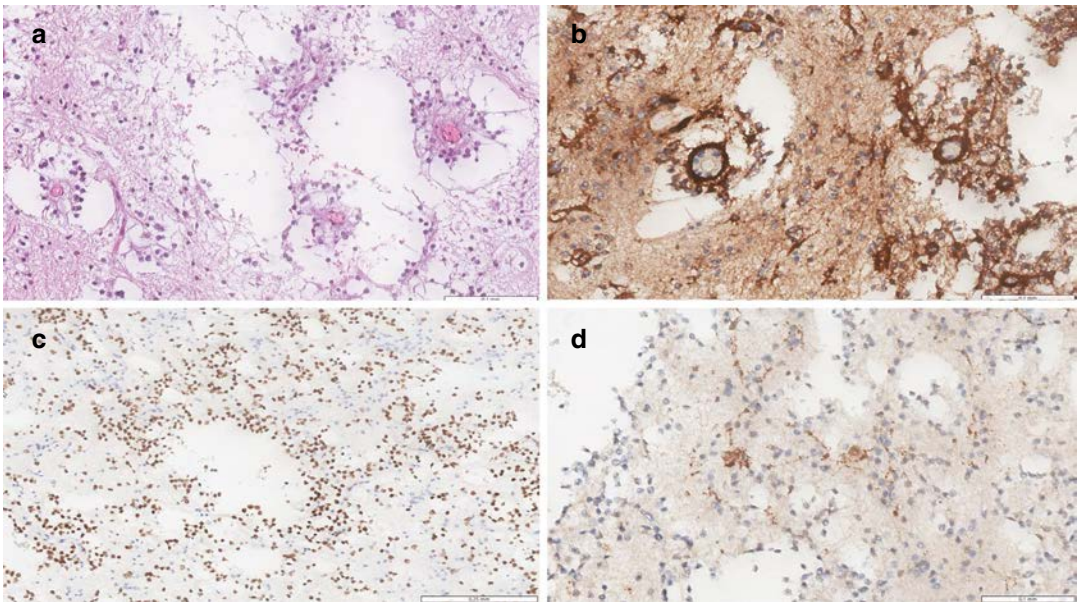


Fig. 30.10 Rosette-forming glioneuronal tumor (RGNT). (a) Rosette-forming glioneuronal tumor, characterized by neurocytic rosettes. (b) Synaptophysin stains

the centers of the rosettes. (c) Olig2 selectively stains the nuclei of tumor cells. (d) NeuN immunoreactivity is evident in neurocytic tumor cells

30.4.1.6 Ependymal Tumors

(a) *General features* (Table 30.10; Figs. 30.11 and 30.12)

(b) *Myxopapillary ependymoma* [16, 19]

(c) *Subependymoma* [16, 19] (Table 30.11; Figs. 30.13 and 30.14)

Table 30.10 Major locations, demographic and molecular features, and outcome of ependymal tumors [15, 16, 23]

Site	Type	Age	Sex	Molecular features	Outcome	WHO grade
Supratentorial	ST-SE	Adult	M = F	<i>Balanced genome</i>	Good	1
	ST-ZTFA	Infant, adolescent, adult	M > F	<i>ZTFA fusions, Chromothripsis CDKN2A and/or CDKN2B loss</i>	Intermediate	2/3
	ST-YAP1	Infant, adult	M < F	<i>YAP fusions</i>	Good	2/3
Infratentorial	PF-SE	Adult	M > F	<i>Balanced genome</i>	Good	1
	PF-PFA	Child, adult	2M – 1F	<i>EZH1P mutations H3 p.K28M (K27M) mutations Chr. 1q gain</i>	Worse	2/3
	PF-PFB	Child, young adult	M = F	<i>Chromosomal instability</i>	Good	2/3
Spinal	SP-SE	Adult	M = F	<i>Chr. 6p deletion</i>	Good	1
	SP-EP	Adult	2M – 1F	<i>NF2 mutations</i>	Intermediate	2/3
	SP-MP	Adult	M = F	<i>Chromosomal instability</i>	Good	2
	SP-MYCN	Child, adult	M = F	<i>MYCN amplification</i>	Good	Grade not yet assigned

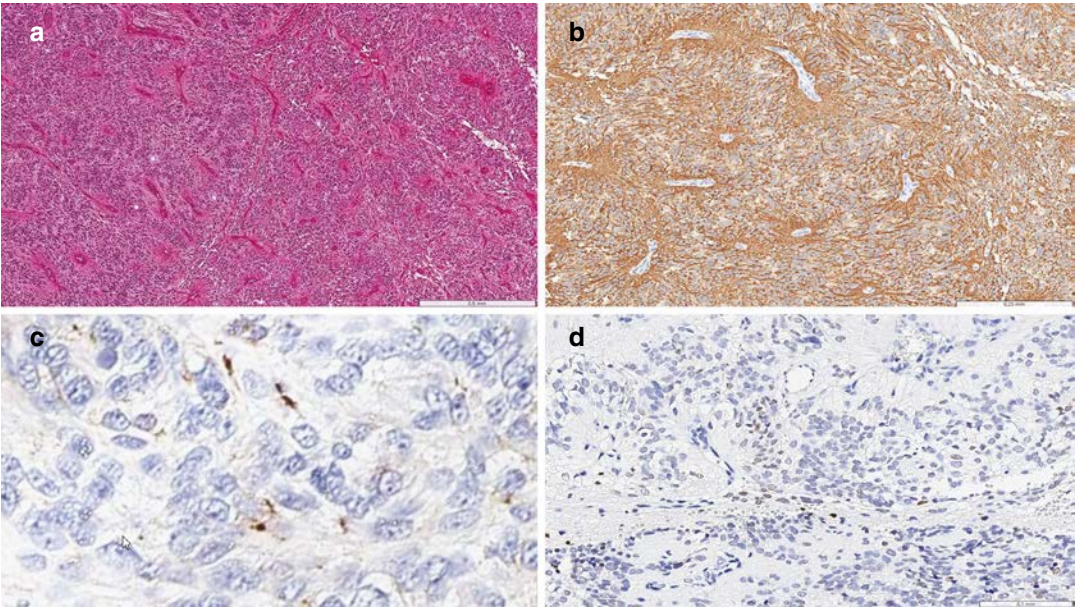


Fig. 30.11 Supratentorial ependymoma. (a) The tumor consisted of uniform cells with a complex vasculature. (b) GFAP stains the tapered cytoplasmic extensions of tumor

cells surrounding vessels. (c) Specific EMA reactivity reveals dots near the nuclei. (d) There is sparse expression of Olig2 by tumor cells

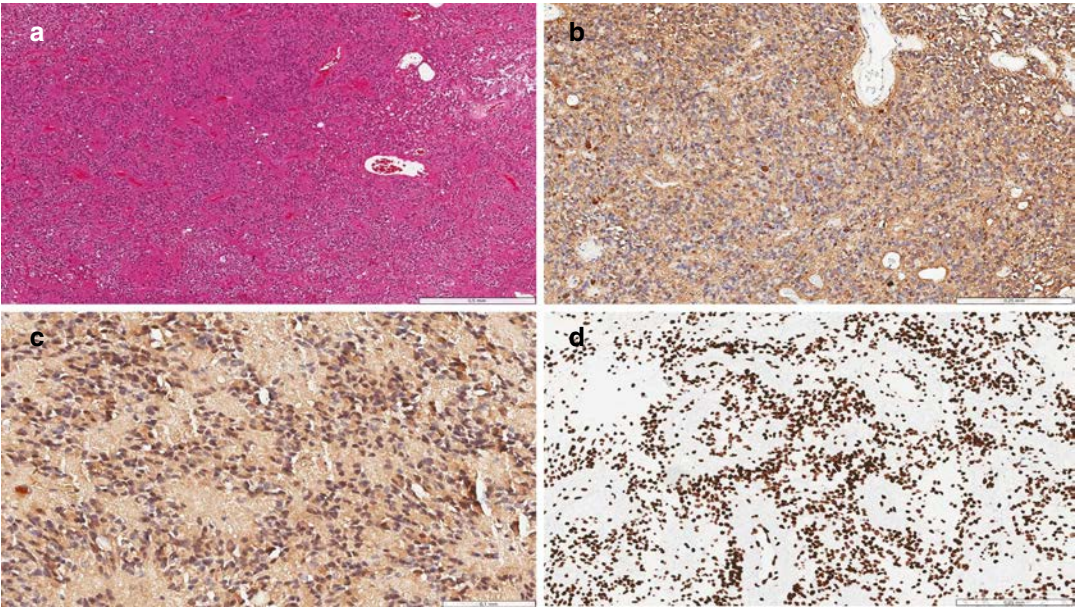


Fig. 30.12 Infratentorial ependymoma (PFB). (a) Ependymoma cells are arranged radially around blood vessels, with an intervening anucleate zone. (b) GFAP+ cells create perivascular pseudorosettes. (c) Tumor cells exhibit immunoreactivity with YAP1. (d) There is diffuse and strong immunoreactivity to H3K27m3

Table 30.11 Major histopathologic and immunohistochemical features of myxopapillary ependymoma and subependymoma

Type		Location	Histopathologic features	Immunohistochemistry	WHO grade
Subependymoma		Septum pellucidum	Nuclei clusters, ependymal cells, mitosis unusual, calcification	GFAP+,S100+,EMA–	1
Myxopapillary ependymoma		Filum terminale	Papillary structures, mucoid background, occasional mitosis	GFAP+,S100+,EMA–	2

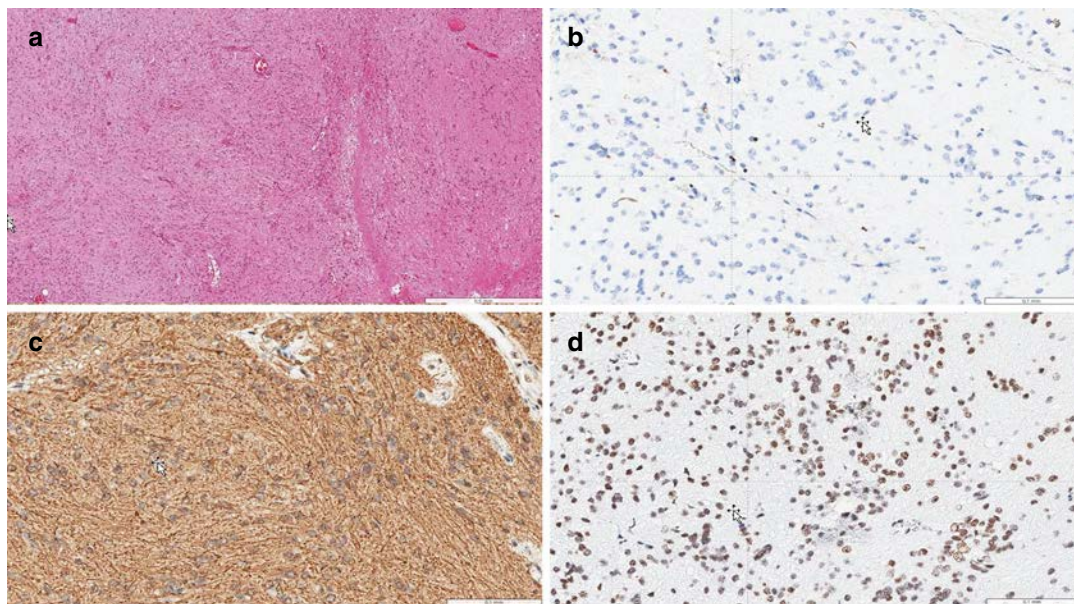


Fig. 30.13 Subependymoma. (a) Tumor cell clusters are characterized by small, monotonous nuclei embedded in a neuropil. (b) EMA shows immunopositive perinuclear

dots. (c) GFAP-reacting cells display a diffuse and strong affinity for this antibody. (d) Tumor cells exhibit diffuse ATRX immunoreactivity

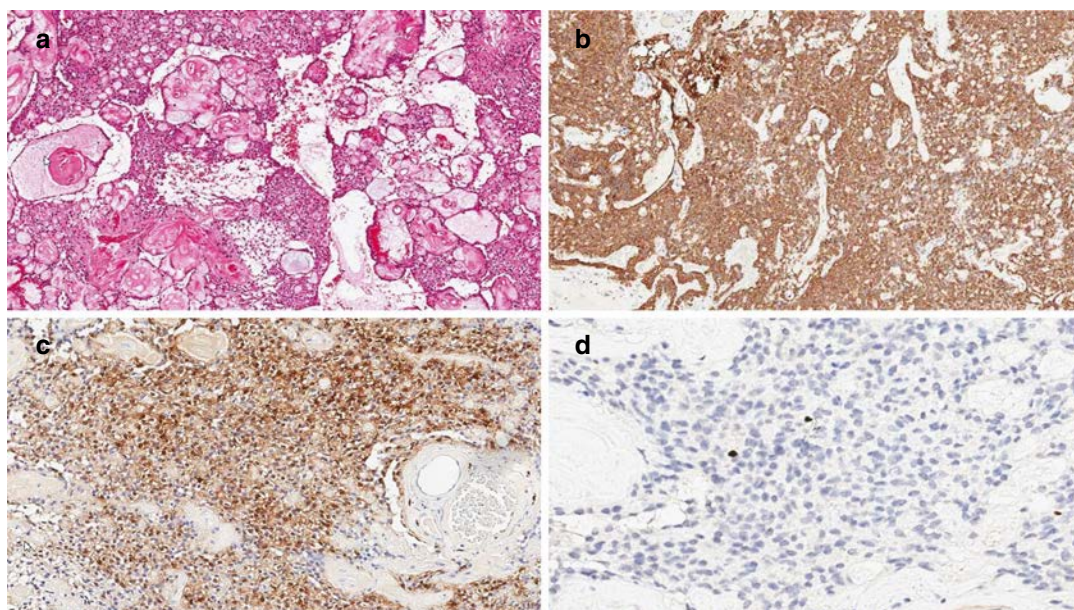


Fig. 30.14 Myxopapillary ependymoma. (a) Tumor cells with epithelioid features are clustered around fibrovascular cores. (b) The tumor cells exhibit strong immunoreac-

tivity to GFAP. (c) The tumor cells demonstrate strong immunoreactivity to S100. (d) The Ki67 proliferation index is low (<1%)

30.4.2 Choroid Plexus Tumors
(Table 30.12; Fig. 30.15)

Table 30.12 Major histopathologic and immunohistochemical features of choroid plexus tumors [16, 19, 24, 25]

Types	Histopathologic features	Immunohistochemical findings	WHO grade
Choroid plexus papilloma	Predominantly composed of bland epithelial-type cells on collagen-vascular cores, minimal atypia, mitotic activity (<2/10 HPF)	CK7+, CK20–, Kir7.1+, S-100+, transthyretin+ GFAP+ (focal) Fig. 30.9a–d	1
Atypical choroid plexus papilloma	Increased mitotic activity (≥ 2 mitoses/10 HPF), increased cellularity and nuclear atypia, blurring of papillary architecture, focal necrosis	CK7+, CK20–, Kir7.1+, S-100+, transthyretin+ GFAP+ (focal)	2
Choroid plexus carcinoma	Atypia, increased mitoses, solid growth, necrosis, and brain invasion (4/5 parameters should be counted)	TP53 mutations (50% associated with Li-Fraumeni syndrome)	3

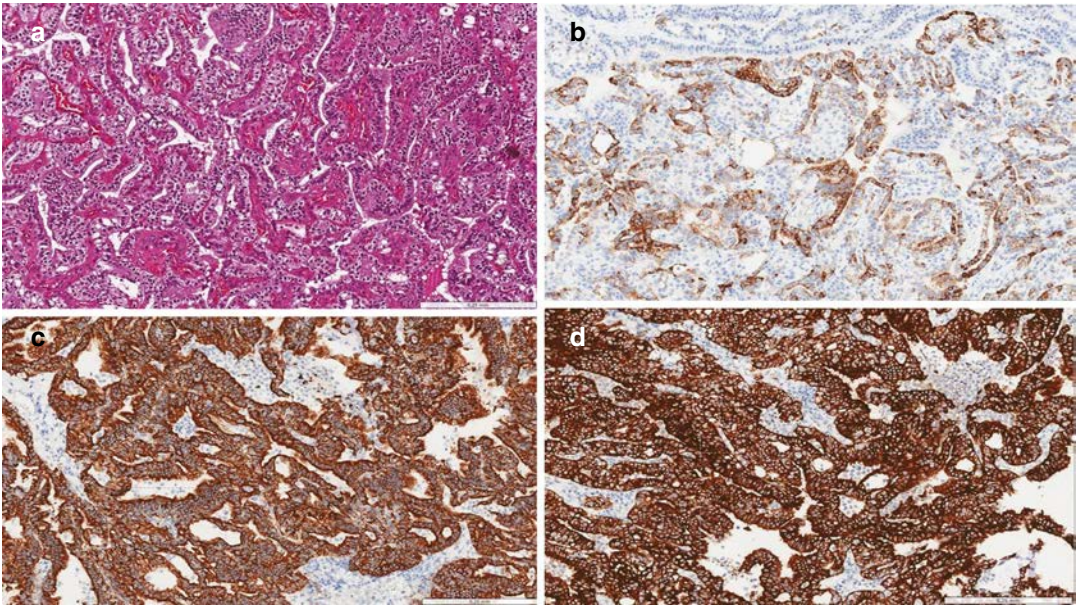


Fig. 30.15 Choroid plexus papilloma. (a) The characteristic papillary pattern consists mainly of a single layer of uniform cuboidal cells. (b) Epithelial cells are reactive to

CK17. (c) PanCK reactivity is both diffuse and strong. (d) Tumor epithelial cells show strong reactivity with synaptophysin

30.4.3 Embryonal Tumors

30.4.3.1 Medulloblastoma [16, 26] (Tables 30.13, 30.14, and 30.15; Fig. 30.16)

Table 30.13 Embryonal tumors, WHO Classification 2021 (CNS5)

<i>Medulloblastomas</i>
Medulloblastoma, WNT-activated
Medulloblastoma, SHH-activated, and TP53-wildtype
Medulloblastoma, SHH-activated, and TP53-mutant
Medulloblastoma, non-WNT/non-SHH
Medulloblastomas, histologically defined
<i>Other CNS embryonal tumors</i>
Atypical teratoid/rhabdoid tumor
Cribriiform neuroepithelial tumor
Embryonal tumor with multilayered rosettes
CNS neuroblastoma, FOXR2-activated
CNS tumor with BCOR internal tandem duplication (ITD)
CNS embryonal tumor NOS

Table 30.14 Genetic subtypes of medulloblastoma [16, 24]

Genetic type	Histological types	Age and M/F ratio	Prognosis
WNT-activated	Classic	Childhood 1:2	>95% survival
SHH-activated, P53-wildtype	Desmoplastic/ nodular	Infants and adults 1:1	75% survival
SHH-activated, P53-mutant	Large cell/ anaplastic	Childhood 1:1	40% survival
Group 3 MYC-amplification in 20%	Classic Large cell/ anaplastic	Infants and childhood 2:1	Poor prognosis
Group 4 Chromosome 17 alteration in 80%	Classic	All ages	Intermediate prognosis (poor if metastatic disease at presentation)

Table 30.15 Genetic subtypes of medulloblastoma [16, 24]

Genetic type	Histological types	Age and M/F ratio	Prognosis
WNT-activated	Classic	Childhood 1:2	>95% survival
SHH-activated, P53-wildtype	Desmoplastic/ nodular	Infants and adults 1:1	75% survival
SHH-activated, P53-mutant	Large cell/anaplastic	Childhood 1:1	40% survival
Group 3 MYC-amplification in 20%	Classic large cell/ anaplastic	Infants and childhood 2:1	Poor prognosis
Group 4 Chromosome 17 alteration in 80%	Classic	All ages	Intermediate prognosis (poor if metastatic disease at presentation)

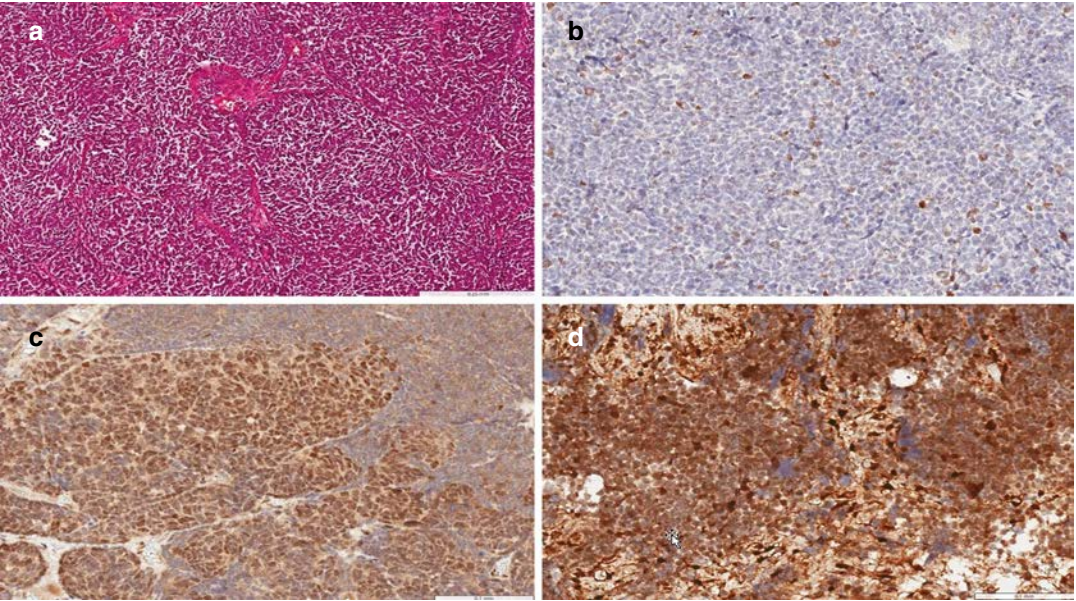


Fig. 30.16 Medulloblastoma, SHH-activated and *TP53*-wildtype. **(a)** This group primarily exhibits desmoplastic/nodular morphology, consisting of small cells with round nuclei and scant cytoplasm. **(b)** p53 is positive in a few scattered cells (wildtype). **(c)** YAP1 shows diffuse immunoreactivity. **(d)** GAB1 is also strongly immunoreactive

30.4.3.2 Atypical Teratoid/Rhabdoid Tumor [16, 19, 24, 25] (Table 30.16)

Table 30.16 Clinico-pathological and genetic characteristics of AT/RT molecular subgroups

Molecular subgroups	AT/RT-SHH	AT/RT-TYR	AT/RT-MYC
Incidence	44%	34%	22%
Age	2–5 years (median age: 20 months)	0–1 years (median age: 12 months)	>3 years (median age: 27 months)
Location	More frequently supratentorial	More frequently infratentorial	More frequently supratentorial (rarely spinal)
Copy number alteration of chromosome 22	None	Complete loss (monosomy)/partial loss	None
SMARCB1 alterations	Point mutations/focal deletions	Point mutations/focal deletions	Extensive deletions
Involved pathway	SHH and NOTCH pathway	BMP and melanosomal pathway	Overexpression of MYC gene and HOX cluster genes

**30.4.3.3 Embryonal Tumor
with Multilayered Rosettes**
[16, 19, 24, 25, 27]
(Table 30.17)

Table 30.17 Major histopathologic and molecular findings of embryonal tumors with multilayered rosettes

Tumor	Histopathologic and IHC features	Molecular alteration
Common findings	Multilayered rosettes composed of pseudostratified tumor cells arranged around blood vessels IHC: LIN28	C19MC alteration, chromosome 19q rearrangements, DICER1 mutation (rare)
Embryonal tumor with abundant neuropil and true rosettes (ETANTR)	Biphasic with areas of mature neuropil and ganglioid differentiation and other areas with embryonal appearance and multilayered rosettes	C19MC alteration, chromosome 19q rearrangements, DICER1 mutation (rare)
Ependymoblastoma	Numerous multilayered rosettes	C19MC alteration, chromosome 19q rearrangements, DICER1 mutation (rare)
Medulloepithelioma	Papillary, trabecular or tubular, structures	C19MC alteration, chromosome 19q rearrangements, DICER1 mutation (rare)

30.4.4 Pineal Parenchymal Tumors
(Table 30.18; Figs. 30.17,
30.18, and 30.19)

Table 30.18 Major histopathologic and immunohistochemical findings of pineal parenchymal tumors [16, 19]

Type	Histopathologic features	Immunohistochemical findings	Grade
Pineocytoma	Pineocytomatous rosettes—largely hypocellular zones with central fibrillarity Fibrillary zones have neural nature	Synaptophysin+, neuron specific enolase+, and neurofilament protein+	1
Pineal parenchymal tumor of intermediate differentiation	Increased cellularity and mitotic activity compared to pineocytoma	Synaptophysin+, NFP+, small in-frame insertions of KBTBD4	2–3
Pineoblastoma	Hyperchromatic tumor cells with high N:C, numerous mitotic figures, necrosis common, Homer-Wright and Flexner-Wintersteiner rosettes	Four distinct DNA methylation subgroups, associated with RB1 tumor predisposition syndrome	4
Papillary tumor of the pineal region	Epithelioid tumor with prominent papillary structures	Cytokeratins+(CK18),S-100+,GFAP+/-	2–3
Desmoplastic myxoid tumor of the pineal region, SMARCB1-mutant	Monotonous, hyperchromatic, oval cells, myxoid and collagenous stroma Positive CD34, EMA; loss of INI1 expression	CD34+, EMA+ loss of SMARCB1 expression	Undetermined

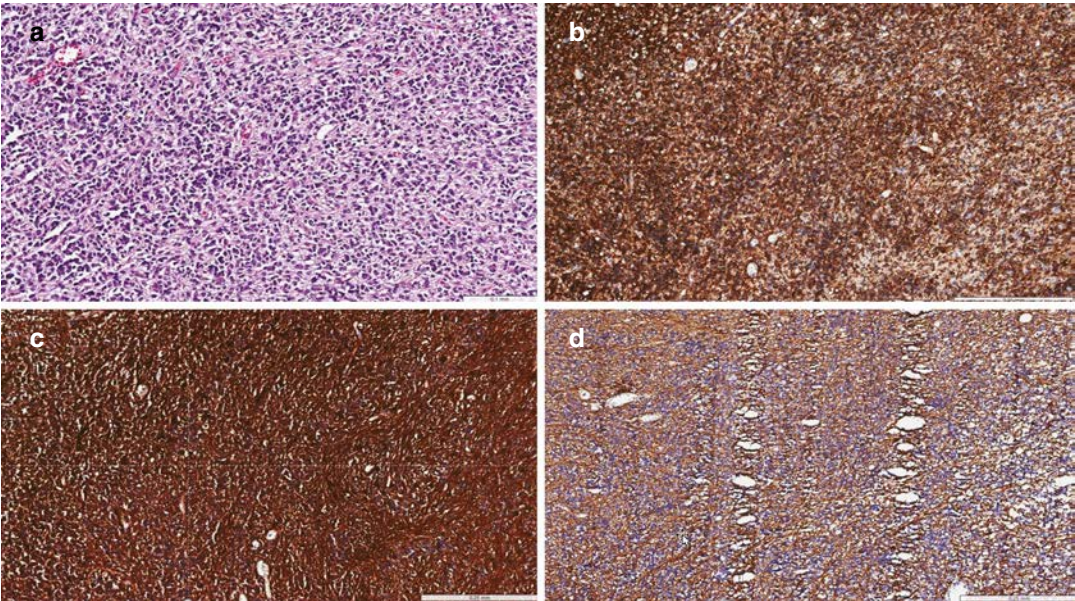


Fig. 30.17 Pineoblastoma. (a) Pineoblastoma is mainly characterized by highly cellular sheets of densely packed small cells that lack a defined pattern. (b) The tumor cells show strong reactivity to synaptophysin. (c) Additionally, they also react to S100. (d) Notably, GFAP immunoreactivity is not a consistent feature of this tumor

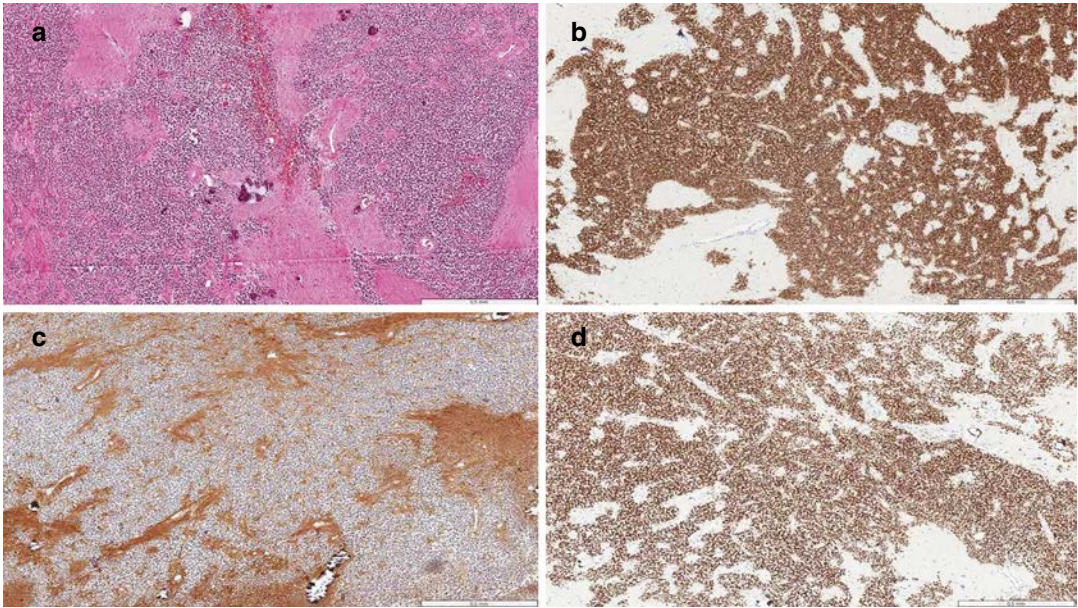


Fig. 30.18 Pineal parenchymal tumor of intermediate differentiation. (a) Tumor cells appear monotonous with scant cytoplasm and lack nucleoli. (b) Nearly all cells

show synaptophysin reactivity. (c) S100 immunoreactivity is a distinguishing characteristic. (d) Tumor cells display diffuse NFP reactivity

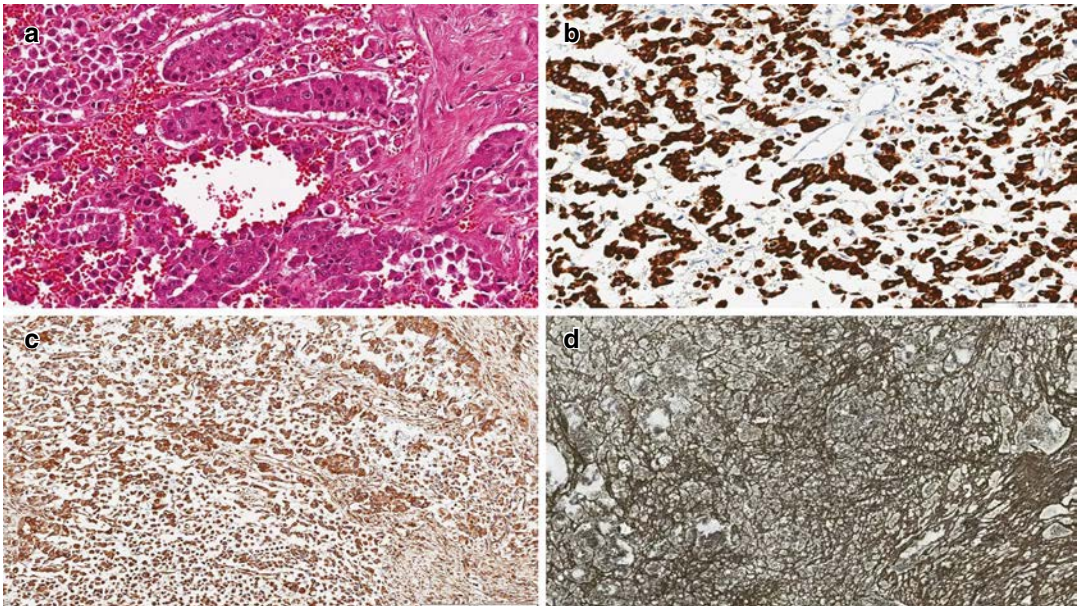


Fig. 30.19 Papillary tumor of the pineal region. (a) The typical papillary structures are integrated within solid tumor areas. (b) Papillae are lined with CK18-positive

cells. (c) Almost all tumor cells are reactive to vimentin. (d) Both solid and papillary regions exhibit a pronounced reticulin framework

30.4.5 Cranial and Paraspinal Nerve Tumors [16]

30.4.5.1 Schwannoma (Table 30.19; Figs. 30.20, 30.21, and 30.22)

Table 30.19 Major histopathologic and immunohistochemical features of cranial and paraspinal tumors

Type	Histopathologic features	Immunohistochemical findings	Syndromic association	Grade
Schwannoma	Spindled cells, Antoni A, Antoni B patterns, Verocay bodies, cystic changes, hyalinized blood vessels	S-100+, SOX10+, GFAP–, H3K27me3 (retained)	NF2	1
Cellular schwannoma	Hypercellular, mostly Antoni A pattern, increased mitotic activity	Same as above		1
Melanotic schwannoma	Melanotic cells	Pigmented cells	Carney complex, NF2	1
Neurofibroma	Admixture of Schwann cells, perineurial-like cells, and fibroblasts in a mucoid/loose matrix Hypercellular, brisk amitosis, necrosis	S100+, loss of nuclear H3K27me3 expression	NF1	1
MPNST (Malignant peripheral nerve sheath tumor)	Histopathologically consistent malignant spindle cell tumor in a patient with NF1 <i>OR</i> in a pre-existing neurofibroma	Loss of H3 p.K28me3 (K27me3) Loss of neurofibromin expression	NF1	4
Perineuroma	Perineurial cells in endoneurium around nerve fibers (pseudo-onion bulbs)	EMA+, claudin-1+, GLUT1+ S100–	Nil	1

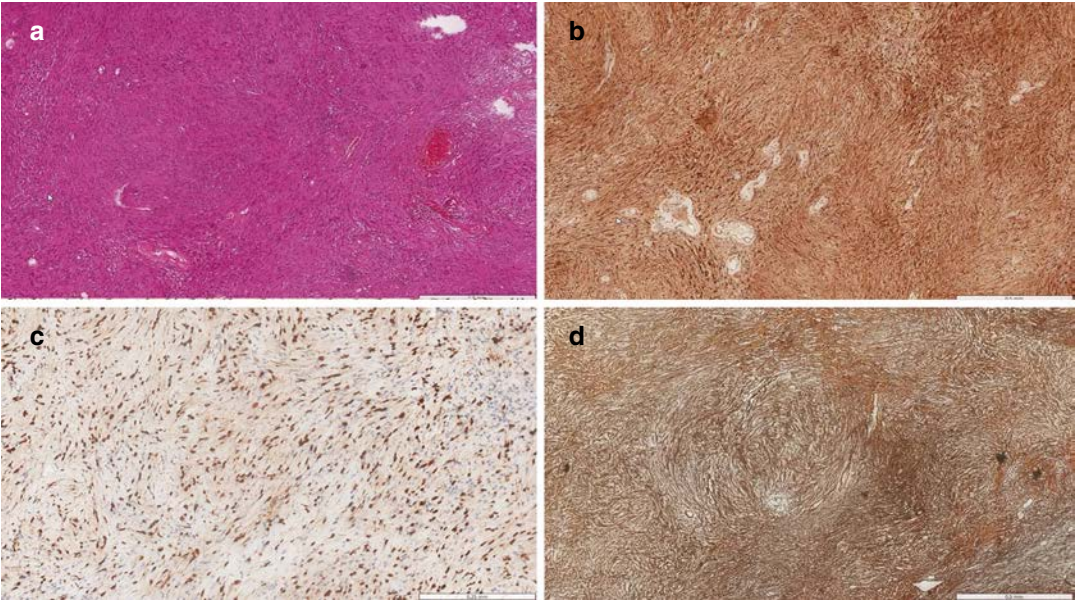


Fig. 30.20 Schwannoma. (a) Spindle-shaped cells with centrally aligned nuclei are a characteristic feature of schwannoma. (b) Almost all tumor cells are reactive to

S100. (c) Nuclear SOX10 positivity is commonly observed in schwannoma. (d) A dense reticulin framework serves as a valuable diagnostic tool for peripheral nerve tumors

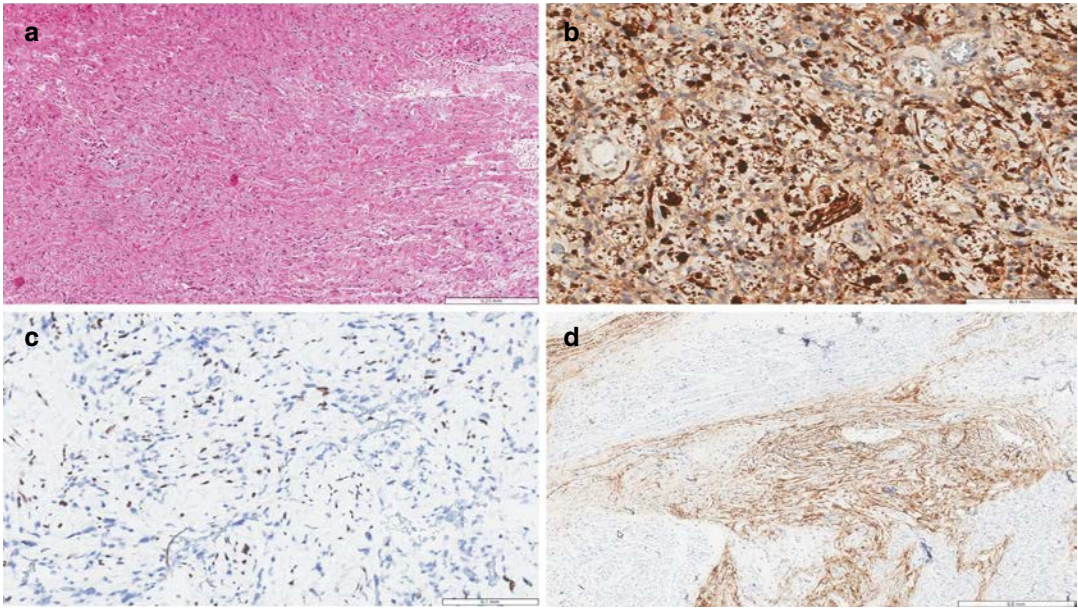


Fig. 30.21 Neurofibroma. (a) Spindle-shaped cells with wavy nuclei and cytoplasmic processes between a collagenous matrix. (b) Spotted areas within the tumor tissue are

S100 reactive. (c) Random distribution of SOX100-positive cells in the tumor. (d) Fascicles of EMA-reactive cells in tumor tissue

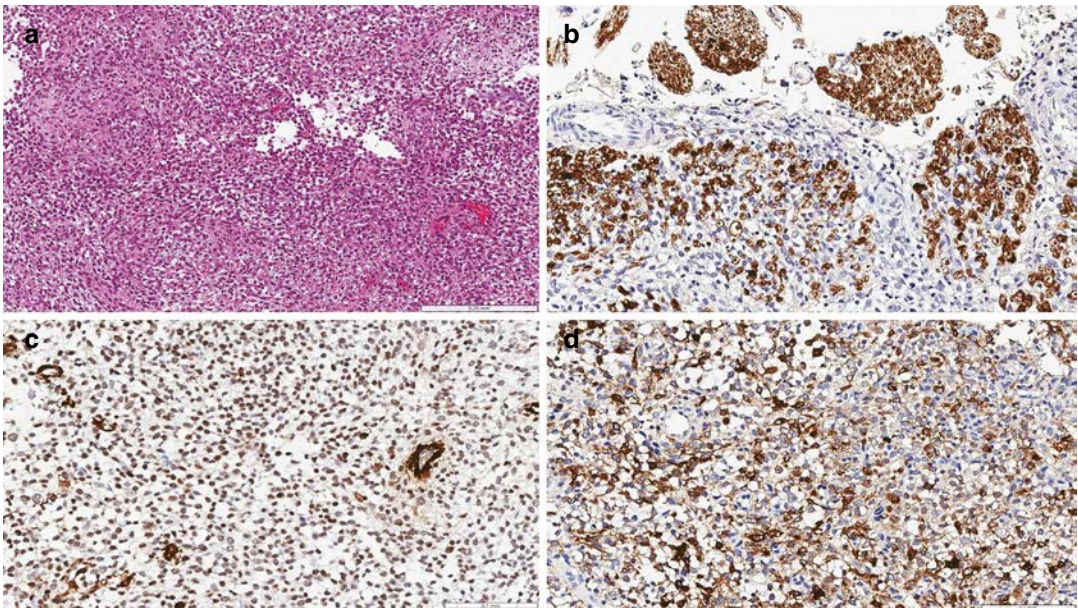


Fig. 30.22 MPNST (malignant peripheral nerve sheath tumor). (a) The tumor primarily consists of small cells that stain darkly and lack a recognizable pattern. (b) There are localized areas of reactive cell aggregates marked by

S100. (c) Blood vessel walls reactive to SMA-actin are surrounded by uniformly stained small tumor cells. (d) There are areas with densely stained aggregates of cells that react to EMA

30.4.6 Meningioma and Other Mesenchymal Tumors [16, 28, 29]

30.4.6.1 Meningioma (Table 30.20; Fig. 30.23; Tables 30.21 and 30.22; Figs. 30.24 and 30.25)

Table 30.20 Overview of histological subtypes of meningiomas belonging to various WHO grades [28]

Histological subtype	Immunohistochemical marker	Molecular marker
<i>WHO grade 1</i>		
Meningothelial	EMA, vimentin, SSTR2A	<i>TRAF7, AKT1, POLR2A, PIK3CA</i>
Fibrous	EMA, vimentin, SSTR2A	<i>NF2</i>
Transitional	EMA, vimentin, SSTR2A	<i>NF2, AKT1, PIK3CA</i>
Psammomatous	EMA, vimentin, SSTR2A	<i>NF2</i>
Secretory	EMA, vimentin, SSTR2A, CEA, cytokeratins	<i>KLF4/TRAF7</i>
Angiomatous	EMA, vimentin, SSTR2A, inhibin-negative	Trisomy 5
Microcystic	EMA, vimentin, SSTR2A	
Lymphoplasmacyte-rich	EMA, vimentin, SSTR2A	
Metaplastic	EMA, vimentin, SSTR2A	
<i>WHO grade 2</i>		
Atypical features (irrespective of histological subtype)	EMA, vimentin, SSTR2A	<i>NF2, TRAF7, TERT</i>
Clear cell	EMA, vimentin, SSTR2A	<i>SMARCE1</i>
Chordoid	EMA, vimentin, SSTR2A	
<i>WHO grade 3</i>		
Anaplastic features (irrespective of histological subtype)	EMA, vimentin, SSTR2A	<i>NF2, TERT</i>
Papillary	EMA, vimentin, SSTR2A	
Rhabdoid	EMA, vimentin, SSTR2A, BAP1	<i>BAP1</i>

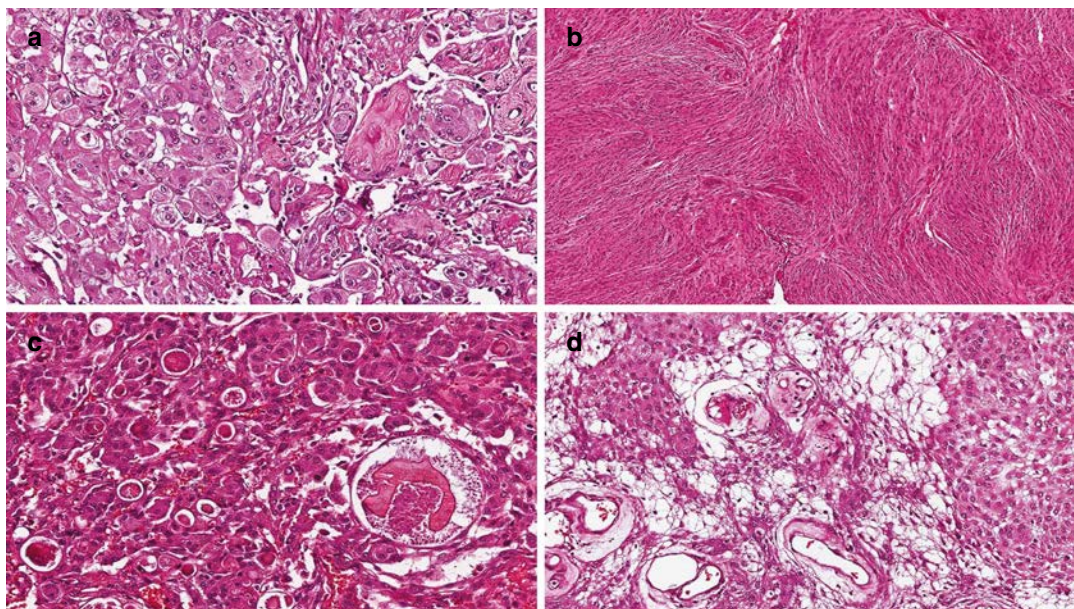


Fig. 30.23 Typical meningiomas. (a) Meningothelial meningioma featuring prominent whorls. (b) Fibroblastic meningioma resembling spindle-celled fibroblasts. (c)

Secretory meningioma with striking pseudopsammomatous bodies. (d) Microcystic meningioma is characterized by a cobweb pattern and a pseudomicrocystic component

Table 30.21 Review of genetic alterations noted among non-NF2 mutated meningiomas [28]

Gene mutation	Chromosome locus	Prevalence	Histology and grade	Location	Co-existent with	Exclusive of	Prognostic significance
<i>TRAF7</i>	16p13.3	15–25%	Meningothelial, low grade (<i>TRAF7/KLF4</i> -secretory)	Anterior skull base	<i>KLF4</i> , <i>AKT1</i> , <i>PIK3CA</i>	<i>NF2</i>	Dependent on co-existent mutations
<i>KLF4</i>	9q31	9–12%	Secretory, grade 1	–	<i>TRAF7</i>	<i>NF2</i>	–
<i>AKT1</i>	14q32.33	7–12%	Meningothelial, grade 1	Anterior skull base	<i>TRAF7</i>	<i>NF2</i> , <i>SMO</i>	Decreased time to recurrence
<i>SMO</i>	7q32.1	1–5%	Meningothelial, grade 1	Midline anterior skull base	–	<i>NF2</i> , <i>AKT1</i>	Recurrence in olfactory groove meningioma
<i>PI3KCA</i>	3q26.32	4–7%	Meningothelial and transitional, low grade (rarely grade 2 and 3)	Anterior and middle skull base	<i>TRAF7</i> , <i>KLF4</i> (rare)	<i>NF2</i> , <i>AKT1</i> , <i>SMO</i>	Poor prognosis in grade 2 and 3 tumors
<i>POLR2A</i> (DNA directed RNA polymerase II subunit A)	17p13.1	6%	Meningothelial, grade 1	Tuberculum sellae meningioma	–	All others	Good prognosis
Focal adhesion kinase (<i>FAK</i>)	8q24.3	Rare	High-grade	–	–	<i>NF2</i>	–
<i>BAP1</i>	3p21	Rare	High-grade, rhabdoid meningioma	–	–	–	Increased recurrence, systemic metastases, lower time to progression
<i>SMARCB1</i> and <i>SMARCE1</i>	22q11.23 and 17q21.2	Rare	Clear cell, anaplastic meningioma, grade 2/3	Spinal or cranial	<i>NF2</i>	–	Moderately aggressive, high risk of recurrence
<i>BRAF V600E</i>	7q34	Very rare	Rhabdoid, high-grade	–	–	–	Anecdotal response to dabrafenib
Checkpoint kinase 2 (<i>CHEK2</i>)	22q12.1	Rare	–	–	<i>NF2</i>	–	Aggressive behavior
<i>CDKN2A</i> and <i>CDKN2B</i>	9p21.3	74% of anaplastic meningiomas	Anaplastic, grade 3	–	–	–	Brain invasion, decreased survival
Duchenne Muscular Dystrophy (<i>DMD</i>)	Xp21.2-p21.1	32% of progressive meningioma	High-grade	–	<i>TERT</i>	–	Shorter overall survival independent of <i>TERT</i>
<i>TE</i>	5p15.33	20% of grade 3 meningioma	High-grade, secondary atypical meningioma	–	–	–	Shorter time to progression, in grade 1—high recurrence and malignant transformation

Table 30.22 Epigenetic subclassification of meningiomas based on DNA methylation profiling [28, 29]

Feature	Group A			Group B		
	MC-ben1	MC-ben2	MC-ben3	MC-intA	MC-intB	MC-mal
Histological subtypes	Fibroblastic Atypical Transitional	Meningothelial Secretory Transitional	Angiomatous Atypical Transitional	Fibroblastic Transitional Atypical	Atypical Anaplastic	Anaplastic
Cytogenetic profile	22q del (95%)	Absent copy number variations	Multiple chromosomal gains (Chr 5 in 47%)	Del 22q (84%) Del 1p (70%)	Del 1p (89%), 10 and 22 (89%)	Del 1p (89%), 10 and 22 (89%)
Genetic alterations	<i>NF2</i> (63%)	<i>TRAF7</i> (49%) <i>AKT1</i> (33%) <i>KLF4</i> (15%) <i>SMO</i> (7%) <i>NF2</i> (7%)	<i>NF2</i> (32%) <i>PIK3CA</i> (11%)	<i>NF2</i> (53%)	<i>NF2</i> , <i>TERT</i> , suppressor of fused (<i>SUFU</i>)	<i>NF2</i> , <i>TERT</i> , <i>SUFU</i> , <i>CDKN2A</i> (70%)
Prognosis	Good			Intermediate		Poor

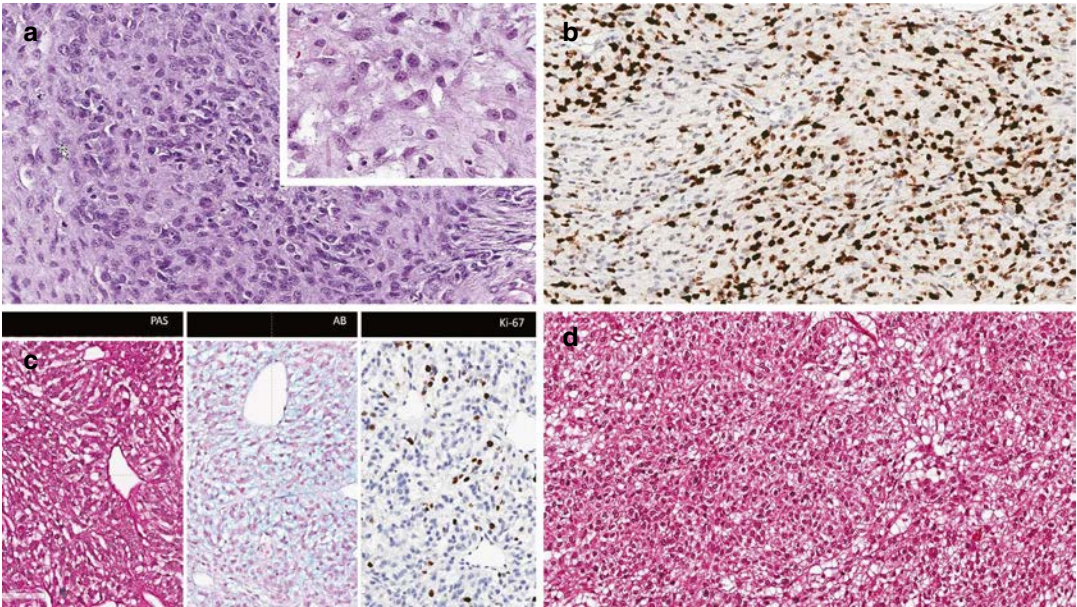


Fig. 30.24 Atypical meningioma. **(a)** Tumor cells are disorganized and display prominent nucleoli (see inset). **(b)** The Ki67 proliferation index is high, 60% (MIB-1). **(c)** Chordoid meningioma shows PAS-positive cytoplasmic granules (left), an alcianophilic matrix (middle), and an intermediate Ki67 proliferation index of 15% (right). **(d)** Clear cell meningioma exhibits distinct clear cytoplasmic features

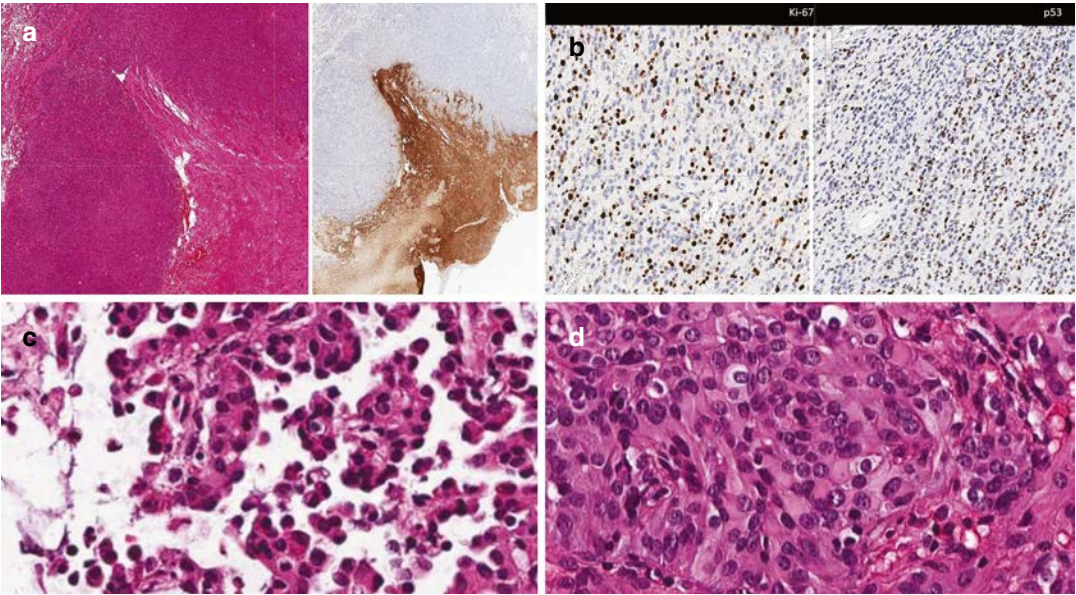


Fig. 30.25 Malignant meningioma. (a) A poorly differentiated neoplasm is invading the brain parenchyma (left), with masses of meningioma infiltrating the GFAP-positive neuropil. (b) The Ki67 proliferative index is 45% (left),

indicating a high p53 index (right). (c) Delicate papillary formations are observed in a papillary meningioma. (d) Nuclei are being displaced by eosinophilic globular paranuclear inclusions in the cytoplasm

30.4.7 Other Mesenchymal, Nonmeningotheial Tumors

30.4.7.1 Solitary Fibrous Tumor (Table 30.23; Fig. 30.26)

Table 30.23 Major histopathologic and immunohistochemical features and outcome of solitary fibrous tumor [16, 24, 25]

Type	Histologic features	Immunohistochemistry	WHO grade
Solitary fibrous tumor	Random spindle cells, staghorn vessels	CD34+, STAT6+ PR–, SSTR2a– NAB2-STAT6 fusion	<5 mitosis/10 HPF = 1 >5 mitosis s without necrosis/10 HPF = 2 >5 mitosis s with necrosis/10 HPF = 2

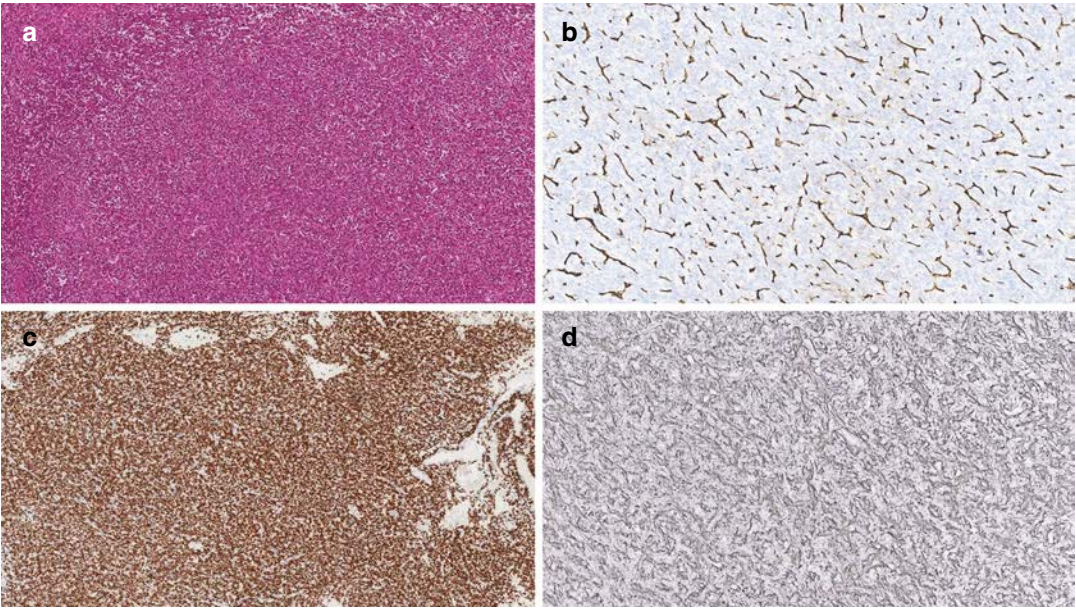


Fig. 30.26 Solitary fibrous tumor. **(a)** The tumor consists of short, spindle-shaped, or oval cells that have minimal cytoplasm, set against a patternless background. **(b)** A delicate network of blood vessels can be identified using

CD34 immunoreactivity. **(c)** There is diffuse and strong immunoreactivity with STAT6. **(d)** A dense reticular framework provides support to the background

30.4.7.2 Hemangioblastoma
(Table 30.24)

Table 30.24 Major histopathologic and immunohistochemical features and grading of hemangioblastoma [16, 19]

Type	Histologic features	Immunohistochemistry	WHO grade
Hemangioblastoma	Rich capillary network and intermixed vacuolated stromal cells, few mitosis, occasional necrosis	Inhibin+, EMA–, PAX8–PAX2–	1

30.4.7.3 Tumors of Uncertain Differentiation (Table 30.25)

Table 30.25 Major histopathologic, immunohistochemical, and molecular alterations of tumors of uncertain differentiation [16, 30]

Primary intracranial sarcoma, <i>DICER</i> mutated	Oval to spindle-shaped cells arranged in a patternless pattern, sheets, fascicular, or whorling. Some authors have described the presence of rhabdomyoblasts or rhabdomyoblast-like cells. Cytoplasmic eosinophilic globules are often identified. Mitoses and necrosis are frequent	Desmin, smooth muscle actin (SMA), and occasionally myogenin: positive GFAP, OLIG2, cytokeratins, EMA, S100, SOX10: negative Nuclear positivity for TLE1 is often noted Patchy to diffuse loss of H3K27me3	Metastatic pleuropulmonary blastoma Other rare sarcomas in CNS: rhabdomyosarcoma, fibrosarcoma, synovial sarcoma	<i>DICER1</i> mutations
Intracranial mesenchymal tumor, <i>FET-CERB</i> fusion-positive	Lobulated or sheet-like arrangement of cells, separated by thick fibrous septa. Some examples have an abundant matrix, ranging from thick collagenous to abundant myxoid stroma; tumor cells are round, oval, spindled to stellate shaped, with some exhibiting epithelioid/rhabdoid morphology. Mitotic activity is usually low and necrosis is an uncommon finding. Whorling may be seen in some cases. Other findings include dense lymphoplasmacytic cuffing at the periphery of the tumor, collection of dilated and thin-walled blood vessels	Desmin, CD99, and EMA: positive S100, CD68, and synaptophysin expression: variable GFAP, myogenin, and HMB-45: negative	Sarcomas or meningioma	<i>FET-CERB</i> fusion
CIC-rearranged sarcoma	Tumor cells are undifferentiated small, round cells present in sheets interrupted by foci of necrosis. May have a variably lobulated growth pattern, and desmoplastic stroma. Neoplastic cells have prominent nucleoli and eosinophilic cytoplasm	CD99: patchy and weak. WT1, ETV4: variable positive NKX2.2: negative	Ewing sarcoma	<i>CIC-NUTM1</i> fusion: majority <i>CIC-DUX4</i> fusion

30.4.7.4 Chordoma [16, 19, 24, 25]
(Table 30.26; Fig. 30.27)

Table 30.26 Major histopathologic and immunohistochemical features and grading of chordoma

Type	Histologic features	Immunohistochemistry	WHO grade
Chordoma	Cords/ribbons of epithelioid cells within a mucoid matrix Physaliphorous cells	PanCK+, EMA+, S100+, brachyury+ SMARB1: preserved	4

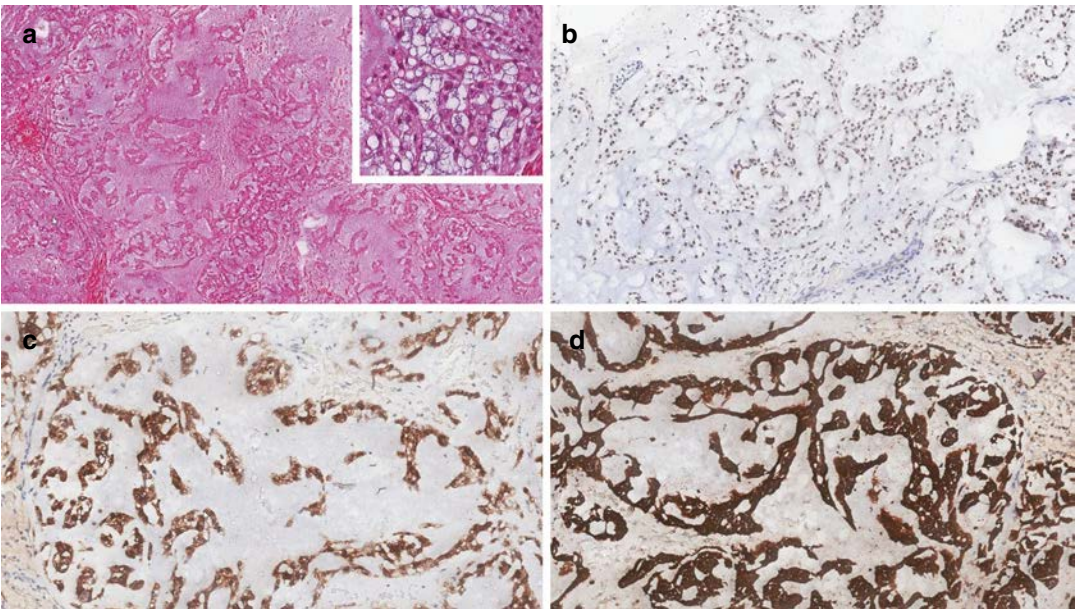


Fig. 30.27 Conventional chordoma. (a) Trabecular architecture is spread over a myxoid matrix, featuring characteristic physaliphorous (bubble-bearing) cells (inset). (b) A notable feature of chordoma is the nuclear

brachyury reactivity. (c) Positive EMA expression distinguishes conventional chordoma. (d) There is diffuse and strong immunoexpressivity of PanCK

30.4.7.5 Other Primary Soft Tissue Tumors of the CNS (Table 30.27)

Table 30.27 Major histopathologic and immunohistochemical features of primary soft tissue tumors of the CNS

Subgroup	Items
Benign	Lipoma, angioliipoma, hibernoma, benign fibrous histiocytoma, leiomyoma, EBV-associated smooth muscle tumor, chondroma, hemangioma, osteoma, osteochondroma
Malignant	Liposarcoma, fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, osteosarcoma, chondrosarcoma, angiosarcoma, undifferentiated pleomorphic sarcoma, Ewing sarcoma, and Kaposi's sarcoma

30.4.8 Melanocytic Tumors

Unusual lesions, mainly distributed in leptomeningeal areas (Table 30.28).

Table 30.28 Major histopathologic, immunohistochemical, and molecular alterations of melanocytic tumors [16, 19]

Histologic type	Histopathologic findings	Immunohistochemistry and molecules
Melanocytoma	Monomorphic spindled or epithelioid cells rich in melanin, vesicular chromatin, and prominent nucleoli	Mutations in GNAQ or GNA11
Diffuse melanocytosis	Diffuse leptomeningeal-based proliferation of nevoid cells	–
Primary meningeal melanoma/melanomatosis	Cytologic atypia, high mitotic counts (>3 mitoses per 10 high power fields), necrosis, hemorrhage	S-100+, HMB45+, melan-A+, SOX10+ NRAS mutations

30.4.9 Hematolymphoid Neoplasms

30.4.9.1 Lymphoma

Incidence in about 0.8–6.6% of primary intracranial neoplasms. CSF examination shows pleocy-

tosis observed in 35–60% of patients, cytology diagnostic in 5–30% of primary CNS lymphomas and 70–95% of metastatic lymphomas (Table 30.29).

Table 30.29 General histopathologic and immunohistochemical features of hematolymphoid neoplasms [16, 19, 24, 25]

Types	Histopathologic findings	Immunohistochemistry and molecules
General features	Marked by angiocentric, atypical lymphoid cell infiltrate	B cell receptor, toll-like receptor, NF- κ B pathway activation; <i>MYD88</i> , <i>CD79B</i> mutations
Diffuse large B cell	Admixed with variable numbers of smaller tumor infiltrating T lymphocytes	PAX5+, CD19+, CD20+, CD22+, CD79a+, BCL6+, (60–80%), IRF4 (MUM1)+ (90%), BCL2+ (82%)
Intravascular lymphoma	Cells are confined primarily to vascular lumens	D20+, CD79a+, PAX5+
Hodgkin's lymphoma	Reed-Sternberg cells	CD30 and CD15 positive
Anaplastic large cell lymphoma	Large cells, N/C reversed	ALK positive or negative
Multiple myeloma	Atypical plasma cells	Light chain markers
MALT lymphoma most common primary lymphoma of dura (low-grade Bcell lymphoma)	Small lymphocytes and marginal zone cells, often with plasmacytic differentiation, areas of reactive follicles with follicular colonization	CD20+, CD79a+, CD5–, CD10–, CD23–

30.4.9.2 Histiocytic Tumors
(Table 30.30; Fig. 30.28)

Table 30.30 General histopathologic and immunohistochemical features of histiocytic tumors [16, 19, 24, 25]

Histologic type	Histopathologic findings	Immunohistochemical findings
<i>Langerhans cell histiocytosis</i>	Mixed inflammatory infiltrates (lymphocytes, plasma cells, and eosinophils) marked by Langerhans cell histiocytes Eccentric nuclei, convoluted nucleus, inconspicuous nucleoli, abundant eosinophilic cytoplasm	CD1a+, S100+, langerin+ BRAF V600E, MAPK mutation
<i>Non-Langerhans cell histiocytoses</i>		
Rosai-Dorfman disease	Large histiocytes associated with emperipolesis (phagocytosis of lymphocytes and plasma cells by histiocytes)	CD68+, CD1a+, langerin–, S100+
Erdheim-Chester disease	Lipid-laden macrophages, fibrosis, multinucleated Touton giant cells	CD68+, CD1a+, langerin–, S100+
Hemophagocytic lymphohistiocytosis	Lymphocytes, macrophages with hemophagocytosis and variable necrosis; histiocytic cells	CD1a+, S-100+, CD11c+, CD68+
Juvenile xanthogranuloma	Lipid-laden macrophages, occasional Touton giant cells, mixed inflammation	
Histiocytic sarcoma	Large, pleomorphic histiocytic cells with abundant eosinophilic cytoplasm, mitotic activity	CD68+, CD163+, lysozyme+, CD11c+

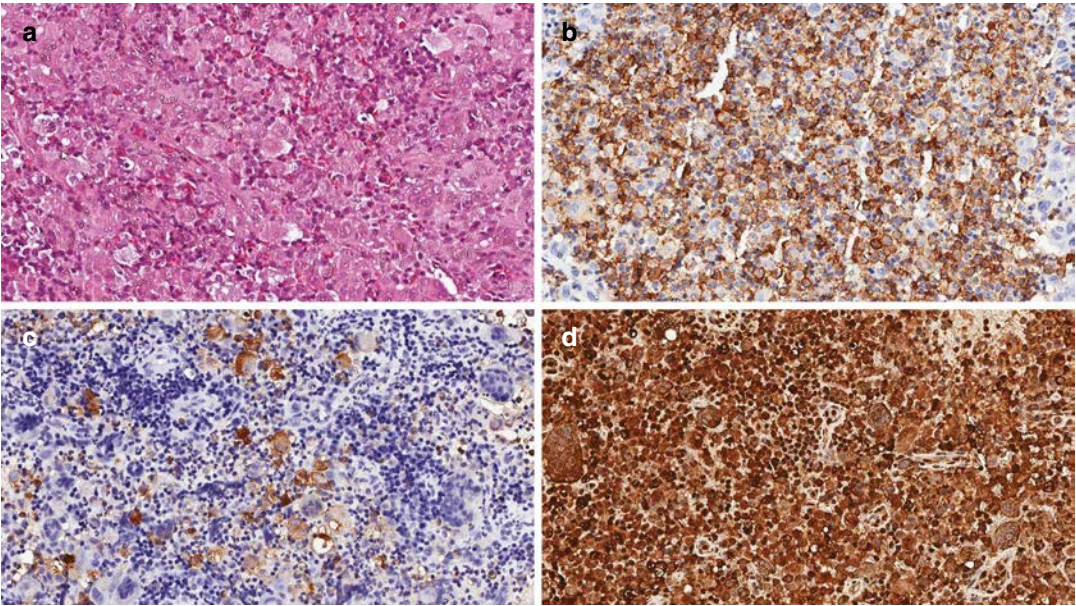


Fig. 30.28 Langerhans cell histiocytosis. (a) The tumor was characterized by nuclei, delicate nuclear membranes, and lightly eosinophilic cytoplasm. (b) Diffuse CD1a expression serves as a diagnostic feature. (c) Notable areas of tumor cells displayed S100 reactivity. (d) CD68 is a characteristic marker associated with the tumor

30.4.10 Germ Cell Tumors

Most commonly located in the midline, suprasellar region, and pineal (Table 30.31; Figs. 30.29 and 30.30).

Table 30.31 General histopathologic and immunohistochemical features of germ cell tumors [16, 19, 24, 25]

Histologic type	Immunohistochemical features
Germinoma	PLAP+, D2–40+, CD117+
Yolk sac tumor	Alpha-fetoprotein+, PanCK+
Embryonal carcinoma	CD30+, PLAP+, PanCK+
Choriocarcinoma	Beta-HCG+, HPL+, PanCK+
Malignant mixed germ cell tumor	Various combination of germ cell antibodies

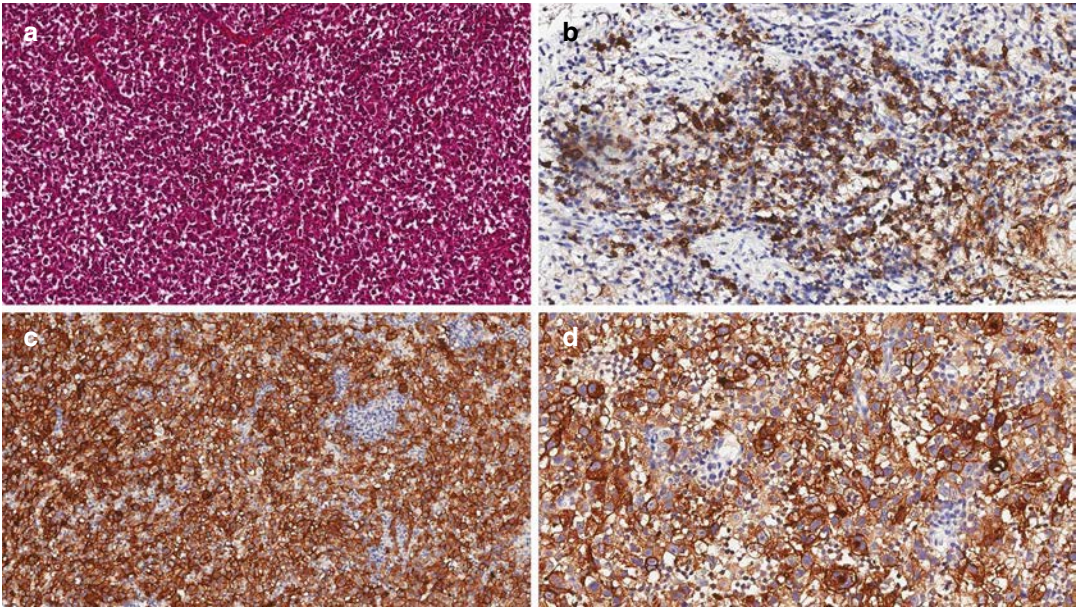


Fig. 30.29 Germinoma. (a) The predominant cell type is primordial germ cells. (b) There are clusters of EMA-positive tumor cells. (c) A diffuse membranous expression

of c-kit is a prominent finding. (d) Although inconsistent, some cases may show a strong reaction with PLAP

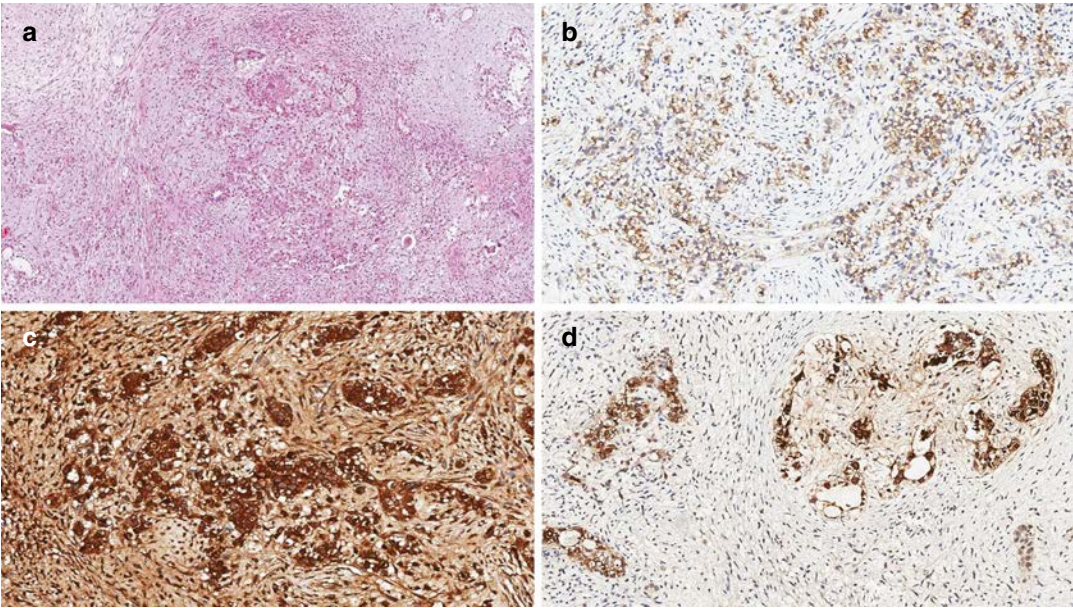


Fig. 30.30 Malignant mixed germ cell tumor. (a) Hypercellular matrix bears distinctive areas filled with irregular gland-like structures and nests lined by pleomorphic cells. (b) Irregular sheets and gland-like structures reacting with KIT (germinoma). (c) Spotted tumor cell aggregates are HCG positive (choriocarcinoma). (d) Disperse gland-like elements express AFP (yolk sac tumor)

Table 30.32 Craniopharyngioma with various histopathology findings and specific molecules [16]

	Histopathology	Molecules	WHO grade
Adamantinomatous	Peripheral palisading of epithelial cells admixed with a loose “stellate reticulum”	CTNNB1 mutation, aberrant beta-catenin expression	1
Papillary	Non-keratinizing squamous epithelium organized in papillary structures	BRAF V600E	1

30.4.11 Sellar Region Tumors

30.4.11.1 Craniopharyngioma, CNS
WHO Grade 1

Rare tumors of the sella. Bimodal age distribution (young adults and elderly) (Table 30.32).

30.4.11.2 Pituitary Adenoma/
Pituitary Neuroendocrine
Tumor (PitNET)

Most common tumors net to meningiomas and metastatic tumors (Table 30.33; Figs. 30.31 and 30.32).

Table 30.33 Common histopathologic features and transcription factors expressed in PitNETs [16, 19]

	Histopathology	Transcription factors
Pituitary adenoma/pituitary neuroendocrine tumor (PitNET)	Monotonous cells accompanied by delicate vascular network, cells with granular cytoplasm, lack mitosis, diffuse pattern	PIT-1: GH, PL and TSH T-PIT: ACTH SF1: FSH and LH
Aggressive types	Sparsely granulated somatotroph Crook cell tumors—intense Silent corticotrophs Plurihormonal PIT-1 positive tumors Lactotroph tumors in men	GH, CAM 5,2, fibrous body Perinuclear, ring-like CAM5.2 Nil PIT-positive LH
Pituitary carcinoma	Rare	May show any neuroendocrine expressivity

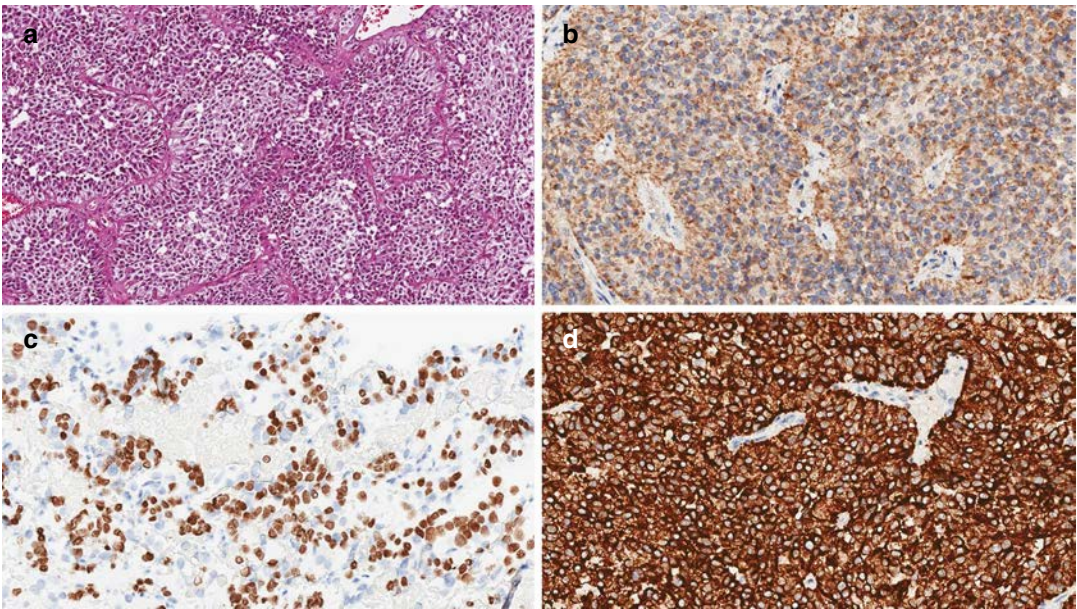


Fig. 30.31 Somatotroph adenoma, densely granulated. (a) Clusters of homogeneous cells with eosinophilic cytoplasm. (b) Immunohistochemically, the cells are positive for GH. (c) The transcription factor PIT-1 serves as a reliable diagnostic aid. (d) Diffuse positivity for CAM 5.2 indicates a densely granulated pituitary adenoma

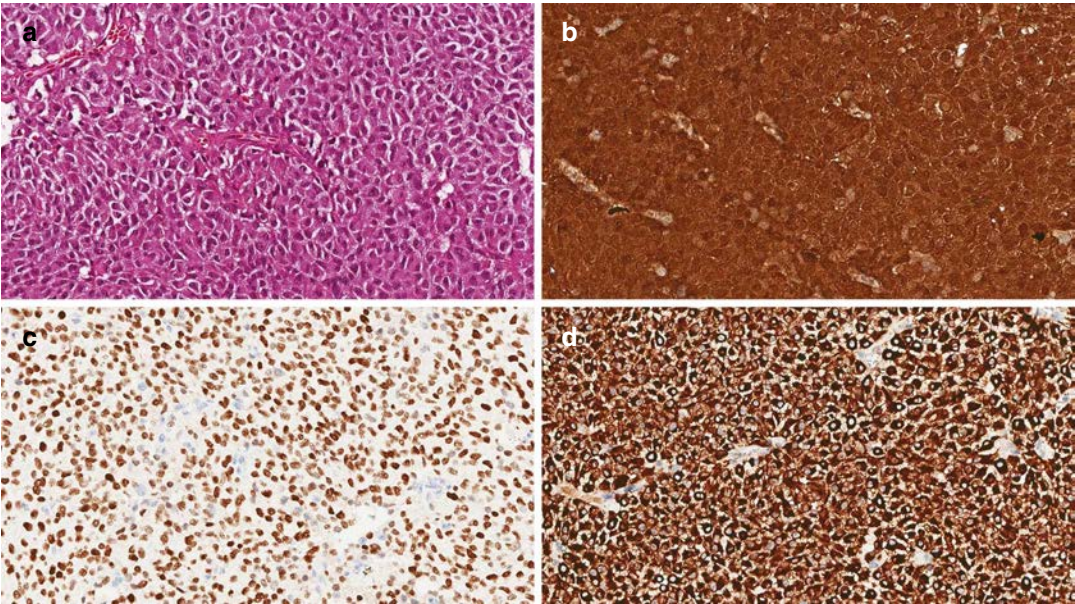


Fig. 30.32 Corticotroph adenoma, densely granulated. (a) There is a diffuse proliferation of monotonous cells with basophilic cytoplasm. (b) Immunohistochemical analysis shows that the cells are positive for ACTH. (c)

The transcription factor TPIT (TBX19) is a reliable diagnostic tool. (d) Diffuse positivity for CAM 5.2 indicates the presence of a densely granulated pituitary adenoma

30.4.11.3 Pituicyte Lineage Tumors

Posterior pituitary tumors TTF-1 positive (Table 30.34; Figs. 30.33 and 30.34).

Table 30.34 Common histopathologic features of PitNETs [16, 19]

Type	Histopathologic features
Pituicytoma	Cells in sheets and fascicles
Granular cell tumor of the sella region	Polygonal cells with granular eosinophilic cytoplasm
Spindle cell oncocytoma	Spindled to epithelioid cells with granular, eosinophilic cytoplasm

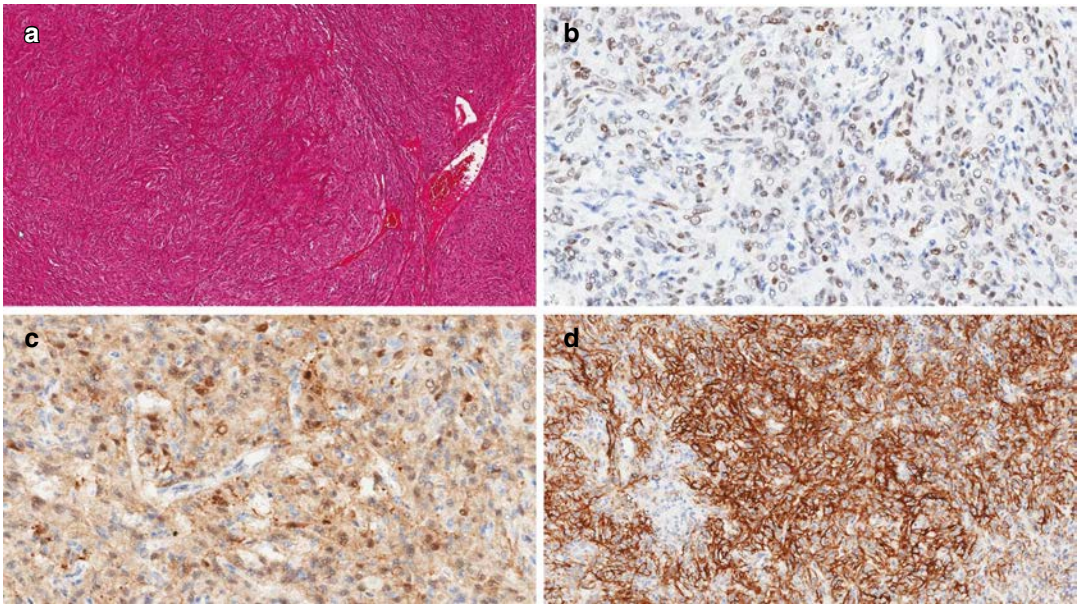


Fig. 30.33 Pituicytoma. (a) Spindle cells are forming fascicles that mimic fibroblastic meningioma. (b) There is diffuse and strong nuclear reactivity with TTF-1. (c)

Tumor cells exhibit paranuclear dot-like reactivity. (d) There is diffuse CD56 immunoreactivity

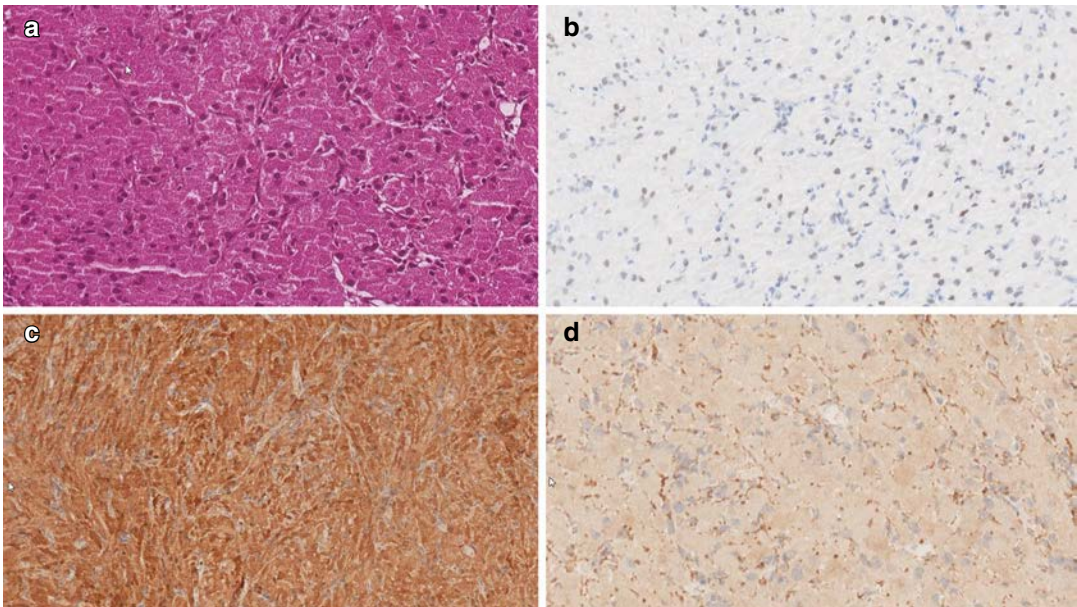


Fig. 30.34 Granular cell tumor of the sella. (a) The characteristic feature is large cells with abundant, fine granular cytoplasm. (b) There is diffuse and strong nuclear reactivity for TTF-1. (c) Tumor cells exhibit variable immunoreactivity for S100. (d) There is typical dot-like reactivity with CD68

ity for TTF-1. (c) Tumor cells exhibit variable immunoreactivity for S100. (d) There is typical dot-like reactivity with CD68

Table 30.35 Most common metastatic tumors to the CNS and immunohistochemical clues for diagnosis [16, 19, 24, 25]

Primary site	IHC
Carcinomas	CK7+, CK20+
Breast cancers	ER+, PR+, mammaglobin
Lung and thyroid carcinomas	Thyroid transcription factor—TTF-1+
Gastrointestinal/colorectal cancers	CDX2+
Renal, Müllerian, and thyroid carcinomas—	Paired box gene 8—PAX8+
Melanoma	S-100+, HMB45+, Melan-A+

30.4.12 Metastases to the CNS

Most common malignancy of CNS. Predominant types are lung, melanoma, breast, renal cell, and gastrointestinal tumors (Table 30.35).

30.5 Conclusions

Nearly 50 years have passed since the World Health Organization (WHO) first proposed its classification system for brain tumors in 1979. The core framework of these classifications has remained largely consistent, focusing primarily on the morphological characteristics of brain tumors. However, the 2021 fifth edition has introduced significant advancements by better integrating molecular data into the classification process. This update includes the addition of new entries, the introduction of subtypes and subtyping, as well as addressing the complexities surrounding the grading of major tumor groups, thereby broadening the spectrum of neoplastic lesions.

While the histopathological basis of previously described tumor characteristics has largely remained unchanged, the molecular genetic approach has introduced various classification methods. Some tumors can still be evaluated primarily based on histology, while others are assessed entirely on molecular features. This technological progress has greatly enhanced our understanding of central nervous system (CNS)

tumor biology, leading to the identification of new entities and more precise categorization of existing ones. As a result, this updated classification is expected to improve diagnostic accuracy, while also paving the way for more accurate prognostic insights and targeted treatment options.

On the other hand, despite these improvements, there are challenges ahead. Investing in accelerated molecular testing and navigating the complexities involved in enrolling patients for specific clinical trials remain hurdles. Nonetheless, it is clear that scientific advancements are opening new avenues in tumor biology that cannot be overlooked.

References

1. Pobereskin LH, Chaddock JB. Incidence of brain tumours in two English counties: a population based study. *J Neurol Neurosurg Psychiatry*. 2000;69(4):464–71.
2. CBTRUS. CBTRUS statistical report: primary brain tumors in the United States, 2004–2008. Hinsdale: Central Brain Tumor Registry of the United States; 2012.
3. Zülch KJ. Histological typing of tumors of the central nervous system, vol. 21. Geneva: World Health Organization; 1979.
4. Kleihues P, Burger PC, Scheithauer BW. Histological typing of tumors of the central nervous system. Berlin: Springer Verlag; 1993.
5. Kleihues P, Cavenee WK. World Health Organization classification of tumors of the nervous system. Lyon: WHO/IARC; 2000.
6. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, editors. World Health Organization histological classification of tumors of the central nervous system. 4th ed. Lyon: International Agency for Research on Cancer; 2007.
7. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK. World Health Organization classification of tumors of the central nervous system. Revised 4th ed. Lyon: International Agency for Research on Cancer; 2016.
8. Louis D, Wesseling P, Brandner S, Brat D, Ellison D, Giangaspero F, Hattab E, Hawkins C, Judge M, Kleinschmidt-Demasters B, Komori T, Mclean C, Paulus W, Perry A, Reifenberger G, Weller M, Rous B. Data sets for the reporting of tumors of the central nervous system: recommendations from The International Collaboration on Cancer Reporting. *Arch Pathol Lab Med*. 2020;144(2):196–206.

9. Louis DN, Wesseling P, Aldape K, Brat DJ, Capper D, Cree IA, Eberhart C, Figarella-Branger D, Fouladi M, Fuller GN, Giannini C, Haberler C, Hawkins C, Komori T, Kros JM, Ng HK, Orr BA, Park SH, Paulus W, Perry A, Pietsch T, Reifenberger G, Rosenblum M, Rous B, Sahm F, Sarkar C, Solomon DA, Tabori U, van den Bent MJ, von Deimling A, Weller M, White VA, Ellison DW. cIMPACT-NOW update 6: new entity and diagnostic principle recommendations of the cIMPACT-Utrecht meeting on future CNS tumor classification and grading. *Brain Pathol.* 2020;30(4):844–56. <https://doi.org/10.1111/bpa.12832>. Epub 2020 Apr 19. PMID: 32307792; PMCID: PMC8018152.
10. Louis DN, Wesseling P, Paulus W, Giannini C, Batchelor TT, Cairncross JG, Capper D, Figarella-Branger D, Lopes MB, Wick W, van den Bent M. cIMPACT-NOW update 1: not otherwise specified (NOS) and not elsewhere classified (NEC). *Acta Neuropathol.* 2018;135(3):481–4. <https://doi.org/10.1007/s00401-018-1808-0>. Epub 2018 Jan 25. PMID: 29372318.
11. Louis DN, Giannini C, Capper D, Paulus W, Figarella-Branger D, Lopes MB, Batchelor TT, Cairncross JG, van den Bent M, Wick W, Wesseling P. cIMPACT-NOW update 2: diagnostic clarifications for diffuse midline glioma, H3 K27M-mutant and diffuse astrocytoma/anaplastic astrocytoma IDH-mutant. *Acta Neuropathol.* 2018;135(4):639–42. <https://doi.org/10.1007/s00401-018-1826-y>. Epub 2018 Mar 1. PMID: 29497819.
12. Brat DJ, Aldape K, Colman H, Holland EC, Louis DN, Jenkins RB, Kleinschmidt-DeMasters BK, Perry A, Reifenberger G, Stupp R, von Deimling A, Weller M. cIMPACT-NOW update 3: recommended diagnostic criteria for “Diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV”. *Acta Neuropathol.* 2018;136(5):805–10. <https://doi.org/10.1007/s00401-018-1913-0>. Epub 2018 Sept 26. PMID: 30259105; PMCID: PMC6204285.
13. Ellison DW, Hawkins C, Jones DTW, Onar-Thomas A, Pfister SM, Reifenberger G, Louis DN. cIMPACT-NOW update 4: diffuse gliomas characterized by MYB, MYBL1, or FGFR1 alterations or BRAF^{V600E} mutation. *Acta Neuropathol.* 2019;137(4):683–7. <https://doi.org/10.1007/s00401-019-01987-0>. Epub 2019 Mar 8. PMID: 30848347.
14. Brat DJ, Aldape K, Colman H, Figarella-Branger D, Fuller GN, Giannini C, Holland EC, Jenkins RB, Kleinschmidt-DeMasters B, Komori T, Kros JM, Louis DN, McLean C, Perry A, Reifenberger G, Sarkar C, Stupp R, van den Bent MJ, von Deimling A, Weller M. cIMPACT-NOW update 5: recommended grading criteria and terminologies for IDH-mutant astrocytomas. *Acta Neuropathol.* 2020;139(3):603–8. <https://doi.org/10.1007/s00401-020-02127-9>. Epub 2020 Jan 29. PMID: 31996992; PMCID: PMC8443062.
15. Ellison DW, Aldape KD, Capper D, Fouladi M, Gilbert MR, Gilbertson RJ, Hawkins C, Merchant TE, Pajtler K, Venneti S, Louis DN. cIMPACT-NOW update 7: advancing the molecular classification of ependymal tumors. *Brain Pathol.* 2020;30(5):863–6. <https://doi.org/10.1111/bpa.12866>. Epub 2020 Jun 23. PMID: 32502305; PMCID: PMC8018155.
16. WHO Classification of Tumors Editorial Board. World Health Organization classification of tumors of the central nervous system. 5th ed. Lyon: International Agency for Research on Cancer; 2021.
17. Lacruz CR, editor. Central nervous system tumors, diagnostic pathology. Springer; 2023.
18. Santosh V, Rao S. A review of adult-type diffuse gliomas in the WHO CNS5 classification with special reference to astrocytoma, IDH-mutant and oligodendroglioma, IDH-mutant and 1p/19q codeleted. *Indian J Pathol Microbiol.* 2022;65(Supplement):S14–23. https://doi.org/10.4103/ijpm.ijpm_34_22. PMID: 35562130.
19. Prayson RA, Ahrendsen JT. Neuropathology. 3rd ed. Springer; 2024.
20. Purkait S, Mahajan S, Sharma MC, Sarkar C, Suri V. Pediatric-type diffuse low grade gliomas: histomolecular profile and practical approach to their integrated diagnosis according to the WHO CNS5 classification. *Indian J Pathol Microbiol.* 2022;65(Supplement):S42–9. https://doi.org/10.4103/ijpm.ijpm_1043_21. PMID: 35562133.
21. Rao S, Sahay A, Epari S. Paediatric type diffuse high grade gliomas in the WHO CNS5 classification: what the pathologist needs to know? *Indian J Pathol Microbiol.* 2022;65(Supplement):S50–8. https://doi.org/10.4103/ijpm.ijpm_1202_21. PMID: 35562134.
22. Köy Y, Tihan T. Circumscribed astrocytic gliomas: contribution of molecular analyses to histopathology diagnosis in the WHO CNS5 classification. *Indian J Pathol Microbiol.* 2022;65(Supplement):S33–41. https://doi.org/10.4103/ijpm.ijpm_1019_21. PMID: 35562132.
23. Gupta RK, Sharma A, Sharma MC. Overview of recent advances in the classification of ependymomas in WHO CNS5 classification: simplified approach to their integrated diagnosis. *Indian J Pathol Microbiol.* 2022;65(Supplement):S68–72. https://doi.org/10.4103/ijpm.ijpm_1212_21. PMID: 35562136.
24. Hilton DA, Shivane AG. Neuropathology simplified: a guide for clinicians and neuroscientists. 2nd ed. Springer; 2021.
25. Sarkar C, Santosh V, Chacko G. Essentials of diagnostic surgical Neuropathology. 2nd ed. Thieme Medical Publisher; 2023.
26. Gianno F, Miele E, Antonelli M, Giangaspero F. Embryonal tumors in the WHO CNS5 classification: a review. *Indian J Pathol Microbiol.* 2022;65(Supplement):S73–82. https://doi.org/10.4103/ijpm.ijpm_1049_21. PMID: 35562137.
27. Kleinschmidt-DeMasters BK, Pekmezci M, Rodríguez F, Tihan T. Diagnostic pathology: neuropathology. 3rd ed. Elsevier; 2022.

28. Goyal-Honavar A, Jayachandran R, Chacko G. Meningiomas—transition from traditional histological grading to molecular profiling in WHO CNS5: a review. *Indian J Pathol Microbiol.* 2022;65(Supplement):S83–93. https://doi.org/10.4103/ijpm.ijpm_1085_21. PMID: 35562138.
29. Prayson RA. Meningiomas: from diagnosis to treatment. 1st ed. Nova Science Pub Inc; 2022. ISBN-10: 1685077153, ISBN-13: 978-1685077150.
30. Chatterjee D, Gupta K. Miscellaneous newly recognized types of CNS tumors in the WHO CNS5 classification (other than gliomas, glioneuronal and embryonal tumors). *Indian J Pathol Microbiol.* 2022;65(Supplement):S94–8. https://doi.org/10.4103/ijpm.ijpm_1038_21. PMID: 35562139.

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