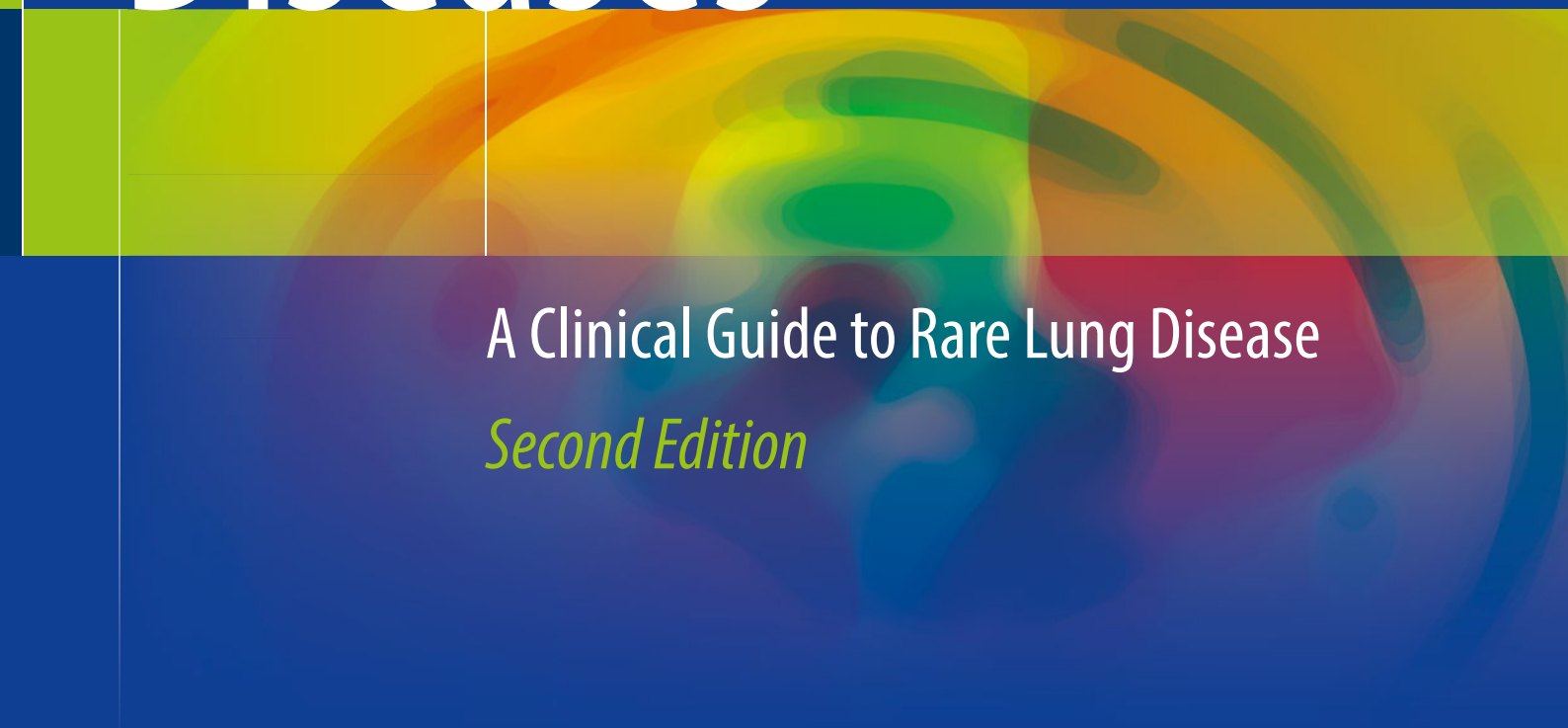
Vincent Cottin ·
Luca Richeldi · Kevin Brown ·
Francis X. McCormack *Editors*

Orphan Lung Diseases



A Clinical Guide to Rare Lung Disease

Second Edition

Springer

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This book is dedicated to Claudia, and to patients who suffer from rare pulmonary diseases and serve as a constant reminder of the importance of our commitment.

Vincent Cottin

Preface to the First Edition

So-called orphan diseases are those conditions that attract little interest by physicians and scientists, which are not widely researched, and where specific treatments are lacking. Orphan diseases are nevertheless characterized by particularly high needs and expectations from patients, who feel abandoned in the world of health care and expect their treating physician to make every possible effort to help them by managing at best their disease. However, as one cannot expect physicians to be knowledgeable with each of the 6000–8000 orphan diseases, they generally lack experience of most orphan diseases and are left with insufficient knowledge to manage these patients. Indeed, most orphan diseases are rare, at least in Europe and North America. Not all orphan diseases are rare, however, and especially neglected tropical infectious diseases are endemic in Africa, Asia, and the Americas, affecting one billion people worldwide and causing tremendous morbidity and mortality.

Rare diseases are defined numerically. In Europe, a disease is rare if it affects fewer than 1 person in 2000. In the USA, a rare disease is a disease that affects fewer than 200,000 people or that affects more than 200,000 but for which there is no reasonable expectation to be economically profitable, with the cost of drug development and availability for such a disease to be recovered from sales. Overall, given the plethora of different conditions, rare diseases are a major health-care burden worldwide. Regarding lung medicine alone, it is estimated that 1.5–3 million Europeans and 1.2–2.5 million Americans are affected by a rare lung disease.

Despite the many difficulties and obstacles, the new millennium witnessed an astonishing gain in the momentum to improve our understanding and the management of many rare diseases, some of which are, therefore, no longer orphan. Interest in rare diseases has increased greatly worldwide. Patients with orphan diseases have joined associations providing them with a previously unknown sense of community, unprecedented awareness, and strong advocacy for more research and better treatments. A steadily increasing number of international organizations and websites contribute to education, support, and research. Governments and agencies have introduced incentives to encourage the pharmaceutical industry to invest in research despite the small target populations. Specialized centers and clinical networks are now developing and have been identified in many countries: This crucial step provides up-to-date management to patients, allows basic and clinical research, establishes registries, interacts with regulatory agencies, and supports patient associations. Novel conditions and syndromes are discovered. The genetic determinants of many diseases and their underlying pathophysiology are progressively better understood. An increasing number of drug candidates are identified and may be granted an orphan drug designation with more clinical trials completed, thereby leading to the approval and licensing of drugs in diseases heretofore considered not treatable. Diseases such as pulmonary arterial hypertension and idiopathic pulmonary fibrosis, formerly devoid of any treatment, are now treatable although they are still deadly severe and not curable.

In this context, diagnosing and managing patients with orphan pulmonary diseases is an increasing challenge to pulmonologists and internal medicine specialists as it is increasingly difficult to keep up to the current pace of growth of knowledge, especially in basic science. To witness the evolution of this field is tremendously stimulating since progress made in pathophysiology, organization of care, and management rapidly translates into clinical practice for

the benefit and better-being of patients. As progress continues, it is sure that additional diagnostic instruments and treatment options will soon be available. We, as doctors, should not let our patients miss any opportunity to get the correct diagnosis (avoiding unnecessary procedures) and the best management. Our goal in this book is to provide synthesized and easily accessible information about the main orphan lung diseases. Although some literature is available through original articles and review articles, it is often difficult to find in a timely manner the answers to questions that clinicians caring for patients are facing. They will find here information oriented toward clinical practice, especially the diagnostic approach (including manifestations suggesting the disease, methods for diagnostic confirmation, diagnostic criteria, and differential diagnosis). The reader will understand that although comprehensive and covering most rare and orphan pulmonary diseases, this textbook is not fully exhaustive in an attempt to keep its size reasonable. Topics are divided into five parts, respectively, on diseases affecting the airways, systemic disorders with lung involvement, orphan conditions limited to the lung, interstitial lung diseases, and miscellaneous conditions with lung involvement (for which information is not readily available elsewhere). We are very grateful to the authors, all leading experts experienced in the field, who contributed time and effort to this endeavor and committed to provide clinically oriented manuscripts with a comprehensive overview, rich illustrations, real case examples, and guidance for the diagnostic process. They shared their expert opinion when evidence base was lacking, as it is often the case in this setting. We hope people will like this book and find it useful and look forward to hearing comments, suggestions, and feedback so that the next edition can be even better.

Successful examples have demonstrated that despite constraint resources, the concerted effort of dedicated patient organizations, clinicians, academic researchers, pharmaceutical companies, and health authorities can translate into major progress. We strongly hope that this book will contribute to the better sharing of knowledge on orphan lung diseases for the immediate benefit of our patients.

Lyon, France — Vincent Cottin
Roma, Italy — Luca Richeldi
Lyon, France — Jean-François Cordier

Preface to the Second Edition

The first edition of *Orphan Lung Diseases: A Clinical Guide to Rare Lung Disease* was published in 2015. The book was very well received, as rare lung diseases are increasingly attracting attention, especially in the context of very active research on new treatments, with the milestone represented by the approval in 2014 of antifibrotic drugs to treat idiopathic pulmonary fibrosis. The book covers the field of rare pulmonary diseases as a whole, and not just interstitial lung diseases, which of course represent the largest share. Due to the progress in the field, the variably limited number of patients with each condition, and the number of conditions involved, it is very difficult for clinicians to remain current in this field. However, patients with rare pulmonary diseases collectively represent a significant fraction of the patients followed by practicing pulmonologists, as well as rheumatologists, internists, and other specialists. With the possible exception of idiopathic pulmonary fibrosis and progressive pulmonary fibrosis, rare pulmonary diseases typically receive less attention by clinicians, researchers, and industry than those more frequently seen in daily clinics. This textbook is oriented toward clinical practice and is accessible online, to provide busy practitioners with ready access to information needed in a timely manner.

The main change for the second edition is that the number of chapters has been increased from 36 in the previous edition to the current 43, now divided into seven parts. This enabled us to create new chapters on topics that have become increasingly relevant, such as pleuropulmonary fibroelastosis, unclassifiable interstitial lung disease, complex thoracic lymphatic disorders of adults, and interstitial pneumonia with autoimmune features and overlap interstitial pneumonia. The parts on interstitial lung diseases and on systemic disorders with lung involvement have been expanded to better cover these important fields, and new chapters were created on diagnostic modalities, including separate chapters on imaging, bronchoscopic and integrated diagnostic approaches to interstitial lung diseases. A new part on rare lung diseases of genetic origin has been included: genetic and familial pulmonary fibrosis related to monogenic diseases, diffuse bronchiectasis of genetic or idiopathic origin, pulmonary vascular manifestations of hereditary hemorrhagic telangiectasia, pulmonary alveolar microlithiasis, and rare diffuse lung diseases of genetic origin. Although no book could hope to cover the immense and ever-growing area of rare pulmonary diseases, we welcome suggestions for the next edition.

The editorial board was joined by two new editors, Dr Kevin K. Brown and Dr Francis McCormack, who brought new ideas and expertise. As Prof. J.F. Cordier has now retired, this new edition was supervised by four editors. We also welcome new authors coming from a variety of countries and regions. As in the previous edition, our goal in this book was to synthesize and organize emerging clinical and research advances in an easily accessible format that is oriented toward the practicing clinician. We thank all authors who have dedicated time to this textbook, and have provided clinically oriented manuscripts, comprising numerous illustrations, representative case examples, and guidance for both the diagnostic process and the practical management, often without the luxury of official diagnostic criteria or guidelines.

In rare diseases, expert opinion is key when evidence is lacking, and we are very grateful to the authors to have shared their experience to guide the clinicians in their practice. Our sincere wish is that this book may benefit the care of our patients.

Lyon, France — Vincent Cottin
Roma, Italy — Luca Richeldi
Denver, CO, USA — Kevin Brown
Cincinnati, OH, USA — Francis X. McCormack

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Part I

Introduction

Orphan Lung Diseases: From Definition to Organization of Care

1

Vincent Cottin

Definitions

The term "orphan" has been coined to describe rare diseases because of the affected sense by patients that many physicians are uncomfortable with the management of their disease, and, as such, hope for the future is dim because so little research has been devoted to understanding such rare disorders in patients and improving their quality of life [1]. Their feeling of abandonment is intensified by comparisons with patients who suffer from common diseases and who benefit from extensive research and continuous drug development. The struggle for equal access to care and research by patients and the organizations that represent them is common to all orphan lung diseases. The associated ethical and social issues are complex and drive many of the particularities of how the care for these conditions is organized. In fact, in some countries, patients have a legal right to equal access to health care, regardless of the epidemiology of their condition [2].

The definition of a rare disease in Europe is a condition with a prevalence of less than 1 in 2000 people (equivalent to a prevalence of less than 50 in 100,000 people) and affecting fewer than 200,000 people in the USA (which equates to about 1 in 1700 people). Although arbitrary, these definitions are not trivial, as they have practical implications for all stakeholders including patients, regulatory bodies, drug developers, and payers (Fig. 1.1). In contrast, currently, there is no established definition for the so-called "ultra-rare" diseases, which affect even smaller populations, with a prevalence as low as 1 in 2,000,000 or even less [1]. The distinction between "somewhat rare" and "ultra-rare" lung diseases is useful to consider. Somewhat rare diseases include conditions that may or may not fit the definition of a rare disease, depending on the epidemiological method used or geographic or ethnic disparities (e.g., sarcoidosis) [3, 4]. This category of ultra-rare lung diseases was introduced by the National Institute for Health and Care Excellence for drugs with indications for diseases that have a prevalence of <1 per 50,000 persons [2]. Studies in ultra-rare lung diseases must be conducted at a national or regional level to assemble even a handful of patients, which poses major challenges to conducting clinical trials of robust methodology [5, 6]. Examples of rare lung diseases in this category would include pulmonary alveolar microlithiasis [7], pulmonary alveolar proteinosis of genetic origin [8], light chain deposition disease [9], ataxia telangiectasia [10], Birt–Hogg–Dubé syndrome [11], and others.

It is worthwhile mentioning that not all orphan diseases are rare. Some conditions may be common but neglected because they affect people in poor countries (e.g., chronic infectious tropical diseases) [12]. Conversely, not all rare diseases are orphan, as progress in organization of care and research can eventually lead to progress in the management of rare diseases, sometimes with highly active research in networks of specialized centers and efficient drug development. Examples of rare lung diseases, which to some may not be considered orphan anymore, include idiopathic pulmonary fibrosis, pulmonary arterial hypertension, and lymphangioleiomyomatosis (LAM).

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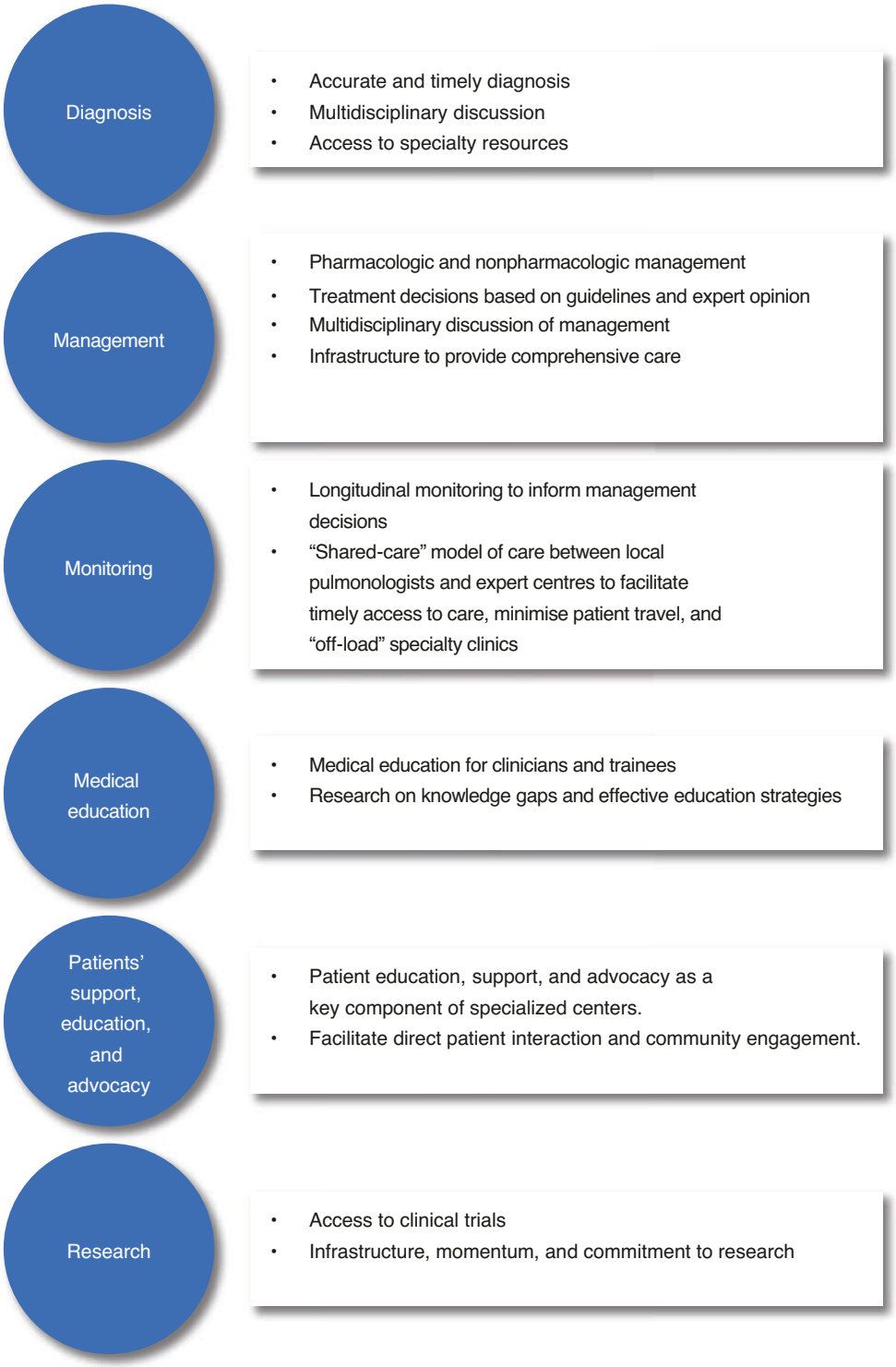

Fig. 1.1 The main stakeholders in the care of patients with orphan lung diseases

The Wide Spectrum of Rare Pulmonary Diseases

The number of "all" rare diseases and syndromes has not been hitherto established, although rough estimates range between 6000 and 8000, with a large proportion being of genetic origin. Despite being rare, "collectively" rare diseases may affect up to 5% of the population, translating into ~30 million in Europe and the USA [1]. Although most rare "lung" diseases are idiopathic and chronic rather than of

genetic origin, DNA mutations are being identified in an increasing proportion of familial interstitial lung diseases (ILDs) [13, 14].

Rare pulmonary diseases may be limited to the lungs or may result from pulmonary involvement of systemic diseases. Rare diseases limited to the lungs may be acquired (e.g., hypersensitivity pneumonitis) or of genetic origin (e.g., diffuse interstitial lung disease in children and young adults associated with mutations in surfactant- or telomere-related genes).

Pulmonary involvement may occur in acquired rare systemic disorders (e.g., pulmonary manifestations of granulomatosis with polyangiitis) or in disorders of genetic origin (e.g., pulmonary lymphangioleiomyomatosis in tuberous sclerosis complex). In such conditions, solitary or dominant pulmonary involvement may be the presenting manifestation with only minor or silent systemic features (e.g., glomerulonephritis in microscopic polyangiitis with diffuse alveolar hemorrhage). Overlapping and distinct phenotypes of rare diseases are common: sporadic pulmonary lymphangioleiomyomatosis may be solitary or associated with kidney angiomyolipoma(s) or part of the systemic manifestations of tuberous sclerosis complex.

The spectrum of the rare pulmonary diseases presented in this book includes a variety of disorders, which themselves may present diagnostic challenges when similar clinical and/or imaging features are present. This is especially the case for rare pulmonary tumors (e.g., primary pulmonary lymphomas) or rare infections (e.g., atypical mycobacterial infections), which can mimic a variety of conditions. The differential diagnosis of any rare pulmonary disease should thus always take into consideration the possibility of neoplastic or infectious disorders. Conversely, some rare conditions have a particularly protean presentation (e.g., sarcoidosis, lymphoproliferative lung disorders) [15] or have unusual presentations (e.g., lymphangioleiomyomatosis [16]), leading to diagnostic challenges.

Diagnostic Challenges

Diagnostic delays are a major complaint of patients with rare disorders, with a definite diagnosis obtained only after several years in a large proportion of cases [17]. This issue is reflected in the vast majority of surveys of patients and patient associations [18–21].

It is evident that a general practitioner cannot be aware of the thousands of rare diseases with their phenotypes and diverse presentations. However, medical education should emphasize the need for systematic consideration of a possible rare disease for any patient with atypical features of a suspected common disease (Box 1.1). Resources are now available online, allowing nonspecialist physicians to quickly get synthetic information about most rare lung diseases (e.g., https://www.orpha.net/, https://www.ncbi.nlm.nih.gov/guide/genetics-medicine/).

Such patients should be referred to a respiratory specialist for either confirming an atypical presentation of a common disease or seeking assistance in the diagnosis of a rare pulmonary disease. Because of the complexity involved, we recommend that any patient suspected of having a rare disease should be offered the benefit of a second opinion at an expert center, for confirmation (or making) of a precise and definitive diagnosis and for outlining a program of specialized care. In the field of interstitial lung diseases, for example, referral to an expert center frequently corrects the diagnosis or suggests a diagnosis or investigation when no diagnosis has yet been contemplated [22], and early referral to an expert center is associated with an improved outcome [23]. Such patients must be advised to contact patient organizations and especially meet expert patients [24]. They should further be informed about possible participation in studies and clinical trials.

Box 1.1 Methodical Doubt for a Rare Disease

The main practical difficulty in the diagnosis of rare pulmonary diseases is that most of them present with common and not specific features. Thus, an astute clinician has to raise the suspicion of a rare disease when faced with any atypical clinical features or unusual findings. The "methodical doubt" for the eventuality of a rare disease is a prerequisite for an accurate diagnosis of atypical common disorders, which eventually prove to be distinct rare diseases.

Some examples are as follows:

- Idiopathic bilateral lower lobe bronchiectasis in a 34-year-old man with further chronic rhinitis and sinusitis (could it primary be ciliary dyskinesia?)
- Rapidly progressive dyspnea with diffuse infiltrative lung disease on chest X-ray with severe worsening anemia (could it be alveolar hemorrhage?)
- Pneumothorax in a patient with polydipsia (could it be Langerhans cell histiocytosis?)
- Increasingly severe asthma with heart failure in a 25-year-old man (could it be eosinophilic granulomatosis with polyangiitis?)
- Relapsing episodes of hemoptysis, bruises of the lower limbs, and history of shoulder luxation in a 35-year-old man (could it be Ehlers–Danlos disease?)
- Bilateral, thin-walled, central, cystic bronchiectasis and a right apical bulla in a nonsmoking 56-year-old man with repeated infections, cough, and wheezing (could it be Williams–Campbell syndrome?)

Expert Centers

In rare disease care, the experience of any single physician is limited, and a well-organized, multidisciplinary approach at an expert center leads to better outcomes than more traditional models [25–27]. The goals of a specialized center are multifold and are centered around providing timely access to an accurate diagnosis and an effective care plan. Other deliverables include management of treatment side effects and patient comorbidities, patient education and support groups, medical education of both practicing clinicians and trainees, and access to clinical trials, lung transplant, and end-of-life care. Organization models for the care of orphan lung diseases are exemplified by those employed for the care of interstitial lung diseases. A multidisciplinary team is integral to providing such complex care delivery and requires access to pulmonology, rheumatology, pathology, thoracic surgery/interventional pulmonology, radiology, palliative care, lung transplant, pharmacy, nursing, social work, and administrative support (both clinical and research), with expertise in orphan lung diseases [26]. The key components of the role of a specialized center are presented in Fig. 1.2.

Facilitating multidisciplinary discussions is a key function of expert centers, and such discussions are the current gold standard for the diagnosis of interstitial lung diseases. They integrate clinical, radiological, and, where available, pathological features in order to reach a consensus diagnosis [28–31] and further incorporate a variety of information that contribute to the diagnosis, including autoimmune serology, precipitins, clinical or molecular biology genetic information, molecular classifiers, or reports from other health-care providers (e.g., occupational medicine specialist, domiciliary visit looking for exposures that may cause hypersensitivity pneumonitis, etc.). Diagnoses of interstitial lung diseases in multidisciplinary discussions have been shown to improve diagnostic confidence and decrease interobserver variability [22, 32–34]. The expertise of an ILD center allows for better assessment of the risk inherent in diagnostic procedures and may reduce the number of cases in which a biopsy is contemplated and performed [35], as compared to centers with less familiarity with interstitial lung diseases [36].

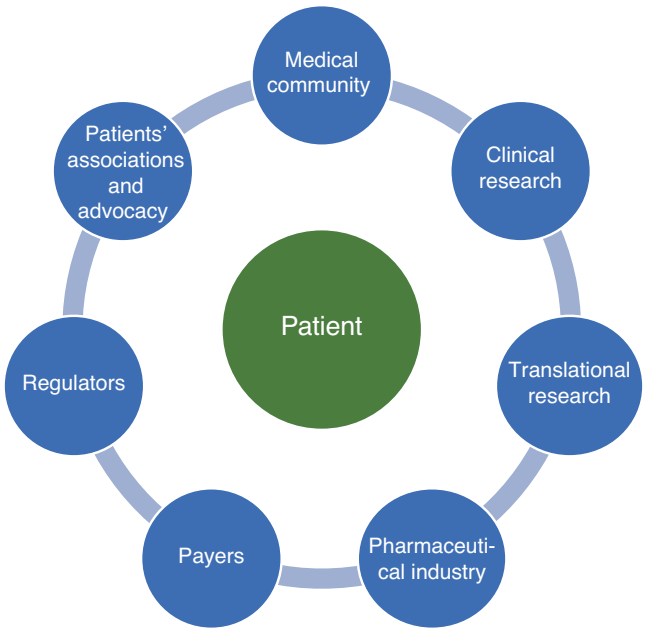

Fig. 1.2 The key components of the role of a specialized center for orphan lung diseases

There is significant heterogeneity in the conduct of multidisciplinary meetings in interstitial lung disease centers and no established composition of the panel of participants. Multidisciplinary discussions, at minimum, include a pulmonologist and a radiologist with expertise in the field [31, 37]. Specialized diagnostic resources, including extensive autoimmune serology and histopathology obtained by videothoracoscopic surgical lung biopsy or cryobiopsy, may be needed to make an accurate diagnosis. Depending on the individual case, other specialty involvement, such as pathology, rheumatology, or genetics, may be useful [31, 38]. A quiet setting with a visual projection system, high-quality high-resolution computed tomography of the chest, and a standardized template summarizing collated patient data are the essential components [31]. Multidisciplinary groups that do not include all interstitial lung disease-specific experts benefit from access to larger and better versed panels for their more complex cases [39]. Innovative strategies are needed to overcome geographic barriers and facilitate access to multidisciplinary discussions and expert diagnostic testing for patients with rare diseases [40].

Although there are no established criteria of expertise, there is informal agreement that expert centers should have ample expertise, infrastructure, and resources for a given rare disease (or for a group of rare diseases, e.g., interstitial lung diseases), associating clinical experience with an adequate volume of patients with the disorder together with active clinical research (international scientific publications), commitment to education and training, and open collaboration with translational research laboratories in the field. European countries including France have pioneered the formal identification of expert centers, with advantages of greater visibility of centers and more efficient referrals of patients to experienced physicians, data collection [41], and initiation of a virtuous circle with larger patient cohorts, increased physician experience, improved medical education, and greater participation in research. As an example, the designation of expert centers in France has validated renewable 5-year mandates of national "reference centers" with further "regional competence (referral) centers" in the specialty departments of large university hospitals. The role of these

reference centers, especially, comprises the production of diagnostic and management procedures and guidelines, evaluation of referred individual complex cases, development of registries, design and coordination of clinical research, and epidemiological studies. These "competence (referral)" centers together with their "reference" centers form a tight network, allowing equity in the access to care and clinical research for all patients in the country. One further layer of organization of care by organ involved (e.g. all expert centers in the respiratory field) ensures that the care pathway to the respective expert centers (reference or competence centers) is smooth and efficient. This ensures especially, that some centers be designated to organize the care of the rarest of conditions (e.g., referral of a patient with alveolar microlithiasis to a national reference center that specializes in all rare interstitial lung diseases including genetic conditions).

The European Union Committee of Experts on Rare Diseases (EUCERD), entrusted with aiding the European Commission (EU), has laid down the foundation for the rare disease community regarding the centers of expertise, European Reference Networks, patient registries and databases, newborn screening, and indicators for national rare disease plans/strategies [42]. The overarching aim of the European Reference Networks is to facilitate access to highly specialized health care for patients requiring a concentration of resources or expertise [43]. The European Reference Network for the lungs (ERN-LUNG, https://ern-lung.eu/) is one of the 24 established European Reference Networks. It has been established for patients with rare respiratory diseases seeking care and advice on all aspects of rare respiratory diseases and facilitates collaboration of expert centers throughout Europe for exchange of knowledge [44], cross-border cooperation, and health-care organization [43].

Patient Organizations

National patient organizations and advocacy groups have been developed for most rare diseases throughout the world [45, 46]. These, most often, have resulted from the efforts of obstinate pioneering individuals (or members of their family), progressively aggregating the skills of both patients and their families. The partnership of patients, clinicians, and scientists has resulted in major advances in the diagnosis and treatment of many rare diseases. The raising of funds, organization of annual meetings where patients (and their families) and doctors from expert centers meet, and national and international cooperation of patients have dramatically increased in the last few decades [24].

Often, these organizations work only with patients in a single country, limited in many cases by language barriers. However, international federations of patient associations are increasingly overcoming this limitation. One example for this is the European Idiopathic Pulmonary Fibrosis and Related Disorders Federation (EU-IPFF), which federates 21 member organizations representing countries all over Europe (https://www.eu-ipff.org). Further alliances of patients' organizations have been developed at the international level, especially in the USA (National Organization for Rare Disorders, NORD, https://rarediseases.org/) and in Europe (European Organization for Rare Diseases, EURORDIS, www.eurordis.org). The EURORDIS website contains the contact details of dozens of organizations that work on individual diseases or rare diseases in general.

The LAM Foundation is a clear example of how advances can be made when patients and researchers work together toward a common goal [47]. Founded in 1995 and driven by the tremendous motivation of a mother of a young patient with lymphangioleiomyomatosis and the networking power of the Internet, the LAM Foundation has funded landmark studies that have substantially improved our knowledge of the disease pathobiology [48] and has been instrumental in the conduct of a randomized controlled trial that demonstrated the benefit of targeting mammalian target of rapamycin, providing patients with an effective treatment [49].

Clinical Trials

Definitive clinical trials of drugs and procedures for patients with rare diseases are challenging because patients are geographically dispersed and the recruitment of an adequate number of subjects is difficult. In addition to the rarity of patients, a major challenge is the recruitment of patients early enough in their disease course to be amenable to improvement (or at least stabilization) of their condition (e.g., idiopathic pulmonary fibrosis, which is too often diagnosed only at a late stage when characteristic end-stage irreversible honeycombing is present) [17].

In highly rare diseases, standard, randomized, double-blind, placebo-controlled trials for the evaluation of new drugs may be logistically impossible, often leading to adoption of alternative suboptimal study designs and methods and less clinically meaningful end points. However, innovative adaptive designs and statistical approaches are increasingly being developed to overcome the barriers due to small sample sizes [50–56].

Research in Orphan Lung Diseases

Patients with orphan lung diseases seek global access to a definite diagnosis and expert management as well as to cutting-edge clinical and basic research.

Advances in rare diseases often begin with early observations in curious single cases initially based on dysmorphol-

ogy. Over time, morphological and pathological features of single cases or short series of patients can lead to characterization of specific syndromes or diseases. Advances in morphological studies may be followed by basic research that often includes extended genetic analysis. The identification of the pathophysiological mechanisms of diseases supported by public and private institutions, furthered by the advocacy of patients and patient groups [24], forge the path to comprehensive care from onset symptoms to efficient treatment.

Orphan Drugs

Orphan drugs are specifically designed to treat rare diseases. The US Orphan Drug Act was signed into law in 1983, providing incentives to the pharmaceutical industry to improve the development of drugs for rare diseases [46]. The "orphan" status allows sponsors to benefit from incentives, research subsidies, and extended patent protection, for the development of drugs (and further medical devices or drug products). More than 500 new orphan therapies have been approved since passing the Act. In Europe, the regulations for orphan medical products were adopted in 1999. Marketing exclusivity for orphan drugs spans 7 years in the USA and 10 years in the EU.

Although these regulations have been effective in supporting the development of new drugs for rare diseases, they also have some downsides, with fewer drugs going through the traditional process, less rigorous trials conducted for orphan drugs, and unaffordable prices for orphan disease therapies. Some authors, therefore, believe that the Orphan Drug Act and the approach to orphan drug development may need to be updated [57, 58].

Orphanet

Orphanet (www.orpha.net) is a portal for rare diseases and orphan drugs. It provides comprehensive information about the classification of rare diseases and an encyclopedia of rare diseases, and offers services including assistance-to-diagnosis tools, emergency guidelines, inventory of orphan drugs, directory of expert centers and patient organizations, directory of professionals and institutions, etc..

Empowerment of Patients

The empowerment of patients is a necessity in rare diseases because these are chronic and difficult-to-manage disorders that require coordinated efforts to make progress [45, 47]. The ideal expert patient with a rare disease should have both personal and collective experiential knowledge of the illness as well as academic involvement including knowledge of the disease and its treatment, academic training as an educator/teacher with health professionals in patient education (including self-management), willingness to take into account patient values and priorities for decision-making, collaborative relationships with academic specialists, responsibilities in patients' associations (e.g., as a board member), attendance and active participation in regional/national/international patient meetings, and participation as a partner in the design of clinical studies/therapeutic trials [47].

Conclusions

Comprehensive care delivery for orphan lung diseases has several key components including diagnosis, treatment, monitoring, support/advocacy, education, and research. The overarching goal of improving patient care and advancing the field of orphan lung diseases can only be achieved in specialized centers with multifaceted care delivery models. With the exponential pace of knowledge generation, orphan lung diseases including interstitial lung diseases have become a subspecialty. Effective knowledge translation and dissemination have become more complex, benefiting from sharing of expertise, and international collaborations are the key to facilitate research. Creative and innovative strategies are needed to find ways to deliver optimal care to the highest possible number of patients with orphan lung diseases.

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Challenges of Clinical Research in Orphan Diseases

2

Paolo Spagnolo and Nicol Bernardinello

Introduction

Rare diseases are a large and highly heterogeneous group of disorders that collectively represent a significant healthcare burden. Indeed, according to current estimates, there are approximately 7000 such conditions, which share the common qualities of being infrequent and unusual. In the United States, where as many as 30 million individuals are living with a rare disease, the Rare Disease Act of 2002 and the US Orphan Drug Act define a rare disease or condition as one that "(a) affects less than 200,000 persons in the United States, or (b) affects more than 200,000 in the United States but for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug" [1]. However, the concept of rare disease is not uniform around the world. For instance, the European Union (EU) considers as rare a disease that affects fewer than 1 in 2000 people, whereas in Japan, a rare disease is one that affects less than 1 in 2500 people [2].

Rare diseases are generally poorly studied and incompletely understood; consequently, often no effective therapy is available for these conditions. Individuals who have the misfortune to be diagnosed with a rare disease feel isolated and orphaned; hence, the commonly applied term "orphan" disease. An estimated 27–36 million people are affected by a rare or ultra-rare condition in Europe and about 350 million are affected worldwide. Overall, about 10% of all diseases are classified as rare, and their cumulative prevalence ranges between 6% and 8% [3]. Despite an urgent need, boosting research in rare diseases is difficult for several reasons:

1. Many diseases lack a real "research community."
2. Experts are often scattered within a country or even internationally, which makes gathering different expertise in a multidisciplinary approach unfeasible.
3. Resources needed to conduct research may be similarly scattered or altogether lacking, e.g., databases, biobanks, and registries.
4. Research into rare diseases is more costly and time-consuming than in other areas, and funding is generally scarce and uncertain.
5. Scientists are often more interested in mechanisms than in how mechanistic interventions might improve disease management, so they may fail to collaborate with clinicians-scientists to identify novel treatments.
6. Clinicians and scientists may be reluctant to pursue a career in the field of rare diseases due to the limited commercial interest in these conditions.

These factors need to be overcome in order to make substantial advances in the implementation of research and clinical care for rare diseases to take place and for gaps in knowledge to be filled.

Challenges to Overcome in Order to Undertake Quality Clinical Research

In order to undertake clinical research, there needs to be adequate numbers of patients gathered, either in a single center or through clinical networks, to enable obtaining meaningful data. However, in rare diseases, this task is problematic for a number of reasons, including a general paucity of prevalence and incidence data, often despite the existence of registries; small numbers of patients with any individual disease; variable genetic effects with incomplete penetrance that affect disease expression and phenotype; occurrence of some genetic diseases in only certain populations worldwide; and limited knowledge of gene–environment interactions. Due to considerable challenges to an accurate diagnosis, patients

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often present late in their disease when it may be inappropriate to enroll them in clinical research studies.

Lack of Reliable Data on Prevalence

In order to plan clinical studies, a number of feasibility issues need to be addressed, especially how many individuals are likely to be enrolled. The prevalence of rare lung diseases varies widely and may be difficult to estimate for a number of reasons. For instance, the prevalence of a "common" rare disease, such as sarcoidosis, is as high as 160 per 100,000 people in Sweden but is much lower in other countries [4–6]; conversely, disorders such as pulmonary alveolar microlithiasis, surfactant protein (SP)-A-related lung disease, or idiopathic pulmonary hemosiderosis are exceedingly rare, having only been described in case reports or small case series. The lungs may also be involved as a rare manifestation of more common disorders, including, among others, Marfan syndrome, Ehlers–Danlos syndrome, Gaucher disease, or Niemann–Pick type C disease.

Small Number of Patients

When planning clinical studies of rare diseases or trials of orphan drugs, investigators are faced with a number of challenges that are usually not encountered in clinical trials of common diseases [7]. Obvious drawbacks include the small size of the trial population and the fact that patients are often geographically dispersed [8]. This is particularly true for disorders with a geographic predilection (e.g., Hermansky–Pudlak syndrome in individuals of Puerto Rican ancestry) or gender predominance (lymphangioleiomyomatosis (LAM) in women of childbearing age). In these circumstances, it is particularly difficult to undertake randomized, double-blind, placebo-controlled studies, which represent the most robust and highest quality data for developing evidence-based recommendations. In addition, in order to prove efficacy in a study with small patient numbers, the compound under investigation needs to show a stronger treatment effect compared to studies with large numbers of patients; furthermore, small studies need more robust methods of data analysis. Indeed, drawing conclusions from trials performed in a limited number of patients may be misleading, if not dangerous. Good examples include initial studies investigating antiestrogen therapy—consisting of surgical castration by oophorectomy, administration of tamoxifen, progesterone, and a gonadotropin-releasing hormone (GnRH) agonist or a luteinizing hormone-releasing hormone—that claimed beneficial effects in LAM [9, 10]. Subsequent careful scrutiny of some of these studies revealed that while the treatment under investigation might have improved some aspects of the disease, such as chylothorax or chylous ascites, other affected organs, including the lungs, were not affected and, in some instances, showed disease progression. Accordingly, the most recent American Thoracic Society/Japanese Respiratory Society Clinical Practice Guidelines have suggested not using hormonal therapy (i.e., progestins, gonadotropin-releasing hormone (GnRH) agonists, selective estrogen receptor modulators like tamoxifen, and oophorectomy) as treatment for LAM [11, 12].

Genetic Component, Variable Degree of Penetrance, and Environmental Interactions

It is estimated that approximately 70% of rare diseases have a genetic origin [2]. However, the importance (and the complexity) of the interactions between host/genetic factors and environmental triggers has become clear only recently. Idiopathic pulmonary fibrosis (IPF), the most common and severe of the idiopathic interstitial pneumonias, is a complex and heterogeneous disease associated with sequence variants in many genes, including genes involved in telomere biology (i.e., *TERT*, *TERC*, *RTEL1*, TINF2, *PARN*, and *DKC1*), alveolar stability (i.e., *SFTPC*, *SFTPA, SFTPA2*, and *ABCA3*), cell–cell adhesion (*DSP* and *DPP9*), and host defense (*MUC5B*) [13]. However, a common gain-of-function variant in the promoter region of *MUC5B* (rs35705950) is the strongest risk factor for both sporadic and familiar IPF, accounting for approximately 30% of the total risk of developing the disease [14]. Familial pulmonary fibrosis (FPF), which is defined by the presence of at least two cases of pulmonary fibrosis (not only IPF) in the same family, represents approximately 10% of all cases and is inherited in an autosomal dominant manner with incomplete penetrance [15]. FPF is characterized by substantial phenotypic heterogeneity, which may be due to a complex interaction between genetic factors and fibrogenic triggers, including cigarette smoke, outdoor pollution, microaspiration of gastric content, and viral infection (a "two-hit" concept) [16]. Different combinations of genetic abnormalities and individual triggers may also account for the variable disease course and prognosis. Another good example of gene–trigger interactions includes chronic beryllium disease in which a strong genetic component requires less antigenic stimulus (i.e., beryllium) to cause the disease, whereas stronger environmental exposures are needed in individuals with "weaker" susceptibility genotypes [17, 18].

Rare genetic lung diseases generally affect individuals from birth through about age 60 and are uncommon in the elderly. Some conditions display racial and ethnic prevalence. For instance, sarcoidosis varies in prevalence and severity across ethnic boundaries [5]. Available measures of prevalence suggest that it is not a common disease. Mass sur-

veys in the United Kingdom in the 1950s and 1960s disclosed radiographic abnormalities consistent with sarcoidosis in 9 [17, 18] to 36 [19] per 100,000 persons screened. Similar studies in Scandinavia, carried out over the same decades, revealed a combined prevalence of 28 per 100,000 examined persons [20]. In 1964, Bauer and Lofgren summarized the findings from 29 surveys carried out in 24 countries; the results varied widely from a prevalence of 0.2 per 100,000 in Portugal, Brazil, and Uruguay to the highest figure of 64 per 100,000 in Sweden [21]. In general, the prevalence is higher, the greater the degrees of latitude from the equator for reasons that are not understood. In the United States, sarcoidosis is more common in African Americans than in Whites. Applying cumulative incidence estimates, the lifetime risk of sarcoidosis is 2.4% for African Americans and 0.85% for American Whites [22]. The wide variation in these estimates presumably reflects the differences in diagnostic labeling and in the age, gender, and morbid distributions of the screened populations. In addition, specific sarcoidosis phenotypes are more prevalent in certain populations, such as uveitis and cardiac involvement in Japanese, Löfgren syndrome (an acute and generally self-limiting form of sarcoidosis characterized by bilateral hilar lymph adenopathy, erythema nodosum/arthralgia, and uveitis) in Scandinavians, and lupus pernio (a chronic purplish indurated lesion mainly seen on the ears, cheeks, lips, and nose) in Puerto Ricans. Rare lung diseases may also display regional variations. This is the case of Hermansky–Pudlak syndrome (HPS), a rare autosomal recessive disorder characterized by oculocutaneous albinism, bleeding diathesis, and lung fibrosis [23]. HPS has a prevalence of 1 in 1800 in Puerto Rico but is exceedingly rare in the rest of the world [24, 25]. Pulmonary alveolar microlithiasis, a rare autosomal recessive disease characterized by calcium phosphate deposits in the distal airspaces, is another example of a condition with a geographic predilection, occurring predominantly in Japan and Turkey [26, 27].

Identifying Causation/Disease Pathogenesis

The cause and pathophysiology of the majority of rare diseases are unknown. However, over the past two decades, research has led to the identification of genes responsible for approximately 50% of the estimated 7000 rare monogenic diseases. This markedly increased discovery rate of causative genes is the result of dramatic improvements in DNA sequencing technologies (i.e., next-generation sequencing, whole-exome sequencing, and whole-genome sequencing) and the associated data analysis [28]. However, interactions between causative and disease-modifier genes remain largely unknown. The environment, including microorganisms, may also play a role in disease pathogenesis, particularly in the presence of a patient's compromised immune system, making these disorders phenotypically heterogeneous and complex. Incomplete knowledge of the disease pathogenesis, in turn, complicates disease management, which is often based on expert opinions.

Unclear/Imprecise Definitions

Rare lung diseases are often difficult to diagnose because of inconsistent case definitions. For instance, hepatopulmonary syndrome, a rare disorder defined by the triad of liver disease, intrapulmonary vascular dilatation, and abnormal gas exchange [29], may also be a rare complication of more common chronic liver diseases, such as liver cirrhosis [30]. Because the definition of an "abnormal gas exchange" varies widely in the published literature [31], the use of diverse diagnostic thresholds has led to variable disease prevalence, thus rendering it difficult to compare studies and complicating patient recruitment due to inconsistent selection criteria. Expert consensus statements and guidelines—not available for most rare diseases—would undoubtedly facilitate consistent disease definitions.

Disease Complexity

Pulmonary involvement in rare diseases may represent only one end of a spectrum of clinical manifestations. This is the case, for instance, of Birt–Hogg–Dubé (BHD) syndrome, an autosomal dominant disorder caused by germline mutations in the *FLCN* (folliculin) gene located on chromosome 17p11.2 and characterized by skin fibrofolliculomas, multiple lung cysts, spontaneous pneumothorax, and renal cancer [32]. BHD-associated skin lesions may also include angiofibromas, which are more typically associated with tuberous sclerosis. In turn, tuberous sclerosis may manifest with pneumothorax (caused by rupture of lung cysts), renal cysts, or tumors and should therefore be considered in the differential diagnosis of BHD syndrome [33]. The diagnosis of BHD syndrome is based on both clinical features and histology. However, the wide variability of clinical expression and the sporadic (in the majority of cases) occurrence of renal cancer or pneumothorax make the diagnosis challenging.

Several Forms of Disease: The Paradigm of Pulmonary Alveolar Proteinosis (PAP)

Pulmonary alveolar proteinosis (PAP) is a rare condition characterized by the accumulation of surfactants within alveolar macrophages and alveoli. PAP is now recognized as a highly heterogeneous syndrome belonging to a large group

of disorders of surfactant production (A) and clearance (B)—collectively referred to as "disorders of surfactant homeostasis" [34]. The former group (i.e., A) includes conditions secondary to mutations in genes encoding surfactant proteins (SPs)-B and -C [35] or proteins involved in surfactant lipid metabolism (i.e., ABCA3) [36, 37]. Conversely, PAP syndrome belongs to the second category of disorders (i.e., B) and is classified as "primary," which can be either autoimmune (accounting for more than 90% of all cases) or hereditary, or as "secondary" to inhalation of dust, such as silica, or underlying immunological or hematological diseases that alter macrophage function. Autoimmune PAP is characterized by the presence of neutralizing autoantibodies directed against granulocyte macrophage colony-stimulating factor (GM-CSF) [38]. Conversely, hereditary PAP cases carry autosomal recessive mutations within the *CSF2RA* or *CSF2RB* gene, which encode the alpha and beta subunits of the GM-CSF receptor, thus resulting in decreased protein expression on the cell surface [39]. Defective GM-CSF activity, in turn, results in altered function of alveolar macrophages, which are unable to maintain surfactant homeostasis and display defective phagocytic and antigen-presenting capabilities [40], leading to increased susceptibility to lung infections [41]. Despite the complexity of the different conditions that are included under the "disorders of surfactant homeostasis" umbrella, this is a nice example of how basic, animal-based research can facilitate the understanding of the basis of human disease that, in turn, stimulates the development of an effective, novel treatment strategy.

Lack of Access to a Correct Diagnosis

Delay in Diagnosis

For many individuals with a rare disease, the period between the emergence of the first symptoms and the appropriate diagnosis often involves unacceptable and highly risky delays; in addition, in many instances, a wrong diagnosis leads to the administration of inappropriate, if not dangerous, treatments. The European Organization for Rare Diseases (EURORDIS), in collaboration with 67 European rare disease organizations, has conducted a survey about the delay in diagnosis for 8 rare diseases in Europe [3]. One of the main findings of this survey was that 25% of patients had to wait between 5 and 30 years from emergence of early symptoms to a confirmatory diagnosis of their disease. Before receiving a secure diagnosis, 40% of patients first received an erroneous one and others received none. In all, 25% of patients had to travel to a different region to obtain the final diagnosis and 2% had to travel to a different country. The diagnosis was announced in unsatisfactory terms or conditions in 33% of cases and in unacceptable conditions in 12.5% of cases. The genetic nature of the disease was not communicated to the patient or family in 25% of cases. Intuitively, the consequences of a misdiagnosis include clinical worsening of the patient's health—even leading to death—and loss of confidence in the health-care system. This is utterly unacceptable—imagine if this had occurred to a member of one's own family—and should not continue.

Clinical features alone usually do not allow discrimination between rare and common lung diseases. In fact, the diagnostic delay of a rare disease is mainly accounted for by the fact that in early stages symptoms may be absent, masked, misunderstood, or confused with other more common diseases [42]. This implies that the goal of primary care should be the early recognition that a rare lung disease might be present and the determination of an appropriate threshold for referral to centers with specific expertise. The need for more global, accessible educational tools is clear. "You only see what you look for and you only look for what you know."

From a research perspective, these delays present barriers to recruitment, whereas from a clinical perspective, they contribute to patient morbidity. For instance, most patients suffer from several episodes of pneumothorax before being diagnosed with LAM. In addition, a misdiagnosis not only leads to inappropriate—and ineffective—treatments but also to unnecessary risks, such as pregnancy or air travel in the case of LAM. Similarly, in patients with Hermansky–Pudlak syndrome, invasive procedures should be avoided because of the patient's tendency to bleed. In the latter case, a correct diagnosis allows other family members to be screened for the syndrome, with the demonstration of absent dense bodies on whole mount electron microscopy of platelets being diagnostic. Diseases caused by a single, mutated gene—such as alpha-1 antitrypsin deficiency, surfactant protein disorders, and cystic fibrosis—lend themselves to family screening. This is essential as diseases diagnosed at an early stage are more likely to be properly treated, and, with the knowledge that a rare disease is present in the family, other individuals are less likely to fall victim to an erroneous diagnosis.

Challenges But Not Negativity

These challenges should not be seen as insurmountable and, in some cases, have been successfully overcome (Table 2.1). This requires a clear appreciation of the fundamental pathological aspects of the disease in order to identify how to best deal with it; an ivory tower, purely mechanistic research, without keeping an eye on the disease that gave rise to the research question, can lead to false dawns (see excellent reviews in Moeller et al. [43] and Jenkins et al. [44], on the bleomycin model of lung fibrosis as a purported "model" for IPF and how this has failed to provide any novel therapy for this disease).

Table 2.1 Major challenges to research in rare lung diseases and possible ways to address them

Challenge	Possible solution
Limited awareness of rare diseases throughout society	Establish effective educational programs; disclose stories about people, especially celebrities, with rare diseases; stimulate government attention
Incomplete knowledge of disease pathophysiology, potential biomarkers, and therapeutic targets	Encourage and fund basic research; strengthen national and international research networking for fund applications
Difficulties in making a timely diagnosis	Promote task forces to develop guideline documents
Incomplete knowledge of the natural history of the disease	Encourage collection of patient-reported outcomes through social networking
Difficulties in undertaking clinical trials	Promote multi-institutional and international collaborations aimed at creating registries of phenotypically well-defined patients. Patient advocacy groups may also facilitate recruitment by notifying patients of opportunities to participate in clinical trials
Insufficient research funding	Promote and facilitate partnership between industry, patient advocacy groups, and research funding agencies
Need for continuous interaction between specialists from different disciplines	Timely referral to expert centers with available multidisciplinary teams
Limited interest in pursuing a career in rare disease research	Provide financial incentives and guarantee career opportunities for young investigators. The potential of having a major impact on clinically and scientifically underserved populations of patients is a fascinating challenge and this aspect should be emphasized
Lengthy development of novel therapies	Promote and develop interactions between industry, academia, regulatory authorities, research funding bodies, and patient associations

Some Success Stories

Two examples, among others, are illustrative of the way clinical science, diagnostic precision, and multinational networking can be combined to obtain therapeutic benefit: IPF and LAM. In IPF, the combination of an improved understanding of the disease pathogenesis, refined consensus diagnostic criteria, and international multicenter collaboration has led to the worldwide approval of two drugs (nintedanib and pirfenidone) that are able to slow down functional decline and disease progression. These substantial advances represent new hopes for patients and a new vision of the disease for dedicated researchers and physicians. Similarly, a better understanding of the processes underpinning LAM [45] together with the emergence of a strong international network of clinicians-scientists and supported by a highly efficient patient organization (see below) has resulted in the completion of a successful study of an agent, sirolimus, which was predicted to block the key pathogenetic mechanisms and indeed was found to lead to stabilization of lung function and improved quality of life [46, 47].

Both of these examples demonstrate that progress in the pathogenesis and treatment of rare diseases requires a team approach and an equipoise in collaboration that transcends individual interests to result in a successful outcome. These two examples may provide a template for other rare and orphan diseases that require the same sort of concerted organization that would attract research funding together with pharmaceutical company interest in developing focused therapies.

The Means to Overcome the Challenges of Clinical Research: Get Bigger Numbers of Well-Characterized Patients

One of the more fundamental obstacles to undertaking research in rare diseases is the absence of sufficient patient numbers to study disease causation, susceptibility, and phenotypes. Once these numbers are gathered, expertise and knowledge of the disease improve, patients become aware of research into their condition, and this becomes an iterative process of knowledge acquisition. An international survey conducted in 2018 by Rare Barometer Voices (a group of patients living with rare diseases and participating in EURORDIS studies) found that 64% of patients did not participate in any clinical trials for their condition [48]. Increasing patient numbers is the essential starting point, and there are a number of strategies that could be employed to facilitate this process.

The Importance of Patient Organizations

Patient organizations are vital in rare diseases as they form associations for patients to acquire better information, to become aware of the ways in which their disease might be managed, and to find their way to experts who can offer therapy and guidance. In this manner, small numbers of individuals become larger cohorts who are generally all too willing to become participants in research studies. Patient advocacy organizations are valuable allies in the fight against rare dis-

eases as they provide education and support to patients and families. The LAM Foundation illustrates the impact of patient–parent advocacy groups on basic and clinical research into rare diseases. Until recently, a diagnosis of LAM has been a medical anomaly and a patient who received this diagnosis had little cause for hope due to both doctors being unfamiliar with the disease and the unavailability of effective drugs. The tremendous motivation of a mother of a young patient with LAM and the networking power of the Internet changed all this. Founded in 1995 and headquartered in Cincinnati, Ohio, the LAM Foundation has rapidly evolved into an organization described by the National Heart, Lung, and Blood Institute as "a model for voluntary health agencies." The Foundation embraces women with LAM and their families, provides support and education, engages doctors and scientists, and raises funds for the study of LAM. The LAM Foundation has funded a number of studies that have dramatically improved our knowledge of the pathobiology of the disease [45], and we now know that LAM results from the aberrant proliferation of smooth muscle-like cells ("LAM cells"), which infiltrate organs, especially the lungs and the kidneys, via the blood and lymphatics [49, 50]. With an increasing understanding of the disease, clinical trials not only have become possible but also successful [46]. The LAM Foundation is a clear example of how advances can be made when patients, researchers, and funding bodies work together toward a common goal: the research community provides ideas and scientific knowledge and patients contribute their personal insights, provide biological samples, and show dedication and courage as they put themselves at risk in clinical trials of potential treatments for their disease. In turn, the results of the clinical trials may lead to more focused basic research in what can be referred to as a "bench-to-bedside-and-back" research strategy. Other organizations, including the Raynaud's and Scleroderma Association in the UK and the Pulmonary Fibrosis Foundation in the United States, have similar templates that combine education, support, and research in their drive for better treatment for patients.

Patient organizations have also been a huge driving force in treatment development in cystic fibrosis and in neuromuscular disorders. An example of a successful clinical research network is the Cystic Fibrosis Therapeutics Development Network, an international network of about 50 centers formed by the Cystic Fibrosis Foundation in 1988. In just over a decade, this network has conducted more than 150 studies, involving hundreds of patients [51]. Finally, patient organizations are essential in order to identify specific unmet medical needs, which, in turn, represent the main driver of research. In this regard, a study conducted by EURORDIS in 2009 showed that funding from patient organizations is mainly used to fund basic science, whereas public funding is mainly used for clinical, diagnostic, and therapeutic studies [52].

National and International Networks

Increasing the sample size of studies on rare diseases requires collaboration among research centers. This is essential in order to build up patient registries and databases, which, in turn, are vital to assess the feasibility and facilitate the planning of appropriate clinical trials and to support the enrollment of patients. In addition to building meticulous datasets, this approach would also serve to limit overlapping and competitive research efforts and avoid wasteful use of resources by replicating efforts that could have been more profitably developed as collaborations. Rare disease research typically requires multiple sites to recruit sufficient numbers of participants. However, even when a disorder is clustered in specific ethnicities or geographic areas, recruitment may be challenging. For instance, the prevalence of hereditary hemorrhagic telangiectasia is high (1/200) in Dutch Antilles owing to a founder effect. Nevertheless, recruitment from these islands has been limited by remote geography, patients' fear of foreign medical institutions, and transportation costs. Ideally, registries and databases should be international, although there may be some heterogeneity in data sources and regulations across countries. For instance, alkaptonuria (AKU) is an ultra-rare autosomal recessive disorder characterized by high circulating levels of serum amyloid A and spondyloarthropathy, resulting in reduced quality of life. Cicaloni et al. developed an AKU-dedicated precision medicine "ecosystem" in which genetic, biochemical, and clinical resources can be shared among registered researchers [53]. One other approach would be to export the expertise rather than import the patients. With the widespread use of Internet and the explosion of social networks, it should not be long before research and even diagnoses can be developed remotely. Certainly, major international funding bodies need to invest in longer-term strategies at least at the pump-priming stage. The practicalities should not be insurmountable. For the moment, where disease prevalence is such that it is often impossible to study large patient cohorts, trials can be designed using methodologies that allow efficacy and safety to be balanced even with small patient numbers [54–58]. Such studies, provided they are well-designed, can result in regulatory approval despite their small size [59]. Further impetus could be provided by the creation of registries that would accurately capture the true prevalence and incidence of rare diseases across nations; this is not a trivial task as evidenced by the flaws and difficulties observed in some of the existing registries. This requires significant resource to optimize the capture and audit of data. A second advance requires the continuing development of guidelines that would allow the harmonization of diagnostic criteria and management principles across nations [60, 61], as it has been done for IPF and LAM, for example.

End Points for Trials: Getting Them Right When Numbers Are Small and Change Is Modest

Clinical trials in the field of rare diseases suffer from a number of weaknesses: (1) due to the small number of participants, a statistically significant benefit may be difficult to reach; (2) clinical trials are often too short to capture the complex natural history of a rare disease; (3) defining benefit in disorders in which there are often no well-defined and validated markers/surrogates for monitoring disease progression and treatment response is difficult; and (4) access to health care, which is different across countries, often limits patient enrollment in clinical trials. As a result, only 57% of approved orphan drugs have been tested in a randomized clinical trial before approval [62]. Furthermore, rare diseases are frequently diagnosed and managed in childhood, and this presents a challenge to clinical studies, since designing trials of pharmacological interventions in children can be problematic and/or extremely slow.

Orphan Drug Development

To date, only about 5% of all rare diseases have a targeted treatment [63]. Generally, the first stage in drug development is research into the mechanisms and pathogenesis of a given disease. Once a promising compound has been identified, the next stage is to test its safety and efficacy in animals. The lack of knowledge about the pathogenesis of most rare diseases limits identification of pharmaceutical targets, and the scarcity of animal models that authentically recapitulate human disease is a huge obstacle to preclinical studies and orphan drug development. In turn, the scarcity of funds invested and human resources devoted to investigating rare diseases accounts for the difficulty faced by pharmaceutical companies to invest in this area. Furthermore, for some conditions, clinical trials need to be multinational and geographically dispersed owing to limited regional expertise and the small number of patients affected by the disease. These hurdles, combined with the estimated low return on investment due to extremely small markets and costly drug development, discourage pharmaceutical company interest and hamper development of drugs for rare diseases, despite the huge unmet medical need.

However, there has been some important progress with regard to drug research that has eased the pathways to developing drugs and obtaining approval in rare diseases [64–68]. These include regulatory and economic incentives for pharmaceutical companies willing to develop drugs for rare diseases via the orphan drug acts [69]; the recognition by regulatory agencies of the highly individualistic nature of problems encountered in drug development for rare diseases, such as demonstrating the efficacy of novel therapies in trials of relatively small numbers of patients; and the development of public–private partnerships with a goal to facilitating the discovery of effective new therapies.

Importance of Referral Centers

Who should or is able to adopt a broad clinical perspective on the needs of patients affected by rare diseases? Given the number and diversity of these disorders, it is impossible for community physicians to have knowledge about all of them. Although the "optimum" for a general lung specialist, going forward, may be to better incorporate rare disease training into the pulmonary fellowship curriculum, at this time, referral to centers with expertise in the specific lung disease or group of diseases is strongly encouraged. Joint clinics that share expertise are also important. A tuberous sclerosis clinic, for example, should comprise geneticists, neurologists, psychiatrists, nephrologists, and pulmonologists. Similarly, a neurofibromatosis clinic should have a geneticist working alongside pulmonologists, pediatric neurologists, endocrinologists, and ophthalmologists, to cite only two rare disorders. Multidisciplinary specialist clinics and coordinated services are the key to delivering proper care in rare disorders, but they can only be found in dedicated centers. This, in turn, allows patients to have the highest possible chance of success through sharing of expertise and resources and maximizing cost-effective use of resources by concentrating them where appropriate. A multidisciplinary approach through specialist centers has proven successful in diagnosing and treating cystic fibrosis, which is now included in neonatal screening programs in several countries with ready access to genetic counseling and support for parents of children diagnosed at birth [70]. This model now needs to be reproduced for other disorders.

Looking at the Future

In addition to exploring areas in which short- and medium-term progress can be made, there is a requirement for a long-term vision. This must include attention to education. Primary and secondary care providers need to be aware of the range of rare diseases, whereas patients need education and guidance on the implications of their disease and on where they can reach out for information in order to not be left truly orphaned and disenfranchised. Most importantly, future generations of doctors need to develop a lower index of suspicion for rare diseases. This can only be achieved by creating and providing structured training to medical students, which involves courses on all the diagnostic and management skills required in caring for patients with rare diseases. It would be highly desirable if the content of these courses could be harmonized across national boundaries, which would have the added advantage of enhancing the

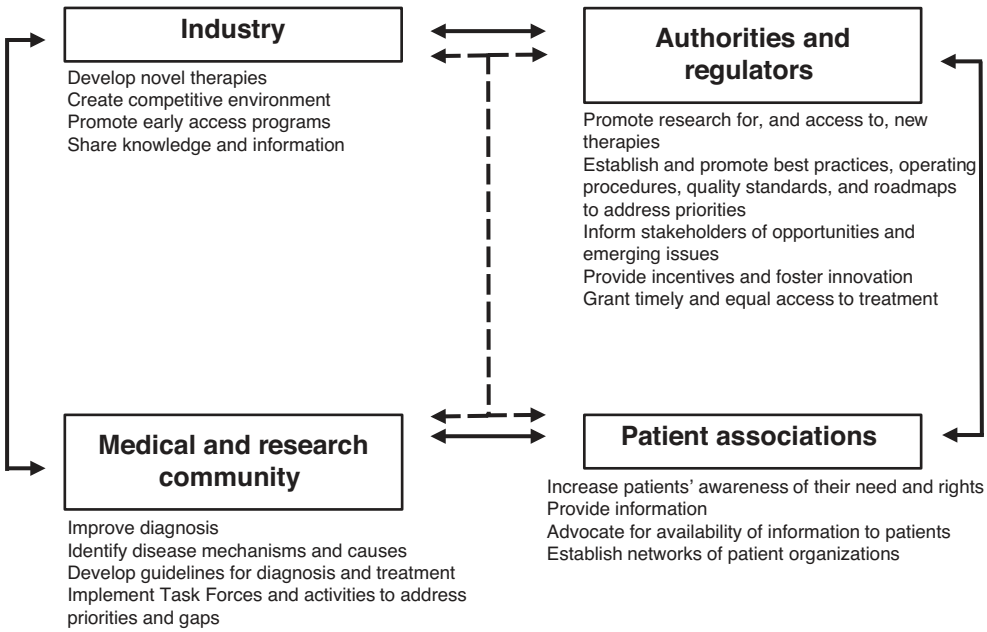

Fig. 2.1 Research priorities and roles of stakeholders in rare lung diseases

opportunities for national and international collaborations in the future. The incentive should not be only in teaching but also in terms of sharing. In the big data era, artificial intelligence, medical technology, and biobanks are excellent ways to exchange information worldwide. According to a recent survey by the EURORDIS Rare Barometer Programme, most patients, regardless of the severity of their disease, have been willing to share their data to foster research and improve health care [71]. However, particularly in the field of rare diseases, it is important to know "where to go" and to set realistic goals [72] always with an eye on the available resources. The International Rare Diseases Research Consortium (IRDiRC), which unites national and international governmental and nonprofit funding bodies, companies, patient advocacy organizations, and scientific researchers to promote international collaboration and advance rare disease research worldwide, has set some ambitious (but not unrealistic) goals to be achieved in the next decade, including faster diagnosis, more therapies, and better access to care (Fig. 2.1).

The Arguments for Progress

Economic Burden The burden of rare diseases in terms of suffering and human life loss is enormous. Similarly, though difficult to estimate, the economic load of rare diseases is massive [73]. With an overall prevalence of at least one to two million people and conservative approximations of average yearly health-care costs of $5000 per patient, the annual total cost in the United States only is in billions of dollars, according to the National Institutes of Health Office of Rare Diseases. In addition, the rarer the condition, the more tests and health-care visits are usually required to make a correct diagnosis, which, in turn, results in greater expenses, unnecessary tests, and missed opportunities for early intervention. In recent years, the European Union has allocated one billion for rare disease research, which funded 270 projects; hopefully, this effort will boost innovative therapeutic approaches and eventually improve the life of people living with a rare disease [74].

Ignorance Can be More Expensive Than the Research Aimed at Improving Knowledge Too many health professionals are still unaware of too many rare diseases. Consequent delays or errors in diagnosis are stressful for patients and their families, affect their quality of life, and can be costly or even dangerous by delaying access to appropriate treatments; all this translates into an increase of expenses and a waste of resources for the health-care and social systems. This is particularly unacceptable considering that some rare diseases may be compatible with a normal life if diagnosed on time and properly managed. Therefore, any research that could improve the diagnosis, understanding, or treatments of just some of the estimated 6000–7000 different rare diseases would substantially reduce costs for health-care systems. A patient affected by a rare disease, when properly treated, stops being a consumer of irrelevant tests, ineffective, if not dangerous, treatments, or superfluous hospital admissions.

Patients Deserve Better The low prevalence of rare diseases means that the numbers of patients who are affected by any given condition are small or extremely small; those affected,

therefore, feel particularly isolated. The isolation felt by these patients is not only geographical but can also lead to marginalization within the society and within health-care systems that are designed for common diseases. In a survey conducted in 2017 in 48 countries, more than 70% of patients reported difficulty in daily activities and more than 50% mentioned that the disease affects their social life [52]. Indeed, 70% of patients reported that they are forced to reduce or discontinue their work and 69% face a reduction in their income. Scientific knowledge on rare diseases is scarce overall; when it does exist, it is fragmented and scattered across national territory. For most rare conditions, the causes, pathogenetic mechanisms, and epidemiology are unknown, which makes diagnostic methodologies and therapies difficult to develop. In turn, this aggravates patients' vulnerability and puts them at a disadvantage relative to the rest of the society and to patients affected by more common diseases.

The Goal of Clinical Research in Rare Diseases

Rare lung diseases are often chronic and debilitating and, once diagnosed, may require unconventional, expensive, and long-term treatments. This is the case, for example, of subcutaneously administered GM-CSF for pulmonary alveolar proteinosis [75], alpha-1 antitrypsin replacement for hereditary emphysema [76], or glucocerebrosidase therapy for Gaucher disease [77]. As with more common diseases, the ultimate goal of research in rare diseases is to identify the underlying pathogenetic mechanisms and new targets for therapeutic intervention. The success of sirolimus—a mammalian target of rapamycin (mTOR) signaling inhibitor—in stabilizing lung function, reducing respiratory symptoms, and improving the quality of life of tuberous sclerosis/LAM patients is proof of concept that therapy targeting defective genetic and biochemical pathways can be successful [46, 78].

Concluding Remarks

Rare lung diseases represent a heterogeneous group of disorders with complex pathogenesis, diverse histopathology, and variable natural history and prognosis. In the last decade, there have been major advances in the field, but much work remains to be done. Most of these conditions are genetically determined. However, unraveling how multiple susceptibility alleles interact with each other and with environmental factors to determine disease risk and phenotypes remains challenging. Studies on rare diseases have several beneficial effects, apart from facilitating the diagnosis and treatment of specific entities. The establishment of partnership between academic researchers/clinicians, pharmaceutical companies, patient–parent support groups, and government agencies to solve problems related to rare diseases will also serve as a paradigm for the studies of other diseases. Basic and clinical studies on rare lung disorders are also likely to improve our understanding of the physiological and pathological processes as well as treatment of more common diseases. The development of central databases, registries, and research networks is vital in order to the design and performance of much-needed robust clinical studies across the spectrum of rare lung diseases.

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Part II

Orphan Diseases of the Airways

Chronic Bronchiolitis in Adults

3

Talmadge E. King Jr.

Introduction

Bronchiolitis (or bronchiolitis obliterans) primarily affects the small conducting airways (3 mm or less in diameter), with limited involvement of the interstitium. The small airways, bronchioles, are divided into terminal (membranous) and respiratory bronchioles (Fig. 3.1). Bronchiolitis results from damage to the bronchiolar epithelium, resulting in some degree of inflammation, narrowing, or obliteration of the small airways. The severity and persistence of the injury may determine whether there is resolution and recovery or progression to a less reversible intramural or intraluminal fibrotic state.

There may be extensive damage to the small airways before the patient becomes symptomatic or develops detectable abnormalities on lung function testing. Most cases have an insidious onset characterized by cough or dyspnea. Initially, patients are assumed to have more common problems, such as asthma or chronic obstructive pulmonary disease (COPD).

The epidemiology of bronchiolitis is poorly understood. Bronchiolitis in infants and children is recognized worldwide and is often associated with outbreaks of infection (especially respiratory syncytial virus and rhinovirus) [1]. Adult bronchiolitis is rare and has not been well-studied. Many cases are associated with accidents that result in inhalation injuries.

This chapter reviews the clinical, radiographic, and histopathological findings of the bronchiolar syndromes in adults and is orientated toward practical management. More exhaustive reviews can be found elsewhere [2, 3].

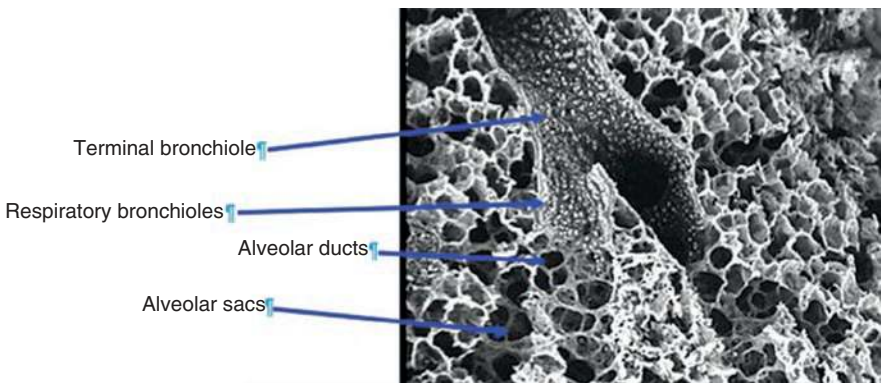

Fig. 3.1 The junctional area between the purely conductive airways and the respiratory portion of the lung. The terminal (non-respiratory) bronchiole has a continuous cuboidal epithelium, whereas the alveoli open off the respiratory bronchiole. (Courtesy of Marco Chilosi, MD, Dipartimento di Patologia, Università di Verona)

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Classification

"Bronchiolitis" is often confusing because the term describes both a clinical syndrome and a constellation of histopathological abnormalities that may occur in a variety of disorders. Thus, two classification schemes appear useful in defining cases of bronchiolitis: (1) a clinical classification based on the etiology (Table 3.1) and (2) a histopathological classification, which includes two major morphological types (proliferative bronchiolitis and constrictive bronchiolitis) [3].

Table 3.1 Clinical syndromes associated with histological bronchiolitis

Inhalation injury	Selected examples
Toxic fumes or irritant gases	• Fire smoke
	• Nitrogen dioxide (e.g., silo gas, chemical, electric arc, or acetylene gas welding, contamination of anesthetic gases)
	• Sulfur dioxide (e.g., burning of sulfur-containing fossil fuels, fungicides, refrigerants)
	• Ammonia (e.g., fertilizers and explosives, production, refrigeration)
	• Chlorine (e.g., bleaching, disinfectant and plastic making)
	• Phosgene (e.g., chemical industry, dye and insecticide manufacturing)
	• Ozone (e.g., arc welding and air, sewage, and water treatment)
	• Cadmium oxide (e.g., smelting, alloying, welding)
	• Methyl sulfate
	• Hydrogen sulfide
	• Hydrogen fluoride
	• Other agents (e.g., chloropicrin, trichloroethylene, hydrous magnesium silicate, stearate of zinc powder)
Organic dusts	
Mineral dusts	
Volatile flavoring agents	
Vaping-associated lung injury	
Post-infectious	• Respiratory syncytial virus
	• Parainfluenza (types 1, 2, and 3)
	• Adenovirus (types 1, 2, 3, 5, 6, 7, and 21)
	• *Mycoplasma pneumoniae*
Drug-induced reactions	• Penicillamine
	• Gold
	• Amiodarone
	• Busulfan
	• Free-base cocaine use
	• Sulfasalazine
	• Bleomycin
	• Sauropus androgynus
	• Paraquat poisoning
	• Nitrofurantoin
Idiopathic	No associated diseases
	• Cryptogenic bronchiolitis
	• Respiratory bronchiolitis (cigarette smoke)
	• Cryptogenic organizing pneumonia, diffuse
	Associated with other diseases
	• Associated with organ and hematopoietic stem cell transplantation
	• Associated with connective tissue disease
	• Aspiration pneumonitis
	• Ulcerative colitis
	• Primary biliary cirrhosis
	• Vasculitis
	• Paraneoplastic pemphigus

Cellular Bronchiolitis

"Cellular bronchiolitis" is a descriptive histological term that refers to inflammatory infiltrates that involve the lumen, the walls of bronchioles, or both. The inflammation may be acute, chronic, or both.

Follicular Bronchiolitis

Follicular bronchiolitis is a distinctive subset of cellular bronchiolitis characterized by the dramatic proliferation of lymphoid follicles with germinal centers along the airways and an infiltration of the epithelium by lymphocytes (lymphoid hyperplasia of bronchus-associated lymphoid tissue (BALT)) (Fig. 3.2) [4, 5]. Most cases occur in patients with connective tissue diseases (e.g., rheumatoid arthritis (RA) and Sjögren's syndrome) [4, 6]. Other associations include immunodeficiency syndromes, familial lung disorders, chronic infections, and a heterogeneous group of patients with a hypersensitivity-type reaction [4].

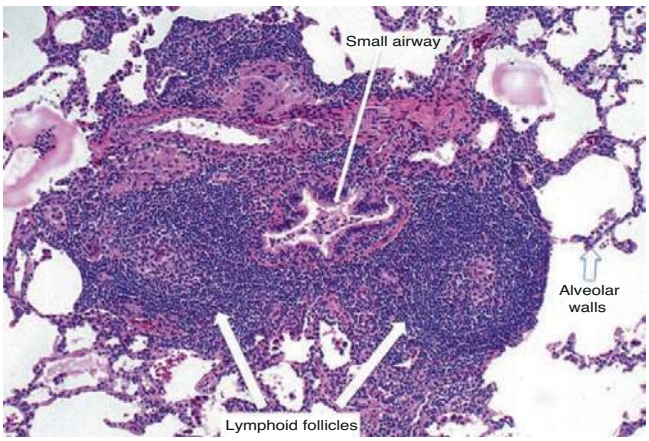

Fig. 3.2 Follicular bronchiolitis. Prominent lymphoid follicles adjacent to and impinging on the distal airways. (Courtesy of Jeffrey L Myers, MD, Department of Pathology University of Michigan)

Respiratory Bronchiolitis

Respiratory bronchiolitis is characterized by a cellular reaction in and around respiratory bronchioles. There is mild inflammation of the walls of the respiratory bronchioles, which extends to involve the adjacent alveoli [7]. Slight fibrosis may be present. This lesion is common in smokers and is often associated with a prominent increase in pigmented macrophages in the airway lumina and alveolar spaces.

Airway-Centered Interstitial Fibrosis

Airway-centered interstitial fibrosis (ACIF), also called idiopathic bronchiolocentric interstitial pneumonia and chronic bronchiolitis with fibrosis, is characterized by centrilobular and bronchiolocentric inflammatory infiltrates with peribronchiolar fibrosis and an absence of granulomas [8, 9]. The typical patient is a middle-aged woman (40–50 years old) with a chronic nonproductive cough. Many cases are believed to be characteristic of hypersensitivity pneumonitis on clinical grounds, although no specific antigen has been identified [10]. Unlike hypersensitivity pneumonitis, the percentage of lymphocytes on bronchoalveolar lavage (BAL) is less than 40% [9]. Many of the reported patients have a history of smoking, raising concerns that cigarette smoking may be a contributor to airway injury. Chronic silent microaspiration and toxic or hypersensitivity reactions may contribute to the development of this pattern of injury in some patients.

Diffuse Panbronchiolitis

Diffuse panbronchiolitis is an inflammatory process characterized by mononuclear cell inflammation of the respiratory bronchioles and the presence of foamy macrophages in the bronchiolar lumina and adjacent alveoli (Fig. 3.3). These findings often produce nodular lesions [11]. This distinctive form of small airway disease is relatively common in Japan, China, and Korea; it is rare in other parts of the world [11, 12].

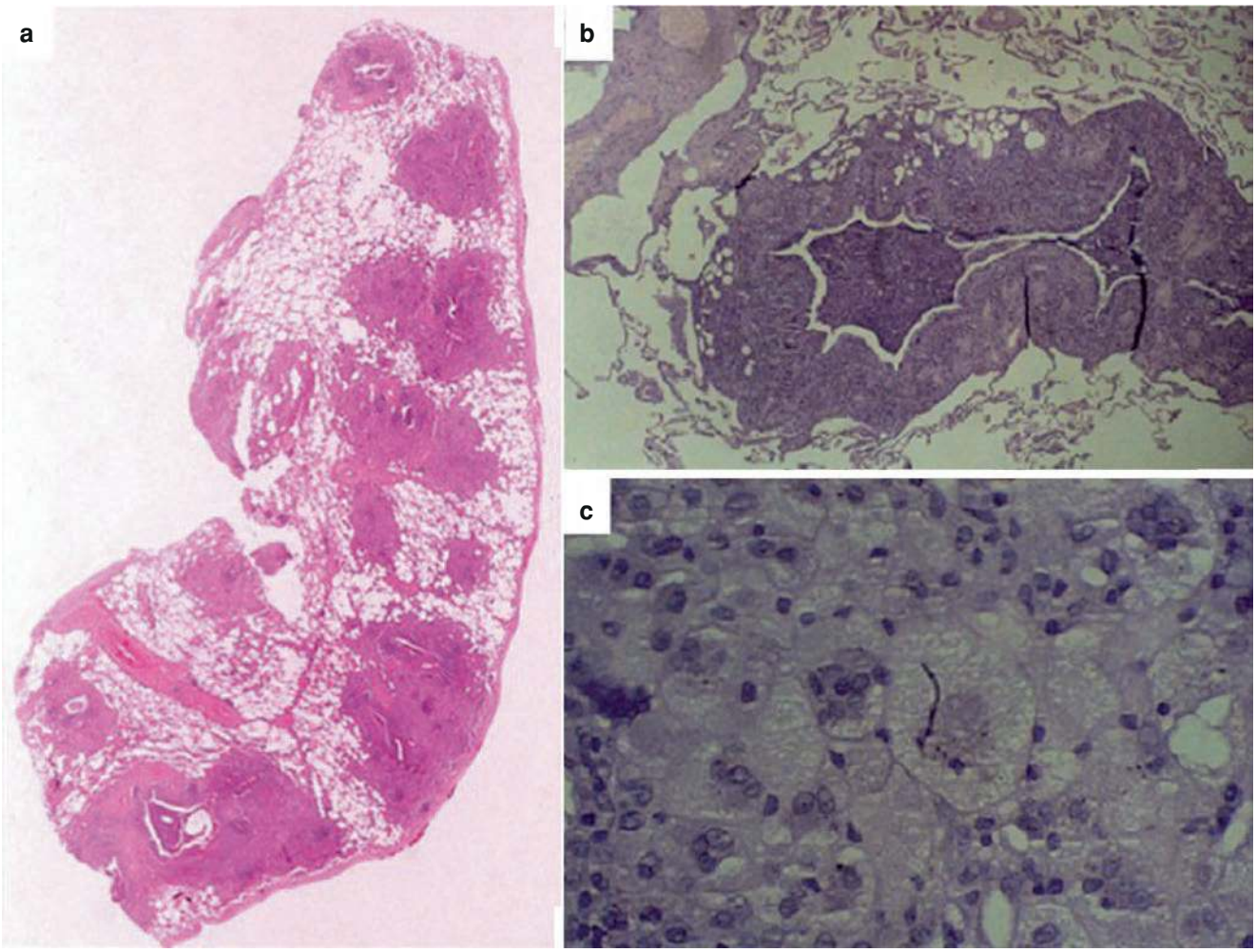

Fig. 3.3 Diffuse panbronchiolitis. (**a**) Scattered nodules are seen at a low power. The primary lesion is an inflammatory process of the respiratory bronchioles with marked associated foam cell accumulation. (Courtesy of Jeffrey L Myers, MD, Department of Pathology University of Michigan). (**b**) Inflammatory process in the respiratory bronchioles characterized by mononuclear cell inflammation in the wall. (**c**) Numerous foamy macrophages are present in the bronchiolar lumina (and adjacent alveoli)

Proliferative Bronchiolitis

Proliferative bronchiolitis is characterized by an organizing intraluminal exudate and is extensive and prominent in organizing pneumonia [13]. The intraluminal fibrotic buds (Masson bodies) are seen in the respiratory bronchioles, alveolar ducts, and alveoli. Proliferative bronchiolitis is most frequently associated with diffuse alveolar opacities on chest radiographs and CT scans [14]. A restrictive defect is found on pulmonary function testing.

Diagnosis

Patients who present with a chronic, insidious onset of cough and dyspnea, especially when the symptoms and signs do not follow a typical pattern, should raise the consideration of bronchiolitis.

Clinical Vignette

A 42-year-old female never smoker presented with a 12-week history of dyspnea with exertion and a nonproductive cough. She is a secondary school science teacher and an avid runner. She first experienced a nonproductive cough with chest tightness about 15 weeks following accidental exposure to a sulfur-based chemical that overheated, giving off fumes. She has had progressive worsening of her dyspnea such that she is now not able to run. She has no chest pain, tightness, or heaviness. She is afebrile. Her respiratory rate is 16 breaths/min, and pulse oximetry shows 96% saturation on room air. Pulmonary examination shows slight expiratory wheezing and occasional bibasilar rhonchi that clear with coughing. Results of cardiac examination are normal, and no ankle edema is present. Lung function testing revealed moderate airflow obstruction

with moderate overdistension. The diffusing capacity was slightly reduced. A chest X-ray showed findings suggestive of hyperinflation. Inspiratory HRCT demonstrated mild bronchiolar dilatation. Expiratory HRCT showed multifocal lobular air trapping in several lobes of her lungs. A surgical lung biopsy was performed and showed marked concentric narrowing of the bronchiolar lumen. Step sectioning of the tissue specimen confirmed the presence of complete obliteration of the bronchiolar lumen due to fibrosis (Fig. 3.4). Following treatment with bronchodilators and oral prednisone, her lung function stabilized with persistent reduction in her exercise capacity.

The differential diagnosis includes severe asthma, chronic obstructive pulmonary disease, hypersensitivity pneumonitis, and sarcoidosis. A multidisciplinary approach that considers the clinical setting and radiographic pattern is often helpful. When bronchiolitis is suspected, the most helpful tests are chest imaging, usually a high-resolution CT (HRCT) scan, and pulmonary function testing (see Box 3.1).

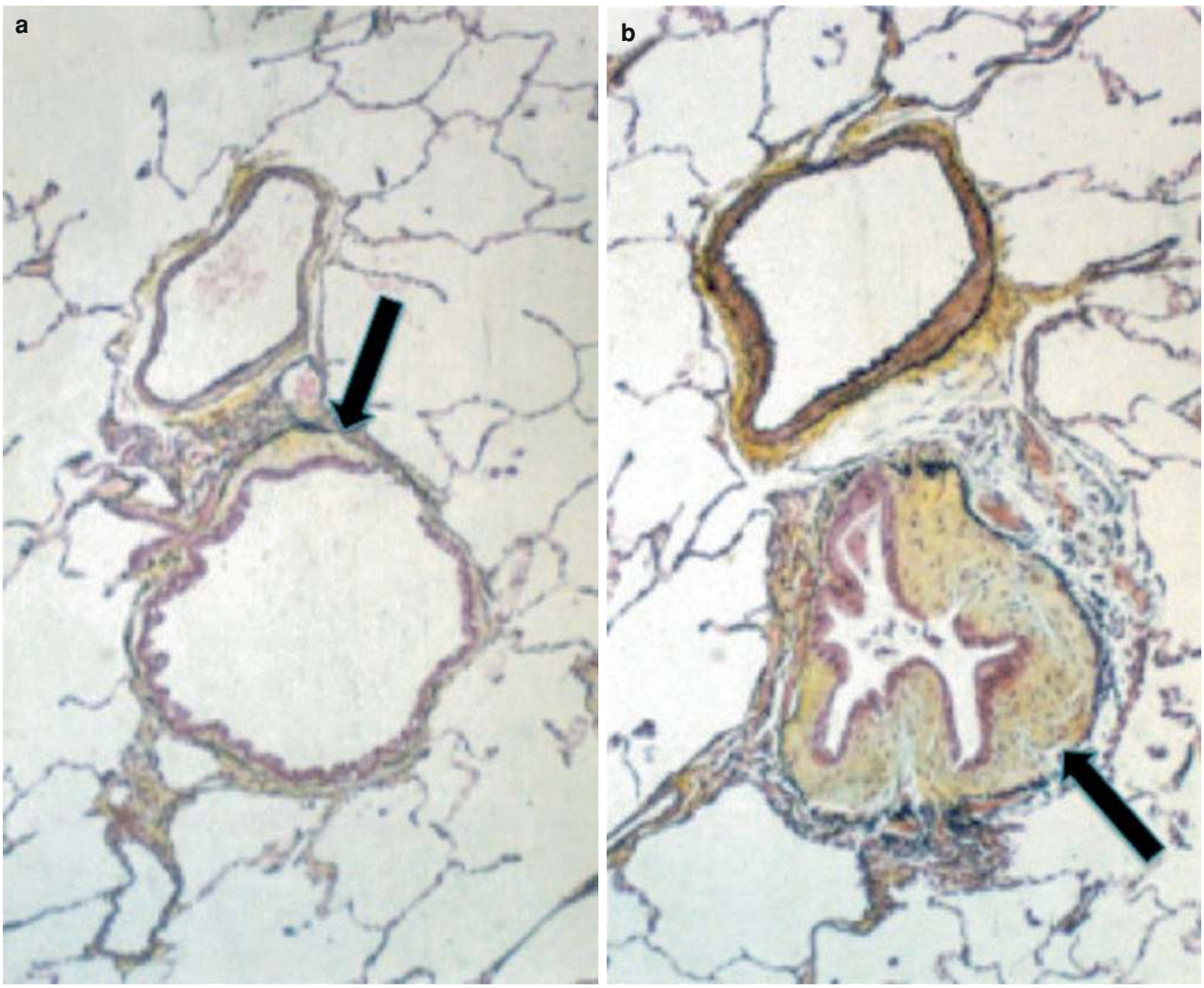

Fig. 3.4 (**a**) Slightly dilated bronchiole with minimal fibrosis (arrow) and a normal intervening lung (pentachrome stain; ×156 original magnification). (**b**) Severe concentric narrowing of the bronchiolar lumen due to fibrosis (arrow) (pentachrome stain; ×156 original magnification). (Adapted from King [2])

Box 3.1 Diagnostic Criteria

1. **Bronchiolitis in adults should be diagnosed based on history, physical examination, chest imaging, and lung function studies**

   The wide range of clinical symptoms and severity can make diagnosis challenging. Useful clinical features consistent with the diagnosis include:

   (a) Preceding upper respiratory symptoms, including rhinorrhea and fever.

   (b) Signs/symptoms of respiratory distress: cough, dyspnea, tachypnea, wheezing, inspiratory crackles, and a mid-inspiratory squeak.

2. When bronchiolitis is suspected, **the most helpful tests are chest imaging, usually a high-resolution CT (HRCT) scan, and pulmonary function testing**. Viral testing is not routinely recommended.

   (a) Chest imaging studies

   - A **chest X-ray** is obtained most commonly to rule out bacterial pneumonia and to assess disease severity. Chest radiography is of limited usefulness in the diagnosis and may be normal or may show varying combinations and degrees of any of the following: hyperinflation, peripheral attenuation of the vascular markings, and nodular or reticular opacities.
   - **High-resolution chest CT scans** are most useful in identifying findings consistent with bronchiolitis.
     - Constrictive bronchiolitis:

       Inspiratory CT scans show the presence of centrilobular thickening, bronchial wall thickening, bronchiolar dilatation, the tree-in-bud pattern, and the mosaic perfusion pattern.

       Expiratory CT scans may show air trapping (the principal finding on CT and its severity correlates with lung function).
     - Proliferative bronchiolitis and organizing pneumonia: The predominant CT findings are bilateral areas of consolidation.

   (b) Pulmonary function testing

   - Constrictive bronchiolitis: normal or show obstructive changes with air trapping.
   - Proliferative bronchiolitis: a restrictive pattern is common.
   - Diffusing capacity is usually reduced in both types.
   - Resting hypoxemia is frequently present in both patterns.

Chest Imaging Studies

Chest radiography is of limited usefulness in the diagnosis and follow-up of patients with bronchiolitis and may be normal or may show varying combinations and degrees of any of the following: hyperinflation, peripheral attenuation of the vascular markings, and nodular or reticular opacities [15].

Inspiratory and expiratory CT scans are most useful in identifying findings consistent with bronchiolitis (Fig. 3.5). Bronchiolitis is suggested on inspiratory CT scans by the presence of centrilobular thickening, bronchial wall thickening, bronchiolar dilatation, the tree-in-bud pattern, and the mosaic perfusion pattern [15–21].

Cylindrical bronchiectasis is frequently associated with bronchiolitis [18]. Expiratory CT scans are important in the assessment of air trapping, which is a characteristic finding of partial airway obstruction [22]. Small peripheral centrilobular nodular parenchymal densities are nonspecific indirect signs of small airway diseases [21].

These hazy nodular opacities appear as focal rounded areas of increased ground glass attenuation, measuring less than 1 cm in size [21]. The predominant CT findings associated with proliferative bronchiolitis and organizing pneumonia are bilateral areas of consolidation. These are usually found in a predominantly peribronchial or subpleural distribution of the consolidation [20]. The findings are asymmetric and vary over time.

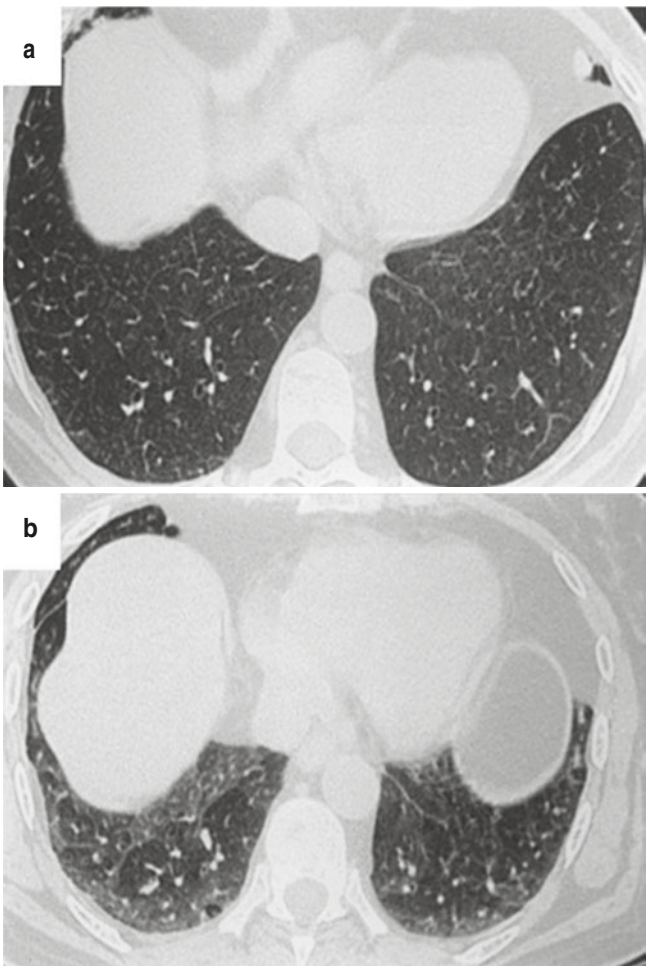

Fig. 3.5 (**a**) Normal inspiratory high-resolution CT scan image. (**b**) Expiratory high-resolution CT scan image showing characteristic mosaic pattern with areas of decreased and increased attenuation reflecting air trapping. Note that areas in which lung density remains virtually unchanged are indicative of substantial air trapping

Pulmonary Function Testing

In constrictive bronchiolitis, lung function may be normal or may show obstructive changes with air trapping. In proliferative bronchiolitis, a restrictive pattern is common. Diffusing capacity is usually reduced in both types, particularly as the disease progresses. Resting hypoxemia is frequently present in both patterns of bronchiolitis.

Lung Biopsy

In the majority of cases, an open or thoracoscopic lung biopsy is required to make a definitive diagnosis [3]. A transbronchial lung biopsy is often inadequate for diagnosis. Tissue confirmation may not be necessary in patients with a clear predisposition and typical HRCT. The histopathological lesions are often subtle, and specific attention must be directed at examination of the small airways, including step sectioning of the tissue with special stains (elastic stains) to identify remnants of the small airway walls.

Clinical Syndromes Associated with Bronchiolitis

Bronchiolitis Secondary to Inhalational Lung Injury

The inhalation of fumes, gases, mists, mineral dusts, or organic material can result in either a subtle or severe clinical illness. Silo-filler's disease is a well-studied example of bronchiolitis from the inhalation of nitrogen dioxide and dinitrogen tetroxide from air on the surface of the silage in agricultural silos [23]. After recovery from the acute illness, or in patients with no symptoms following exposure, recurrence or new onset of clinical illness is characterized by the progressive onset of cough and dyspnea associated with mild hypoxemia. Tachypnea is present, and crackles are usually heard. The radiographic pattern in this late stage may vary. A normal chest film may be seen; however, a miliary or discretely nodular pattern is believed to be characteristic of bronchiolitis obliterans. Physiological disturbances include hypoxemia at rest or with exercise and associated with a progressive and irreversible obstructive ventilatory defect.

Mineral Dusts

Pathological changes in the small airways (respiratory bronchiolitis) secondary to exposure to inorganic mineral dusts, including asbestos, silica, iron oxide, aluminum oxide, several different sheet silicates, and coal have been reported [24, 25]. The clinical relevance of the lesions found in these subjects awaits a better definition. Nevertheless, the development of airflow obstruction, rather than the classic restriction, is seen in subjects with inorganic mineral dust exposure.

Organic Dusts

Numerous agents are associated with the development of hypersensitivity pneumonitis. Although interstitial pneumonitis is seen in virtually 100% of patients with hypersensitivity pneumonitis and granulomas are seen in approximately 70%, bronchiolar lesions are seen in essentially all cases. The bronchioles contain granulomata within the walls or lumina or show tufts of granulation tissue as seen in bronchiolitis obliterans.

Volatile Flavoring Agents

Several reports have described the development of severe obstructive lung diseases in workers exposed to flavoring chemicals at microwave popcorn plants and flavoring production plants [26–30]. Chest radiographs showed hyperinflation in several cases. HRCT findings included diffuse cylindrical bronchiectasis and a mosaic pattern suggestive of air trapping [31]. This pattern suggests a predominant constrictive bronchiolitis pattern. Pathology consistent with obliterative bronchiolitis has been found [28].

Electronic cigarettes (e-cigarettes) are devices that produce an aerosol by heating a liquid containing various chemicals, including harmful substances, e.g., nicotine, flavorings, vitamin E acetate, volatile organic compounds, heavy metals, ultrafine particles, and carbonyl compounds [32, 33]. E-cigarettes can also be used to deliver tetrahydrocannabinol (THC). The use of e-cigarettes ("vaping" or "dabbing") has been associated with the development of severe lung diseases, including bronchiolitis obliterans [34, 35].

Infectious Causes of Bronchiolitis

Infection is the most common cause of acute bronchiolitis. Infectious causes of bronchiolitis are more commonly found in children than in adults. Acute bronchiolitis in older children and young adults has been primarily associated with *Mycoplasma pneumoniae*; however, a number of other viruses (e.g., respiratory syncytial virus (RSV), especially in the elderly) and bacterial agents have been identified [2, 3]. The clinical presentation of infectious bronchiolitis in adults is not well-defined, and no systematic study has been reported. Most have a history of an upper respiratory tract illness that precedes the onset of dyspnea with exertion, cough, tachypnea, fever, and wheezing. Measles, varicella zoster, and pertussis have been reported to cause bronchiolitis obliterans in adults. A number of adults have developed an acute or subacute diffuse ventilatory obstruction that has occasionally been fatal.

Idiopathic Forms of Bronchiolitis

Several idiopathic clinicopathological syndromes associated with prominent involvement of the bronchioles have recently been reported. Although no specific etiology has been identified for these syndromes, the constellation of findings in reported cases suggests that these are unique syndromes that must be distinguished from more common problems, such as COPD, pneumonia, or pulmonary fibrosis.

Cryptogenic adult bronchiolitis is a rare clinicopathological syndrome that is found in middle-aged women who have a nonproductive cough, shortness of breath, or other nonspecific chest complaints, usually of a relatively short duration (6–24 months) [36–39]. Few cases have been reported, and it is not entirely clear whether all of those reported are the same entity. The disorder is largely diagnosed by exclusion and requires a high index of suspicion, along with an awareness of its unique clinical features.

Airway-centered interstitial fibrosis is characterized by chronic cough and progressive dyspnea [8]. Most cases have not been smokers [40]. A history of possible inhalational exposures has been found in the majority of cases [9]. It is speculated that this is not a unique and specific disease but may be a response to some occupational or environmental agent (especially hypersensitivity pneumonitis) or chronic aspiration [9, 10, 41–45]. Pathologically, airway-centered interstitial fibrosis is characterized by central-bronchiolar or centrilobular patchy distribution, peribronchiolar fibroplasia associated with smooth muscle hyperplasia, and hyperplasia of smooth muscles in vessel walls and extending around toward the lung parenchyma. Pulmonary architectural reconstruction, metaplastic bronchiolar epithelium (honeycomb lung formation under a microscope), and subpleural focal pulmonary fibrosis were also seen.

Connective Tissue Diseases

Bronchiolitis occurs infrequently in connective tissue diseases and is common in patients with rheumatoid arthritis (especially in association with Sjögren's syndrome), both constrictive bronchiolitis and follicular bronchiolitis. The majority of patients are middle-aged women with seropositive rheumatoid arthritis. The clinical manifestations include an abrupt onset of dyspnea and dry cough, often associated with inspiratory crackles and a mid-inspiratory squeak. A positive rheumatoid factor is present, often at high levels (1:640–1:2560). Most patients have a chronic course. The prognosis is poor, with early deaths reported [46].

Organ Transplantation

"Bronchiolitis obliterans syndrome (BOS)," manifested by progressive airflow obstruction, is a frequent, noninfectious, post-transplantation respiratory complication [47]. The incidence of bronchiolitis obliterans among single lung recipients is approximately 20%; in double or bilateral sequential single lung recipients, the incidence is 12% [48]; however, double lung recipients showed a better chance of survival despite developing BOS compared to single lung recipients [49]. Bronchiolitis obliterans is the main pulmonary complication in long-term survivors of heart–lung transplantation. The prevalence has been estimated to be as high as 65% at

5 years. This syndrome has a variable clinical course. Common symptoms include nonproductive cough, mild malaise, and fatigue. Eventually, all subjects develop dyspnea. Physical examination is usually normal, but inspiratory squeaks may be heard. Crackles are uncommon. Progressive airflow limitation, secondary to small airway obstruction, is the hallmark of the bronchiolitis obliterans syndrome. A reduction in the diffusing capacity of the lungs for carbon monoxide (DLCO) is common. Hypoxemia and hypocapnia are almost always present. Approximately 50% of all deaths after the first year post-transplantation are due to bronchiolitis obliterans.

Hematopoietic Stem Cell Transplantation

Bronchiolitis obliterans syndrome may affect up to 6% of HSCT recipients and dramatically alters survival, with overall survival of only 13% at 5 years. Cases appear after the first 100 days post-transplantation, usually in the setting of chronic graft-versus-host disease [50]. Graft-versus-host disease has been postulated to play a role in the development of this lung disease. Bronchiolitis obliterans is most prevalent in patients following allogeneic transplantation but is also seen with autologous bone marrow transplantation. The prognosis is variable—patients have had progressive or persistent disease; many have died secondary to respiratory failure (40–65% of subjects).

Drug-Induced Bronchiolitis

Bronchiolitis, usually with organizing pneumonia, has been reported in association with a number of drugs. Most reports are of single cases or small case series.

Diffuse Panbronchiolitis

A familial occurrence has been described, with a significant increase in human leukocyte antigen (HLA)-Bw54 (63% frequency) [51]. Because HLA-Bw54 or its related haplotype is primarily confined to some mongoloid races (e.g., Japanese, Chinese, and Koreans), the genetic and ethnic background observed with this unique syndrome may be explained. Environmental factors also appear important because the disorder is highly uncommon in persons of Asian ancestry living abroad.

Diffuse panbronchiolitis is more prevalent in men, with a 2:1 men-to-women ratio. The peak incidence occurs between the fourth and seventh decades of life; the mean age at presentation is 50 years. Chronic sinusitis is present in 75–100% of cases. Sinus symptoms often precede chest symptoms by years or decades. Chronic cough with expectoration of copious purulent sputum, exertional dyspnea, and wheezing are the most common clinical manifestations. Cigarette smoking or occupational exposures have not been shown to be predisposing factors. Physical examination reveals coarse crackles; clubbing is not a feature.

The most characteristic laboratory abnormality is persistent marked elevation of serum cold agglutinins. Mycoplasma antibody titers are negative. Rheumatoid factor may be elevated. Immunoglobulin levels are usually normal. BAL fluid studies reveal marked neutrophilia.

A chest radiograph often reveals diffuse small nodular opacities up to 2 mm in diameter. A reticular "airway" pattern may be evident with more advanced disease. Hyperinflation may also be present. HRCT better reflects the clinical stages and pathology. On HRCT scans, the nodular shadows are distributed in a centrilobular manner, often extending to small branching linear areas of attenuation. The nodular and linear densities correspond to thickened and dilated bronchiolar walls with intraluminal mucus plugs. Peripheral air trapping may be present. Bronchiectasis may be prominent in advanced disease. Pulmonary function tests reveal marked obstruction and hypoxemia.

Treatment

Constrictive Bronchiolitis

Constrictive bronchiolitis tends to be progressive and less responsive to therapy. Macrolide antibiotics are commonly used in the long-term management of bronchiolitis, largely based on their success in improving symptoms, lung function, and mortality in patients with diffuse panbronchiolitis (see below) [52]. Inhaled bronchodilators and cough suppressants are used to control the cough.

In the setting of rheumatoid arthritis, any potential culprit medications (e.g., penicillamine, gold) should be discontinued. High-dose systemic glucocorticoids have been used with variable success. The tumor necrosis factor-alpha (TNF-alpha) inhibitors etanercept and infliximab have been suggested as possible treatment for constrictive bronchiolitis associated with rheumatoid arthritis [53]. It is not known whether they would be beneficial in other forms of constrictive bronchiolitis.

A variety of therapies have been tried for BO/BOS, but no well-established protocol has been developed [47]. Bronchiolitis obliterans following organ transplantation is often managed by intensification of immunosuppression. Gastroesophageal reflux disease (GERD) is prevalent in lung transplantation recipients, and non-acid reflux has been associated with the development of bronchiolitis obliterans syndrome [47, 54]. Aggressive therapy for GERD, possibly including surgery, has been proposed to prevent progression

of bronchiolitis obliterans syndrome, although additional studies are needed [47]. Other potential approaches include photopheresis, total lymphoid irradiation, long-term azithromycin, plasmapheresis, and inhaled cyclosporine [47].

Diffuse Panbronchiolitis

The optimal therapy is still unknown. Low doses of oral erythromycin (200–600 mg/day) or clarithromycin (250 or 500 mg/day) or azithromycin have been used for most patients [55]. Erythromycin impairs neutrophil chemotaxis, neutrophil superoxide production, and neutrophil-derived elastolytic activity and decreases the number of neutrophils in BAL fluid, following challenge with Gram-negative bacteria [2, 3]. Erythromycin has also been shown to reduce the circulating pool of T lymphocytes bearing HLA-DR, a marker of cellular activation. Azithromycin appears to work by targeting cytokine production, proliferation, apoptosis, and autophagy of T cells [56].

Follicular Bronchiolitis

Follicular bronchiolitis is usually treated as part of the underlying disease, whether it is a connective tissue or associated with immunodeficiency [3]. Successful treatment of RA-related follicular bronchiolitis with macrolides has been reported [57]. Corticosteroids have been used, with relapses occurring when steroids are tapered [58].

Airway-Centered Interstitial Fibrosis

The optimal treatment for airway-centered interstitial fibrosis is not known. Glucocorticoid therapy has been tried with limited success.

Proliferative Bronchiolitis

Glucocorticoids are commonly employed and are quite effective in cases of proliferative bronchiolitis, particularly when it is associated with organizing pneumonia (e.g., cryptogenic organizing pneumonia). A common approach is to start with prednisone 0.5–1 mg/kg lean body weight per day to a maximum of 60 mg per day, administered as a single oral dose in the morning. Prednisone is gradually tapered over 3–6 months. Relapses have been reported with the premature cessation of glucocorticoid therapy in some of these patients.

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Allergic Bronchopulmonary Aspergillosis

4

Danielle Stahlbaum, Karen Patterson, and Mary E. Strek

Clinical Vignette

A 30-year-old man with a history of severe persistent asthma since childhood was referred for consultation for presumed chronic *Aspergillus* infection that was being treated with voriconazole therapy.

He was a lifelong nonsmoker. His lifelong asthma was associated with atopic dermatitis and chronic allergic rhinosinusitis. He was treated with an inhaled corticosteroid and a long-acting beta-agonist. Two years prior to the current presentation, he was diagnosed at an outside hospital with "semi-invasive" *Aspergillus* pulmonary infection after presenting with chills, cough productive of sputum, and shortness of breath. Chest CT imaging showed a right middle lobe pulmonary opacity. Sputum culture and CT-guided lung biopsy grew *Aspergillus fumigatus*. He was treated with oral itraconazole for 6 months with clinical and radiographic improvement.

Two years later, he noted fever, cough productive of brown sputum, dyspnea, and wheezing. Repeat chest CT imaging showed a large right lung opacity and smaller left lung opacities, and the sputum culture grew *Aspergillus fumigatus* for which he was begun on voriconazole 200 mg twice a day (BID) for presumptive recurrent *Aspergillus* infection. Our evaluation revealed a thin man with no distress. On auscultation, he had no wheezing. There was no clubbing. White blood cell count was 13.4 k/μL with 8.3% eosinophils. Serum immunoglobulin E was 5355 IU/mL. Spirometry showed moderately severe airflow obstruction with a forced vital capacity (FVC) of 4.30 L (78% predicted) and a forced expiratory volume in the first second (FEV_1) of 2.28 L (53% predicted) with 32% improvement after the use of the inhaled bronchodilator. Reviews of prior and current chest radiographs (Fig. 4.1) and CT chest imaging (Fig. 4.2) by thoracic radiology revealed additional findings of central bronchiectasis, hyperdense mucus plugging, and fleeting parenchymal opacities.

The constellation of severe persistent asthma, bronchiectasis, eosinophilia, elevated IgE level with *Aspergillus* in the sputum, and CT scans showing hyperdense mucus plugging with fleeting pulmonary parenchymal opacities was highly suggestive of allergic bronchopulmonary aspergillosis (ABPA). The diagnosis was further solidified by a high-titer positive serum IgE to *A. fumigatus*. The patient declined oral corticosteroids but preferred to continue on voriconazole with resolution of the cough, sputum, dyspnea and wheezing, a decline in the absolute eosinophil count to 500 and serum IgE to 2425 IU/mL, and improvement in the parenchymal opacities. After 6 months of therapy, he required dose reduction of the voriconazole to 200 mg daily for elevated levels of hepatic function tests. After a total of 12 months of therapy, at which time the serum IgE was 1000 IU/mL, voriconazole was discontinued. Two months later, he noted fatigue, cough with brown mucus plugs, and wheezing. His serum IgE was increased to 3814 IU/mL. He was restarted on voriconazole 200 mg daily, but, despite therapeutic levels, he did not improve. What therapies should be prescribed?

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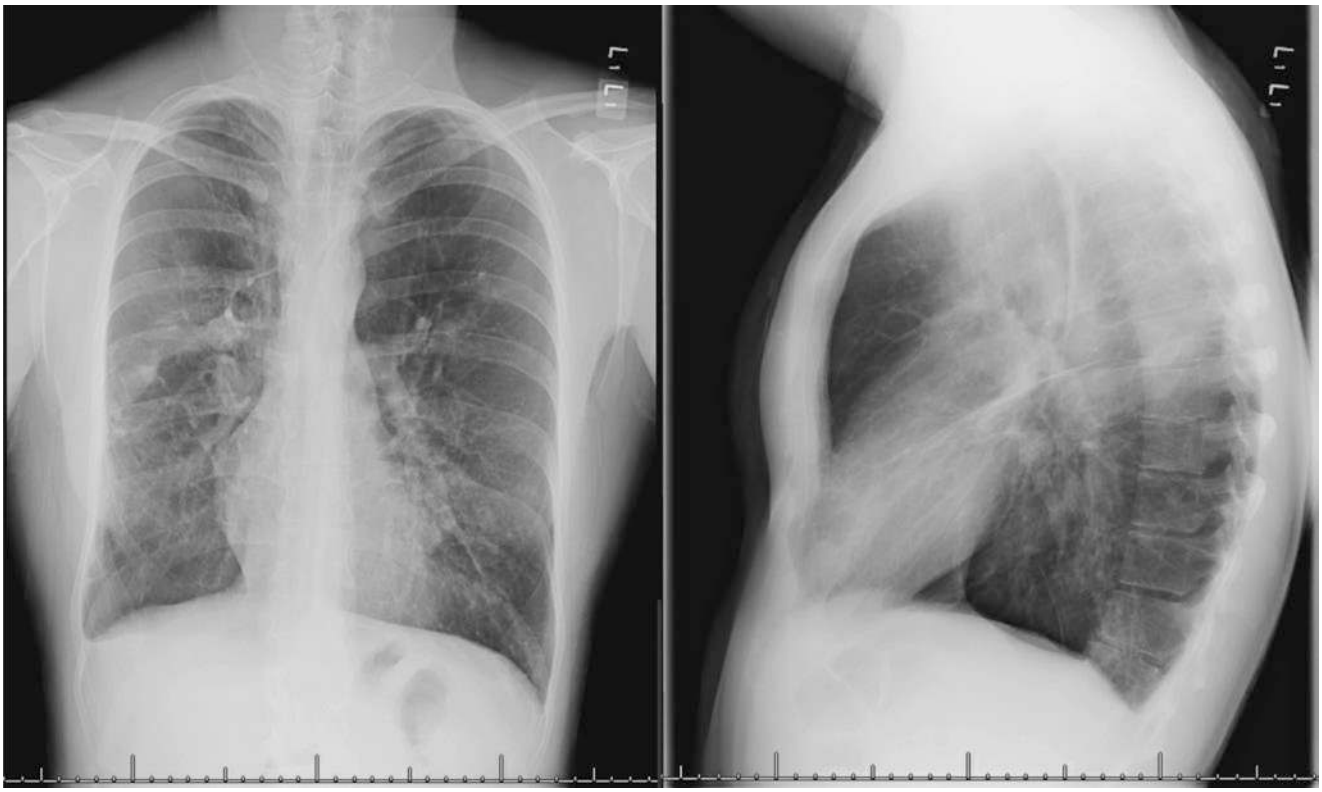

Fig. 4.1 PA (left) and lateral (right) radiographs demonstrating hyperinflated lungs and bronchiectasis with mucoid impaction in a patient with ABPA

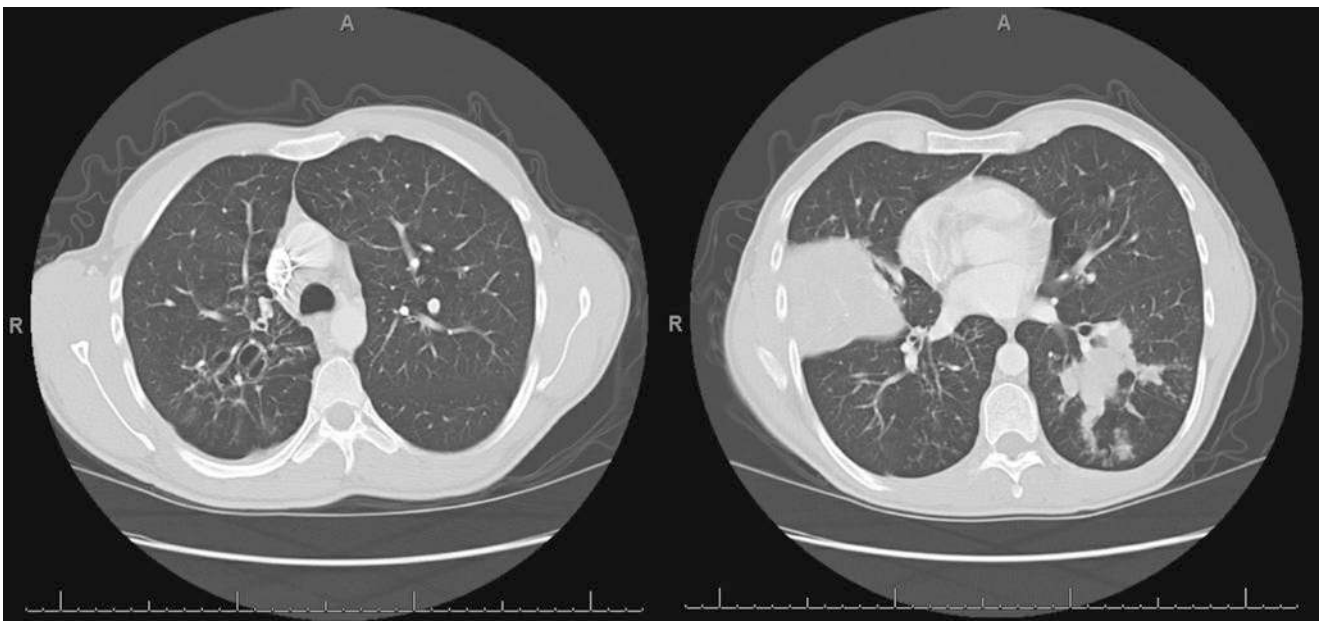

Fig. 4.2 Axial HRCT images of a patient with ABPA demonstrate cylindrical bronchiectasis of the right lower lobe (left) as well as bronchiectasis and severe mucoid impaction of the left lower lobe and pulmonary consolidation of the right upper lobe (right)

Background and Epidemiology

Aspergillus is a genus of mold that is commonly found in soil and decaying organic material [1]. It is not the most prevalent fungi worldwide; however, it is one of the most ubiquitous with airborne conidia [1, 2]. The conidia are small enough in diameter to remain airborne both outdoors and indoors when released into the atmosphere. Analysis of air samples from various settings demonstrate that humans inhale hundreds of *Aspergillus* conidia daily [3–6]. The conidia reach the distal and terminal airways where they germinate and grow if a favorable environment is present. The pathogenicity of *Aspergillus* depends on the characteristics of the host. Allergic bronchopulmonary aspergillosis (ABPA) is a complex pulmonary disease resulting from an allergic immune response to *Aspergillus*, complicating the clinical course of patients with asthma or cystic fibrosis (CF). A similar syndrome called allergic bronchopulmonary mycosis (ABPM) can also occur with exposure to other mycoses.

In ABPA, germination of *Aspergillus* and growth of hyphae in the airways trigger an airway-centric T helper 2 (Th2) cell- and immunoglobulin E (IgE)-mediated hypersensitivity response, leading to bronchospasm and bronchiectasis. Patients with ABPA commonly present with wheezing, cough, and pulmonary infiltrates with central bronchiectasis. These features are nonspecific and overlap with other pulmonary diseases, which can lead to delays in diagnosis [7]. ABPA is often underdiagnosed, especially in areas with high rates of tuberculosis in which a misdiagnosis of ABPA as pulmonary tuberculosis may occur [8].

Patients with underlying airway diseases related to asthma and CF are most susceptible to ABPA. The prevalence of ABPA in patients with asthma widely varies depending on the region studied: Ireland 0.7% [9], New Zealand 3.5% [10], Saudi Arabia 2.7% [11], China 2.5% [12], Russia 4% [13], and North India 12.9–21.7% [14, 15]. A meta-analysis demonstrated a pooled prevalence of 12.9% of ABPA in patients with asthma in specialty referral clinics [16]. The global burden of ABPA is estimated to be 4.8 million patients of 193 million asthma patients according to a scoping review by Denning et al. [17].

The prevalence of ABPA appears to be higher in patients with CF than in those with asthma. As is the case with ABPA in asthma, the prevalence of ABPA in CF varies geographically. The Epidemiologic Registry of Cystic Fibrosis found a pooled ABPA prevalence of 7.8% in patients with CF in Europe [18]. The Epidemiologic Study of Cystic Fibrosis, a large multicenter observational registry from the United States and Canada, found a prevalence of 2% with a range of 0.9% in the southwestern region to 4% in the west [19]. Obtaining more definite prevalence rates of ABPA is limited by the small number of studies and the inconsistency with which diagnostic criteria are used. There is no clear gender predilection among all patients with ABPA; a male predominance was reported in one study of CF patients with ABPA, but this finding was not replicated in another study [18, 20]. There are also rare cases of ABPA that have been reported in patients without asthma or cystic fibrosis including patients with chronic obstructive pulmonary disease (COPD) [21], sarcoidosis following infliximab therapy, [22] and previous tuberculosis [23, 24].

Pathophysiology

The pathophysiology of ABPA is complex, involving genetic alterations in innate and adaptive immunity in an allergic host and resulting in persistence of germinated *Aspergillus* in the airways. Although the pathogenesis of ABPA is incompletely understood, the continued presence of fungal hyphae, in turn, leads to T-lymphocyte activation and inflammatory cell recruitment with cytokine and immunoglobulin release. The resultant airway inflammation causes increased mucus production, bronchial hyperreactivity, and, over time, bronchiectasis and pulmonary fibrosis.

In people with an appropriate milieu of genetics and a predisposing condition, the presence of fungal hyphae in the airways leads to a robust hypersensitivity reaction. *Aspergillus* conidia lack immunogenicity due to the presence of a surface hydrophobin layer, which prevents recognition by the immune system [25]. Thick mucus in the airways as well as decreased mucociliary clearance in the case of patients with CF may disrupt the normal process of conidia removal, allowing the fungus to germinate into hyphae that are immunogenic [26]. Proliferation of *Aspergillus* leads to a high antigen burden. *Aspergillus* produces proteases that damage the airway epithelium, leading to desquamation and loss of the mechanical barrier [20, 27]. The proteases also induce the release of pro-inflammatory proteins such as interleukin (IL)-6, IL-8, and monocyte chemoattractant protein-1 [27]. Serine protease activity in *Aspergillus fumigatus* has been shown to induce expression of the *MUC5AC* gene in bronchial epithelial cells, leading to mucin synthesis, which also contributes to decreased airway clearance [28]. Along with these events, the innate immune system responses lead to the release of further pro-inflammatory cytokines and chemokines with a significant inflammatory response [29].

Antigen-presenting cells such as dendritic cells process the fungal antigens for presentation and release a variety of specific cytokines. Antigen presentation to naïve T lymphocytes in the bronchoalveolar lymphoid tissues primes and activates the T cells [30]. In ABPA, the T-cell response is polarized toward a Th2 phenotype [29]. The Th2 phenotype is not dependent on a specific *Aspergillus fumigatus* antigen and

occurs irrespective of which *Aspergillus* antigen is recognized [31]. Th2 cells release IL-4, IL-5, and IL-13, which causes an influx of additional inflammatory cells such as neutrophils, eosinophils, and mast cells [27]. IL-4 is associated with B-cell isotype conversion to immunoglobulin E production. IL-4 and IL-13 increase expression of the vascular cell adhesion molecule-1 (VCAM-1) protein on endothelial cells, which increases recruitment of eosinophils and other immune cells and enhances IgE and IgA Fc receptor expression on eosinophils [29, 32]. Locally produced IgE activates mast cells. The degranulation of mast cells and eosinophils results in vasodilation and bronchoconstriction [29].

Host Characteristics

ABPA predominantly afflicts patients with underlying airway diseases, such as asthma or CF. Although the prevalence rate of ABPA among patients with CF is higher than that among patients with asthma, more patients with ABPA have asthma as their comorbidity, given the much higher background prevalence of asthma in the general population.

Aspergillus is ubiquitous in the environment and frequently inhaled, yet only a small fraction of patients with asthma or CF develop ABPA [3–6, 17–19]. The reason for this remains unclear, but genetic attributes are believed to contribute to ABPA risk. A study of 164 patients with asthma and ABPA demonstrated a familial rate of 4.9% of ABPA in first-degree relatives [33]. Gene association studies have demonstrated an association between ABPA and single-nucleotide polymorphisms in the following genes: *IL4RA* [34, 35], *IL10* [36], *IL13* [35], *TLR3* [35], *TLR9* [37], *MBL2* [38], and *SP-A2* [39]. Mutations in the *cystic fibrosis transmembrane conductance regulator (CFTR)* gene have also been associated with ABPA [40]. There is a higher-than-expected frequency of ΔF508 mutations in patients with non-CF-related ABPA compared to that in the general population [41]. A study by Chauhan et al. found that allelic diversity in the major histocompatibility complex class II genes for human leukocyte antigen (HLA)-DR2 and HLA-DR5 contributes to the susceptibility to ABPA, whereas the HLA-DQ locus may confer resistance to the development of ABPA [42]. Taken together, these studies suggest a complex relationship between potentially multiple genetic factors in a host genetically susceptible to developing ABPA.

Beyond genetic risk factors, most patients also have concomitant atopy including allergic rhinitis and atopic dermatitis in addition to asthma or cystic fibrosis [32].

Asthma often presents in childhood, but ABPA associated with asthma is largely a disease of adulthood [33]. Although speculative, aging-related changes in airway function and immune responses, or airway damage accumulated over many years of disease, may contribute to the higher risk in adulthood. Age of onset for ABPA associated with CF is more variable; childhood disease is observed but in one study was rare among patients younger than 6 years of age [18]. Historically, patients with CF had a reduced life expectancy, and reaching adulthood was uncommon. With dramatic improvements in clinical care, many patients with CF now reach adulthood with the average life expectancy ranging from 37 to 40 years of age [43]. Updated studies documenting the burden of ABPA among adults with CF are needed and will be illuminating with regard to the role of age in ABPA risk.

The regional rates of ABPA in asthma vary around the world [44]. Yet, when corrected for variations in the background rates of asthma, geography and other environmental factors have not been shown to vary the risk of ABPA. *Aspergillus* spores are ubiquitous in the environment around the globe and are virtually impossible to avoid. Even as environmental conditions differentially promote fungal growth and aerosolization of spores, the finding that geography is not implicated as an asthma-independent risk factor for asthma-associated ABPA argues against a dose-dependent effect of exposure in most cases. More comprehensive global surveys, which compare ABPA rates among patients with asthma according to the geographic region, are necessary to confirm this. These findings in asthma are in contrast to those in CF, in which regional differences in the prevalence of ABPA have been demonstrated, although not explained [19]. Modeling, which incorporates predicted climate changes, indicates that sensitization to fungal antigens may increase. Fungal spore production increases with increased environmental CO_2 concentrations [45]. Therefore, it will be important to track the incidence of ABPA in coming years and continue surveillance for the role of environmental factors in the development of allergic fungal pulmonary diseases.

Clinical Manifestations

Symptoms

The symptoms of asthma and CF typically worsen with the development of ABPA. Accordingly, patients with ABPA can present with new or worsening cough, shortness of breath, wheezing, and increase in sputum production [46, 47]. Patients may also develop fevers, fatigue, and weight loss. Thick, viscous mucus production is common with expectoration of tan to brownish black mucus plugs noted in some but not all patients. Hemoptysis secondary to airway inflammation and bronchiectasis can occur. Patients may experience mild or minimal symptoms but may otherwise present with immunological and radiographic signs, which support a diagnosis of ABPA [48]. ABPA should be suspected in patients with difficult-to-control or corticosteroid-

dependent asthma as well as in patients with CF who have a progressive pulmonary function decline.

Laboratory Evaluation

Skin Testing

Immediate cutaneous hypersensitivity to *Aspergillus* antigens is a classic finding in ABPA and part of the current diagnostic criteria. The test can be performed with a skin prick test or an intradermal injection. Development of a wheal and erythema within 1 min of administration of the antigen reflects the presence of immediate cutaneous hypersensitivity. In ABPA, the sensitivity of a positive result to antigens derived from *Aspergillus fumigatus* is around 90% [49].

Serum Precipitins

The presence of precipitating IgG antibodies against extracts of *Aspergillus fumigatus* in patients with ABPA was first described by Pepys et al. in 1959 [50]. Longbottom and Pepys further refined the significance of the presence of serum precipitins with an agar gel double-diffusion test and immunoelectrophoresis on *Aspergillus* in a study comparing the serum from 60 presumed normal controls, 397 asthma patients, 93 asthma patients with transitory pulmonary infiltrations and blood eosinophilia, 66 patients with radiographic, surgical, or postmortem evidence of mycetoma, and 185 patients with other pulmonary diseases [51]. A higher percentage (63%) of the patients with asthma with transitory pulmonary infiltrations and blood eosinophilia had positive and stronger precipitation reactions compared to patients with only asthma (9%). An additional study found positive *Aspergillus fumigatus* precipitins in 69% of patients with similar ABPA-type features [52].

Eosinophil Count

Peripheral eosinophilia is a common finding in ABPA. It is incorporated into the diagnostic criteria, but its presence is not obligatory to make a diagnosis. The cutoff value for elevated peripheral eosinophil count is >500 cells/μL in a corticosteroid-naïve patient [46]. Sputum eosinophilia is also present in ABPA with increasing levels of sputum eosinophilia demonstrated to correlate with the severity of bronchiectasis present on a high-resolution CT scan (HRCT) [53].

Total Serum Immunoglobulin E Levels

In 1972, Patterson et al. demonstrated that elevated total serum IgE levels may aid in diagnosis of ABPA and that they were associated with acute flares of disease [54]. Total serum IgE levels are incorporated as part of the formal diagnosis of ABPA with a level > 1000 IU/mL the criteria for a positive result; although if a patient meets all other ABPA criteria, a lower level may be acceptable [46]. The earliest measurement of total serum IgE should be used in the diagnosis of ABPA as levels may decline with treatment. Of note, serum IgE levels are often reported in different units around the world, leading to misapplied cutoff values and misinterpretation of the normalcy of results (1 IU/mL is equivalent to 2.4 ng/mL) [46]. Total serum IgE levels very often do not return to normal ranges even when patients are in remission. Serial monitoring of total serum IgE levels should be done while following patients, as an increase in the IgE levels may signal an impending exacerbation.

Serum Antibodies Specific to *Aspergillus fumigatus*

An elevated level of *Aspergillus fumigatus*-specific IgE is a characteristic finding of ABPA and is included as part of the diagnostic criteria. Experts recommend a value >0.35 kUA/L as positive [46]. The presence of *Aspergillus fumigatus*-specific IgG is also included in the diagnostic criteria; however, it is not required for the diagnosis of ABPA if the other additional criteria are present [46]. *Aspergillus fumigatus*-specific IgG is not specific to ABPA and can be found in other *Aspergillus*-related pulmonary diseases.

Recombinant Antigens

New technology permits the cloning of specific proteins of *Aspergillus fumigatus*, allowing for the creation of recombinant antigens rather than crude extracts of *Aspergillus*. Studies have demonstrated that antibodies against the recombinant antigens rAsp f1, rAsp f3, rAsp f4, and rAsp f6 are elevated in patients with ABPA [55, 56]. Their use in the diagnosis of ABPA is under investigation.

Radiographic Imaging

Chest radiographs with fleeting pulmonary opacities and bronchiectasis should raise a suspicion for ABPA, especially in patients with underlying asthma or CF. Pulmonary opacities can reflect eosinophilic infiltration as well as mucus plugging, atelectasis, bronchoceles (mucus-filled dilated bronchi), or lobar collapse [57]. HRCT more precisely characterizes the pulmonary findings in ABPA compared to chest radiographs. HRCT classically shows consolidation with central cystic or varicose bronchiectasis involving multiple lobes (Fig. 4.3) and mucus-filled bronchi (Fig. 4.4) [58]. Bronchiectasis is defined as central if it is confined to the medial two-thirds or the medial half of the lungs [59]. Although central bronchiectasis is a characteristic finding in ABPA, bronchiectasis may extend to the periphery in some cases. Bronchiectasis typically involves the upper lobes. Centrilobular nodules, tree-in-bud opacities, and mosaic attenuation are other radiographic findings, which may be observed. Transient air-fluid levels may be seen in dilated

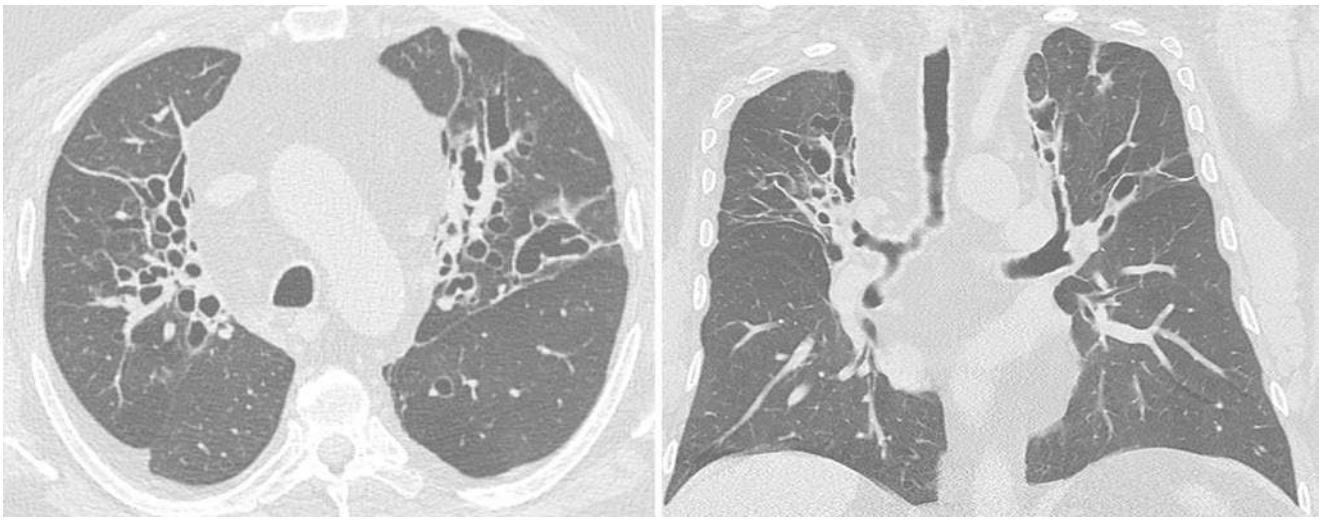

Fig. 4.3 Axial (left) and coronal (right) HRCT images depicting upper lobe predominate central varicose bronchiectasis and volume loss in a patient with ABPA

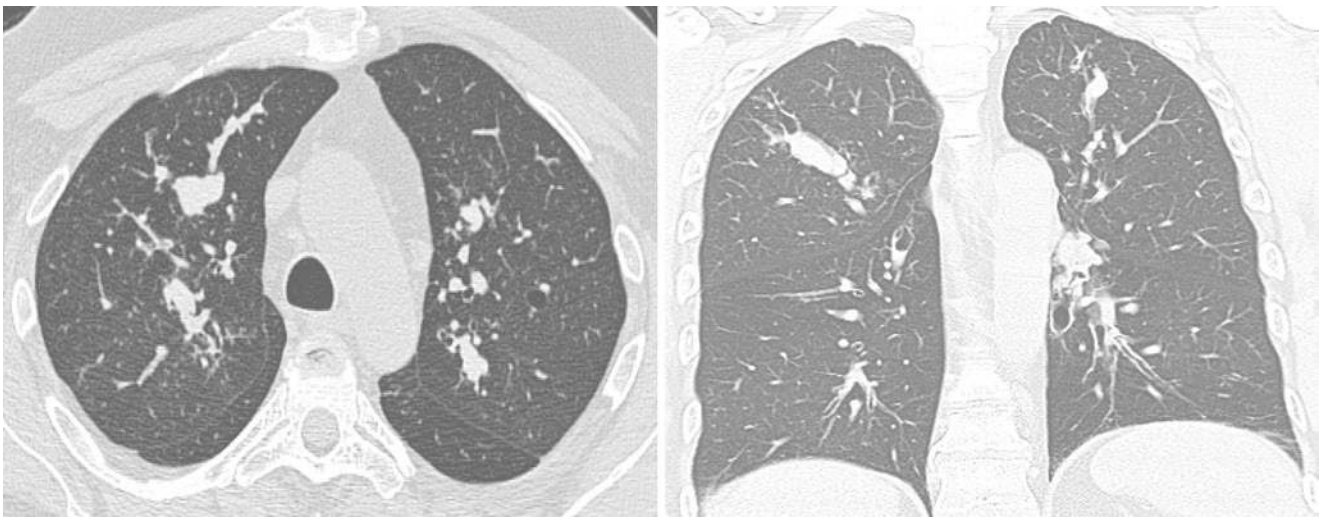

Fig. 4.4 Axial (left) and coronal (right) HRCT images depicting cylindrical bronchiectasis with severe mucoid impaction in a patient with ABPA

bronchi. Varying appearances of mucus plugging can occur, which have been described as "V," inverted "V," and "Y"-shaped shadows, toothpaste shadows, and finger-in-glove opacities [59]. High attenuation mucus, in which the mucus plug is visually denser than the paraspinal skeletal muscle or has a density of 100–170 Hounsfield units, is a characteristic radiologic sign in ABPA. High attenuation mucus was the most specific finding in the diagnosis of ABPA in a study of more than 300 patients [49]. In a setting of untreated or progressive disease, extensive bronchiectasis with airway cavitation and pleuropulmonary fibrosis can develop.

Pulmonary Function Testing

Pulmonary function test findings are nonspecific in ABPA, given the high frequency of additional pulmonary pathology [60]. Airflow obstruction is a common finding, but spirometry may also be normal. Partially reversible airflow obstruction is often noted in early or mild ABPA with fixed airflow obstruction seen in more advanced diseases. Decreased lung volumes can be seen if interstitial fibrosis has developed. The diffusing capacity may be normal or decreased. The primary role of pulmonary function testing in ABPA is to monitor disease progression over time.

Histology

Histology is not a requirement to diagnose ABPA. If a lung tissue is obtained, histopathological features include bronchocentric granulomatosis, tissue eosinophilia, and bronchial mucoid impaction with the mucin containing large numbers of eosinophils and Charcot–Leyden crystals [61]. Noninvasive fungal hyphae may also be present.

Diagnostic Criteria

Historical Diagnostic Criteria

There is no single test to diagnose ABPA. Rather, the diagnosis is based on a constellation of clinical, serological, and radiographic findings. The diagnostic criteria for ABPA have evolved over time. ABPA was first described in a case series of three patients in 1952 in England [62]. The patients had intermittent wheezing, fevers, sputum with brown plugs or flecks, eosinophilia in both the blood and sputum, and pulmonary infiltrates noted on chest X-ray. Hinson et al. suggested the following diagnostic criteria: recurrent pyrexial attacks, purulent sputum containing plugs or brown flecks, growth of *Aspergillus* from sputum culture, radiographic evidence of recurrent pulmonary collapse and consolidation in different areas, and peripheral eosinophilia of >1000 per mm^3. Following this initial report, Henderson described an additional series of 32 patients in which 22 patients presented with eosinophilia, sputum with abundant hyphae, episodic airway obstruction, and transient pulmonary opacities in multiple sites, which he referred to as allergic aspergillosis [63].

Rosenberg and Patterson Diagnostic Criteria

Rosenberg and Patterson published a case series of 20 patients with ABPA in 1977 in which they proposed a formal diagnosis of ABPA defined by the following seven primary criteria: episodic bronchial obstruction (asthma), peripheral blood eosinophilia, immediate skin reactivity to an *Aspergillus* antigen, precipitating antibodies against an *Aspergillus* antigen, elevated serum IgE concentrations, history of transient or fixed pulmonary infiltrates, and central bronchiectasis [64]. They proposed that the diagnosis of ABPA is highly likely if six of the seven criteria are met and certain if all seven criteria are present. Secondary criteria of finding *Aspergillus fumigatus* in repeated sputum samples from culture or microscopic examination, history of expectoration of brown flecks or plugs, and Arthus reactivity (late skin reactivity) to the *Aspergillus* antigen were supportive of a diagnosis of ABPA but were not required.

The Rosenberg–Patterson criteria for ABPA were the generally accepted diagnostic criteria for many years. Critiques of the Rosenberg–Patterson criteria include the equal importance given to each finding and lack of defined cutoff values for total IgE levels and eosinophil counts. In 1986, it was recognized that limited disease without central bronchiectasis could be present in patients who otherwise met the clinical and serological criteria for a diagnosis [65]. ABPA was subsequently further classified into allergic bronchopulmonary aspergillosis serological (ABPA-S) and allergic bronchopulmonary aspergillosis with central bronchiectasis (ABPA-CB). The 1977 Rosenberg–Patterson criteria were updated in 1991 by Schwartz and Greenberger [66]. In the updated criteria, elevated levels of *Aspergillus fumigatus*-specific IgE and *Aspergillus fumigatus*-specific IgG were included as the diagnostic criteria.

ISHAM Diagnostic Criteria

More recently, the International Society for Human and Animal Mycology (ISHAM) has formed a working group focused on ABPA in asthma patients to further refine the diagnostic criteria and proposed new diagnostic criteria in 2013 [46]. In these new criteria, a predisposing condition of asthma or CF must be present (Box 4.1). Both obligatory criteria and two of three additional criteria are then needed for a diagnosis of ABPA. Obligatory criteria are an elevated total serum IgE level and either immediate cutaneous hypersensitivity to an *Aspergillus* antigen or elevated levels of *Aspergillus fumigatus*-specific IgE. Additional criteria are the presence of precipitating or IgG-specific antibodies against *Aspergillus fumigatus,* radiographic pulmonary opacities consistent with ABPA, and a total eosinophil count >500 cells/μL in glucocorticoid-naïve patients. The elevated total eosinophil count may be a historical abnormality occurring at any point in the patient's clinical course. The ISHAM group removed the presence of bronchiectasis as a requirement for a diagnosis, given that ABPA may be present without bronchiectasis. The group established a total IgE level of >1000 IU/mL as the cutoff level for a diagnosis in an attempt to differentiate from severe asthma with fungal sensitization (discussed below); however, a diagnosis of ABPA should still be considered in patients with total IgE levels less than 1000 IU/mL if the other diagnostic criteria are met.

Box 4.1 ISHAM Group Diagnostic Criteria

Predisposing conditions
Asthma, cystic fibrosis
Obligatory criteria (both must be present)
Immediate cutaneous hypersensitivity to the *Aspergillus* antigen or elevated *Aspergillus fumigatus*-specific IgE levels
Elevated total IgE levels (>1000 IU/mL)
Additional criteria (at least two of the following)
Total eosinophil count >500 cells/μL in a steroid-naïve patient, may be historical
Positive precipitating antibodies or *Aspergillus fumigatus*-specific IgG antibodies
Radiographic pulmonary opacities consistent with ABPA

ISHAM International Society for Human and Animal Mycology, *IgE* immunoglobulin E, *IgG* immunoglobulin G

Box 4.2 Cystic Fibrosis Foundation Consensus Criteria

Obligatory criteria (all must be present)
Acute or subacute clinical deterioration not attributable to another cause
Elevated total serum IgE levels (>500 IU/mL, >1200 ng/mL)
Immediate cutaneous reactivity to the *Aspergillus* antigen or presence of *Aspergillus fumigatus*-specific IgE antibodies
Additional criteria (at least one of the following)
Demonstration of precipitins to *Aspergillus fumigatus*
Presence of *Aspergillus fumigatus*-specific IgG antibodies
New or recent chest imaging abnormalities that have not resolved with standard
Chest physiotherapy or antibiotics

IgE immunoglobulin E, *IgG* immunoglobulin G

Cystic Fibrosis Foundation Diagnostic Criteria

The diagnosis of ABPA presents unique challenges in patients with CF. The clinical manifestations of CF overlap with those seen in ABPA with many patients with CF demonstrating thick mucus, mucus plugging, and bronchiectasis at baseline. Diagnosing ABPA in patients with CF requires a high index of suspicion and often relies on serological testing to differentiate ABPA from a CF exacerbation. It is recommended to check annual serum IgE levels in patients with CF to screen for ABPA [20]. In 2003, the Cystic Fibrosis Foundation published consensus criteria for diagnosing ABPA in patients with CF [20]. According to this statement, the minimal diagnostic criteria for ABPA in CF require evidence of acute or subacute clinical deterioration not attributable to an alternative etiology, demonstration of *Aspergillus fumigatus*-specific IgE antibodies or immediate cutaneous reactivity to *Aspergillus* antigens, total serum IgE level > 500 IU/mL (1200 ng/mL) while off corticosteroids, and one of the following: serum precipitins to *Aspergillus fumigatus, Aspergillus fumigatus*-specific IgG antibodies, or new abnormalities on chest imaging that do not respond to antibiotics and chest physiotherapy (Box 4.2). The CF Foundation recommends repeating a total serum IgE level in 1–3 months in patients for whom there is a high suspicion for ABPA but prior total serum IgE levels were not sufficiently elevated to meet the diagnostic criteria.

Baxter ABPA in Cystic Fibrosis Diagnostic Criteria

Baxter et al. suggested new diagnostic criteria for ABPA complicating CF with incorporation of real-time quantitative polymerase chain reaction (PCR) (RT-PCR) for *Aspergillus* DNA and the galactomannan antigen [67]. In these criteria, four classes are proposed, with each class representing a diagnostic group. Class 1 consists of non-diseased CF patients with or without *Aspergillus* growth in sputum cultures but without a measurable immunological response and negative galactomannan. Class 2 represents serological ABPA with all immunological markers high as well as positive RT-PCR and positive galactomannan. Patients in class 3 are *Aspergillus* IgE-sensitized with or without *Aspergillus* noted in sputum but test negative for *Aspergillus fumigatus*-specific IgG and galactomannan. Patients in class 4 have *Aspergillus* bronchitis with negative IgE markers but positive *Aspergillus fumigatus*-specific IgG, RT-PCR, and galactomannan. Although this proposed class system addresses the potential confounders of *Aspergillus* sensitization and *Aspergillus* bronchitis, the RT-PCR and galactomannan testing may be impractical in non-tertiary care centers.

General Diagnostic Recommendations

In summary, when a diagnosis of ABPA is suspected in a patient with asthma or CF, a total serum IgE level and *Aspergillus fumigatus*-specific IgE levels should be obtained. If the total serum IgE level is >1000 IU/mL and the *Aspergillus fumigatus*-specific IgE levels are positive, then *Aspergillus fumigatus*-specific IgG or serum precipitins to *Aspergillus* and absolute eosinophil count should be measured and a CT of the chest performed to look for radiographic signs of ABPA.

Differential Diagnosis

"ABPA" is the diagnostic term associated with allergic bronchopulmonary diseases driven by the *Aspergillus* species; however, a range of other fungi, including the

Penicillium and *Curvularia* species, can cause a nearly identical clinical course and are described by the diagnostic term "allergic bronchopulmonary mycosis (ABPM)" [68]. When *Aspergillus*-specific testing is negative, but clinical features otherwise suggest ABPA, testing for allergic responses to other fungal agents may be helpful. Although *Candida albicans* has been implicated in a few case reports of ABPM, coexisting *Aspergillus* growth and allergic responses are often present and definitive evidence for *Candida*-driven disease is lacking.

Severe asthma with fungal sensitization (SAFS) is another disease that may be confused with ABPA, particularly in patients with ABPA without bronchiectasis. The diagnostic criteria of SAFS include the presence of asthma severe enough to warrant high-dose inhaled corticosteroids and frequent systemic corticosteroid use (which are not requirements for the diagnosis of ABPA) and a positive skin prick test for individual fungi, which does not have to be specific to the *Aspergillus* species [68]. The total IgE level may be elevated but is less than the threshold for ABPA, and serum precipitins testing should be negative. An important distinction from ABPA is the absence of radiographic findings suggestive of ABPA in SAFS.

Beyond ABPA and SAFS, a range of other serious pulmonary diseases are caused by the *Aspergillus* species, including chronic necrotizing aspergillosis, and should be considered in the differential diagnosis, given the potential overlap in clinical features. In contrast to ABPA, in which fungal growth does not violate the epithelial airway barrier, local tissue invasion is a feature of chronic necrotizing aspergillosis, which often leads to progressive tissue damage and parenchymal destruction if untreated. Progressive peribronchial opacities on serial chest imaging in patients with evidence of immune responses to *Aspergillus* should raise a strong suspicion for chronic necrotizing aspergillosis, particularly in the setting of systemic symptoms such as weight loss or fevers. Rather than elevated total and *Aspergillus*-specific IgE levels, anti-*Aspergillus* IgG immune responses are the hallmark serological finding. Moreover, rather than asthma, the underlying pulmonary conditions associated with an increased risk of chronic necrotizing aspergillosis include chronic obstructive pulmonary disease, sarcoidosis, a history of pulmonary tuberculosis, and prior radiation treatment.

Less frequently, other *Aspergillus* pulmonary diseases, such as aspergilloma, *Aspergillus* tracheobronchitis, or invasive pulmonary aspergillosis, may be confused with ABPA. Consideration of the underlying immune status of the patient and radiographic findings on HRCT imaging of the chest are often instrumental in directing the differential toward the most likely disease.

Allergic *Aspergillus* Sinusitis (AAS)

Allergic *Aspergillus* sinusitis is a noninvasive fungal rhinosinusitis that can sometimes be seen in patients with ABPA [69]. Similar to ABPA, allergic *Aspergillus* sinusitis is believed to be secondary to a hypersensitivity response to fungal hyphae in the sinus and is often found in patients with atopy and asthma [70]. The diagnostic criteria for allergic *Aspergillus* sinusitis include demonstration of sinusitis of one or more paranasal sinuses on imaging and nasal polyps in a patient with histopathological confirmation of a characteristic, eosinophil-rich, viscous sinus material called "allergic mucin" and the presence of fungal elements without an invasive fungal disease. Patients may also have peripheral blood eosinophilia, elevated total serum and *Aspergillus fumigatus*-specific IgE levels, and precipitating antibodies to *Aspergillus* antigens [71]. Potential treatments for AAS are systemic corticosteroids in combination with topical intranasal corticosteroid instillations and sinus surgery [72]. The use of systemic or topical antifungal therapy in the treatment of allergic *Aspergillus* sinusitis has unclear benefit [73, 74]. Referral to a specialist in otolaryngology is recommended.

Natural History

The natural history of ABPA is not well-defined, and the clinical course varies among patients [48, 65, 75]. ABPA may be quiescent and asymptomatic for long periods of time interspersed with episodes of relapsed symptoms and increased inflammation. The percentage of patients with ABPA that relapse ranges from 19% to 49% [48, 76, 77]. If untreated, the inflammatory process in the airways may result in irreversible tissue damage including development of bronchiectasis and pulmonary fibrosis in long-standing diseases. The latter, in turn, can lead to serious complications such as respiratory failure and cor pulmonale.

Previously, ABPA had been classified into five stages: acute, remission, exacerbation, corticosteroid-dependent asthma, and fibrotic [78]. The acute stage is defined by the presence of classic symptoms and signature laboratory findings at the time of diagnosis. Remission is defined as the period of time after diagnosis and treatment in which decreasing levels of total serum IgE and clearing of pulmo-

nary opacities on imaging are observed. Disease exacerbation is defined by the recurrence of symptoms of active disease after a period of remission or by the presence of worsening serological markers and imaging findings without a concomitant increase in symptoms in the case of an asymptomatic exacerbation. Corticosteroid-dependent asthma is defined by the occurrence of severe asthma when systemic corticosteroid treatment is stopped without an intervening period of clinical remission. Patients in the fibrotic stage typically have had ABPA for a prolonged duration with subsequent development of pulmonary fibrosis and fixed airflow obstruction.

In addition to proposing new diagnostic criteria, the ISHAM working group on ABPA created a new staging classification with more precise definitions (Box 4.3) [46]. They proposed a new stage 0 in which patients are asymptomatic with well-controlled asthma but are diagnosed with ABPA on routine screening for allergic response to *Aspergillus*. Stage 1 patients present with acute or subacute symptoms of ABPA and can be further divided into subgroups based on the presence or absence of mucoid impaction on imaging. A response to treatment defined as clinical improvement, clearing of radiographic opacities, and decrease in total serum IgE levels by at least 25% in 8 weeks defines stage 2, where an exacerbation of ABPA qualifies patients as having stage 3 disease. The ISHAM working group defined an ABPA exacerbation as an increase in total serum IgE levels by at least 50% compared to baseline with a concomitant worsening of clinical symptoms and radiological abnormalities. Patients are considered to be in stage 4 with clinical remission if there are no ABPA exacerbations for the first 6 months after discontinuing treatment. Patients in stage 5 have difficult-to-control asthma due to ongoing ABPA disease activity in spite of treatment. Stage 5 is further divided into two subtypes: treatment-dependent ABPA with patients requiring repeated courses of systemic corticosteroids and/or antifungal therapy to control ABPA and corticosteroid-dependent asthma with patients requiring systemic corticosteroids for control of asthma but with ABPA controlled based on radiographic findings and IgE levels. Finally, patients in stage 6 have advanced ABPA with significant bronchiectasis and/or pulmonary fibrosis with type 2 respiratory failure and/or cor pulmonale.

Articulating the concise and definitive stages of ABPA allows for standardization and clarity in communication within the medical field for the purposes of patient care and research; however, the numerical system can be misleading. Patients do not necessarily start and progress through the stages in a sequential order. Some patients are diagnosed at stage 6, whereas others may remain at stage 0. It is unclear how to identify which patients will have recurrent or progressive disease.

Box 4.3 ISHAM Stages of ABPA

Stage 0: Asymptomatic
Diagnosed with ABPA on routine screening
Stage 1: Acute
Acute or subacute symptoms of ABPA and fulfills the diagnostic criteria for ABPA without a prior diagnosis of ABPA
1A: Mucoid impaction documented on chest imaging or bronchoscopy
1B: Without mucoid impaction
Stage 2: Response
Response to treatment defined as clinical improvement, clearing of radiographic opacities, and decrease in total serum IgE levels by ≥25% of baseline in 8 weeks
Stage 3: Exacerbation
Worsening of clinical symptoms and radiographic abnormalities with an associated increase in total serum IgE levels by ≥50% of baseline
Stage 4: Remission
Clinical remission with no ABPA exacerbations for ≥6 months after discontinuing treatment
Stage 5: Treatment-dependent
Difficult-to-control symptoms due to ongoing ABPA disease activity or uncontrolled asthma in spite of treatment
5A: Treatment-dependent ABPA
Patients requiring prolonged systemic corticosteroids and/or antifungal therapy to control ABPA
5B: Corticosteroid-dependent asthma
Patients requiring systemic corticosteroids for asthma but ABPA controlled based on radiographic findings and IgE levels
Stage 6: Advanced ABPA
Significant bronchiectasis and/or pulmonary fibrosis with type 2 respiratory failure and/or cor pulmonale

ISHAM International Society for Human and Animal Mycology, *IgE* immunoglobulin E

Treatment

The overall goal of treatment of ABPA is to induce remission by suppressing the inflammatory process, thereby preventing further damage to the lungs while also minimizing the harmful side effects. Remission is defined as an improvement in clinical symptoms with an associated decrease in serum IgE levels and resolution of pulmonary opacities on chest imaging [46, 78]. There have been many different medications used in the treatment of ABPA with varying results (Table 4.1). These include inhaled and systemic corticosteroids, antifungal therapies, and monoclonal antibodies such as omalizumab and mepolizumab. Corticosteroids decrease the inflammatory response to *Aspergillus* but do not inhibit fungal growth. Antifungal therapy decreases the antigen bur-

Table 4.1 Selected studies of therapy for allergic bronchopulmonary aspergillosis (ABPA)

Medication	Study design	Outcomes	Reference
Inhaled corticosteroids			
Beclomethasone 400 μg QD vs. placebo for 6 mo	Double-blind trial of 32 asthma patients	No benefit over placebo	Br J Dis Chest 1979 [87]
Budesonide/formoterol 1600/24 μg QD	Retrospective case series of 21 oral corticosteroid naïve asthmatic ABPA-S patients	Control of asthma symptoms but continued rise in total IgE levels	Agarwal 2011 [88]
Systemic corticosteroids			
Prednisone 0.5 mg/kg QD × 1 wk then QOD	Case series of 20 asthma patients	"Complete remission" in all patients	Rosenberg 1977 [64]
Prednisone 0.5 mg/kg QD × 2 wk then QOD × 3 mo	Case series of 84 asthma patients	16 (19%) "remission without recurrent exacerbation," 38 (45%) corticosteroid dependent	Patterson 1986 [65]
Prednisolone 0.75 mg/kg QD × 6 wk, 0.5 mg/kg QD × 6 wk, then taper 5 mg every 6 wk	Case series of 126 asthma patients	All had "remission" at 6 wk, 25 (20%) "relapsed" during course of treatment, 17 (13.5%) corticosteroid dependent	Agarwal 2006 [48]
Methylprednisolone IV 10–15 mg/kg QD × 3 days every 4 wk until remission vs. prednisone 0.5–2 mg/kg QD for 2–4 wk with taper over 1–3 mo; all itraconazole 200–400 mg QD	Case series of 14 CF patients (9 IV vs 5 PO)	All with clinical improvement, increased FEV_1, reduced serum IgE levels, IV less medication adverse events than PO	Cohen-Cymberknoh 2009 [85]
High: prednisolone 0.75 mg/kg QD × 6 wk, 0.5 mg/kg QD × 6 wk, then taper 5 mg every 6 wk vs. Medium: prednisolone 0.5 mg/kg QD × 2 wk then QOD × 8 wk, then taper 5 mg every 2 wk	Prospective open label RCT of 92 asthma patients with acute ABPA	No difference in time to first exacerbation (H: 132 vs M: 100 days) and number of exacerbations (H: 18/44, 42%, M: 24/48, 50%). Similar improvement in lung function between both groups, less cumulative corticosteroid dose, and corticosteroid related adverse reactions in medium-dose group	Agarwal 2016 [84]
Antifungal therapy			
Itraconazole 200 mg BID vs. placebo × 16 wk; all prednisone >10 mg QD	Randomized double-blind trial of 55 asthma patients	Decreased prednisone dose and decreased serum total IgE levels in itraconazole (13/28, 45%) vs. placebo (5/27, 19%)	Stevens 2000 [90]
Itraconazole and prednisolone vs itraconazole 200–600 mg QD	Retrospective study of 21 CF patients (9 both, 12 itraconazole monotherapy)	Improved FEV_1 and decreased precipitins in all, total IgE levels decreased 42% itraconazole vs. 56% itraconazole/prednisolone	Skov 2002 [96]
Itraconazole 400 mg QD vs. placebo × 16 wk	Randomized double-blind trial of 29 asthma patients	Decreased serum total IgE and Aspergillus-specific IgG levels as well as fewer exacerbations with itraconazole vs placebo	Wark 2003 [92]
Voriconazole 300–600 mg QD or posaconazole 800 mg QD	Retrospective study of 20 asthma patients	"Clinical response" at 6 mo in 73% with voriconazole and 78% with posaconazole	Chishimbra 2012 [97]
Isavuconazole 200 mg TID × 2 days then 200 mg QD	Case report of 1 patient with asthma	Symptomatic improvement, decreased inhaled steroid dosing, and normalization of FEV_1	Jacobs 2017 [98]
Itraconazole 200 mg BID × 4 mo vs. prednisolone 0.5 mg/kg QD × 4 wk, 0.25 mg/kg QD × 4 wk, 0.125 mg/kg × 4 wk, then taper 5 mg every 2 wk	Prospective open label RCT of 131 asthma patients with acute ABPA	Higher rate of composite response at 6 wk in prednisolone (63/63, 100%) vs itraconazole (60/68, 88%), similar time to first exacerbation, number of exacerbations, and change in lung function. Higher rate of adverse events in prednisolone group	Agarwal 2018 [99]
Voriconazole 200 mg BID × 4 mo vs. prednisolone 0.5 mg/kg QD × 4 wk, 0.25 mg/kg QD × 4 wk, 0.125 mg/kg × 4 wk, then taper 5 mg every 2 wk	Open label RCT of 50 asthma patients with acute ABPA	No difference in rates of composite response, time to first exacerbation, number of exacerbations, and change in lung function. Higher rate of adverse events in prednisolone group	Agarwal 2018 [100]
Monoclonal antibodies			
Omalizumab 375 mg SQ every 2 wk × 4 mo vs placebo then 3 mo washout followed by cross-over	Open label RCT of 13 asthma patients with chronic ABPA	Decrease in exacerbations compared to placebo (2 vs 12 events), decrease in FeNO	Voskamp 2015 [103]
Omalizumab 300–600 mg SQ every 15 days	Retrospective study of 18 pediatric CF patients	Stabilization of lung function decline, decrease in corticosteroid daily dose, improvement in nutritional status, no adverse events	Perisson 2017 [104]

(continued)

Table 4.1 (continued)

Medication	Study design	Outcomes	Reference
Omalizumab 375 mg SQ every 2 wk, Mepolizumab 100 mg SQ every 4 wk	Case report of 1 asthma patient	Omalizumab—wean to prednisone 20 mg daily and stabilization of clinical decline, addition of Mepolizumab—complete weaning off of prednisone and improvement in functional status, decreased supplemental oxygen needs	Altman 2017 [107]
Omalizumab 600 mg SQ QD vs placebo × 6 mo, all patients receiving itraconazole and oral corticosteroids	Industry sponsored double-blind RCT of 14 CF patients	Terminated early due to lack of enrollment. High dropout rate (9/14). One or more serious side effects in Omalizumab 6/9 (67%) vs placebo 1/5 (20%)	Jat 2018 [105]
Mepolizumab 100 mg SQ every 4 wk	Case series of 2 asthma patients who refused treatment with steroids and antifungals	Improved symptoms, decrease in peripheral blood eosinophilia, improved FEV_1, no change in serum total IgE levels	Soeda 2019 [106]

ABPA allergic bronchopulmonary aspergillosis, *BID* twice a day, *CF* cystic fibrosis, *FeNO* exhaled nitric oxide, *FEV1* forced expiratory volume in 1 s, *Ig* immunoglobulin, *mo* months, *IV* intravenous, *PO* oral, *QD* every day, *QOD* every other day, *RCT* randomized control trial, *SQ* subcutaneous, *TID* three times a day, *wk* weeks

den, thereby also decreasing the immune response with a subsequent decrease in airway inflammation. In some cases of refractory ABPA, treatment with monoclonal antibodies is utilized but efficacy data are limited. Avoiding exposure to higher-than-average background fungal levels, such as during home renovation or farming, is a prudent recommendation. Smoking marijuana has been associated with *Aspergillus* exposure, and patients should be counseled that this may be an additional risk factor for ABPA and should be avoided [79]. When bronchiectasis is present, an airway clearance regimen may be beneficial. In a small clinical trial, the use of 7% hypertonic saline nebulization in addition to chest physiotherapy in patients with stable bronchiectasis led to an increase in the yield of mobilized sputum and increased the ease of sputum expectoration with decreased sputum viscosity [80]. The optimal treatment of ABPA depends on the severity of illness, exacerbation frequency, patient response to therapy, and medication adverse effects. Details regarding each medication class are considered below.

Corticosteroids

Systemic corticosteroids are the initial treatment of choice for ABPA [81, 82]. Corticosteroids are initiated at a medium or high dose and then tapered off to the lowest dose possible to maintain remission. There are no placebo-controlled studies of systemic corticosteroid use in ABPA, but years of clinical experience have demonstrated their effectiveness [64, 65, 78]. There are two common dosing regimens. In the medium-dose regimen, patients are started on prednisone 0.5 mg/kg/day for 1–2 weeks, then maintained on 0.5 mg/kg/day on alternate days for 6–8 weeks, followed by tapering of 5–10 mg every 2 weeks [83]. In the high-dose regimen, patients are started on prednisolone 0.75 mg/kg/day for 6 weeks, then 0.5 mg/kg/day for 6 weeks, followed by tapering of 5 mg every 6 weeks [48]. A randomized control trial of 92 patients with stage 1 ABPA complicating asthma in India found that the medium-dose regimen was as effective at preventing exacerbations and progression to the glucocorticoid-dependent stage of ABPA as the high-dose regimen with significantly smaller cumulative corticosteroid doses and fewer corticosteroid-related adverse reactions [84]. There is a paucity of data regarding treatment of ABPA complicating CF, but, similar to ABPA complicating asthma, corticosteroids are the foundation of treatment.

An alternative regimen of intermittent pulse dose intravenous corticosteroids was investigated in two open-label series of 13 patients with CF, with corticosteroid-dependent ABPA, who were not able to tolerate daily oral corticosteroid dosing due to significant side effects or because their disease remained uncontrolled on the oral daily regimen [85, 86]. They were administered 10–20 mg/kg per day of intravenous methylprednisolone on three consecutive days every 3–4 weeks. This regimen was generally safe, effective, and well-tolerated; however, long-term follow-up data are not available and the sample size was small.

Inhaled corticosteroids have been studied for the treatment of ABPA in an attempt to avoid the adverse effects associated with systemic corticosteroid therapy. A double-blind trial of 32 ABPA patients with asthma treated with inhaled beclomethasone showed no benefit of the inhaled corticosteroid over placebo therapy [87]. In a study of 21 patients with asthma and ABPA-S who were naïve to oral corticosteroids and who were administered the high-dose inhaled corticosteroid budesonide with formoterol, it was observed that asthma control improved but total serum IgE levels rose throughout the duration of the therapy, suggesting that the immunological activity underlying ABPA was not controlled [88]. If patients are also receiving itraconazole, then it is important to carefully consider the choice of the inhaled corticosteroid and also consider avoiding or reducing the dose of budesonide or fluticasone propionate, given known drug–drug interactions

[89]. Inhaled corticosteroids should not be used as monotherapy to treat ABPA but may be useful if additional control of the underlying asthma is required.

Antifungal Therapy

Antifungal therapy is generally used as adjunctive therapy along with corticosteroids to reduce the dose of corticosteroids or if corticosteroids alone are insufficient to induce remission [90–92]. In patients with recurrent exacerbations of ABPA, it is recommended to treat with a combination of glucocorticoids and itraconazole [90–92]. If antifungal therapy is used, then the selected drug should exhibit activity against the *Aspergillus* species. Of the triazoles exhibiting *Aspergillus* activity, itraconazole has the most clinical experience and data demonstrating its effectiveness in the treatment of ABPA. Itraconazole is administered at a dose of 200 mg twice a day for 4–6 months and then tapered off over 4–6 months. Itraconazole is a strong inhibitor of the cytochrome P450 3A4, so it is important to consider drug–drug interactions prior to initiation of therapy. Of particular note in this patient population, coadministration of itraconazole increases levels of budesonide, fluticasone propionate, dexamethasone, and methylprednisolone, which may lead to inadvertent toxicity from higher-than-intended doses of corticosteroids [89, 93, 94]. Drug levels should be monitored to ensure adequate bioavailability in patients with severe disease, patients not responding to therapy, or in those taking medications that may interact with itraconazole [95]. The suspension formulation has higher bioavailability than that of the capsule formulation. Absorption is improved in an acidic environment, so the medication should not be taken with antacids [95]. The most common side effects of azole therapy include elevated hepatic transaminases, gastrointestinal intolerance, peripheral neuropathy, rash, and headache as well as the risk of multiple drug–drug interactions.

Data from two randomized, double-blind placebo-controlled trials demonstrated the effectiveness of itraconazole in the treatment of ABPA complicating asthma. In a multicenter study of 55 patients in the United States, Stevens et al. found a higher rate of treatment response in the group randomized to receive itraconazole compared to placebo with a response defined as a ≥50% reduction in corticosteroid dosing, a ≥25% decrease in total serum IgE levels, and at least one of the following: resolution or absence of pulmonary infiltrates, improvement of pulmonary function tests, and/or improvement in exercise tolerance by at least 25% [90]. In a single center study in the UK, Wark et al. found a decrease in total serum IgE and *Aspergillus*-specific IgG levels, normalization of sputum eosinophilia, and fewer ABPA exacerbations in patients treated with itraconazole compared to placebo [92]. In the 2016 practice guidelines for the diagnosis and treatment of *Aspergillosis,* the Infectious Diseases Society of America (IDSA) recommends treating symptomatic asthmatic patients with known bronchiectasis or mucoid impaction despite oral or inhaled corticosteroids with oral itraconazole with therapeutic drug monitoring [91].

Similar to the treatment of ABPA associated with asthma, adjunctive therapy with itraconazole in ABPA complicating CF has also been reported to be beneficial. In a retrospective study of 21 patients, Skov et al. found an improvement in FEV_1 to pre-exacerbation levels and decreased precipitins in all patients as well as decreased total serum IgE levels in 56% of patients on combination therapy with itraconazole and prednisone [96]. The Cystic Fibrosis Foundation recommends the addition of itraconazole in cases of ABPA in which there is a poor response to corticosteroids, relapse, or corticosteroid toxicity or dependence [20]. The IDSA also recommends treating CF patients with ABPA, who have frequent exacerbations and/or declining lung function with oral itraconazole with therapeutic drug monitoring [91].

There are emerging data regarding the use of newer triazoles for the treatment of ABPA. In a study by Chishimba et al., treatment of ABPA complicating asthma with voriconazole led to a clinical response in 73% of patients and treatment with posaconazole led to a clinical response in 78% of patients [97]. In a case study of one patient with difficult-to-control ABPA complicating asthma with repeated relapses and who was unable to tolerate itraconazole or voriconazole, isavuconazole was used with symptomatic improvement and increasing FEV_1 as well as subsequent weaning of the inhaled corticosteroid dose [98]. In an attempt to minimize corticosteroid use, the IDSA recommends consideration of alternative mold-active azole therapy in patients requiring antifungal therapy if unable to achieve therapeutic levels of itraconazole [91]. Further research is needed on the potential role of voriconazole, posaconazole, or isavuconazole in the treatment of ABPA.

Use of mold-active azoles as monotherapy for treatment of ABPA has been proposed. In an open-label randomized controlled trial in India of 131 patients with acute-stage ABPA complicating asthma randomized to monotherapy with prednisolone versus itraconazole, prednisolone was more effective than itraconazole (100% vs. 88%) in causing a treatment response, but there was no difference in timing to first exacerbation or number of exacerbations [99]. There were also significantly higher rates of adverse events in the prednisolone group such as weight gain, cushingoid habitus, and acne. In patients taking itraconazole monotherapy, 9/60 (15%) developed liver function test abnormalities. The same research group in India conducted a similar open-label randomized control trial comparing monotherapy with prednisolone versus voriconazole in 50 asthmatic patients with acute-stage ABPA [100]. The proportion of patients demonstrating a positive treatment response was similar between

the two groups (prednisolone 25/25, 100% and voriconazole 24/25, 96%). There was again no significant difference in timing to first exacerbation or number of exacerbations between the groups, but higher rates of adverse events were noted in the prednisolone group. Given the results of these two trials, monotherapy with a mold-active azole with close monitoring for treatment failure may be an effective potential treatment option for acute ABPA, especially in patients in whom a glucocorticoid sparing agent is necessary.

Monoclonal Antibodies

Multiple case reports and small studies have reported on the use of monoclonal antibodies to treat refractory ABPA. Omalizumab is a humanized monoclonal IgG_1 antibody that binds to free IgE. Approved for treatment of severe allergic asthma, dosing is based on the patient's total IgE level and body weight up to a maximum of 750 mg monthly [101]. Given the high degree of total serum IgE elevation, patients with ABPA frequently exceed these dosing parameters. Despite the dosing limitations, there are reports of omalizumab used in the treatment of ABPA. A meta-analysis of 102 patients with ABPA treated with omalizumab found a 59% average decline in total serum IgE levels with an improvement in clinical symptoms and a decrease in the exacerbation rate [102]. There were no reported adverse events including no reported episodes of anaphylaxis. In a partially industry-supported, open-label, placebo-controlled randomized trial in Australia of 13 asthmatic patients with chronic ABPA, there was a significant decrease in the rate of exacerbations with omalizumab use compared to placebo [103]. Furthermore, each patient who had an exacerbation in the placebo phase experienced fewer exacerbations in the omalizumab crossover phase. In a retrospective study of 18 pediatric patients with ABPA complicating CF in France, treatment with omalizumab was associated with stabilization of lung function and a decrease in the average daily corticosteroid dose without any adverse events noted [104]. In contrast, an industry-sponsored, double-blind randomized controlled trial evaluating the safety and efficacy of omalizumab for treatment of ABPA complicating CF noted higher rates of adverse events, with 6/9 (67%) patients in the omalizumab group experiencing one or more serious side effects [105]. In that trial, an omalizumab dose of 600 mg subcutaneous injection daily for 6 months was higher than those in other studies and there was significant drop out of participants. The study was terminated early due to insufficient enrollment.

Mepolizumab is a monoclonal antibody against IL-5. Approved for treatment of severe eosinophilic asthma, it has also been utilized for the treatment of ABPA complicating asthma. In two patients in Japan with ABPA complicating asthma who declined treatment with systemic corticosteroids, initiation of mepolizumab for treatment of severe asthma led to improved symptoms with a decrease in peripheral blood eosinophil count and improved FEV_1 but no change in total serum IgE levels [106]. The two patients were treated with mepolizumab for more than 20 months without any adverse events. There is also a case report of mepolizumab used in combination with omalizumab successfully treating a patient with ABPA complicating asthma that remained refractory to treatment despite initiation of omalizumab [107]. Further studies including randomized controlled trials are necessary prior to formally recommending treatment of ABPA with omalizumab or mepolizumab.

Monitoring for Treatment Response

Patients should be closely monitored when initiating treatment for ABPA with serial total serum IgE levels, lung function testing, and chest radiograph every 6–8 weeks until remission is achieved, as discussed above. Treatment can be considered successful if there is symptomatic improvement, a decrease in total serum IgE levels, and clearing of opacities on chest imaging. Since, in most patients, ABPA is a chronic process, in our clinical practice, we follow patients regularly in outpatient pulmonary clinics after remission is achieved with continued periodic monitoring of serum IgE levels and lung function testing as well as intermittent chest imaging.

Conclusions

Significant progress has been made in the awareness of ABPA as an important disease entity in patients with asthma and CF, with recent proposed expert panel guidelines increasing the ease of diagnosis in patients with asthma. Nonetheless, recognition of ABPA still requires thoughtful clinical assessment, with annual screening serum IgE levels recommended in CF. An improved understanding of the pathophysiology of ABPA has led to an expansion of treatment options, which, in addition to systemic corticosteroids, now includes antifungal azole agents, and, in some circumstances, anti-IgE and anti-IL-5 asthma therapies. It is imperative to induce clinical remission with long-term surveillance monitoring once remission has been achieved. The role of prevention of disease by limiting exposure to *Aspergillus* in at-risk patients requires further study.

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Orphan Tracheopathies

5

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Introduction

Within the scope of respiratory medicine, central airway diseases have overall received less attention than parenchymal disorders. This is perhaps based on the incorrect assumption that disease processes involving the trachea and main bronchi are relatively rare and often clinically inconsequential. It may also be based on the unfounded belief that severe cases may only be successfully managed by complex and invasive surgical interventions often associated with high surgical risks. Tracheal diseases encompass a variety of disease processes that may be primary or secondary to underlying systemic diseases, whether inflammatory, infectious, or neoplastic in nature. Central airway diseases can generally be successfully managed by a variety of endoscopic procedures, which, within this past decade, have grown exponentially in both number and complexity. In that regard, central airway diseases present unique challenges and opportunities for respiratory physicians and can be largely credited for the development of the subspecialty of interventional pulmonary medicine.

Anatomical Considerations

The trachea extends from the lower border of the larynx (at the inferior edge of the cricoid cartilage) to the carina where it separates into right and left main stem bronchi. The angle between the right and left main stem bronchi is approximately 70°, with the right main stem bronchus being slightly more vertical than the left. The trachea is lined by a series of 18–22 semicircular cartilaginous rings located anteriorly and laterally, which are responsible for its relatively rigid structure. Conversely, the posterior (membranous) trachea consists of a relatively thin muscular layer made of longitudinally arranged smooth muscle fibers and a fibrous connective tissue forming the "trachealis."

The trachea is an irregular tube that is mostly intrathoracic (lower two-thirds). The average tracheal length is 10 cm in women and 12 cm in men (range, 8–13 cm) [1, 2]. The normal tracheal diameter in men is 13–25 mm coronal and 13–27 mm sagittal, with an average diameter of 19.5 mm [1–3]. In women, the respective values are 10–21 mm coronal and 10–23 mm sagittal, with an average diameter of 17.5 mm [1–3]. Pathological alteration in the size of the trachea refers to tracheal dimensions greater or less than these normal range values.

Clinical Presentation

Although stridor or a central "monophonic" wheeze can occasionally suggest the diagnosis of a tracheal disease, these symptoms are often reported late in the course of the disease and are preceded by less specific symptoms of dyspnea on exertion, cough, and, sometimes, hemoptysis. Tracheal diseases are unfortunately not always evident on plain chest radiography, and, as such, a clinical suspicion should lead to additional investigations.

Significant advances in imaging technologies have transformed our diagnostic approach to central airway lesions. Standard and dynamic computed tomography

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(CT) of the chest including two- and three-dimensional reformatting of images can now identify most tracheopathies and often suggest a precise diagnosis. In addition, chest CTs offer detailed information on the structures surrounding the airways, allowing the distinction between extrinsic compression from extraluminal processes versus endotracheal disease. Pulmonary function studies, particularly when they include a flow–volume curve, are equally invaluable. Fiberoptic bronchoscopy remains the gold standard for the diagnosis of the vast majority of tracheal diseases.

Etiological Considerations

Diseases involving the trachea often lead to debilitating symptoms for patients, and the diagnosis of central airway involvement is often delayed by erroneous diagnoses of more common respiratory diseases, such as asthma and chronic obstructive pulmonary disease (COPD).

Diseases of the trachea have been classified by several parameters including luminal narrowing versus widening, focal versus diffuse, congenital versus acquired disorders, and combinations thereof [1, 2, 4, 5]. In addition, tracheal diseases may be classified by an underlying cause. What is considered optimal classification depends on the type of tracheal disease being discussed and the purpose.

The majority of disorders involving the trachea are neoplastic or infectious in nature. However, there are several uncommon tracheal disorders that are of an unknown cause but are associated with characteristic features. Malignancy may occur in the trachea directly by endoluminal involvement, such as squamous cell carcinomas, adenoid cystic carcinomas, or metastases, or indirectly by extrinsic compression from tumors arising from the surrounding structures (e.g., esophageal carcinomas, thyroid carcinomas) or malignant lymphadenopathy. Similarly, traumatic injuries to the trachea from prolonged intubation or previous tracheostomy may ultimately result in significant narrowing or excessive compliance of the trachea, resulting in airflow limitation, or in post-tracheostomy fistula, resulting in massive tracheal bleeding. Other uncommon tracheal diseases are occasionally encountered and often present complex challenges to clinicians due to the lack of evidenced-based guidelines regarding diagnosis and optimal management. These include idiopathic subglottic stenosis, tracheobronchopathia osteochondroplastica, idiopathic tracheomalacia, tracheobronchomegaly, and tracheal involvement in systemic diseases (including granulomatosis with polyangiitis, relapsing polychondritis, sarcoidosis, and tracheal amyloidosis). These so-called "orphan diseases" constitute the topic of this chapter and will be reviewed here, with a particular emphasis on practical management.

Idiopathic Subglottic Stenosis

Clinical Vignette

A 45-year-old Caucasian woman presents to the pulmonary clinic for shortness of breath that has been slowly progressing over the past 2 years. She was diagnosed with asthma several months ago and prescribed various inhalers (bronchodilators and inhaled steroids) but showed no significant improvement. She is otherwise healthy and is not taking any other medications. She had several endotracheal intubations for minor surgical procedures in the past but never remained intubated for prolonged periods of time. She reports occasional heartburn and indigestion that has not been severe enough for her to seek medical attention. Chest radiography is obtained and interpreted as normal. Pulmonary function studies reveal the presence of a moderate airflow obstruction with a normal diffusing capacity. Both inspiratory and expiratory portions of the flow–volume curve are flattened, raising concerns for the possibility of fixed central airway obstruction. A fiberoptic bronchoscopy is performed and reveals a 70% concentric narrowing in the subglottic area without evidence of inflammation or neoplastic infiltration. Biopsies are consistent with nonspecific inflammation, without evidence of granulomas or malignancy. A diagnosis of idiopathic subglottic stenosis is established.

Introduction

Tracheal stenosis may be encountered in a variety of different clinical situations. Tracheal traumas, whether related to prolonged intubation with excessive endotracheal tube cuff pressure, tracheostomy, infections (such as tuberculosis or rhinosclerosis associated with *Klebsiella rhinoscleromatis*), or post-transplant (heart–lung transplant, in which the anastomosis is tracheal rather than bronchial), are causes of secondary tracheal stenosis. Rarely does tracheal stenosis occur as a complication of tracheal malignancy, radiation therapy, inhalational injury, or even congenital causes (such as airway hypoplasia, complete tracheal rings, or extrinsic compression from vascular rings) [6–9]. In a minority of cases, no obvious cause can be identified, and the diagnosis of idiopathic subglottic stenosis (ISS) is established. Of course, the diagnosis is one of exclusion and requires careful exclusion of all other potential causes.

Etiology and Pathogenesis

The first case of ISS was described in 1972 by Brandenburg [10]. Relatively few and small case series have been pub-

lished since, and, overall, our understanding of the underpinnings of this rare entity remains limited.

The vast majority of affected individuals are women, which has led to theories on the role played by the hormonal environment [10–13]. In that context, several investigators have assessed for the presence of overexpressed estrogen and progesterone receptors on the cellular membranes of epithelial and fibroblastic cells involved in the disease process with overall unconvincing results [14, 15].

Although a hormonal basis for the disease remains unsubstantiated at this time, the evident gender predilection remains to be explained otherwise. One hypothesis suggests that other initiating factors may contribute to the disease process, perhaps facilitated by a specific hormonal milieu. Others have postulated that repeated cough trauma, with "telescoping" of the first tracheal ring into the cricoid cartilage, may be followed by an abnormal wound repair process, perhaps driven by specific hormonal influences, though this remains purely speculative [11]. The possibility of the limited form of granulomatosis with polyangiitis (GPA) is always difficult to confidently exclude, as the presentation is by definition limited to the upper airway and the specific serum antibodies may be lacking in up to 40% of the cases of GPA. In addition, biopsies of the upper airway will frequently miss the typical granulomatous changes associated with the disease. Clearly, limited GPA is unlikely to be responsible for more than a small minority of these cases as it would not account for the female predominance observed. Smoking does not appear to play a role.

More convincing arguments have been advanced for the role played by gastroesophageal reflux disease (GERD). Multiple observational studies have reported a higher frequency of GERD in this patient population compared to that in the general population [9, 16–18]. Furthermore, treatment with anti-reflux agents has been associated with improvement in the severity of lesions observed and symptoms experienced by patients. More recently, an elegant case–control study has lent support to this hypothesis by showing increased levels of pepsin, a gastric enzyme generally absent from the upper airway, in tracheal biopsies of patients with ISS [19]. Although causality remains in question, these observations suggest that GERD treatment should be at least considered as part of the management of these patients.

Clinical Features

The most common symptom reported by patients with ISS is exertional dyspnea. Patients generally do not experience dyspnea until the tracheal lumen is severely reduced to less than 10 mm in diameter. Thus, the diagnosis is often delayed as symptoms generally occur late in the course of the disease when a monophonic wheeze or even stridor becomes apparent. Coughing may be present in some patients.

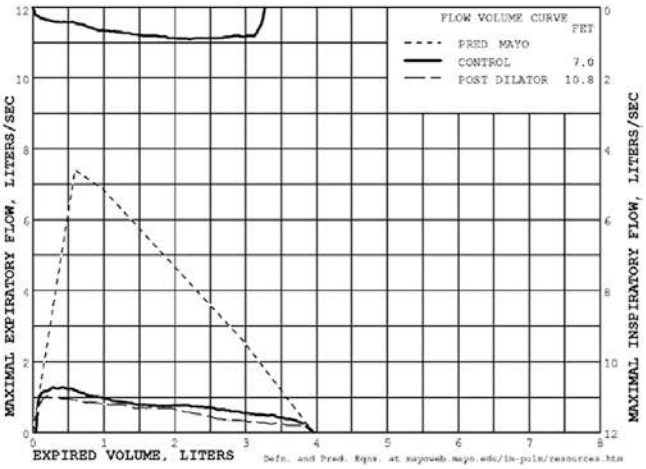

Fig. 5.1 The flow–volume loop in fixed upper airway obstruction (subglottic stenosis) revealing blunting of both the inspiratory and expiratory portions of the loop

Pulmonary Function Studies

Pulmonary function testing in patients with ISS usually demonstrates fixed (versus variable) airflow limitation with a plateau manifesting on both inspiratory and expiratory flow–volume loops (Fig. 5.1) [20, 21]. This is because the airway caliber does not significantly change with variations in intraluminal pressure in most patients with ISS.

Imaging Studies

Conventional chest radiography may reveal narrowing of the tracheal air column but is neither sensitive nor specific to the diagnosis of ISS. A chest CT allows a more precise assessment of the tracheal anatomy and also provides information on the mediastinum, which by definition should appear normal in ISS (i.e., no extrinsic compression). High-resolution CT using multi-row detectors now allows for two- and three-dimensional reconstruction and virtual bronchoscopic images that can help define the type (concentric, complex, hourglass) and extent of stenosis prior to invasive techniques. In addition, dynamic CT with expiratory views allows identification of dynamic collapse due to tracheomalacia occasionally associated with ISS [1, 2].

Bronchoscopy

Bronchoscopy is the gold standard for the diagnosis of tracheal stenosis (Fig. 5.2). Typically, flexible bronchoscopy is used first in order to determine the location, extent, and complexity of the stenosis. Endobronchial ultrasound (EBUS) can document the thickening of the lamina propria of the tracheal mucosa without cartilage involvement. This diagnostic tool can be helpful both in differentiating ISS from other

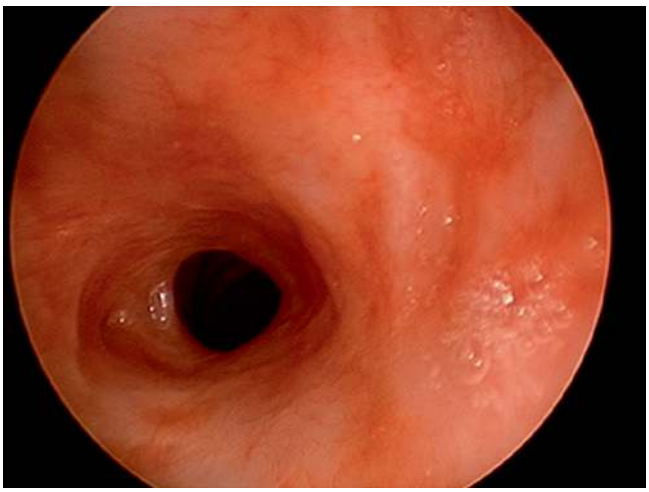

Fig. 5.2 Bronchoscopic view of idiopathic subglottic stenosis in a 38-year-old woman. The tracheal lumen is narrowed to a 4 mm diameter

diseases that usually involve the cartilage (i.e., chondromalacia, relapsing polychondritis) and in assessing the extent and complexity of the tracheal stenosis. Occasionally, the stenosis is severe enough that only pediatric or ultrathin bronchoscopes may be used. In this situation, however, extreme caution is needed as procedure-related edema or inflammation can result in life-threatening airway obstruction. In such cases, proceeding directly to rigid bronchoscopy in a controlled operating room setting may allow better management of the airways. High-frequency ventilation can be used with rigid bronchoscopy and is extremely helpful in this setting.

When obtained, biopsies, by definition, show no evidence of granulomatous inflammation or malignancy. The typical histological finding consists of cheloidal fibrosis with dilatation of the mucous glands and normal cartilage [14]. As mentioned above, studies evaluating the presence of estrogen and progesterone receptors have not been conclusive.

Treatment

The definitive treatment of ISS consists of single-stage laryngotracheal resection with or without a posterior membranous tracheal wall flap. The largest series published by Ashiku et al. from the Massachusetts General Hospital included 73 patients, 67 of whom had excellent long-term results without the need for further endoscopic or surgical interventions with a mean follow-up of 7.9 years [22]. In contrast, the largest case series on endoscopic management of ISS reported recurrence requiring re-intervention in 30% of patients at 6 months and in 87% at 5 years [23]. Although the results would argue for surgical interventions in the majority of patients, it cannot be overemphasized that such patients should be referred to centers of excellence with expertise in the management of this exceedingly rare disease. Cartilage grafting has been used in the surgical management of complex stenotic lesions [24].

Endoscopic treatment varies and is based on expert opinion. It may include simple dilatation using rigid bronchoscopy with barrels of increasing diameter, which may be preceded by radial cuts using laser. Others have used flexible bronchoscopy with balloon dilatation. We tend to favor rigid bronchoscopy, which offers the safety of a more secured airway. Applications of mitomycin C and/or intralesional injections of corticosteroids are sometimes used to prevent recurrences, though the evidence for this practice is scarce. Mitomycin C should not be used during pregnancy. In addition, some reports suggest that the excessive use of mitomycin C may be associated with subsequent tracheal stenosis from excessive fibroproliferation [25]. Airway stents are occasionally considered, but their use may be associated with recurrent tracheal trauma that could jeopardize future definitive surgical treatment. Tracheostomy is believed to present the same risks and is usually discouraged. The value of empiric medical therapy including inhaled steroids and empiric proton pump inhibitors remains unclear at this time, though documented gastroesophageal reflux disease should be aggressively treated.

Idiopathic Subglottic Stenosis: Key Points

- Female predominance
- Location: subglottis
- Histology: cheloidal fibrosis of the lamina propria with preservation of the tracheal cartilage
- By definition of the diagnosis of exclusion, secondary causes of tracheal stenosis should be excluded

Tracheobronchopathia Osteochondroplastica

Clinical Vignette

A 55-year-old man is referred to the urology clinic for prostatectomy after being diagnosed with prostate adenocarcinoma. He is a never smoker but was diagnosed with chronic obstructive pulmonary disease (COPD) a few years back and uses a beta-2 agonist inhaler as needed as well as inhaled steroids. He has moderate obstruction on his pulmonary function test, but his diffusing capacity is normal. He is considered at a low risk for surgery from a respiratory standpoint and undergoes an uneventful radical prostatectomy. After the procedure, the anesthesiologist recommends a pulmonary consultation because of difficulties encountered during endotracheal intubation, requiring placement of a smaller-diameter endotracheal tube. A chest CT scan shows prominent calcified tracheal nodules sparing the posterior membrane with normal lung parenchyma. Fiberoptic bronchoscopy confirms the diagnosis of tracheobronchopathia osteochondroplastica.

Introduction and Clinical Presentation

With less than 400 cases reported in the literature, tracheobronchopathia osteochondroplastica (TPO) is one of the rare tracheal diseases [26]. It is characterized by the nonmalignant growth of cartilaginous and/or osseous submucosal nodules of varying sizes (generally 1–3 mm) that protrude into the lumen of the trachea and proximal main stem bronchi. As they arise from the tracheal cartilages, these nodules typically spare the posterior membrane, which generally helps distinguishing this diagnosis from those of other tracheal diseases. This entity is likely underreported as affected patients are generally asymptomatic or have mild respiratory symptoms.

Etiology and Pathogenesis

TPO affects both males and females with equal frequency and does not appear to be influenced by smoking [27]. Most patients are middle-aged adults, though few cases have been reported in children [26–29].

The pathogenesis of the disease remains obscure, although some have suggested that ongoing irritation from chronic cough may eventually lead to metaplasia of the elastic connective tissue. Biopsies of the lesions of TPO have revealed the presence of bone morphogenetic protein 2 and transforming growth factor beta-1, cytokines involved in extracellular matrix and bone formation [30]. An association with amyloidosis has been described, and some have suggested that TPO could be a manifestation of tracheobronchial amyloidosis, though the evidence supporting this assertion is limited to a few case reports. More likely, these two entities represent distinct tracheal diseases with overlapping clinical manifestations. Finally, *Klebsiella ozaenae*, a bacterium responsible for the development of atrophic rhinitis, has been suggested as a possible cause for TPO as its presence was demonstrated in 20% of TPO patients in a large case series [26–28].

Clinical Features

In the majority of cases, the presence of TPO is incidentally identified on the basis of a chest CT demonstrating calcified submucosal nodular thickening or during bronchoscopy. Occasionally, the confluence of osseous and cartilaginous nodules can lead to mass-like formation, resulting in luminal narrowing and symptomatic tracheal stenosis. Laryngeal involvement may occasionally be seen as well. Hemoptysis, due to ulceration of the mucosa overlying these nodules, is a rare manifestation of the disease and is generally minimal and self-limited. Cough, wheezing or stridor, hoarseness, and recurrent infections (due to poor mucociliary clearance and post-obstructive infections) can occur as well. A characteristic presentation, as described in the case above, is that of difficult endotracheal intubation, eventually leading to the diagnosis.

Pulmonary Function Studies

Pulmonary function studies are frequently normal but may occasionally demonstrate an obstructive defect when the degree of tracheal narrowing causes significant airflow limitation. The central airway location of the disease can be identified by a flow–volume loop showing the plateau of the inspiratory or expiratory portion of the curve depending on whether the level of obstruction is extra- versus intrathoracic, respectively. In some cases (extensive disease or fixed obstruction), both the inspiratory and the expiratory portions may be abnormal [27].

Imaging Studies

Chest radiography is rarely sensitive enough to suggest the diagnosis but may occasionally show narrowing and irregularity of the tracheal air column with calcified deposits. A chest CT reveals the characteristic calcified nodules arising from the anterior and lateral walls of the trachea with varying degrees of narrowing and irregular lumen (Fig. 5.3) [27, 28, 31]. As mentioned earlier, the posterior membrane is typically spared and, if involved, should suggest the possibility of alternative diagnoses, specifically amyloidosis and relapsing polychondritis, which can both result in significant central airway calcifications.

Bronchoscopy

Bronchoscopy typically establishes the diagnosis and reveals obvious abnormalities in the vast majority of patients, which may range from mild to severe. Submucosal nodules protruding into the airway can be seen at all levels of the trachea (Fig. 5.4) but result in clinically significant narrowing

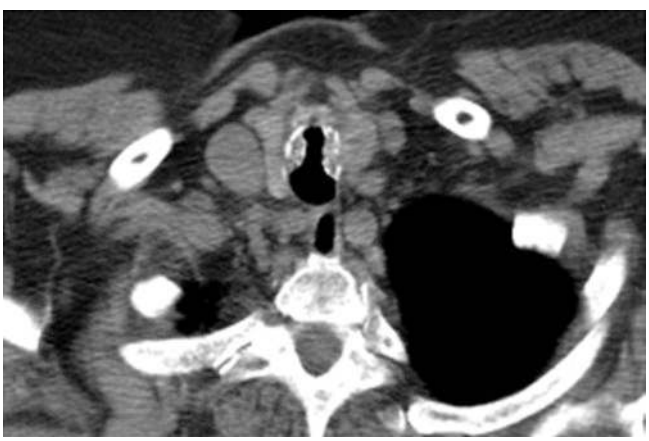

Fig. 5.3 A CT scan of the chest of an 89-year-old woman with tracheobronchopathia osteochondroplastica. Partially calcified submucosal nodules are present in the tracheal walls with sparing of the posterior membranous wall

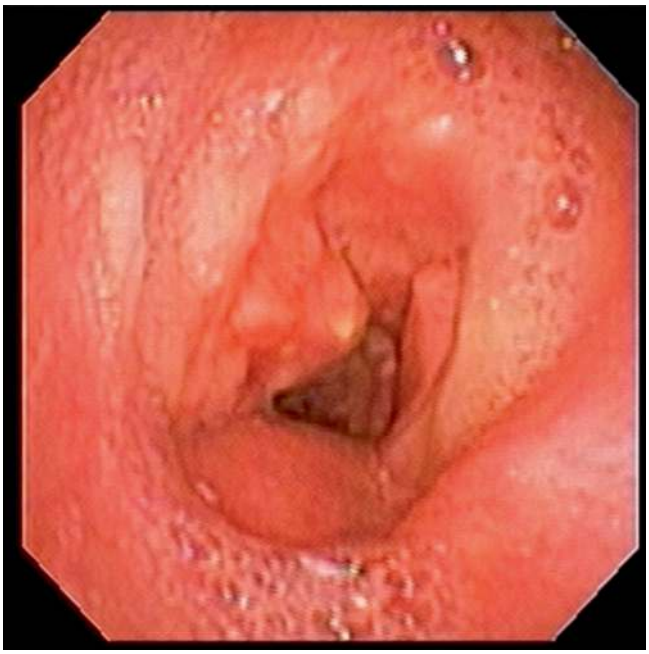

Fig. 5.4 Bronchoscopic view of tracheobronchopathia osteochondroplastica revealing osseous submucosal nodules projecting into the tracheal lumen

(>50%) in only a minority of patients. While the posterior membrane is generally spared, progression of the nodule formation may eventually extend posteriorly in 15% of patients. Biopsies are not mandatory to establish the diagnosis when palpation with forceps confirms the firmness of the calcified and/or osseous nodules. When biopsies are obtained, which can be difficult, they reveal the presence of submucosal cartilage and bone formation with occasional intraosseous bone marrow formation. Proximal main stem bronchi may be involved as well, but more distal airways are involved in less than 20% of patients [27, 29].

Treatment

In the absence of respiratory symptoms, patients with TPO do not require any specific treatment. In symptomatic patients, treatment of TPO remains mainly supportive. Bronchopulmonary hygiene measures aimed at improving secretion clearance are of paramount importance in patients with recurrent infections due to impaired mucociliary function and post-obstructive infections. Immunizations should be updated. The definitive treatment of TPO is difficult, as the firm, calcified, and osseous nodules do not lend themselves well to endoscopic resection. Furthermore, the diffuse extent of the lesions along the tracheal walls often precludes any consideration of reconstructive surgery. When indicated, rigid bronchoscopy with resection of the nodules using gentle and careful pressure with the bevel of the bronchoscope is usually the most efficient but may result in tracheal injury. Other techniques have been described, including laser-assisted mechanical debulking. An important caveat is that any consideration of endoscopic treatment should be symptom-driven, as the lesions of TPO are minimally progressive in most patients and follow a benign course [27, 29, 32].

TPO: Key Points

- No gender predilection
- Tracheal involvement typically spares the posterior membrane
- Biopsies are not needed in typical cases
- Differential diagnosis on CT imaging includes amyloidosis and relapsing polychondritis

Tracheomalacia

Clinical Vignette

A 55-year-old man with known COPD is admitted to the pulmonary ward for his third episode of pneumonia this year. His cough has worsened with production of purulent sputum and increased shortness of breath. Chest radiography reveals consolidation in the right lower lobe. Pulmonary function studies reveal severe obstruction, markedly worse than that noted 2 years prior to admission during an outpatient evaluation. A chest CT scan confirms the right lower lobe infiltrate but is otherwise unremarkable. A bronchoscopy is undertaken to explore the possibility of an endobronchial lesion. The bronchoscopy reveals severe tracheobronchomalacia from excessive dynamic airway collapse secondary to severe laxity of the posterior membrane. The pulmonary service is consulted for management recommendations.

Introduction

Tracheomalacia (from the Greek word *malakia*, i.e., softness) refers to a weakness of the trachea that results in increased compliance and excessive reduction in the tracheal luminal dimensions during normal or forced expiration and/or inspiration. Because the trachea is mainly intrathoracic (lower two-thirds approximately), most of the changes noted occur during expiration, as the airways tethered to the surrounding thoracic structures remain relatively normal during inspiration [33, 34]. The extrathoracic portion of the trachea is occasionally involved as well, and

inspiratory collapse with audible stridor may then occur. When the proximal bronchi are involved, the appropriate term is "tracheobronchomalacia." The distinction is essentially semantic as the manifestations and clinical implications are identical.

Tracheomalacia may be diffuse, as seen in excessive dynamic airway collapse, or focal, as seen in complications of tracheostomy, for example. In general, focal lesions are more easily amenable to endoscopic or surgical treatment, emphasizing the importance of a careful endoscopic examination. It has been argued that tracheomalacia should only refer to excessive tracheal weakness from structural insufficiency of the tracheal cartilaginous rings and should be distinguished from excessive dynamic airway collapse, related to excessive laxity of the posterior membrane. As these conditions may result in similar manifestations and management strategies, this distinction is not particularly helpful and, rather, management should be guided by symptoms and evidence of airflow limitations during dynamic respiratory maneuvers.

Etiology and Pathogenesis

The vast majority of cases described in children is congenital and include mucopolysaccharidoses (such as Hurler syndrome and Hunter syndrome) and Williams–Campbell syndrome (the absence of cartilages, resulting in loss of structural support) [1, 35, 36]. Other causes of tracheomalacia in children include compression of the trachea by vascular rings or the right-sided aortic arch. The persistent compression of the trachea is believed to result in chronic ischemic changes and cartilage destruction, eventually leading to focal tracheomalacia. Bronchiectasis is likely to develop over time as a consequence of recurrent lung infections from retained secretions, and, as such, tracheomalacia should be considered in the differential diagnosis of diffuse bronchiectasis.

Various types of tracheomalacia are described in adults. As for children, prolonged tracheal compression from surrounding structures may eventually result in focal tracheomalacia. This includes chronic endotracheal intubation with excessive cuff pressure, tracheostomy or other forms or trauma to the airways, extrinsic compression from tumoral processes or lymph nodes, and thyroid goiters. Other causes include infections (such as tuberculosis) or, rarely, heart–lung transplant (as the anastomosis is located in the lower trachea). Some inflammatory conditions may result in diffuse tracheomalacia, such as relapsing polychondritis (discussed separately) and inhalational injuries (including recurrent aspirations). Tracheomalacia from excessive dynamic airway collapse is typically observed in COPD, though occasionally occurring in never smokers. In this condition, documentation of central airflow limitation should precede therapeutic interventions as excessive dynamic airway collapse may be secondary to peripheral airflow limitation and may not contribute to the patient's respiratory symptoms [37].

Idiopathic tracheomalacia is relatively rare. One type of idiopathic tracheomalacia is Mounier-Kuhn syndrome, or tracheobronchomegaly, which typically manifests in adult life (also discussed separately) [33–35, 38–42]. Another example is Williams–Campbell syndrome, which is a congenital disorder characterized by the absence or severely diminished cartilages in the tracheobronchial tree (mainly affecting the fourth- through sixth-order bronchi) and results in bronchiectasis and, in some patients, tracheomalacia [38, 39, 41]. This condition is usually diagnosed in children or young adults.

There are few descriptions of the histopathological changes associated with tracheomalacia. Autopsy studies have revealed atrophy of the longitudinal muscle fibers with or without cartilaginous destruction or absence of the cartilaginous support structure [33, 34]. Inflammatory cellular infiltrates may also be noted in some instances, such as in relapsing polychondritis [43].

Clinical Features

Clinical manifestations are nonspecific and vary based on the degree of luminal narrowing, often resulting in delayed diagnosis or misdiagnosis as having chronic bronchitis or refractory asthma [33, 34]. Some asymptomatic patients may decompensate only during episodes of respiratory infections or during sleep (due to sleep-related respiratory changes and recumbent position). Symptomatic patients may experience wheezing, typically described as monophonic and, rarely, stridor when the extrathoracic portion of the trachea is involved.

Recurrent infections are secondary to impaired mucous clearance and are a common presentation. They may eventually lead to the development of bronchiectasis, aggravating the obstructive syndrome and predisposing patients to yet further infections. Cough may be severe and occasionally result in cough-induced syncope.

Pulmonary Function Studies

Pulmonary function studies usually reveal airflow obstruction. The severity of this obstruction is directly proportional to the degree of tracheomalacia [33, 34]. Obstruction that is considered out-of-proportion to the smoking history of a COPD patient should suggest tracheomalacia from excessive dynamic airway collapse. One clue to the diagnosis is the presence of a plateau on the expiratory portion of the flow–volume curve, following a reduced peak expiratory flow rate.

Oscillations of flow, similar to those noted in obstructive sleep apnea patients, have been reported as well. If the extrathoracic portion of the trachea is involved, then a plateau may also be noted on the inspiratory curve [33, 34, 44]. In some instances, a cardiopulmonary exercise test with flow–volume loops may help to document central airflow limitation as exercise-limiting.

Imaging Studies

Chest radiography is usually inadequate for the diagnosis of tracheomalacia. Chest CT images may also be misleading if obtained only during inspiration, as the tracheal dimensions are generally normal under these conditions (unless the extrathoracic trachea is involved as well). If a diagnosis of tracheomalacia is suspected, then a dynamic CT study should be obtained by requesting dynamic expiratory imaging. The diagnostic accuracy of dynamic CT approaches that of bronchoscopy and allows precise measurements of the luminal diameter changes and extent of tracheomalacia [1, 2]. Multirow detector spiral CT allows for image acquisition within seconds and is generally obtainable even in the most dyspneic patients. The type of luminal narrowing can be accurately characterized by CT. Reduction in the anteroposterior diameter is described as crescent-shaped (a "frown sign" on CT images) (Fig. 5.5), whereas reduction in the sagittal diameter has been referred to as "saber-sheath trachea." This latter presentation is more common in patients with emphysema and is believed to result from chronic cough with microfractures of the cartilages and lateral compression from hyperinflated upper lobes.

The criteria for tracheomalacia on CT are identical to those used during bronchoscopy. By convention, airway collapse is considered significant if the minimum luminal diameter is 50% or less than the maximum diameter. Luminal narrowing down to 25% is considered moderate, and complete collapse is designated as severe [33]. These criteria are supportive of the diagnosis but should be considered diagnostic only in the appropriate clinical setting, as several studies have shown that a majority of healthy controls can experience narrowing >50% during forced expiratory maneuvers [45, 46]. For this reason, a 75% narrowing cutoff has been proposed by some authors for diagnosing tracheomalacia [45–47].

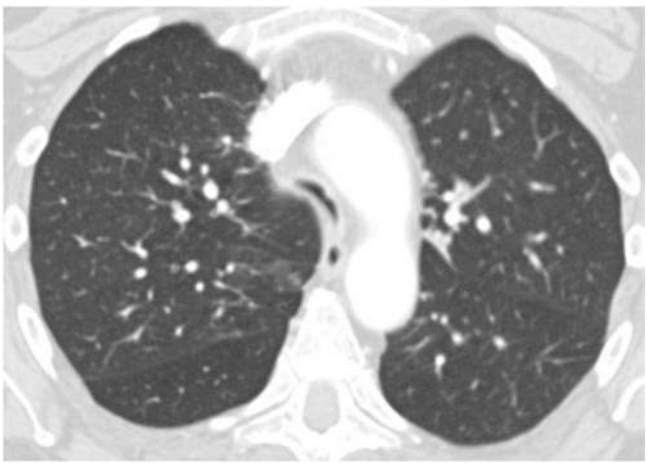

Fig. 5.5 A CT scan of the chest of a 57-year-old man with severe tracheomalacia demonstrating the "frown sign"

Bronchoscopy

Bronchoscopy remains the diagnostic gold standard, although it does not provide the same quantitative measurements of airway diameter assessed by CT imaging. Again, a narrowing >50% is considered consistent with the diagnosis but is based on a semiquantitative assessment by bronchoscopists.

Bronchoscopy should be performed with conscious sedation as it allows maneuvers of cough and forced expiration that are not possible under general anesthesia. Morphometric bronchoscopy has been proposed as a potential tool to allow quantitative analysis of airway dimensions via software analysis of digital bronchoscopic images, but its use remains experimental at the present time. One major advantage of bronchoscopy over CT is the possibility of identifying endoluminal pathology responsible for the tracheal narrowing, which may be missed by CT. In addition, bronchoscopic interventions may be possible in the same setting or allow adequate planning for further interventions.

Treatment

Treatment of tracheomalacia should be individualized according to the type, extent, and etiology of the tracheomalacia. Treatment of the underlying cause, when possible, is warranted (such as systemic anti-inflammatory treatment of relapsing polychondritis or resection of mediastinal mass). If possible, tracheomalacia in children should be observed as it may spontaneously resolve as the patients get older and the cartilaginous support structures mature. Noninvasive measures such as continuous positive airway pressure (CPAP) therapy during sleep have been suggested, particularly in the context of excessive dynamic airway collapse, and may allow improved airflow and decreased compliance, though the supportive evidence overall remains scarce [33, 34, 48].

Focal lesions are sometimes amenable to tracheal resection and end-to-end anastomosis, which is considered the definitive treatment. When the tracheomalacia is diffuse, or when the patient is not deemed an appropriate candidate for surgical treatment, endoscopic interventions may be helpful. Rigid bronchoscopy with silicone stent placement may result in significant improvement in lung function and symptoms.

Migration of the choke point beyond the extremities of the stent may limit its efficacy, however, and excessive stent length can lead to further impairment of mucous clearance and predispose patients to recurrent infections. Inhalation of nebulized saline is warranted after stent placement to avoid inspissation (thickening) of mucous and occlusion of the stent. Metallic stents, while similarly efficacious in re-establishing airway patency, should be avoided in benign airway diseases, as they are associated with serious long-term complications. As opposed to silicone stents, they can be difficult to remove when left in place for prolonged periods of time.

An alternative option for diffuse diseases is surgical tracheobronchoplasty, which consists of reinforcing the posterior membrane of the central airways with prosthetic material such as Marlex mesh, effectively resulting in splinting of the airways [49–51]. Potential candidates for this procedure should be selected on the basis of a favorable response to silicone stenting [33]. Long-term stenting is an option for those who do respond but are not considered acceptable candidates for this invasive procedure. Airway stabilization via tracheoplasty or stenting for COPD-associated excessive dynamic airway collapse can result in significant improvement in quality of life and physiological parameters [52]. In some cases, tracheostomy may occasionally be performed if the area of narrowing can be successfully bypassed.

Tracheomalacia: Key Points

- Increased compliance of the trachea with collapsibility
- May be idiopathic or secondary
- May be focal or diffuse
- Effects of endotracheal stent placement can predict response to surgical management

Tracheobronchomegaly

Clinical Vignette

A 30-year-old man with a history of recurrent respiratory infections and refractory asthma presents to the emergency department for a sudden onset of shortness of breath. Chest radiography reveals a right-sided pneumothorax, and chest tube thoracostomy is performed for management. A chest CT is obtained to assess for the underlying parenchymal lung disease, which reveals significant bronchiectasis that predominates in the lower lobes with marked enlargement of the central airways. A bronchoscopy later confirms the diagnosis of tracheobronchomegaly. Several tracheal diverticula are noted during the bronchoscopic examination.

Introduction

Idiopathic tracheobronchomegaly, also called Mounier-Kuhn syndrome, was first reported in an adult patient in 1932. Since then, more than 100 cases have been reported in the literature [33]. It is considered a congenital disease affecting the trachea and proximal bronchi, resulting in abnormal enlargement of the airways, leading to tracheobronchomalacia with impaired secretion clearance and recurrent infections. Although occasionally identified during childhood, the disease more often presents later in life after development of bronchiectasis and recurrent infections prompt further investigations.

Etiology and Pathogenesis

Abnormal enlargement of the central airways has been described in association with a variety of conditions including connective tissue diseases such as Marfan syndrome, Ehlers–Danlos syndrome, and ankylosing spondylitis [53–59]. Congenital diseases have also been reported in association with tracheobronchomegaly and include Bruton agammaglobulinemia, Kenny–Caffey syndrome, ataxia telangiectasia, and Brachman de Lange syndrome. Finally, similar to traction bronchiectasis, fibrotic infiltrative lung processes have occasionally been reported to cause enlargement of the central airways tethered to the surrounding fibrotic lung parenchyma. These conditions include idiopathic pulmonary fibrosis and other chronic parenchymal lung diseases such as sarcoidosis, rheumatoid-associated interstitial lung disease, chronic histoplasmosis, and idiopathic pleuroparenchymal fibroelastosis [60, 61]. The term "Mounier-Kuhn syndrome" should be reserved for the idiopathic form of the disease and is also called idiopathic giant trachea. Several familial cases have been described [62].

Clinical Features

Mounier-Kuhn syndrome tends to affect males with a higher frequency [4, 56, 63, 64]. Although the anatomical anomalies are generally present in childhood, the symptoms usually become evident in adulthood, in the 30s or 40s. A significant percentage of patients with Mounier-Kuhn syndrome are asymptomatic and are diagnosed on the basis of abnormalities identified on imaging studies (typically chest CT) obtained for other reasons. Associated symptoms mainly consist of chronic cough and shortness of breath, recurrent infections, increased sputum production, and bronchiectasis. Occasionally, patients may report episodes of hemoptysis. Rare cases of pneumothorax have been reported [65].

Pathophysiology

The pathophysiology of Mounier-Kuhn syndrome remains to be elucidated. Histopathology data are limited but suggest that the tracheal and bronchial walls contain an abnormal connective tissue responsible for weakness of the central airways, leading to significant tracheobronchomalacia. Atrophy of the smooth muscles and elastic component of the airway walls has been described in autopsy studies [66–68]. The resultant tracheobronchomalacia causes reduction of airflow, impaired secretion clearance, and recurrent infections, ultimately leading to bronchiectasis. Outpouchings of the tracheal mucosa, or airway diverticula, may develop over time, and are highly suggestive of the diagnosis when identified by chest CT imaging. These may result in additional secretion retention, potentially further increasing the risk of infectious complications.

Pulmonary Function Studies

Pulmonary function studies are typically consistent with an obstructive pattern. As described in other types of tracheomalacia, an expiratory plateau may be identified, suggesting central airway obstruction. Restrictive defects are rare but may occasionally be seen when pulmonary fibrosis is present.

Imaging Studies

Chest radiography may occasionally suggest the diagnosis, which is confirmed by the presence of central airway enlargement on chest CT (Fig. 5.6). The diagnosis is established when the airway diameter exceeds the following cutoffs, which represent three standard deviations above the norm: 24 mm for the right main stem bronchus, 23 mm for the left main stem bronchus, and 30 mm for the trachea [1, 3].

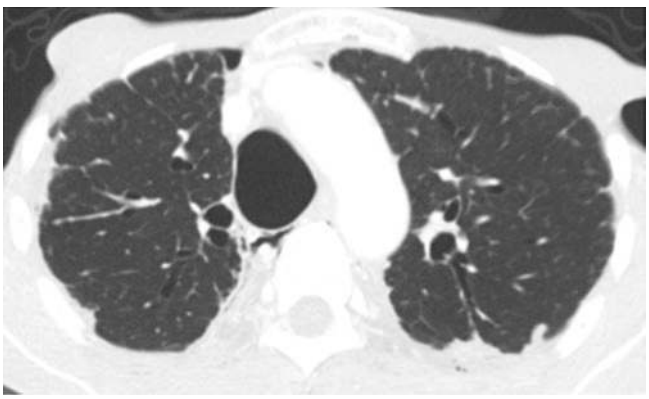

Fig. 5.6 A CT scan of the chest of a 66-year-old man with tracheobronchomegaly. The anteroposterior diameter is 37 mm

Treatment

Treatment of Mounier-Kuhn syndrome is challenging. The size of the central airways often precludes endoscopic stenting due to the lack of appropriately sized stents. The largest stent deployed in a case of tracheomegaly in association with Marfan syndrome had an outer diameter of 2.8 cm and had to be custom-made [69]. Despite this, a recent case series has reported improvements in quality-of-life indices and physiological parameters after both endoscopic stenting and surgical tracheobronchoplasty in patients with Mounier-Kuhn syndrome [70]. One anecdotal report described lasting improvement with low-power yttrium aluminum perovskite laser treatment of the posterior membrane of a Mounier-Kuhn patient, causing effective retraction of the tissues, though the safety of this approach remains questionable [71].

Supportive interventions such as noninvasive positive pressure ventilation at night, bronchopulmonary hygiene measures, and appropriate and timely antibiotic treatments and immunizations are recommended. The prognosis of the disease varies widely, but severe cases can progress to respiratory failure [4, 56, 63, 64]. Few patients with Mounier-Kuhn syndrome have undergone lung transplantation, and, as for cases of severe bronchiectasis, a bilateral lung transplant is preferred over a single lung transplant [72].

Tracheobronchomegaly: Key Points

- Male predominance
- Diagnosis is typically made in early adulthood
- Recurrent infections and bronchiectasis are common
- Endoscopic treatment is difficult due to the large size of the affected airways

Tracheopathies Associated with Systemic Diseases

The trachea and proximal main bronchi are sometimes involved in a variety of systemic diseases occasionally discovered during the workup of respiratory symptoms. Consideration of these diseases in patients with central airway disorders is warranted as they may influence management and prognosis. As a comprehensive review of all clinical entities potentially associated with central airway involvement is clearly beyond the scope of this chapter, we will review herein the most common offenders: relapsing polychondritis, granulomatosis with polyangiitis, sarcoidosis, and amyloidosis.

Relapsing Polychondritis

Clinical Vignette

A 42-year-old woman presents with shortness of breath and stridor. She has a past medical history significant for hearing loss of unclear etiology and mitral regurgitation. Physical examination reveals a saddle nose deformity and central wheezing on lung auscultation. Chest radiography reveals no apparent abnormalities. Blood work reveals increased inflammatory markers with elevated sedimentation rate and C-reactive protein. A chest CT suggests tracheal narrowing, and a bronchoscopy is performed. Endoscopic examination reveals subglottic stenosis, marked inflammation throughout the tracheobronchial tree, and severe tracheobronchomalacia. Upon further questioning, the patient reports recurrent episodes of ear inflammation and a diagnosis of relapsing polychondritis is established.

Introduction

Relapsing polychondritis is a rare type of autoimmune connective tissue disease that affects both males and females with equal frequency [73]. It is characterized by recurrent episodes of inflammation involving various cartilaginous structures including the ears, nose, upper airway (including the larynx), joints, and cardiac valves (mitral and/or aortic valve regurgitation). In addition, the disease may also result in life-threatening complications affecting the kidneys and central nervous system (CNS). It is most commonly diagnosed in middle-aged adults [43, 73–75].

Unilateral or bilateral ear inflammation is the most common presenting symptom and ultimately occurs in the vast majority of patients during the course of the disease [73, 76]. Approximately 30% of patients will report hearing loss or dizziness related to vestibular involvement. This constellation of symptoms in patients with central airway involvement should suggest the diagnosis of relapsing polychondritis. The characteristic auricular chondritis seen in the majority of patients with relapsing polychondritis is not a feature of granulomatosis with polyangiitis. However, differentiating relapsing polychondritis from granulomatosis with polyangiitis can sometimes be difficult because both diseases can manifest saddle nose deformity and tracheobronchial involvement; the possible overlap between these two entities has been discussed earlier. A biopsy of the tracheal cartilage shows degeneration with fibrous changes and inflammatory cell infiltration. The histological picture is not absolutely characteristic, and specific diagnostic tests are lacking.

Clinical Features

Central airway involvement is common in patients with relapsing polychondritis [77]. The largest case series reported by Ernst et al. [78] included 145 patients, 31 of whom had evidence of airway involvement (21%) with a majority being female (70%). The respiratory manifestations consisted of subglottic stenosis in eight patients (26%), focal or diffuse tracheobronchomalacia in 15 patients (48%), and focal stenosis in the remainder [78]. Other reports suggest that central airway manifestations may occur over time in approximately half of patients with relapsing polychondritis [74, 78, 79]. Presenting manifestations are nonspecific and include chronic cough, wheezing and/or stridor, and hoarseness in case of laryngeal involvement [74, 79].

Laboratory Findings

Laboratory abnormalities are also generally nonspecific, and the diagnosis remains essentially clinical. Anemia of chronic disease may be present, and eosinophilia is noted in approximately 10% of patients. Inflammatory markers are elevated during periods of active disease but may be normal between exacerbations. They are helpful for monitoring the disease and for treatment decisions but do not exclude the diagnosis when normal. Autoantibodies are sometimes present, consisting of antinuclear antibodies in approximately half of the patients. Rheumatoid factor and antiphospholipid antibodies are occasionally noted. Anti-neutrophil cytoplasmic antibodies (ANCAs) have also been described in relapsing polychondritis. Since patients with active limited granulomatosis with polyangiitis have a 30% chance to be ANCA-negative, this laboratory test does not always allow a clear distinction between relapsing polychondritis and granulomatosis with polyangiitis.

There is strong support for an autoimmune process directed at some extracellular components of the cartilage, but no particular antibody has been identified as either sensitive or specific to the disease. Anti-type II collagen antibodies, in particular, are found in a variety of other conditions and are believed to result from a nonspecific immune reaction to cartilage destruction, rather than being true pathogenic antibodies. The utility of identifying these antibodies in clinical practice is unclear [80, 81].

Pulmonary Function and Imaging Studies

Pulmonary function studies reveal findings consistent with central airway obstruction that may predominate during expiration in case of tracheobronchomalacia or may be present during both inspiration and expiration with a fixed stenosis pattern on the flow–volume curve if subglottic stenosis is present. Chest radiography is generally not helpful in the diagnosis. A chest CT reveals

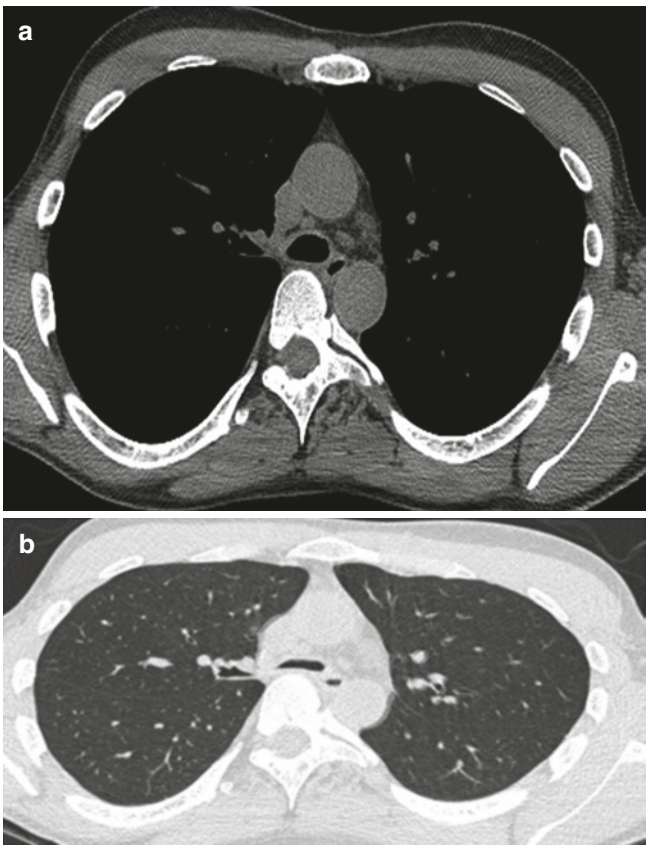

Fig. 5.7 A CT scan of the chest of a 32-year-old man with relapsing polychondritis. (**a**) Inspiratory view demonstrating a thickened tracheal wall with mild narrowing. (**b**) On expiration, there is collapse of the tracheal lumen

changes consistent with tracheobronchomalacia on dynamic images (Fig. 5.7a, b) or subglottic stenosis. One clue for the diagnosis of relapsing polychondritis is the presence of extensive calcification of the walls of the trachea and main bronchi, also seen in a few other conditions (age-related changes, tracheobronchial amyloidosis, and tracheobronchopathia osteochondroplastica). In a retrospective study of 18 patients with relapsing polychondritis referred to chest CT with expiratory images, abnormalities were noted in the majority of patients and consisted of malacia in 13 patients, air trapping in 17, and calcification of the airway wall in seven [82].

Magnetic resonance imaging has been proposed as a way to distinguish inflammation from fibrosis of the soft tissues of the central airways, but problems with resolution and prolonged image acquisition time in patients with respiratory compromise limit its usefulness in clinical practice [83]. Positron emission tomography using ^{18}F-fluorodeoxyglucose has also been suggested to assess for ongoing inflammation, but its use remains largely experimental [84–86].

Treatment

Treatment of the underlying disease using anti-inflammatory and immunomodulating agents is warranted during periods of active inflammation. First-line agents include dapsone or glucocorticoids. Severe life-threatening manifestations of the disease (including cardiac and central nervous system disease) should be treated with high-dose glucocorticoids, often combined with cyclophosphamide or other immunomodulatory agents such as azathioprine, cyclosporine, and methotrexate. Biologics, including tumor necrosis factor inhibitors, have been reported to be effective in some patients [77, 87]. In general, the evidence supporting their use is comprised of observational data and anecdotal reports. Supportive measures should include prophylaxis for *Pneumocystis jirovecii* while on immunosuppressive therapy, prompt initiation of antibiotics when needed, and appropriate immunizations.

The management of airway manifestations should be individualized. Treatment of subglottic stenosis and tracheobronchomalacia should follow the general guidelines outlined in the previous chapters (see Idiopathic Subglottic Stenosis and Tracheomalacia). Endobronchial ultrasound (EBUS) can be useful in the diagnosis and treatment of relapsing polychondritis. EBUS can reveal changes in the tracheobronchial cartilage characterized by fragmentation and edema. Evaluation of the complexity and extent of the stenosis and of the size of residual tracheal lumen facilitates stent placement. Noninvasive positive pressure ventilation may be of help in patients with significant tracheobronchomalacia. It should be emphasized that endoscopic treatment of airway lesions should preferably be performed during inactive phases of the disease as airway manipulations during exacerbations may result in paradoxical inflammatory reactions, resulting in additional airway compromise. Overall, airway manifestations of relapsing polychondritis can usually be controlled with a combination of anti-inflammatory agents and airway-specific interventions, leading to better outcomes than reported in earlier studies [43, 74, 79].

Relapsing Polychondritis: Key Points

- Inflammation of the cartilages, particularly the ears
- Saddle nose deformity and central airway obstruction may mimic granulomatosis with polyangiitis
- Treatment of the underlying inflammation is warranted, when present

Granulomatosis with Polyangiitis

Clinical Vignette

A 32-year-old woman with a long-standing history of granulomatosis with polyangiitis (initially diagnosed by proteinase 3 (PR3)-ANCA positivity and nasal biopsy) is admitted to the pulmonary ward for worsening shortness of breath. She has been treated with various immunosuppressive agents over the years and most recently has been started on rituximab for worsening renal function and several episodes of pulmonary capillaritis with alveolar hemorrhage. Although these manifestations have been well-controlled, she now presents with significant dyspnea on exertion with obvious stridor on deep inspiration. A chest CT excludes obvious pulmonary embolism or parenchymal infiltrates. A bronchoscopy reveals severe subglottic stenosis without evidence of inflammation or other tracheobronchial lesions.

Introduction

Granulomatosis with polyangiitis is an autoimmune multisystem disease characterized by necrotizing granulomatous inflammation involving small-to-medium-sized blood vessels and capillaries. The disease is characterized by the presence of circulating anti-neutrophil cytoplasmic antibodies (ANCAs) with cytoplasmic staining (c-ANCA) directed against the PR3 antigen. PR3-ANCAs are present in 90% of patients with active disease [88].

The respiratory system and the kidneys are most commonly affected (pulmonary renal syndrome), but many other organs may be involved as well, including the central or peripheral nervous system, eyes, heart, gastrointestinal system, and skin. A limited form of the disease is characterized by manifestations in the respiratory system (sinuses and lungs) without kidney involvement. c-ANCAs are positive in only 60% of those with the limited form of the disease [2, 89, 90].

Clinical Features

Respiratory manifestations vary and include chronic rhinosinusitis, pulmonary nodules that may cavitate, diffuse alveolar hemorrhage, and tracheobronchial involvement [88]. Thromboembolic disease is also relatively common during the active phase of the disease.

Tracheobronchial involvement occurs in approximately 15–55% of patients and mostly consists of subglottic stenosis [90]. This subglottic stenosis is indistinguishable from the idiopathic form, and, in general, biopsies fail to show typical necrotizing granulomas or vasculitis. Occasionally, palisading granulomas and microabscesses may be identified. Subglottic stenosis may be the only manifestation of limited GPA. Other less common but well-described airway lesions include concentric lower tracheal or bronchial stenosis, synechial bands resulting in obliteration of smaller airways, submucosal tunnels, polypoid mass lesions (inflammatory pseudotumors), and, less commonly, tracheobronchomalacia. Distal airways may be involved as well with follicular bronchiolitis, bronchiectasis, and, rarely, bronchiolitis obliterans [2, 89, 90].

Pulmonary Function Studies

Pulmonary function studies are important in the evaluation and follow-up of patients with GPA. Obstructive pattern is common, and the flow–volume loop may be consistent with intrathoracic obstruction (a plateau on the expiratory portion of the loop) or a combined intra- and extrathoracic (fixed upper airway) obstruction pattern, as in cases of subglottic stenosis (both inspiratory and expiratory plateaus are present).

Imaging Studies

A chest CT is extremely useful in characterizing the type and extent of the airway lesions. Expiratory images may reveal dynamic airway changes not otherwise obvious on conventional inspiratory images. The tracheal wall may be thickened and occasionally calcified. Although bronchoscopy remains the gold standard for the diagnosis of airway involvement in GPA, a chest CT allows for precise quantitative analysis of the type and extent of the stenosis and helps plan appropriate endoscopic interventions.

The utility of positron emission tomography in granulomatosis with polyangiitis has been reported in few case reports [91]. We have occasionally used positron emission tomography to document ^{18}F-fluorodeoxyglucose uptake in the subglottic region and to identify other possible localizations of the inflammatory process.

Bronchoscopy

Bronchoscopy remains the gold standard for the diagnosis of airway involvement in GPA. It also helps determine the activity of the disease, by showing significant inflammation not evident by other imaging methods. Mucosal erythema, ulcerative lesions, and cobblestoning of the mucosa are common during the active phase of the disease, whereas noninflammatory fibrotic stenoses are seen between exacerbations [89, 90, 92]. EBUS shows circumferential thickening of the submucosa with an intact bronchial cartilage. It is important to avoid aggressive endoscopic airway interventions during exacerbations as procedure-induced inflammatory reactions may result in further complications.

Treatment

Treatment should consist of remission induction regimens if GPA is active, using a combination of corticosteroids and immunosuppressive agents, such as cyclophosphamide or rituximab. Once the inflammation is controlled, bronchoscopic interventions consist of airway dilatation using balloon tracheo- or bronchoplasty, occasionally preceded by radial cuts using laser or electrocautery. The management of subglottic stenosis follows the same general guidelines described in a previous chapter (see Idiopathic Subglottic Stenosis above). Mucosal applications of mitomycin C and submucosal injections of steroids are occasionally performed in the same episode to prevent recurrence, though the evidence supporting this practice is limited [89, 90, 93]. Similarly, inhaled corticosteroids are of unclear benefit in this situation. Stent placement should generally be avoided but is occasionally necessary. Surgery is sometimes an option for patients who fail to respond to the above measures but should also be considered only after remission.

Granulomatosis with Polyangiitis: Key Points

- May be limited (i.e., limited vasculitis), mostly involving the upper airway
- Subglottic stenosis is the most common form of upper airway involvement
- Biopsies are frequently nondiagnostic (consider instead kidney or sinus biopsies)
- Treatment of the underlying inflammation is warranted, when active disease is present

Tracheobronchial Amyloidosis

Clinical Vignette

A 55-year-old man is referred to a tertiary center for management of tracheobronchial amyloidosis. The diagnosis was established after a bronchoscopy was conducted during an episode of pneumonia and revealed subtle infiltration of the tracheal mucosa including the posterior wall; biopsies demonstrated amyloid deposition. Although the patient is now completely asymptomatic, he has read extensively about his condition and inquires about the risk of cardiac complications and the role for external beam radiation as a potential treatment for tracheobronchial amyloidosis.

Introduction

Amyloidosis refers to a broad and heterogeneous group of diseases caused by the abnormal extracellular accumulation of insoluble fibrillar proteins [94]. This accumulation ultimately results in organ dysfunction and related clinical manifestations. Virtually all organs may be involved, though cardiac, renal, and pulmonary manifestations are generally responsible for the most severe manifestations of the disease. More than 30 different serum proteins have been shown to be responsible for amyloidosis, the most common being related to light chains (AL amyloidosis), serum amyloid A protein (AA amyloidosis), and transthyretin (ATTR amyloidosis) [94]. Amyloidosis may be congenital or acquired and may be limited to one organ or may result in multisystem manifestations.

Clinical Features

Pulmonary manifestations of amyloidosis include pulmonary edema associated with amyloid cardiomyopathy, pleural disease, interstitial lung disease with characteristic septal thickening, pulmonary nodules (amyloidomas), pulmonary hypertension, laryngeal amyloidosis, and tracheobronchial amyloidosis [95]. Tracheobronchial amyloidosis is a rare manifestation of the disease overall and is usually present as a form of localized amyloidosis (i.e., limited to the airways) [95, 96]. It is more common in men and becomes apparent in the fifth or sixth decade of life.

Symptoms are nonspecific and may include cough, sputum production, hemoptysis, wheezing, or stridor, depending on the severity of the airway obstruction. Associated laryngeal amyloidosis may result in significant hoarseness. Distal endobronchial involvement may also be present, potentially leading to post-obstructive pneumonia or atelectasis.

Pulmonary Function Studies

Pulmonary function studies reveal findings that generally correlate with the degree of airway involvement and may be normal in mild cases or reveal airflow obstruction in more severe cases. The flow–volume loop may reveal plateauing of the inspiratory and/or expiratory loop, depending on the anatomical level and extent of obstruction (see preceding chapters). Mixed obstructive/restrictive lung disease is possible in cases of combined airway and interstitial lung disease but is uncommon.

Imaging Studies

Chest radiography is generally not helpful in the diagnosis of tracheobronchial amyloidosis. A chest CT may reveal an irregular and thickened tracheal wall with occasional mass-like lesions protruding into the lumen (Fig. 5.8) [96, 97]. One characteristic finding is tracheal and bronchial calcifications,

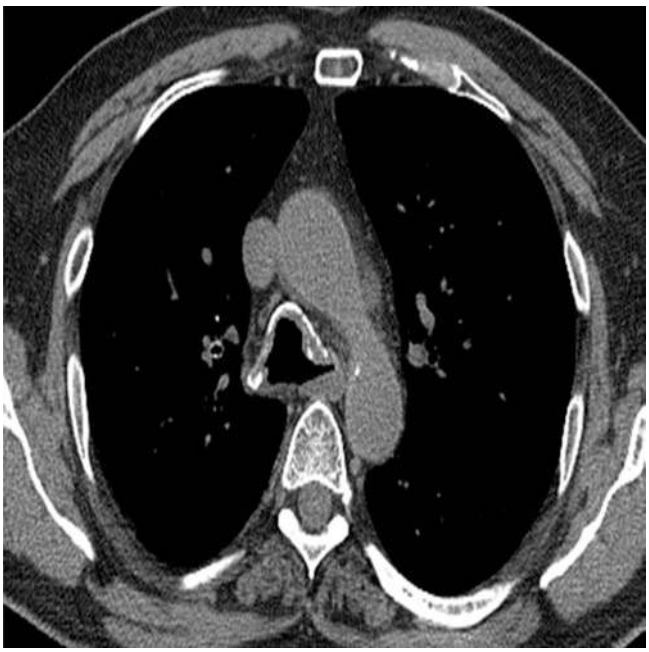

Fig. 5.8 A CT scan of the chest of a 64-year-old man with tracheobronchial amyloidosis demonstrating nodular thickening of the tracheal wall with calcifications

for which a limited differential diagnosis exists (age-related changes, relapsing polychondritis, and tracheobronchopathia osteochondroplastica). The main differential diagnosis is tracheobronchopathia osteochondroplastica, with the notable difference that the posterior membrane is typically uninvolved in tracheobronchopathia osteochondroplastica, though both conditions have been shown to occasionally occur in the same individual. Imaging using positron emission tomography may help distinguish amyloid deposits from malignancy, showing limited ^{18}F-flurodeoxyglucose uptake on delayed images in amyloidosis [98].

Bronchoscopy

Bronchoscopy is warranted to establish the diagnosis. Tracheobronchial amyloidosis is typically characterized by the presence of raised waxy yellowish or erythematosus nodules that may bleed easily on contact or during biopsies. Cobblestoning of the mucosa due to submucosal amyloid deposition may also been seen. Lesions may be focal or diffuse in extent. EBUS shows a thickening of the bronchial mucosa without infiltration of the deeper tissues. EBUS can be helpful in directing the site of biopsy to avoid bleeding, assisting in the choice of the more appropriate endobronchial intervention as reported for other nonmalignant causes of tracheal stenosis (relapsing polychondritis, granulomatosis with polyangiitis, and idiopathic subglottic stenosis). The diagnosis is established on the basis of positive staining with Congo Red, with a typical apple-green birefringence when viewed under polarized light.

Treatment

Treatment for tracheobronchial amyloidosis should be individualized based on the severity of the clinical manifestations and the extent of the disease. Rigid bronchoscopy is often needed in the management of cases of severe endoluminal obstruction using mechanical debulking with or without laser therapy. Endotracheal and/or endobronchial stents are rarely needed unless tracheobronchomalacia is present. Surgery is rarely an option, but tracheostomy may be considered if it can successfully bypass the area of narrowing. As tracheobronchial amyloidosis most often is an organ-limited disease, systemic therapies are generally not needed. Several reports suggest that external beam radiotherapy may be of benefit in patients with symptomatic tracheobronchial disease [99, 100]. As usual, supportive care should include appropriate antibiotics when needed, immunizations, and bronchopulmonary hygiene measures. Prognosis varies widely with some patients remaining stable over many years, whereas others gradually deteriorate with a poor 5-year survival [96].

Tracheobronchial Amyloidosis: Key Points

- Usually limited to the respiratory tract (i.e., no extrapulmonary involvement)
- Congo Red stain of the biopsy specimen demonstrating apple-green birefringence seen under polarized light establishes the diagnosis
- Biopsy may result in significant bleeding
- Treatment is symptomatic and external beam radiation therapy may have a role

Sarcoidosis

Clinical Vignette

A 35-year-old man with a past medical history of stage I sarcoidosis develops hoarseness and shortness of breath. Chest radiography suggests mediastinal lymphadenopathy, unchanged when compared to previous chest radiographs. A chest CT reveals slightly enlarged mediastinal and hilar lymphadenopathy but no obvious infiltrates. Narrowing of the proximal right main stem bronchus is noted, and bronchoscopy is performed. Infiltration of the laryngeal tissue is noted with limitation of the vocal cord movements but no true paralysis. The trachea is diffusely involved with inflammation and cobblestoning with marked narrowing of the origin of the right main stem bronchus. Biopsies confirm the presence of non-necrotizing granulomas without evidence of malignancy.

Introduction

Sarcoidosis is a multisystem disease characterized by the presence of non-necrotizing granulomas in the absence of an identifiable cause. Multiple organs may be affected by the disease, but the predominance of the respiratory manifestations (>90% of the cases) suggests that an inhaled offender may trigger an exuberant type IV immune reaction responsible for the manifestations of the disease. Sarcoidosis can also affect many other organs including the heart, eyes, skin, peripheral and central nervous systems, joints, and kidneys.

Respiratory manifestations of sarcoidosis are varied and include mediastinal and hilar lymphadenopathy, micronodular parenchymal infiltrates, and pulmonary fibrosis. Rare manifestations of the disease include cavitary lesions (as in necrotizing sarcoid granulomatosis), pleural effusions, pulmonary hypertension, and airway involvement including laryngeal and tracheobronchial sarcoidosis [101, 102].

Pulmonary Function Studies

Pulmonary function studies may be normal in mild cases of airway involvement in sarcoidosis or may reveal various combinations of obstructive and/or restrictive defects depending on the extent and severity of intrathoracic involvement. Central airway involvement can result in characteristic abnormalities in the flow–volume curve with an inspiratory and/or expiratory plateau depending on the location and extent of the tracheobronchial lesions.

Imaging Studies

Although bronchoscopy remains the gold standard, imaging studies may offer supportive evidence of the diagnosis. Chest radiography is rarely normal in sarcoidosis and typically reveals mediastinal and/or hilar lymphadenopathy with varying degrees of reticular or reticulonodular infiltrates, but the central airways are difficult to evaluate. A chest CT may show airway distortion or extrinsic compression from adjacent enlarged lymph nodes. Mucosal involvement may manifest as thickening of the wall of the trachea or main stem bronchi. Additional findings suggestive of sarcoidosis include micronodular infiltrates in a perilymphatic distribution and reticular, fibrotic changes that typically predominate in the upper and mid lungs.

Bronchoscopy

Central airways are less commonly involved than distal airways in sarcoidosis. Granulomatous inflammation results in thickening of the tracheal and bronchial mucosa with a characteristic "cobblestone" appearance and may lead to significant obstruction of the airway lumen [102]. Other manifestations include hypervascularity of the mucosa, granular infiltration, plaques, and polypoid lesions. Although symptomatic tracheobronchial sarcoidosis is relatively uncommon, up to 60% of patients with sarcoidosis will exhibit some types of endobronchial abnormalities, making bronchoscopy the diagnostic method of choice when sarcoidosis is suspected [102]. In fact, non-necrotizing granulomas are frequently observed on random endobronchial biopsies in patients with asymptomatic sarcoidosis, particularly when the biopsies are relatively deep and include submucosal lymphatic vessels. Occasionally, the airways may be narrowed as a consequence of extrinsic compression by enlarged mediastinal and hilar lymph nodes. A typical presentation is that of the "right middle lobe syndrome" in which the right middle lobe bronchus is easily compressed by regional lymphadenopathy, leading to impaired secretion clearance and recurrent infections. Finally, severe cases of upper lobe fibrosis may result in airway distortion with resultant fibrostenosis and central airway obstruction [101–103].

Treatment

The treatment is tailored to the severity of the airway involvement. In asymptomatic disease, monitoring without specific treatment is generally appropriate. In advanced disease, systemic corticosteroids may be warranted, whereas mild cases may be treated with only inhaled steroids. Bronchoscopic interventions can include balloon tracheo- and/or bronchoplasty and laser resection with or without stent placement [104–108].

Respiratory Tract Sarcoidosis: Key Points

- Tracheal stenosis is a rare manifestation of sarcoidosis. Biopsies are usually diagnostic, revealing non-necrotizing granulomas
- Treatment with inhaled or systemic steroids may be beneficial

Orphan Tracheopathies: Conclusions

Diseases specifically affecting the trachea are uncommon compared to other respiratory diseases. As such, the diagnosis of tracheopathy is often delayed and affected patients are commonly misdiagnosed to have other conditions such as asthma or COPD. Clues hinting at the possibility of central

airway lesions include stridor or monophonic "central" wheezing and poor response to bronchodilator therapy. Pulmonary function studies can provide important clues, particularly when the shape of the inspiratory/expiratory flow–volume curve is evaluated. Advances in the acquisition protocols of CT imaging and image resolution have considerably improved the identification and characterization of tracheal diseases, but bronchoscopy remains the gold standard in the diagnostic evaluation and can allow assessment for specific interventions. Treatment of the underlying cause is warranted whenever possible. The approach to diagnosis and management should include a multidisciplinary team of clinicians, radiologists, pathologists, and interventional pulmonologists.

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Part III

Systemic Disorders with Lung Involvement

Amyloidosis and the Lungs and Airways

6

Helen J. Lachmann and Jennifer H. Pinney

Introduction

Amyloids occur due to the deposition of soluble plasma proteins within the extracellular space in an abnormal insoluble fibrillar form. Amyloidosis describes a group of diseases caused by the resulting disruption of the tissue structure and organ function. The diagnosis is often made late in the disease course, frequently as an unexpected histological finding when a failing organ is biopsied. It may be either acquired or inherited, and at least 30 different proteins can form amyloid fibrils in humans [1] (Table 6.1). In the right conditions, almost any polypeptide chain can be driven towards misfolding and aggregation but relatively few proteins are amyloidogenic in vivo. There are essentially three circumstances in which amyloid deposition occurs. The first is when there is a sustained, abnormally high abundance of proteins that are normally present at low levels, such as serum amyloid A protein (SAA) in chronic inflammation or beta-2 microglobulin in chronic renal failure. The second is when there is normal abundance of a normal but inherently amyloidogenic protein over an extremely prolonged period, such as transthyretin. The third situation is the presence of an abnormal protein, which is markedly amyloidogenic, such as monoclonal immunoglobulin light chains in AL amyloidosis and genetic variants of transthyretin, apolipoprotein AI, fibrinogen Aα chain, etc. in autosomal dominant hereditary amyloidosis.

The ultrastructural morphological and histochemical properties of all amyloid fibrils, regardless of the precursor protein type, are remarkably similar. Diffraction studies of amyloid fibrils have confirmed that they all share a common core structure consisting of anti-parallel β-strands lying perpendicular to the long axis of the fibrils. This extremely abnormal, highly ordered conformation underlies the distinctive physicochemical properties of amyloid fibrils. The fibrils are relatively stable and are resistant to proteolysis. All amyloid fibrils possess the ability to bind molecules of the dye Congo Red in a spatially organised manner, which results in a pathognomonic apple-green birefringence when viewed under crossed polarised light. Amyloid deposits also always contain the normal plasma glycoprotein, serum amyloid P component (SAP) as a non-fibrillar constituent. The universal presence of SAP in amyloid deposits reflects its specific binding to an as yet uncharacterised ligand common to all amyloid fibrils, which forms the basis for diagnostic scintigraphic imaging of amyloids with radiolabelled SAP [2].

The phenotypes associated with amyloid deposition are diverse, ranging from an asymptomatic, small, localised deposit to a systemic, rapidly lethal multi-system disease [3]. Clinically important amyloid deposits accumulate in the extracellular space, progressively disrupting the structure, integrity and function of the tissues and organs. The natural history of amyloidosis is usually of progressive accumulation, although as amyloid deposits are constantly turned over, clinical progression reflects the fact that the fibrillar deposits are laid down faster than they are cleared away [4]. Amyloid deposits can therefore regress if this balance is tipped in favour of clearance; current treatment strategies have focused on reducing the supply of fibrils by halting the production of the culpable plasma protein. Although treatment is not always effective as many of the conditions that underlie systemic amyloidosis are progressive and unremitting, there are numerous reports describing regression of amyloidosis when associated inflammatory and other diseases have been successfully treated.

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Table 6.1 Classification of the more common types of systemic amyloidoses in humans

Type	Fibril protein precursor	Clinical syndrome
AA	Serum amyloid A protein	Reactive systemic amyloidosis associated with chronic inflammatory diseases
AL	Monoclonal immunoglobulin light chains	Systemic amyloidosis associated with monoclonal plasma cell dyscrasias
AH	Monoclonal immunoglobulin heavy chains	Systemic amyloidosis associated with monoclonal plasma cell dyscrasias
$A\beta_2M$	Normal plasma β_2-microglobulin	Periarticular and, occasionally, systemic amyloidosis associated with long-term dialysis
$A\beta_2M$	Variant β_2-microglobulin	Autosomal dominant hereditary systemic amyloidosis
ATTR	Normal plasma transthyretin	Wild-type systemic TTR amyloidosis with prominent cardiac involvement
ATTR	Genetically variant transthyretin	Autosomal dominant systemic amyloidosis
		Familial amyloid polyneuropathy or cardiomyopathy
ACys	Genetically variant cystatin C	Autosomal dominant Systemic amyloidosis
		Hereditary cerebral haemorrhage with cerebral and systemic amyloidosis
AGel	Genetically variant gelsolin	Autosomal dominant systemic amyloidosis
		Predominant cranial nerve involvement with lattice corneal dystrophy
ALys	Genetically variant lysozyme	Autosomal dominant systemic amyloidosis
		Non-neuropathic with prominent visceral involvement
AApoAI	Genetically variant apolipoprotein AI	Autosomal dominant systemic amyloidosis
		Predominantly non-neuropathic with prominent viscera involvement
AApoAII	Genetically variant apolipoprotein AII	Autosomal dominant systemic amyloidosis
		Non-neuropathic with prominent renal involvement
AApoAIV	Apolipoprotein AIV	Sporadic systemic amyloidosis with predominant cardiac and renal involvement
AApoCII	Genetically variant apolipoprotein CII	Autosomal dominant systemic amyloidosis
		Non-neuropathic with prominent renal involvement
AApoCIII	Genetically variant apolipoprotein CIII	Autosomal dominant systemic amyloidosis
		Non-neuropathic with prominent renal involvement
AFib	Genetically variant fibrinogen A alpha chain	Autosomal dominant systemic amyloidosis
		Non-neuropathic with prominent renal involvement
ALect 2	Leukocyte chemotactic factor 2	Sporadic slowly progressive renal amyloid with nephrotic syndrome and liver involvement
ALys	Genetically variant lysozyme	Autosomal dominant systemic amyloidosis
		Non-neuropathic with prominent renal and hepatic involvement

Diagnosis and Evaluation of Amyloidosis

As amyloidosis is a remarkably heterogeneous disease, it may present to a variety of different medical specialties. There are several reasons for patients with amyloidosis to present to a respiratory physician. Chronic pulmonary conditions can themselves give rise to systemic amyloidosis, most commonly of the AA type. Although these patients rarely present with symptomatic involvement of the lungs, the underlying pulmonary disease is the driver of the amyloidogenic protein production and it is therefore important to recognise those patients at risk. Patients with systemic amyloidosis may also present with respiratory symptoms as a consequence of the amyloidosis itself, whereby amyloid deposits are found in the lungs as a component of a more systemic process. Localised, isolated pulmonary and respiratory tract amyloid deposits are also well-described and may either present with symptoms or may be detected incidentally on chest radiography or a biopsy [5]. Finally, it is important to recognise that, especially in the context of AL amyloidosis, pulmonary complications may also arise from treatment.

The diagnostic gold standard of amyloidosis is histological confirmation through Congo Red staining, which produces a red-green birefringence under crossed polarised light [6, 7] (Fig. 6.1). Most tissue specimens, ranging from needle biopsies to open surgical resections, can be studied, although small biopsies are open to sampling errors. A biopsy of any organ can be hazardous in amyloidosis as there is an increased risk of haemorrhage; significant bleeds having been reported

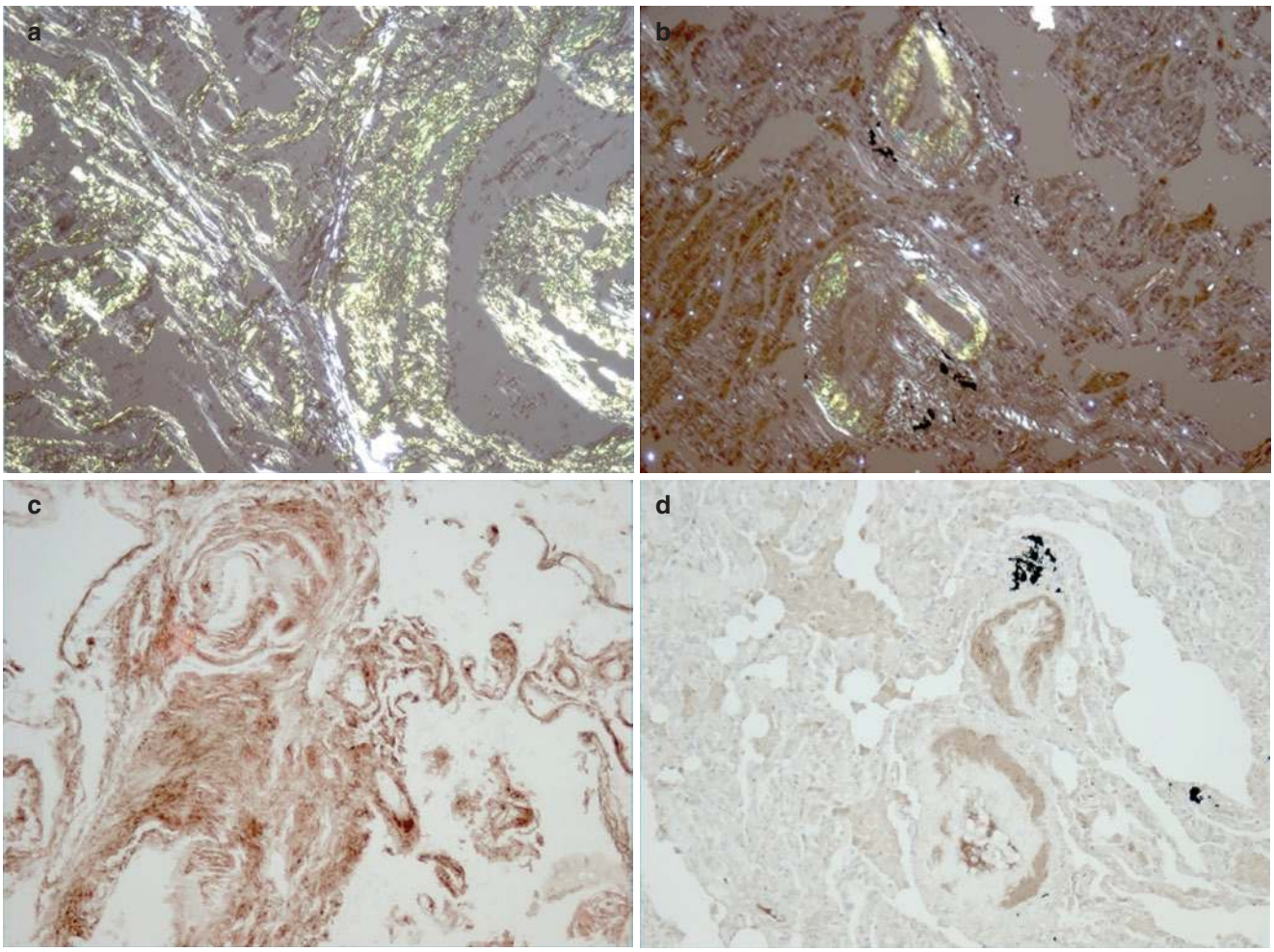

Fig. 6.1 (**a**) Bronchial biopsy showing characteristic histological appearance of amorphous amyloid deposits stained with Congo Red. (**b**) The same section viewed under crossed polarised light demonstrating an apple-green birefringence. Confirmatory testing is shown by immunohistochemistry using anti-lambda light chain antibodies (**c**) and anti-transthyretin antibodies (**d**)

in 5% of liver biopsies [8], although recent data from renal biopsies have been more reassuring [9]. A case report from 1987 described fatal lung haemorrhage following a transbronchial biopsy in a patient with amyloidosis. The postmortem findings showed that the biopsied blood vessels were infiltrated by amyloids [10]. A further case series by Utz et al. published in 1996 reported no major complications in 11 patients, following transbronchial lung biopsies; however, 2 of the 11 cases were reported to have 100 mL blood loss [11]. More encouragingly, a study from a single centre in 2017 reported no bleeding in 25 cases diagnosed by transbronchial biopsy [12]. Haemorrhage in amyloidosis is due to the increased fragility of the involved blood vessels, reduced elasticity of the amyloidotic tissues and, very occasionally, in the AL type, an acquired deficiency of clotting factors IX or X [13–15]. A less invasive alternative in suspected disease is fine needle aspiration, and this has been successfully used in the respiratory tract [16–18]. Immunohistochemical stains are then used to determine the fibril protein type [5, 19]. Suitable antibodies are widely available, but, although immunohistochemistry is usually definitive in AA amyloidosis, it is non-diagnostic in about 20% of AL deposits [20, 21]. Expertise in the typing of hereditary amyloids is restricted, and definitive immunohistochemical typing of amyloid deposits cannot always be achieved. Mass spectrometry is extremely useful in those patients who cannot be confidently diagnosed through immunohistochemical typing; its use is limited by current availability but will become more routine in future practice [22].

If a genetic variant is suspected, then more detailed analyses examining for mutations in the gene giving rise to the amyloidogenic fibrils should be performed (Fig. 6.2). In general, sequencing is the preferred modality, and ideally samples should be sent to a reference laboratory with expertise in this area. A web-based repository reviewing all currently known mutations in genes with amyloidogenic potential helps guide these investigations (http://amyloidosismutations.com).

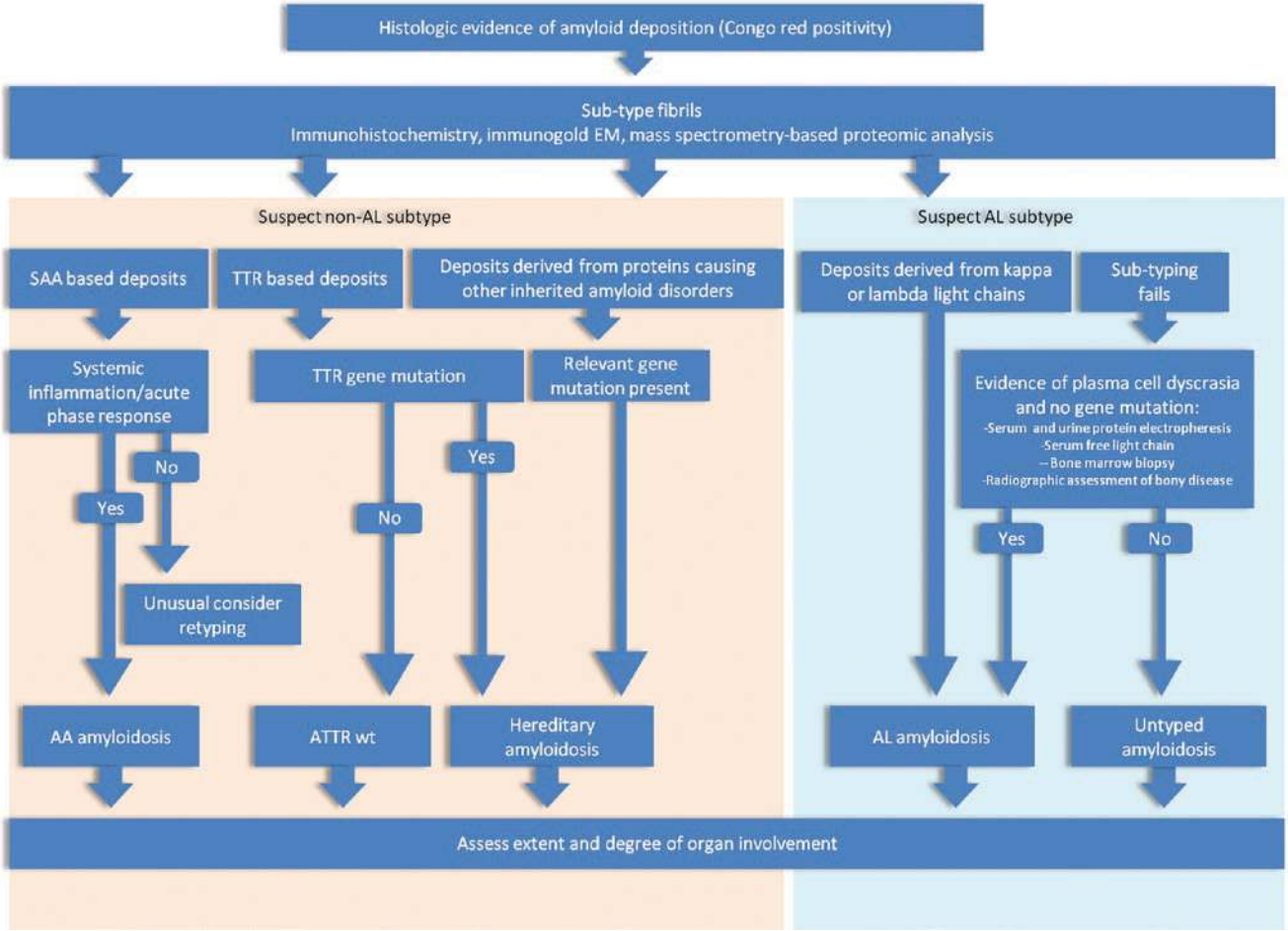

Fig. 6.2 Algorithm for investigations of patients with suspected amyloidosis

Once there is histological confirmation of amyloidosis, the extent of deposits needs to be ascertained. In respiratory tract amyloidosis, this can be challenging and the optimum imaging technique can vary depending upon the distribution of deposits. Plain radiography as an initial assessment can be helpful but may be normal in many cases. Computed tomography (CT) scanning is particularly useful in further defining interstitial diseases. In combination with positron emission tomography (PET) imaging, it can also help to better define the metabolic activity of a solid lesion, thus aiding in differentiation from more typical intrathoracic malignancies or metastases as well as rare entities such as plasmacytomas [23]. In addition, magnetic resonance imaging (MRI) and bronchoscopy may also be useful in combination with comprehensive pulmonary function tests (PFTs). PFTs are an important objective tool to formally establish the severity of clinically relevant diseases and are useful in guiding therapeutic decisions [5, 24]. Evidence of systemic diseases should be sought clinically by performing haematological and biochemical profiles. The plasma cell clones that underlie systemic AL amyloidosis are often subtle and may not be detected by bone marrow examination or immunofixation of the serum and urine; use of a serum-free light-chain assay increases diagnostic sensitivity [25–28]. Immunoglobulin gene rearrangement studies may identify subtle clones in either the bone marrow or, in the case of localised AL, within the amyloid biopsy material [29] (Fig. 6.1c, d).

Radiolabelled SAP specifically localises to amyloid deposits in vivo in proportion to the quantity of amyloids present and thereby enables diagnosis, quantification and monitoring of the amyloids [2]. SAP scintigraphy is useful in visualising amyloids in solid organs; localisation to the lungs is poor and not routinely used for monitoring amyloid deposits in the respiratory tract (Fig. 6.3a, b). Cardiac amyloidosis is best evaluated by a combination of echocardiography, electrocardiogram (ECG) and cardiac magnetic resonance imaging (CMR). Two-dimensional Doppler echocardiography classically reveals concentric biventricular wall thickening with a restrictive filling pattern [30] (Fig. 6.3b). Amyloidosis causes diastolic dysfunction with preserved contractility until an extremely late stage [31]. The ECG may be normal in patients with substantial cardiac

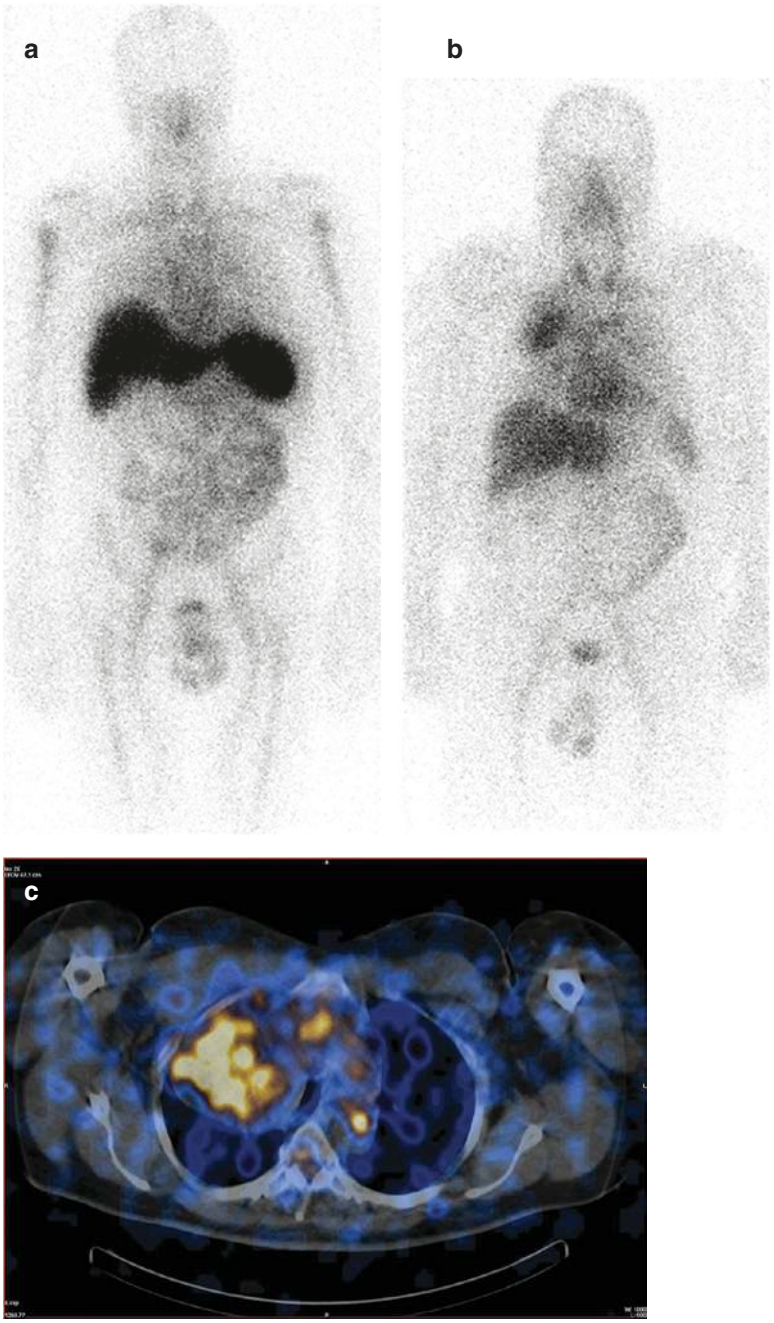

Fig. 6.3 Scintigraphic assessments using ^{123}I-human SAP. An anterior whole body scintigraphic image from a patient obtained following intravenous injection of ^{123}I-human SAP showing abnormal uptake into the amyloid deposits within the spleen, liver and bone marrow (**a**). An anterior plasmacytoma and deposition in the spleen. An anterior whole body scintigraphic image from a patient with a solitary intrathoracic amyloidoma (**b**) with corresponding SPECT-CT (**c**)

amyloidosis, but, in advanced disease, it commonly shows small voltages, pathological 'Q' waves (a pseudo-infarct pattern) in the anterior chest leads and conduction abnormalities. CMR is extremely useful in identifying cardiac amyloidosis. Typical appearances are of homogeneous late gadolinium enhancement [32]. ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) scintigraphy is a specific test indicative of fibril deposition within the heart, with data suggesting that the degree of uptake and pattern of distribution in the extracardiac soft tissue may be specific for amyloid transthyretin (ATTR) amyloidosis [33, 34]. Elevation of N-terminal pro-brain natriuretic peptide (NT-Pro-BNP) and cardiac troponins can also be helpful in establishing whether a patient has cardiac amyloidosis [35, 36]. These enzymes are not specific and can be elevated for other reasons such as renal impairment and other forms of cardiomyopathy; however, a normal NT-Pro-BNP can exclude cardiac involvement [37].

The key to effective monitoring of amyloidosis and its treatment is relatively frequent repetition of these investigations, bearing in mind that organ dysfunction may not closely reflect amyloid load.

Systemic Amyloidosis Complicating Respiratory Diseases

Systemic AA Amyloidosis

Systemic AA amyloidosis is a potential complication of any disorder associated with a sustained acute-phase response, and the list of chronic inflammatory, infective or neoplastic disorders that can underlie it is almost without limit (Table 6.2). Biopsy and postmortem series suggest that the prevalence of AA amyloid deposition in patients with chronic inflammatory diseases is between 3.6% and 5.8%, though a smaller proportion of patients have clinically significant amyloidosis [38–40]. The amyloid fibrils are derived from cleavage fragments of the circulating acute-phase reactant, SAA [41]. SAA is an apolipoprotein of high-density lipoprotein (HDL), which is synthesised by hepatocytes under the transcriptional regulation of cytokines including interleukin (IL)-1, IL-6 and tumour necrosis factor-α (TNF-α) [42]. In health, the circulating concentration of SAA is around 1 mg/L, but this can rise by more than a 1000-fold in the presence of inflammation. The circulating concentration of SAA tends to be parallel to that of the much more frequently measured C-reactive protein (CRP). A sustained high plasma level of SAA is a prerequisite for the development of AA amyloidosis, but the reason why amyloidosis develops in only a small proportion of cases remains unclear. AA amyloidosis can present anytime between childhood and old age with a median age at presentation of 48 years in the UK. It is slightly more common in men and, although the disease can develop extremely rapidly, the median latency between presentation with a chronic inflammatory disorder and clinically significant amyloidosis is almost two decades [43].

Table 6.2 Conditions with respiratory manifestations associated with systemic AA amyloidosis

Chronic infections	**Neoplasia**
Bronchiectasis	Adenocarcinoma of the lung
Q fever	Carcinoid tumour
Subacute bacterial endocarditis	Castleman's disease
Tuberculosis	Hodgkin disease
Immunodeficiency states	Mesothelioma
Common variable immunodeficiency	**Inflammatory arthritis**
Cyclic neutropenia	Adult Still's disease
Hyperimmunoglobulin M syndrome	Ankylosing spondylitis
Hypogammaglobulinaemia	Rheumatoid arthritis
Sex-linked agammaglobulinaemia	**Systemic vasculitis**
HIV/AIDS	Behcet's disease
Other conditions predisposing to chronic infections	Systemic lupus erythematosus
Cystic fibrosis	**Others**
Kartagener syndrome	SAPHO syndrome
Quadriplegia	Sarcoidosis
Sickle cell anaemia	Sinus histiocytosis with massive lymphadenopathy

The most common respiratory disease underlying AA amyloidosis in the United Kingdom is bronchiectasis, accounting for 5% cases. A study of 16 patients with end-stage renal failure secondary to AA amyloidosis due to bronchiectasis in Turkey reported the mean duration of bronchiectasis to be 22.18 years, with a wide range of ±12.02 years. The mean age at presentation was 50.6 ± 13.5 years. Eight cases (50%) had cystic bronchiectasis and four of these eight patients died from suppurative pulmonary infections. The other eight patients had chronic fibrotic changes, and four of these were considered to be the sequelae of previous tuberculosis (TB) infections [44]. The prevalence of bronchiectasis is falling due to earlier treatment of necrotising pneumonia and prevention of pulmonary infections via routine immunisation programmes; hopefully, this will also lead to a reduction of patients with AA amyloidosis from this cause.

Lung neoplasia including Castleman's tumours, lymphomas and adenocarcinomas account for 3% of cases of AA amyloidosis. Castleman's disease [45], or angiofollicular lymph node hyperplasia, is a rare B-cell lymphoproliferative disorder characterised by giant hyperplastic lymph node follicles, capillary proliferation and plasma cell infiltration, and it is often associated with marked constitutional symptoms. It comprises solitary and multicentric forms, and there are hyaline vascular and plasma cell variants histologically [46]. Multicentric disease, commonly of the plasma cell type, usually has an aggressive and rapidly fatal course. Unicentric disease tends to occur in younger patients and is of the hyaline vascular type in more than 70% of cases and of the plasma cell type or mixed histology in the remainder [47, 48]. Most solitary tumours occur within the mediastinum and consist of a dominant mass surrounded by multiple enlarged lymph nodes, which, histologically, may appear merely reactive. Constitutional symptoms including night sweats, fever and weight loss are common and laboratory abnormalities including anaemia, elevation of the erythrocyte sedimentation rate (ESR) and polyclonal hypergammaglobulinaemia are almost universal. Acquired systemic amyloidosis is a recognised rare complication of all forms of angiofollicular lymph node hyperplasia and is usually of the systemic AA type, occurring as a result of the persistent acute-phase response [49–52]. In Castleman's disease, there is production of IL-6 by the tumour and anti-IL-6 therapies can be highly effective [51–56]. In other lymphomas, the exact pathophysiology resulting in a systemic acute-phase response is less well-understood [57]. A surgical resection of unicentric tumours can result in complete remission and excellent long-term outcome [49].

Other purely respiratory causes of AA amyloidosis are now fairly rare in the UK, although in the first half of the last century, tuberculosis was common, and this remains the case in parts of the developing world and is likely to be underreported [58, 59]. Other rare associations include cystic fibrosis [60, 61], sarcoidosis [62] and Kartagener syndrome [63].

AA amyloidosis usually presents with proteinuria, which can be heavy. Progressive renal dysfunction follows, often accompanied by nephrotic syndrome [64]. Splenic amyloid deposits are almost universally present but are often asymptomatic and frequently impalpable. Hepatic involvement and autonomic neuropathy are well-recognised in advanced disease. Cardiac amyloidosis is extremely rare, occurring in less than 2% of cases. Respiratory tract involvement has not been a clinical feature among more than 400 patients with systemic AA amyloidosis evaluated in our unit, and although there have been a few reports of systemic AA amyloidosis affecting the lungs, fibril typing was generally imperfect [65], and all studies in which the fibril protein has actually been sequenced have been identified to be of the AL type.

A diagnosis of amyloidosis relies on a high index of clinical suspicion. The most effective form of basic screening in medical or respiratory practice is to target patients at a risk of developing AA amyloidosis with ongoing poorly controlled inflammation and to perform urinalysis on each clinic attendance. More than 95% of patients with AA amyloidosis will have significant proteinuria on dipstick testing, which should prompt investigation. The prognosis of AA amyloidosis depends on the degree of renal dysfunction at presentation and whether the underlying chronic inflammatory disease can be effectively suppressed so that the median plasma SAA is maintained below 10 mg/L. When the supply of the fibril precursor protein is substantially reduced for sustained periods, AA amyloid deposits frequently regress and renal function can improve [43, 64, 66]. If the acute-phase response continues unabated, then progressive amyloid deposition often results in end-stage renal failure. In individuals who present with advanced renal disease, even complete suppression of their inflammatory disease may not be sufficient to preserve their renal function and in all cases renal deterioration is accelerated by hypertension. Treatment depends on the underlying diagnosis and may include surgery for cytokine secreting tumours or localised bronchiectasis, long-term antimicrobials and postural drainage for chronic infections associated with structural lung problems in cystic fibrosis or Kartagener and immunosuppression in inflammatory diseases such as sarcoidosis.

Almost 40% of patients with AA amyloidosis eventually develop dialysis-dependent renal failure. Renal outcomes on dialysis are equivalent to those of age-matched non-diabetic patients on the end-stage programme with a median survival of 53 months. Mortality is higher in the first year, and this has been attributed to ongoing heavy urinary protein losses and increased risk of sepsis [67, 68]. Nephrotic syndrome is a major risk factor for sepsis, particularly in patients predisposed to infection, such as those with bronchiectasis, in whom the risk of further infection is even greater and outcome may well be poor. A minority of patients go on to receive renal transplants [68–70]. The published outcomes are rather variable, but our series of almost 40 highly selected patients with well-suppressed SAA levels had a 5-year graft survival of 82%.

Systemic AL Amyloidosis

This is the most common type of systemic amyloidosis accounting for more than 60% of cases [71] and may potentially occur in association with any form of monoclonal B-cell dyscrasia. The precursor proteins are monoclonal immunoglobulin light chains and generally consist of the whole or part of the variable (V_L) domain [72].

A number of conditions localised to the thoracic cavity can underlie systemic AL amyloidosis. An isolated plasmacytoma presenting as a chest mass can secrete enough monoclonal-free immunoglobulin light chains into the circulation to produce systemic AL amyloid deposits [73] (Fig. 6.4a, b). Castleman's tumours, both unicentric and multicentric, can be associated with monoclonal immunoglobulin light-chain production and are a rare cause of AL amyloidosis [74]. The most common condition managed by respiratory physicians, which can cause both systemic and respiratory localised AL amyloid deposits, is Sjögren's syndrome, which is discussed later.

A degree of amyloid deposition is seen in up to 15% of patients with myeloma, but the vast majority, more than 80%, who present with clinically significant AL amyloidosis have an extremely low grade and otherwise 'benign' monoclonal gammopathies [75]. AL amyloidosis usually presents over the age of 50 years, although it can occur in young adults [75]. Clinical manifestations are extremely variable since almost any organ other than the brain can be directly involved [76]. Although specific clinical features can be strongly suggestive of AL amyloidosis (Table 6.3), and multiple vital organ dysfunction is common, many patients present with non-specific symptoms such as malaise and weight loss. The outlook of untreated AL amyloid is far worse than that of the AA type, with a 5-year survival of approximately 10% and a 10-year survival of less than 5% [75]. Most affected individuals eventually die of heart failure, uraemia or autonomic failure.

In most cases, there is substantial histological cardiac involvement, and restrictive cardiomyopathy is the presenting feature in up to one-third of patients and ultimately the cause of death in one-half [77]. Renal involvement is frequent in AL amyloidosis and presents in the same manner as renal AA amyloidosis [78]. Gut involvement can cause motility disturbances (often secondary to autonomic neuropathy), malabsorption, perforation, haemorrhage or obstruction [79]. Peripheral neuropathy occurs in one-fifth of cases and typically presents with a painful sensory polyneuropathy, followed later by motor deficits [75]. Autonomic neuropathy causing orthostatic hypotension, impotence and gastrointestinal disturbances may occur in isolation or with a peripheral neuropathy [76].

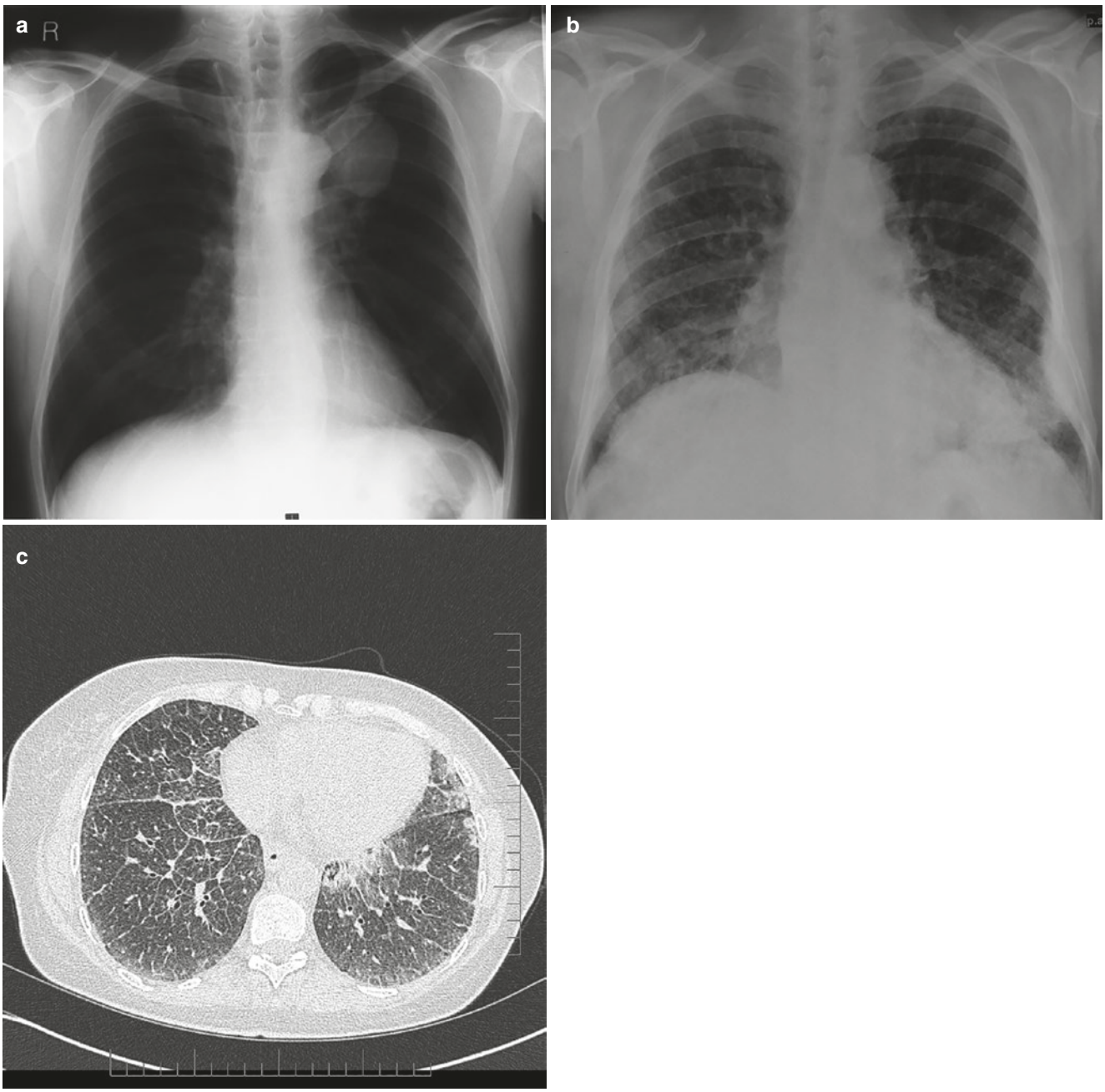

Fig. 6.4 (**a**) A CXR demonstrating a mass in the left upper lobe; this was diagnosed as a plasmacytoma with associated AL amyloid deposition following a biopsy. (**b**) A posterior whole-body scintigraphic image from the same patient obtained following an intravenous injection of ^{123}I-human SAP, showing abnormal uptake into the amyloid deposits within the plasmacytoma and deposition in the spleen. High resolution CT of the chest on the same patient confirming intersitial infi ltration (**c**)

Although microscopic deposits of amyloids are universally present in the lungs, in the vast majority of cases, dyspnoea is secondary to cardiac involvement. The chest radiograph is usually normal in systemic AL amyloidosis but may demonstrate a diffuse alveolar septal pattern, and this can be associated with pulmonary hypertension and respiratory failure [80]. When pulmonary symptoms do develop, the outlook is grave and responds poorly to therapy [80, 81]. Patients are often highly dyspnoeic, which may be further compounded by amyloid-induced cardiac dysfunction. The pathophysiology is due to deposition of amyloid fibrils within the small airways and the capillary alveolar membrane, leading to impaired gas exchange and respiratory failure detectable by decreased carbon monoxide diffusion capacity. With more widespread involvement, a restrictive defect can occur similar to that seen in pulmonary fibrosis. Pulmonary function testing provides a quantitative means of both assessing a patient's baseline dysfunction and tracking the progression or response to treatment. Lung function tests may show a restrictive pattern and more rarely reduced gas transfer [82].

Table 6.3 Clinical features associated with systemic AL amyloidosis

Organ involvement	Clinical manifestation
Soft tissue infiltration	Bruising—especially periorbital; macroglossia; muscle/joint pseudohypertrophy
Renal	Proteinuria; nephrotic syndrome; nephrotic syndrome; hypertension very rarely
Cardiac	Restrictive cardiomyopathy; arrhythmias; congestive cardiac failure
Hepatic	Hepatomegaly; liver failure very rarely
Peripheral nervous system	Carpal tunnel syndrome; symmetrical sensorimotor neuropathy
Autonomic nervous system	Orthostatic hypotension; impotence; disturbed bowel motility; impaired bladder emptying
Gastrointestinal	Weight loss; blood loss; disturbed bowel motility
Lymphoreticular	Splenomegaly; lymphadenopathy
Adrenal axis	Hypoadrenalism (rare)

Radiographically, the features can mimic a number of interstitial infiltrative diseases [83]. Plain films often show a reticular pattern, and, on CT, interstitial infiltrates are seen mimicking more common interstitial lung diseases. Fine interlobular thickening is often seen peripherally and/or subpleurally. The findings may be somewhat patchy depending on whether the amyloidosis arises from local parenchymal populations of clonal plasma cells or from a population of cells residing in the marrow. MRI often does not add to the diagnosis in this form of the disease. Similar to nodular amyloid deposits, the lesions are largely inert, showing low or no metabolic activity on PET imaging [84]. Persistent pleural effusions have been described in 5.5% of patients and are mostly associated with amyloid heart disease. Chronic effusions secondary to pleural amyloids are often refractory to diuretics and require recurrent drainage or pleurodesis [85]. Sleep-disordered breathing and sleep apnoea are increasingly recognised in systemic AL amyloidosis and other types of amyloidoses, presumably reflecting cardiomyopathy, macroglossia, neuropathy and myopathy [86, 87].

The aim of treatment in AL amyloidosis is to suppress proliferation of the underlying B-cell clone and, therefore, production of the amyloid fibril precursor protein; there are, however, many difficulties [88]. Chemotherapy regimens are based on those used in multiple myelomas, but the plasma cell dyscrasias in most AL patients are relatively low-grade and may be less chemosensitive. Diagnosis is difficult and can be delayed, and many patients have advanced multi-system disease, which limits their options for chemotherapy. Regression of amyloidosis is a gradual process, which may not lead to measurable clinical improvement or recovery of organ function for months, or even years, after successful suppression of the causative plasma cell dyscrasia [89, 90]. The rate of mobilisation of amyloid deposits varies depending on the organ. Cardiac amyloid deposits are slower to show signs of regression compared to those of the liver or kidneys, and patients with cardiac or multi-system dysfunction may not live long enough to benefit from chemotherapy [91]. However, despite these problems, many patients with AL amyloidosis do benefit substantially and chemotherapy has led to improved survival outcomes in this disease [92]. Treatment approaches need to be tailored to the individual patient based on their organ involvement. Staging systems have been developed to help guide treatment rationale and prognosis. The Mayo staging system is based on cardiac dysfunction, using cut-off values of 0.035 μg/L for troponin T and 332 pg/mL for NT-Pro-BNP. Patients can be classified into three stages: stage I, in which both biomarkers are below the cut-off value; stage II, in which one biomarker is elevated and stage III, in which both biomarkers are elevated. The reported median survivals are 26.4 months, 10.5 months and 3.5 months, respectively, for stages I, II and III [93]. Rigorous patient selection for high-dose chemotherapy is essential as procedure-related mortality is extremely high in individuals with multiple organ involvement [94, 95] and stage III patients should be excluded from stem cell transplantation [96]. The aim of treatment is to achieve adequate suppression of light-chain production with minimal treatment toxicity. Treatment response is routinely monitored using a serum-free light-chain assay. Reduction in serum-free light-chain levels is associated with improved survival [97–99]. The degree of response needed to halt production may be different for individual patients. Achieving a >90 dFLC response has been associated with improved patient outcome and organ response with a higher chance of renal recovery [100].

Immunomodulatory therapies such as bortezomib, lenalidomide and thalidomide are now routinely used in patients with AL amyloidosis. Serious pulmonary side effects are extremely rare but are well-recognised complications following the use of the proteasome inhibitor bortezomib [101]. Patients present with fever and asthma-like symptoms and progress to respiratory failure with pulmonary infiltrates on CT imaging [102]. There have also been case reports of lung toxicity, following the use of thalidomide [103] and lenalidomide [104] with toxic granulomatous interstitial pulmonary disease, which is reported to be steroid-responsive.

Thromboembolic risk is increased in some patients with AL amyloidosis, nephrotic syndrome incurs an increased risk and treatment with thalidomide and lenalidomide has also been associated with higher rates of thrombosis [105]. The recommendation is therefore to consider anticoagulation in patients on treatment for nephrotic syndrome.

Amyloidosis Localised to the Respiratory Tract

First described by Lesser in 1877, localised amyloidosis of the respiratory tract ranges from asymptomatic pulmonary nodules to diffuse parenchymal deposits [83, 106]. Presenting

symptoms can mimic a variety of lung pathologies, and initial investigations with routine imaging can be unhelpful in confirming the diagnosis. A number of classifications have been suggested based upon radiographic or bronchoscopic findings [11, 107]. In general, amyloidosis is best classified by fibril proteins (Table 6.1) and then by the sites that are clinically involved [108]. Localised amyloid deposition is not uncommon, although often undiagnosed, and results from either local production of fibril precursors [109, 110] or properties inherent to the particular microenvironment, which favour fibril formation of a widely distributed precursor protein [111]. The vast majority of localised amyloid deposits are AL in type [106, 112–114], and symptomatic deposits occur most frequently in the eyes [115], skin [116] or respiratory [11, 117] or urogenital tracts [118, 119]. They are often associated with extremely subtle focal monoclonal B-cell proliferation confined to the affected site, and surgical resection of these localised 'amyloidomas' can sometimes be curative [119]. Symptomatic and apparently localised amyloid deposits can rarely be manifestations of a systemic disease, and patients should always be fully investigated to exclude more generalised amyloid deposition [19].

A thorough evaluation of respiratory tract amyloidosis and biopsy confirmation is required to determine the need for treatment and the most suitable modality. The paucity of controlled clinical trials means that management decisions have to be made on an individual basis. Broadly speaking, systemic chemotherapy is usually indicated for systemic AL amyloidosis and local intervention, according to symptoms for its localised forms.

Laryngeal Amyloidosis

The larynx is the most frequent site of localised amyloidosis, affecting the head and neck [120, 121]. It represents 0.5–1% of benign laryngeal disease and its incidence increases with age, but it occasionally affects young adults or children [122]. Discrete nodular and diffuse infiltrative types of laryngeal amyloidoses were described in 1949 [123], with the diffuse pattern with an intact mucosa being more common, sometimes with tracheobronchial extension [114]. Macroscopic appearance is often seen as diffuse subepithelial oedema without a mucosa or nodular alterations [124]. The amyloid deposits most commonly occur in the ventricles followed by the subglottis, the aryepiglottic folds and the true vocal cords [114]. Presentation is usually with hoarseness or rarely stridor but can cause a sensation of 'fullness' in the throat, choking and dyspnoea on exertion [125]. The aetiology remains unclear, and there is no reported association with alcohol use, smoking, vocal abuse or infections [120]. One proposed explanation for the predilection of the larynx is that the production of light chains may be arising from the mucosa-associated lymphoid tissue (MALT) [117, 126]. Light-chain restriction is predominantly lambda in origin [118, 127].

A diagnosis is usually made following laryngoscopy and biopsy. It is important to identify the extent of infiltration with an MRI to decipher whether there is tracheobronchial extension. On MRI imaging, laryngeal amyloidosis has been reported to produce intermittent T1-weighted signal intensity and low T2-weighted signal intensity similar to the skeletal muscle. An MRI is believed to be superior to a CT scan when evaluating amyloidosis of the pharynx, larynx and trachea [128]. Systemic amyloidosis should be excluded, and investigation for an underlying plasma cell dyscrasia is imperative [121, 129]. There are case reports of extramedullary plasmacytomata with amyloid deposition affecting the larynx, and it is important to distinguish this from a localised deposit of amyloids [130].

Localised laryngeal amyloidosis is usually relatively benign but can be progressive or recur after treatment. Fatal haemorrhage has been reported [131]. Following a complete histological diagnosis and evaluation of the disease extent, endoscopic surgery [132, 133] or carbon dioxide laser excision [134, 135] is the treatment of choice, aiming to preserve voice quality and maintain airway patency [136]. As the underlying clonal plasma cell population is often diffuse and not excised, patients may require repeated removal of the amyloid deposits. Local and systemic corticosteroids have no effect on laryngeal amyloidosis [137]. There is some evidence of successful results, following external beam radiation therapy. The numbers of reported cases are small, and one patient developed grade one dysphagia and odynophagia following radiotherapy with hyperpigmentation of the skin over the treated area. However, the patient did achieve a significant improvement in voice strength and hoarseness and the treatment was deemed a success [138].

Very rarely, apparently localised laryngeal amyloid deposits can occur due to a feature of hereditary systemic apolipoprotein AI amyloidosis (AApoAI). Four separate apolipoprotein variants have been reported to cause this [110, 139–141], and, in three of these, the major site of organ damage is the heart. Apolipoprotein AI is a major constituent of high-density lipoprotein (HDL) [142]. Wild-type apolipoprotein AI is amyloidogenic and is present as traces of amyloids in human aortic atherosclerotic plaques in 10–20% of autopsies [143]. Numerous amyloidogenic variants have been reported, and, depending on the mutation, patients can present with massive abdominal visceral amyloid involvement [144], predominant cardiomyopathy [139] or a polyneuropathy syndrome [145]. Case reports suggest that the macroscopic appearances of the larynx in AApoAI amyloidosis differ from the localised AL form with deposits visible as small, irregular, floppy proliferations affecting the borders of the vocal folds in contrast to firm, bulky deposits in the localised AL form [146]. AApoAI amyloidosis is autosomal dominant inherited with variable penetrance, and a family history

of the disease is therefore often lacking. Performing immunohistochemistry on biopsy specimens for both kappa and lambda light chains and apolipoprotein AI is recommended. Genetic sequencing for Apo AI should also be performed.

Tracheobronchial Amyloidosis

Tracheobronchial amyloidosis is an uncommon diagnosis, although it too may well be underreported. It is characterised by amyloid deposits primarily in the trachea and large bronchi, with extension at times into the segmental bronchi and frequent involvement of the submucosal vessels, single or multiple nodules, luminal stenosis and obstruction; luminal wall thickening and rigidity; rough or uneven inner luminal walls and oedema of the mucosa with contact bleeding [11, 147, 148]. A literature review in 1983 identified 67 cases, of which 57 were diffusely infiltrative (multifocal submucosal plaques) and the remainder were nodular or 'tumour-like' [107]. Subsequently, 107 cases seen in China over a 34-year period have been reported [149] with a mean age at onset of 52.16 (±11.33) years and a median disease duration of 2 years.

Presenting symptoms include dyspnoea, persistent cough, which may be productive, haemoptysis, chest tightness and hoarseness [150]. Narrowing of the airways can cause wheezing, and cases of tracheobronchial amyloidosis simulating asthma have been reported. Deposits may cause distal atelectasis, recurrent pneumonia or lobar collapse [151], and solitary nodules may be mistaken for endobronchial neoplasia [152]. In the large Chinese series, 45% of cases were initially misdiagnosed; a CT was performed in 82 cases, and the major abnormalities were tracheal stenosis, tracheal wall thickening and calcification, patchy shadows, atelectasis and hilar lesions. Chest X-ray examination was reported in 59 patients with described features including increased lung markings, atelectasis, patchy shadows, bronchitis, emphysema, luminal stenosis and enlarged hilar shadows. In a review of 64 cases, 70% had normal radiographic findings [153]. Magnetic resonance imaging (MRI) may be more helpful in demonstrating more specific features suggestive of amyloidosis. Typically, deposits have intermediate T1-weighted signal intensity and low T2-weighted signal intensity similar to the skeletal muscle [128]. Dual-phase fluorodeoxyglucose (FDG) PET/CT imaging can be used to differentiate between a malignancy and amyloid deposits. Early phase FDG metabolic activity can be seen, but delayed images show reduced activity, which would not be seen with a malignancy [154]. Given the non-specific nature of the imaging of tracheobronchial amyloidosis, the diagnosis is often delayed and made following bronchoscopy and biopsy [155]. Tracheobronchopathia osteoplastica, characterised by calcified or cartilaginous submucosal nodules within the airways [156–158], and relapsing polychondritis are the principle differential diagnoses [159, 160].

Although symptomatic tracheobronchial amyloidosis is usually localised, its course is not always benign, and overall survival has been reported in only 31–43% of patients at 4–6 years: 8 of 66 cases followed up by Lu died and three of four Mayo Clinic patients died within 79 months of diagnosis, although survival in the more recent Chinese series seems better over a limited follow-up [11].

The management of tracheobronchial amyloidosis is largely dependent upon symptoms; there is no proven drug therapy for tracheobronchial amyloidosis, although systemic chemotherapy has been tried in patients with progressive disease [150] with some anecdotal reports of success using dimethyl sulphoxide. The most common management strategies reported in the large series of Lu were bronchoscopic with 53 patients receiving interventions including Nd-YAG laser, argon plasma coagulation, cryotherapy, topical drugs, clamping, resection, high-frequency electrotome cautery, stent implantation and microwaves. Among these patients, 20 received bronchoscopic therapy alone, 32 received bronchoscopic therapy combined with drug therapy, whereas one received bronchoscopic therapy combined with external beam radiation therapy. The series did considerably better than previously reported cases as 51 patients improved, one worsened and one died. Extensive airway involvement may require open resection [161]. Endobronchial brachytherapy has been reported in a handful of cases with encouraging early results [162]. Management will always need to be tailored to each patient depending on the degree of amyloid infiltration.

Parenchymal Pulmonary Amyloidosis

Amyloids within the lung parenchymal tissue are the most frequently detected respiratory manifestations of amyloidosis [163]. It can be radiographically divided into solitary/multiple nodules or a diffuse alveolar septal pattern [164, 165] (Fig. 6.4c); the latter is usually a manifestation of systemic amyloidosis, most commonly AL, but is also reported with the TTR type [5].

Nodular pulmonary amyloidosis is almost always due to localised AL deposits and is usually an incidental finding on chest radiography. Although the lesions may be dramatic and need to be differentiated from neoplasia, the prognosis is usually excellent. In theory, CT/PET should be useful in distinguishing between amyloid nodules and malignancies, but case reports suggest that PET imaging can yield false-positive results in nodular pulmonary amyloidosis and thus, although it may be a helpful investigation, it must be a confirmed histological diagnosis. Amyloid nodules in the lung parenchyma are usually peripheral and subpleural, occurring preferentially in the lower lobes; they may be bilateral and range in diameter from 0.4 to 15 cm. They grow slowly and may cavitate or calcify [163, 164, 166]. Larger nodules can

occasionally produce space-occupying effects or pneumothorax, but, otherwise, no treatment is required. Rarely pulmonary amyloid nodules have been reported to be transthyretin amyloids in type; wild-type transthyretin amyloidosis is also known as senile systemic amyloidosis and usually presents with cardiac involvement [148, 167]. Pulmonary nodules associated with AA amyloidosis have been found in patients with rheumatoid arthritis [168], Crohn's disease [169] and AA amyloidosis secondary to intravenous drug abuse [65], all of which have run a reportedly benign course.

Pulmonary Amyloidosis Associated with Sjögren's Disease

Sjögren's disease is a chronic organ-specific autoimmune disease characterised by lymphocytic infiltration into the salivary and lacrimal glands with an estimated prevalence of 0.5%, predominantly affecting women in middle life [170]. It is associated with a 44-fold increase in lymphoproliferative disorders and can be divided according to the extent of organ damage and disease progression: in mild disease, accounting for 45%, patients complain of dry eyes and mouth, sometimes associated with fatigue, depression and myalgia; more advanced cases have evidence of damage to the pulmonary, renal, hepatic, haematological and/or skin tissues, and approximately 5% of patients develop malignant lymphomas. This evolution from polyclonal lymphoproliferation to clonal disease to mucosa-associated lymphoid tissue (MALT) lymphoma and finally to high-grade malignant lymphoma is associated with an increasing risk of AL amyloidosis as monoclonal breakthrough occurs. Sjögren's disease is associated with a wide spectrum of respiratory manifestations, ranging from bronchial sicca and obstructive small airway disease to interstitial lung disease, pulmonary hypertension and pleural involvement [171]. Pulmonary amyloidosis is a rare but well-recognised complication of Sjögren's disease; it is most often associated with localised nodular pulmonary amyloidosis [172] but can also affect the breast tissues [173] and can result in systemic disease [174]. A recent case series has identified 33 cases in the literature [175], and 96.5% of cases were women with a median age at presentation of 59 years (range 29–79). The most common symptoms were cough and dyspnoea. The majority of cases (91%) occurred in primary Sjögren's disease, and a lymphoma was associated with 9% of cases. The diagnosis of pulmonary amyloidosis was generally made some years after the initial symptoms of Sjögren's presented, with a median of 7 years (range 0–30). Amyloidosis associated with Sjögren's is predominantly AL; however, there have been a few isolated case reports of diffuse septal AA amyloidosis without evidence of amyloid deposition elsewhere [176, 177].

Mediastinal and Hilar Amyloid Lymphadenopathy

Infiltration of the lymphoid tissue by amyloid deposits resulting in massive lymphadenopathy is not uncommon. Hilar and mediastinal lymphadenopathy can rarely be associated with localised pulmonary amyloidosis; a literature review of 55 patients with nodular pulmonary amyloidosis reported only three cases with associated mediastinal adenopathy [107]. Sjögren's syndrome complicated by a secondary lymphoma is a recognised cause [107, 178]. The majority of patients with amyloid lymphadenopathy have a detectable, circulating, monoclonal immunoglobulin, typically associated with extremely low-grade lymphoplasmacytic lymphoma or Waldenstrom macroglobulinemia [179]. The presentation of hilar and mediastinal amyloid lymphadenopathy and initial investigations can be highly suspicious of lung cancer or granulomatous diseases, and false-positive PET findings have been described [180]. CT imaging of amyloid lymphadenopathy has demonstrated considerable variety; calcification is not uncommon and low-density areas within the lymph nodes have also been described [165, 181]. The diagnosis is often made incidentally following a biopsy, and the discovery of amyloidosis should prompt the search for an underlying B-cell dyscrasia. Disease progression may be exceptionally slow and node calcification is well-recognised [165, 182]. Amyloid adenopathy has occasionally been reported to cause tracheal compression and superior vena cava obstruction. Treatment centres on treating the underlying lymphoproliferative disease without surgical resection may become necessary.

Conclusions

Amyloidosis is an extremely heterogeneous disease, which can impact the respiratory system in a number of ways. Long-standing respiratory conditions can lead to systemic amyloidosis, which requires treatment of the underlying condition in order to suppress the fibril precursor protein and halt the disease. Respiratory conditions can arise as a complication of systemic amyloidosis and its management. Localised amyloid deposits can affect any part of the respiratory tract and may be asymptomatic and require no treatment or can lead to complications, which require intervention. Lack of clinical trials in this area has meant that management of localised amyloid deposits are guided by small case series and treatment needs to be tailored on a patient-by-patient basis. The development of drugs, which prevent translation of genes encoding amyloid genic precursors, acts to stabilise the protein in its folded state and inhibit the process of aggregation; inhibitors of the specific proteases, which produce amyloidogenic fragments and immunotherapies to enhance clearance of existing deposits are on the horizon and may pave a new way of treating this disease in the future [1].

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Eosinophilic Granulomatosis with Polyangiitis

7

Yann Nguyen and Loïc Guillevin

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA), previously known as Churg–Strauss syndrome, is a systemic necrotizing vasculitis that predominantly affects small- and medium-sized vessels and is characterized by asthma and blood eosinophilia [1, 2]. Although anti-neutrophil cytoplasm antibody (ANCA) presence is not constant, EGPA is classified as a small-sized vessel, ANCA-associated vasculitis (AAV) [3]. Clinical phenotypes and pathogenic mechanisms of this rare disease have now been partly described, but gaps in our knowledge persist. Recent advances in EGPA management have included several novel immunomodulatory drugs and biotherapies, the efficacies of which have been or are currently being evaluated. In this review, EGPA epidemiology, pathophysiology, clinical manifestations, outcomes, and the different therapeutic options now available, including therapeutic perspectives, are addressed.

Pathophysiology

EGPA pathogenesis is not yet completely understood, but genetic background and immune dysregulation seem to be implicated.

Genetic Predisposition

Genetic studies have revealed associations between specific human leukocyte antigen (HLA) alleles and EGPA. Indeed, genetically distinct AAV–subset associations with major histocompatibility complex (MHC) and non-MHC determinants were identified in a genome-wide association study (GWAS) on granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) but not EGPA [4]. The strongest associations were with ANCA antigen specificities but not with the clinical phenotype. Anti-myeloperoxidase (MPO) and anti-proteinase-3 (PR3)-ANCAs were associated with *HLA-DQ* and *HLA-DP*, respectively. An earlier study found an association with the *HLA-DRB4* gene, for EGPA patients harboring an *HLA-DRB1*04*, *HLA-DRB1*07*, or *HLA-DRB1*09* allele (odds ratio (OR) 2.49 (95% confidence interval (95% CI) 1.58–3.09)), but *HLA-DRB3* gene frequency was lower in EGPA patients than that in controls (OR 0.54 (95% CI 0.35–0.84)) [5].

A more recent GWAS conducted on 676 EGPA patients and 6809 healthy controls from 9 European countries has identified at least 4 significant associations with EGPA ($P < 5 \times 10^{-8}$), regardless of the ANCA status [6]. The strongest association was with the MHC, supporting the hypothesis that EGPA is a polygenic disease. This study was able to differentiate two subentities genetically and clinically, according to ANCA positivity with distinct genotypes. Compared to the general population, MPO-ANCA-positive EGPA was associated with *HLA-DQ* (OR 5.68; $P = 1.1 \times 10^{-28}$), whereas ANCA-negative EGPA had no HLA. These results might suggest potential genetic differences between MPO-ANCA-positive and MPO-ANCA-negative EGPA.

Immune Dysregulation

Because blood and tissue eosinophilia are among the major EGPA characteristics, eosinophils are believed to be the key players in EGPA pathogenesis. Immune dysfunction results in massive eosinophilic proliferation, impaired apoptosis, and elevated tissue toxicity attributed to eosinophil products. Defective CD95 (Apo-1/Fas)-mediated apoptosis seems to be involved in eosinophil proliferation [7]. Blood eosinophils from patients with active EGPA primarily

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express less proapoptotic genes (e.g., *BLC2L13* (mitochondrion-localized protein with conserved B-cell lymphoma-2 homology motifs), *CASP2* (*caspase-2*), *CARD4* (caspase recruitment domain family member-4)) involved in nuclear factor-kappa B (NF-κB) regulation [8]. Aggression of respiratory epithelial cells following exposure to the triggering factors (see below) could induce production of cytokines, such as interleukin (IL)-25. Indeed, IL-25 is elevated in EGPA patients' blood, where it could drive $CD4^+$ T lymphocytes toward a skewed T-helper cell type-2 (Th2) phenotype, thereby maintaining eosinophil proliferation via cytokines synthesized by Th2 cells [9]. High levels of eosinophilic cytotoxic proteins (e.g., eosinophil cationic protein, eosinophil peroxidase), directly involved in damaging tissues, are also found in EGPA patients' sera, urine, and tissues [10].

As in asthma patients, EGPA patients' $CD4^+$ T lymphocytes, mostly Th2 phenotype, are activated. EGPA patients' sera and bronchoalveolar lavage (BAL) fluid also contain elevated concentrations of Th2 ILs (e.g., IL-4, IL-5, and IL-13) [11]. IL-5 plays a central role in eosinophil survival and maturation, and strong associations have been found between IL-5 expression and clinical parameters of EGPA activity (Birmingham Vasculitis Activity Score, eosinophilia). Moreover, EGPA pathogenesis also seems to implicate Th1 and Th17 responses [12].

Although the precise role of B lymphocytes in EGPA has not yet been fully elucidated, their involvement in EGPA pathogenesis is being more thoroughly investigated, in light of the efficacy of anti-CD20 monoclonal antibodies against GPA and MPA [13, 14]. Higher percentages of $CD80^+$, $CD27^+$, or $CD95^+$ B cells and lower rates of $CD19^+$ B cells have been found in patients with frequently relapsing EGPA [15]. Furthermore, immunoglobulin (Ig)G4 levels, an indirect surrogate of B-lymphocyte activation, were elevated during EGPA flares [16]. In addition, ANCA positivity, found in one-third of EGPA patients, is also indicative of B-lymphocyte activation, and direct EGPA pathogenesis via anti-MPO-ANCAs was demonstrated in vitro and in mouse models [17, 18].

Epidemiology

Incidence and Prevalence

EGPA is a rare disease, the prevalence of which ranges between 7.3 and 17.8/million inhabitants [19, 20], with an annual incidence of 0.9–2.4/million inhabitants [21, 22]. EGPA prevalence seems to be similar in Europe, Japan, and the United States [20]. The mean age at diagnosis is ~50 years [23], which is lower than that for MPA, GPA, or polyarteritis nodosa (PAN). Childhood-onset EGPA is extremely rare [24]. No male/female sexual predominance has been reported.

Triggering Factors

Because of the asthma prodrome, allergens have been suspected of being EGPA triggers. However, when frequent allergens were systematically tested, less than a third of EGPA patients had documented allergies [25]. Thus, although potentially responsible molecules may still not have been identified, allergens alone do not seem to be responsible for the onset of EGPA manifestations.

Although no common EGPA-triggering event or cause has yet been identified, many environmental factors implicated in its pathogenesis have been described, e.g., inhaled antigens (dark diesel fumes, grain dust, cereal dust, dust), desensitization, or vaccinations [26, 27]. However, these exposures may merely be disease accelerators in patients, with undiagnosed EGPA already present, rather than its true cause.

Some medications, mainly leukotriene receptor antagonists (e.g., montelukast) or, more recently, anti-IgE antibodies (e.g., omalizumab), are still considered potential triggers, but because they are often used to taper glucocorticoid doses, their role remains unclear [28–32]. In a study on 79 EGPA patients, montelukast use was significantly associated with the risk of developing EGPA within 3 months (OR 4.5 (95% CI 1.5–13.9)) [29]. However, that association was not specific, as other drugs used to treat asthma, e.g., long-lasting β_2-agonists and oral glucocorticoids, were also associated with EGPA with comparable risk ratios. These associations may be confounded by indication due to gradually worsening asthma.

Clinical Manifestations

EGPA generally evolves in three stages: first with asthma or sometimes symptoms attributed to allergy, then eosinophilia and lung infiltrates, and, finally, systemic vasculitis manifestations. The time between the first manifestations and overt EGPA is usually around 9 years, but all three stages can simultaneously appear. Its main clinical manifestations are described in Table 7.1.

Table 7.1 EGPA patients' clinical features according to the main published series (from Nguyen and Guillevin [33])

	Chumbley et al. 1977 [91]	Lanham et al. 1984 [50]	Guillevin et al. 1987 [27]	Gaskin et al. 1991 [92]	Guillevin et al. 1999 [45]	Solans et al. 2001 [93]	Comarmond et al. 2013 [23]	Durel et al. 2016 [94]
Patient demographics								
Number included	30	16	43	21	96	32	383	101
Male/female sex ratio, *n*	21/9	12/4	24/19	14/7	45/51	9/23	199/184	43/58
Mean age (years)	47	38	43.2	46.5	48.2	42	50.3	49.2
[Range]	[15–69]		[7–66]	[23–69]	[17–74]	[17–85]	[35–66]	
Clinical features								
General symptoms			72		70	69		
Arthritis, arthralgias	20	51	28	43	41		29.8	68.3
Myalgias		68			54		38.9	82.2
Allergic rhinitis and/or ENT involvement	70	70	21		47		48	96
Asthma	100	100	100	100	100	100	91.1	53.4
Pulmonary infiltrates	27	72	77	43	38	53	38.6	53.5
Pleural effusion		29				19	8.9	3
Skin involvement	67			50	51	69	39.7	46.5
Purpura		48	28		31	41	22.5	24.7
Nodules	27	30	21		19	6	9.7	8.9
Mononeuritis multiplex	63	66	67	70	78	44	46	54.5
GI involvement	17	59	37	58	33	38	23.2	25
CV involvement	16	47	49	15	30	28	27.4	20.8
Renal involvement	20	49	16	80	16	13	21.7	26

Values are expressed as percentages, unless stated otherwise. *ENT* ear, nose, and throat, *GI* gastrointestinal, *CV* cardiovascular

General Symptoms

Constitutional symptoms, like fever, asthenia, or weight loss, are common before systemic manifestations, and, as for patients in our EGPA series at diagnosis, 38.9% were febrile with myalgias, 29.8% had arthralgias, and almost 50% had lost weight (mean ± standard deviation (SD) loss during the preceding 3 months, 7.8 ± 4.7 kg) [23].

Pulmonary Manifestations

Asthma is the main EGPA characteristic, affecting 91–100% of the patients, most often before systemic vasculitis symptoms (mean ± SD interval 9.3 ± 10.8 years). It is a criterion in the American College of Rheumatology (ACR) classification criteria (Box 7.1). Asthma is often late-onset, appearing around 30–40 years of age, but can start during childhood. Asthma is generally severe and glucocorticoid-dependent, and its severity tends to increase 3–6 months before the systemic disease becomes apparent. In a retrospective study on 157 EGPA patients, asthma was mild, moderate, or severe in 17%, 26%, or 57%, respectively [38]. All patients required high-dose, inhaled glucocorticoids and bronchodilators. The mean ± SD post-bronchodilator FEV_1 (forced expiratory volume in 1 s) was 69.7 ± 24.9% of the predicted value, and post-bronchodilator FEV_1/FVC (forced vital capacity) was <0.7 for 54% of tested patients.

Box 7.1 1990 American College of Rheumatology criteria for the classification of Churg–Strauss syndrome (Adapted from Masi et al. [2])

Criterion		Definition
1.	Asthma	History of wheezing or diffuse high-pitched rales on expiration
2.	Eosinophilia	Eosinophilia >10% of white blood cell differential count
3.	Mononeuropathy or polyneuropathy	Development of mononeuropathy, multiple mononeuropathies, or polyneuropathy (i.e., glove/stocking distribution) attributable to vasculitis
4.	Pulmonary infiltrates, non-fixed	Migratory or transitory pulmonary infiltrates on radiographs (not including fixed infiltrates), attributable to systemic vasculitis

Criterion		Definition
5.	Paranasal sinus abnormality	History of acute or chronic paranasal sinus pain or tenderness or radiographic opacification of the paranasal sinuses
6.	Extravascular eosinophils	Biopsy including the artery, arteriole, or venule, showing accumulations of eosinophils in extravascular areas

For classification purposes, a patient with vasculitis is said to have EGPA, when at least four of these six criteria are present. The presence of any four or more criteria yields 85% sensitivity and 99.7% specificity.

Compared to MPA, the alveolar hemorrhage frequency attributable to pulmonary vasculitis is lower (4%), but patients can sometimes experience massive hemoptysis (often associated with renal involvement). However, in most patients, alveolar hemorrhage is usually mild, with only bloody sputum or diagnosed by BAL. Eosinophilic, exudative, pleural effusions have been described, with rare pleural biopsies showing signs of vasculitis and infiltrated by eosinophils [39]. Lung infiltrates are common (38.6%) and can be uni- or bilateral, transitory and often disappear after a few days of glucocorticoids [40]. Phrenic paralysis has been described but is extremely rare [41].

Rarely, EGPA can be lung-limited and present without any systemic extra-respiratory organ involvement [42]. The diagnosis might be challenging, and a lung biopsy is needed to evidence eosinophilic, granulomatous, and necrotizing vasculitis.

Ear, Nose, and Throat (ENT) Manifestations

Asthma can be associated with other ENT symptoms. Maxillary sinusitis is common in EGPA and is one of the ACR classification criteria (Box 7.1). Allergic rhinitis and nasal polyposis are found in 17% and 41% of EGPA patients, respectively, but must be distinguished from the ENT manifestations of GPA, which are often destructive and severe. Rhinitis and polyposis are usually present in EGPA patients before the vasculitis symptoms become evident.

Although these ENT manifestations are considered EGPA symptoms, they could represent an underlying predisposition to the vasculitis, rendering patients more susceptible to developing vasculitis symptoms. Once a vasculitis flare has been successfully treated, most patients have polyps and symptoms at some time during the evolution of the disease, which supports the hypothesis advanced above of a predisposition.

Neurological Manifestations

Peripheral neuropathies are frequent (affecting 46–75% of EGPA patients), mainly mononeuritis multiplex (46% in our series) [23]. Therein, the most frequently involved nerves, in decreasing order of frequency, are the common peroneal, internal popliteal, then those of the arms (radial, cubital, and/or median), and, finally, cranial nerves. Patients may complain of paresthesia or sometimes painful hyperesthesia before sensory and motor deficiencies become apparent, when mild, only superficial sensitivity is affected. According to the Five-Factor Score (FFS) [42], peripheral nerve involvement is not a poor prognosis factor and does not influence mortality, but motor or sensory deficiency sequelae can worsen the functional prognosis because recovery is long and unpredictable, mostly for sensory symptoms.

Central nervous system involvement, indicating cerebral vasculitis, is uncommon (5.2% in our series [23]). Its clinical manifestations are nonspecific: seizures, hemiplegia, brain, or subarachnoid hemorrhages. Although computed tomography (CT) scans can visualize hemorrhagic or some ischemic events, magnetic resonance imaging (MRI) can detect T2-weighted cortical and subcortical signals, more specific to cerebral vasculitis. Since the FFS was revised in 2011, central nervous system involvement is no longer considered to be factor of poor prognosis [42].

Skin Manifestations

Small-vessel vasculitis or extravascular granulomas can lead to cutaneous involvement, which is common and affects 40–70% of patients in our EGPA series. Vascular purpura, preferentially affecting the lower limbs, is the most frequent skin sign, affecting 22–50% [23]. Subcutaneous nodules, often bilateral, symmetrical, red, and predominantly affecting the fingers, elbows, and upper limbs, are found in 10–30% of EGPA patients. When nodule biopsies are obtained, they can contain extravascular granuloma(s), which are nonspecific for EGPA, as they also occur in other vasculitides or inflammatory bowel diseases. Skin symptoms can also include Raynaud's phenomenon, urticaria, livedo reticularis (3.9%), and gangrenous necrotic lesions.

Cardiac Manifestations

Heart involvement is one of the most severe EGPA manifestations and is the primary cause of death of EGPA patients. It is also an FFS prognostic item [42]. The pathophysiology of these cardiac manifestations includes coronary vasculitis, extravascular granuloma(s), and eosinophilic interstitial

infiltrate. In our EGPA series, clinical manifestations included hypertension, pericarditis (15.1%), valvopathy, eosinophilic myocarditis, and/or congestive heart failure (16.4%), and 31% of the deaths were attributed to cardiac involvement [23].

However, the real frequency of EGPA cardiac disease may be underestimated. Detailed cardiac workups of 32 ambulatory EGPA patients considered to be in remission revealed that 62% had cardiac involvement: among them, 60% had echocardiographic defects, 66% had electrocardiogram (EKG) abnormalities, and 62% had MRI anomalies, but only 26% of those patients were symptomatic [43].

Gastrointestinal Involvement

Gastrointestinal involvement, often severe, is another FFS poor prognosis factor [35, 42]. Clinical manifestations are often nonspecific, with abdominal pain, nausea, vomiting, diarrhea, and/or intestinal hemorrhage. Bowel perforation, the most severe digestive event, is associated with high mortality [42]. Ischemic colitis or mesenteric ischemia may require surgical intervention [44]. When obtained, biopsies can show signs of vasculitis, extravascular granulomas, sometimes mimicking pseudopolypoid lesions, and eosinophilic infiltrates. Thickening of the esophageal wall and sometimes other parts of the gastrointestinal tract could be indicative of eosinophilic infiltration; it disappears under glucocorticoids.

Renal Manifestations

EGPA kidney manifestations are less common than in other AAVs, affecting 16–22% of EGPA patients. In our series, the mean ± SD creatinine level at diagnosis was 89.1 ± 38.6 µmol/L (1.01 ± 0.44 mg/dL), and 12.8% of the patients had abnormally elevated proteinuria [23]. Histology of EGPA patients' renal biopsies usually finds crescentic glomerulonephritis, which can be focal or diffuse, and less frequent renal vasculitis, eosinophilic infiltrates, or granuloma(s) [45]. Glomerulonephritis in EGPA is usually associated with anti-MPO-ANCA positivity. Ureteral stenosis has been described but only rarely [46].

Ophthalmological Manifestations

Ophthalmological involvement, including uveitis, episcleritis, ischemic vasculitis, and/or orbital inflammatory pseudotumor with conjunctival involvement, has been described [47].

Complementary Investigations

Blood eosinophilia is an EGPA constant; it is also an ACR classification criterion, with eosinophil counts exceeding 15,000/mm^3 or 10% of total leukocytes as a diagnostic criterion. The mean ± SD eosinophil count for patients in our series was 7569 ± 6428/mm^3 [23], but eosinophil counts can exceed 50,000/mm^3 [48]. Eosinophilia may rapidly decline within a few days of starting EGPA treatment. Although isolated eosinophilia can be a marker of EGPA evolution, it is probably not enough to diagnose a relapse. During follow-up, eosinophil counts rise frequently without engendering clinical manifestations, usually during glucocorticoid tapering, so close monitoring is essential.

Inflammatory syndrome is documented in ~80% of EGPA patients, with elevated C-reactive protein at 66.9 mg/L or a high erythrocyte sedimentation rate of 56% in our series [23].

About a third of EGPA patients are ANCA-positive, mostly with a perinuclear immunofluorescence labeling (P-ANCA) pattern, and, according to enzyme-linked immunosorbent assay (ELISA), ~70% of the ANCAs are MPO-specific. Antinuclear antibodies are not found, but rheumatoid factor can be present [49].

For EGPA patients with alveolar hemorrhage, BAL fluid can contain red blood cells and the Golde score is elevated. In other contexts, BAL can contain inflammatory cells, predominantly eosinophils [38].

When biopsies are obtained, histological examination has good sensitivity for confirmation of the EGPA diagnosis [34, 44]. Biopsies may contain three types of lesions, but rarely simultaneously: (1) necrotizing small-to-medium-sized vessel vasculitis, showing fibrinoid necrosis of the media and pleomorphic cellular infiltrate(s), mainly eosinophils; (2) typical but nonspecific extravascular granuloma(s), with central necrosis and epithelioid cells, which can also be seen in other vasculitides (e.g., GPA) or autoimmune diseases; and (3) eosinophil infiltration of arterial walls and adjacent tissues of any organ [50].

Chest radiographs can contribute to diagnosing EGPA and its lung manifestations. In a study on 91 patients, chest X-ray abnormalities were seen in 58% of the patients at diagnosis and included ground glass attenuation (29%), consolidation (29%), pleural effusion (10%), and/or nodules or mass(es) (9%). These anomalies were frequently bilateral (58%) [38]. Chest CT scans can evaluate lung abnormalities more precisely, as they can visualize ground glass opacities (39%), bronchial wall thickening (32%), and/or micronodules <3 mm (24%).

Echocardiography or cardiac MRI can identify cardiac involvement and detect abnormalities in 38% of patients who are asymptomatic or have EKG abnormalities [43]. However,

MRI abnormalities must be interpreted prudently, as the meaning of T1-weighted cardiac MRI abnormalities remains unknown for asymptomatic patients. Indeed, among a series of 42 non-cardiomyopathic (diagnosed independently of MRI findings) EGPA patients, those with cardiac MRI abnormalities had EGPA outcomes similar to those without. Thus, cardiac MRI alone cannot be used to diagnose cardiomyopathy [51, 52]. In certain situations, coronary arteriography might be useful to distinguish EGPA cardiomyopathy from the underlying ischemic cardiopathy.

Diagnosis

Diagnostic Criteria

Initially, the three EGPA-defining histological lesions mentioned above served as the basis of the diagnosis. However, because the simultaneous presence of all three lesions types is uncommon, EGPA diagnosis remained clinical. In 1984, Lanham et al. devised the following criteria: asthma, blood eosinophilia >1500/mm^3, and clinical or pathological evidence of vasculitis involving at least two organs [34]. However, because asthma onset can follow the vasculitic phase and because blood eosinophil counts may fluctuate, these criteria could lack sensitivity.

Thus, the 1990 ACR EGPA classification criteria [2] required at least four of the following criteria (Box 7.1): asthma, eosinophilia (>10% of white blood cell count), mononeuropathy or polyneuropathy, pulmonary infiltrates, paranasal sinus abnormality, and/or extravascular eosinophils. However, these descriptive criteria were established for clinical studies; they are not diagnostic.

The more recent 2012 Chapel Hill Consensus Conference Nomenclature has defined EGPA as an "eosinophil-rich and necrotizing granulomatous inflammation, frequently involving the respiratory tract, and necrotizing vasculitis predominantly affecting small-to-medium-sized vessels and associated with asthma and eosinophilia" [3].

Differential Diagnosis

Clinical manifestations dictate the entities included in the differential diagnosis of EGPA. Prior to the onset of vasculitis manifestations, it may be difficult to differentiate EGPA among eosinophilic asthma, parasitic infections, or allergic bronchopulmonary aspergillosis.

Idiopathic chronic eosinophilic pneumonia has no known etiology and is a rare disease with nonspecific respiratory symptoms and eosinophilia [53–55]. Pertinently, it has no vasculitic and extrapulmonary signs and, thus, remains an exclusionary diagnosis.

Once vasculitis symptoms become overt, the main differential diagnoses are other systemic vasculitides, especially GPA and MPA. Although eosinophilia is also seen in GPA, EGPA can usually be differentiated by the presence of asthma, nondestructive ENT manifestations, and anti-MPO-ANCAs (as opposed to anti-PR3-ANCAs in GPA).

Hypereosinophilic syndrome (HES) can also be difficult to distinguish from EGPA. Although HES can also be associated with cardiopathy, pulmonary manifestations, and/or nerve involvement, vasculitis symptoms are absent, as are histological signs of vasculitis [56]. Two HES variants are recognized: one is the lymphocytic variant, with a predominance of skin and soft tissue involvements, resulting from abnormal $CD3^-CD4^+$ T-cell subsets responsible for IL-5 synthesis [57], and the second is the myeloid form. Because HES myeloid variants have specifically elevated tryptase and vitamin B_{12} levels, these biological determinations can be useful for excluding HES, the diagnosis of which can be confirmed by genetic testing for *FIP1L1–PDGFRA* fusion and *JAK2* mutations [58].

Recently, the EGPA Consensus Task Force experts have recommended complementary investigations to exclude the main differential diagnoses [59]: toxocariasis and human immunodeficiency virus serology, specific IgE and IgG dosages for *Aspergillus* spp., the search for *Aspergillus* spp. in sputum and/or BAL specimens, tryptase and vitamin B_{12} dosages, peripheral blood smears to look for dysplastic eosinophils or blasts, and thoracic CT scan.

In addition, asthma with eosinophilia is another entity in the differential diagnosis of EGPA. In the absence of extrapulmonary manifestations, making a distinction between the first EGPA manifestations and asthma with eosinophilia can be difficult, especially when ANCAs are absent.

Prognosis and Outcomes

The use of glucocorticoids and immunosuppressants have revolutionized EGPA prognoses, with a 5-year survival rate rising from 10% in the 1950s to 90% today. However, prognoses for all EGPA patients differ according to the presence or absence of several clearly identified prognostic factors. Multivariate analyses of the characteristics of 260 polyarteritis nodosa and 82 EGPA patients, the foundation of the original 1996 prognostic FFS, retained 5 items significantly associated with mortality and accorded each presence with 1 point: proteinuria >1 g/day; gastrointestinal bleeding, perforation, infarction, and/or pancreatitis; renal insufficiency (with serum creatinine >1.58 mg/dL or 140 μmol/L); central nervous system involvement; and cardiomyopathy. FFS = 0, 1, or 2 corresponded to respective 5-year mortality rates of 12%, 26%, or 46%. The FFS was revisited in 2011, and, this time, it was based on the analysis of 1108 vasculitis patients

including 230 EGPA patients [42]. The revised FFS retained the following 5 factors associated with a higher mortality risk rate: serum creatinine >150 μmol/L, severe gastrointestinal involvement, myocardial involvement, age > 65 years, and the absence of ENT manifestations, each accorded 1 point; then, the points were added. Adding the points yielded the FFS; scores = 0, 1, or 2 were associated with respective 5-year mortality rates of 9%, 21%, or 40%. Hence, calculation of the revised FFS with these readily available parameters can help identify vasculitis patients at a high risk of death who require aggressive therapy with immunosuppressants. In our series, 11.7% of the patients died at a mean ± SD of 50.4 ± 60.1 (median 21.4) months post-diagnosis. The leading cause of death was heart-related (31%; i.e., myocardial infarction, cardiac insufficiency, or arrhythmia), followed by infections or malignancies (11% each), active vasculitis, and respiratory failure (severe asthma attacks and/or end-stage chronic pulmonary obstructive disease, 9% each) [23].

Vasculitis relapses remain a major concern for EGPA. They are defined as the new appearance, recurrence, or worsening of clinical EGPA vasculitis signs (excluding asthma and/or ENT) that require adjunction, change, or intensification of the glucocorticoid and/or other immunosuppressant dose(s) [60]. Although almost 90% of EGPA patients achieve remission, 25.3% of those in our series relapsed and 18% experienced asthma flares, sinusitis, and/or enhanced eosinophilia levels, justifying the prolonged use of glucocorticoids for about 85% of patients in the series [23]. The relapse-free survival rate was 78.6% (95% CI 64.3–84.3) for all patients, and most relapses occurred during the first year post-diagnosis.

Phenotypes According to the ANCA Status

Depending on the ANCA status, EGPA clinical findings and prognoses differ markedly, defining two distinct phenotypes [61, 62].

Based on a series of 93 patients, Sinico et al. showed that ANCA positivity was associated with more frequent pulmonary hemorrhages (20% vs. 0%, $P = 0.001$), renal involvement (51.4% vs. 12.1%, $P < 0.001$), mononeuritis multiplex, and purpura but less frequent lung infiltrates (34.2% vs. 60.3%) and cardiac involvement (5.7% vs. 22.4%, $P = 0.042$) [61]. Similar findings were reported for another series of 112 EGPA patients, with ANCA positivity associated with more frequent renal involvement (35% vs. 4%), peripheral neuropathy (84% vs. 65%), and biopsy-proven vasculitis (79% vs. 39%) [62]. Thus, ANCA positivity might be associated with more frequent vasculitis-associated symptoms, whereas ANCA negativity would be associated with more eosinophilic infiltrates. Patients' prognoses also differ according to the ANCA phenotype: in our series, ANCA positivity was associated with more frequent relapses (35.2% vs. 22.5%, $P = 0.01$) but fewer deaths (5.6% vs. 12.5%, $P < 0.5$) [23]. These events could be representative of two distinct EGPA phenotypes, defined by ANCA positivity and distinct genetic profiles.

However, in a series of 157 patients, definite features of vasculitis were found in 28% of patients who had no ANCAs, suggesting that ANCAs per se are not sufficient to dichotomize patients with or without vasculitis features [63]. Some authors suggested a more precise nomenclature, distinguishing EGPA, with definite vasculitis features, definite surrogates of vasculitis, mononeuritis, and/or ANCAs and any systemic manifestation, from hypereosinophilic asthma with systemic manifestations [63].

Treatment

Therapeutic Strategies

EGPA patients can benefit from glucocorticoids, immunosuppressants, and now targeted therapies. As for other AAVs, the treatment strategy for EGPA comprises remission induction and maintenance phases. However, treating EGPA can be difficult because of asthma and/or ENT manifestations, which can persist even after vasculitis remission has been obtained. In 2015, the EGPA Consensus Task Force published recommendations for the evaluation and management of EGPA patients [59].

In our opinion, each patient should receive a tailored regimen, adapted to different parameters, e.g., disease severity, organ involvement, prognosis, and comorbidities. While the FFS was devised to assess prognosis, using this score to guide the choice of therapeutic regimen remains debated; international recommendations also remain contradictory as to whether to do so [64].

For patients with a 1996 FFS = 0, i.e., without poor prognosis factors, we recommend starting glucocorticoids alone, as their efficacy to induce and maintain remissions and safety have been demonstrated. In the prospective randomized CHUSPAN trial that enrolled 72 EGPA patients without poor prognosis factors, 93% achieved remission with glucocorticoids alone and 97% achieved a 5-year survival rate [63]. However, 35% of them relapsed, mainly during the first year of treatment, and, eventually, immunosuppressant adjunction was needed to limit relapses. Again, controversy persists as to immunosuppressant efficacy for those EGPA patients. In the randomized, prospective CHUSPAN2 trial, azathioprine adjunction to glucocorticoids did not impact the remission or relapse rate [65]. In addition, no steroid-sparing was achieved with azathioprine. The recent European League Against Rheumatism/European Renal Association–European

Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations have not stratified treatment guidelines according to the FFS, despite the results of several prospective trials clearly highlighting its pertinence [66]. Other immunosuppressants, e.g., methotrexate or mycophenolate mofetil, could be other therapeutic options, but prospective, controlled trial findings did not demonstrate the efficacy of one or the other and results obtained with azathioprine were better.

For patients with FFS ≥ 1, i.e., with poor prognosis factors, and/or with other life- threatening manifestations, including those not part of the FFS (i.e., possible blindness due to eye involvement, severe alveolar hemorrhage, and/or fulminant mononeuritis multiplex), it is our opinion that an immunosuppressant should be added to glucocorticoids [59].

Remission Induction

The induction-phase goal is to achieve, as rapidly as possible, clinical remission, defined as the absence of clinical vasculitis manifestations. Glucocorticoids represent the cornerstone of induction regimens. The initial dose of prednisone (or its equivalent of methylprednisolone) should be ~1 mg/kg/day for 2–3 weeks, followed by gradual tapering. When life-threatening symptoms are present, intravenous (IV) methylprednisolone pulses should be administered (usually 7.5–15 mg/kg/day for 3 days) because of their rapid action. A rapid therapeutic response is usually obtained, with attenuation of asthma and vasculitis symptoms, along with eosinophilia levels. No consensus has been published for glucocorticoid tapering, but the dose should be decreased extremely gradually to the lowest effective dose until withdrawal, when possible. Nevertheless, patients often require long-term glucocorticoids because of steroid-dependent asthma. A daily prednisone dose <7.5 mg could be targeted to reduce glucocorticoid-related adverse events (AEs), but, even at low doses, AEs may occur, and steroid toxicity is cumulative.

When immunosuppressant adjunction is deemed necessary, cyclophosphamide has been the most investigated. In a prospective study on 48 EGPA patients with poor prognosis factors comparing 12 vs. 6 pulses of cyclophosphamide, both with glucocorticoids but with no subsequent maintenance therapy, no statistically significant differences were found between the two regimens. Although the complete remission rate for all patients was 78.5% [67], relapses rates remained too high (28.6% vs. 66.7% for 12-versus 6-pulse groups), suggesting the necessity of prescribing maintenance therapy. In an analogy to the induction regimen prescribed for GPA and MPA in our 1997 prospective trial [68], IV pulses or continuous oral cyclophosphamide (2 mg/kg/day) were considered equally effective, as subsequently confirmed by the CYCLOPS trial [69]. However, oral intake has been associated with higher cumulative cyclophosphamide doses and more severe leukopenia. A post hoc, long-term, follow-up analysis showed that although IV pulses were associated with a higher risk of relapse (39.5% vs. 29.8%, $P = 0.029$), the mortality rate was not higher [70]. In addition, IV pulses might have the potential advantage of favoring compliance. By analogy with other AAVs, the standard of care has since become 6 cyclophosphamide pulses for induction (3 infusions at 0.6 g/m^2 or 15 mg/kg every 2 weeks, followed by 3–6 additional pulses at 15 mg/kg or 0.7 g/m^2 every 3 weeks), followed by maintenance therapy [59].

The prospective, randomized, CORTAGE trial evaluated the impact of fixed, low-dose, IV cyclophosphamide pulses (500 mg/m^2 every 2–3 weeks until remission) versus the standard regimen with limited glucocorticoid exposure on 108 AAV patients ≥65 years old (including 14 with EGPA) [71]. Although the two arms were comparable for remission rates, the patients prescribed the "lighter" regimen suffered fewer serious AEs.

Maintenance Therapy

After remission, a maintenance regimen should be prescribed for poor prognosis patients with an FFS ≥ 1, as they are at an extremely high risk of relapse (73.8–85.7%) [67]. It should start 2 weeks after the last induction cyclophosphamide pulse or a few days after stopping oral cyclophosphamide.

Although many immunosuppressants have been prescribed for EGPA remission maintenance, unlike GPA or MPA, no randomized trial has compared them to identify the more effective agent. As for GPA and MPA, azathioprine can be prescribed, initially at 2 mg/kg/day, but its dose can be adjusted to the clinical response and toxicity. Because mycophenolate mofetil has been shown to be less effective than azathioprine in GPA and MPA remission maintenance therapy, it is not prescribed very often [72]. Finally, based on the results of a prospective trial for GPA and MPA remission maintenance therapy, methotrexate, at an initial dose of 0.25 mg/kg/week, seems to be an acceptable alternative to azathioprine [73].

Although the optimal maintenance therapy duration has not yet been determined, it should last for at least 18–24 months after remission. No consensus criteria to completely stop treatment have been formulated to date. However, according to the long-term follow-up of 118 EGPA patients, relapses occurred at a mean of 2 years post-induction, i.e., when immunosuppression had been terminated for almost all patients, again suggesting the potential long-term need for immunosuppressive therapy [74].

Other Treatments

As suggested by some authors, based on case series [75, 76], IV immunoglobulins are another option for second-line therapy for EGPA flares of some patients, after other therapeutic agents have failed, especially those with myocardial or neural involvement.

As for other AAVs, selected ANCA-positive patients with rapidly progressive glomerulonephritis or severe pulmonary renal syndrome [77] might benefit from therapeutic plasma exchanges, even though their efficacy continues to be debated [78].

Although interferon-alpha has successfully induced remission of refractory EGPA, its efficacy to maintain remission seems limited, and, its numerous AEs lead us to think that it is probably not a good choice, if other options are still available [79, 80].

Rituximab is a chimeric monoclonal antibody directed against CD20-expressing B lymphocytes. Its efficacy and safety to induce and sustain GPA and MPA remissions have been clearly demonstrated [13, 14]. However, so far, prescribing rituximab to treat EGPA has been limited to case reports and case series [81–84]. Notably, rituximab indeed seems to induce remissions effectively and safely, mainly for ANCA-positive patients [85]. The ongoing French Vasculitis Study Group's prospective, randomized, REOVAS trial (NCT02807103) is evaluating rituximab efficacy to induce remissions, and its prospective randomized MAINRITSEG trial (NCT03164473) is examining its use as maintenance therapy. Until those results become available, rituximab should be reserved for second-line therapy of severe EGPA refractory to conventional therapy or when that strategy is not possible.

Omalizumab, a monoclonal antibody targeting IgE, is prescribed to treat allergic asthma and allergic rhinitis, but controversy surrounds its efficacy against EGPA. It could be effective against active disease, but a possible association between omalizumab administration and EGPA onset has been suggested [31, 32, 36, 37]. In a French retrospective study on 17 EGPA patients, omalizumab indeed had a glucocorticoid-sparing effect, as the median prednisone dose could be lowered from 16 mg/day at baseline to 9 mg/day at month 12 [86]. However, possible safety questions have emerged, with 8 patients stopping omalizumab because of relapses (50%) and refractory disease (25%) and 2 stopping omalizumab because of severe asthma flares.

The efficacy of mepolizumab, an anti-IL-5 monoclonal antibody, was proven in a double-blind, multicenter, phase 3 trial on 136 patients with relapsing or refractory EGPA who received a stable prednisone dose for at least 4 weeks [87]. Mepolizumab, compared to placebo, obtained significantly higher percentages of participants with ≥24 weeks of accrued remission (28% vs. 3%, respectively; $P < 0.001$). Moreover, glucocorticoid tapering was possible. Although its efficacy as induction therapy remains to be investigated in randomized controlled trials, mepolizumab was used to induce remissions in a single-center, phase 2, uncontrolled trial on ten consecutive patients with active refractory or relapsing EGPA; eight of them entered remission [88].

Prevention of AEs

EGPA prognosis has improved to such an extent that it is now considered a chronic relapsing disease. Because most patients remain on long-term glucocorticoids, prevention of glucocorticoid-related complications is a major issue (i.e., calcium, vitamin D, and bisphosphonates).

Moreover, cyclophosphamide is also associated with serious AEs (e.g., hemorrhagic cystitis and gonadal toxicity) that can be prevented, and concomitant cotrimoxazole or pentamidine aerosol prophylaxis should be prescribed to avoid *Pneumocystis jiroveci* infections.

Although vaccinations have been a suspected of being a factor triggering EGPA [27], immunization with inactivated vaccines against influenza and *Streptococcus pneumoniae* is supported to counter the high risk of potentially mortal infections under immunosuppressants. According to a prospective vaccine phase III study on 199 patients with autoimmune diseases, including 20 with EGPA, seasonal flu vaccines were safe and effective; notably, 80.3% patients obtained seroprotection [89]. However, seroprotection rates were impacted by EGPA therapeutic agents as follows: 86.7% for patients with autoimmune diseases and no immunosuppressant, 79.8% for those with immunosuppressants alone, or 60% for those administered targeted biotherapy (including rituximab). Concerning AAVs, the ongoing French Vasculitis Study Group's prospective, the PNEUMOVAS trial (NCT03069703), is testing different vaccination regimens against pneumococcal pneumonia in GPA and MPA patients treated with rituximab.

Finally, patients must still be encouraged to quit smoking and participate in specific patient education programs [90].

Conclusions

Our understanding of the pathophysiology and disease management of EGPA has progressed notably over the past few decades, as attested by patients' improved prognoses. Two distinct ANCA-status phenotypes have been defined, and investigations to elucidate their different clinical findings, prognoses, and genetic backgrounds are being conducted.

However, EGPA relapse rates remain persistently high, and it is not unusual for patients to experience several treatment-related AEs. Thus, additional studies are needed to further improve the overall care of EGPA patients.

Clinical Vignette

Mr. J., 65 years old, was hospitalized for atrial fibrillation and cardiac insufficiency, in the context of severe chronic asthma, necessitating long-term treatment with bronchodilators and inhaled and oral glucocorticoids (7 mg/day). Over 3 months, his asthma worsened and oral prednisone (30 mg/day) was prescribed for the asthma flare. Eosinophilia, which had been ~500/mm^3 during the last few years, rose to 2000/mm^3 at the time of hospitalization. The patient was febrile and complained of arthralgias, myalgias, and extreme fatigue. A chest X-ray showed multiple lung infiltrates (Fig. 7.1). Some purpuric lesions were present on the lower limbs. A histology of a skin biopsy found fibrinoid necrosis of small-sized arteries.

Eosinophilic granulomatous with polyangiitis (EGPA) was diagnosed. Treatment was immediately started with prednisone (1 mg/kg/day) and intravenous cyclophosphamide (0.6 g/m^2 on days 0, 14, and 28, and then every 4 weeks, until 6 pulses, followed by maintenance therapy with azathioprine (2 mg/kg/day)). Oral prednisone was progressively tapered to 10 mg/day, under which asthma flared again.

Treatment also comprised of a combination of diuretics, enzyme-converting inhibitors, and an antiarrhythmic.

The patient improved quickly, with lung infiltrates resolving within a week. Eosinophilia was normalized. His general condition improved, and the general symptoms disappeared.

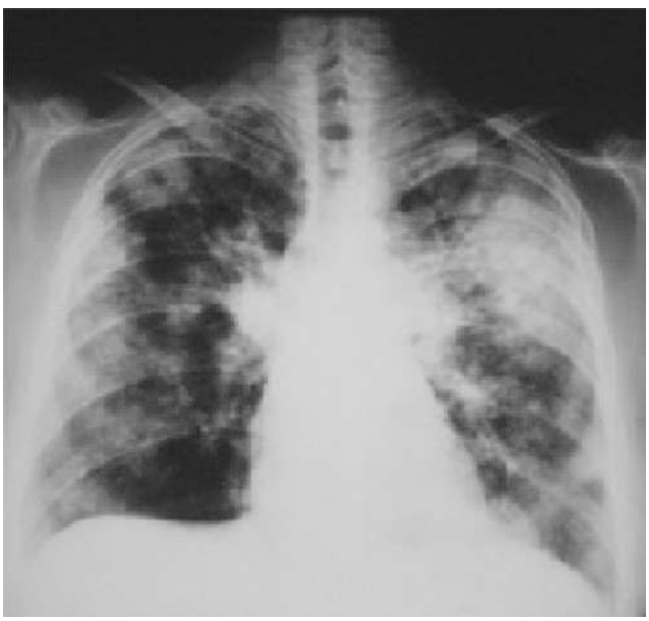

Fig. 7.1 Chest X-ray showing multiple lung infiltrates

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Granulomatosis with Polyangiitis

8

Christian Pagnoux and Alexandra Villa-Forte

Granulomatosis with polyangiitis (GPA; previously known as Wegener's granulomatosis) is a systemic vasculitis characterized by necrotizing granulomatous inflammation predominantly affecting small-sized vessels, including the arterioles and arterial capillaries [1, 2]. It is rare, but the incidence has increased within the past few decades, at least in some northern countries, in part, possibly but not exclusively, because of better recognition [3, 4]. GPA primarily affects adults between 45 and 60 years of age but can also affect people of all ages. Upper and lower respiratory tract and/or kidney manifestations are the cardinal signs of the disease; several are quite suggestive, such as saddle nose deformity, subglottic stenosis, or lung nodular cavitations [5]. GPA is typically associated with anti-neutrophil cytoplasm antibodies (ANCAs) directed toward proteinase 3 (PR3-ANCAs) on ELISA. The etiology remains unknown, although knowledge of the major pathogenic mechanisms, however complex, has greatly improved in the past two decades [6].

The current modalities of treatment, when promptly initiated and properly applied, lead to remission in most patients, with a relatively low risk of side effects. Besides potent therapies used for more than 50 years, such as cyclophosphamide and glucocorticoids, others (namely, rituximab) have been found to be effective in inducing remission while also being less toxic, and additional therapeutic changes are expected to happen in the near future with the recent development of C5a and C5a receptor complement inhibitors. However, given the relapsing nature of the disease, maintenance immunosuppressive therapy needs to be prolonged, although its optimal duration remains unknown, and may vary according to several patient and disease characteristics [7, 8]. The search for newer therapies continues [9], as a few patients experience refractory disease, unrelenting relapses despite treatment, and/or particularly challenging manifestations such as subglottic stenosis or an orbital tumor, for which treatment can be particularly difficult [10].

A Brief Historical Overview

The clinical picture of nasal cartilage destruction, consistent not only with the diagnosis of GPA but also with that of nasal natural-killer (NK)-cell lymphoma (previously known as lethal midline granuloma), was described in 1897 by McBride, an English otorhinolaryngologist. The subsequent published cases of GPA with histological evidence of vasculitis date back to 1931, when Klinger and Rössle at the Berlin Institute of Pathology reported two patients with "granulomatous polyarteritis" who died the following year after onset of the first signs of the disease. In 1933, Rössle described two other patients with necrotizing vasculitis affecting the nasal cavities and upper airways. Then, in 1936 and 1939, Friedrich Wegener, a colleague of Klinger, reported three cases, all with rapidly fatal outcomes. In 1954, Churg, Fahey, and Godman defined the disease more precisely, clinically, and histologically and named it Wegener's granulomatosis. Classification criteria were proposed in 1990 by the American College of Rheumatology [11] and then by the Chapel Hill Consensus [2], which confirmed in 1994 the position of the disease within the necrotizing, systemic, small-sized vessel vasculitides (Table 8.1). In 2011, Wegener's granulomatosis was officially renamed GPA after delayed gathering of evidence that Wegener had some involvement in the Nazi Party during World War II and in a broader effort to eliminate medical eponyms [12]. International efforts since the 2012 Chapel Hill ANCA and vasculitis workshop include a revised nomenclature of the systemic vasculitides, incorporating the new name of GPA and further emphasizing that it is an ANCA-associated disease [13]. New classification criteria

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Table 8.1 Classification criteria and definition of granulomatosis with polyangiitis (Wegener's granulomatosis), according to the American College of Rheumatology (1990) [11], 2021 [14], the nomenclature of the consensus conference held in Chapel Hill (NC) in 1993 [2] and revised in 2012 [13]

1990 American College of Rheumatology classification criteria for Wegener's granulomatosis		
For purposes of classification, a patient shall be said to have Wegener's granulomatosis if at least 2 of these 4 criteria are present. The presence of any 2 or more criteria yields a sensitivity of 88.2% and a specificity of 92.0%		
1. Nasal or oral inflammation: Development of painful or painless oral ulcers or purulent or bloody nasal discharge 2. Abnormal chest radiograph: Chest radiograph showing the presence of nodules, fixed infiltrates, or cavities 3. Urinary sediment: Microhematuria (>5 red blood cells per high power field) or red cell casts in urine sediment 4. Granulomatous inflammation on biopsy: Histologic changes showing granulomatous inflammation within the wall of an artery or in the perivascular or extravascular area (artery or arteriole)		
2021 American College of Rheumatology classification criteria for granulomatosis with polyangiitis		
The classification criteria for granulomatosis with polyangiitis can be considered only in patients in whom: (1) diagnosis of small- or medium-sized vessel vasculitis has been made and (2) all alternate diagnoses have been excluded, and are:		
Clinical criteria	Nasal involvement: bloody discharge, ulcers crusting, congestion, blockage or septa defect/perforation	+3
	Cartilaginous involvement (inflammation of ear or nose cartilage, hoarse voice or stridor, endobronchial involvement, saddle nose deformity)	+2
	Conductive or sensorineural hearing loss	+1
Laboratory, imaging, and biopsy criteria	Cytoplasmic antineutrophil cytoplasmic antibody (cANCA) or antiproteinase 3 ANCA (PR3-ANCA) positivity	
	Pulmonary nodules, mass or cavitation on chest imaging	
	Granuloma, extravascular granulomatous inflammation, or giant cells on biopsy	
	Inflammation, consolidation or effusion of the nasal/paranasal sinuses, or mastoiditis on imaging	
	Pauci-immune glomerulonephritis on biopsy	
	Perinuclear ANCA (pANCA) or antimyeloperoxidase ANCA (MPO-ANCA) positivity	*−1 (subtract)*
	Blood eosinophil count ≥1 × 109/L	*−4 (subtract)*
A cumulative, sum score of ≥5 is needed for classification of granulomatosis with polyangiitis. The sensitivity of these criteria was 93% (95% CI; 87–96%) and specificity 94% (95% CI; 89–97%)		
Definition of Wegener's granulomatosis in the nomenclature of systemic vasculitis adopted in 1994 by the Chapel Hill consensus conference		
Large vessel vasculitis: Giant cell (temporal) arteritis; Takayasu's arteritis		
Medium-sized vessel vasculitis: Polyarteritis nodosa; Kawasaki's disease		
Small vessel vasculitis:		
Wegener's granulomatosis[a]		
Granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small to medium-sized vessels, e.g., capillaries, venules, arterioles, and arteries ***Necrotizing glomerulonephritis is common***		
Churg-Strauss syndrome[a] Microscopic polyangiitis[a] Henoch-Schönlein purpura Cryoglobulinemic vasculitis Cutaneous leukocytoclastic angiitis		
Small artery refers to distal arterial radicals that connect with arterioles. Small vessels include small arteries, arterioles, venules, and capillaries		
Definition of granulomatosis with polyangiitis (Wegener's) in the 2012 revised international Chapel Hill consensus conference nomenclature of vasculitides		
Large vessel vasculitis: Giant-cell arteritis; Takayasu arteritis		
Medium vessel vasculitis: Polyarteritis nodosa; Kawasaki disease		
Small vessel vasculitis:		
ANCA-associated vasculitis		
Microscopic polyangiitis		
Granulomatosis with polyangiitis (Wegener's)		
Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotizing vasculitis affecting predominantly small to medium vessels (e.g., capillaries, venules, arterioles, arteries, and veins). Necrotizing glomerulonephritis is common		
Eosinophilic granulomatosis with polyangiitis (Churg Strauss)		
Immune complex vasculitis		
Anti-GBM disease cryoglobulinemic Vasculitis IgA vasculitis (Henoch-Schönlein) Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis)		
Variable vessel vasculitis: Cogan's syndrome; Behçet's disease		
Single organ vasculitis		
Vasculitis associated with systemic disease		
Vasculitis associated with probable etiology		
Large vessels are the aorta and its major branches and the analogous veins. Medium vessels are the main visceral arteries and veins and their initial branches. Small vessels are intra-parenchymal arteries, arterioles, capillaries, venules, and veins		

[a] These vasculitides are associated with ANCA

have been conjointly developed by the American College of Rheumatology and the European League Against Rheumatism (EULAR) and have been officially published in 2021, which reinforces the role of PR3-ANCAs in the definition of GPA [14].

Epidemiology

GPA affects both genders equally. Only a few studies, mostly those of localized/limited GPA, have suggested a relatively greater frequency in women. The median age at diagnosis is in the fifth decade (Table 8.2), but young children and older adults can also be affected. Most patients (93–98%) are white (Caucasian and Hispanics). The estimated annual incidence is 2–30 cases per million people, and the prevalence is 20–260 cases per million people [3, 4, 15]. A north-south gradient is suggested, at least in Europe, because the reported annual incidence is twice higher in Norway, for example, than in Spain (15 vs. 4.9 per million inhabitants) [16]. Conversely, PR3-ANCA + GPA is rare in Japan, where anti-myeloperoxidase (MPO-ANCA) + disease (mostly of the microscopic polyangiitis-type) represents most cases of ANCA vasculitis. Notably, the incidence of the disease also seems to have increased within the past few decades, according to several European studies, although some of these changes could be related, at least in part, to a better understanding and awareness of the disease and thus more frequent and earlier diagnoses [4, 15, 17]. A British study also suggested peaks of incidence every 8–10 years (17.4 per year per million people during peaks vs. only 4.53 per year per million people during no peaks) [16]. Seasonal variations in GPA incidence have been reported but with conflicting results [18].

The existence of these potential geographic and temporal variations in GPA incidence suggests a potential pathogenic, or at least a participating, role of environmental (allergic, chemical, and/or infectious) and/or genetic factors in the development of the disease. The association between GPA and silica exposure, industrial pollutants such as cadmium, mercury derivatives, or other heavy metals such as lead, volatile hydrocarbons, or organic solvents has been reported. Other studies have suggested links between GPA and the inhalation of dust, especially during livestock activities [19]. However, GPA does not seem more frequent in rural areas, and exposure to such environmental agents is found in no more than 10% of all GPA patients [20]. Finally, an inverse relation between the intensity of sun exposure, specifically ultraviolet rays, and GPA prevalence suggests a possible link to vitamin D deficiency, as has been suggested in many other autoimmune diseases [21].

GPA is not an inherited or genetic disease. Familial forms are extremely rare, with a small and insignificant relative risk of GPA among first-degree relatives of GPA patients (hazard ratio (HR) 1.56; 95% confidence interval (95% CI) 0.35–6.90), as compared with the general population. However, first-degree relatives may be more likely to develop other autoimmune diseases (HR 1.32, 1.18–1.49), including multiple sclerosis (HR 1.92), Sjögren's syndrome (HR 2.00), or rheumatoid arthritis (HR 1.54) [22]. Personal (and probably also familial) history of autoimmune thyroiditis has been found more frequently in GPA patients than in the general population (13% of GPA patients) [23]. Some genetic predisposition is thus likely, although not enough to explain or trigger the disease by themselves. Several international teams have conducted studies on

Table 8.2 Characteristics of patients with granulomatosis with polyangiitis and frequency (percent), according to the main studies published between 1958 and 2020

Characteristic	Range	Mean
Mean age at diagnosis (years)	14–58	48
Clinical presentations/organ involvement (%)		
Ear, nose, and throat	56–99	70
Kidney	18–100	58
Lung	40–100	57
Arthralgias	15–77	52
Fever	17–72	45
Eye	2–61	34
Skin	12–50	29
Peripheral nervous system	7–68	20
Heart	0–30	13
Gastrointestinal	0–42	12
Central nervous system	0–13	8

genome-wide associations with GPA. Many, and sometimes variable, genetic associations have been reported, with the two most reproducible being those for molecules of major histocompatibility complex (MHC) *HLA-DPB1*0401* (odds ratio (OR) 3.38 for patients with ANCAs) and, to a lesser degree, allele deficiency of alpha-1 antitrypsin (serpin A1; *PI*Z* alleles in 5–27% of GPA patients, *PI*S* alleles in 11.58%, homozygosity for deficiency ZZ, SS, or SZ having more severe forms) [24]. Many other genetic associations have been reported, including certain alleles of PR3-coding genes (-564 A/G), type IIa and IIIa/b Fc-gamma or Fc-alpha receptors, intracellular tyrosine phosphatase *PTPN22* (620W allele), transforming growth factor beta-1, interleukin-10 (IL-10) promoter, CTLA-4, or CD226 (Gly307Ser) polymorphism allele [24, 25]. GPA has been associated with other MHC molecules, including DR2 and DR4 alleles HLA-DRB1*04, B8, DR1-DQw1, B50-DR9, and DR9 in Japanese patients. Conversely, the DR13-DR6 phenotype was found to be less frequent among Norwegians with GPA than among healthy subjects.

More importantly, perhaps, the most recent studies have shown that genetic susceptibility is more linked to the ANCA type (PR3-ANCAs with *HLA-DP* and the genes encoding α1-antitrypsin (*SERPINA1*) and proteinase 3 (*PRTN3*) versus MPO-ANCAs with *HLA-DQ*) than to the clinical phenotype (GPA versus microscopic polyangiitis) [26]. Whether the classification of ANCA-associated vasculitides should be modified according to these results remains under debate [8, 27].

Pathogenesis

GPA is considered an autoimmune inflammatory disease. Defining its pathogenic mechanisms has advanced enormously within the past three decades, especially since the discovery of ANCAs in 1985 [17]. However, the *primum movens* of the disease remain(s) to be identified [6, 28].

The hypothesis of an infectious agent, such as *Staphylococcus aureus*, (over)activating the immune system has been repeatedly suggested. Chronic nasal carriage of *S. aureus* is considered a risk factor for relapse, as is observed in some but not all patients and as shown in one study, possibly by maintaining a local inflammatory immune response within the nasal mucosa [29]. A selective cross-reactivity of T cells toward PR3 and *S. aureus* antigens has been suggested. The experimental model of Pendergraft et al. suggested that some antigenic motives of *S. aureus* have a molecular similarity with the protein synthesized from the complementary DNA segment coding for human PR3, which can trigger the production of antibodies against PR3 by a complementary protein idiotype–anti-idiotype mechanism [30]. The *S. aureus* infection found in GPA patients is not from a particular strain and does not produce specific toxins or lead to a specific T-cell repertoire selection through superantigenic mechanisms [31]. Other organisms could have also been involved, such as *Staphylococcus pseudintermedius* or *Corynebacterium tuberculostearicum*, based on recent nasal microbiome studies [32–36].

Irrespective of the signal for their synthesis, PR3-ANCAs are detected in more than 80% of patients with generalized GPA. However, their pathogenic role is less well-documented than that of MPO-ANCAs (most characteristic of microscopic polyangiitis). Animal models of vasculitis associated with PR3-ANCAs remain less convincing and require many preliminary alterations of the immune system of the animal model as compared with those associated with MPO-ANCAs. In the mouse model of Pfister et al., vasculitis induced by transfer of PR3-ANCAs remained localized to the mouse footpads, was not granulomatous, and required prior sensitization with subcutaneous injections of tumor necrosis factor-α (TNF-α) [37]. In the BALB/c murine model of Pendergraft et al., mice did not develop overt vasculitis [30]. Two other subsequent murine models of PR3-ANCA-associated vasculitis have been developed and are more convincing but require specific genetic backgrounds and prior subtle and complicated immune manipulations (including the humanization of the mouse immune system because of the lack of PR3 expression in murine neutrophils and low human and murine PR3 homology) [38, 39]. Specific alterations and "maturation" may be necessary for PR3-ANCAs to become pathogenic, including the selection of higher-affinity ANCAs in the nasal mucosa granulomas or modulation of their sialylation levels [40]. Whereas results from recent studies of therapies targeting B cells (i.e., rituximab) have seemed to provide indirect evidence for the potential pathogenic role of PR3-ANCAs, these biological agents may (also) act through other more complex pathways [41–43].

Other factors or mechanisms involved in GPA can favor or enhance the PR3 and PR3-ANCA interaction and thereby the immune response. Besides the frequent functional and/or genetic deficit in 1-antitrypsin, the physiological inhibitor of PR3, overexpression of PR3 on the neutrophil membrane, genetically determined, has also been reported. More recently, circulating microparticles derived from platelets, neutrophils, or endothelial cells as well as neutrophil extracellular traps (NETs, the cellular activation debris produced in response to inflamma-

tory signals) have been found to express PR3 and MPO, thus perpetuating the presentation of self-antigens and production of ANCAs, and could trigger or increase inflammatory responses in the endothelia, especially in the kidneys [44]. Changes, maturation (such a glycosylation level), and epigenetic changes in PR3-ANCA production and/or conformation can also lead to increased pathogenicity of the autoantibodies [40, 45]. GPA has been associated with excess production of certain soluble factors of stimulation and proliferation of B lymphocytes (B-cell-activating factor (BAFF) of the TNF family, also called B-lymphocyte stimulator). In parallel, functional abnormalities of the regulatory T lymphocytes CD4 + CD25 + FoxP3+ and abnormal expression of certain T-cell costimulatory molecules, including increased membrane expression of CTLA4, can lead to rupture of immune tolerance mechanisms.

The binding of ANCAs results in activation of the alternative complement pathway and production of reactive oxygen species by neutrophils, all of which lead to endothelial injury. Both the depletion of neutrophils and the blockade of the complement pathway prevent the development of MPO-ANCA-induced vasculitis in experimental models [46, 47].

Granuloma formation, an important histological characteristic of GPA, involves lymphocyte subpopulations, with not only a preferential cytokine secretion profile of TH1 lymphocytes (interferon-gamma) but also other complex cytokine imbalances, cell populations, or immune pathways of a more recent discovery, such as TH17 lymphocytes, a source of IL-17, dendritic, or natural killer cells.

Finally, functional abnormalities of endothelial cells have been described, and serum autoantibodies against endothelial cells have been found in some patients.

Clinical Manifestations

The main clinical manifestations of GPAs and their frequencies are displayed in Table 8.2. The most frequent target organs or systems are the upper and lower respiratory tracts and kidneys (necrotizing crescentic pauci-immune glomerulonephritis), but any organ can be affected. Disease damage and possible complications of treatment are discussed in another section of this chapter.

Constitutional Symptoms

Constitutional and musculoskeletal symptoms are common and include asthenia, fever, weight loss, diffuse myalgias, arthralgias, or sometimes genuine inflammatory arthritis with reported cases of oligo- or polyarthritis.

Ear, Nose, and Throat (ENT) Manifestations

More than two-thirds of patients have ear, nose, and throat manifestations, which often represent the first symptoms of the disease. When isolated, such symptoms can result in diagnostic delays. Persistent nasal obstruction, nasal or sinus pain, sinusitis, rhinitis, recurrent epistaxis and/or nasal crusting, or serous otitis media and/or hypoacousia should alert physicians to the possibility of GPA [5]. Hyposmia and/or hypogeusia are frequent.

The destruction of the nasal cartilage, which can lead to nasal septum perforation and/or saddle nose bridge deformity (Fig. 8.1), is highly suggestive, although not pathognomonic of GPA [48, 49]. The cartilage of the ears can also be affected (chondritis), as can the osteochondral tissues of the face and skull, with a rare occurrence of palate perforation or development of fistulas between the sinus and orbital cavities.

Another classic but rarer upper respiratory tract lesion (7–15% of patients) is subglottic stenosis, which is responsible for dysphonia and dyspnea with or without stridor and may require emergency procedures (dilatation with local injections of glucocorticoids or tracheostomy) [10, 49, 50]. Subglottic stenosis can be associated with endobronchial stenoses or can be isolated. It can occur in parallel with other manifestations or continuously progress despite control of disease elsewhere [51].

A computed tomography (CT) scan of the sinuses may show unilateral or bilateral sinusitis, osteochondral destruction and/or osteosclerosis (Fig. 8.2), otitis media, and/or mastoiditis. Granulomatous inflammatory tumors can also occur and can infiltrate the sinuses, skull base, and/or orbits and be responsible for pain, proptosis, or contiguous pachymeningitis, which incur the risk of compression of the surrounding structures, such as the cranial (ophthalmoplegia) or optic nerves. CT scan findings of subglottic stenosis should be studied in parallel with the results of a careful endoscopy (biopsies of subglottic stenosis are relatively sensitive but risky). Biopsies of nasal and/or sinus lesions can reveal granulomatous inflammation or vasculitis in about half of cases, when sufficiently deep in and under the mucosa [52, 53]. In routine practice, nasal and sinus biopsies are often superficial and rarely contribute to the diagnosis (abnormal in <25% of cases).

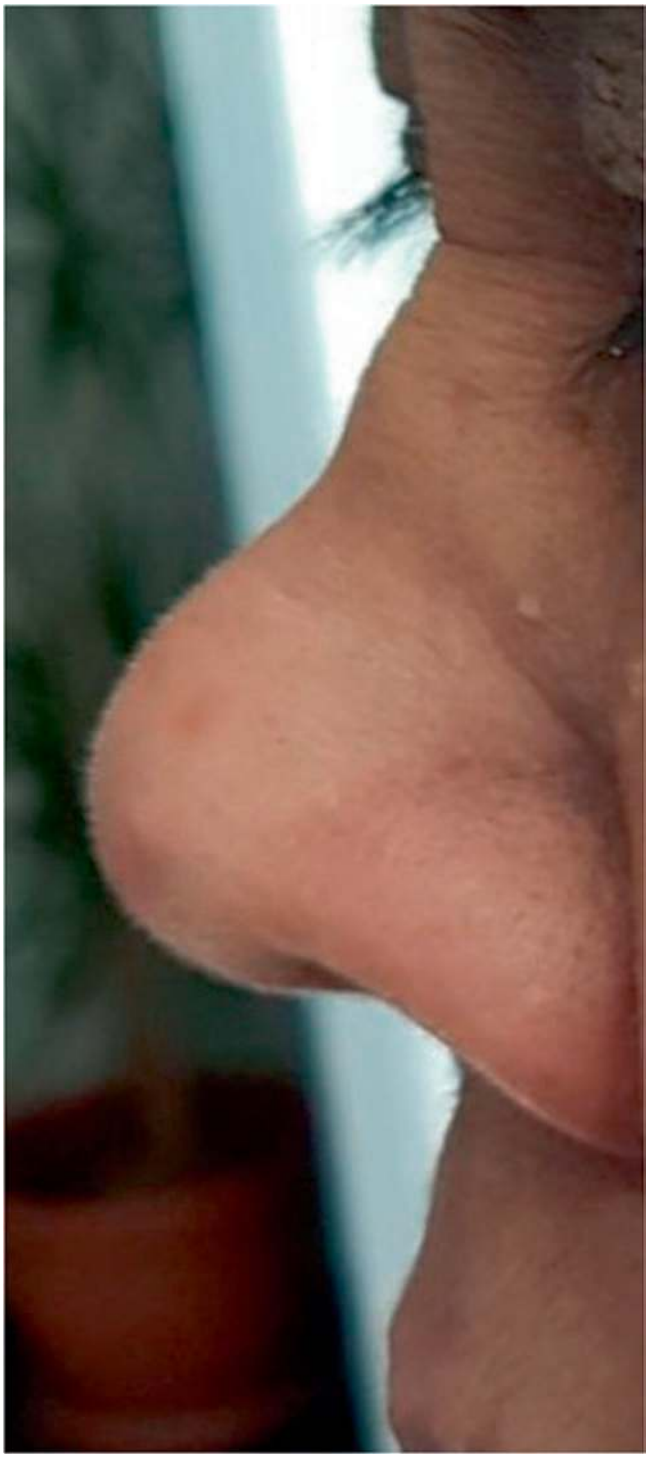

Fig. 8.1 Nasal deformity (bridge erosion) in a patient with granulomatosis with polyangiitis

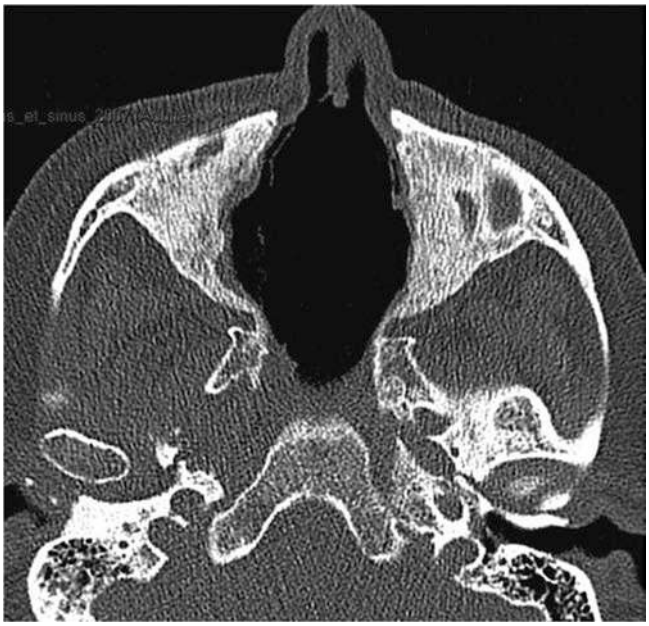

Fig. 8.2 A sinus CT scan (horizontal) in a patient with granulomatosis with polyangiitis. Major destruction of the septum and midline cartilaginous structures, along with bilateral maxillary sinus osteosclerosis and atrophy

Pulmonary Manifestations

The lungs are involved in 70–100% of patients, with clinical manifestations ranging from mild cough, dyspnea, chest pain, and intermittent hemoptoic expectoration to acute respiratory distress syndrome due to massive alveolar hemorrhage. In 6% of cases, lung involvement can remain asymptomatic, especially with lung nodules.

Lung nodules are among the most characteristic signs. A chest X-ray and a CT scan can show nodules in 40–66% of patients [54]; they are unilateral or bilateral, single or multiple (generally <10), measuring 0.5–10 cm in diameter, and excavated in half of cases (Figs. 8.3, 8.4, 8.5, and 8.6) [55]. A high-resolution chest CT should be obtained for all patients with respiratory symptoms because small nodules, early alveolar hemorrhage, and other early lesions may be missed on a chest X-ray. The differential diagnosis, including primary or metastatic tumors, and infections, especially tuberculosis or fungal infections, can be difficult.

Alveolar hemorrhage (8–30% of patients) can occur at disease onset or later and can be associated with lung nodules [5]. It can be limited to a few bloody expectorations or become rapidly massive and be responsible for acute respiratory failure. However, sometimes, hemorrhage is suspected only on a chest CT scan (Figs. 8.6, 8.7, and 8.8; patchy, ground-glass opacities) and/or as unexplained anemia and then confirmed by bronchoalveolar lavage (persistently demonstrating hemorrhagic fluid on sequential samples). Even when bleeding is obvious, bronchoalveolar lavage should be considered to rule out concurrent infection, even at disease onset.

Other pulmonary infiltrates or lung consolidation (Fig. 8.5), unilateral or bilateral, may be observed in

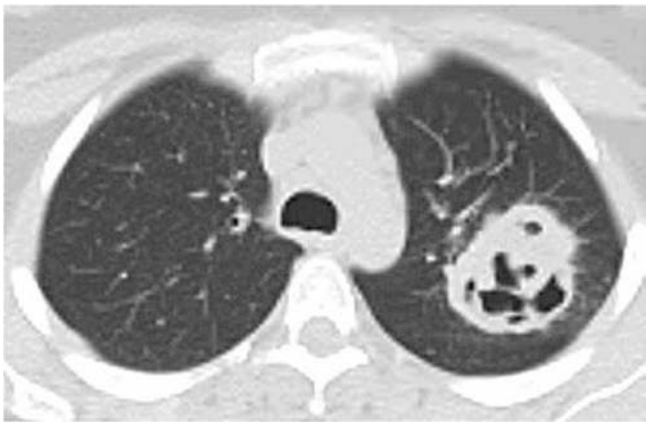

Fig. 8.3 A chest CT scan (horizontal) in a patient with granulomatosis with polyangiitis. Large parenchymal excavated nodule (left lung)

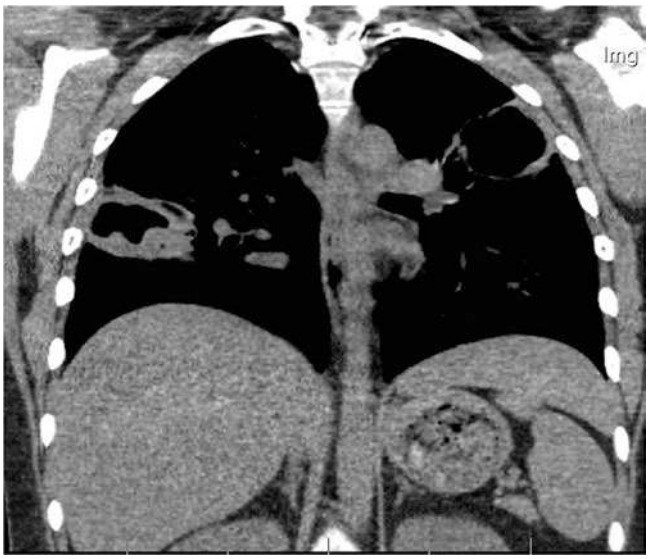

Fig. 8.4 A chest CT scan (coronal) in a patient with granulomatosis with polyangiitis. Large parenchymal excavated nodules in both the lungs

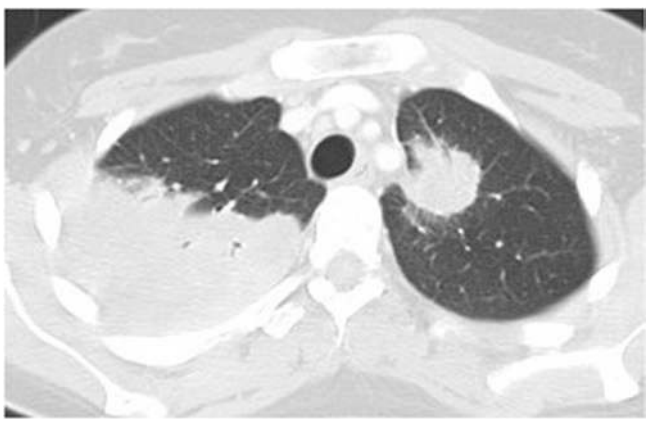

Fig. 8.5 A chest CT scan (horizontal) in a patient with granulomatosis with polyangiitis. Parenchymal plain nodule (left lung) associated with right lung posterior consolidation (and mild pleural effusion)

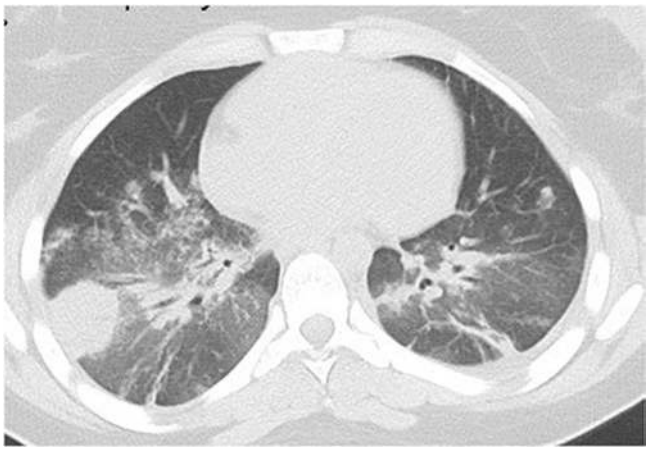

Fig. 8.6 A chest CT scan (horizontal) in a patient with granulomatosis with polyangiitis. Parenchymal plain nodule (right lung) associated with multiple bilateral patchy opacities and diffuse posterior ground-glass opacities (probably corresponding to moderate alveolar hemorrhage)

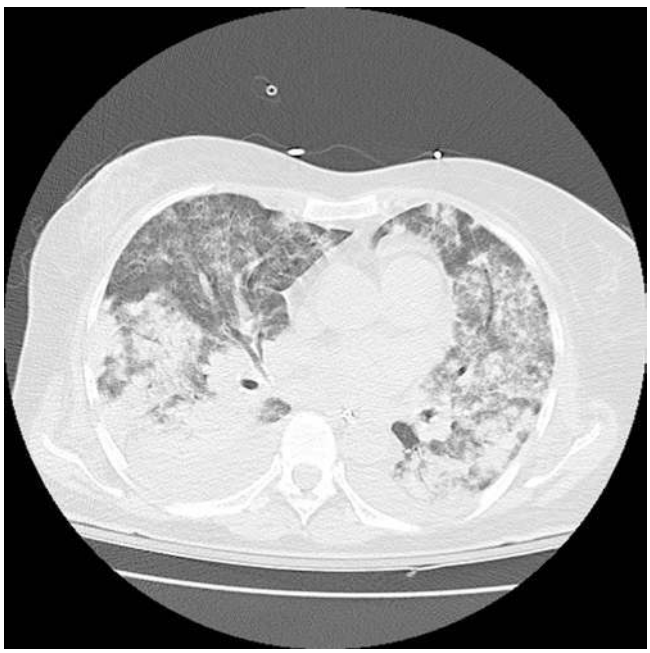

Fig. 8.7 A chest CT scan (horizontal) in a patient with granulomatosis with polyangiitis. Diffuse bilateral ground-glass infiltrate corresponding to massive alveolar hemorrhage

30–50% of patients and pleural effusion in 9–28% [5, 54]. Bronchial stenoses, usually on the main bronchia and/or first branches, can occur and are often difficult to manage, as mentioned previously (frequently associated with subglottic stenosis). These are best studied with a CT scan of the lungs (Fig. 8.9) and fiberoptic bronchoscopy, which can reveal multifocal strictures and/or granulomatous endobronchial lesions. Spontaneous pneumothorax or pyopneumothorax are rare. Bronchiectasis is rarer in GPA than in MPO-ANCA-associated vasculitis [56]. Similarly,

chronic interstitial lung disease with fibrosis is not a classical feature of GPA. It is possible but more commonly seen in the presence of MPO-ANCAs with or without systemic vasculitis (microscopic polyangiitis).

Surgical and open-wedged lung biopsies, targeting nodules or consolidation lesions, have a good diagnostic yield of up to 91% [5, 53]. In practice, obtaining these biopsies can be difficult, but they can be necessary to confirm the diagnosis, especially in patients with disease limited to the lungs.

Pulmonary embolism (<5% of patients at diagnosis) may be a sign of active GPA, especially in patients with otherwise unexplained chest pain and sudden and/or persistent shortness of breath.

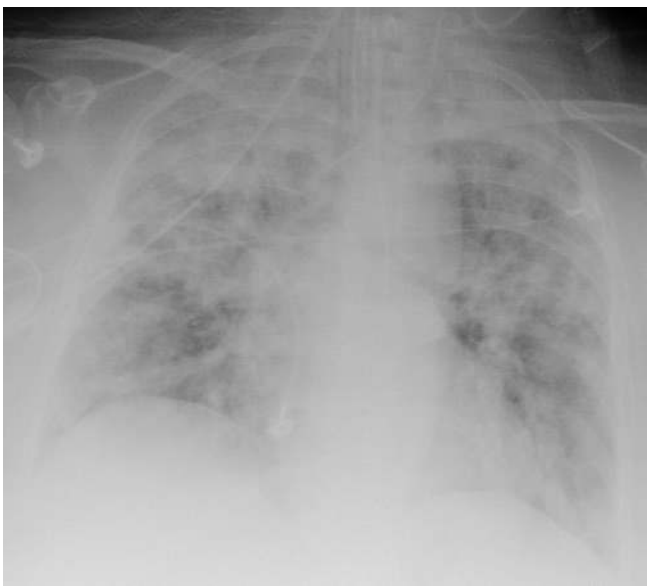

Fig. 8.8 A chest radiograph (anteroposterior) in a patient with granulomatosis with polyangiitis. Diffuse bilateral bronchoalveolar infiltrate corresponding to massive alveolar hemorrhage

Asthma is not a feature of GPA and may suggest eosinophilic granulomatosis with polyangiitis. A coincidental association of the two conditions remains possible, and an eosinophilic variant form of GPA has been described, sometimes with asthma [57, 58] and/or as a possible overlapping form of immunoglobulin (Ig)4-related diseases [59, 60].

Kidney and Urological Manifestations

Kidney Manifestations

Renal disease represents the third most frequent manifestation of GPA and presents as focal, segmental, crescentic, necrotizing, and pauci-immune glomerulonephritis. The first sign is microscopic hematuria, with (or without) red blood cell casts. Increased proteinuria usually follows before renal function worsening, which can rapidly lead to end-stage renal disease. The combination of alveolar hemorrhage and renal disease defines pulmonary renal syndrome, which can occur in GPA as well as in microscopic polyangiitis, anti-glomerular basement membrane (GBM) antibody disease (Goodpasture syndrome), and systemic lupus erythematosus. A kidney biopsy is sensitive in patients with urine sediment abnormalities, and histology can help in predicting renal prognosis (with a simple classification: focal, crescentic, mixed, and sclerotic) [61].

Rarer renal manifestations include granulomatous nephritis, interstitial granulomatous renal masses, and aneurysms of the branches of the renal arteries, including their intraparenchymal portions [62, 63]. A possible (but low) increase in the frequency of kidney cancer has been suggested by some studies or case reports, but most were probably related to bladder toxic treatments [64].

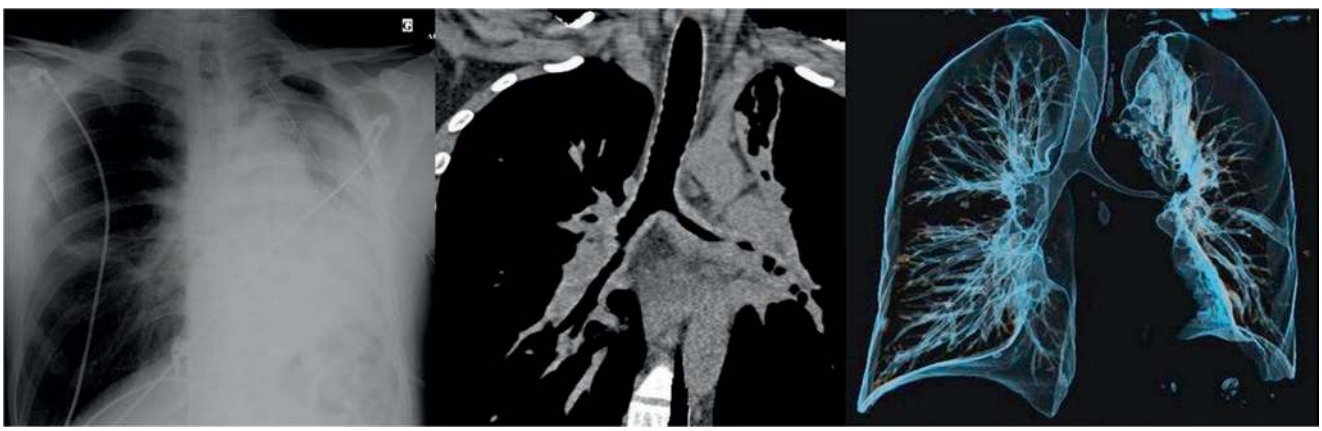

Fig. 8.9 A chest radiograph (anteroposterior), a CT scan (coronal), and a 3D volume reconstruction of the tracheobronchial tree in a patient with granulomatosis with polyangiitis. Major lengthy and multisegmental stenosis of the left main bronchus causing partial left lung atelectasis (bronchus intermedius is also laterally narrowed). Note the thickening of the narrowed bronchial wall, suggesting granulomatous infiltration

Urological Manifestations

Ureteral (or, less frequently, urethral) stenosis, uni- or bilateral, single or multifocal, secondary to ureteral arteriolitis, peri-ureteral granulomatous infiltrates, and/or sheathing in retroperitoneal fibrosis can occur and cause hydronephrosis and/or obstructive renal insufficiency [63]. Granulomatous prostatitis, ischemic and/or granulomatous orchitis, and penile ulcers have been reported [63]. Vulvar ulcerations have been reported in women.

Bladder involvement is rare, and inflammation and/or hematuria originating from the bladder should suggest an infection and/or hemorrhagic cystitis in patients receiving cyclophosphamide, bladder cancer in those receiving cyclophosphamide, and/or in heavy smokers [65].

Neurological Manifestations

Peripheral Nervous System (PNS) Manifestations

The peripheral nervous system (PNS) is affected in 11–68% of patients [66]. Clinically, mononeuritis multiplex (asymmetrical and asynchronous) represents the principal pattern of peripheral nervous system involvement (45–79% of cases), most frequently involving the ulnar and peroneal nerves, followed by sensorimotor (symmetrical) polyneuropathy, both related to axonal ischemia due to vasculitis of the vasa nervorum of the small epineurial vessels.

Central Nervous System (CNS) Manifestations

The central nervous system is more rarely involved in 6–13% of patients and often later and more progressively (except for the exceptional strokes) than the PNS [67, 68]. Central nervous system involvement can result from the extension of sinus and/or orbital granulomatous lesions, causing pachymeningitis and sometimes (post- or pan-) pituitary gland involvement (diabetes insipidus) or a new development of cerebral granulomatous lesions and/or intracranial artery vasculitis. Headache, meningeal irritation, cranial nerve palsy, hypoacousia, and sensorimotor deficit are the most frequent clinical features, but hemiparesis, hemiplegia, or seizures can also occur (usually ischemic). Rare cases of cerebral venous thrombosis with cortical venous infarction have been reported.

Spinal Cord and Cranial Nerve Involvement

Spinal cord or cauda equina involvement is rare and is usually due to compression by a meningeal granulomatous infiltrate rather than spinal cord ischemic vasculitis [69]. Cranial nerve involvements are more common (4–14% of patients), primarily affecting the optic nerves II, VI, and/or VII and V, uni- or bilaterally, and occur due to compression by extensive meningeal or pseudotumoral intraorbital lesions or, more rarely, nerve ischemia and/or inflammation.

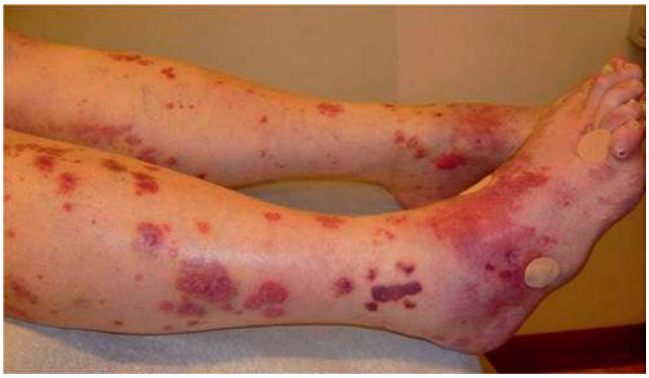

Fig. 8.10 Diffuse ecchymotic, necrotic, and purpuric lesions in a patient with granulomatosis with polyangiitis

Skin and Oral Mucosal Manifestations

In total, 10–50% of patients have skin lesions, primarily palpable purpura (Fig. 8.10). Macules, papules, ulcers, digital gangrene, or, more rarely, subcutaneous nodules can occur [70]. Palpable purpura is more common in the lower extremities, but involvement of the elbows (nodules, ulcerated nodules) and hands, including the dorsal face and digital pulps, is not infrequent. Lesions can sometimes mimic erythema elevatum diutinum, pyoderma gangrenosum, or hidradenitis suppurativa, which can also occur as a rare complication or an associated condition.

Skin biopsies most often reveal nonspecific perivascular infiltrates and/or aspects of leukocytoclastic vasculitis of small vessels, which are not specific to GPA. Sometimes, blatant necrotizing vasculitis of superficial vessels of the dermis and/or deep subcutaneous layers is seen. Vascular or extravascular granulomatous infiltrates can be seen in nodular or papular lesions [71].

Oral mucosal lesions can occur in 10–50% of patients and include ulcerations; persistent canker sores, especially on the lateral edges of the tongue; and gingival hypertrophy or "strawberry" gum, which is often painful and relatively evocative of GPA [70]. Infiltrations of the parotid and/or accessory salivary glands have been described. Very destructive lesions of the soft palate are rare in GPA, and more suggestive of levamisole-cocaine induced GPA-like vasculitis/vasculopathy.

Eye Manifestations

Ocular and/or orbital manifestations are relatively common (14–60% of patients) and can be inaugural and/or remain isolated for a long time.

Proptosis, possibly associated with ophthalmoplegia, is usually due to the local extension of a granulomatous retro-orbital tumor or from the ear, nose, throat, and/or meningeal lesions (Fig. 8.11).

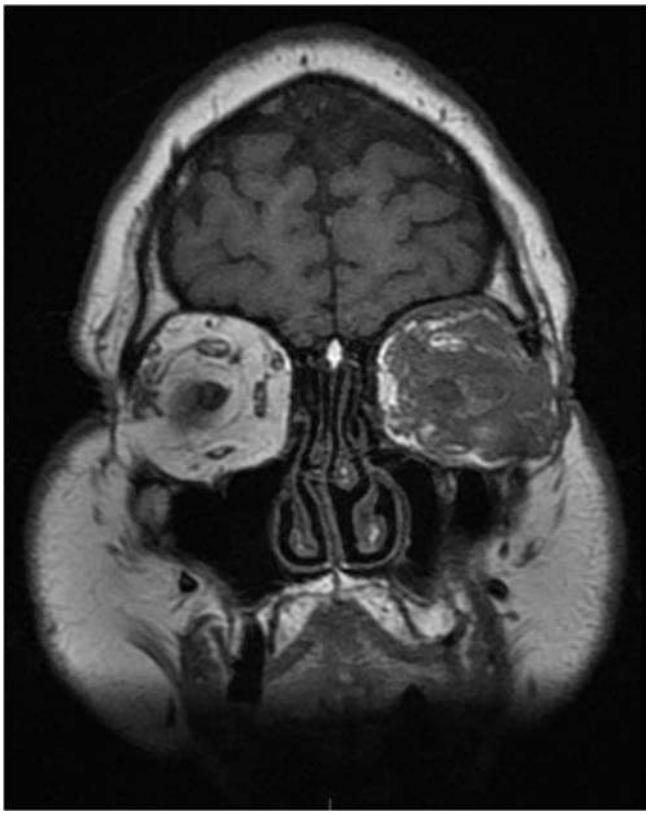

Fig. 8.11 A sinus and orbital CT scan (coronal) in a patient with granulomatosis with polyangiitis. Massive infiltration of the left orbital cavity by a tumoral tissue (likely granulomatous on biopsy and exerting compression on the eye and ocular muscles)

Conjunctivitis and episcleritis are relatively common and benign. Inflammation of the lacrimal gland (dacryocystitis or dacryoadenitis) is also common and leads to dry eye sensation, watery eyes, or suprainfection because of clogged tear ducts, which may require surgical debridement procedure and/or stenting. Corneal ulcers and scleritis, often necrotizing and nodular, are more of a concern because of the risk of eye perforation, loss of vision, and endophthalmitis. Retinal vasculitis is rarer but can also cause blindness [72]. Extensive xanthelasma has been reported, especially after the regression of an orbital tumor [70].

Cardiac Involvement

Cardiac involvement is rare (about 10% of patients but up to 30% in an autopsy series) [73, 74]. Magnetic resonance imaging (MRI) or sophisticated echocardiography (such as two-dimensional (2D) speckle-tracking) of the heart or electrophysiological investigations can reveal subclinical abnormalities, the prognostic value of which remains to be determined [75].

Sinus tachycardia is common during the active phases of the disease, as are arrhythmias, especially atrial fibrillation. Conduction disorders due to granulomatous infiltration of the cardiac conductive tissue can lead to an atrioventricular block or a bundle branch block, which may require transient pacing but usually regresses with medical treatment. Pericarditis, sometimes progressing to tamponade and/or constrictive pericarditis, and coronary artery inflammation, most often clinically silent, account for half of the reported cardiac manifestations in GPA. Myocardial infarction, diagnosed during the patient's life, represent about 10% of the reported cases of GPA, with cardiac involvement and valvular disease, primarily aortic, in 21% of such cases [74].

Gastrointestinal Manifestations

Gastrointestinal manifestations are less frequent in GPA than in other medium- and small-sized vessel vasculitides and are rarely isolated or present at disease onset; they range from mild abdominal pain to more severe ischemic bowel perforations [76, 77]. Inflammatory granulomatous ileocolitis, gastritis, or anorectitis are more characteristic but are not specific (differentiating between GPA, Crohn's disease, and ulcerative colitis can be difficult). Biopsies performed endoscopically rarely reveal vasculitis (10–50%) and are not without risks.

The involvement of the appendix or pancreas (sometimes with challenging tumoral presentation) and/or the gallbladder has been reported [78]. Hepatic involvement is rare in clinical practice and usually remains limited to laboratory abnormalities (transaminitis). Splenic involvement is exceptional but can be responsible for infarction or a nontraumatic rupture. Hepatic artery aneurysms, which can rupture, have been reported.

Gynecological and Obstetric Manifestations

Few cases of mastitis have been described but can present as breast masses or ulcerated skin lesions. Uterine and vulvar lesions are rare.

Few pregnancies in GPA patients have been reported in the literature, in part because the average age of onset of the disease is about 45 years and because cyclophosphamide, often used as treatment, can lead to infertility or subfertility in women of childbearing age, depending on the cumulative dose received [79, 80]. Decreased fertility resulting from the disease itself is possible, but overt ovarian involvement has rarely been described. Measurement of the anti-Mullerian hormone at treatment onset (and thereafter) can help evaluate the remaining follicles in young women.

Few women develop GPA during pregnancy, and few others with known GPA experience disease flares or worsening during pregnancy post-partum or post-abortion [81–83], some with fatal outcome. However, more than half of the reported pregnancies with GPA have been uneventful or with only minor disease manifestations. The risk of GPA worsening or relapse is an estimated 25% if the disease is in remission at the onset of pregnancy and is 40% if the disease is active. The existence of organ damage from previous flares, especially renal and/or heart failure, must be taken into consideration when evaluating the risk with pregnancy. GPA flares and complications during pregnancy must be managed in referral centers for vasculitis and high-risk pregnancies.

Among pregnancies carried to term with GPA, newborn and child outcomes appear to be favorable, perhaps with a slightly higher frequency of preterm deliveries [80, 81].

Venous Thrombosis and Other Vascular Events

Many studies have now reproducibly demonstrated an increased risk of venous thromboembolic events (deep vein thrombosis and/or pulmonary embolism) with GPA, mainly during the active phases of the disease [84–88]. The incidence of these events was an estimated 7 per 100 patient-years in one of the first studies reporting this complication, which is a 20-fold higher risk than in the general population [85]. The events are probably favored by systemic and vessel wall inflammation and frequent, reduced patient mobility because of the disease and/or neuropathy in some patients. Additional autoimmune mechanisms may lead to the development of these thromboses (antibodies against plasminogen have been detected in some patients, and PR3-ANCAs may cross-react with plasminogen in certain conditions) [89].

Besides digital ischemia, stroke, and/or coronary artery involvement, limb ischemia or carotid artery thromboses can occur, although rarely [90]. A few cases of ascending aorta inflammation (aortitis), pseudotumor (periaortitis), or aneurysms of the aorta, subclavian arteries, popliteal, renal, hepatic, and/or spleen have been reported. There is also an increased risk of ischemic heart disease, possibly because of endothelial function abnormalities, some of which are reversible in part with immunosuppressive therapy and prolonged use of glucocorticoids [91].

Other Manifestations

Other rare manifestations include periostitis, almost exclusively of the tibia, or prevertebral dorsal lesions, which can mimic fibrosing mediastinitis but are usually not erosive or compressive [92, 93]. Retroperitoneal fibrosis is exceptional and should raise suspicion of a IgG4-related disease.

Granulomatous involvement of the thyroid gland is rare, but autoimmune hypothyroidism (Hashimoto) or hyperthyroidism (Graves' disease) can occur. Other endocrine glands that can be affected include the adrenal and pituitary glands (as described with CNS manifestations). Pancreatic involvement does not usually result in secondary diabetes mellitus.

Limited/Localized Versus Severe/Diffuse/Systemic Forms

Despite the variation in definitions among studies and authors (Table 8.3), GPA can be differentiated into two

Table 8.3 Definitions of forms of granulomatosis with polyangiitis. Adapted from Hellmich et al. [94]

Study group	Clinical subgroup	Systemic vasculitis outside ENT and lungs	Threatened vital organ function	Other definitions	Serum creatinine (μmol/L)
EUVAS (European group)	Localized	No	No	No constitutional symptoms, ANCA typically negative	<120
	Early systemic	Yes	No	Constitutional symptoms present ANCA-positive or -negative	<120
	Generalized	Yes	Yes	ANCA-positive	<500
	Severe	Yes	Organ failure	ANCA-positive	>500
	Refractory	Yes	Yes	Refractory to standard therapy	Any
WGET Research Group/VCRC (North American group)	Limited	Allowed, but not required	No	Not severe	≤124, if hematuria, but no red blood cell casts
	Severe	Yes	Yes	Organ- or life-threatening disease implies the need for cyclophosphamide (or rituximab) for remission induction	Any

EUVAS European Vasculitis study group, *VCRC* Vasculitis Clinical Research Consortium, *WGET* Wegener-Etanercept trial

subgroups: generalized/diffuse/severe, characterized by the involvement of one or more major organ(s), including progressive renal disease and/or extensive alveolar hemorrhage, and limited/localized/early systemic, which predominantly presents as isolated ear, nose, and throat diseases and is not directly life-threatening [23, 94–96]. Localized/limited forms account for up to 29% of GPA at diagnosis, particularly in women, who are slightly younger than those with diffuse GPA (41 years vs. 50 years of age at diagnosis). ANCAs are found in more than 90% of patients with systemic/diffuse/severe GPA but only in 50–78% of those with limited forms. However, transition from a localized to a systemic form and vice versa is possible during the disease. Strictly and persistently localized GPA is exceptional (<5% of patients in both German and French cohorts after 3 years of follow-up) [97, 98].

Pediatric GPA

GPA is rare in children. Clinical manifestations are similar to those for adults, but girls are more frequently affected than are boys, and nasal deformities and subglottic stenosis are more frequent [99, 100] (Table 8.4). Kidney damage is also frequent and often with a poorer prognosis than in adults. Venous thrombosis may also occur more frequently (in up to 16% of children with GPA). In contrast, neurological manifestations seem less frequent (18% of cases) [101]. However, the overall prognosis is similar but with significant morbidity from disease damage and treatment side effects.

Diagnosis

Diagnostic Approach

Classification criteria have been defined (Table 8.1 for adults and Table 8.4 for children), and new ones by the American College of Rheumatology and the European League Against Rheumatism have been published in 2021, which reinforce the role of PR3-ANCA. Conversely, and importantly, there are no diagnostic criteria [14]. However, diagnosis of GPA is relatively simple in patients with typical clinical features (Box 8.1) such as a combination of nasal crusting and erosive rhinitis, lung nodules, renal involvement with microscopic hematuria and proteinuria, skin purpura on lower limbs, and mononeuritis multiplex. Still, in practice, the diagnosis is often delayed by weeks or months because the first manifestations are often not specific (lingering rhinitis, for example) and are isolated for a while, before more suggestive manifestations of the disease develop. The presence of PR3-ANCAs will almost definitively support the diagnosis, when it is clinically suspected, without the need for a biopsy. However, even in this setting, as well as in less obvious ones, a histological confirmation may be necessary. A renal biopsy in the setting of renal impairment may also provide prognostic information for renal recovery [61]. In addition, several mimickers that must be ruled out, including infections (endocarditis, which can be associated with positive ANCA testing or fungal infections affecting the ENT or lungs, causing granulomatous inflammation on biopsies) and cocaine-levamisole use, can also be associated with PR3-ANCAs and/or MPO-ANCAs (or anti-elastase ANCAs, which are not routinely tested) [102].

Table 8.4 EULAR/PRINTO/PreS criteria and classification definition of granulomatosis with polyangiitis (Wegener) in children, Ankara 2008. Adapted from Ozen et al. [99]

Children GPA is a systemic inflammatory disease characterized by at least three of the six following criteria:	
Criterion	**Glossary**
1. Histopathology	Granulomatous inflammation within the wall of an artery or in the perivascular or extravascular area
2. Upper airway involvement	Chronic purulent or bloody nasal discharge or recurrent epistaxis/crusts/granulomata Nasal septum perforation or saddle nose deformity Chronic or recurrent sinus inflammation
3. Laryngo-tracheo-bronchial involvement	Subglottic, tracheal, or bronchial stenoses
4. Pulmonary involvement	Chest x-ray or CT showing the presence of nodules, cavities, or fixed infiltrates
5. ANCA	ANCA positivity by immunofluorescence or by ELISA (MPO/p or PR3/c ANCA)
6. Renal involvement	Proteinuria >0.3 g/24 h or >30 mmol/mg of urine albumin/creatinine ratio on a spot morning sample Hematuria or red blood cell casts: >5 red blood cells/high power field or red blood cells casts in the urinary sediment or ≥2+ on dipstick Necrotizing pauci-immune glomerulonephritis

EULAR European League Against Rheumatism, *PRES* Paediatric Rheumatology European Society, *PRINTO* Paediatric Rheumatology International Trials Organisation

Box 8.1 Main Diagnostic Features of Granulomatosis with Polyangiitis (GPA)—There Is Presently No Official and Validated Set of Diagnostic Criteria

Nonspecific clinical and radiological features
• Constitutional symptoms: fever, arthralgias, myalgias, weight loss (in severe/generalized GPA)
• Skin purpuric lesions, sometimes necrotic (common to several medium and small vessel vasculitides)
• Mononeuritis multiplex (also common in several medium and small vessel vasculitides)
More suggestive clinical and radiological features
• Signs of glomerulonephritis: microscopic hematuria (>5 red blood cells per high power field) with proteinuria and red cell casts in urine sediments (also in other small vessel vasculitides), and then renal function impairment
• Ear, nose, and throat manifestations: nasal or oral ulcerations, recurrent serous otitis media, painful eroding sinusitis, purulent or bloody nasal discharge with nasal crusting, septum perforation and/or saddle nose deformity, subglottic stenosis
• Lung manifestations: alveolar hemorrhage (also in some other small vessel vasculitides), parenchymal nodules or cavities, bronchial stenosis
• Other "granulomatous-type" lesions: pachymeningitis, orbital (pseudo-)tumor, dorsal prevertebral lesions
• Eye lesions: scleritis, dacryocystitis or dacryoadenitis, retinal involvement
Laboratory investigations to support the diagnosis
• Detection of serum ANCAs (mainly, but not always and not exclusively, PR3-ANCAs; 50–75% of the patients with limited GPA, 80–90% of those with severe/generalized GPA)
• Evidence of granulomatous inflammation within the wall of a small artery or arteriole on biopsy of an affected organ/tissue with/without fibrinoid necrosis (the diagnostic yield varies depending on which organ is biopsied—highest for open-lung biopsies, lowest for nasal mucosa biopsies)

Laboratory Investigations

Biology

Nonspecific inflammatory syndrome is common at diagnosis and during disease flares, with an increased neutrophil count, normochromic normocytic anemia (50–73% of patients, usually worse in patients with alveolar hemorrhage), and thrombocytosis (30–65%) [5]. Erythrocyte sedimentation rate in the first hour and C-reactive protein level are increased in almost every patient with active disease [103].

Transient and moderate eosinophilia can occur, in less than 12% of patients and rarely above 2000/mm^3, sometimes with a concomitant increase in the serum IgE level. High levels of IgE and/or atypical findings, including asthma, should suggest eosinophilic granulomatosis with polyangiitis. IgG4 levels are sometimes elevated, raising the question of possible overlapping presentations [59, 60]. Moderate lymphopenia, 700–750/mm^3, is common at diagnosis (and during active disease) but can also result from and/or be induced by glucocorticoid therapy [104].

Routine laboratory tests should systematically be a part of the initial workup and monitoring during the disease course. Analysis of fresh urine sediments is important for all patients for the detection of red blood cell casts, which are more suggestive of a glomerular disease than a tubular or interstitial condition.

Immunology

The 2017 revised international consensus statement recommends high-quality antigen-specific immunoassays such as enzyme-linked immunosorbent assay (ELISA), capture ELISA, or multiplex microbead immunoassay as the initial screening test for PR3-ANCAs and MPO-ANCAs [105]. This position is now widely adopted by most groups [106]. In the case of a negative result with a high clinical suspicion, a testing through indirect immunofluorescence (IIF) can still be considered, which demonstrates variable performance across laboratories and detection methods. Patients with PR3-ANCAs would most often be positive in IIF with a cytoplasmic (C-ANCA) fluorescence pattern.

As already stated, the frequency of ANCA detection is lower in patients with limited GPA (50–75%) than generalized GPA (80–90%). A negative ANCA thus does not rule out ANCA-associated vasculitis (AAV) in the appropriate clinical context of active disease [23]. Conversely, ANCAs can also be present in other conditions, some of which can mimic vasculitis, such as endocarditis, tuberculosis, or amebiasis. Few patients with microscopic polyangiitis (or, exceptionally, with eosinophilic granulomatosis with polyangiitis) can have PR3-ANCAs rather than MPO-ANCAs, and the diagnosis of GPA may be difficult to establish with certainty. Use of cocaine, through any route and especially if cut with levamisole, can cause vasculitis-like necrotic skin lesions and nasal septum perforation similar to that seen in GPA and can be associated with various ELISA results (MPO-ANCAs or PR3-ANCAs, both, or ANCAs directed toward different antigens such as elastase) [107]. Patients with associated inflammatory bowel disease, chronic liver diseases (chronic hepatitis C or autoimmune liver diseases), or certain infections (endocarditis, fungal infections, tuberculosis) can also show low and, usually, transient titers of ANCAs (and/or other autoantibodies).

In addition, patients with high ANCA titers can test positive, usually transiently, for other autoantibodies. The detection of rheumatoid factor has been reported in some series, in up to 70% of patients, but is not specific and is usually seen at low titers, and anti-cyclic citrullinated peptide test results are usually negative. Patients with alveolar hemorrhage and/or renal

involvement should undergo systematic testing for anti-glomerular basement membrane (GBM) antibodies. An association of the two antibodies (ANCA and anti-GBM) can occur in a few (<5%) patients with pulmonary renal syndrome, who have worse global and renal prognosis than do patients with only one of the two autoantibodies, and require a specific treatment approach (including plasma exchange therapy) [108].

Radiology, Endoscopy, and Other Nonbiological Investigations

Ideally, imaging of the chest must always be performed with a CT scan. Other radiological investigations (CT scan of sinuses, MRI or MR angiography of the head, ultrasonography, or CT scan of the abdomen and pelvis) should be performed depending on clinical findings. Abdominal angiography (conventional or CT) is not part of the usual diagnostic evaluation (as opposed to polyarteritis nodosa). If performed, physicians should not forget that microaneurysms of the renal, splenic, and/or liver arteries, although primarily characteristic of polyarteritis nodosa, can occasionally be seen in GPA or other small-sized vessel vasculitides [109].

Nasal fibroscopy can be useful in patients with ear, nose, or throat manifestations but is cautioned in patients with subglottic stenosis (because of the risk of spasm or post-traumatic inflammatory edema), to assess the extent of lesions and/or to perform biopsies, although sensitivity may be low. Bronchial endoscopy with bronchoalveolar lavage can help support a diagnosis of alveolar hemorrhage, identify and assess inflammatory bronchial stenosis or lesions, and, perhaps more importantly, exclude infections (or neoplasia). When the patient's condition allows for it, transbronchial biopsies can be performed; however, sensitivity is not as good as with open-lung biopsies [5, 53]. In the presence of digestive symptoms, upper endoscopy and/or colonoscopy may be needed. These can reveal ulcers, especially in the ileocolon or anorectal junction, sometimes with a similar appearance as in Crohn's disease, and also in the stomach or esophagus. A gastrointestinal biopsy incurs some risks (i.e., perforation) in these patients, and the sensitivity is low.

Patients with peripheral neurological symptoms, especially those as subtle and nonspecific as tingling in the fingers or feet, should undergo electromyography with a nerve conduction study to confirm or exclude peripheral neuropathy. Subclinical nerve involvement can been seen and may dictate a more aggressive treatment [66]. Electromyography results may also guide nerve or muscle and nerve biopsy, when considered. Many patients have transmission (up to 33% of patients) and/or neurosensory perception (47%) hypoacousia, which can ideally be quantified on audiography.

Pathology

GPA affects small-sized vessels, capillaries, and, sometimes, venules, less commonly medium-sized vessels, and rarely large-sized ones (the aorta). Therefore, biopsies of the affected organs can help support the diagnosis and reveal (1) vessel wall infiltration, mainly by neutrophils and lymphocytes (sometimes also with some eosinophils), (2) fibrinoid necrosis, and/or (3) poorly formed granulomas, sometimes with palisading organization and/or giant cells. The coexistence of these three histological aspects may be considered to be highly suggestive of the diagnosis, but they are not always present in the same sample. The decision to seek a histological diagnosis must be balanced with the risk of the biopsy itself, especially when the clinical features suggestive of GPA and PR3-ANCAs are positive.

Biopsies of skin lesions are easy to perform and can reveal nonspecific leukocytoclastic vasculitis. Some other aspects are a little bit more (but not totally) specific, such as the presence of extravascular poorly formed granulomas, vasculitis with granulomas, or sterile abscesses with granulomas. Nasal and sinus mucosa biopsies are also relatively simple to perform but should be deep enough, and multiple samples should be obtained because of low sensitivity (less than half of the sinus biopsies and only 20% of the nasal biopsies contribute to the diagnosis [52]).

Tracheal biopsies, in patients with subglottic stenosis, can be associated with an increased risk, are often superficial, and are therefore not highly sensitive or helpful in clinical practice (<18% show some histological features). Biopsies of lung nodules usually require surgical procedures, but they can show vasculitis in >60% of cases. In alveolar hemorrhage, the usual aspect on histology is capillaritis. In the study by Duna et al., transbronchial biopsies revealed vasculitis in 7% of cases and evidence of both vasculitis and granulomas in 5% [110]. However, open-lung biopsies showed vasculitis and necrosis in 89% of cases, granulomas and necrosis in 90%, and all three features in 91% (Fig. 8.12). ENT and lung biopsies may also be extremely helpful to rule out infections, especially fungal infections (using different and specific staining methods).

A renal biopsy (in patients with renal involvement) typically shows pauci-immune glomerulonephritis (little or no immunoglobulin and complement deposition), also called necrotizing crescentic or rapidly progressive glomerulonephritis. Granulomas can be observed in up to 20% of patients. The extent of lesions is associated with renal recovery after treatment [61]. Focal glomerular lesions (>50% of normal glomeruli) and crescentic categories (crescent in >50% of the glomeruli) have a better prognosis than do sclerotic (>50% of glomeruli) or mixed categories.

Nerve, muscle, and/or neuromuscular biopsies (mainly of the branches of the peroneal nerves) can show vasculitic

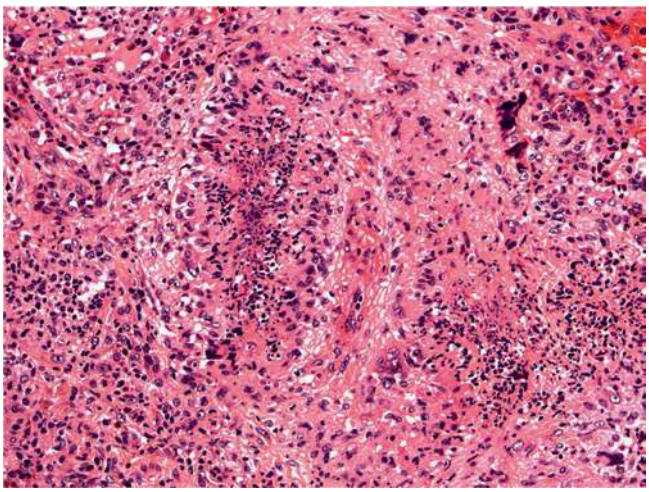

Fig. 8.12 A lung biopsy in a patient with granulomatosis with polyangiitis. Histiocytes line a microabscess with central basophilic necrosis involving the small artery (center); scattered giant cells (upper and lower right) are also present (Hematoxylin and eosin; 100×). (Courtesy of Dr. Carol Farver, Cleveland Clinic, OH)

features in up to 60% of patients with clinical symptoms of peripheral neuropathy but are rarely necessary for a diagnosis and should be avoided because they carry a risk of permanent neurological (sensory) damage around the site of biopsy. A temporal artery biopsy in case of headache can be considered; temporal artery involvement has been described [111].

Differential Diagnosis

The main differential diagnoses of GPA are listed in Table 8.5. Besides other systemic vasculitides, secondary vasculitis to other systemic diseases, granulomatous diseases (sarcoidosis, Liebow's lymphomatoid granulomatosis, beryllium disease, Crohn's disease), IgG4-related diseases, infections (especially tuberculosis and fungal infections), or malignancies (mainly primary or metastatic lung cancers) can mimic GPA.

Pulmonary renal syndrome is not the hallmark of GPA or microscopic polyangiitis and can also occur in systemic lupus erythematosus and anti-GBM disease. However, one should keep in mind the possible association of the latter with GPA (patients with high titers of both ANCAs and anti-GBM antibodies). Saddle nose deformity, although highly suggestive, is not specific of GPA. It can occur in relapsing polychondritis, sarcoidosis, T-cell/NK lymphomas (centrofacial angiocentric lymphomas), congenital syphilis or other acquired and eroding infections like mucormycosis or leprosy, or after nasal traumas. Cocaine-levamisole-induced vasculopathy is another important differential for patients with multiple and necrotic skin and ENT eroding lesions, with massive nasal septum perforation and/or frequent soft palatus perforation, which is not common in GPA. Other drugs, including propylthiouracil or minocycline, can induce vasculitis or several vasculitic features, most of the time associated with atypical or MPO-ANCAs rather than PR3-ANCAs.

Table 8.5 Main differential diagnoses of granulomatosis with polyangiitis (Wegener's granulomatosis)

Other vasculitides	
Primary	Microscopic polyangiitis Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) Polyarteritis nodosa IgA vasculitis (Henoch-Schonlein purpura) Cryoglobulinemic vasculitis Other primary vasculitis
Secondary	Relapsing polychondritis Drug-induced vasculitis (propylthiouracil, hydralazine, allopurinol, etc.) Inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, primary Sjogren's syndrome, etc.
Granulomatous diseases	Lymphomatoid granulomatosis (Liebow; Epstein-Barr virus-associated) Nasal NK/NK-T cell lymphoma Sarcoidosis Berylliosis Inflammatory bowel disease
Infections	Tuberculosis Atypical mycobacterial infections Actinomycosis, Nocardiosis *Burkholderia cepacia* or *B. pseudomallei* infection Syphilis (aortitis) Aspergillosis, Histoplasmosis, Blastomycosis, Coccidioidomycosis, Cryptococcosis, Mucormycosis, and other fungal infections
Pulmonary-renal syndrome	Anti-GBM antibody disease (Goodpasture syndrome)[a] Post-streptococcal glomerulonephritis Systemic lupus erythematosus
Cancers and hemopathies	Lymphomas, histiocytosis, Castleman disease ENT cancers Lung cancer/metastases
Miscellaneous	Cocaine-induced vasculopathy (nasal septum perforation, necrotic skin lesions; mainly with levamisole-altered cocaine) TAP1 deficiency (HLA type 1 deficiency/bare lymphocyte syndrome)

ENT ear, nose, and throat, *GBM* glomerular basement membrane, *HLA* human leukocyte antigen, *TAP1* antigen peptide transporter 1

[a] Now classified as a primary vasculitis in the revised 2012 Chapel Hill nomenclature (cf. Table 8.1)

Disease Activity, Prognosis, and Damage Scores

Various scores have been designed to monitor disease activity and assess damage, primarily for therapeutic trials and cohort studies. These scores are easily accessible online (e.g., http://www.canvasc.ca/tools.htm). The need to use the scores and their usefulness in routine practice is debatable. However, the items contributing to the scores can help physicians assess patients in a more systematic manner and not forget some important symptoms and signs. The Birmingham Vasculitis Activity Score (BVAS) and the Vasculitis Activity Index (VAI) include clinical and biological factors to assess the degree of activity of systemic vasculitis, not specifically GPA [112]. The BVAS/GPA (WG) was developed specifically for GPA [113]. The Damage Extent Index (DEI) is a rarely used activity score, and the result is also related to prognosis [114].

The Five-Factor Score (FFS) is a prognostic score that was initially designed and validated only for polyarteritis nodosa, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis [115]. After a subsequent analysis of the French Vasculitis Study Group database, the FFS was revised and can also be used for GPA [116]. Five factors, assessed at the initial diagnosis of GPA, are associated with a poor prognosis (lower survival): a serum creatinine level ≥150 μmol/L, specific GPA-related cardiomyopathy, age >65 years, severe and specific GPA-related gastrointestinal involvement, and the absence of ear, nose, or throat manifestations. The 5-year mortality for an FFS = 0 is <10% and is 60% for an FFS ≥ 2 [116]. This revised FFS is not an activity score to be repeatedly calculated during the course of the disease, must not be used to determine treatment choices (as opposed to the original FFS, which can be used to guide treatment for patients with polyarteritis nodosa, microscopic polyangiitis, or eosinophilic granulomatosis with polyangiitis), and has not been validated for GPA relapse.

Although the BVAS, BVAS/GPA (WG), and DEI can quantify some of the persistent clinical signs and damage, while the disease is no longer active, assessment of disease- and/or treatment-related damage can be more accurate with the Vasculitis Damage Index (VDI) or the Combined Damage Assessment Index (CDAI), which was developed later than the VDI and is more comprehensive but also takes longer to complete [117].

The European League Against Rheumatism (EULAR) recommends use of the BVAS, VDI, and DEI for all vasculitis as well as the Medical Outcomes Survey Short Form 36 (SF-36) to assess quality of life [118]. The Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) 10 recommends the BVAS (original and/or version 3/2003 and/or BVAS/GPA (WG)) for assessing disease activity, the VDI for evaluating damage (Combined Damage Assessment Index remaining under validation), and the SF-36 [119].

Treatment

Without treatment, GPA was almost always fatal within 6–12 months in historical reports and series [73]. Since the introduction of glucocorticoids in the early 1960s for vasculitis, and the use of glucocorticoids combined with cyclophosphamide since the early 1970s, survival has greatly improved. In the 1992 study by Hoffman et al., more than 87% of patients achieved remission and were alive at 8 years [5]. Patient outcomes have continued to improve, with most of the advances made in optimizing treatment strategies, mainly to limit treatment-related toxicity. A major advance in the early 2000s was the demonstration that rituximab was equally effective as cyclophosphamide in remission, which increased the therapeutic armamentarium, and, then, it was also proven superior to conventional azathioprine for remission maintenance. New agents have been studied and more are still being investigated, which may further alter how patients with GPA can be optimally treated.

Treatment has two phases: induction therapy, currently with a combination of glucocorticoids and a second immunosuppressive agent and, then, once remission is achieved, maintenance therapy (to maintain remission).

Induction Treatment for Systemic/Severe/Generalized Forms

Glucocorticoids

Glucocorticoids can rapidly improve the symptoms and signs of active GPA, but if prescribed alone, they will not induce sustained remission [73]. The initial dose of glucocorticoids is 1 mg/kg/day prednisone equivalent, sometimes preceded by 1–3 intravenous (IV) boluses of methylprednisolone (7.5–15 mg/kg/day) [120]. After the first couple of weeks of treatment, the dose of glucocorticoids is usually reduced by about 10% every 1–2 weeks to achieve a half dose (0.5 mg/kg/day) at about the second or third month of treatment. The optimal tapering regimen and duration of treatment with glucocorticoids are still unclear and controversial. The recent results of the PEXIVAS trial have suggested that a rapid tapering schedule, as of Week 1, was as effective as a slower, more conventional one and associated with a reduction in infections [121]. In the United States, some centers consider glucocorticoids beyond 6–9 months of little benefit or even with an increased risk of long-term toxicity [122, 123]. Most of the other centers prescribe glucocorticoids for a longer duration but at low doses (5–10 mg/day) for 1 year or more. An analysis of several trials conducted prior to 2010 suggested that low-dose prednisone beyond 6 and 12 months may be associated with a low risk of relapse [124]. Trials are ongoing to determine whether this is true or not.

Cyclophosphamide

The combination of glucocorticoids and cyclophosphamide had been the first-line standard treatment for severe GPA until around 2010 [125]. Cyclophosphamide induces remission in >80% of patients [126]. It can be administered as intravenous "pulses" (boluses at regular intervals) or continuous (daily) oral tablets. Oral daily cyclophosphamide is prescribed at a dose of 2 mg/kg/day (not exceeding 200 mg/day). Intravenous boluses of cyclophosphamide are administered every 14 days for 1 month at 0.6 g/m^2 or 15 mg/kg (at Days 0, 14, and 28) and then at 0.7 g/m^2 or 15 mg/kg every 3 weeks [126]. The dose of each pulse should not exceed 1200 mg. Pulsed oral administration is another option but is rarely used (the total dose of each pulse—15 mg/kg/day—is usually divided and administered over 3 days; i.e., 5 mg/kg/day for 3 consecutive days every 2 weeks for the first month and then every 3 weeks). Proper hydration should be ensured during the administration of cyclophosphamide. If cyclophosphamide is administered intravenously at >600 mg, then mesna should also be prescribed to reduce the bladder toxicity with cyclophosphamide [127, 128]. The dose of oral or intravenous cyclophosphamide should be adjusted (i.e., lowered by 25–50%, with a minimal dose of 500 mg per IV pulse) in patients aged >65 years old, with renal impairment, low leukocyte count (white blood cell count <4 G/L), and low hemoglobin level [106].

Several studies have established that the two routes of cyclophosphamide administration (intravenous bolus or continuous oral) are comparable in achieving remission and time to achieve remission. However, the cumulative dose of cyclophosphamide is higher with the continuous oral route and has been associated with an increased frequency of neutropenia [129] and, in some (but not all) studies, with infections [126]. The risk of infertility and/or late complications (i.e., cancers, mainly bladder cancer, and also late lymphomas or skin cancers) is directly associated with the cumulative dose of cyclophosphamide. Therefore, in France and most European countries, the intravenous route is most often used first and the oral route represents an alternative for patients without remission as escalation therapy. However, the long-term follow-up (median 4.3 years) in one study comparing pulsed intravenous and oral continuous routes for induction (followed by azathioprine maintenance) suggested that oral continuous cyclophosphamide (i.e., eventually a higher cumulative dose of about 16 g, as compared with 8 g for patients who achieved remission with the intravenous regimen) is associated with a lower subsequent relapse rate (20% instead of 40%) [130].

Irrespective of the route of administration, the 2003 CYCAZAREM study showed that oral continuous cyclophosphamide could be stopped as soon as the patient achieves clinical remission (defined as the absence of clinical disease activity, confirmed by a BVAS score of 0), thus possibly after only 3 months in most patients [125]. Thereafter, cyclophosphamide can be switched to a less toxic immunosuppressive agent for maintenance. This format has also been used with intravenous bolus cyclophosphamide, even though not proven directly; thus, the prescription of three additional boluses to consolidate the achieved remission is no longer seen as needed [131]. Once remission is achieved, usually after 6–9 boluses, therapy can also be switched to a less toxic immunosuppressive therapy. By limiting the duration of exposure and cumulative doses of cyclophosphamide, the risk of subsequent malignancies, as reported in earlier studies, is greatly reduced [5].

Rituximab

Rituximab is a chimeric monoclonal anti-CD20 antibody and a cornerstone agent for treating lymphomas, which was first tested in the early 2000s in GPA for treating refractory disease. It has been subsequently evaluated in two randomized trials (RAVE and RITUXVAS) as an alternative to cyclophosphamide to induce remission and was officially approved in April 2011 by the US Food and Drug Administration (FDA) for treating severe forms of ANCA-positive GPA (and microscopic polyangiitis) in adults, combined with glucocorticoids [41, 43], and, subsequently, in late 2019, in children aged 2 years and older. The treatment of severe ANCA-negative GPA, which is a rarer form, should follow the same therapeutic approach, but access to the drug may be more difficult in some countries. In both the RAVE and RITUXVAS studies, rituximab was not inferior to cyclophosphamide in inducing remission at 6 months. Tolerance to rituximab was good, but the infection rate was (disappointingly) comparable in the two arms and mainly consisted of community-acquired upper and lower respiratory tract infections. At 18 months, the rates of relapse (around 30%) and adverse events were the same in both arms [132]. Neither the RAVE or the RITUXVAS trial involved maintenance therapy after the induction courses of rituximab.

The doses of rituximab used in these studies were four infusions of 375 mg/m^2 at 1-week intervals. Data from various cohorts support that a different protocol of two infusions of 1 g at a 2-week interval, as used for rheumatoid arthritis, has comparable effectiveness and is now used very often [106].

In practice, the choice of cyclophosphamide or rituximab for induction is based on several factors, including several of the disease and patient characteristics, patient's plans for pregnancy, comorbidities, and the higher cost of rituximab. Rituximab use as a first-line induction agent, combined with glucocorticoids, has increased over the past decade, after initially being mostly limited to patients with contraindication to cyclophosphamide, those with frequent relapses, and/or those who had already received large cumulative doses of cyclophosphamide (>20 or 30 g, but consensus is lacking on

the threshold dose at which the risk of cancer becomes unacceptable). Being female and of childbearing age is an important consideration (as well as males wishing to be a father), even though the risk of infertility in a 20-year-old patient after receiving a cumulative dose of 6–9 g of cyclophosphamide is probably low. Other factors influence the therapeutic choice. The response to rituximab appears to differ also depending on the form of the disease, with a poorer and/or slower response for granulomatous than vasculitic manifestations and some better results with rituximab than cyclophosphamide in PR3-ANCA-positive patients, especially in those with relapsing disease [132–134]. Of note, rare cases of progressive multifocal leukoencephalopathy have been reported in patients receiving rituximab for other conditions (lymphoma, lupus), as well as potentially serious allergic reactions, and, rarely, interstitial "immunoallergic" pneumonias.

Other Current Induction Approaches

The combined use of glucocorticoids and either cyclophosphamide or rituximab represents the current standard of care for the treatment of severe GPA. The combined use of rituximab plus cyclophosphamide could be considered in severe or refractory cases, although most experts do not favor such an option because the added efficacy of this combination is likely negligible, whereas the risk of complications, especially infectious, would increase. However, some groups are investigating this combination therapy with study designs aimed at limiting the use of glucocorticoids. Recent preliminary results have shown that this combination allowed for good disease control, with highly limited use (1–2 weeks only) of glucocorticoids or even none, with less infections as a result [135, 136].

Plasma exchange, avacopan, and a few other therapies rarely used at present or still under investigation are further discussed in section on "Other Treatments in GPA". Avacopan may lead to radical changes in the treatment of GPA, by allowing for an effective and safe steroid-free option, but, it is not yet readily accessible in every country.

Maintenance Therapy for Systemic/Severe/Generalized Forms

Maintenance therapy follows induction therapy once remission is achieved. The continuation of oral cyclophosphamide in early studies, in patients induced with cyclophosphamide, found a relapse rate as low as 13% at 5 years [126]. Continuing intravenous boluses of cyclophosphamide in gradually longer intervals were not as effective, with a relapse rate of about 60% at 5 years [126, 137]. However, the cumulative toxicity of cyclophosphamide, administered orally or intravenously, precludes its prolonged use, and, thus, use of this agent must remain limited to induction therapy (3–6 months).

Other immunosuppressive agents, including azathioprine or methotrexate, have first been found as effective as continuing oral cyclophosphamide in maintaining remission but with less toxicity. More recently, rituximab has been found to be superior to those agents, thereby gradually becoming the most frequently used and recommended agent for maintenance, whether the induction includes rituximab or cyclophosphamide [106].

After therapy induction with cyclophosphamide, maintenance therapy can be initiated as early as remission is achieved, usually after 3–6 months of cyclophosphamide [125]. After therapy induction with rituximab, maintenance therapy can be considered (and started) at around 4–6 months after the last rituximab infusion [138, 139]. Whereas maintenance appears mandatory after cyclophosphamide-based induction therapy, a few authors suggested that patients in remission after rituximab-based induction, especially (or exclusively, for some more prudent authors) those with a new diagnosis of GPA, could be simply monitored and only retreated with rituximab (induction doses) if a clinical relapse occurs, as was done for the RAVE study patients [132]. The latter approach encompasses risks, including that of a major, acute, and life-threatening flare, but might be an option for some specific, highly selected patient subsets. MAINRITSAN, a prospective study of the French Vasculitis Study Group, the results, of which were published in 2014, showed rituximab infusions (500 mg at the time of remission, then at Day 15 and at months 6, 12, and 18) to be superior to azathioprine for maintenance therapy [139]. In this study, patients had newly diagnosed or relapsing GPA (or microscopic polyangiitis) and were treated with IV cyclophosphamide and glucocorticoids for remission induction. The rate of major relapses at 28 months post-enrollment was 5% with rituximab compared to 29% with azathioprine. Based on these results, in October 2018, the FDA approved the use of rituximab for "follow-up" (i.e., maintenance) in GPA (or microscopic polyangiitis). In the subsequent similarly designed international study (RITAZAREM), patients with relapsing GPA (or microscopic polyangiitis), who achieved remission with a rituximab-based regimen this time, were randomized to receive maintenance azathioprine or 1 g rituximab infusions every 4 months for 2 years. Again, rituximab proved superior, with a lower relapse rate (major and minor combined) at 20 months after randomization (13% compared to 38% in the azathioprine group—the preliminary results were presented as Abstract in November 2019) [140].

Mainly because of the high cost of rituximab, approaches other than systematic rituximab reinfusions have been inves-

tigated. The MAINRITSAN 2 study investigated the value of an "on-demand, tailored" maintenance treatment, with repeat 500 mg infusions of rituximab only if a change in the ANCA status from negative to positive, an increase in the ANCA titer by at least twice the previous value, and/or a CD19+/CD20+ B-cell repopulation occurred (all measured serially every 3 months). Such a strategy was associated with a statistically comparable rate of (major and minor) relapses at 28 months (17.3% vs. 9.9% with the fixed schedule reinfusions of 500 mg every 6 months) [141]. This "tailored" approach requires repeat ANCA testing and CD19+ B-cell monitoring every 3 months and thus can be more cumbersome in practice than reinfusions systematically scheduled every 6 months for 2 years. A post hoc analysis of MAINRITSAN 2 also showed that the second dose of 500 mg of maintenance rituximab at Day 15 was not required, thus rendering the MAINRITSAN regimen simpler (500 mg at Month 6, then every 6 months, for at least three more doses) [142].

When rituximab is not available, contraindicated, or not the preferred agent for some reason, azathioprine can be administered for maintenance at a dose of 2 mg/kg/day orally or methotrexate at the dose of 0.3 mg/kg/week (up to 25 mg/week), orally or subcutaneously [125, 131, 143]. These two drugs are equally effective and safe, at least at a 2-year follow-up. However, methotrexate should not be used for patients with renal insufficiency or a serum creatinine level ≥2 mg/day/L (>175 μmol/L). With these two agents, the relapse rate (following a cyclophosphamide-based induction) is around 16% at 18 months, 37% at 25 months, 52% at 32 months, and 51–64% at 7 years, with a relapse-free survival rate of only 42% at 5 years [125, 131, 137, 144, 145]. Both azathioprine and methotrexate can increase the risk of opportunistic infections and cause liver toxicity and/or myelosuppression. Methotrexate-induced lung hypersensitive pneumonia is a rare adverse event. Pharmacogenetic and/or genotypic study to measure the activity of thiopurine methyltransferase may be performed before prescribing azathioprine, to identify the rare patients at an increased risk of hematological toxicity [146]. Close laboratory monitoring is anyhow mandatory after the start of these maintenance drugs.

In a single randomized controlled study, terminated prematurely because of the higher-than-expected relapse rate in the control methotrexate arm, the rate of severe relapse with leflunomide was only 5% at a 2-year follow-up [147]. Leflunomide (at the standard dose of 20 mg/day, possibly increased to 30 or 40 mg/day after 3–6 months) could thus be another option for maintenance therapy. However, side effects were frequent (especially a dose >20 mg/day) and included respiratory infections, arthralgia, high blood pressure, liver toxicity, diarrhea, and, rarely, peripheral neuropathy. The first open studies of mycophenolate mofetil for maintenance therapy reported a relapse rate of only 11% [148], but the following studies reported higher rates, up to 43–48% [149]. The results of the European IMPROVE trial, comparing azathioprine and mycophenolate mofetil as maintenance therapy, showed mycophenolate mofetil to be inferior to azathioprine: at 4 years, the relapse rate was 55% and 38%, respectively [150].

The optimal duration of all these maintenance treatments remains unknown, and several prospective studies have been conducted, with some still ongoing, to determine when and for whom it is safe to stop therapies. The results of several completed controlled trials agree that the total duration of treatment (induction + maintenance) must not be <18 months. The results of the European REMAIN trial (4 years of maintenance therapy with azathioprine and low-dose prednisone as compared with discontinuing therapy at 2 years) showed that the continuation of therapy for 4 years was associated with fewer relapses (22% versus 63% at Month 48 post-enrollment), especially for patients with persistent ANCAs at remission. The MAINRITSAN 3 trial compared rituximab maintenance (500 mg at Day 1, Day 15, and then every 6 months) for 18 months (a total of five infusions) vs. 46 months (a total of none infusions) and showed a greater major relapse-free survival rate of 100% at 56 months with the longer treatment vs. (an "only slightly lower") 87% when stopping after the 18-month infusion [151]. As mentioned previously, glucocorticoids should not be unduly prolonged, but maintaining low-dose glucocorticoids of about 5 mg/day over an additional 6–12 months may reduce the risk of relapse [124]. Two studies are ongoing to further address this latter issue (ClinicalTrials.gov Identifiers: NCT01933724 and NCT03290456).

Treatment of Localized/Limited/Early Systemic GPA

In patients with localized GPA, mainly with ear, nose, and throat manifestations, cyclophosphamide should be avoided, with other less toxic treatment strategies used as first-line therapy. Glucocorticoids alone can improve disease in half of such patients but are unlikely to achieve or sustain remission [96, 143]. Few patients have achieved treatment success with cotrimoxazole (at 2 tablets/day, double-strength) alone or most often combined with glucocorticoids [97, 98, 152]. However, the results with this cotrimoxazole-based treatment have been disappointing in the few prospective studies, some of which had to be stopped earlier than planned because of frequent disease progression and worsening [153]. In the European NORAM trial, methotrexate (0.3 mg/kg/week for 12 months) led to remission as often and as quickly as cyclophosphamide with early-systemic GPA [94]. The remission rate with glucocorticoids and methotrexate was 90% (as

compared with 94% with cyclophosphamide). However, in this study, the relapse rate and progression to a systemic form was higher in the methotrexate than in the cyclophosphamide arm (70% versus 47% at 18 months), which indicated the need for a longer methotrexate treatment duration (>12 months) if initially effective.

More recent studies with mycophenolate mofetil have also suggested that it could be used instead of cyclophosphamide in non-severe GPA disease, with mild renal involvement. However, and again, the subsequent relapse rates were high [154].

Finally, data on rituximab for limited GPA are promising but limited to small case series and are not approved for this indication (existing approvals for rituximab are only for severe ANCA-positive GPA; and limited GPA is often ANCA-negative).

Other Treatments in GPA

Intravenous Immunoglobulins

Intravenous immunoglobulins have been mainly used to treat refractory or recurrent GPA and/or GPA with ongoing and concomitant serious infection. The dose is 2 g/kg/month, over 2–5 days, with good immediate results, but is often only transient and/or not sustained (the disease often recurs after their discontinuation) [155]. However, the therapy has lower toxicity than with conventional immunosuppressants, particularly in terms of infection, and does not result in late neoplastic complications, which explains its transient use for GPA patients with ongoing infection, pregnant female patients, and/or children.

Plasma Exchange

Plasma exchange combined with induction chemotherapy has been proposed for patients with GPA and rapidly progressive necrotizing glomerulonephritis and/or alveolar hemorrhage, by analogy with anti-GBM antibody disease. However, the benefit of plasma exchange in such patients with ANCA vasculitis was mainly suggested by case series. Only one small prospective randomized study of patients with severe renal impairment, defined as a serum creatinine level >500 μmol/L, was conducted prior to 2010 and showed that plasma exchange improved the probability of good renal function at only 12 months but not later and had no impact on global survival [156]. The subsequent randomized international trial PEXIVAS included 704 patients with severe renal disease (20% required dialysis initially) and/or alveolar hemorrhage (18.5% had non-severe alveolar hemorrhage, 8.6% had severe alveolar hemorrhage) and showed no benefit of plasma exchange in terms of global survival or renal survival. Death from any cause or end-stage renal disease at the end of follow-up was 28.4% in the plasma exchange group versus 31% in the group not treated with plasma exchange ($p = 0.27$), with similar findings in main subgroup analyses. There may still be a role for plasma exchange in patients with refractory disease and/or with kidney biopsy showing acute disease and minimal scarring, as a rescue adjunctive option, but with limited expectations, and a possible increased risk of infection (related to the procedure itself, although the reasons for this remains poorly understood).

Avacopan (and Other Complement Inhibitors/Blockers): A Major Upcoming Change in the Treatment of GPA

Avacopan, an oral C5a receptor antagonist, was tested in an animal model of MPO-ANCA-induced vasculitis, and then in two open-label phase II studies, administered in addition to standard induction therapy with rituximab or cyclophosphamide with or without glucocorticoids, with promising results [46, 157, 158]. The safety profile of the drugs was extremely good. A larger randomized controlled study has thus been conducted and recently completed (ADVOCATE), which have confirmed these earlier results [159]. This double-blind, randomized study included 330 patients with newly diagnosed or relapsing ANCA-positive GPA or microscopic polyangiitis. Sustained BVAS remission at Weeks 26 and 52 was achieved in 65.7% of the patients who received oral avacopan (30 mg, twice daily for 52 weeks) versus 54.9% in those treated instead with a conventional 5-month prednisone course (in addition, in both arms, to rituximab- or cyclophosphamide-based induction, followed by azathioprine for the latter; $p = 0.007$). Of note, the renal parameters, including proteinuria, improved to a greater and faster level in avacopan recipients. Serious adverse events (excluding worsening vasculitis) occurred in 37.3% of the patients receiving avacopan versus 39% of those receiving prednisone. Patients with GPA could thus be treated with rituximab or cyclophosphamide and avacopan, instead of the conventional glucocorticoid treatment. Initial glucocorticoid pulses or a short initial course of glucocorticoids may still be considered (and were given to most of the ADVOCATE participants in fact) and might be useful [106].

Avacopan was approved by the FDA in late 2021 for the treatment of adult patients with severe GPA and microscopic polyangiitis. Once more largely accessible, this new drug may radically change the treatment of GPA (and microscopic polyangiitis), as it would lead to a (totally or at least partially) steroid-free approach. However, many subsequent questions have now been raised and will have to be studied, such as the optimal duration of avacopan use, its long-term safety, and cost-efficiency [160]. Other complement inhibitors or blockers are also under investigation (ClinicalTrials.gov Identifier: NCT03712345 and NCT03895801).

CTLA4-Ig (Abatacept)

An open-label study reported promising results with abatacept for relapsing or refractory limited GPA [161], which will need to be further confirmed by the ongoing, prospective controlled study ABROGATE (ClinicalTrials.gov Identifier: NCT02108860).

Cotrimoxazole

Besides basic science evidence suggesting an association between GPA and *Staphylococcus aureus* carriage (in the nostrils; cf. Pathogenesis), some early studies in the 1980s reported that the prescription of antibiotics, especially cotrimoxazole (trimethoprim–sulfamethoxazole), combined with other treatments, could provide better disease control and reduce the relapse rate [29, 152]. When administered at a high dose (320 mg trimethoprim/day, sulfamethoxazole 1600 mg/day), combined with or following the usual maintenance treatments of GPA, cotrimoxazole further reduced the relapse rate by 40% at 1 year in one small controlled study, regardless of the presence of *S. aureus* on nasal swabs [29]. However, recent meta-analyses of all the studies on cotrimoxazole in GPA, including that only one, former randomized controlled study, have seriously questioned that finding [162]. Cotrimoxazole (trimethoprim–sulfamethoxazole) cannot substitute for immunosuppressive maintenance, as it is clearly not as effective [153]. In addition, such a high dose can be hazardous for patients with end-stage renal disease and is not compatible with the use of methotrexate because of increased bone marrow toxicity.

However, and importantly, low-dose cotrimoxazole (160 mg trimethoprim with sulfamethoxazole 80 mg every day or, alternatively, 320 mg trimethoprim and sulfamethoxazole 1600 mg three times per week; dose to be adjusted in case of renal impairment) must be prescribed for prophylaxis against *Pneumocystis jiroveci* pneumonia in patients with GPA [120]. The risk of *P. jiroveci* pneumonia is relatively small but real in patients with GPA receiving cyclophosphamide or rituximab combined with high-dose glucocorticoids. Such a low dose likely has no benefit in terms of preventing relapse or controlling disease manifestations, but it was also shown to reduce the risk of infectious complications of other immunosuppressive treatments [162, 163], more common bacterial infections, especially upper respiratory tract infections. In case of allergy or intolerance to cotrimoxazole, prevention of *Pneumocystis jiroveci* pneumonia can be based on aerosolized pentamidine (300 mg every 4 weeks), oral dapsone (100 mg/day, which can cause hemolysis even without glucose-6-phosphate dehydrogenase deficiency or more rarely methemoglobinemia), or atovaquone (1500 mg/day).

Other Agents

Smaller series or open-label studies have also been reported, most often with some encouraging results, but in highly specific patient subsets, either with refractory GPA and/or at different points of their disease course, such as gusperimus (15-deoxyspergualin) or alemtuzumab (antiCD52), with interesting results, but their use has remained extremely limited, mainly because of their associated risks of adverse events [164, 165]. Other small series have also reported interesting results with ofatumumab, a fully humanized monoclonal antibody directed against CD20 on B cells, obinutuzumab, another anti-CD20 monoclonal, belimumab, a human monoclonal antibody that inhibits B-cell-activating factor (BAFF), tocilizumab, a humanized monoclonal antibody against the IL-6 receptor, or streptococcal enzymes IgG-degrading enzyme of *Streptococcus pyogenes* (IdeS) and endoglycosidase S (EndoS), which can to degrade and disarm IgG ANCAs.

Anti-TNF-α blockers such as infliximab and etanercept have been used in refractory ANCA vasculitis but are now seldom used, despite some beneficial results with infliximab (at 5 mg/kg on Days 0, 15, and 45 and then every 1–2 months) [166]. The results of the Wegener's Granulomatosis Etanercept Trial (WGET) combined with conventional treatments were disappointing: etanercept added no benefit in preventing relapses as compared to placebo, and, more importantly, solid cancers, including unusual ones, developed in a concerning number of patients who had received etanercept (combined with glucocorticoids and cyclophosphamide), including several years after the end of the study [167]. Thus, the use of anti-TNF-α is not recommended for GPA.

Other potential therapeutic targets are constantly being identified or studied, such as IL-17, IL-23, NETs, the Janus kinase/signal transducers and activators of transcription (JAK-STAT) signaling pathway, or dipeptidyl peptidase I (cathepsin C), but are all at extremely early stages of consideration. Intensive chemotherapy followed by autologous bone marrow or stem cell transplantation remain the anecdotal therapy for GPA and are under investigation in few selected centers.

Specific Treatments for Certain Manifestations of GPA

GPA patients often need multiple other treatments, including local treatment of sinus inflammation with nasal rinses, myringotomy, dialysis for severe renal disease, local treatment of episcleritis, surgery for intestinal perforation, or pacing for severe conduction disorders. Kidney transplant for patients with end-stage renal disease or surgical reconstruction of nasal deformities can be considered in patients with sustained disease remission.

Treatment for subglottic and tracheobronchial stenoses is highly challenging and complex, especially because this complication often relapses and/or can worsen despite con-

trol of other GPA manifestations. The response to systemic therapy, including glucocorticoids, can be as low as 22–44% [49, 50]. Response to cyclophosphamide or rituximab seems limited (but these should still be considered and may help a subsequent proportion of patients). Thus, local treatment based on (repeated) dilation with bougies or balloons is often required, followed, at least for subglottic stenosis and main bronchi, by local injections of glucocorticoids. The use of lasers seems to lead to more adherent fibrous scars. Some groups also end the dilation session with local application of mitomycin. Stenting and laryngotracheal reconstruction with partial tracheal resection should only be performed in highly specialized centers and as a last resource. Surgical management of bronchial stenoses is limited to stenosis of the main bronchi, is hazardous, and is not standardized.

Adjuvant Measures and Prevention of Treatment Adverse Effects

Maintenance of a good nutritional status during all treatment phases is essential, with nutritional supplementation, enteral or parenteral, if necessary. Physical therapy can help patients, especially those with PNS or CNS involvement [168]. Potential adverse effects of prolonged steroid therapy are numerous and require at least the prescription of calcium (500–1000 mg/day, depending on diet intake), vitamin D (2000 IU/day), and, often, bisphosphonates, according to updated recommendations by rheumatology societies. *Pneumocystis jiroveci* pneumoniae, annual vaccinations for influenza (flu), COVID vaccination (and/or other agents to decrease to risk of severe COVID infection), and vaccinations every 3–5 years for *Pneumococcus* spp. and *Haemophilus influenzae* should be considered in every patient, along with ensuring that all mandatory vaccines are up to date. There is no evidence suggesting that vaccinations could trigger a GPA onset or flare. Conversely, in patients receiving high-dose prednisone and potent immunosuppressants, the efficacy of most vaccines remains unpredictable [169, 170], and, as usual, patients on immunosuppressive therapies should not receive live virus vaccines.

Managing traditional cardiovascular risk factors (smoking, dyslipidemia, diabetes, hypertension) is also essential, from the beginning of GPA treatment, to limit the cardiovascular consequences of glucocorticoid therapy in addition to specific pro-atherothrombotic complications associated with GPA [91]. The risk of late neoplasia induced by treatments must be considered in treatment decisions [65] as well as that of infertility induced by some cytotoxic agents (when conceivable, sperm cryopreservation and egg preservation can be offered).

Principles of Treatment for Relapsing and Refractory GPA

New, persistent, or worsening symptoms during treatment of GPA should always raise suspicion of an infectious complication or, more rarely, a GPA mimicking condition, such as lymphoma, cancer, or cocaine-levamisole-induced vasculopathy.

Treatment of GPA relapse occurring during maintenance treatment or in patients off immunosuppressants should be based on conventional induction treatment strategies, as described previously. The RAVE study revealed that rituximab is more often effective than cyclophosphamide in patients with relapsing disease [41], which was further confirmed by the pre-enrollment phase of the RITAZAREM study (patients with relapsing GPA, all treated with rituximab for induction) [140].

In the rare case of a patient with truly refractory GPA to glucocorticoids and cyclophosphamide, a switch to the alternative agent (rituximab) should be made, or vice versa if rituximab was used for induction [171]. For patients with disease resistant to all of these treatments, administered at sufficient doses, at recommended intervals, and after having excluded all other conditions that can mimic vasculitis, other strategies must be considered on a case-by-case basis and in collaboration with reference centers for vasculitis.

Outcomes and Prognostic Factors

Survival and Causes of Deaths

With current therapies, the remission rate exceeds 80% and the overall mortality rate is <15% at 5 years. However, mortality remains higher than in the general population of similar age, with a standardized mortality ratio of 1.58 (95% CI 1.14–2.13), particularly among men (1.8 vs. 1.23 for women) [144]. The main causes of early mortality in recent studies have been infections and poor disease control. After the first year post-diagnosis, the leading causes are cardiovascular complications, infections, and late cancers [118, 172, 173].

As mentioned previously, five factors, present at the time of initial diagnosis of GPA, are associated with a poor prognosis/survival: serum creatinine ≥150 μmol/L, specific cardiomyopathy, age >65 years, severe gastrointestinal involvement, and absence of ear, nose, and throat involvement [116]. Previous studies have reported a poor prognosis with renal failure (defined by a serum creatinine level >160 μmol/L or a granular filtration rate <15 mL/min) and/or age >50–52 years, whereas ear, nose, and throat symp-

toms had a good prognostic value in terms of survival [118]. Pulmonary disease was identified as a poor prognostic factor in one study [145]. Although alveolar hemorrhage may be responsible for massive and acute respiratory distress syndrome, it has not been clearly identified to be associated with a poor prognosis with appropriate treatment. An analysis of patients from several trials of the European Vasculitis Society (EUVAS) group reported an increased, but not significant, risk of death in patients with alveolar hemorrhage (HR 1.35, 95% CI 0.70–2.64) [174].

MPO-ANCA + GPA is rare and is associated with increased mortality as compared with anti-PR3+ GPA (which, in contrast, may be associated with a better survival but an increased risk of relapse) [118]. A high rate of PR3-ANCAs at diagnosis has been associated with a lower survival rate as well as anemia because of inflammation, alveolar hemorrhage, and/or renal failure [118].

Relapse

The high risk of relapse, sometimes on multiple occasions in the same patient, has been a hallmark of GPA. The rate of relapse-free survival did not exceed 42–57% at 5 years with conventional treatments (i.e., induction with cyclophosphamide and maintenance with azathioprine or methotrexate), but it has dramatically improved in the past decade, especially since the wider use of rituximab for maintenance [137, 144].

Relapse may occur more frequently in PR3 than in MPO-ANCAs or ANCA-negative GPA [175–177]. The predictive value of monitoring ANCA titers during treatment is controversial. The persistence of ANCA titers during treatment, especially when switching to conventional, non-rituximab-based maintenance therapy, was found to be associated with a high relapse rate, 86%, as compared with 20% with ANCA results that became negative in one study and a relative subsequent risk of relapse 2.6 times higher in another study [178]. However, these results emphasize that relapses are not systematic, even with persistent ANCA positivity [179]. Conversely, relapses can occur in patients negative for ANCAs [180]. An increase in the titer or a recurrence of ANCA positivity has been observed in about 40% of patients with relapse within the following weeks or months (6 months) [181]. The magnitude of the increase in ANCA titers was believed to improve the predictive value of this factor, with a relative risk of relapse of 14.5 with ANCA titers increased by more than four times the previous value [179]. However, 29% of patients with increased PR3-ANCA titers did not experience relapse [182]. A meta-analysis concluded that an increase in titers or persistence of ANCA positivity during remission only modestly predicted future disease relapse, and, thus, serial ANCA measurements during disease remission had limited or no value in guiding non-rituximab-based treatment decisions [183]. The value of PR3-ANCA monitoring might be greater in patients with renal vasculitis and/or in those receiving rituximab maintenance (see section on "Maintenance Therapy for Systemic/Severe/Generalized Forms") [184]. However, not all patients with PR3-ANCA-positive GPA become ANCA-negative while on rituximab therapy. In the MAINRITSAN 2 study, 37% of patients were persistently ANCA-positive after 28 months of maintenance with systematic reinfusions of rituximab every 6 months [141]. In the MAINRITSAN 3 study, 50% of patients who had a relapse had become ANCA-positive again and only one patient with persistent ANCA negativity had a relapse [151]. However, 15% of those who did not relapse also had become ANCA-positive again. The addition of CD19+ B-cell count monitoring may not only add to the predictive value of serial ANCA monitoring but also to its cost. After (or during) rituximab therapy, relapses are rare in patients with both negative ANCA and CD19+ B-cell counts, with only one such case in the RAVE trial and none in the MAINRITSAN 3 study [132]. However, in the MAINRITSAN 2 study, 18% of the patients who relapsed were both ANCA-negative and B-cell-depleted at the time of their relapses.

Several other clinical factors have been identified as potentially predicting relapse in different patient cohorts. The most reproducible factors are the presence of a cardiac disease at diagnosis, a "less intense" initial treatment (defined by a cumulative dose of cyclophosphamide <10 g after the first 6 months of treatment and/or a decrease in the dose of glucocorticoids <20 mg/day before the third month), a previous relapse, and pulmonary and/or ear, nose, and throat [175, 176, 181] diseases. Conversely, the presence of more severe renal disease (and/or serum creatinine level >100 μmol/L at diagnosis) is associated with a lower risk of relapse. These results suggest a greater association of relapse in predominantly granulomatous GPA forms (i.e., with ear, nose, and throat involvement, pulmonary nodules, orbital tumors) than predominantly "vasculitic" manifestations (i.e., with glomerulonephritis and/or pulmonary capillaritis), which, by contrast, carry a high mortality rate. A longer duration of low-dose glucocorticoids (about 5 mg/day after 1 year post-diagnosis) may be associated with a low risk of relapse, but, this observation, as mentioned previously (cf. Treatment), remains controversial [122, 124].

Studies are under way to identify new and more useful biological factors to help differentiate between infections and disease flares, assess disease activity, and predict relapse, as are studies of cytokine profiles and genomic investigations [185].

Damage and Disease Burden on Quality of Life

Only 11–14% of patients surviving GPA remain without any damage [186]. Among the most frequent complaints and damage after 10 years of follow-up are dyspnea (46% of survivors), hearing loss (30–45%), hypertension (31%), and nasal deformities (23%) [48]. The socio-professional impact of GPA is substantial: only 44% of patients are able to continue or return to work after diagnosis and treatment. Finally, late complications, such as late cancers or early atherosclerosis, responsible for late cardiovascular events, have become frequent and may continue to increase with improved patient survival [91, 187]. Thus, regular cardiovascular monitoring seems essential.

Conclusions

GPA is a severe and potentially life-threatening disease, which often becomes and follows the path of a chronic disease with a risk of relapse in survivors. With proper and prolonged treatment, patient survival exceeds 80% at 5 years. Based on advances in our understanding of the pathogenesis of the disease, and many epidemiological and clinical studies, more effective drugs have been developed over the past decade, and newer ones are upcoming. Rituximab has almost become the standard for both induction, in combination with glucocorticoids, and maintenance therapies, although older immunosuppressive drugs such as cyclophosphamide are still used and, often, useful. New drugs, such as avacopan, will certainly be incorporated into the treatment of patients with GPA, which will allow for a more limited use of glucocorticoids, thus having less complications. Other strategies should increasingly target each manifestation of the disease and, ultimately, each patient, individually. Better treatments to prevent ear, nose, and throat erosive lesions and nasal deformities for subglottic and bronchial stenoses are still needed. More therapeutic trials need to be conducted, on an international level, to further improve the generalizability of results and patient outcomes.

Clinical Vignette

A 30-year-old female was hospitalized for recent-onset fatigue and dyspnea. She also had recurrent episodes of sinus and ear pain for the prior 6 months and intermittent nose bleeds. On examination, she had nasal mucosa ulcerations and bilateral chest rales. Initial laboratory tests revealed a hemoglobin level of 6.5 g/dL, a serum creatinine level of 2.0 mg/dL (176 μmol/L), and an erythrocyte sedimentation rate of 78 mm/h. Her urine sediment analysis revealed microscopic hematuria and several red blood cell casts. A chest computed tomography showed bilateral lung infiltrates and nodules, up to 25 mm in diameter. Further tests revealed positive anti-neutrophil cytoplasm antibodies (ANCAs) against proteinase 3 (PR3) in ELISA. A diagnosis of granulomatosis with polyangiitis (GPA) was made, and a treatment with rituximab (1 g on Day 1 and Day 15) and glucocorticoids was initiated. The patient had excellent response to therapy, and, 6 months later, glucocorticoids were stopped. The patient remained asymptomatic, with repeat rituximab infusions (500 mg) every 6 months for maintenance for 2 years.

Four years later, off medications, she presents for a routine follow-up visit. She has had polyarthralgia, moderate leg edema, bloody-tinged rhinorrhea, dry cough, and bilateral ear fullness for the past couple of weeks. Her serum hemoglobin is 12 g/dL, serum creatinine is 3.5 mg/dL (309 μmol/L), and C-reactive protein is >200 mg/L. A diagnosis of GPA relapse is suspected.

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Alveolar Hemorrhage

9

Yosafe Wakwaya and Stephen K. Frankel

Introduction

Diffuse alveolar hemorrhage (DAH) is a clinical syndrome defined by generalized intra-alveolar bleeding originating from the pulmonary microcirculation. Patients commonly present with dyspnea, hemoptysis, anemia, diffuse radiographic pulmonary infiltrates, and hypoxemia. The severity can range from mild dyspnea to severe hypoxemic respiratory failure requiring mechanical ventilation. Diagnosis is frequently made at the time of bronchoscopy, when serial aliquots of bronchoalveolar lavage (BAL) fluid reveal a progressively hemorrhagic return. However, the presence of DAH carries a broad differential diagnosis (Table 9.1) and is associated with a number of histopathologic patterns. This chapter will review the approach to the diagnosis and the management of DAH.

Case Vignettes

Case 1

A 19-year-old man presented to the emergency room complaining of 1 week of progressive dyspnea on exertion and non-productive cough, initially thought to be a respiratory infection. On further history, he revealed a 1-month history of a non-pruritic rash on his legs and ankles. He denied any fever, chills, chest pain, sputum production, inhalational injury, cocaine or other drug use, or any human immunodeficiency virus (HIV) risk factors. Review of systems was positive for fatigue, malaise, abdominal pain that was worse after meals, and diffuse arthralgias, particularly of the large joints. He also endorsed multiple episodes of hematochezia (passing bright red blood per rectum) over the past month. He denied any sinus disease, gross hematuria, focal weakness, or paresthesias. His only medications were non-steroidal anti-inflammatory agents on an as needed basis.

Physical exam revealed tachycardia, tachypnea, increased respiratory effort with accessory muscle use and significant hypoxemia with an oxygen saturation of 92% while on high-flow oxygen through a non-rebreather mask. He was anxious and speaking only in short sentences. His pulmonary exam revealed diffuse bilateral crackles. His abdominal examination revealed diffuse tenderness, and the patient was positive for fecal occult blood testing. His skin exam was notable for irregular, palpable, slightly raised, purpuric lesions with surrounding petechiae on his lower extremities.

The patient's respiratory status deteriorated over the ensuing 4–5 h, ultimately requiring intubation and mechanical ventilation. Laboratory testing was notable for an elevated white blood cell count of 17,000 cells/mm^3 and an elevated erythrocyte sedimentation rate of 87 mm. His laboratory testing also indicated acute renal failure with a creatinine of 1.8 mg/dL, and his urinalysis revealed both granular casts and microscopic hematuria, but no red blood cell casts. Chest imaging revealed patchy, heterogenous, diffuse, and bilateral infiltrates, and bronchoscopy revealed an increasingly bloody return on serial aliquots. Skin biopsy confirmed a leukocytoclastic vasculitis and IgA-positive immunofluorescence. The patient was diagnosed with Henoch-Schönlein purpura complicated by diffuse alveolar hemorrhage.

The patient was treated with intravenous corticosteroids, cyclophosphamide, and plasmapheresis. He had resolution of his respiratory failure and was liberated

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from mechanical ventilation on hospital day #5. His renal function also subsequently returned to normal, and he was discharged to home on hospital day #16.

Case 2

A 28-year-old man presented to clinic for progressive dyspnea and fatigue. The patient had a complex past medical history notable for multiple episodes of deep venous thrombosis and a known diagnosis of antiphospholipid antibody syndrome. Further work-up for systemic lupus erythematosus and other collagen vascular diseases was negative. The patient has been maintained on chronic oral anti-coagulation for the past 4–5 years.

Approximately, 1 year ago the patient had a "flare" of his disease that began with a non-productive cough, fatigue, and dyspnea, similar to his current presentation. However, with the earlier episode, he went on to develop hemoptysis and respiratory distress. Surgical lung biopsy at an outside hospital revealed alveolar hemorrhage and an underlying fibrotic non-specific interstitial pneumonitis. He was treated with intravenous corticosteroids and improved. Since that time, his oral corticosteroids have slowly been weaned, and at the time of the current presentation, he was down to 10 mg of oral prednisone every other day. Of note, the patient also reported that he had recently resumed smoking ¼–½ pack of cigarettes per day.

Physical examination was notable for a mildly elevated heart rate of 100 beats/min and a mildly elevated respiratory rate of 20 breaths/min. Auscultation revealed crackles at the right base, but breathing was otherwise easy, symmetric, and unlabored. Pulmonary function testing revealed a forced vital capacity that was 65% predicted and FEV1 that was 70% predicted, but a normal diffusing capacity of carbon monoxide (DLCO) at 90% predicted that corrected to 108% predicted when adjusted for alveolar volume. High-resolution computed tomography (HRCT) of the chest demonstrated patchy ground-glass opacities (Fig. 9.1a, b). Bronchoscopy revealed diffuse alveolar hemorrhage on BAL.

The patient was diagnosed with DAH secondary to recurrent antiphospholipid antibody syndrome and was successfully treated with increased doses of oral corticosteroids and the addition of a steroid-sparing, cytotoxic agent. Upon achieving a goal maintenance dose of cytotoxic agent, the corticosteroids were successfully tapered to 5 mg of oral prednisone daily.

Case 3

The patient was a 75-year-old gentleman who was in good health and quite active until 6–8 months prior to presentation. At that time, he was noted to develop dyspnea on exertion by family members and was encouraged to seek medical attention. Pulmonary evaluation revealed significant functional impairment, and HRCT demonstrated a basilar predominant, reticular pattern of interstitial lung disease. Autoimmune serologies including antinuclear antibodies, anti-neutrophil cytoplasmic antibodies, rheumatoid factor, anti-Scl-70, anti-SS-A, and anti-SS-B antibodies were all negative. Surgical lung biopsy revealed usual interstitial pneumonitis, and the patient was diagnosed with idiopathic pulmonary fibrosis (IPF).

Over the first few months following the diagnosis, the patient noticed a slow, steady decline in function, but over the 2–3 weeks prior to presentation, he became dramatically worse with markedly increased oxygen requirements and dyspnea that occurred with ambulating room to room. Upon presenting to clinic, he was found to be in respiratory distress with a respiratory rate of 32 breaths/min, accessory muscle use, and increased work of breathing. The patient was admitted to the Intensive Care Unit.

Further evaluation included HRCT of the chest which revealed diffuse ground-glass infiltrates superimposed on an underlying fibrosing interstitial pneumonia consistent with his known diagnosis of IPF (Fig. 9.2a, b). White blood cell count was normal, but his hematocrit was reduced at 35%. Bronchoscopy revealed DAH (Fig. 9.2c). Differential cell counts from the BAL revealed a 60% neutrophilia, but no infectious organisms were isolated. Echocardiography confirmed normal left ventricular function and filling pressures and was otherwise unremarkable. No evidence of pulmonary embolus or other precipitant of respiratory decline could be identified. Given that no specific precipitant for the patient's acute respiratory decline could be identified and that infection, heart failure, thromboembolic disease, and other potential causes of acute lung injury were all excluded, the patient was diagnosed with an acute exacerbation of IPF with DAH being an accessory, accompanying feature. Furthermore, the bronchoscopic finding of alveolar hemorrhage did not prove to represent clinically significant hemorrhage and repeat serologies, ANCA testing, and anti-basement membrane antibodies were all negative. Following a prolonged ICU course, he died of respiratory failure.

Table 9.1 Differential diagnosis of DAH based on pathology

Histology	Etiologies
Pulmonary capillaritis	Granulomatosis with polyangiitis
	Microscopic polyangiitis
	Isolated pulmonary capillaritis
	Systemic lupus erythematosus
	Primary antiphospholipid antibody syndrome
	Other collagen vascular disorders/connective tissue diseases
	Henoch-Schönlein purpura
	Behçet Syndrome
	Goodpasture syndrome
	Acute lung transplant rejection
	Hematopoietic stem cell transplantation
	Cryoglobulinemia
	Drugs and medications (e.g., propylthiouracil)
Bland pulmonary hemorrhage	Idiopathic pulmonary hemosiderosis
	Goodpasture syndrome
	Systemic lupus erythematosus
	Coagulation disorders
	Inhalational exposures (e.g., trimellitic anhydride, isocyanates)
	Drugs and medications (e.g., penicillamine, amiodarone, nitrofurantoin)
	Mitral stenosis/valvular heart disease
	Left ventricular dysfunction
	Obstructive sleep apnea
	Pulmonary veno-occlusive disease
Diffuse alveolar damage	Acute respiratory distress syndrome
	Acute idiopathic pneumonia
	Hematopoietic stem cell transplantation
	Drugs and medications (e.g., cocaine inhalation)
	Acute exacerbation of interstitial lung disease
Miscellaneous	Human immunodeficiency virus infection
	Pulmonary capillary hemangiomatosis

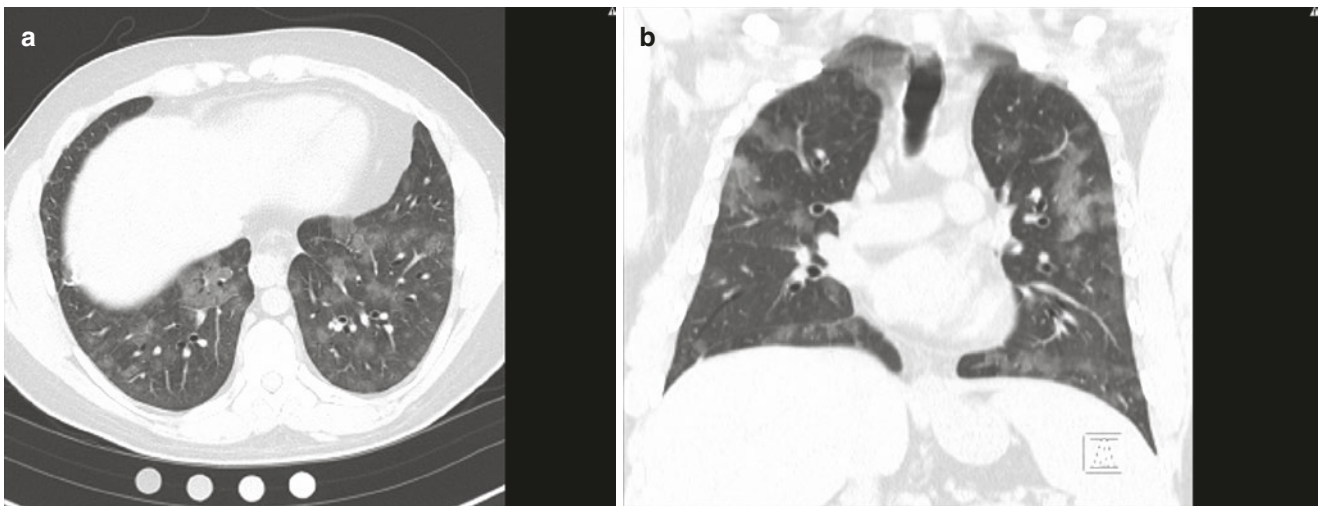

Fig. 9.1 (**a**, **b**) High-resolution computed tomography images demonstrating patchy ground glass opacities consistent with alveolar hemorrhage

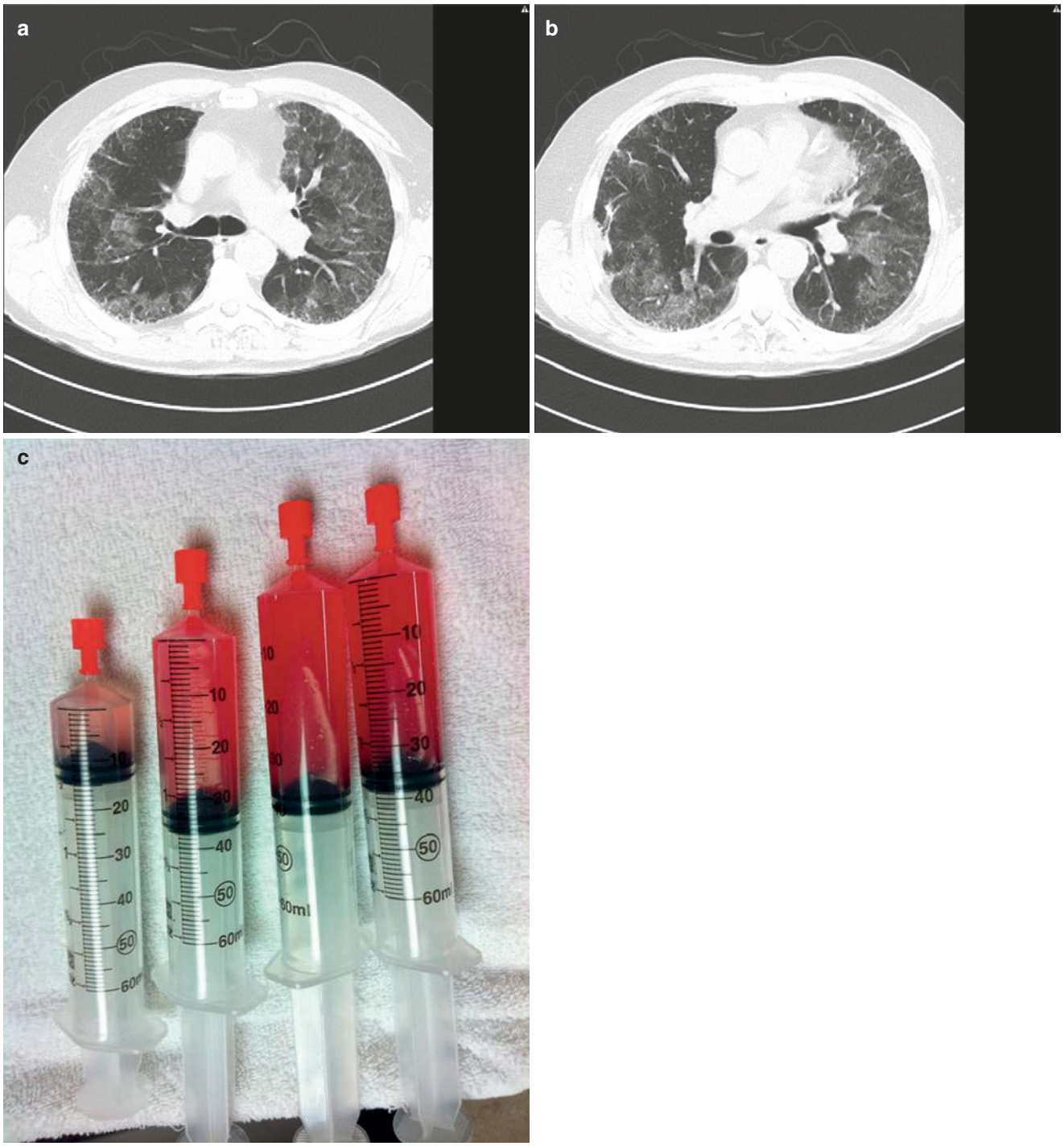

Fig. 9.2 (**a**, **b**) High-resolution computed tomography images demonstrating patchy ground glass opacities superimposed on peripheral-predominant reticular infiltrates and early honeycomb changes. (**c**) Serial aliquots of bronchoalveolar lavage fluid demonstrating an increasingly hemorrhagic return diagnostic of alveolar hemorrhage

Clinical Presentation

Patients who present with DAH can present at any age. Patients may have a known predisposing condition such as a systemic vasculitis, collagen vascular disease, or mitral stenosis, or the DAH may represent the initial manifestation of their disease state. DAH may occur as an isolated event or with repeated episodes of bleeding. Hemoptysis, the most characteristic sign of DAH, may evolve slowly over a period of weeks (i.e., antiphospholipid antibody syndrome [1]) or more dramatically over a period of days or hours (i.e., crack

cocaine inhalation [2]). However, it has also been reported that up to one-third of cases of DAH will present without evidence of hemoptysis [3]. Additional pulmonary symptoms may include dyspnea, non-productive cough, exercise intolerance, and/or vague chest discomfort or heaviness. As mentioned, patients may present earlier in a disease course with more mild symptoms of dyspnea or hemoptysis with or without new onset anemia, or they may present with fulminant disease including profound hypoxemia or respiratory failure. Constitutional symptoms are commonly also seen including fatigue, malaise, anorexia, fever, and myalgias.

In evaluating any patient with DAH, a comprehensive and detailed history is very important. Areas to consider include: (1) Does the patient have any elements to suggest a systemic autoimmune or collagen vascular disorder? The identification of extra-pulmonary signs and symptoms may be helpful in revealing a potential underlying etiology for the DAH. For example, the identification of skin lesions consistent with a cutaneous leukocytoclastic vasculitis, the presence of destructive upper airway lesions, or the finding of inflammatory ocular disease may point the clinician towards the diagnosis of a primary small-vessel vasculitis. Similarly, does the patient have a malar rash or synovitis to suggest possible systemic lupus erythematosus? (2) Does the patient have any underlying cardiac disease? Specifically, does the patient have valvular heart disease (i.e., mitral stenosis or rheumatic heart disease) or disease that might result in elevated left-sided filling pressures? (3) Does the patient take any potentially causal medications such as penicillamine or propylthiouracil? Or engage in illicit drug use, such as crack cocaine? (4) Does the patient have a coagulation disorder or take any anti-coagulants that might contribute to hemorrhage?

Physical examination findings in DAH are non-specific. Objective findings may include fever, tachypnea, tachycardia, hypoxemia, diffuse crackles/rales, bronchial breath sounds, or other findings consistent with alveolar consolidation on chest auscultation. The search for extra-pulmonary findings, however, may be extremely fruitful as regards identifying an inciting underlying systemic disease. Such findings may include palpable purpura, conjunctivitis, septal perforation, iridocyclitis, synovitis, or focal neurologic deficits/mononeuritis multiplex.

On laboratory testing, patients will be noted to have a low and/or falling hemoglobin. However, the presence of a normochromic, normocytic anemia in acutely-ill patients tends to be a non-specific finding. In the case of subclinical bleeding or recurrent bouts of DAH, iron deficiency anemia may develop as well. Generally speaking, elevations of the white blood cell counts and platelets will be noted, although thrombocytopenia may be seen in conjunction with DAH in entities such as idiopathic thrombocytopenic purpura, thrombotic thrombocytopenia purpura, hemolytic uremic syndrome, and disseminated intravascular coagulation [4, 5]. Of note, these conditions are generally associated with bland pulmonary hemorrhage rather than a capillaritis lesion. Additionally, the presence of thrombocytopenia with DAH should also raise suspicion for possible systemic lupus erythematosus (SLE) [6] or primary antiphospholipid antibody syndrome [7].

Coagulation studies are critical to excluding coagulopathy as the inciting etiology of DAH (bland hemorrhage). Elevated inflammatory markers such as erythrocyte sedimentation rate and C-reactive protein are commonly elevated but are non-specific findings. Serologic testing for specific autoimmune disorders and immune-complex-mediated diseases is a necessary part of the evaluation of DAH and extremely helpful when positive. Urinalysis should be obtained in all patients with DAH to evaluate for the presence of a "pulmonary-renal syndrome" which is defined as the presence of DAH plus glomerulonephritis. Glomerulonephritis in turn is characterized by the presence of (1) proteinuria, (2) microscopic (or gross) hematuria, ideally with dysmorphic, crenulated red blood cells, and (3) red blood cell casts. Renal insufficiency and renal failure will commonly ensue such that the presence of a pulmonary-renal syndrome calls for rapid treatment to prevent permanent renal failure.

Chest radiography is extremely informative and is characterized by diffuse alveolar infiltrates but is difficult to distinguish from other diseases characterized by an alveolar filling pattern (i.e., acute respiratory distress syndrome, congestive heart failure or pneumonia.) The alveolar opacities themselves may vary from a patchy, focal process to confluent, diffuse alveolar filling. Still, those cases that initially present with unilateral or lobar infiltrates will usually rapidly progress to diffuse alveolar filling if unrecognized or untreated. HRCT of the chest can confirm the presence of airspace disease. While DAH will typically be characterized by patchy, bilateral ground-glass opacities +/− consolidation with a central and lower lobe predominance, the higher-resolution images tend to add only a marginal amount of information over a standard chest radiograph. Finally, despite not commonly recognized, repeated bouts of DAH may lead to findings of fibrosis or even obstructive lung disease on chest radiography [8, 9].

Pulmonary function testing may be performed in patients in whom the disease onset is less acute, and in these cases, the diffusing capacity for carbon monoxide (DLCO) may be elevated, or if measured sequentially, may be noted to increase. This increase in DLCO is secondary to the presence of carbon monoxide-avid hemoglobin in the airspaces. However, in patients who present with more acute disease, pulmonary function testing is rarely feasible. Longitudinally, pulmonary function testing can be useful in cases of DAH in which the bleeding may be chronic or recur frequently, such as in idiopathic pulmonary hemosiderosis or antiphospholipid antibody syndrome, as these patients may go on to develop obstructive and/or restrictive physiology.

Diagnosis (Table 9.1, Fig. 9.3)

While the presence of DAH may be strongly suggested in a patient with marked hemoptysis, bilateral alveolar infiltrates, anemia and respiratory distress, this classic presentation appears to represent a minority of cases. Ultimately, DAH remains on the differential diagnosis of any patient with bilateral or diffuse alveolar infiltrates, hypoxemia, and dyspnea, and in point of fact, autopsy studies have shown that 2–4% of patients with clinical acute respiratory distress syndrome (ARDS) who died of their disease will be found to have unsuspected DAH [10, 11]. Thus, although pneumonia, heart failure, and ARDS are all much more common than DAH, in those cases where the diagnosis is less than certain, bronchoscopy with BAL should be considered.

When performing the procedure, the BAL should always be performed prior to any concomitant procedure such as biopsy to avoid precipitating any confounding bleeding or even bronchoscope trauma. When choosing the anatomic location for the BAL, the operator should choose the areas most involved by chest radiograph or, in diffuse disease, may choose the right middle lobe or lingula so as to optimize the return volumes. The bronchoscope should be advanced until "wedged" or impacted in a segmental or subsegmental bron-

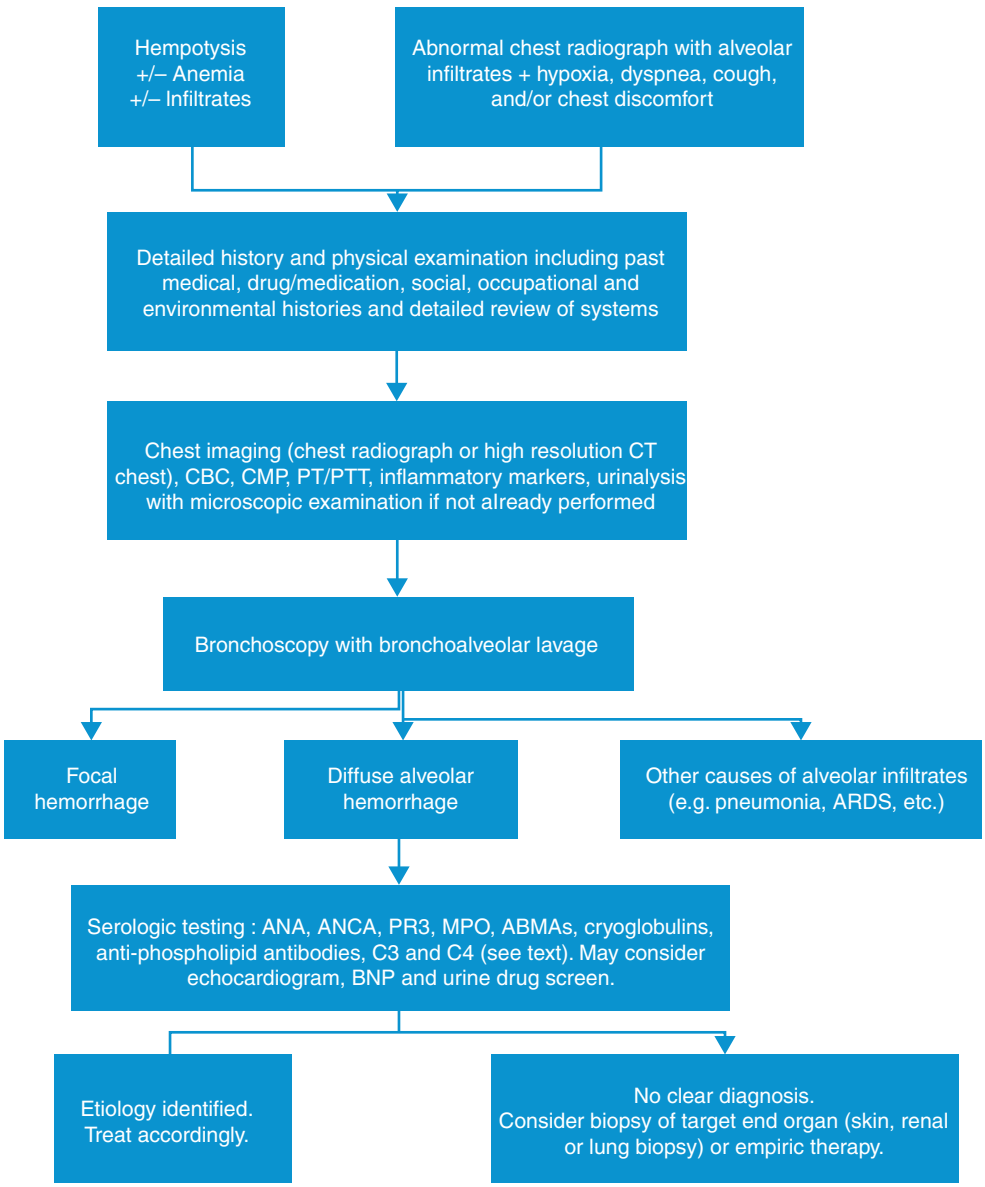

Fig. 9.3 A generalized approach to the diagnosis of diffuse alveolar hemorrhage

chus. Once a position has been secured, four to five standard saline aliquots of between 30 and 60 mL should be serially instilled and removed via the bronchoscope up to a total lavage volume of no less than 100 mL and no more than 300 mL (and ideally >30% of the total instilled volume should be obtained on return to assure the accuracy of differential cell counts) [12]. In DAH, the recovered fluid will become increasingly hemorrhagic from aliquot to aliquot, or at a minimum, will not clear with serial lavage. This bronchoscopic finding is diagnostic of DAH (Table 9.2). Nevertheless, the finding of DAH is not a final diagnosis in and of itself, as the general presence of DAH carries an extended differential diagnosis and cannot by itself define the underlying etiology for the DAH.

As mentioned above, serologic testing is central to the evaluation of DAH, and in specific cases, serologic studies can confirm a diagnosis without the need for surgical biopsy. In anti-basement membrane antibody disease or Goodpasture syndrome, diagnosis may be confirmed by the presence of serum anti-basement membrane antibodies (ABMAs) [13]. Similarly, serum anti-cardiolipin antibodies (and Russell Viper Venom Time) should be measured to assess for primary antiphospholipid antibody syndrome [1]. The presence of serum anti-neutrophil cytoplasmic antibodies (ANCA) and/or a positive anti-proteinase-3 or anti-myeloperoxidase enzyme-linked immunosorbent assay (ELISA) will assist with the diagnosis of a primary, small-vessel, ANCA-associated vasculitis (AAV) such as granulomatosis with polyangiitis, microscopic polyangiitis, pauci-immune idiopathic pulmonary capillaritis, or eosinophilic granulomatosis with polyangiitis (EGPA) [14]. In cases of DAH complicating SLE, the diagnosis of SLE is usually established [3].

Table 9.2 Diagnosis of diffuse alveolar hemorrhage

Entities
Diffuse alveolar hemorrhage is diagnosed at the time of bronchoscopy. With the bronchoscope in "wedge position" in a segmental or subsegmental bronchus, four to five standard saline aliquots of between 30 and 60 mL are serially instilled and removed for a total lavage volume of no less than 100 mL and no more than 300 mL. A diagnosis of diffuse alveolar hemorrhage is made when the recovered fluid is identified to be increasingly hemorrhagic from aliquot to aliquot, or at a minimum, does not clear with serial lavage. Alternatively, a diagnosis of DAH may also be made at time of surgical lung biopsy when a pathologic finding of diffuse alveolar hemorrhage is made (red blood cells filling the alveolar spaces.) If a diagnosis of DAH is made at the time of surgical lung biopsy, a concurrent pathologic diagnosis of capillaritis or bland hemorrhage may also be identified.

However, in cases where DAH is the presenting manifestation, serum testing for low serum complement (specifically C3 and C4), serum antinuclear antibodies, and the presence of anti-double-stranded deoxyribonucleic acid antibodies will help point to the diagnosis. Anti-SS-A (Ro) and SS-B (La) antibodies are less specific but may be associated with SLE as well as primary Sjogren syndrome and scleroderma. Cryoglobulins and hepatitis serologies are helpful in the assessment of cryoglobulinemia.

Additional testing that is less specific but may be helpful in diagnosis includes a complete blood count, liver function testing, renal function testing, inflammatory markers, urinalysis with sediment examination, and coagulation studies. In point of fact, as mentioned earlier, the identification of findings of glomerulonephritis upon urinalysis can be extremely helpful, especially if it leads to the identification of a pulmonary-renal syndrome. Echocardiography is often required to evaluate for mitral stenosis, severe diastolic dysfunction, and other causes of elevated left-sided filling pressures that potentially may cause bland hemorrhage. Additional imaging studies, beyond chest radiography, and HRCT that may yield diagnostic information depending upon the clinical scenario include CT of the sinuses (i.e., to assess for evidence of granulomatosis with polyangiitis), CT/MRI of the brain, and CT of the abdomen and pelvis.

In some cases, surgical lung biopsy may be required to establish the underlying cause if serologic testing and clinical evaluation are unrevealing. The decision to proceed to surgical lung biopsy should not be taken lightly as the procedure, whether done as a less invasive video assisted thoracoscopic procedure or a more invasive thoracotomy, requires general anesthesia and is a significant thoracic surgical procedure in a moderately or severely ill patient. On the other hand, surgical lung biopsy may be safely accomplished in the hands of an experienced surgeon in the vast majority of cases. Ultimately, the decision to proceed or not to proceed to surgical lung biopsy must take into account a careful weighing of the risks, benefits, and alternatives. It should be clear that the biopsy is necessary to obtain critical diagnostic information that cannot be obtained in other ways and that this information will affect treatment decisions.

Three broad categories of pulmonary histopathology are associated with DAH, namely (1) capillaritis, (2) bland hemorrhage, and (3) diffuse alveolar damage with hemorrhage, and the identification of the underlying histopathologic pattern can often be used to focus the differential diagnosis.

Pulmonary Capillaritis

Histology (Fig. 9.4)

Pulmonary capillaritis, also known as alveolar capillaritis, necrotizing alveolar capillaritis, and neutrophilic capillaritis, is one of the three core histologic patterns that may be associated with DAH. Pulmonary capillaritis is characterized by neutrophils infiltrating the alveolar septa along the pulmonary capillaries and hemorrhage. Capillaritis may, in some cases, also involve other small vessels such as the venules and arterioles. There is associated disruption of the alveolar-capillary basement membrane, and red blood cells, edema fluid, fragmented neutrophils, debris, and fibrin leak into the alveolar spaces [15]. The alveolar interstitium itself is broadened by the presence of edema, fibrinoid necrosis, inflammatory cells, and red blood cells. The neutrophils in the interstitium and vessel walls degranulate and undergo apoptosis, and as such, often appear pyknotic and undergo karyorrhexis leaving behind characteristic basophilic nuclear debris. Other features that may occur or be identified on this background pattern of lung injury include small-vessel thrombosis, organizing pneumonia, and type II alveolar epithelial cell hyperplasia. Lastly, it should be noted that pulmonary capillaritis is a subset of pulmonary vasculitis in which the microcirculation of the lung (alveolar capillaries, arterioles, and venules) is predominantly affected and the larger pulmonary vessels are spared [16].

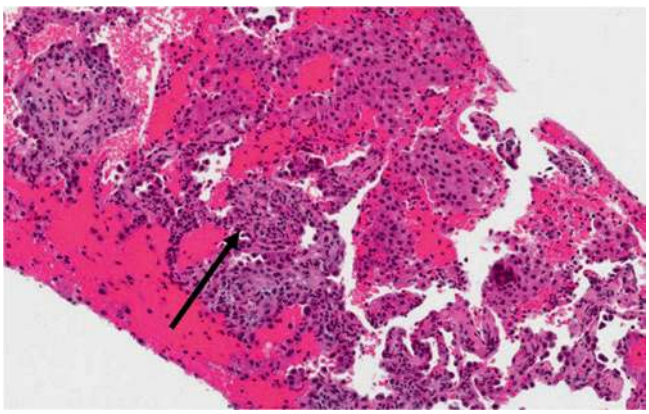

Fig. 9.4 Photomicrograph (20× magnification) of an H&E-stained section showing lung parenchyma with diffuse airspace filling by hemorrhage and scattered macrophages. The arrow points to a region of capillaritis in which the alveolar septa are expanded by necrotic neutrophils and karyorrhexitic nuclear debris. (Courtesy of Dr. Steven Groshong, Division of Pathology, Department of Medicine, National Jewish Health, Denver, Colorado, USA)

Etiologies

ANCA-Associated Small Vessel Vasculitis: Granulomatosis with Polyangiitis (GPA)

Granulomatosis with polyangiitis is the entity formerly known as Wegener granulomatosis and represents one of the more common etiologies associated with pulmonary capillaritis as well as pulmonary-renal syndrome. GPA is one of the ANCA-associated vasculitides (AAV) and is characterized by granulomatous inflammation of the upper and lower respiratory tract and a necrotizing small-vessel vasculitis. While the American College of Rheumatology and Chapel Hill Consensus Conference have developed criteria for the classification of the AAV, these criteria perform poorly when used to diagnose an individual patient. The diagnosis of GPA and the other AAV rests upon the clinician integrating clinical, laboratory, radiographic and pathologic data, and making an informed clinical judgment that the data do or do not support a diagnosis of GPA.

DAH is estimated to occur in 5–15% of patients with GPA. Indeed, the presence of DAH alone should raise the possibility of GPA and the other AAV within the differential diagnosis [17]. DAH can occur as an initial manifestation of the disease or it may occur during an exacerbation of a previously established case. DAH may occur as an isolated finding or in conjunction with other pulmonary manifestations of GPA. In a patient series published by Cordier and colleagues, pulmonary capillaritis was identified in 31% of open lung biopsies obtained in patients with GPA [18]. The presence of DAH, by definition, represents severe, life-threatening disease and correlates with a considerably increased mortality [19].

As mentioned above, GPA commonly presents with upper airway involvement (>80%) and may manifest with epistaxis, nasal discharge or crusting, septal perforation, otitis, hearing loss, or subglottic or tracheal stenosis. Similarly, the lower respiratory tract is also frequently involved (>80%), and patients may manifest with cough, dyspnea, chest discomfort, or hemoptysis. Radiographically, patients may have infiltrates, consolidation, nodules, cavities, and/or effusion(s). Extra-pulmonary manifestations will commonly include renal involvement/glomerulonephritis, constitutional symptoms, myalgias, arthralgias/arthritis, cutaneous involvement, ocular involvement, and cardiac manifestations [20].

Anti-neutrophil cytoplasmic antibodies (ANCA) are a hallmark of GPA and contribute to the pathogenesis of AAV. Three distinct ANCA-staining patterns have been identified, namely cytoplasmic, peri-nuclear, and atypical, and it is the cytoplasmic or c-ANCA that have been most closely

associated with GPA. c-ANCA in turn, have been shown to recognize the proteinase-3 (PR3) antigen in the vast majority of cases. 85–90% of patients with generalized active GPA will be c-ANCA and/or anti-PR3 positive [17]. While ANCA titers correlate with disease activity, a rise in ANCA titers needs to be considered within the context of the full clinical assessment, as a change in ANCA titers alone lacks sufficient sensitivity and specificity for predicting disease relapse [21]. Also, it should be noted that while a positive c-ANCA or PR3 is very helpful in diagnosing AAV, a negative test does not exclude GPA or AAV in an individual patient.

Treatment of DAH begins with basic supportive care elements such as a secure airway, oxygen therapy, and ventilatory support. Once the patient has been stabilized and the "A, B, Cs" of airway, breathing, and circulation have been addressed, and any potential coagulopathic state or bleeding diathesis similarly addressed, treatment directed towards the underlying precipitating disease may begin.

Treatment of GPA requires the use of immunosuppressive agents (cytotoxic medications, biologic agents, and systemic corticosteroids) that carry the risk of serious adverse side effects. As such, the intensity of the immunosuppression must carefully be titrated to disease activity, and disease activity must be careful assessed in each patient. DAH clearly represents organ and life-threatening disease and as such qualifies as "severe" disease that necessitates the use of more aggressive immunosuppressive regimens to control the disease activity.

The initial regimen of choice for both generalized active and severe life-threatening disease had been oral cyclophosphamide plus oral corticosteroids based upon the original National Institutes of Health studies demonstrating the efficacy of this regimen for the induction of disease remission [22]. Daily oral cyclophosphamide was then compared to a pulse intravenous regimen in the CYCLOPS Trial. This study showed that pulsed cyclophosphamide was as effective as oral cyclophosphamide at inducing disease remission and had fewer side effects (leukopenia) related to an overall dose reduction [23]. Long-term follow-up revealed that there was no difference in survival or renal function despite an increased rate of relapse in the pulsed cyclophosphamide cohort [24]. Although CYCLOPS-enrolled patients had generalized active disease and not severe disease, these data are often extrapolated to inform management of severe disease.

The utility of plasma exchange in the treatment of AAV-related DAH is a rapidly evolving question. In 2007, Jayne and colleagues published the MEPEX trial (Randomized Trial of Plasma Exchange or High-Dosage Methylprednisolone as Adjunctive Therapy for Severe Renal Vasculitis) in which patients with severe renal disease were treated with corticosteroids and oral cyclophosphamide and additionally randomized to plasma exchange or high-dose intravenous methylprednisolone [25]. Dialysis-independent survival was higher in the plasma exchange group than the intravenous corticosteroid group such that the addition of plasma exchange to corticosteroids and cyclophosphamide became the standard of care for the management of patients with severe renal disease. However, long-term follow-up of the MEPEX trial revealed no statistically significant benefit from plasma exchange [26]. The attenuated efficacy over time of plasma exchange seen in the MEPEX follow-up data may have been related to study design limiting the use of pulse dose steroids to the control arm or insufficient power at the time of follow-up. Thus, the long-term benefit of plasma exchange remained unclear. Plasma exchange itself is not a benign intervention and carries the risk of exacerbating pulmonary hemorrhage by the removal of clotting factors as well as increases the risk of infection secondary to the removal of serum antibodies [27].

In 2018, Walsh and colleagues presented the results of the PEXVIS trial (a two-by-two factorial randomized trial evaluating plasma exchange and two different oral glucocorticoid regimens in severe AAV) which found that in patients with either lung hemorrhage or glomerulonephritis (eGFR <50 mL/min/1.73 m^2), neither plasma exchange nor reduced-dose oral steroids had a statistically significant difference in the primary composite outcome of death from any cause and end-stage renal disease [28]. Of the 704 patients recruited, 27% had alveolar hemorrhage. The results from this trial demonstrated that plasma exchange does not reduce the risk of end-stage renal disease or death in patients with severe AAV [28]. Also, PEXVIS demonstrated that reduced-dose steroids were non-inferior when compared to a more aggressive steroid dosing regimen and resulted in fewer infections during the first year of immunosuppression [28]. Mitigating infectious risk is imperative in the management of vasculitis. A study by Flossmann et al. illustrates this point, as the investigators found that 48% of deaths in vasculitis patients during the first year of therapy were related to infection, and infection remained the third leading cause of death at 20% after the first year of therapy [29].

In 2010, the Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis (RAVE) trial evaluated the anti-CD-20 monoclonal biologic rituximab for the management of generalized active and severe AAV and found that rituximab was non-inferior when compared with cyclophos-

phamide [30]. No significant differences in total or severe adverse events were found between the treatment groups. Subgroup analysis further showed that rituximab was equally effective as cyclophosphamide for the management of alveolar hemorrhage and more efficacious for inducing remission in relapsing disease. Thus, rituximab may be used as a potential alternative to cyclophosphamide in severely ill patients, including those with DAH. A subsequent 18-month follow-up of the RAVE trial demonstrated that rituximab was non-inferior to conventional immunosuppressive maintenance therapy over 18 months [31]. In addition to relapsing disease, rituximab has been shown to achieve higher rates of remission in diffuse alveolar hemorrhage secondary to AAV and patients who are anti-PR3 positive [32, 33]. Finally, the RITAZAREM trial comparing rituximab to azathioprine head to head for maintenance of disease remission should provide definitive results regarding the effectiveness of rituximab for maintenance therapy in the near future [34]. As a result, rituximab has been gaining favor as a first-line therapy for the treatment of severe GPA/DAH in conjunction with corticosteroid therapy.

ANCA-Associated Small Vessel Vasculitis: Microscopic Polyangiitis

Microscopic polyangiitis (MPA) is another of the small-vessel ANCA-associated vasculitides and has a predilection for the microvasculature of the kidney and the lung. MPA is universally associated with a focal segmental necrotizing glomerulonephritis and is characterized by marked constitutional symptoms. MPA can be differentiated from classic polyarteritis nodosa by the lack of involvement of medium-sized blood vessels and the absence of systemic hypertension. Distinguishing MPA from GPA can be difficult, but MPA lacks the granulomatous inflammation seen in GPA, only affects the upper airway in <15% of patients, and is commonly associated with a peri-nuclear ANCA-staining pattern (p-ANCA) rather than a c-ANCA pattern. DAH due to pulmonary capillaritis occurs in up to one-third of patients with MPA and represents by far the most common pulmonary manifestation of the disease. In patients with recurrent bouts of DAH related to MPA, both obstructive lung disease and pulmonary fibrosis have been reported [20, 35].

As mentioned above, a diagnosis of MPA essentially requires that the patient has a focal segmental necrotizing glomerulonephritis. Other common clinical manifestations include arthralgias/arthritis, myalgias/myositis, gastrointestinal disease, peripheral nervous system involvement, and cardiac disease. As seen in other AAV, non-specific inflammatory markers are elevated (erythrocyte sedimentation rate and C-reactive protein), and non-specific increases in both serum antinuclear antibodies and rheumatoid factor may be present. ANCA is frequently present in patients with MPA, but less so than with GPA, on the order of 50–75%. Additionally, 85% of the ANCAs will have a p-ANCA-staining pattern that in turn is more commonly associated with anti-myeloperoxidase (MPO) antibodies [17, 35, 36].

As with GPA, DAH in MPA represents life-threatening disease and is associated with an increased mortality. Indeed, an episode of DAH secondary to MPA is associated with up to 30% mortality. For those patients who do survive, the 1-year and 5-year survival is reduced to 82% and 68%, respectively [35, 37].

Treatment of DAH secondary to MPA is very similar to GPA and consists of supportive care elements plus glucocorticoids and cyclophosphamide or rituximab. Additionally, recombinant factor VIIa has been tried at the case report level as a modality by which to control refractory alveolar hemorrhage and unremitting respiratory failure in severe cases of DAH due to MPA [38].

Isolated Pulmonary Capillaritis

Isolated pulmonary capillaritis or idiopathic pauci-immune pulmonary capillaritis refers to a small-vessel vasculitis that is confined to the lungs. Some experts liken this entity to a lung-limited MPA. DAH in isolated pulmonary capillaritis may or may not be p-ANCA positive, and while no differences can be discerned between those patients who are ANCA positive and ANCA negative, this may be due to inadequate longitudinal follow-up. In one case series of 29 patients, isolated pulmonary capillaritis was the most common cause of DAH with biopsy proven pulmonary capillaritis, followed by GPA and MPA [39]. In this study, isolated pulmonary capillaritis accounted for 28% of the cases, and there were no clinical, serologic, or histologic features of an alternative systemic disorder. Clinically, three quarters of patients presented with respiratory distress and half required mechanical ventilation. Despite this, there was an 88% in hospital survival and an overall favorable prognosis for the group. Isolated pulmonary capillaritis is treated along the same lines as AAV and responds well to standard therapy with corticosteroids and cytotoxic medications [36, 40]. Similarly, rituximab has been described as a potential therapy for recurrent DAH in isolated pulmonary capillaritis previously treated with cyclophosphamide [41].

Systemic Lupus Erythematosus

DAH affects only 4% of patients with SLE, but along with acute lupus pneumonitis represents one of the most devastating pulmonary complications of SLE with a mortality rate approaching 50%. Histopathologically, DAH due to SLE is associated with pulmonary capillaritis in the vast majority of cases, but bland pulmonary hemorrhage and DAH secondary

to diffuse alveolar damage may also be seen. That said, patients with DAH (and acute lupus pneumonitis) are often critically ill and rarely proceed to biopsy as the risks associated with lung biopsy are rarely justified, and the diagnosis can generally be made without biopsy. Finally, co-morbid and/or precipitating infectious complications should excluded as a contributing factor to the DAH [3, 42, 43].

As with SLE itself, there is a strong female preponderance in DAH secondary to SLE, and patient is on average in their third to fourth decade. In the majority of cases of DAH associated with SLE, glomerulonephritis is also present at the time of presentation. As with other cases of DAH, patients present with dyspnea, hemoptysis, hypoxemia, and respiratory distress/respiratory failure; however, this clinical presentation is common to both DAH and acute lupus pneumonitis (ALP) and distinguishing between these entities can be exceedingly difficult. In point of fact, 20% of cases of ALP may present with hemoptysis. Still, the majority of DAH cases occur in patients with a known diagnosis of SLE and will frequently have concomitant glomerulonephritis, whereas 50% of cases of ALP are an initial presentation of SLE. Ultimately, as with most cases of DAH, diagnosis is made at time of BAL. In those patients who undergo biopsy, ALP is characterized by diffuse alveolar damage complicated by hemorrhage and may also have features of organizing pneumonia but should not demonstrate frank capillaritis [3, 6].

As mentioned previously, mortality rates associated with DAH in SLE are high and have traditionally ranged from 50% to 90%, although more recent data suggests that the use of aggressive immunosuppressive treatment, increased recognition of concomitant infections, and advances in the management of critically ill patients, survival is far better. Negative prognostic factors include the need for mechanical ventilation, the presence of infection, and the requirement for cyclophosphamide therapy [3, 6, 43].

Treatment of DAH secondary to SLE includes the use of intravenous, high-dose methylprednisolone, and cyclophosphamide. Ednalino and colleagues published a systematic review of 174 cases of DAH in 140 patients with SLE. Treatment varied with the most common therapeutic agent being corticosteroids (98%), followed by cyclophosphamide (54%) [44]. Other therapies included plasmapheresis (31%), azathioprine (7%), rituximab (6%), and IVIG (5%). Of these, only the use of cyclophosphamide showed improved survival (71% vs. 49%) [44]. While plasmapheresis is also used for DAH complicating SLE, it is unclear whether or not this intervention provides additional benefit [36, 43, 45]. An increasing number of case reports have been published regarding the successful use of rituximab in cases of SLE complicated by DAH. In the majority of these cases, rituximab is used in combination with cyclophosphamide for recurrent DAH [46–48].

Antiphospholipid Antibody Syndrome

Antiphospholipid antibody syndrome, along with GPA, MPA, idiopathic pauci-immune capillaritis, and SLE, represents one of the more common etiologies of capillaritis. As with the other entities, DAH may be an initial presentation or later complication of the disease. Symptoms again include cough, dyspnea, fatigue, malaise, fever, hemoptysis, hypoxemia, and acute respiratory failure. Thrombocytopenia may be present at the time of the DAH episode helping to focus the differential diagnosis on antiphospholipid antibody syndrome along with SLE, disseminated intravascular coagulation, and thrombotic thrombocytopenic purpura. On histology, there is evidence of pulmonary capillaritis with or without concomitant microvascular thrombosis [7, 49].

The management of antiphospholipid antibody syndrome is commonly complicated by thromboembolic disease and the need for anti-coagulation. When an episode of DAH occurs in a patient with an established diagnosis of antiphospholipid antibody syndrome, the presence of capillaritis and diffuse hemorrhage may be further worsened by the presence of therapeutic anti-coagulation (as well as the possibility of concomitant pulmonary thromboemboli.) Nevertheless, it must be recognized that more often than not, it is the capillaritis driving the DAH and controlling the vasculitis is key to achieving therapeutic success. At the same time, diagnosing, treating, and/or preventing the thromboembolic manifestations of the disease, as well as controlling the DAH, cannot be ignored. Thus, even in centers experienced in the management of complex autoimmune diseases, the management of these patients is extremely challenging and referral to a center of expertise is recommended when feasible. Nevertheless, first-line therapy for DAH associated with antiphospholipid antibody syndrome is intravenous corticosteroids combined with optimal supportive care. Rapid resolution of most cases of DAH is typically seen after treatment with corticosteroids. In cases of catastrophic antiphospholipid syndrome, IVIG or plasma exchange may be added to the intravenous corticosteroids and supportive care. Most recently, case reports describing the use of rituximab for refractory antiphospholipid antibody syndrome, including when complicated by refractory DAH, have suggested that this agent may ultimately prove to have a role when more conventional therapies are unsuccessful [1, 49–52].

As with other cases of chronic and/or recurrent DAH, fibrosis and/or obstructive disease may evolve over time. Lastly, it should be noted that in catastrophic cases of antiphospholipid antibody syndrome (Asherson syndrome), ARDS and multi-system organ dysfunction may develop. In these cases, the pathology will demonstrate diffuse alveolar damage, capillaritis, and diffuse small-vessel occlusion and obliteration [14, 51].

Anti-Basement Membrane Antibody Disease (Goodpasture Syndrome)

Anti-basement membrane antibody (ABMA) disease is an autoimmune disorder mediated by antibodies directed against the non-collagenous domain-1 (NC1) of the alpha-3 chain of type IV collagen (and to a lesser degree the alpha-5 chain) found in basement membranes [53]. The majority of patients, approximately 60–80%, present with a pulmonary-renal syndrome of DAH and glomerulonephritis. Indeed, the presence of a true pulmonary-renal syndrome helps focus the differential diagnosis upon ABMA disease, GPA, MPA, and SLE. Still, 15–30% of cases may present with isolated glomerulonephritis, and conversely, up to 10% of patients may present with DAH alone without renal involvement. Interestingly, although type IV collagen is found elsewhere in the body, including the skin, eye, and gastrointestinal tract, end-organ damage in ABMA disease is limited to the kidneys and lung. DAH represents a major cause of mortality in patients with ABMA disease, and among the competing causes of DAH, ABMA disease has a relatively poorer prognosis. On the other hand, in those cases of ABMA disease in which the pulmonary manifestations are dominant, renal outcomes are better when compared to patients who present with renal disease alone [13, 53].

The clinical presentation of DAH due to ABMA disease is very similar to other cases of DAH of differing etiologies with the caveat that glomerulonephritis is present in most albeit not all cases. Again, patients will complain of dyspnea, cough, hemoptysis, hypoxemia, and/or constitutional symptoms (fatigue, fever, anorexia, weight loss, arthralgias, and myalgias). ABMA disease preferentially affects men more than women (approximately 2:1) and has a predilection for young adults (the average patient age reported ranges between 20 and 30). In those patients with ABMA who develop DAH, a history of smoking is extremely common (50–90%), although recent viral infection or other inhalation exposures (e.g., hydrocarbons, marijuana, fire smoke, cocaine) may also be seen immediately antecedent to the onset of DAH. In point of fact, it is hypothesized that cigarette smoking (or alternatively, infection or other inhalational exposure) plays a pathophysiologic role in the development of DAH either through a secondary injury to the alveolar-capillary unit, facilitating antigen presentation, or allowing ABMAs entry into the lung [13]. On laboratory testing, anemia will commonly be present and frequently will be accompanied by an elevated blood urea nitrogen or serum creatinine consistent with renal insufficiency. Urinalysis frequently reveals microscopic hematuria, proteinuria, and red blood cell casts diagnostic of glomerulonephritis. Interestingly, 3–7% of patients will be p-ANCA positive, suggesting the possibility of an overlap syndrome with MPA. ABMA disease has also been shown to have an association with specific human leukocyte antigen (HLA)-DR alleles, specifically HLA-DRB1*1501 [53]. Chest imaging studies, as with other cases of DAH, will show patchy diffuse alveolar infiltrates that appear as ground-glass infiltrates or consolidation on HRCT. While it is rare to obtain pulmonary function testing in acutely ill patients, in more chronic cases or more slowly evolving cases, an increased diffusing capacity of carbon monoxide may be identified.

Diagnosis may be made by identifying the presence of serum anti-basement membrane antibodies (ABMA) in a patient with a compatible clinical presentation, and circulating antibodies may be identified in two thirds to three quarters of patients at time of diagnosis [53]. At the bedside, it may be necessary to make a tentative clinical diagnosis and initiate therapy while awaiting the results of the serologic testing which frequently must be sent to a referral laboratory. Of note, while antibody titers appear to correlate with the severity of the renal disease, no such correlation has been identified with the pulmonary manifestations of the disease.

Alternatively, patients may be diagnosed via lung or kidney biopsy and immunofluorescence studies. In general, a biopsy is pursued when there is diagnostic uncertainty and when the preponderance of the available data does not make a compelling case for a diagnosis. For example, a patient with evidence of glomerulonephritis on urinalysis, negative serologies, including ANCA, PR3, MPO, ABMA, ANA, and dsDNA, and a non-diagnostic bronchoscopy, e.g., hemosiderin-laden macrophages on differential cell counts but a BAL that clears with serial lavage, would be a patient that would benefit from a diagnostic biopsy. In this example, the clinician knows that the kidneys are an involved target end organ based upon the sediment, and a renal biopsy that includes both routine studies and immunofluorescence studies would be a very reasonable approach to the diagnosis. On the other hand, if this same patient had had detectable serum anti-basement membrane antibodies, a biopsy would not be required for diagnosis.

On light microscopy, the histopathology of the lung in ABMA disease may demonstrate either bland hemorrhage or capillaritis (although the appearance of the capillaritis in ABMA disease tends to lack some of the more aggressive and destructive features seen in MPA or GPA). Similarly, the renal biopsy will demonstrate a focal, segmental, rapidly progressive glomerulonephritis with crescent formation that is indistinguishable from other etiologies of rapidly progressive glomerulonephritis. However, the frozen sections should demonstrate a positive immunofluorescence pattern with a linear, continuous, “ribbon-like” appearance, reflecting antibody that has bound to the basement membrane. This immunofluorescence pattern is distinct from the punctate, patchy staining pattern seen in SLE and the negative or “pauci-immune” pattern associated with the AAV, and hence, is diagnostic for ABMA disease [54].

DAH associated with ABMA disease is managed very similarly to other cases of DAH and begins with the ABCs.

Interestingly, plasmapheresis combined with corticosteroids and a cytotoxic agent (i.e., cyclophosphamide) has been shown to be effective and is associated with improved mortality and renal recovery [55]. Early diagnosis and prompt institution of therapy are crucial to optimizing outcomes, and as such, it is sometimes necessary to initiate therapy pending a definitive diagnosis. The similarities in the therapeutic recommendations for diseases characterized by a pulmonary-renal syndrome, whether it is due to ANCA-associated vasculitis, SLE or ABMA disease, combined with the adverse effects associated with delays in therapy support the early institution of steroids and a cytotoxic or biologic agent. The role of plasmapheresis is well supported in patients with ABMA disease unlike patients with GPA or MPA. Steroids alone, or steroids combined with cytotoxic agents without the use of plasmapheresis do not achieve equivalent results in patients with ABMA disease. While there is no definitive data informing the optimal duration of plasmapheresis, the duration of therapy in ABMA disease tends to be on the order of 10–14 exchanges, or until ABMAs become undetectable. With regard to choice of cytotoxic agent, intravenous cyclophosphamide is the most common agent utilized for life-threatening alveolar hemorrhage. In more mild cases or as the patient's conditions improve, azathioprine (and more recently mycophenolate mofetil) has been used [20]. Still, rituximab has been proposed by some experts as a potential therapeutic agent for Goodpasture syndrome based upon its mechanism of action and the pathogenetic role of ABMAs in the disease. Currently, data supporting this hypothesis are limited to small case series that have successfully utilized rituximab as both the primary induction agent and salvage therapy to cyclophosphamide refractory disease [56, 57].

In terms of prognosis, patients with more severe renal disease have a worse outcome. A retrospective review of patients with ABMA disease by Levy and colleagues, and patients with a creatinine concentration of <5.7 mg/dL had a 1-year survival of 100% and a renal survival of 95%, those with a creatinine ≥5.7 mg/dL but who did not require immediate hemodialysis had a 1-year survival of 83% and renal survival of 82%, and those who required immediate hemodialysis had a 1-year survival of 65% and renal survival of only 8% [58]. A similar pattern is seen if one assesses renal involvement via biopsy in that patients with ≥70% crescentic glomeruli and renal insufficiency may be expected to have persistent renal failure whereas patients with less than 30% of their glomeruli having undergone crescent formation have improved survival and renal function. In a 28 patient case series of patients with ABMA disease and DAH reported by Lazor and colleagues, patients with pulmonary predominant disease (a paucity or absence of renal involvement) had a lower requirement for immunosuppressive therapy and plasma exchange than patients with a combined pulmonary-renal syndrome. Interestingly, this cohort was characterized by frequent worsening of their pulmonary or renal disease but 100% survival [13]. Unlike ANCA-associated vasculitis, ABMA disease has generally been characterized more as a monophasic process without multiple recurrences, and those cases characterized by recurrence have tended to relapse in close proximity to disease onset [53].

Lung Allograft Rejection

Pulmonary capillaritis as a manifestation of acute lung transplant rejection was first noted in a case series of five patients in 1998, four of which were confirmed histopathologically on surgical lung biopsy [59]. Interestingly, immunofluorescence studies identified septal capillary deposition of antibodies specific for complement factors and immunoglobulin subtypes. To differentiate between acute cellular rejection and post-transplant capillaritis, a biopsy is required; however, these conditions can be found concomitantly in greater than 50% of cases. When post-transplantation capillaritis is identified, intensification of immunosuppressive regimen is recommended. Plasmapheresis has also been tried on a compassionate use basis, but remains unproven [60].

Others

In addition to SLE and antiphospholipid syndromes, DAH has been documented in other collagen vascular diseases. While exceedingly rare, there have been case reports of pulmonary capillaritis in rheumatoid arthritis, scleroderma, mixed connective tissue disease, polymyositis/antisynthetase syndrome, and undifferentiated connective tissue disease [40, 61]. Distinguishing DAH from other pulmonary manifestations and complications of the underlying autoimmune disease may be difficult, especially given the rarity of DAH in these other entities, and the fact that hemoptysis needs not be present. Competing considerations include diffuse alveolar damage (i.e., acute interstitial pneumonitis, acute exacerbation of ILD, or lupus pneumonitis), organizing pneumonia, infection, pulmonary edema/heart failure, and drug toxicity. Treatment for DAH associated with these other connective tissue disease entities is similar to that recommended for DAH in SLE. Ultimately, these entities are all considered to be a secondary, autoimmune-mediated, small-vessel vasculitis secondary to an underlying collagen vascular disease, and therapy must be directed at the underlying process.

Henoch-Schönlein purpura is an immune-complex-mediated autoimmune disorder most commonly seen in pediatric populations which may also occur, albeit less frequently, in young adults. Patients typically present with a palpable, purpuric rash, most prominently over the lower extremities, and a focal segmental glomerulonephritis. Constitutional symptoms, arthralgias with synovitis, and gastrointestinal tract manifestations are common. Pulmonary

capillaritis has been reported in patients with Henoch-Schönlein purpura, but it is exceedingly rare. Indeed, a large case series of 37 adult patients revealed no cases of DAH [62]. In those cases where DAH is found to complicate Henoch-Schönlein purpura, IgA immune complexes may be demonstrated in the serum, lung, and kidney. Once again, management centers upon best supportive care combined with immunosuppressive therapy (corticosteroids and cytotoxic agents).

Behçet disease, or Behçet syndrome, is a clinical syndrome of unclear pathophysiology, characterized by mucocutaneous oral and genital ulcers, skin lesions and pathergy, ocular disease (pan-uveitis, iridocyclitis, retinal vasculitis), arthritis, and vascular disease, generally manifested as thrombophlebitis, venous thrombosis, and/or arterial aneurysms and/or occlusions. The syndrome not only preferentially affects individuals of Middle Eastern origin but is also found with increased incidence in Japanese populations. The most common pulmonary manifestation of Behçet disease is pulmonary artery aneurysms, and these occur in 1–8% of all individuals with Behçet. The presence of pulmonary artery aneurysms, however, is associated with a 50% mortality. Pulmonary hemorrhage may occur either due to involvement of the microvasculature that in turn leads to DAH, or alternatively, patient may present with massive hemorrhage secondary to the erosion of an aneurysm into the airway [63–65]. As with the other entities, management centers upon best supportive care combined with immunosuppressive therapy (corticosteroids and cytotoxic agents) [66].

DAH from pulmonary capillaritis has also been documented in mixed cryoglobulinemia, a vasculitis of small- to medium-sized vessel, mediated by immune complexes and complement, and frequently seen in association with hepatitis B and C infection. Patients often present with cutaneous vasculitis and glomerulonephritis, but rare cases of DAH have been reported [67].

Finally, some rare causes of pulmonary capillaritis include inflammatory bowel disease, idiopathic glomerulonephritis, IgA nephropathy, EGPA, myasthenia gravis, and drug-sensitivities due to diphenylhydantoin, retinoic acid, and propylthiouracil. With regard to inflammatory bowel disease, a number of pulmonary complications have been associated with both ulcerative colitis and Crohn disease including bronchiolitis (panbronchiolits and bronchiolitis obliterans), bronchiectasis, and interstitial lung disease [68]. There are at least two case reports of DAH with a capillaritis lesion associated with ulcerative colitis. Both cases responded to corticosteroids and cytotoxic therapy. A number of cases of propylthiouracil-associated p-ANCA-positive vasculitis with DAH have also been reported, and these patients in general responded to therapy with corticosteroids and the discontinuation of propylthiouracil [69].

Bland Pulmonary Hemorrhage (Fig. 9.5)

Histology

While both bland pulmonary hemorrhage and capillaritis show intra-alveolar filling by red blood cells, fibrin, and hemosiderin-laden macrophages along with septal expansion, edema and reactive type II cell hyperplasia, the vessel walls of bland pulmonary hemorrhage lack the inflammatory cell infiltrates and necrotic features seen in capillaritis. After repeated episodes of hemorrhage from any cause, fibrotic changes and/or microvascular "drop out" may evolve. In some cases of bland hemorrhage due to idiopathic pulmonary hemosiderosis, electron micrographs have demon-

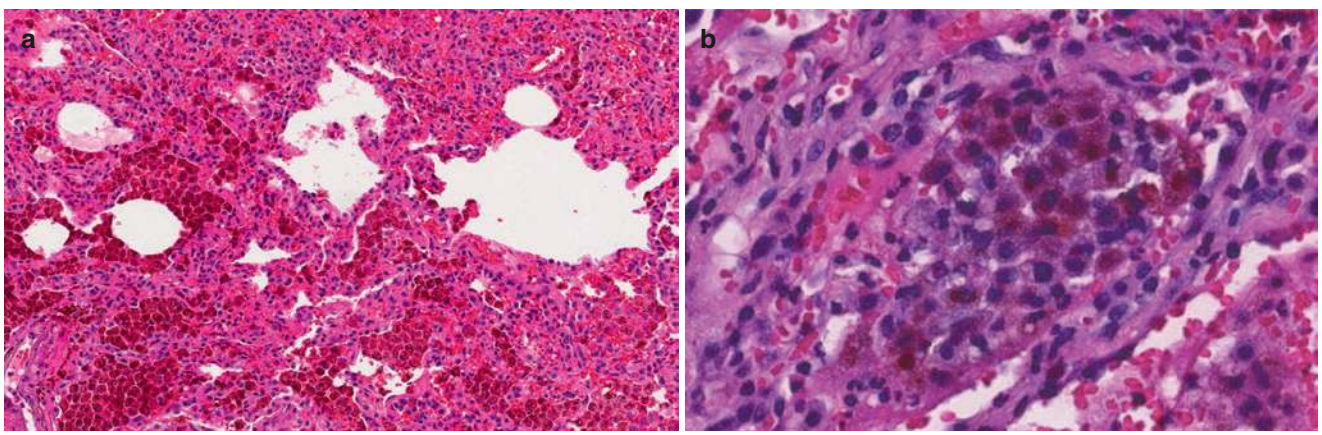

Fig. 9.5 (**a**) Photomicrograph (20× magnification) of a histopathologic section of lung demonstrating diffuse alveolar hemorrhage without features of capillaritis (bland hemorrhage). (**b**) Photomicrograph (60× magnification) of hemosiderin-laden macrophages filling the alveolar space. (Courtesy of Dr. Steven Groshong, Division of Pathology, Department of Medicine, National Jewish Health, Denver, Colorado, USA)

strated abnormalities in the integrity of the alveolar-capillary membrane suggesting a possible etiology. Finally, cases of capillaritis that have undergone a course of treatment or partial treatment may histopathologically appear as bland hemorrhage confounding the diagnostic algorithm [15, 70].

Etiologies

Idiopathic Pulmonary Hemosiderosis

The diagnosis of idiopathic pulmonary hemosiderosis (IPH) is a diagnosis of exclusion, and by definition, is the presence of bland diffuse alveolar hemorrhage in the absence of an identifiable etiology. Patients who present with IPH typically are children (80%) and young adults (20%). Males are preferentially affected relative to females (2:1). Familial cases have been reported. Clinically, the disorder is characterized by recurrent episodes of DAH. As such patients present with cough, dyspnea, hemoptysis, constitutional symptoms (fever, fatigue, malaise, anorexia), anemia (especially iron deficiency anemia), hypoxia, recurrent pulmonary infiltrates, and/or exercise intolerance. The severity of individual episodes of hemorrhage may vary from asymptomatic to fulminant respiratory failure requiring mechanical ventilation. Given the recurrent nature of the episodes of DAH, pulmonary fibrosis and restrictive lung disease will develop in up to a quarter of patients. Alternatively, patients with more chronic and refractory courses may also develop obstructive lung disease. Impaired gas exchanged with a reduced DLCO has similarly been reported in patients with chronic and relapsing disease. An isolated elevation of serum IgA may be seen in up to half of pediatric patients with IPH and may help raise the possibility of IPH in the differential diagnosis of a younger patient with DAH [14, 71].

By definition, in IPH, there should be no evidence of a systemic disorder (vasculitis, immune-complex-mediated disease, collagen vascular disease, etc.), no potentially inciting drugs or exposures, no significant cardiac lesions, no coagulopathy, and no appreciable pathophysiologic explanation for the disease [71]. As such, a detailed history (including occupational, exposure, drug and medication history), full serologic evaluation for autoantibodies and markers of autoimmune disease, urinalysis with sediment examination, urine toxicology screening (e.g., cocaine), ECG, and echocardiography should all be within normal limits. Even then, given that this is a diagnosis of exclusion, as cases of IPH are followed longitudinally, they may later be re-classified as a disease of known etiology as additional disease manifestations develop or objective data support an alternative diagnosis. It is believed that a number of cases in the published literature would have been classified differently had serum anti-basement membrane antibody testing, ANCA testing, and PR3/MPO ELISA testing that have been widely available at the time of publication. One caveat to this would be an observation that IPH may be associated with celiac disease or jejunal villous atrophy in some patients [72]. Similarly, subtle findings of capillaritis may easily be missed and cases of idiopathic pulmonary capillaritis may be misclassified as IPH. This is especially true in the patient who has started corticosteroid therapy or other disease-modifying therapy prior to surgical lung biopsy. Moreover, this may explain why some patients with IPH are observed to respond to immunosuppression with corticosteroids and cytotoxic agents. Nevertheless, to diagnose IPH, the biopsy must demonstrate bland hemorrhage and an absence of any features of vasculitis/capillaritis [71]. Indeed, to make a definitive diagnosis of IPH, a lung biopsy is essentially required.

As mentioned above, histologic evaluation reveals bland alveolar hemorrhage with filling of the alveolar spaces with red blood cells, fibrin, and hemosiderin-laden macrophages. Alveolar epithelial type II cell hyperplasia may be noted, and the vessels of the microvasculature may appear dilated and/or tortuous. Electron microscopy studies have further revealed subtle alveolar epithelial type I cell injury, basement membrane thickening, excessive collagen deposition, and an absence of immune complexes [71].

As with other cases of DAH, treatment of IPH begins with supportive care elements of oxygen, reversing any bleeding diathesis, and when indicated, ventilatory support and red blood cell transfusion. Pharmacologically, corticosteroids and cytotoxic agents again represent the mainstays of therapy, although their effectiveness specifically in IPH is unproven. Plasmapheresis has been used in severe, refractory episodes of DAH at the case report level [14]. The prognosis is variable—25% of patients will have limited disease characterized by a single episode of hemorrhage without recurrence, 25% will have recurrent hemorrhage but remain free of fibrosis or other major structural lung disease, 25% will have progressive, chronic lung disease as a result of chronic, recurrent hemorrhage, and 25% of patients will die of massive hemorrhage or other major complication of their disease [8, 71].

Drugs and Medications

A number of drugs and chemicals have been associated with the development of DAH and a pathologic correlate of bland hemorrhage including penicillamine, amiodarone, nitrofurantoin, and isocyanates. The reader is directed to the website www.pneumotox.com maintained by Drs. Foucher and Camus and the Groupe d'Etudes de la Pathologie Pulmonaire Iatrogène for up-to-date information regarding medication associated pulmonary toxicity.

DAH and pulmonary-renal syndrome are rare but reported complication of penicillamine therapy regardless of indication (rheumatoid arthritis, Wilson disease, or primary biliary cirrhosis) [73, 74]. As with other drug-induced pulmonary complications, the key to diagnosis is eliciting

a truly complete list of current medications as well as past medication history. On average, patients will have been taking penicillamine for a year prior to the onset of DAH, but the duration of therapy prior to the development of toxicity is highly variable. In patients who have undergone biopsy, the histopathology will demonstrate bland hemorrhage and immunofluorescence studies will show granular deposition of IgG similar to patients with SLE [75, 76]. Pulmonary capillaritis has not been associated with penicillamine therapy. Treatment includes cessation of penicillamine plus corticosteroids, cytotoxic therapy, and plasmapheresis [74].

While the majority of patients with amiodarone pulmonary toxicity will demonstrate "classic" histopathologic features, namely the presence of interstitial edema and fibrosis, copious vacuolated histiocytes, and foamy alveolar macrophages with or without elements of organizing pneumonia and/or diffuse alveolar damage, cases of diffuse alveolar hemorrhage associated with amiodarone therapy have been reported and histopathologically will demonstrate bland hemorrhage [75, 76]. Similarly, nitrofurantoin therapy is most commonly associated with a subacute or chronic cellular interstitial pneumonitis and/or pulmonary fibrosis, but in rare cases, an acute nitrofurantoin toxicity may develop and present with an acute-onset diffuse alveolar hemorrhage [75]. Therapy requires discontinuation of the drug with or without concomitant corticosteroids.

Coagulopathy

Coagulation disorders are among the most common etiologies of DAH associated with bland pulmonary hemorrhage. Thrombocytopenia of a variety of etiologies including idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, drug-induced thrombocytopenia (e.g., chemotherapy), hemolytic uremic syndrome, and disseminated intravascular coagulation may all lead to bland hemorrhage [4, 5]. Similarly, pharmacologic anti-coagulation with vitamin K antagonists, fractionated or unfractionated heparin, direct thrombin inhibitors, factor Xa inhibitors, IIb/IIIa inhibitors, and fibrinolytic therapy may also lead to alveolar hemorrhage [77–80]. Less obvious causes may include vitamin K deficiency and advanced liver disease.

As with other patients with DAH, patients may present with dyspnea, exercise intolerance, hypoxemia, anemia, and pulmonary infiltrates. Hemoptysis appears to be less common than with other etiologies of DAH, but bronchoscopy and lavage are generally diagnostic. Therapy includes supportive care and reversal of the coagulopathy.

Valvular Heart Disease and Left Ventricular Dysfunction

Mitral stenosis may produce DAH in those instances in which the disease is severe enough to produce severe pulmonary venous hypertension and histopathologically appears as bland hemorrhage. Although patients may have a known history of mitral stenosis, a history of rheumatic heart disease or the development of insidious exercise intolerance and dyspnea may herald a diagnosis of valvular heart disease, or patients may have an initial presentation of pulmonary infiltrates or intermittent hemoptysis [81]. DAH has also been reported in patients with markedly elevated left ventricular filling pressures of other etiologies such as severe aortic stenosis, severe diastolic dysfunction and cardiomyopathy, especially in patients with concomitant chronic kidney disease/end-stage renal disease. Treatment in these cases is directed at the underlying cardiovascular pathology.

Other

Inhalation of acid anhydrides and isocyanates has been associated with alveolar hemorrhage. These reactive organic chemicals are used in the manufacturing of plastics, paints, varnishes, and other resins. Hence, obtaining an occupational and exposure history is important in the evaluation of the patient with DAH. In general, the disease process is lung limited, and interestingly, cases related to acid anhydride exposure appear to have a latency period between initial exposure and the development of hemorrhage of 1–3 months suggesting an immunologic mechanism. As with other exposure related processes, treatment requires elimination of the exposure [82, 83].

Extremely severe cases of obstructive sleep apnea and obesity hypoventilation syndrome have also been associated with alveolar hemorrhage. These cases are generally associated with marked pulmonary hypertension, chronic hypoxemia, pulmonary capillary network proliferation, and biventricular heart failure. Histology in these cases demonstrates bland hemorrhage, non-specific injury, and capillary proliferation [84].

Lastly, there are rare cases of pulmonary veno-occlusive disease associated with DAH. Pulmonary veno-occlusive disease may occur in the setting of bone marrow transplantation, chemotherapy-induced lung injury, radiation, collagen vascular disease, HIV, a familial disorder, or as an idiopathic process. Patients most commonly present with signs and symptoms of severe pulmonary hypertension, including exercise intolerance, syncope, lightheadedness, and dyspnea but may report hemoptysis, and in rare cases, may be demonstrated to have DAH. Pulmonary function testing will demonstrate normal lung volumes and spirometry but a reduced diffusing capacity of carbon monoxide. Right heart catheterization will reveal pulmonary hypertension but a normal pulmonary capillary wedge pressure. Histology in these cases demonstrates obliteration, thrombosis, and fibrosis in and around the pulmonary venules and bland hemorrhage. The prognosis in pulmonary veno-occlusive disease is poor, and lung transplantation is the

only definitive therapy, although immunosuppressive therapy (cytotoxics and corticosteroids), pulmonary vasodilator therapy, and anti-coagulation have all been attempted [85, 86].

Diffuse Alveolar Damage

Histology

Diffuse alveolar damage (DAD) is a histopathologic pattern associated with acute lung injury. In those cases in which patients present with an acute illness, such as septic shock, pneumonia, trauma, aspiration or pancreatitis, severe hypoxemia, bilateral alveolar radiographic infiltrates, and a histopathologic correlate of DAD, they are appropriately diagnosed with ARDS. Other etiologies of DAD include acute exacerbations of fibrosing interstitial lung diseases, acute lupus pneumonitis, bone marrow transplantation (idiopathic pneumonia syndrome), and acute interstitial pneumonitis. While DAH is not considered "characteristic" of underlying DAD, DAH may be associated with underlying DAD. Histology in these cases will show a dominant lesion of DAD characterized by noncardiogenic pulmonary edema, alveolar type I cell injury and necrosis, denudation of the basement membrane, hyaline membrane formation in the alveolar spaces, thrombi in the microvasculature, and an influx of plasma cells, histiocytes, lymphocytes, and scattered neutrophils, combined with evidence of focal hemorrhage in the alveolar spaces. As the entity evolves over days, the alveolar spaces and interstitium will fill with loose fibromyxoid tissue, the type II alveolar epithelial cells will proliferate and appear hyperplastic and cuboidal and elements of organizing pneumonia may develop as airspace fibrin begins to organize. While gross examination of the aliquots of serial bronchoalveolar lavage will be largely indistinguishable from cases of bland hemorrhage or capillaritis, in general, the absolute red blood cell counts identified by formal differential cell counts seem to be lower in DAD with hemorrhage, and there is a concurrent pronounced neutrophilia related to the lung injury [15, 87]. In many ways, the presence of DAH in the setting of DAD is more confounder than clinically significant and should not be misinterpreted as being a major manifestation of DAD (Table 9.3).

Table 9.3 Entities characterized by prominent and severe diffuse alveolar hemorrhage

Entities
Granulomatosis with polyangiitis
Microscopic polyangiitis
Isolated pulmonary capillaritis
Systemic lupus erythematosus
Primary antiphospholipid antibody syndrome
Goodpasture syndrome
Hematopoietic stem cell transplantation
Idiopathic pulmonary hemosiderosis
Coagulation disorders

Etiologies

Hematopoietic Stem Cell Transplantation (HSCT)

Both infectious and non-infectious pulmonary complications are extremely common following bone marrow transplantation or hematopoietic stem cell transplantation (HSCT). In 2011, the American Thoracic Society published an official research statement on the spectrum of non-infectious lung injury after HSCT or the idiopathic pneumonia syndrome [88]. Approximately 3–15% of patients who undergo allogenic HSCT will develop a non-infectious lung injury within 120 days of transplantation. A subset of these patients will have DAH. As with other patients with DAH, patients will present with dyspnea, hypoxemia, cough, constitutional symptoms, and bilateral radiographic infiltrates. Hemoptysis occurs less frequently than expected and may be found in perhaps 15% of patients. Respiratory failure requiring mechanical ventilation is common. The onset of DAH usually occurs within 1–5 weeks of the HSCT. Risk factors associated with the development of DAH in these patients include advanced age, total body radiation, type of myeloablative conditioning regimen, and the presence of severe acute graft-vs-host disease. While most cases of clinical DAH will be a subset of IPS, infection as a contributing feature to the development of DAH must be excluded, as hemorrhage in this subset of patients may also be due to infection. Mortality for DAH in this setting is 60–100%. Furthermore, even for the minority of patients that survive an episode of DAH, the follow-up 6-month mortality is on the order of 40%. Treatment for DAH associated with HSCT is high-dose corticosteroids and supportive care, but given the exceedingly high mortality, the efficacy of this strategy is clearly limited. Attempts at protective strategies, including reductions in the intensity of the conditioning regimen, have not been proven to decrease the risk of disease [68–71].

Cocaine Inhalation

Cocaine is an illicit drug derived from leaves of the *Erythroxylon* coca plant. While cocaine may have legitimate medicinal properties as a local anesthetic, its stimulant properties make it an attractive drug of abuse. Cocaine may be inhaled nasally, smoked and inhaled in its free base form ("crack" cocaine), or injected intravenously. Inhaled crack cocaine is commonly associated with an array of pulmonary complications including thermal injuries to the upper airways, cough and carbonaceous sputum, barotrauma (pneumothorax and pneumomediastinum), cardiogenic and noncardiogenic pulmonary edema, bronchospasm and

asthma, eosinophilic lung reactions, organizing pneumonia, "crack lung," hemoptysis, and pulmonary hemorrhage. Acute respiratory symptoms usually develop with several hours of use but may develop in a matter of minutes or may evolve over several days. Presenting complaints will include cough, chest pain (usually pleuritic), shortness of breath, hemoptysis, and wheezing. Hypoxic, tachycardia, tachypnea, and abnormalities on auscultation are common. Imaging findings depend upon the manifestation of cocaine pulmonary toxicity, but in the case of "crack lung" or alveolar hemorrhage, bilateral pulmonary infiltrates are identified. Toxicology screening should reveal the presence of cocaine metabolites in the urine (Fig. 9.6) [2].

DAH as an isolated complication or as part of the more heterogenous "crack lung" pattern of acute parenchymal injury is believed to be relatively common, but data are limited. Histologically, "crack lung" is characterized by DAD, edema, inflammatory infiltrates, and hemorrhage. The mechanism of injury is believed to relate to profound vasoconstriction of the pulmonary vascular bed and its resulting cellular damage. Additionally, a direct toxic effect of the inhaled substances is also believed to play a role [2].

Management is supportive in nature and in most cases, the injury will spontaneously resolve. At present, there appears to be no role for corticosteroids or other immunosuppressive therapy, but substance abuse counseling is critical to the longitudinal management of these patients.

Finally, it should be noted that there are also isolated case reports of DAH occurring with other drugs of abuse, such as cannabis and heroin.

Acute Exacerbation of Interstitial Lung Disease

Acute exacerbation of interstitial lung disease (AE-ILD) is a relatively rare cause of DAD associated DAH, but conversely, it is a common cause of death among patients with fibrosing interstitial lung diseases. While the occurrence of AE-ILD is now well recognized in IPF, collagen vascular disease-associated ILD, hypersensitivity pneumonitis, drug-associated ILD, and fibrotic non-specific interstitial pneumonitis, the pathophysiology remains largely unknown, and the diagnosis remains one of exclusion. By definition, AE-ILD is the presence of an acute respiratory decline in a patient with a pre-existing fibrosing interstitial lung disease accompanied by new radiographic infiltrates (ground glass or consolidation superimposed on pre-existing fibrotic changes) in whom volume overload or cardiac failure cannot be identified [89].

In one large retrospective study focusing on idiopathic pulmonary fibrosis, the incidence of AE-ILD among an at-risk population was 14.2% at 1-year follow-up and 20.7% at 3-year follow-up. In the study, in-hospital mortality was approximately 50% with a 5-year survival of only 18.4%. DAH was noted as the cause of death in 2.2% of patients. Predictors of poor outcome included older age, low FVC and DLCO, mechanical ventilation, and immunosuppressive therapy [89, 90].

In another smaller study of patients hospitalized with suspected AE-ILD, 100% of patients were noted to present with worsening dyspnea and increased oxygen requirements. Most patients were found to have a cough and constitutional symptoms. Bronchoscopy was performed routinely to exclude infectious etiologies for the patients' decline, and surprisingly, diffuse alveolar hemorrhage was identified on

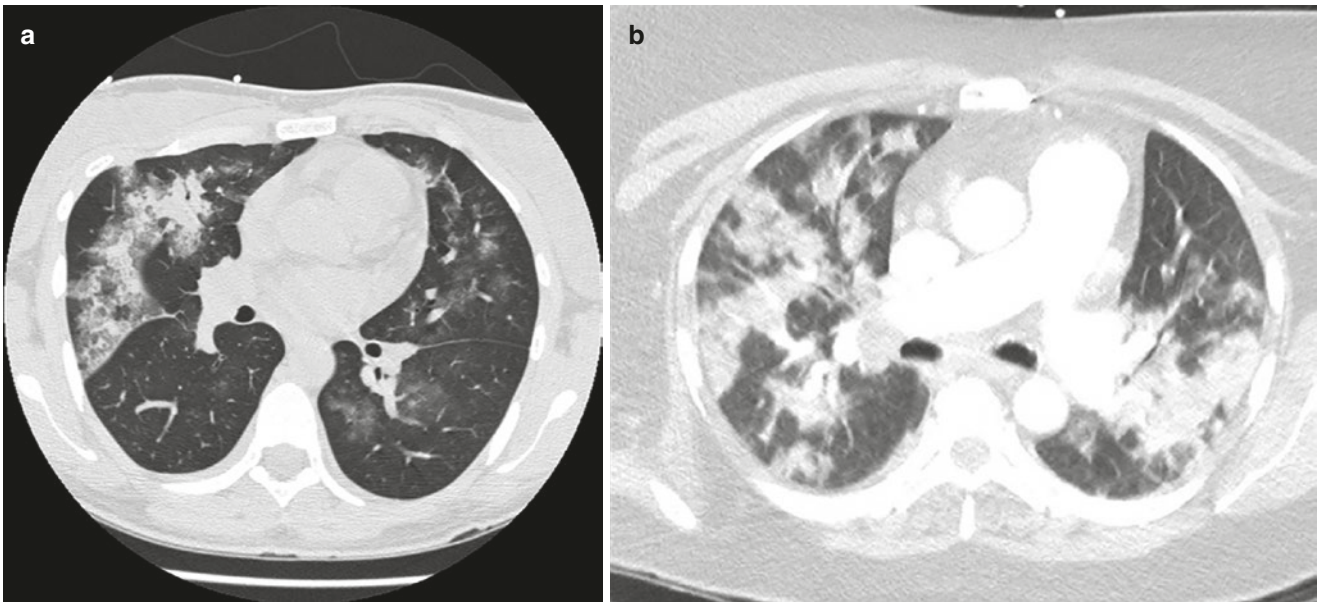

Fig. 9.6 (**a**) High-resolution computed tomography image and (**b**) CT angiography image demonstrating a spectrum of disease associated with alveolar hemorrhage. Note that while both radiograph images demonstrate patchy alveolar filling patterns, the density of the infiltrates may range from ground glass to frank consolidation, and the extent of the proportion of involved lung may similarly vary. (Courtesy of Dr Gregory P. Cosgrove, Division of Pulmonary and Critical Care Medicine, National Jewish Health, Denver, Colorado, USA)

serial lavage in 21.7% of patients. On chest imaging, the majority of patients had diffuse ground-glass opacities superimposed on their underlying lung disease. In the patients that underwent lung biopsy or autopsy, nine out of ten had evidence of DAD superimposed on underlying fibrosis, and one patient demonstrated significant acute and chronic alveolar hemorrhage with no significant acute lung injury. Hospital survival was only 37% and 1-year survival 14.8% in this patient cohort [91].

Treatment of AE-ILD is largely empiric and focused on supportive care. Most experts recommend the administration of broad-spectrum antimicrobial therapy and high-dose corticosteroids, but no significant controlled trials have been performed to confirm their efficacy. In patient who require mechanical ventilation, the mortality approaches 100%, thus, while a lung-protective strategy is recommended given the similarities to ARDS, counseling the patient and family regarding the dismal prognosis is strongly recommended.

Acute Interstitial Pneumonia

Acute interstitial pneumonia (AIP) is unique clinical-histopathologic entity characterized by a rapidly progressive course of respiratory decline over days to weeks that is associated with diffuse bilateral radiographic infiltrates, and the pathologic correlation of organizing DAD [92]. By definition, AIP is an idiopathic interstitial pneumonia, and the clinician must eliminate known causes of DAD in order to make a diagnosis. This can often be difficult, and indeed, some experts have coined AIP to be "idiopathic ARDS."

AIP is very rare with only about 250 cases in the literature. On average, patients are in their fifth through seventh decades, and there appears to be a slight male preference. Most patients develop a viral prodrome that evolves over days to weeks and includes cough, dyspnea, fatigue, malaise, fever, and "flu-like" illness [93]. Symptoms typically progress to include more marked dyspnea, hypoxemia, and respiratory distress [94]. Imaging studies universally reveal bilateral infiltrates, and on more refined HRCT imaging, appear as ground-glass abnormalities and consolidation [95]. The pathologic pattern of AIP is that of fibroproliferative or organizing DAD. Proliferative hyperplastic type II alveolar epithelial cells are seen lining airspaces filled with fibromyxoid tissue, edema, fibrinous exudates, and remnants of hyaline membranes. Subacute and chronic inflammatory infiltrates are noted as is fibroblast proliferation, interstitial widening, and collagen deposition. Occasionally, features of alveolar hemorrhage are also identified on histology [92].

Given the very low numbers of patients reported in the literature, it is difficult to prognosticate in AIP, but overall, it appears to be better than AE-ILD or HSCT-IPS, but worse than ARDS [96]. As with DAD of other etiologies, patients receive supportive care, including lung-protective ventilatory strategies (6 mL/kg tidal volumes) and restrictive fluid strategies if they require mechanical ventilation. High-dose corticosteroids are commonly deployed, but again, objective data supporting their use are lacking and are largely based upon extrapolation from other entities.

Acute Respiratory Distress Syndrome

The acute respiratory distress syndrome (ARDS) is a major cause of respiratory failure and ICU admission. The 2012 Berlin criteria defined ARDS by the acute onset (<7 days), bilateral opacities on chest radiograph, and no clinical suspicion of volume overload [97]. The most common etiologies or precipitants of ARDS are septic shock, pneumonia, aspiration, trauma, and pancreatitis. Other previously described precipitants include fat emboli, thermal burns, transfusion-associated lung injury, and inhalational injuries. Risk factors for the development of ARDS include advanced age and alcohol consumption. Initial evaluation of patients with ARDS is focused on (1) determining and treating the underlying cause of the lung injury and (2) optimally supporting the patient's ventilation and gas exchange. Hence, patients typically are broadly cultured for the presence of infection and cardiogenic causes of pulmonary edema are excluded (e.g., echocardiography, serial electrocardiography, cardiac enzymes). Bronchoscopy may be performed in patients in whom no obvious inciting etiology is identified. A lung-protective ventilatory strategy is recommended in all ARDS patients requiring mechanical ventilation (see below) [98, 99].

The histology of ARDS is DAD, but superimposed intra-alveolar hemorrhage may be seen, especially during the acute phase of DAD [10].

Mortality in ARDS has improved over the past two decades with advances in care informed by large, multicenter clinical trials, in particular the National Heart, Lung and Blood Institute ARDS Clinical Network trials. The landmark ARMA trial published in 2000 of patients with ARDS maintained on mechanical ventilation, demonstrated that a "lung-protective" tidal volume of 6 mL/kg was associated with a 22% reduction in mortality when compared with a tidal volume of 12/mL/kg [100]. In 2013, PROSEVA, a trial examining the utility of prone ventilation in moderate to severe ARDS, found a 50% relative risk reduction in 28-day all-cause mortality with prone ventilation [101]. Further investigation into ventilatory strategies using differing levels of positive-end expiratory pressure was unable to achieve clinically significant differences but re-inforced the desirability of keeping the end inspiratory plateau pressure below 30 mmHg [102]. Despite neuromuscular blockade initially suggesting a 9% absolute risk reduction in 90-day mortality for moderate to severe ARDS patients in a 2010 study, a 2019 re-evaluation of paralytics in moderate to severe ARDS found no mortality benefit when compared to usual care and was associated with an increased risk of ICU acquired weak-

ness [103, 104]. The Fluid and Catheter Treatment Trial compared a liberal versus a conservative fluid management strategy in ARDS as well as methodology for monitoring fluid management, and the investigators found that a conservative strategy of fluid management improved lung function and shortened the duration of mechanical ventilation [105]. Additionally, investigation into the optimal management of analgesia and sedation, liberation strategies from mechanical ventilation, nutritional management, the prevention of hospital acquired conditions (catheter related blood stream infections, ventilator associated pneumonia, pressure ulcers, venous thromboembolic disease, etc.), and restrictive transfusion strategies have all contributed to the improvements seen in the management of the critically ill patient including those with ARDS. Hence, the 28-day mortality has declined from 35% to 40% to approximately 20–25% [99].

Miscellaneous Causes

Etiologies

Human Immunodeficiency Virus (HIV)

Infection with HIV predisposes patients not only to its all too well-known infectious complications but also a broad array of non-infectious pulmonary complications such as Kaposi sarcoma, interstitial lung disease (non-specific interstitial pneumonitis, lymphocytic interstitial pneumonitis, organizing pneumonia), pulmonary hypertension, and alveolar hemorrhage. Vincent and colleagues prospectively analyzed the BAL results of a cohort of HIV-infected patients undergoing bronchoscopy as part of their evaluation for new respiratory symptoms and/or fever and found that approximately one-third of patients had evidence of DAH [106]. Independent risk factors for DAH in this study were (1) pulmonary Kaposi sarcoma, (2) hydrostatic pulmonary edema, (3) cytomegalovirus pneumonia, and (4) thrombocytopenia (platelets <60,000 cell/μL). However, the absolute degree of hemorrhage was relatively mild and did not appear to affect survival. Treatment is largely supportive care combined with treating reversible, underlying pulmonary processes (i.e., pneumonia or Kaposi).

Pulmonary Capillary Hemangiomatosis

Pulmonary capillary hemangiomatosis is an exceedingly rare entity characterized by diffuse proliferation of the pulmonary capillary network. Patients present with signs and symptoms of both alveolar hemorrhage (secondary to capillary rupture into the airspaces) and pulmonary hypertension (secondary to obstruction to flow at the capillary/post-capillary level) [107]. Given its rarity, no effective therapies other than lung transplantation have been identified. There is one case report of clinical improvement following treatment with interferon alpha-2a [108].

Treatment

When approaching a patient with hemoptysis, bilateral infiltrates with hypoxemia, or known lower respiratory tract bleeding, the differential diagnosis remains quite broad, and yet, the bedside clinician must support the patient's vital physiologic functions, and correctly diagnosis and reverse the disease process in an efficient and timely fashion. Moreover, the degree and severity of dyspnea, hypoxia, and/or respiratory distress can vary dramatically between patients from the asymptomatic to profound hypoxemic respiratory failure. Nevertheless, the initial steps of management revolve around supportive care and distinguishing between a focal source of hemorrhage, a non-hemorrhagic diagnosis, and DAH.

From a supportive care standpoint, oxygen therapy titrated to a saturation of arterial hemoglobulin ≥90% is recommended for all patients. Similarly, reversing any contributing coagulopathy is recommended unless firm contraindications or mitigating circumstances exist (i.e., antiphospholipid antibody syndrome with active or life-threatening thromboembolic disease). In those patients who are unable to protect their airway or who require ventilatory support, endotracheal intubation and initiation of mechanical ventilation are recommended. Still, to date, no randomized trials have been performed to determine the most effective mode of mechanical ventilation in DAH. Extrapolating from the extensive data informing the ARDS literature, most experts would recommend a lung-protective, low tidal volume strategy (tidal volumes of 6 mL/kg ideal body weight), goal plateau pressures less than 30 cm H_2O, and potentially, prone ventilation in patients with more severe disease. Given the clinical similarities between DAH complicated by respiratory failure and ARDS, it is reasonable to extrapolate this data to the care of the patient with DAH.

Similarly, volume resuscitation is recommended for patients with clinical evidence of hypovolemia or shock. Following definitive reversal of the hypoperfused state, adopting a conservative fluid strategy, again based on data from the ARDS literature, would also be advisable. For those patients with clinically significant anemia, transfusion may be necessary, but there are no data to specifically inform transfusion thresholds in DAH. Recent data in more general populations of critically ill patients have found that blood transfusions increase the risk of adverse outcomes, particularly in younger and less severely ill patients, and many critical care units will now uniformly deploy restrictive transfusion strategies that transfuse to a goal hemoglobin of no higher than 7.0–9.0 g/dL [109]. Mitigating against this would be the rate of active bleeding and whether or not the hemorrhage is controlled at the time of decision-making.

As outlined earlier, the diagnosis of DAH rests upon bronchoscopy and bronchoalveolar lavage demonstrating an absence of clearing, or paradoxical worsening of hemorrhage during serial lavage. Competing considerations that

may be identified on bronchoscopy include focal hemorrhage (malignancy, arterio-venous malformation, bronchiectasis, necrotizing pneumonia, pulmonary embolus, tuberculosis/Rasmussen aneurysms, etc.), aspirated blood (gastrointestinal or upper airway bleeding), or non-hemorrhagic disease (ARDS, pneumonia, pulmonary edema, etc.). Once a diagnosis of DAH has been established, further distinguishing between capillaritis and non-capillaritis lesions determines whether or not additional targeted therapies may provide benefit. Generally, the specific underlying etiology is not known even when a diagnosis of DAH is established, but rapid intervention may be required depending upon disease severity. Given the significant mortality associated with immune-mediated DAH, the importance of the prompt initiation of disease-modifying therapy cannot be overemphasized. Picard et al. created a scoring system utilizing data present at admission that was highly predictive of pulmonary capillaritis, as opposed to bland hemorrhage or DAD. This scoring system was developed by doing a multivariate analysis of 76 consecutive, symptomatic DAH cases. Four variables were identified as predictive factors of immune-mediated DAH including (1) more than 11 days since respiratory symptom onset, (2) arthralgias, (3) fatigue and/or weight loss, and (4) proteinuria > 1 g/L (Table 9.4) [110]. Validation from an external cohort demonstrated that a score ≥4 yielded a sensitivity of 100%, specificity 88%, positive predictive value 75%, and a negative predictive value of 100% [111]. Although this scale may suggest pulmonary capillaritis, the authors recommend refraining from initiating cytotoxic agents (i.e., cyclophosphamide) or plasma exchange based off of this scale alone.

For patients with suspected pulmonary capillaritis, in whom a diagnosis of GPA, MPA, SLE, or ABMA disease is seriously entertained and who demonstrate respiratory distress, respiratory failure requiring mechanical ventilation and/or demonstrate a clinically significant pulmonary-renal syndrome of DAH and glomerulonephritis, initiating therapy with IV corticosteroids and a cytotoxic or biologic agent should be performed in a timely fashion. Given the known efficacy of plasmapheresis in ABMA disease and potential benefit in SLE, plasmapheresis should be initiated until either the former two entities are ruled out or a confident diagnosis of AAV is made. Although plasmapheresis demonstrated no benefit in AAV, PEXIVAS did not find any statistically significant difference in adverse events with plasma exchange. The data informing these treatment recommendations are derived primarily from the AAV and ABMA disease literature and have been discussed earlier. The optimal timing of the introduction of the cyclophosphamide, rituximab, or other disease-modifying agent in the critical care setting, especially in patients with concomitant infection and/or requiring mechanical ventilation remains subject to debate. With the results of PEXIVS, a reduced steroid dosing strategy seems to be non-inferior in severe AAV and may help mitigate against infectious complications from aggressive immunosuppression. Whether this strategy of corticosteroid dosing is beneficial for other forms of pulmonary capillaritis is unclear at this time. For patients with lesser degrees of disease severity, not requiring mechanical ventilation and without end-organ impairment, clinicians may elect to treat with corticosteroids alone pending the results of the definitive evaluation (which in turn may then drive additional treatment decisions such as the introduction of a cytotoxic or biologic agent). However, these cases can often evolve rapidly, and close, serial observation is required. If patients demonstrate clinical deterioration, then therapy may need to be escalated.

As was discussed earlier, two randomized control trials were performed in generalized, active and severe AAV comparing cyclophosphamide to rituximab for the induction of remission, and based upon the finding of non-inferiority, rituximab may now be considered an alternative first-line agent for the management of AAV [30, 112]. Furthermore, specifically with the RAVE study, rituximab was found to be as effective as cyclophosphamide in patients with alveolar hemorrhage and more efficacious than cyclophosphamide-based regimens for inducing remission of relapsing disease and PR3 positive patients [30, 33]. Thus, one may consider substituting rituximab for cyclophosphamide in patients with AAV and alveolar hemorrhage. However, recognizing that rituximab is a monoclonal antibody, the timing of its administration relative to any use of plasmapheresis must be carefully considered, and in point of fact, most experts would recommend beginning administration after completion of any plasma exchange (or limiting its use to those patients who do not require plasma exchange).

Additional therapies that have been considered in these severe cases of DAH include activated human factor VII and extracorporeal membrane oxygenation (ECMO). Exogenous activated factor VII has been used on a compassionate use basis and reported at the case report level to aid in hemostasis of cases of refractory DAH. ECMO is an advanced form of ventilatory and circulatory support and is used as a salvage therapy for refractory hypoxemia or cardiac failure.

Table 9.4 Predicting immune capillaritis in DAH

Variables	Points
≥11 days since respiratory symptom onset	+2
Fatigue and/or weight loss[a]	+2
Arthralgias/Arthritis	+3
Proteinuria ≥1 g/L	+3

A score ≥4 had sensitivity of 100%, specificity 88%, and a positive predictive value of 75% for diagnosing immune mediated causes of DAH [110, 111]

[a] Includes fatigue that is incapacitating and weight loss of at least 5% for at least 1 month prior to admission

An ECMO circuit consists of a cannula withdrawing blood from a vein, a pump, a membrane oxygenator, and a catheter returning blood either to a central vein (venovenous ECMO) or a central artery (venoarterial ECMO) [113]. Venovenous ECMO (VV ECMO) has been used most frequently in the management of severe ARDS. However, recent trials have shown no mortality benefit with the use of VV ECMO [114]. ECMO requires systemic anti-coagulation to maintain circuit patency and prevent thrombosis. Improved biocompatible circuits have led to a reduction in complications from ECMO usage. In non-bleeding patients, Extracorporeal Life Support Organization (ELSO) guidelines recommend anti-coagulation with heparin titrated to an activated clotting time (ACT) of 180–220 s [115]. In bleeding patients, the ACT goal may be reduced to 180 s [116]. Previously, alveolar hemorrhage was perceived to be a strong relative contraindication to the use of ECMO for fear of exacerbating underlying hemorrhage.

Given the rarity of DAH, the evidence for the use of ECMO in this condition is limited to case series. A review of 21 cases found AAV to be the most common cause for ECMO use in DAH accounting for 48% of cases [113]. Anti-coagulation use was documented in 82% of patients who were on ECMO. Survival to discharge was documented at a surprising 90% [113]. The reported survival with ECMO as salvage therapy for DAH is likely to be related to publication bias as these cases represent the potential discovery of a novel intervention for a life-threatening disease. Prospective randomized control trials are needed to fully ascertain the benefit of the ECMO in refractory cases of DAH.

Conclusions

DAH is a complex and life-threatening clinical-pathologic syndrome associated with a broad differential diagnosis and a number of distinct histopathologic patterns. Accurate and timely diagnosis of DAH and its specific underlying cause permit the bedside clinician to effectively treat the majority of patients such that a detailed knowledge of its diagnosis and management is critical for the Pulmonary/Critical Care physician.

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Pulmonary Involvement in Takayasu Arteritis and Behçet Disease

10

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The term vasculitis encompasses a heterogeneous group of rare disorders, each of which is characterized clinically by the type and location of affected blood vessels, and pathologically by the nature of the cellular infiltrate [1]. Vasculitic involvement of pulmonary blood vessels may be secondary to infectious diseases, connective tissue diseases, malignancies, and hypersensitivity disorders or can be seen as a feature of primary small-vessel antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitides (Granulomatosis with polyangiitis [Wegener's], microscopic polyangiitis, Eosinophilic granulomatosis with polyangiitis [Churg-Strauss]) and idiopathic large-vessel vasculitides (Takayasu arteritis, Giant Cell Arteritis) [2]. Behçet disease should be considered within the latter group because it may also involve the aorta as well as the pulmonary arteries. In this review, we will focus on the epidemiology, diagnosis, and therapeutic management of two of these diseases with characteristic pulmonary artery findings: Takayasu's arteritis (TA) and Behçet disease (BD).

Takayasu Arteritis

Takayasu's arteritis is a rare chronic large-vessel granulomatous vasculitis of unknown etiology predominantly affecting the aorta, its major division branches, and the pulmonary arteries [3]. Classification criteria for adults [4] have been derived in 1990 (Table 10.1), and a set of criteria for childhood TA have been recently published [5].

Table 10.1 The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis

1. Age at disease onset <40 years
Development of symptoms or findings related to Takayasu arteritis at age <40 years
2. Claudication of extremities
Development and worsening of fatigue and discomfort in muscles of 1 or more extremity while in use, especially the upper extremities
3. Decreased brachial artery pulse
Decreased pulsation of 1 or both brachial arteries
4. BP difference >10 mmHg
Difference of >10 mmHg in systolic blood pressure between arms
5. Bruit over subclavian arteries or aorta
Bruit audible on auscultation over 1 or both subclavian arteries or abdominal aorta
6. Arteriogram abnormality
Arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or low extremities, not due to arteriosclerosis, fibromuscular dysplasia, or similar causes; changes usually focal or segmental
For purposes of classification, a patient shall be said to have Takayasu arteritis if at least three of these six criteria are present. The presence of any three or more criteria yields a sensitivity of 90.5% and a specificity of 97.8%

BP blood pressure (systolic; difference between arms)

Epidemiology

Although TA has a worldwide distribution, the disease is thought to be more prevalent in Asian, Middle-East, and Central and South American countries than in North America [6–8] or Europe [3], with some differences in the characteristics of the disease among the various ethnic backgrounds [3, 7, 9, 10]. The greatest frequency of the disease is observed in Japan [11, 12]. Conversely, the incidence of the disease is as low as 0.3–2.6 cases per million per year in the USA, Sweden, Germany, and UK [3], suggesting that TA is one of

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the most infrequent forms of vasculitis. One of the typical epidemiological features of TA is the marked predominance of the disease in women, with a F/M sex ratio known to vary from 29/1 to 1.2/1 [3]. This very wide range may reflect either biases in case collection or differences between ethnic groups. Most TA patients have disease onset during the second or third decade of life. However, neither the occurrence of TA in patients over 50 years nor in children is uncommon [3, 13].

Pathologic Features

Because biopsy of involved vessels is not usually performed in TA, the diagnosis mostly relies on clinical features and vascular imaging. Pathologic findings in the pulmonary arteries have been poorly documented [14] and most available data originate from other arteries. Active inflammation in TA is typically indicated by the presence of mononuclear cells within the vascular wall, predominantly lymphocytes, and macrophages. These cells are mostly recruited in the media and adventitia through the vasa vasorum. Because TA is a granulomatous vasculitis, giant cells, and granulomas are commonly found in the media during active inflammation. Intimal proliferation contributes to the development of stenotic arterial lesions. At a more advanced stage, pathologic features include vascular wall fibrosis, while the destruction of the elastic lamina and the muscular media can lead to aneurismal dilation of the affected vessel. Retrospectively, dense scar tissue remains as an indication of prior vasculitis.

Pathogenesis

While our knowledge of the pathogenesis of TA has considerably improved during the last decade, the exact pathogenic sequence and natural history of vascular lesions remain unknown. By using cluster analysis we have recently shown that paired vascular beds usually clustered with their contralateral counterparts, while vascular lesions extended contiguously in the aorta [15]. Cell-mediated mechanisms are thought to be of primary importance in TA (Fig. 10.1). Therefore, it is currently hypothesized [15] that an unknown stimulus triggers the expression of the 65 kDa Heat-shock protein in the aortic tissue which, in turn, induces the Major Histocompatibility Class I Chain-Related A (MICA) on vascular cells. The γδ T cells and NK cells expressing the NKG2D receptors recognize MICA on vascular smooth muscle cells and release perforin, resulting in acute vascular inflammation. Pro-inflammatory cytokines and chemokines are therefore released and increase the recruitment of mononuclear cells within the vascular wall. Then, T cells infiltrate and recognize one or a few antigens that could be presented by a shared epitope, which is associated with specific major Histocompatibility Complex alleles on the dendritic cells, these latter being activated through their Toll-like receptors. Th1 lymphocytes drive the formation of giant cells through the production of interferon-γ, and activate macrophages with release of vascular endothelial growth factor (VEGF) resulting in increased revascularization and platelet derived growth factor (PDGF), resulting in smooth muscle migration and intimal proliferation. Th17 cells induced by the IL-23 microenvironment may also contribute to vascular lesions through activation of infiltrating neutrophils. Although being very controversial, dendritic cells may cooperate with B lymphocytes and trigger the production of anti-endothelial cell auto-antibodies resulting in complement-dependent cytotoxicity against endothelial cells.

Clinical Vignette

A 23-year-old female originating from Madagascar was referred for fatigue, hypertension, lower limb claudication, and long-standing low-grade fever. Clinical examination revealed diffuse vascular bruits over the carotid arteries, abdominal aorta and iliac arteries, blood pressure asymmetry over 10 mmHg and diminished popliteal, posterior tibial, and dorsalis pedis pulses. Laboratory examination revealed raised acute phase reactants (ESR: 60 mm/first hour, CRP: 5 mg/dL). Computed tomography angiography showed typically thickened thoracic and abdominal aortic wall with subocclusive stenoses of the iliac arteries. Echocardiography was normal. Extensive workup ruled out any ongoing infectious disease. Diagnosis of Takayasu's arteritis was made and she was treated with prednisone 1 mg/kg/day orally followed by slow tapering and tuberculosis prophylaxis (because she was originating from an area where tuberculosis is highly prevalent). Her condition markedly improved within 3 weeks and follow-up at 6 months revealed significant improvement of arterial lesions. Unfortunately, lower limb claudication reoccurred when corticosteroids were tapered down to 15 mg/day. Therefore, prednisone was increased back to 30 mg/kg/day and azathioprine 3 mg/kg/day was added. Corticosteroids were slowly tapered again and azathioprine eventually stopped. Three years later, she is totally asymptomatic under prednisone 5 mg/kg/day, which is our consolidation regimen.

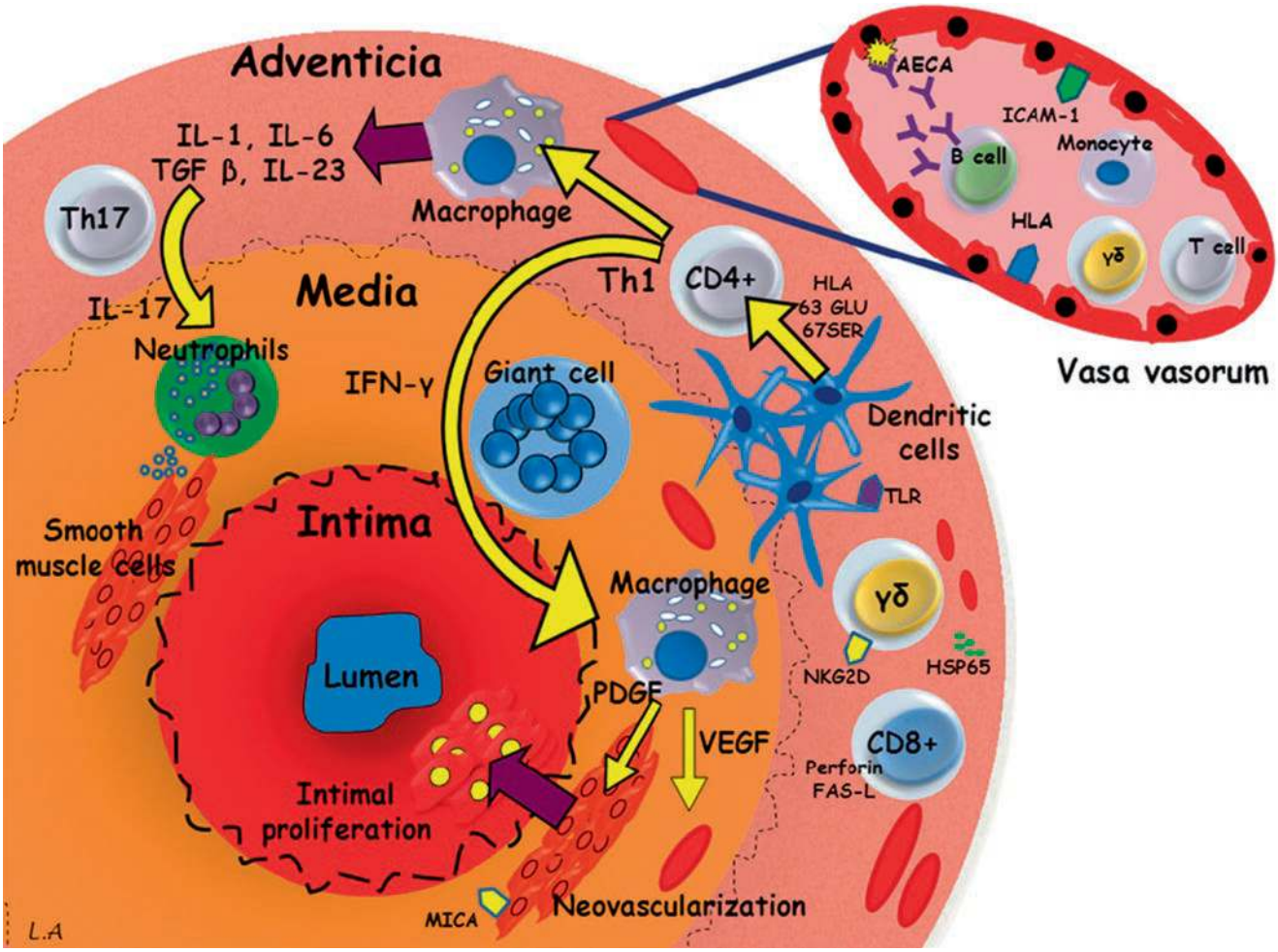

Fig. 10.1 Pathogenesis of Takayasu's arteritis. *AECA* anti-endothelial cell antibodies, *FAS-L* FAS ligand, *HLA* human leukocyte antigen, *HSP65* heat-shock protein 65, *ICAM-1* intercellular adhesion molecule 1, *IFN* interferon, *IL* interleukin, *TLR* toll-like receptors, *MICA* major histocompatibility complex class I-related chain A, *NKG2D* natural killer group 2, member D, *PDGF* platelet-derived growth factor, *TGF* transforming growth factor, *VEGF* vascular endothelial growth factor, *γδ* gamma-delta cell

Clinical Features

The clinical course of TA is classically thought to progress through three distinct stages: first, an early phase with prominent constitutional and systemic symptoms such as fatigue, weight loss, fever, and arthralgia; second a vascular phase occurring months or years later, with clinical manifestations of ischemia due to stenotic or occlusive lesions, or related to aneurysms; and third, a late phase (also called "burnt out phase") with fibrotic and fixed vascular abnormalities [6]. While more than 90% of patients have vascular signs or symptoms during the course of the disease, it is now well recognized that the systemic and vascular phases may overlap, and that a significant proportion of patients may never exhibit any constitutional symptom [3, 6].

The clinical presentation of TA is heterogeneous, and comprises many non-specific findings such as constitutional symptoms (fatigue, fever, and weight loss), musculoskeletal features (arthralgia, arthritis), cardiac and vascular features (vascular bruit, blood pressure asymmetry, claudication of extremities, carotodynia, hypertension, valvular involvement with aortic regurgitation, Raynaud's phenomenon, pericarditis), neurologic features (headache, visual disturbance, stroke or transient ischemic attacks, seizures), dermatologic manifestations (erythema nodosum, pyoderma gangrenosum).

Pulmonary artery involvement of TA is believed to occur in 15–65% of patients [11, 14, 16–22]. It may occasionally be the revealing [23, 24] or foreground feature of the disease [23, 25, 26]. Clinical signs of pulmonary involvement in TA are usually non-specific and therefore may lead to delayed diagnosis [3, 27]. These mostly include chest pain, cough, signs of pulmonary hypertension such as dyspnea, fatigue, angina, syncope [28–31], and hemoptysis [32, 33], with rare cases of pulmonary hemorrhage [34–36]. The exact frequency of pulmonary hypertension is unknown in TA, and is mostly due to pulmonary stenosis or left heart involvement

[37]. However, other causes, including pulmonary capillary hemangiomatosis have been occasionally reported [38]. In a study of 76 Mexican TA patients [39], 10 (13%) developed pulmonary hypertension using transthoracic echocardiography. Pulmonary artery hypertension was observed in 20% of patients with pulmonary artery involvement among patients with pulmonary artery involvement reported in a Chinese study published in 1994 [19]. Pulmonary hypertension in TA was statistically associated with disease activity in a Korean series of 204 patients [40], those with active disease (defined as patients having an elevated ESR or CRP level, thickened arterial wall with mural enhancement on CT or MR angiography, and carotidynia at the time of the initial diagnosis) had a higher incidence of pulmonary hypertension than those with inactive disease. In a Japanese study [41], a significant correlation was found between plasma endothelin-1 levels, which is involved in the pathogenesis of pulmonary hypertension, and erythrocyte sedimentation rates. Occasionally, clinical and radiographic features mimicking pulmonary embolism may be the first manifestation of Takayasu's arteritis [42–44], and pulmonary infarction may occur in this setting [45–47]. Rarely, coronary artery to pulmonary artery collaterals may develop and induce coronary steal and myocardial ischemia [48, 49].

Laboratory Findings

Dealing with TA patients is challenging because there is no sensitive or specific biologic markers for diagnosis and monitoring disease activity in TA [50]. It is well known that clinical assessment alone may underestimate disease activity [6, 51] and current disease activity criteria (Table 10.2) are nonvalidated [6]. Previous studies have shown that ESR and CRP did not correlate with clinical features in about 50% of cases [6, 7]. Interleukin-6, RANTES (Regulated upon Activation, Normal T Cell Expressed and Secreted), and Pentraxin-3 blood levels are believed to correlate with disease activity, but these markers are not widely available [52, 53].

Table 10.2 National Institute of Health Criteria for "active disease" in Takayasu's arteritis [41]

Systemic features, such as fever, musculoskeletal (no other cause identified)
Elevated erythrocyte sedimentation rate
Features of vascular ischemia or inflammation such as claudication, diminished or abolished pulse, bruit, vascular pain (carotodynia), asymmetric blood pressure in either upper or lower limbs (or both)
Typical angiographic features

New onset or worsening of two or more features indicates "active disease"

Imaging Studies

Because the clinical presentation and results of laboratory tests are typically nonspecific, accurate diagnosis of TA commonly depends on imaging studies. While conventional angiography has for long been the "gold standard," this imaging modality is now outdated, while computed tomography (CT) and magnetic resonance imaging (MRI) angiographies are increasingly used (Figs. 10.2, 10.3 and 10.4). These latter offer several advantages, including their noninvasiveness and their capability to demonstrate both mural and luminal changes in the pulmonary arteries, which is of major interest in TA because luminal changes may be delayed [22, 23, 54, 55]. Recently, pulmonary perfusion MRI has been shown to be a new alternative for the evaluation of pulmonary perfusion in TA [22, 56]. In a Japanese study [56], pulmonary MR perfusion images were acquired in 21 TA patients. The presence of perfusion abnormality was determined in both lobe-based (n = 126) and patient-based (n = 21) analyses. Sensitivity, specificity, positive predictive value (PPV), and negative predictive values (NPV) were calculated using perfusion scintigraphy as a standard reference. For lobe-based analysis, sensitivity was 91.7–95.8%, specificity was 92.2–93.7%, and PPV and NPV were 73.3–76.7% and 97.9–99.0%, respectively. For patient-based analyses, sensitivity was 100%, specificity was 72.7%, and PPV and NPV were 76.9% and 100%, respectively. Therefore MR perfusion imaging appeared to be a

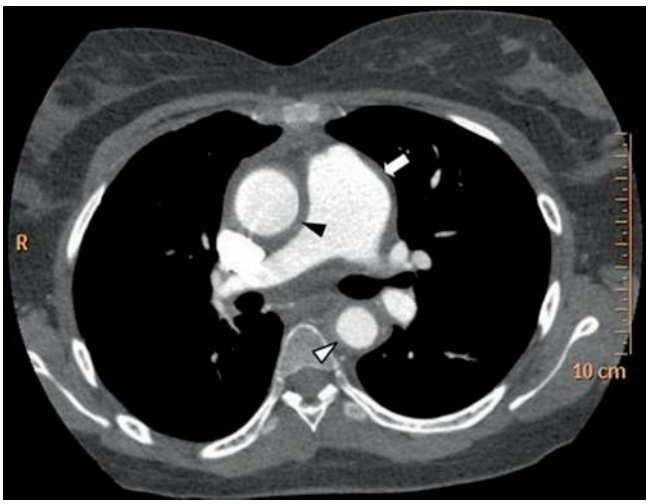

Fig. 10.2 Thoracic CT scan in Takayasu arteritis. Thoracic CT scan in mediastinal windows in an 18-year-old woman with TA showing dilatation of the ascending aorta and increased thickening of the ascending aorta wall (*black arrowhead*), of the thoracic descending aorta wall (*white arrowhead*) as well as thickening and dilatation of pulmonary trunk (*white arrow*)

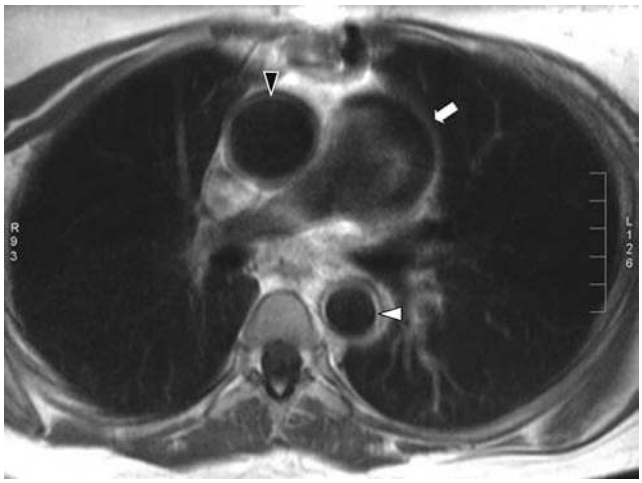

Fig. 10.3 Contrast-enhanced thoracic MRI in Takayasu arteritis. Contrast-enhanced T1-weighted black-blood thoracic MRI (axial view) in an 18-year-old woman with TA showing dilatation of the ascending aorta and increased thickening of the ascending aorta wall with ring-like contrast enhancement (*black arrowhead*), and increased thickening of the thoracic descending aorta wall with ring-like contrast enhancement (*white arrowhead*) as well as thickening and dilatation of pulmonary trunk (*white arrow*)

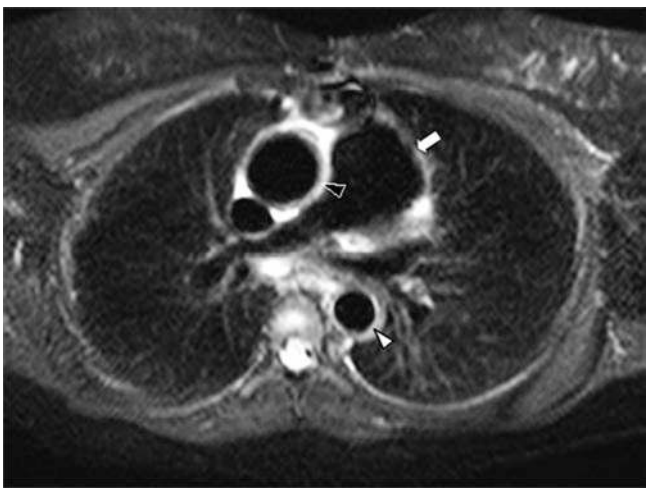

Fig. 10.4 STIR thoracic MRI in Takayasu arteritis. Short tau inversion recovery (STIR) thoracic MRI (axial view) in an 18-year-old woman with TA showing dilatation of the ascending aorta and increased thickening of the ascending aorta wall with hyperintense signal (*black arrowhead*), and increased thickening of the thoracic descending aorta wall with hyperintense signal (*white arrowhead*) as well as thickening and dilatation of pulmonary trunk (*white arrow*)

valuable, non-invasive method to estimate pulmonary artery involvement in TA patients. Pulmonary perfusion scintigraphy has been shown effective to detect presence of pulmonary artery involvement in TA [13, 17, 18, 20, 57] and correlates well with pulmonary angiography [58]. Another convenient way to assess vascular involvement in TA is peripheral vascular Doppler. Unfortunately, vascular Doppler is only suitable for following peripheral disease progression and not pulmonary involvement in TA. ^{18}F-Fluorodeoxyglucose-positron emission tomography (FDG-PET) scanning has been proposed as a new way of assessing disease activity in TA, but its role in the diagnostic and follow-up strategy remains controversial [59].

The most characteristic imaging findings of pulmonary involvement in TA include wall thickening and enhancement in early phases, stenotic or occlusive changes during the vascular phase, and fibrotic and/or calcified stenosis or occlusion in the chronic phase. These lesions mainly involve the segmental and subsegmental arteries, and less commonly the lobar or main pulmonary arteries [60–62]. Unilateral occlusion of a pulmonary artery can occur in advanced cases. Therefore, late-phase TA should always be considered in cases of chronic pulmonary artery obstruction of unknown origin [60]. Occasionally, TA may mimic unilateral pulmonary artery agenesis in children [63]. While being frequent in the aorta and its main branches, vascular dilatation and aneurysms in the pulmonary arteries are uncommon findings among TA patients [14, 16, 19, 21]. In a Chinese study performed in 1994 [19], pulmonary artery involvement was assessed by conventional digital subtraction angiography arteriography in 45 (33.8%) of 133 patients. Stenosis and/or occlusion of segmental and/or lobar pulmonary arteries, and subsegmental branches, were the basic angiographic findings. Pulmonary artery branches in the upper lobes were more commonly affected than those in the lower and middle lobes. Bilateral lesions were more common than unilateral ones. Single lobar and segmental lesions were rare. No main pulmonary artery involvement was detected. In a Japanese study published in 1992 [14], 21 of 30 patients (70%) had pulmonary artery involvement at pulmonary arteriography. Abnormalities were most common in upper lobe pulmonary arterial branches and segmental branches, followed by subsegmental branches. Systemic artery-pulmonary artery communications were seen in six patients (20%). While regional hypoperfusion due to pulmonary arteritis may occasionally be seen on lung CT-scan [64], involvement of the lung parenchyma is atypical in TA, and alternative diagnoses should also be considered [65–67].

Therapeutic Management

Corticosteroids are usually considered the mainstay of medical treatment in active TA with early phase or vascular phase manifestations [68, 69]. However, approximately 40–50% of patients require additional immunosuppressive agents to achieve and maintain remission [3, 7, 70]. Corticosteroids and other immunosuppressive agents have been shown effective to treat pulmonary involvement of TA, as these regimen may reverse pulmonary artery stenosis [28, 71]. Azathioprine [72], methotrexate [73], mycophenolate mofetil [74, 75], cyclo-

phosphamide [76], and anti-TNFα agents [20, 77, 78] have all been recognized effective in open-label trials but no randomized controlled trial data are available. Therefore, the therapeutic choice should be mainly guided by the individual benefit–risk ratio. There is no specific recommendations for the treatment of TA-associated pulmonary hypertension, therefore the latter should be treated according to the current standard of care, while it may occasionally be intractable [29].

Treatment with corticosteroids and immunosuppressive agents is not mandatory during the late phase, as only limited improvement, if any, can be achieved for fibrotic and fixed vascular abnormalities. However, both angioplasty and stenting [28, 79, 80] or vascular bypass [31, 81] may be necessary in TA patients when symptomatic and/or hemodynamically significant stenoses, including pulmonary arterial stenoses, have occurred. Pulmonary artery bypass has been shown effective for in-stent stenosis following angioplasty for isolated pulmonary TA [82]. Bronchial artery embolization may be considered in case of intractable hemoptysis [83].

Prognosis

The early, intermediate, and long-term outcome of angioplasty and vascular bypass procedures in TA is generally considered satisfactory [51, 71, 82, 84–95], even for treatment of pulmonary artery involvement where available experience is more limited [80].

Comparison of survival between TA series is likely biased because different enrollment criteria and care strategies have been used. In most series from developed countries, the 5-year and 10-year survival rates are of ≈95% and ≈90%, respectively [3, 6–8, 96–98]. Park et al. [96] underlined that major prognostic factors in TA were presence of valvular heart disease, cerebrovascular accidents, congestive heart failure, ischemic heart disease, retinopathy, and renovascular hypertension [96]. However, the exact prognostic value of pulmonary involvement in TA remains currently unknown.

Behçet's Disease

Behçet's disease (BD) is a multisystem and chronic disease of unknown etiology characterized by relapsing manifestations, including oral and genital ulcers, uveitis, and vasculitis, cutaneous, articular and central nervous system involvement.

BD's vasculitis is particularly distinctive because both veins and arteries can be affected, mainly in the form of arterial aneurysms and of venous or arterial thrombosis. Pulmonary involvement in BD can almost be summarized as pulmonary artery aneurysm and pulmonary thrombosis. Parenchymal manifestations are less documented and can be either isolated or associated with pulmonary arterial involvement, therefore being a direct consequence of parenchymal ischemia.

Epidemiology

BD occurs worldwide but is most prevalent in the countries of the ancient Silk Road, especially in Turkey with 20–240 cases per 100,000 [99]. Prevalence ranges from 13.5 to 22 cases per 100,000 in Middle East and Asian countries. It is less frequent in Western countries, preferentially affecting migrants from endemic countries with a prevalence ranging from 0.12 to 0.64 per 100,000 [99].

The disease typically affects young adults from 20 to 50 years. BD is as frequent in male as in female but more severe in the former, with increased mortality, and more frequent ocular, major vessel or neurologic involvement [100].

Pathologic Features

Characteristic histopathological features of BD are vasculitis and perivascular inflammatory infiltrates of neutrophils and T-cells [101]. Vasculitis can involve both veins and arteries of all sizes [102]. Studies of pulmonary artery aneurysms reveal perivascular infiltrates and small-vessel vasculitis in the vasa vasorum [103], marked intimal thickening with disruption of the elastic lamina, degeneration of the tunica media, and thrombotic occlusion with recanalization [104].

Pathogenesis

While the pathogenesis of BD remains largely unknown, the disease is thought to be at the frontline between autoimmune and auto-inflammatory diseases [105]. Like many chronic inflammatory diseases, BD is believed to be the consequence of interplay between genetic susceptibility and environmental factors (mainly bacterial infections) [106]. There is a close association between HLA-B51/B5 and BD, suggesting a pivotal role of these alleles in the pathogenesis of the disease [107]. Many infectious agents have been implicated in the pathogenesis of BD [99], with Herpes simplex virus and *Streptococcus sanguis* being most consistent candidates. Both are mainly found in oral mucosa and thus could explain the prominent feature of oral ulcers [108]. However, none of these microorganisms has proven to be the causative agent of BD and it has been hypothesized that many antigens, including bacteria heat-shock proteins, could trigger immune cross-reactive responses [109].

Main pathogenic features of BD are vasculitis, neutrophils hyperactivity and aberrant immunological responses [99]. Perivasculitis is found in BD lesions, including oral and genital ulcers, posterior uveitis and neurologic lesions [110]. Tissue injury seems to be the result of neutrophils infiltration and overproduction of superoxide and lysosomal enzymes [111]. High levels of pro-inflammatory cytokines (TNF, IL-1β, IL-8) have been measured in patients' serum and could explain enhanced chemotaxis [99]. The recruitment of neutrophils within affected tissues could be under control of IL-17 producing T-cells [112, 113]. Pivotal role of gamma-delta T cells have also been shown. Activation of this innate population of T cells by microbial antigens could be the missing link between infectious agents and overreacting neutrophils [114].

Diagnostic Criteria

BD should be considered a diagnosis of exclusion, without any available pathognomonic diagnostic test. International diagnostic criteria were adopted in 1990 (International Study Group, ISG criteria, Table 10.3) [115]. In addition to oral ulcerations, which are a prerequisite, diagnosis of BD requires two of the following features: genital ulcerations, eye lesions, positive pathergy test or skin lesions (folliculitis or erythema nodosum). Pathergy test is not commonly used in Western countries because of its frequent negativity [116]. Altogether, these criteria are questionable as they sometimes fail to diagnose cases of BD without prominent mucocutaneous manifestations, for example, cases where foreground feature is vascular involvement [117].

Table 10.3 International diagnosis criteria of Behçet's disease, International Study Group for Behçet's Disease

Recurrent oral ulceration	Minor aphthous, major aphthous, or herpetiform ulceration observed by physician or patient, which recurred at least 3 times in one 12-month period
Plus 2 of the following, in absence of other clinical explication	
Recurrent genital ulceration	Aphthous ulceration or scarring, observed by physician or patient
Eye lesions	Anterior uveitis or posterior uveitis, or cells in vitreous on slit lamp examination or retinal vasculitis observed by ophthalmologist
Skin lesions	Erythema nodosum observed by physician or patient, pseudofolliculitis or papulopustular lesions or acneiform nodules observed by physician in postadolescent patients not on corticosteroid treatment
Positive pathergy test	Read by physician at 24–48 h

Clinical Features

In the absence of any pathognomonic laboratory test, diagnosis of BD is strictly clinical and requires careful bedside evaluation [99]. In case of inaugural pulmonary manifestations, the diagnosis mostly relies on extra-pulmonary features, as the former are mostly non-specific. It is therefore important to look for a history of recurrent oral and genital ulcers, episodes of eye inflammation or visual loss, and past history of venous or arterial thrombosis. Genital scares are the hallmark of previous BD's flares and must be carefully searched for. Skin examination must look for erythema nodosum and pseudo-folliculitis. Although pathergy test is not often performed in Western countries, hypersensitivity at puncture point can be found in the form of a small pustule. Eye examination is mandatory. Previous uveitis flares can present as anterior synechia. Moreover, retinal vasculitis can be asymptomatic but threatens the visual prognosis.

Prevalence of pulmonary involvement in BD seems to range from 1% to 18% [118]. It mostly affects young males like other severe manifestations of BD [119].

Although inconstant and poorly specific, hemoptysis is the most frequent revealing symptom of BD pulmonary involvement, and may be observed in up to 90% of patients with such involvement [120]. Massive hemoptysis (>500 cm^3) occurs in about 25–45% patients and may warrant surgical or instrumental rescue treatments [120]. Other common symptoms are less specific and include cough, fever, dyspnea, and pleural chest pain. Fever is of particular interest in BD because it has been shown to be associated with ongoing arterial involvement [102].

Pulmonary Artery Aneurysm

Pulmonary artery aneurysm (PAA) is a major and life-threatening complication of BD. It is well recognized as the most specific pulmonary complication of BD, the second most frequent site of arterial involvement and the leading cause of mortality in BD [120]. Like any other severe manifestation of BD (eye or neurological involvement), PAA is more frequent in male than female [119]. Prevalence of PAA in the course of BD is not known in the absence of prospective study but ranges from 0.5% to 1% in retrospective studies [119, 120].

Several Turkish studies [103, 118–121] have helped defining the clinical presentation, prognosis, and treatment of PAA. This complication can either occur at diagnosis or during the course of BD. PAA is more frequent than thrombosis of pulmonary artery in BD [120]. It may precede other

symptoms of BD, including oral ulcerations, and thus make positive diagnosis of BD difficult. In a cumulative study of PAA cases, almost 14% of patients did not fulfil ISG criteria [118]. When lacking mucocutaneous or eye lesions, BD is sometimes referred to as Hughes-Stovin syndrome, which associates PAA and deep venous thrombosis [122]. It is still debated whether Hughes-Stovin syndrome is an incomplete phenotype form of BD or a separate nosologic entity [123–125]. Indeed, pulmonary involvement is indistinguishable between the two entities [122].

Pulmonary Artery Thrombosis

Pulmonary artery thrombosis (PAT) is the second most frequent pulmonary manifestation of BD [120], and can be isolated or associated to PAA. Clinical presentation of PAT is not specific and therefore is indistinguishable from common pulmonary embolism or PAA as it includes cough, pleuritic chest pain, fever, and dyspnea. Hemoptysis can occur but is significantly less frequent [120] and has been reported to be less abundant [118] in PAT than in PAA.

The term PAT is more commonly used than pulmonary embolism in BD because pulmonary artery occlusion seems to be consecutive to in situ thrombosis rather to thromboembolic mechanisms [126, 127]. Nevertheless, PAT is frequently associated to deep venous thrombosis, and therefore the exact mechanism of pulmonary artery occlusion in BD is still debated [128]. It is important to note that in some patients PAT may transform into PAA, and therefore could occasionally be a forerunner of PAA [120].

Pulmonary Parenchymal Involvement

Parenchymal involvement in BD is commonly associated with pulmonary vascular lesions [120]. Only a few cases of patients with isolated parenchymal lesions have been reported. Clinical presentation of parenchymal involvement in BD is non-specific and includes cough, sputum, and chest pain. Differential diagnosis with infection is a major concern in immunocompromised patients [103].

Some authors believe that parenchymal lesions in BD could be small-vessel vasculitis [103], with pulmonary hemorrhage and infarction being the main pathological features [118]. Pathological evaluation of five peripheral lung nodules has recently been reported: in three the lesions comprised both necrosis and pulmonary infarction, in one it was necrotizing granulomatous inflammation, while organizing pneumonia was found in the remaining one [120]. Presence of organizing pneumonia in parenchymal lesions of BD has been reported elsewhere [129]. Thus, two pathogenic mechanisms may explain nodular opacities in BD: those with transient and corticosteroid-responsive nodules may correspond to organizing pneumonia, while slowly-changing nodules evolving to cavitations would be more suggestive of necrosis and infarction [120].

Laboratory Findings

Biological results are not helpful for positive diagnosis of BD and there is no pathognomonic test to date. Laboratory findings are non-specific and are frequently normal. Biological inflammatory syndrome could be suggestive of arterial involvement if infection is ruled out [102]. HLA typing is frequently mentioned but must not be used as diagnostic test as its sensitivity and specificity is low. Furthermore, it is still a matter of debate whether HLA-B51 positive patients have a more severe course of the disease [130]. Therefore, association of HLA B51 to BD is mainly of epidemiological interest.

Imaging Studies

Chest X-ray in BD patients with PAA is often abnormal, showing hilar enlargement and unilateral or bilateral round hilar opacities. Other features associated to PAA are peripheral consolidation consistent with lung infarction, infiltrations related to pulmonary hemorrhage and pleural effusion. Contrary to PAA, chest X-ray in PAT is mostly normal and if abnormal mostly shows only non-specific changes such as pleural effusion and consolidations.

Conventional or digital subtraction angiographies must be avoided in BD because these can enhance aneurysm formation at arterial puncture point [131]. Moreover, completely thrombosed aneurysms may not be apparent in angiography [132].

Spiral CT angiography is mandatory in case of pulmonary symptoms in BD [103, 120]. It is the best way to diagnose both pulmonary artery and parenchymal involvement. PAA and PAT are mostly found in the right lower lobar arteries, followed by the right and left main pulmonary arteries [118, 120, 133]. PAA are saccular or fusiform and may be complicated with mural thrombosis, arteriobronchial fistula, compressive atelectasis or lung infarction [120, 133]. In the majority of cases pulmonary artery aneurysms are multiple, bilateral (57%) and filled with mural thrombosis (85%) [120]. PAA and PAT are frequently associated with various parenchymal lesions: peripheral nodules (85% of patients), cavitary lesions (47%), ground-glass opacities (45%), and pleural effusion or thickening (45%) [120]. Those parenchymal lesions can also be isolated in which cases infection should be considered a major differential diagnosis. Infiltration (nodular or reticulo-nodular) and

wedge-shaped, linear or rounded opacities are the most frequent radiologic abnormalities [118]. These lesions are frequently interpreted as pulmonary infarction, hemorrhage or small-size vasculitis but anatomoclinical correlations are often lacking [121].

Defects on ventilation/perfusion lung scans must be interpreted with caution in BD [118, 119], as they are not the hallmark of pulmonary thrombosis and can be seen in PAA. If anticoagulation is prescribed, pre-therapeutic CT-scan is mandatory to exclude small PAA.

Diagnosis of arterial pulmonary involvement with thoracic magnetic resonance imaging (MRI) has been described in few cases [134–136] and therefore could be an alternative to CT scan for pulmonary vasculitis screening. However, it seems less efficient than thoracic CT scan for evaluation of lung parenchyma [103, 137].

PET scan has rarely been used as a diagnostic tool for vascular pulmonary involvement in BD [120, 138–140] and therefore could not be recommended until further evaluation.

Differential Diagnosis

PAA is closely associated to BD and only a few diagnoses must be ruled out. Differential diagnoses of BD's pulmonary involvement are summarized in Table 10.4. As mentioned before, it is still matter of debate whether Hughes-Stovin syndrome is an incomplete variant of BD or a distinct syndrome [123–125]. Hughes-Stovin syndrome sometimes evolves to full-blown BD.

Pulmonary involvement of Takayasu arteritis is mainly pulmonary thrombosis and stenosis and is therefore easily distinguishable from BD. Systemic infections such as tuberculosis, right-sided endocarditis or fungal infections can present with pulmonary aneurysm and those diseases should be carefully ruled out. The presence of extra-pulmonary symptoms makes distinction with post-traumatic, congenital or idiopathic pulmonary aneurysm easy.

Table 10.4 Differential diagnosis of pulmonary arterial aneurysm

Inflammatory chronic disease
Behçet's disease
Hughes-Stovin syndrome
Takayasu arteritis
Infectious disease
Tuberculosis (Rassmussen's aneurysm)
Syphilis
Mycotic aneurysm (right-sided endocarditis)
Aspergillosis
Congenital heart disease
Pulmonary hypertension
Post-traumatic

Therapeutic Management

Treatment of PAA

No randomized controlled trial for the treatment of PAA is available. However, expert recommendations [141] and retrospective studies [103, 118, 120, 121] advocate the use of high dose corticosteroids and monthly cyclophosphamide pulses. It is recommended to start with methylprednisolone 500–1000 mg pulses 3 days successively, followed by 1 mg/kg prednisone progressively tapered depending on clinical response. Monthly cyclophosphamide must be continued for at least 2 years and followed with azathioprine [141]. Ciclosporine A or tacrolimus have been used in only a few cases and therefore cannot be recommended. Anti-TNF alpha are probably a promising therapy [142, 143] and have effectively been used for other BD's manifestations [144]. It could be considered a valuable option in case of life-threatening or resistant PAA. Colchicine is widely used for other BD's manifestations and is often associated as adjuvant therapy. As mentioned above, immunosuppressive therapy is usually sufficient to induce sustainable and complete remission of PAA [120]. Instrumental treatment must be reserved to rescue situations [145–147]. Surgical treatment in BD is associated with high mortality [118, 148] and must be avoided in most cases. It exposes to a high risk of postoperative complications, prosthetic thrombosis, arteriobronchial fistula, and recurrent anastomotic aneurysms. Arterial embolization should be preferred in case of massive or life-threatening hemoptysis. It must also be considered in case of large aneurysms (>3 cm) that have been associated with fatal outcome [120]. In all cases immunosuppressive treatment must be associated. Anticoagulation should be avoided in all case, even if aneurysm is filled with mural thrombus. A study has shown that anticoagulation used in PAA is associated with high mortality [118]. Moreover, efficacy of anticoagulation on inflammatory and organized thrombi found in BD is questionable [118]. If anticoagulation is indicated, it should be suspended until disappearance of aneurysms, after immunosuppressive therapy.

Treatment of PAT

Prospective studies on the treatment of isolated PAT are lacking. As mentioned before, the mechanism of pulmonary occlusion in BD is rather inflammatory thrombosis than classic thromboembolism. For that reason it is postulated that treatment of PAT should rely on immunosuppressive treatments rather than on anticoagulants [141]. Moreover, one study suggests that immunosuppressive therapy but not anticoagulation is required to prevent recurrence of venous thrombosis in BD [149]. Another study states that immunosuppressive treatment but not anticoagulation is significantly associated with complete remission of arterial lesions in BD (including PAT and PAA) [102]. Immunosuppressive ther-

apy must therefore be the key treatment of PAT. It is difficult to recommend a specific immunosuppressive protocol but corticosteroids must be prescribed with cyclophosphamide pulses or azathioprine [141]. Azathioprine is the only immunosuppressive drug to be validated in a controlled-trial and therefore it should be preferred to other immunosuppressive drugs (MMF, methotrexate) [150]. If anticoagulation is prescribed, pre-therapeutic CT-scan is mandatory to exclude small PAA. One must remember that ventilation/perfusion lung scan is not efficient to diagnose PAT in BD [118].

Prognosis

Until the 1980s, 1-year mortality of patients diagnosed with PAA was as high as 50% [151] and survival rate at 5 years reaches 62% since 1992 versus 40% before that date [119]. This improvement in outcome is supposedly related to earlier recognition and treatment rather than to modification in treatment modalities. In the last study to date, 12 of 47 patients died (from massive hemoptysis in 7/12 patients), in a median interval of 4 years [120]. All others patients survived and aneurysms disappeared after immunosuppressive therapy. Four patients had recurrence of pulmonary aneurysms that disappeared after repeated immunosuppressive treatment. Only two patients had persistent small aneurysms. Aneurysm size >3 cm has been associated to poor outcome [120]. The course of PAT is not well known but seems to be as severe as PAA. Patients with isolated PAT must be carefully followed because some of them can develop associated PAA [120].

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Portopulmonary Hypertension and Hepatopulmonary Syndrome

11

Arun Jose, Shimul A. Shah, Chandrashekar J. Gandhi, Francis X. McCormack, and Jean M. Elwing

Introduction

Portopulmonary hypertension (PoPH) and hepatopulmonary syndrome (HPS) are two distinct, but related, pulmonary vascular diseases that occur exclusively in patients with underlying chronic liver disease (Tables 11.1 and 11.2). Although the mechanisms that drive disease pathogenesis are unclear, developments of PoPH and HPS both likely involve vasoactive mediators that are produced by or bypass metabolism by the diseased liver and result in inappropriate angiogenesis, inflammation, and remodeling in the pulmonary vasculature. Symptoms are nonspecific and difficult to separate from underlying chronic liver disease, but early identification of PoPH and HPS is of paramount importance as these conditions have significant prognostic implications and can substantially affect candidacy for and outcomes of liver transplantation (LT). LT is curative in some cases of PoPH, and for most cases of HPS, but the mechanistic basis of benefit remains to be determined. A high index of suspicion for PoPH and HPS is recommended when evaluating chronic liver disease patients with pulmonary symptoms (Fig. 11.1).

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Table 11.1 Comparison of the clinical presentation, epidemiology, molecular pathogenesis, diagnosis, and therapeutics of HPS and PoPH

	HPS	PoPH
Clinical features	Dyspnea, orthodeoxia, platypnea	Dyspnea, fatigue, weakness, syncope, orthopnea
Physical exam findings	Digital clubbing, cyanosis	Peripheral edema, ascites, pulsatile liver, tricuspid regurgitant murmur, split second heart sound, elevated jugular venous pulsation
Age at diagnosis	40–50	60
Prevalence in patients with liver disease	1–4%	1–6%
Prevalence in patients undergoing liver transplant evaluation	10–47%	5–8.5%
Molecular pathogenesis	ET-1, pulmonary nitric oxide, low BMP-9, low BMP-10, intestinal bacterial translocation into systemic circulation, genetic polymorphisms of endoglin, COL18A1, NOX4, RUNX1	ET-1, thromboxane B-1, low BMP-9, elevated endoglin, nitric oxide, IL-6, serotonin, prostaglandins, activated hepatic stellate cells
Portal hypertension	Usually Present	Always Present
High-resolution computed tomography findings	Nonspecific	Enlarged central PA, enlarged RV, interlobular septal thickening and reticulations
Echocardiographic testing findings	Late bubbles in LA	Dilated or thickened RV, tricuspid regurgitation, pericardial effusion
Characteristic laboratory testing findings	Low PaO_2 and elevated A-a gradient on arterial blood gas	Elevated BNP levels on serum testing
Impact of liver transplantation	Curative	Variable
Additional treatment modalities	Supplemental Oxygen	Pulmonary vasodilator therapy
Effect of pulmonary vasodilator therapy	Can increase shunting	Reduced PA pressures and RV stress, improved cardiac function and PVR, improvement in symptoms, and walk distance

ET-1 endothelin-1, *BMP-9* bone morphogenic protein 9, *BMP-10* bone morphogenic protein 10, *IL-6* interleukin-6, *PA* pulmonary artery, *RV* right ventricle, *LA* left atrium, *PVR* pulmonary vascular resistance, *A-a* alveolar-arterial gradient, *PaO_2* partial pressure of oxygen, *BNP* brain natriuretic peptide

Table 11.2 Classification criteria and definition of PoPH and HPS, as per the 2015 ERS/ESC Guidelines [1], revised at the 6th World Symposium on Pulmonary Hypertension [2], and the most recent American Association for the Study of Liver Diseases Guidelines [3], and International Liver Transplant Society Guidelines [4]

Portopulmonary hypertension (PoPH)
1. Portal Hypertension
(a) Hepatic venous pressure gradient ≥6 mmHg
OR
(b) Presence of clinical sequelae of portal hypertension (splenomegaly, thrombocytopenia, portosystemic shunts, esophageal varices, or portal vein abnormalities) in a patient with an underlying risk factor for portal hypertension (such as chronic liver cirrhosis)
2. Precapillary Pulmonary Hypertension on Right Heart Catheterization at rest
(a) Mean pulmonary arterial pressure >20 mmHg
(b) Pulmonary capillary wedge pressure ≤15 mmHg
(c) Pulmonary vascular resistance ≥3 Woods units (240 dynes/s/cm^{-5})
Hepatopulmonary syndrome (HPS)
1. Chronic liver disease (such as portal hypertension or chronic liver cirrhosis)
2. Arterial deoxygenation present on resting arterial blood gas analysis while breathing ambient air
(a) Alveolar-arterial oxygen gradient ≥15 mmHg (≥20 mmHg in those over age 65)
OR
(b) PaO_2 of <80 mmHg (<70 mmHg in those over age 65)
3. Intrapulmonary vascular dilation
(a) Late bubbles (after 3 cardiac cycles) appearing in the left atrium on contrast-enhanced TTE imaging

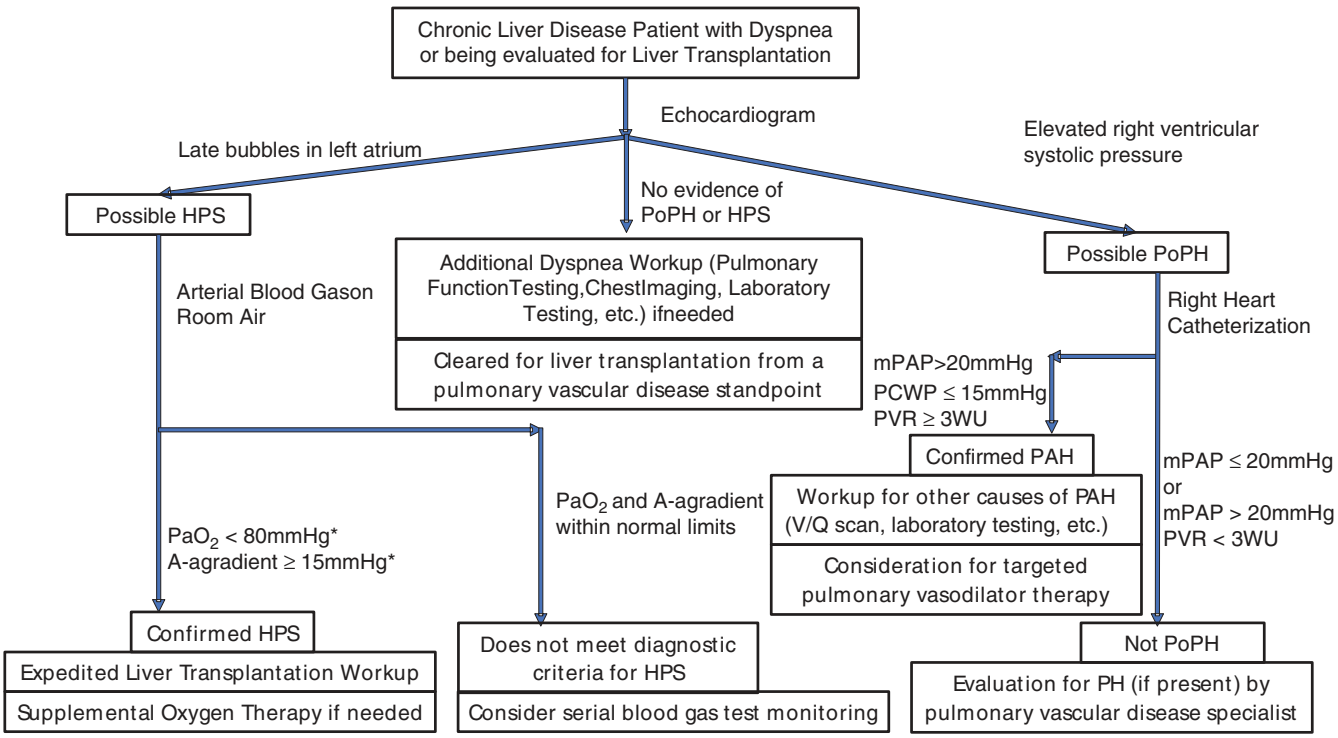

Fig. 11.1 Algorithm for the evaluation of the dyspneic chronic liver disease patient. *PH* pulmonary hypertension, *HPS* hepatopulmonary syndrome, *PoPH* portopulmonary hypertension, *A-a gradient* alveolar-arterial oxygen gradient, PaO_2 partial pressure of oxygen, *V/Q* ventilation-perfusion testing, *mPAP* mean pulmonary arterial pressure, *PCWP* pulmonary capillary wedge pressure, *PVR* pulmonary vascular resistance, *WU* woods units

Portopulmonary Hypertension (PoPH)

Epidemiology and Risk Factors

Portopulmonary hypertension is a pulmonary vascular complication of liver disease, defined by the presence of pulmonary arterial hypertension (PAH) in the setting of portal hypertension [5–7]. Although virtually all patients with liver cirrhosis also suffer from portal hypertension, it is important to note that portal hypertension can also rarely occur in the *absence* of liver cirrhosis, and that PoPH can occur in patients with non-cirrhotic portal hypertension [8]. Portal hypertension is identified either directly by catheter-based portal vein hemodynamic measurements, or inferred by the presence of splenomegaly, thrombocytopenia, portosystemic shunts, esophageal varices, or portal vein abnormalities [5–7]. PAH is best defined by right heart catheterization (RHC) hemodynamic measurement as a mean pulmonary arterial pressure of >20 mmHg at rest, with a pulmonary capillary wedge pressure ≤15 mmHg, and a pulmonary vascular resistance of at least 3 Woods Units (240 dynes/s/cm^{-5}) [1, 2]. Identifying PAH in a patient with portal hypertension, and excluding other causes of PAH (such as connective tissue disease or chronic thromboembolic disease) confirms the diagnosis of PoPH.

Estimates for the prevalence of PoPH vary widely, in part due to challenges in diagnosis and classification [5–7, 9–11]. Among all patients with portal hypertension and chronic liver disease, it is estimated that between 1% and 6% of patients carry a diagnosis of PoPH. In patients who undergo comprehensive diagnostic testing for liver transplant evaluation, the prevalence of PoPH ranges from 5% to 8.5% of patients. PoPH accounts for between 5% and 10% of all PAH diagnoses. From a large study of patients in the United Kingdom, the prevalence of PoPH was estimated at 0.85 per million persons [9]. The diagnosis is typically made in the fourth to fifth decade of life, and often 4–7 years after portal hypertension is diagnosed. Female sex and autoimmune hepatitis are known to be associated with the presence of PoPH, and hepatitis C patients are less likely to develop PoPH [9–13]. There is no known association between either the degree of portal hypertension or liver cirrhotic dysfunction and either the presence and severity of PoPH.

Molecular Pathogenesis

The molecular pathogenesis in PoPH is incompletely understood, but vasoactive mediators that affect the pulmonary vasculature are believed to play a central role (Fig. 11.2). Patients with PoPH demonstrate the same histopathological changes of pulmonary artery intimal fibrosis, smooth muscle medial hypertrophy, in-situ thrombosis, and plexiform lesions that are present in other patients with PAH (Fig. 11.3) [5–7]. Endothelin-1 (ET-1), a vasoactive peptide secreted by vascular endothelial and activated stellate cells, likely plays a central role in PoPH disease pathogenesis. ET-1 is a potent systemic and pulmonary vasoconstrictor that acts on hepatic stellate and endothelial cells to regulate blood flow, extracellular matrix turnover, and fibrosis in chronic liver disease. ET-1 is pleiotropic, and its binding to the ET-A receptor promotes vasoconstriction and smooth muscle cell proliferation, and to the ET-B receptor contributes to pulmonary vascular remodeling and endothelial-to-mesenchymal cell transformation in the pulmonary vasculature [5, 14, 15]. Significantly higher pulmonary arterial concentrations of ET-1 have been observed in PoPH as compared patients with liver cirrhosis without PoPH [5, 11, 16, 17]. Multiple other vasoactive factors, believed to promote disease pathogenesis in other forms of PAH, have also been implicated in PoPH pathogenesis. These candidate mediators, including interleukin-6, thromboxane B-1, serotonin, prostaglandins, and nitric oxide, are believed to interact with ET-1 to promote inflammation, angiogenesis, and pulmonary vascular remodeling [5, 11]. Macrophages are likely also key effectors in disease pathogenesis, and levels of macrophage migration inhibitory factor have been found to be significantly higher in cirrhotic patients with PoPH as compared to those without PoPH [18].

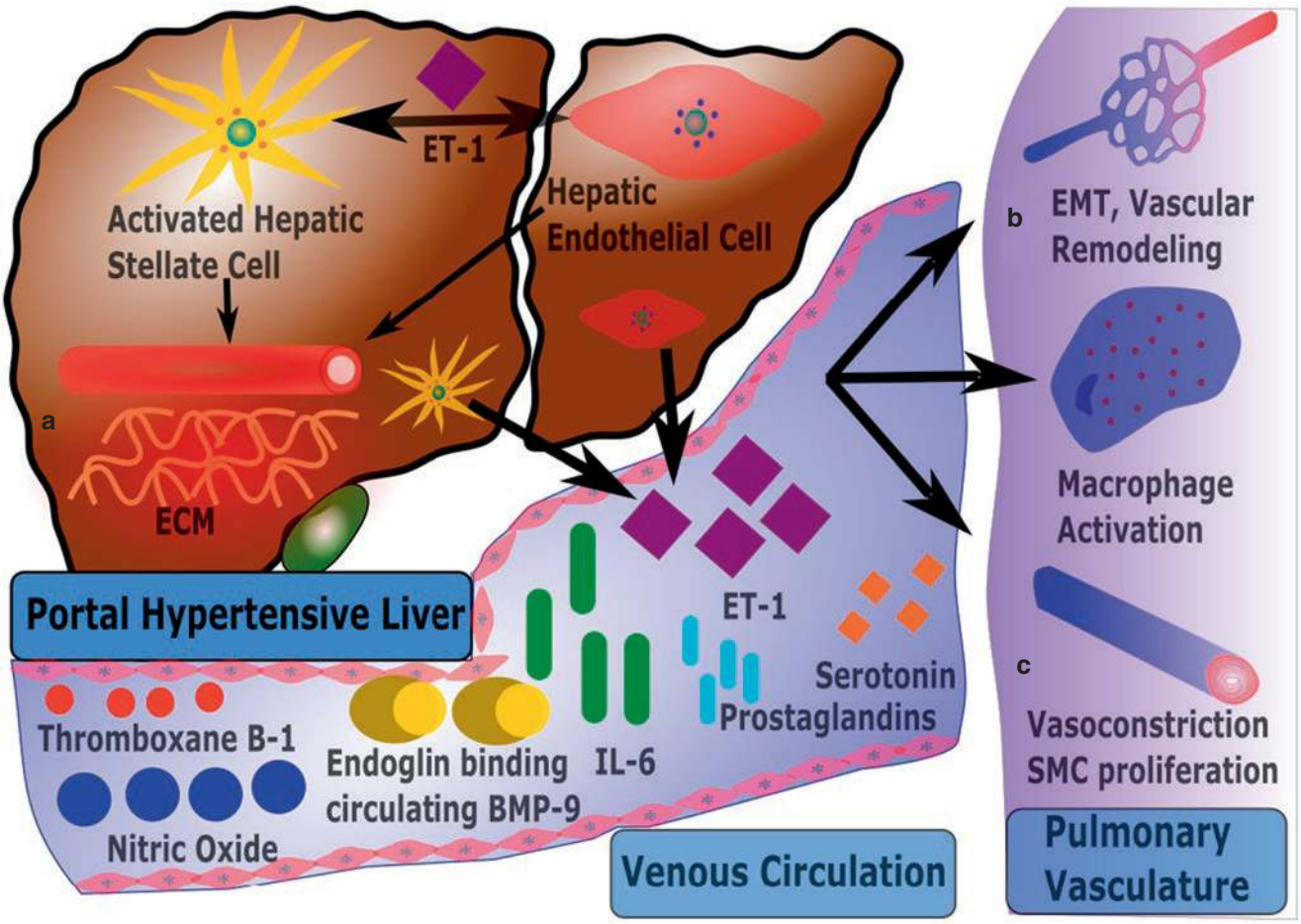

Fig. 11.2 Working Hypothesis for the Molecular Pathogenesis of PoPH. Endothelin-1 (ET-1) derived from hepatic endothelial and activated stellate cells induces these cells to alter regulation of hepatic blood flow, inflammation, and extracellular matrix (ECM) turnover (**a**). ET-1 is also released into systemic circulation, where it acts in concert with circulating thromboxane B-1, nitric oxide, interleukin-6 (IL-6), serotonin, prostaglandins, and in the presence of low BMP-9 levels (due to endoglin binding and sequestration), to activate pulmonary macrophages and promote endothelial-to-mesenchymal cell transition (EMT) (**b**), smooth muscle cell (SMC) proliferation (**c**), and pulmonary vascular remodeling characteristic of PoPH

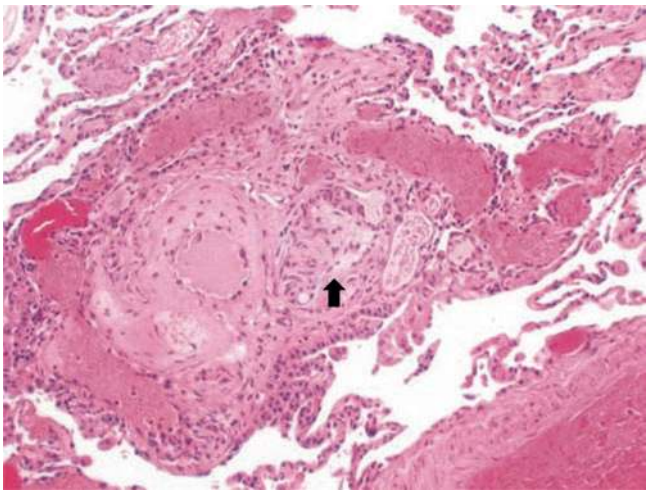

Fig. 11.3 Representative histopathology of lung explant from a 37-year-old woman with primary biliary cirrhosis who underwent heart–lung–liver transplant, showing pulmonary artery medial hypertrophy, intimal fibrosis, and plexiform lesions (Hematoxylin and Eosin stain, black arrow)

The bone morphogenic protein system has also recently been implicated in the pathogenesis of PoPH [19–22]. Bone morphogenic protein 9 (BMP-9), encoded by the growth differentiation factor 2 gene (GDF2), is a protein member of the transforming growth factor beta superfamily produced in the liver. BMP-9 levels were found to be significantly decreased in patients with PoPH as compared to patients with other forms of PAH, or those with non-PoPH liver cirrhosis. This difference persists even after adjustment for age, gender, and severity of liver disease as measured by the Model for End-Stage Liver Disease (MELD) score. Additionally, in a mouse carbon tetrachloride model of liver cirrhosis, while binding of BMP-9 to hepatic stellate cells induces hepatocyte proliferation and mesenchymal transition of hepatic stellate cells, blockade of BMP-9 instead promotes development of pulmonary vascular disease following exposure to hypoxemic conditions [19]. A large study of gene polymorphisms in PoPH and non-PoPH cirrhotic liver disease patients did not identify informative variants in GDF2, bone morphogenic protein type 2, or endoglin (the circulating ligand trap for BMP-9) in PoPH patients, however, highlighting the substantial remaining gaps in our understating of PoPH disease pathogenesis [23]. Recently, single-cell RNA-sequencing techniques have shed new light on the cellular transcriptomics that promote progression from fibrosis to cirrhosis in the liver and show promise in identifying the molecular mechanisms that underlie PoPH disease pathogenesis as well [24].

Screening and Diagnosis

Screening for PoPH is currently recommended for all patients undergoing LT evaluation (Fig. 11.1) [1, 3, 5–7, 11, 25, 26]. Clinical manifestations of PoPH are nonspecific and often difficult to distinguish from underlying portal hypertension and chronic liver disease. The most common symptom is dyspnea, but fatigue and weakness are also common. Physical examination will typically demonstrate the characteristic findings of portal hypertension including peripheral edema, abdominal ascites, a pulsatile liver, and the stigmata of cirrhosis (spider angiomas, scleral icterus, jaundice, and palmar erythema) (Fig. 11.4). In the advanced stages of PoPH, patients can present with signs and symptoms of right heart failure, including syncope, orthopnea, and a physical examination demonstrating an elevated jugular venous pulse, a prominent and split second heart sound, a tricuspid regurgitant murmur, and a palpable right ventricular heave. Electrocardiogram testing can show right-axis deviation, electrical evidence of right ventricular and right atrial enlargement, and occasionally a right bundle branch block pattern. Thoracic imaging (chest radiography and computed tomography) is nonspecific, occasionally demonstrating the presence of an enlarged right ventricle and a dilated central pulmonary artery suggestive of underlying pulmonary vascular disease. Pulmonary function testing will occasionally show a decreased diffusion capacity for carbon monoxide, but this is not diagnostic of PoPH. Serum levels of brain natriuretic peptide, the most widely used biomarker in PAH, are known to be elevated in portal hypertension and chronic liver disease, and are of limited value in screening patients with these conditions for underlying PoPH [27].

Resting transthoracic echocardiographic (TTE) imaging is the optimal screening tool for PoPH and is recommended in all patients undergoing evaluation for LT [3]. Elevations in the estimated right ventricular systolic pressure (RVSP) can identify patients at risk for PoPH who warrant further workup with diagnostic RHC testing. PoPH can rapidly develop in patients with underlying portal hypertension, and therefore, serial TTE screening is recommended for all liver transplant candidates, to avoid the morbidity and mortality associated with performing LT in a patient with undiagnosed PoPH. Although RVSP cutoffs vary across institutions, it is generally accepted that an RVSP lower limit on TTE of 30 mmHg is sufficient (>95% negative predictive value) to exclude clinically significant PoPH. This test value is tempered by a limited specificity (59–77%) for echocardiography in accurately identifying PoPH, as the correlation

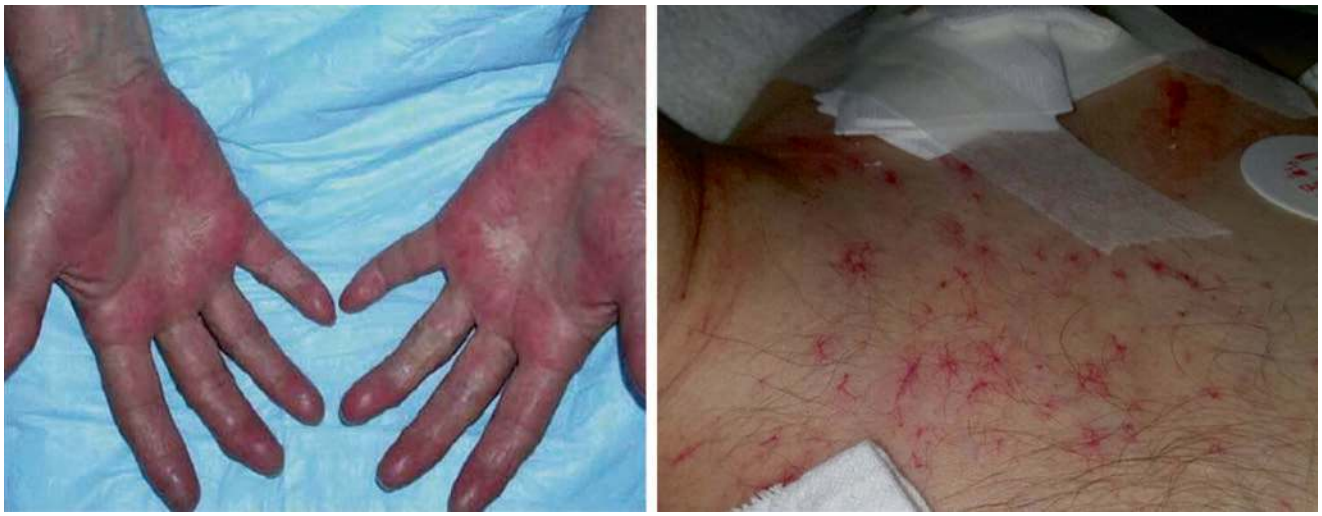

Fig. 11.4 Characteristic physical exam findings of chronic liver cirrhosis including palmar erythema and jaundice (**left panel**) and spider angiomas (**right panel**)

between RVSP on TTE and pulmonary arterial pressures on RHC is moderate at best (linear correlation strength ~0.46–0.78) [3, 28–30].

As with all forms of PAH, the diagnosis of PoPH requires invasive RHC hemodynamic measurements [1, 2, 5–7, 31]. Due to abnormal vascular morphology and alterations in compensatory mechanisms regulated by the estrogen axis and the renin–angiotensin–aldosterone system, the majority of patients with portal hypertension and liver cirrhosis will demonstrate a hyperdynamic circulation, with elevated pulmonary arterial pressures (and elevated RVSP measurements on TTE) as a consequence of an increase in cardiac output, but with normal pulmonary vascular resistance [32, 33]. Patients with PoPH, by contrast, will demonstrate elevations in pulmonary arterial pressure that are in excess of what can be accounted for on the basis of increased cardiac function, resulting in a markedly abnormal elevation in calculated pulmonary vascular resistance. The diagnosis of PAH requires a mean pulmonary arterial pressure >20 mmHg at rest, with a pulmonary capillary wedge pressure ≤15 mmHg, and a pulmonary vascular resistance of at least 3 Wood Units (240 dynes/s/cm^{-5}) [1, 2]. Of note, many chronic liver disease patients will have a pulmonary vascular resistance that does not meet this threshold but still display abnormally elevated pulmonary arterial pressures. It is unclear what the significance of abnormally elevated pulmonary arterial pressures is in this patient population, but increasing evidence suggests that these patients are prone to worse outcomes while awaiting transplantation and have increased mortality post-LT [5–7, 13, 31, 34].

PoPH Treatment

The treatment for PoPH can be divided into two categories: liver transplantation and medical therapy with targeted pulmonary vasodilators. Unfortunately, survival and outcomes in PoPH remain poor regardless of treatment [4–7, 9, 11, 13, 35–38]. A large retrospective study of PoPH patients from the United Kingdom estimated 1-year survival at 85%, and 5-year survival at 35%, even with medical therapy [9]. These estimates aligned with other reports of 1-year survivals between 86% and 91% but are significantly worse than the more commonly cited 67–70% 5-year survival in treated PoPH. Survival in PoPH, similar to other forms of PAH, is highly correlated with the degree of right ventricular failure, as measured by RHC cardiac output, cardiac index, and pulmonary vascular resistance. In PoPH, survival is also associated with the degree of liver disease, as measured by the MELD score. Although PoPH is not an indication for LT, given the high morbidity and mortality in this population, MELD exception points are granted for a diagnosis of PoPH, and LT is generally offered for PoPH patients who are able to achieve a reduction in mean pulmonary arterial pressure to ≤35 mmHg on RHC with a pulmonary vascular resistance of <3 Wood Units [3, 34]. As PoPH can progress rapidly, MELD exception points must be updated every 6 months with repeat RHC testing. Therapeutic reduction in pulmonary vascular pressures improves outcomes of LT. A retrospective single center study of PoPH patients undergoing liver transplantation indicated 100% mortality in those with mean pulmonary arterial pressure of >50 mmHg, and no mortality if mean pul-

monary arterial pressure was less than 35 mmHg, highlighting the importance of pulmonary hemodynamics in facilitating safe LT in these patients [39]. As a consequence of this study, PoPH with a mean pulmonary arterial pressure >45 mmHg is considered an absolute contraindication to LT at most centers.

Even when the above hemodynamic criteria are met, LT in PoPH is still considered high risk and is associated with a significant morbidity and mortality post-transplant. A review of the Multicenter Liver Transplant Database indicated that the post-transplant hospital mortality in PoPH patients undergoing LT was 36%, although these data preceded the modern era of targeted PAH treatment for PoPH, and more recent estimates [37] for post-LT survival in PoPH range from 77% to 91% at 1 year, and 67–80% at 5 years. It is generally accepted that the majority of PoPH patients who undergo LT will experience an improvement in the severity of their pulmonary vascular disease, and some are cured of PoPH post-transplant, but the factors that predict a favorable response to LT are still unknown [40–47]. Additionally, relapse of PoPH has been reported after an initially favorable outcome from LT, and therefore, serial TTE screening is recommended following transplantation [3–5, 11].

Medical therapy represents the other pillar of treatment for PoPH, which complements and facilitates LT. The cornerstone of medical therapy in PoPH mirrors that of other types of PAH and is centered on the use of targeted pulmonary vasodilator therapy to reduce pulmonary vascular resistance [48–60]. As PoPH patients are generally excluded from most PAH clinical trials, the limited efficacy data available in PoPH is primarily derived from case series and small cohort studies, with few randomized controlled studies to support use of these agents. The earliest studied agent for PoPH was epoprostenol, a synthetic analog of a naturally occurring prostacyclin, which has potent vasodilatory properties as well as anti-inflammatory and anti-platelet effects. Data for the use of epoprostenol comes from case series and retrospective cohort data, in which administration of epoprostenol was shown to result in significant improvements in pulmonary vascular hemodynamics (mean pulmonary arterial pressure, cardiac output, cardiac index, and pulmonary vascular resistance), and facilitated successful LT in some patients [54, 58–60]. Given the significant benefits of epoprostenol in other forms of PAH, and the fact that epoprostenol remains the only therapeutic agent to demonstrate a mortality benefit in PAH, it is accepted that intravenous epoprostenol is the preferred therapeutic for PoPH [61, 62].

Oral pulmonary vasodilator medications have also demonstrated clinical benefit in PoPH and remain an important part of the medical armamentarium to treat this condition. Oral phosphodiesterase 5 inhibitor medications, sildenafil and tadalafil, have demonstrated benefit in case series and cohort studies of PoPH [52–57]. Sildenafil monotherapy results in improvements in walk distance, functional capacity, circulating natriuretic peptide levels, pulmonary vascular hemodynamics (mean pulmonary arterial pressure, pulmonary vascular resistance, and cardiac output), and has facilitated successful LT in PoPH patients. A newer class of medications, soluble guanylate cyclase stimulators (riociguat), has also shown efficacy in improving pulmonary vascular hemodynamics and functional capacity in PoPH [51]. Given the potential role of ET-1 in driving PoPH disease pathogenesis, endothelin receptor antagonist medications (ambrisentan, macitentan) have been carefully studied for efficacy in PoPH. Notably, endothelin receptor antagonists are the only medications to show benefit in PoPH in a randomized controlled trial setting and have been successfully used either alone or in combination with phosphodiesterase 5 inhibitors in patients with PoPH [48–50, 55]. The recently published PORTICO study, the largest clinical trial to date in PoPH patients, randomized 85 PoPH patients to either macitentan or placebo, and demonstrated a significant improvement in pulmonary vascular resistance, mean pulmonary artery pressure, and cardiac index on RHC after macitentan treatment for 12 weeks [48]. Smaller case series and open-label studies have shown similar improvements in pulmonary vascular hemodynamics following endothelin receptor antagonist therapy in PoPH, and despite the hepatic metabolism of this class of medications, only a minority of patients experienced liver function abnormalities significant enough to warrant medication cessation. Notably, all targeted pulmonary vasodilator medications are hepatically metabolized except epoprostenol (which is rapidly hydrolyzed in plasma), and therapeutic plans should anticipate the potential for higher drug concentrations and longer half-lives in PoPH compared to other PAH subtypes [63]. Other considerations when using these medications include the increased peripheral edema with endothelin receptor antagonists (which can be dose limiting in patients with pre-existing ascites and edema from portal hypertension), and the enhanced action of phosphodiesterase 5 inhibitors and prostacyclin analogs when co-administered with ethanol (which can occasionally be seen in patients with underlying alcoholic cirrhosis).

In addition to targeted vasodilator therapy for PoPH, there are other therapeutic interventions that merit discussion. Patients with portal hypertension are often treated with beta blocker medications to decrease portal pressure and prevent

variceal hemorrhage; however, these medications may also impair cardiac function and increase pulmonary vascular resistance in PoPH, and as such are generally avoided in this patient population [4, 5, 64–66]. The same concerns apply to the use of calcium channel blocker medications, and consequently patients with PoPH do not typically undergo vasodilator testing during diagnostic RHC as these medications are generally contraindicated. Trans-jugular intrahepatic portosystemic shunting (TIPS) procedures have been shown to relieve portal pressure, decrease the risk of variceal bleeding in patients with advanced portal hypertension and cirrhosis, and decrease mortality in these patients [67, 68]. In PoPH, however, TIPS procedures may result in a marked increase in cardiac output, leading to right ventricular overload and decompensated pulmonary vascular disease, and the decision to proceed with TIPS should be approached with extreme caution in these patients [5, 11, 69]. Although the exact relationship between HPS and PoPH is unclear, administration of targeted pulmonary vasodilator therapy in PoPH has unmasked or exacerbated underlying HPS, both yielding clues regarding the fascinating relationship between these two pulmonary vascular complications of chronic liver disease and offering a cautionary note when utilizing targeted pulmonary vasodilator medication in PoPH [70, 71].

Hepatopulmonary Syndrome (HPS)

Epidemiology and Risk Factors

Hepatopulmonary syndrome is defined by the triad of arterial deoxygenation and intrapulmonary vascular dilation that occurs in the setting of chronic liver disease [5, 72–74]. Arterial deoxygenation is typically confirmed by a resting arterial blood gas analysis while breathing ambient air that demonstrates an alveolar-arterial oxygen gradient of ≥15 mmHg (or, for those over age 65, greater than the expected age-adjusted values) or a partial pressure of oxygen (PaO_2) of <80 mmHg (or, in those over age 65, less than the expected age-adjusted values). Intrapulmonary vascular dilation manifests as intrapulmonary shunting, which is typically identified using contrast TTE imaging.

HPS is typically diagnosed in the sixth decade of life. It is estimated that 1–4% of all chronic liver disease patients have HPS. Among those undergoing evaluation for liver transplantation, between 10% and 47% of patients have some degree of HPS, depending on which diagnostic criteria are used (absolute values or age-adjusted values of arterial blood gas analysis). There is no association between the presence of HPS and either the etiology or severity of chronic liver disease, or with age, gender, or ethnicity. The presence of HPS has been associated with a markedly higher risk of mortality in cirrhotic patients, even after adjustment for severity of liver disease (MELD score) [73, 74].

Molecular Pathogenesis

Although the mechanism(s) of disease pathogenesis in HPS is incompletely understood, it is believed to involve vasoactive mediators that bypass hepatic metabolization and directly affect the pulmonary vasculature (Fig. 11.5). A combination of bacterial translocation into systemic circulation, hepatic endothelin-1 (ET-1) release, and resulting increases pulmonary nitric oxide synthesis and macrophage activation are believed to play key roles [75–82]. Animal models of liver cirrhosis generated by common bile duct ligation have demonstrated increased nitric oxide synthesis in the lungs, increased enteric bacterial translocation into the systemic circulation, and elevated macrophage recruitment into the pulmonary circulation. Additionally, antibiotic treatment or macrophage depletion both serve to reduce intrapulmonary vascular dilations and vascular remodeling characteristic of HPS, and animals with HPS were more likely to have evidence of bacterial invasion of lymph nodes as compared to non-HPS animals, further supporting a potential microbial mechanism for the disease [75–77, 79]. Evidence from common bile duct ligation animal models of liver cirrhosis suggests that ET-1 and pulmonary nitric oxide likely contribute to intrapulmonary vascular dilations and HPS, in that blockage of the endothelin B receptor diminished macrophage accumulation, pulmonary nitric oxide synthesis, and vascular abnormalities [80–82]. The potential role that ET-1 and activated pulmonary macrophages play in both PoPH and HPS pathogenesis also suggest shared mechanisms, however to date the evidence linking these two vascular complications of chronic liver disease remains rudimentary.

The study of the bone morphogenic protein axis appears to be a promising new direction in HPS research [20, 83]. A multicenter case-control study of in cirrhotic liver transplant patient genetics identified a number of gene polymorphisms associated with the bone morphogenic protein system that were significantly associated with HPS, including those involved in regulating angiogenesis (COL18A1), levels of specific bone morphogenic proteins (endoglin, the circulating ligand trap for BMP-9), and the vascular remodeling response induced by hypoxemic conditions (NOX4 and RUNX1). Building upon this, an investigation of the pulmonary vascular complications of liver disease study, a multicenter prospective cohort study of 454 adult patients with portal hypertension undergoing evaluation for liver transplant between 2013 and 2017, identified significantly lower BMP-9 and bone morphogenic protein 10 levels in HPS patients compared to non-HPS control cirrhotic patients, and

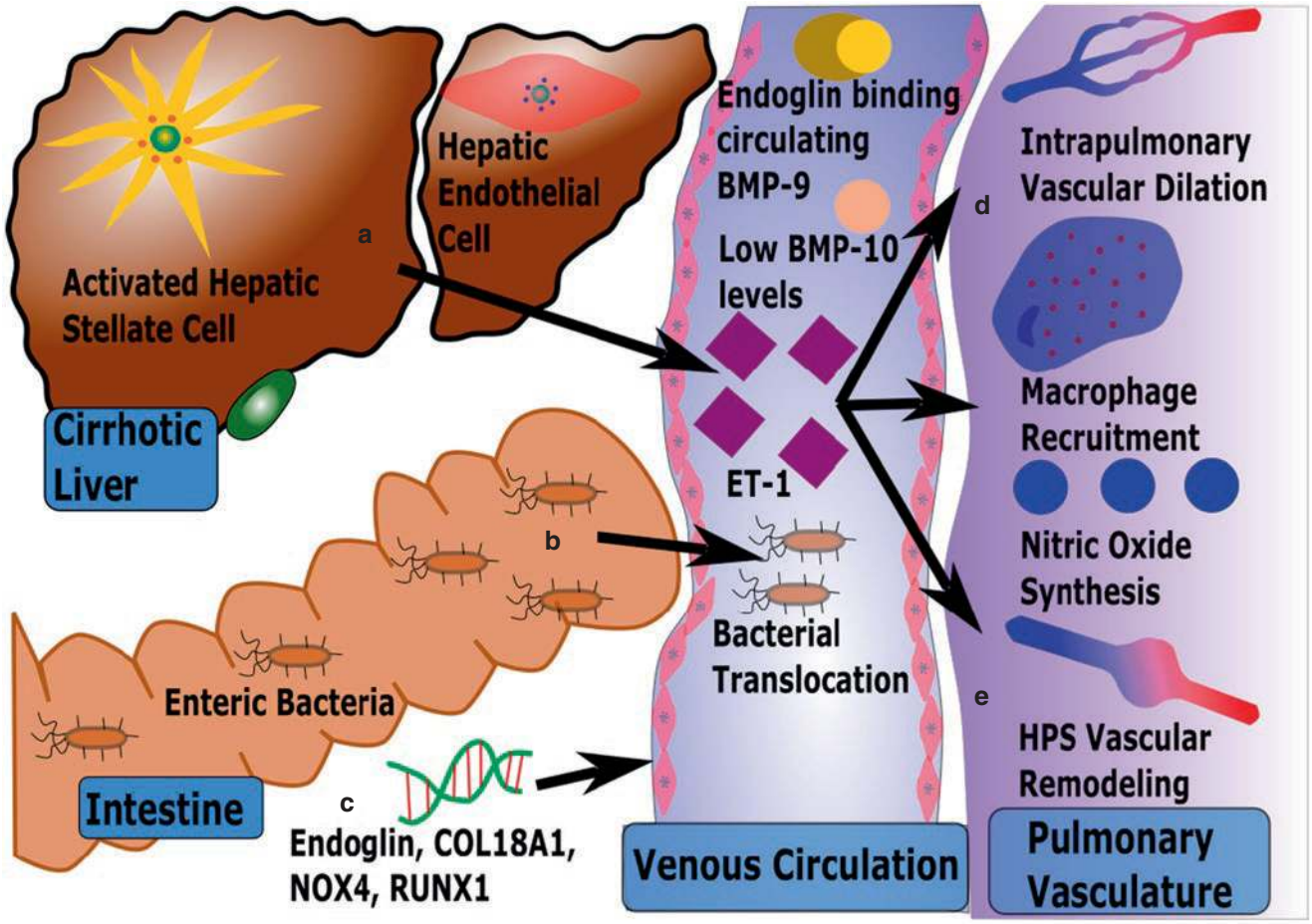

Fig. 11.5 Working hypothesis of molecular pathogenesis of HPS. Release of Endothelin-1 (ET-1) from activated hepatic endothelial cells (**a**), combined with enteric bacterial translocation into systemic circulation (**b**), gene polymorphisms in Endoglin, COL18A1, NOX4, RUNX1 (**c**), and low levels of circulating BMP-9 and BMP-10, result in macrophage recruitment, intrapulmonary vascular dilation (**d**), increased pulmonary nitric oxide synthesis, and vascular remodeling characteristic of HPS (**e**)

an association between BMP-9 levels and widened alveolar-arterial gradients and worse functional capacity in HPS patients. Taken together, these data not only implicate the bone morphogenic protein system in driving the vascular malformations characteristic of HPS but also offer another intriguing link between PoPH and HPS disease pathogenesis. Given their ability to resolve gene expression profiles at the cellular level, single-cell RNA-sequencing techniques may shed new light on the complex interactions between PoPH and HPS [24].

Screening and Diagnosis

As HPS is an indication for LT, screening for the disorder is recommended in all chronic liver disease patients undergoing transplant evaluation (Fig. 11.1). Clinical manifestations reflect the underlying physiology of chronic hypoxemia and liver disease, and include dyspnea, cyanosis, and digital clubbing, as well as the ascites, peripheral edema, jaundice, spider angiomas, and palmar erythema seen in chronic liver disease [5, 74, 84] (Fig. 11.6). Platypnea, dyspnea in the upright position that is relieved by lying supine, and orthodeoxia, hypoxemia in the upright position that is corrected while lying supine, are commonly associated with HPS. None of these findings are pathognomonic for HPS, however, and the most common presenting symptom is dyspnea. Chest radiography is typically unremarkable, and pulmonary function testing can occasionally identify an impaired diffusion capacity for carbon monoxide, but neither are routinely useful in the screening and diagnosis of HPS.

The mainstay of diagnosis in HPS is twofold: confirmation of arterial deoxygenation and identification of intrapulmonary vascular dilation. Arterial deoxygenation can be suggested by pulse oximetry screening, and various cutoffs have demonstrated differing trade-offs between sensitivity

and positive predictive value, but an upright at-rest arterial blood gas is still required for confirmation [85–89]. To enhance the screening value of pulse oximetry, the test can be performed both supine and upright to evaluate for underlying orthodeoxia; however, this screening approach has yet to be fully validated. Arterial deoxygenation requires an elevated alveolar-arterial oxygen gradient of ≥15 mmHg (or, in those over age 65, greater than the expected age-adjusted values) or a PaO_2 of <80 mmHg (or, in those over age 65, less than the expected age-adjusted values).

Contrast-enhanced TTE imaging is performed to identify the presence of intrapulmonary vascular dilations in HPS and is recommended as part of the routine evaluation for all liver transplant candidates [3–5]. The late appearance of bubbles in the left atrium, typically after three cardiac cycles, is consistent with the presence of an intrapulmonary shunt and is sufficient to fulfill the diagnostic criteria for HPS [90, 91] (Fig. 11.7). Parenteral macro-aggregated albumin scanning using radiolabeled albumin, as is routinely performed for ventilation perfusions scanning, can also identify intra-

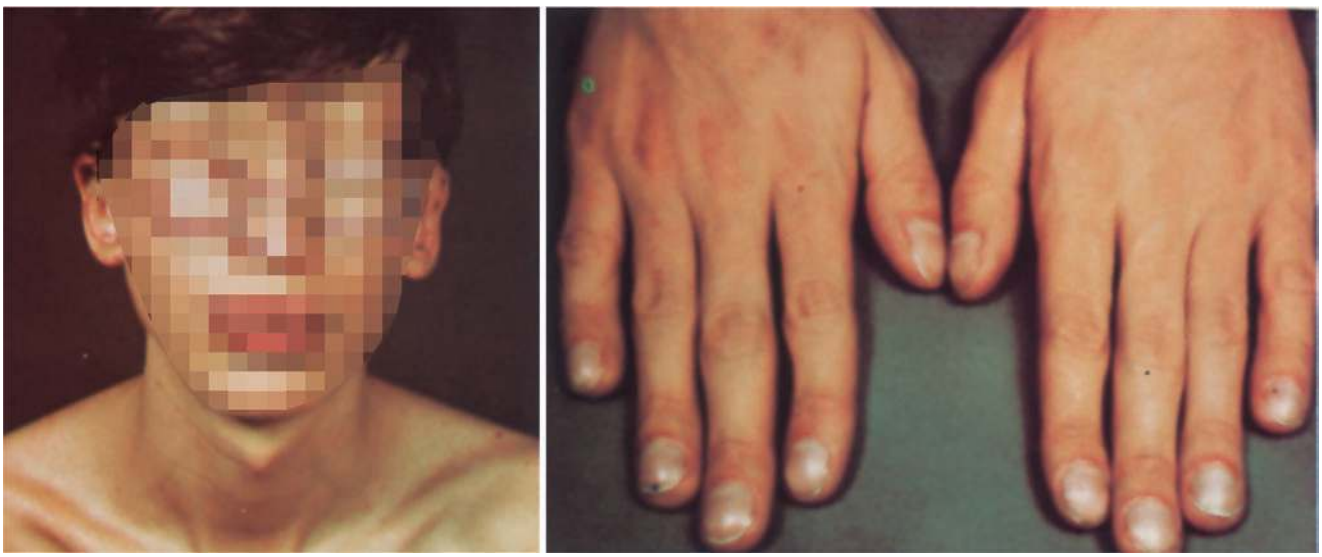

Fig. 11.6 Characteristic physical exam findings of digital clubbing and cyanosis visible in a 16-year-old male with HPS, who required supplemental oxygen therapy for severe hypoxemia

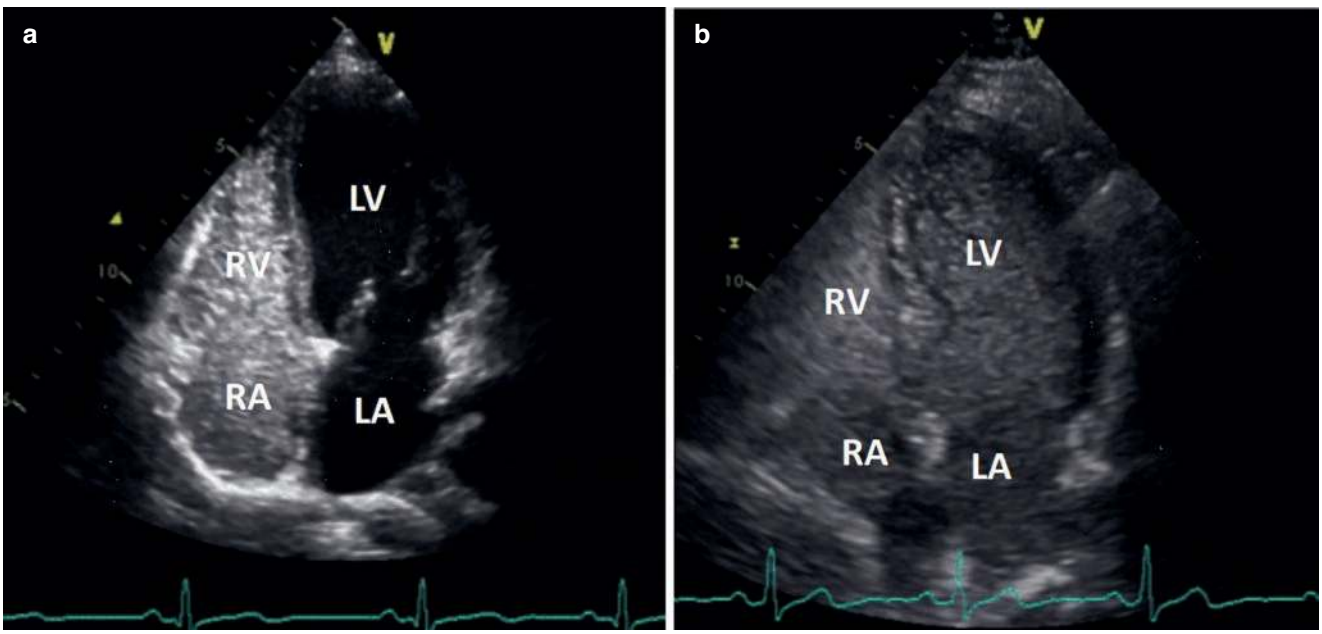

Fig. 11.7 Contrast-enhanced transthoracic echocardiogram showing opacification of right atrium and right ventricle (Panel **a**) with delayed opacification of left atrium and left ventricle (Panel **b**) after three cardiac cycles, consistent with a diagnosis of HPS

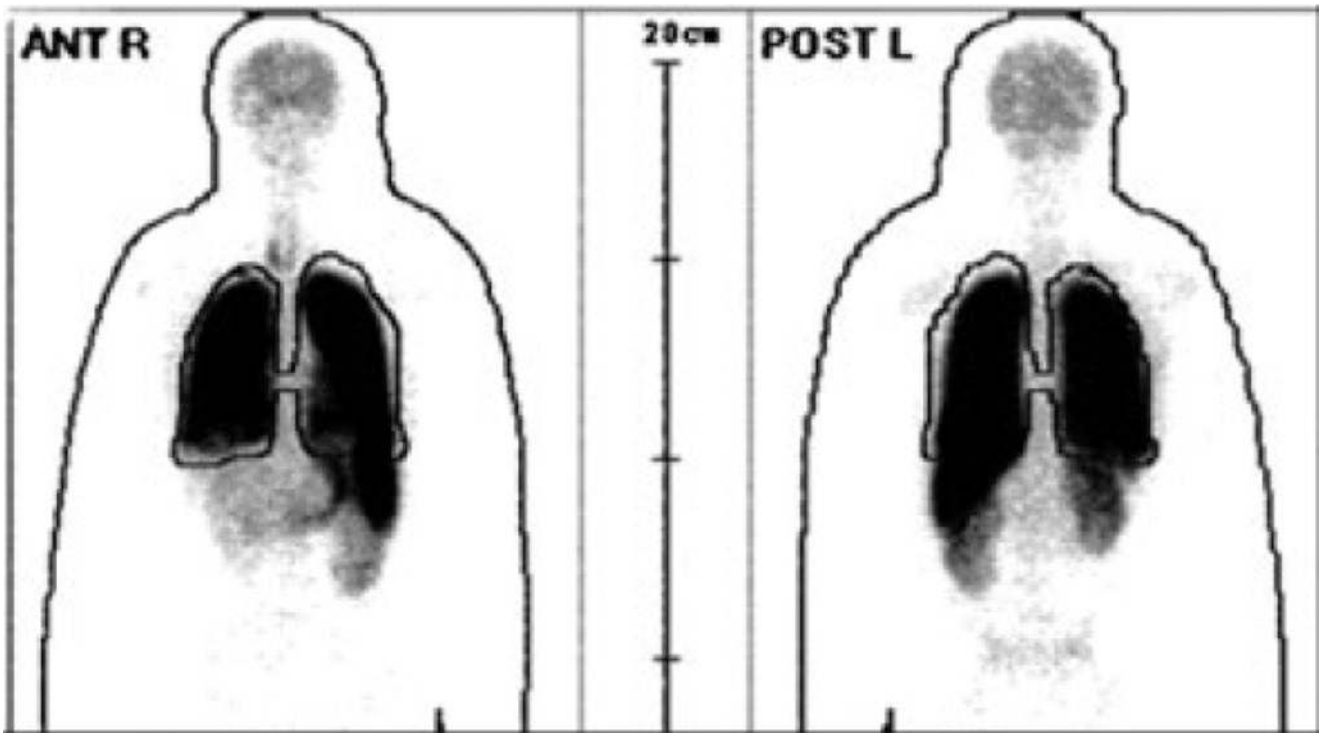

Fig. 11.8 Macroaggregated albumin perfusion imaging in a patient with HPS, demonstrating dramatic extrapulmonary accumulation (brain, kidneys) of intravenously injected radiolabeled albumin, indicative of right-to-left shunting

pulmonary shunts, as well as quantify the severity of shunt. A cutoff of >6% shunt, calculated as the percent of extrapulmonary shunt to the cerebrum, is typically used as a diagnostic threshold in HPS (Fig. 11.8) [92–94]. Rarely patients with HPS demonstrate large intrapulmonary shunts, sometimes referred to as Type-II HPS, which may be amenable to therapeutic embolization, and the use of macro-aggregated albumin scanning and pulmonary angiography can help identify this subset of patients. Neither imaging test is routinely performed in the evaluation of HPS, however, and the precise association between shunt severity and outcomes in HPS remains unclear.

HPS Treatment

HPS is defined by arterial hypoxemia, and supplemental oxygen remains the mainstay of therapy. As LT can be curative, debilitating HPS is an indication for an expedited liver transplant evaluation, and the diagnosis of HPS provides MELD exception points during LT listing [3, 4]. Following LT, HPS is expected to resolve in almost all patients, with 85% of patients cured within 12 months [95–97]. HPS patients experience roughly double the mortality rate of non-HPS cirrhotic patients while awaiting liver transplantation, but survival following LT is comparable in both groups [5, 74, 98, 99]. Predictors of outcomes in HPS before and after LT include both severity of liver disease and degree of hypoxemia, as measured by either alveolar-arterial oxygen gradient or PaO_2 on arterial blood gas [3, 4, 37, 100, 101].

A number of additional therapeutics have been studied in HPS as adjuncts to LT and supplemental oxygen [102–108]. Given the defining feature of intrapulmonary vascular dilation, somatostatin analogs (octreotide) have been evaluated in HPS but have not demonstrated any beneficial effect on arterial oxygenation or degree of shunting and may actually worsen pulmonary vascular hemodynamics in these patients [102, 103]. Inhibition of nitric oxide via L-N^G-Nitro arginine methyl ester has also been studied in HPS and was successful in decreasing nitric oxide levels. Unfortunately, this therapy also decreased cardiac function and increased pulmonary vascular resistance, dampening enthusiasm for this interventional strategy [104]. Treatment with allium sativum (garlic) supplementation did demonstrate improvements in both symptoms of dyspnea and arterial hypoxemia in a small pilot study of HPS patients but has not been validated in larger studies [105]. In an attempt to inhibit angiogenesis, the tyrosine kinase inhibitor sorafenib was studied in HPS patients in a randomized clinical trial, and although it did significantly reduce circulating vascular endothelial growth factor levels, it did not affect the degree of shunting on contrast echocardiography or alveolar-arterial oxygen gradient and significantly worsened quality of life in HPS patients [106]. TIPS procedures have been effective in improving arterial oxygen-

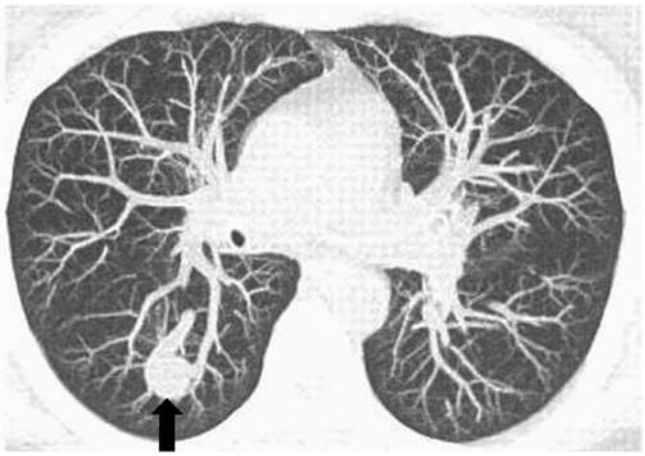

Fig. 11.9 Maximal intensity projection reconstructions showing dilated pulmonary veins and arteriovenous communications (**black arrow**), consistent with underlying Type-II HPS

ation in HPS patients, with concomitant decreases in portal vein pressure, but this benefit must be balanced against the increased rate of hepatic encephalopathy in these patients [107]. In select patients with Type-II HPS and large intrapulmonary shunts, embolization therapy has been reported to improve hypoxemia and dyspnea, but this remains an investigational approach [108] (Fig. 11.9). In summary, in HPS, supplemental oxygen is the only therapeutic modality with proven clinical benefit short of liver transplantation, which remains a limited resource.

Conclusion

PoPH and HPS are uncommon pulmonary vascular complications of chronic liver disease. Signs and symptoms are nonspecific and are easily confused with the manifestations of chronic liver disease. Both conditions confer markedly increased morbidity and mortality in liver disease patients. Mechanisms of disease pathogenesis are unclear but likely involve vasoactive mediators affecting the pulmonary circulation and are likely mechanistically interrelated.

Although the exact circulating factors responsible for PoPH and HPS pathogenesis have yet to be identified, current evidence suggests that abnormalities in the bone morphogenic protein system and dysregulation of ET-1, in the setting of hepatic dysfunction and portal hypertension, favor a state of excess angiogenesis, ECM breakdown, and vascular remodeling. Further hinting at the complex relationship between PoPH and HPS, both conditions can occur independently of one another, occur simultaneously in the same patient, or can transition from one to the other in an individual patient. With respect to the latter, two scenarios have been proposed: (1) low resistance intrapulmonary vascular dilations' characteristic of HPS effectively decreases the pulmonary vascular resistance, masking underlying PoPH until liver transplantation closes these vascular lesions, and (2) elevated pulmonary vascular resistance specific to PoPH limits blood flow through intrapulmonary vascular dilations, hiding HPS until targeted pulmonary vasodilator augments cardiac output and worsens intrapulmonary shunting. Exciting research into the mechanistic relationship between PoPH and HPS is ongoing, including employing state-of-the-art techniques such as single-cell RNA sequencing that promise to resolve the common and divergent molecular pathways driving disease pathogenesis in these two disorders.

Given the significant impact PoPH and HPS have on prognosis, treatment, and candidacy and outcomes of liver transplantation, screening of all chronic liver disease and liver transplant candidates for these disorders is recommended by international guidelines. Pulmonary vasodilator therapy is the mainstay of therapy for PoPH, and although liver transplantation can be helpful in some cases, identifying the patients who are most likely to benefit is challenging. Liver transplant is generally curative in HPS; and the only other therapy demonstrated to have benefit is supplemental oxygen. Given the high morbidity and mortality of both conditions, maintaining a high index of suspicion to promote early diagnosis and management is imperative. As liver transplantation as a therapeutic option is limited and mechanisms of disease pathogenesis remain unclear, additional investigation of targeted therapeutics is crucial to promoting optimal patient outcomes in this high-risk population.

Clinical Vignette

A 50-year-old woman presented with increasing dyspnea on exertion and increased abdominal ascites for the past year. She had a history of hepatitis C virus and alcohol-induced liver cirrhosis and was currently undergoing liver transplant evaluation. She had never had an episode of variceal bleeding but had known esophageal varices that required banding. A contrast echocardiogram on admission (Fig. 11.10) reveals an elevated right ventricular systolic pressure as well as right ventricular dilation and impaired systolic function, suggestive of underlying pulmonary hypertension. There are also a few bubbles appearing in the left atrium after 4 cardiac cycles, but the patient does not demonstrate hypoxemia at rest, and has a normal arterial blood gas analysis. She subsequently undergoes a right heart catheterization, notable for a mean pulmo-

nary arterial pressure of 38 mmHg, a pulmonary capillary wedge pressure of 8 mmHg, and a calculated pulmonary vascular resistance of 6.4 Wood Units. A diagnosis of PoPH is made, and the patient is started on dual oral therapy with sildenafil three times a day, and macitentan once daily. Despite these interventions, the patient's dyspnea progresses, and she is subsequently found to be hypoxemic at rest and placed on supplemental oxygen. A repeat right heart catheterization shows improved pulmonary vascular hemodynamics, with a mean pulmonary arterial pressure of 22 mmHg, and a pulmonary vascular resistance of 2.3 Wood Units. Contrast-enhanced echocardiogram testing is repeated, showing numerous bubbles appearing in the left atrium after 3 cardiac cycles, and resting room air arterial blood gas demonstrates an elevated alveolar-arterial gradient of 30 mmHg. The patient is subsequently diagnosed with HPS, undergoes an expedited liver transplant evaluation, and is placed on the transplant waiting list. Two months later, she undergoes a successful liver transplantation, and follow-up echocardiographic, right heart catheterization, and arterial blood gas testing is normal, indicating resolution of both PoPH and HPS.

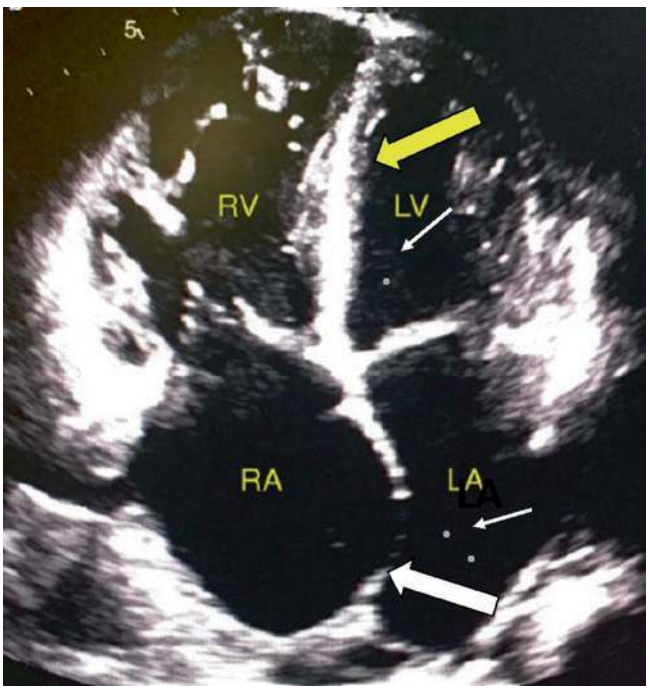

Fig. 11.10 Representative contrast-enhanced transthoracic echocardiogram showing evidence of PoPH (including dilation of right atrium (**thick white arrow**) and a dilated and hypertrophied right ventricle (**thick yellow arrow**)) as well as evidence of HPS (bubbles present in left atrium and left ventricle after three cardiac cycles (**thin white arrows**))

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Systemic Sclerosis and the Lung

12

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Introduction

In systemic sclerosis (SSc), cardiopulmonary involvement, consisting of interstitial lung disease (SSc-ILD) and pulmonary hypertension (SSc-PH) are the most frequent cause of death. Accurate management depends upon the early identification of lung involvement. Apart from interstitial lung disease, the range of primary lung abnormalities in SSc includes sporadic case reports of obliterative airways disease, diffuse alveolar haemorrhage and significant pleural involvement. However, the possibility that these extremely rare complications result from overlap disorders cannot be excluded. In this chapter, we cover the epidemiology, presenting features, prognostic evaluation and management of SSc-ILD.

Epidemiology of SSc-ILD

The pooled prevalence of SSc in 46 studies is 176/million, with a pooled incidence of 14/million person years [1]. SSc-ILD is present in approximately 50% of SSc patients, with the spectrum of disease severity ranging from sub-clinical lung involvement, detected during routine evaluation, to severe pulmonary disease progressing ultimately to respiratory failure and death. Epidemiological studies have been hampered by the rareness of SSc and also by variations in the definition of pulmonary disease. These problems have recently been addressed by large international collaborative databases with standardization of diagnostic criteria and nomenclature [2]. In the EUSTAR database, compiled from over 5800 patients, SSc-ILD is the most frequent cause of death (35% of SSc-related deaths), followed by SSc-PH (26% of deaths). Renal disease was the most frequent cause of death in the last century but now accounts for only 4% of deaths [3]. SSc most commonly occurs in women (female:male ratio 5:1 in pooled studies) aged 30–50 years [1]. In USA series, the risk of SSc-ILD increases in association with African-American ethnicity: other risk factors for SSc-ILD, discussed later, include diffuse cutaneous SSc, older age at disease onset, shorter duration of disease and the presence of anti-topoisomerase antibodies [4–8].

In autopsy studies of patients with SSc, interstitial lung disease is present histologically in most patients [9]. All histological patterns seen in the idiopathic interstitial pneumonias have been reported in SSc-ILD [10]. However, the relative prevalence and prognostic significance of histological patterns differ greatly between idiopathic disease and SSc-ILD. In idiopathic interstitial pneumonia, the most prevalent histological pattern is usual interstitial pneumonia (UIP), corresponding to idiopathic pulmonary fibrosis (IPF). IPF has a strikingly worse outcome than other idiopathic disorders, including fibrotic nonspecific interstitial pneumonia (NSIP). By contrast, NSIP is the most prevalent histological pattern at biopsy and autopsy in SSc-ILD (Fig. 12.1). In a series of 80 SSc-ILD patients undergoing a diagnostic surgical biopsy [11], cellular or fibrotic NSIP (Figs. 12.1a, b and 12.2a) was present in 78%, with less than 25% of patients having predominantly reversible disease. By contrast with idiopathic interstitial lung disease, mortality did not differ between NSIP and UIP but was associated with pulmonary function impairment at presentation and decline in pulmonary function variables during follow-up. These findings are broadly compatible with outcome data in smaller series, although in one reports, the presence of UIP was associated with a trend towards a shorter survival time [12].

High-resolution computed tomography (HRCT) is the primary means of detecting SSc-ILD [13, 14]. Interstitial lung disease is present in over 90% of SSc patients with abnormal pulmonary function tests and in up to 65% of SSc patients overall. HRCT appearances are typically compatible with NSIP, with prominent ground-glass attenuation and a low prevalence of honeycomb change [15]. HRCT has a high

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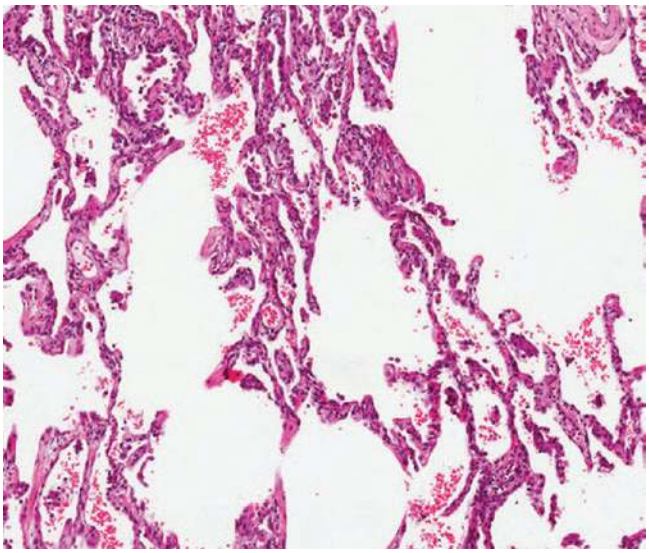


Fig. 12.1 Cellular NSIP. The lung shows diffuse involvement of the alveolar interstitium by a mild chronic inflammatory infiltrate more evident at high power (H&E stain, ×80 magnification)

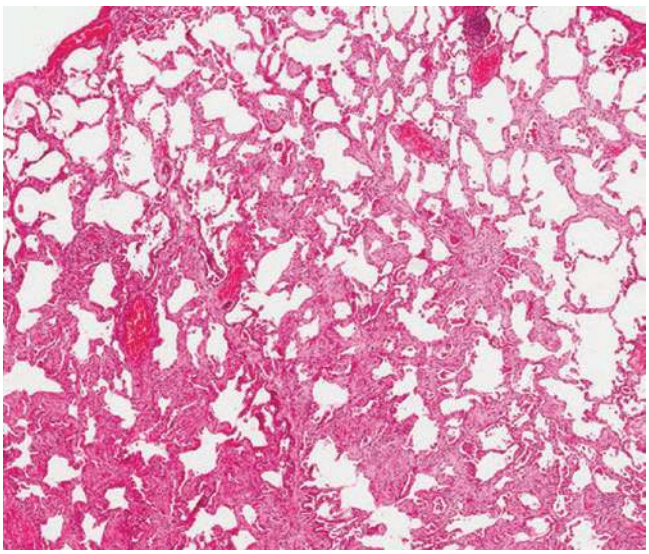


Fig. 12.2 Fibrotic NSIP. The lung shows diffuse involvement of the alveolar interstitium by a homogenous fibrosis with minimal inflammation. No fibroblastic foci were seen at high power (H&E stain, ×10 magnification)

diagnostic sensitivity which has obvious advantages but has also caused difficulties for clinicians as very limited HRCT abnormalities are often disclosed by routine screening tests. As HRCT abnormalities are often limited and difficult to interpret, a multidisciplinary evaluation of disease severity is essential, with the integration of symptoms, pulmonary function tests and the extent of disease on HRCT. The selection of patients for treatment, discussed later, has been facilitated by studies of the natural history and treated course of SSc-ILD in large historical cohorts [16, 17] and especially by HRCT data [18, 19].

Risk factors for SSc-ILD

SSc-ILD has been linked to both the distinction between limited and diffuse cutaneous disease and the autoantibody profile. SSc is sub-classified as limited or diffuse cutaneous disease, according to the extent of skin involvement. In limited disease, skin involvement is distal to the elbows and knees (although facial involvement may occur) whereas in diffuse disease, there is variable involvement of the trunk, shoulders, pelvic girdles and the face and acral areas. Across many series, the prevalence of SSc-ILD has generally been higher in diffuse cutaneous disease, but this association is weaker than the associations between SSc-ILD and autoantibody status [20].

In the EUSTAR database, autoantibody status was a more powerful predictor of major organ involvement than the distinction between diffuse and limited cutaneous disease [21]. Antinuclear antibodies (ANA) are present in more than 90% of SSc patients. Autoantibodies against topoisomerase I (ATA, also known as anti-Scl70 antibody), present in over 20% of SSc patients, are associated with the development of pulmonary fibrosis in over 85% of cases [22]. However, only 40% of patients with SSc-ILD are ATA positive [23]. Reported correlations between ATA levels and the severity of SSc-ILD [24, 25] are not sufficiently consistent to influence the investigation of individual patients. Anti-centromere antibody (ACA) positivity, associated with a very low prevalence of significant SSc-ILD, is linked to limited cutaneous disease and an increased risk of SSc-PH [4, 26].

Genetic Associations

The accumulated evidence indicative of a genetic predisposition to SSc includes associations between specific autoantibodies and major histocompatibility complex (MHC) classes, clustering of SSc with other rheumatic diseases in family members and familial cases of SSc, including in twins [27]. The Choctaw Indians have a tenfold increase in prevalence of SSc and a genome-wide screen has disclosed multiple microsatellite markers in chromosome regions associated with SSc, including the MHC, fibrillin 1 gene (15q), the topoisomerase 1 gene (chromosome 20q) and the SPARC gene (secreted protein, acid rich in cysteine; chromosome 5q) [28]. However, the overall familial linkage to SSc is weak, with less than 3% of patient siblings developing the disease, and the current consensus is that many gene variants

may influence susceptibility, clinical phenotype and disease progression [29]. ATA positivity is strongly linked to the carriage of the HLA-DRB1*11 and HLA-DPB*1301 alleles [23]. ATA positivity, diffuse cutaneous disease and SSc-ILD have been associated with the rs763361 single-nucleotide polymorphism in the CD226 gene [30].

Other genetic linkages to SSc-ILD have included the HLA-C, HLA-DQB1, HLA-DRB1, CD247, IL-1α and IL-1β genes [31]. By contrast, single-nucleotide polymorphisms in the surfactant protein B gene are associated with a lower prevalence of SSc-ILD in Japanese SSc patients [32].

Clinical Presentation of SSc-ILD

In SSc-ILD, respiratory symptoms are notorious for their non-specificity and variability, with the severity of exercise limitation correlating poorly with disease severity, as judged by pulmonary function tests (PFT) and the extent of disease on HRCT. The difficulty in evaluating symptoms lies in the fact that in SSc, dyspnoea may arise from a multiplicity of causes including interstitial lung disease, pulmonary vascular limitation (even when overt PH is not present), cardiac involvement, musculoskeletal disease, loss of fitness due to general debility and anaemia, with more than one factor often coexisting. In some patients, severe systemic disease results in a major reduction in daily activity, and loss of pulmonary reserve is not exposed. By contrast, knowledge of the likelihood of lung involvement leads to concerns about exercise intolerance in other cases, even when interstitial lung disease is absent or relatively limited. Accurate assessment of dyspnoea requires observation of the exercising patient. The absence of oxygen desaturation during a 6-min walk test (or a more strenuous form of exercise) suggests that dyspnoea largely results from extra-pulmonic factors.

A detailed history should include occupational exposures known to result in SSc and the impact of lung symptoms on quality of life. The duration of systemic disease (as judged by SSc symptoms and not by Raynaud phenomenon) may influence treatment decisions, as discussed later. It is also important to explore the evolution of dyspnoea: a long-term lack of change in exertional dyspnoea is reassuring in patients with severe SSc-ILD. Aspiration due to gastro-esophageal regurgitation (GER) has been suggested as a potential cause of SSc-ILD although this hypothesis has yet to be validated. GER may cause troublesome cough (due to a vagally mediated cough reflux) and in occasional patients, episodes of wakening with a choking sensation may be indicative of significant nocturnal aspiration of gastric contents.

Physical examination does not contribute greatly to the assessment of SSc-ILD. The classical finding of fine bi-basal crackles is often absent in limited SSc-ILD. Changes in the intensity of crackles have not been validated as a reliable indicator of disease progression. Finger clubbing is very rare in SSc-ILD. In end-stage SSc-PH, positive clinical findings include a loud pulmonary component of the second heart sound, a right ventricular heave, elevated jugular venous pressure, signs of peripheral oedema—but these signs are not reliably present in less advanced PH. Impairment in chest wall movement due to severe thoracic skin involvement is a rare extra-pulmonic cause of exertional dyspnoea.

Pulmonary Function Tests (PFTs)

PFTs have been used historically for both the staging of disease severity and the serial monitoring of SSc-ILD. It is generally accepted that in these regards, PFTs are more reliable than symptoms or chest radiography. However, the limitations of PFT need to be appreciated by the clinician. In staging severity, the normal PFT range, varying from 80% to 120% of expected values based on age, height and gender [33], is a major confounder. For example, an FVC value of 75% of predicted may equally represent a relatively minor fall of 5% or a very major reduction of 45% from premorbid values of 80% and 120%, respectively. Thus, it is essential that the evaluation of disease severity should be a multidisciplinary exercise, with the integration of PFT, HRCT findings and symptoms. However, it can at least be concluded that severe reductions in lung volumes and measures of gas transfer are reliably indicative of severe pulmonary disease.

The classical PFT profile in SSc-ILD is a restrictive ventilatory defect, with reduced total lung capacity, reduced forced vital capacity (FVC), an FEV1/FVC ratio of >0.8, reduced carbon monoxide diffusing capacity (DLco) and reduced lung compliance. Moderate restriction (FVC 50–75% of predicted) is found in up to 25–30% of SSc patients, with 10–15% having severe restriction [4]. DLco estimation can be viewed as a "gestalt" evaluation of resting pulmonary function, as it captures both ventilatory defects and reductions in blood volume within ventilated lung. Disproportionate reductions in DLco (when compared to lung volumes) can arise in two distinct scenarios. In smokers, the coexistence of interstitial lung disease and emphysema (widely known as the "combined pulmonary fibrosis and emphysema syndrome") results in preservation of lung volumes (even when both processes are extensive) but a devastating reduction in DLco, a combination best documented in idiopathic interstitial pneumonia [34] but also seen in SSc-ILD [35]. A more frequent scenario in SSc-ILD (and in SSc in general) is disproportionate reduction in DLco due to significant pulmonary vascular limitation (with or without overt SSc-PH). In recent series, elevation of the FVC/DLco ratio has been used as a marker of pulmonary vascular limitation

[36, 37]. However, there are theoretical advantages in an alternative variable and the gas transfer coefficient (Kco), which quantifies carbon monoxide uptake per unit volume of ventilated lung. It is often overlooked that DLco is calculated as the product of measured Kco and measured VA [38] (accounting for the higher measurement variability of DLco than other pulmonary function variables). Thus, the use of the FVC/DLco ratio depends upon the accurate measurement of three variables (Kco, VA and FVC) whereas Kco carries the measurement variation of only one manoeuvre.

Spirometric volumes are highly reproducible in laboratories with an acceptable level of quality assurance. Body plethysmography is a more complex measurement performed inside a sealed, air-tight chamber and is used to estimate total lung capacity (TLC) and residual volume (RV). In interstitial lung disease, reductions in TLC and RV tend to mirror reductions in FVC and in most cases add little to FVC measurement. However, plethysmography should be performed at presentation in order to allow an alternative monitoring variable to be used in occasional patients, in whom forced spirometric manoeuvres are contraindicated by glaucoma, significant chest wall discomfort or severe microstomia.

In SSc-ILD, resting arterial gases tend to be normal in mild to moderate disease except when there is concurrent pulmonary hypertension. In advanced disease, hypoxia is usually associated with hypocapnia (reflecting alveolar hyperventilation). The performance of arterial gases can generally be avoided in routine evaluation as simple oximetry is an adequate substitute, despite sometimes confounded by Raynaud phenomenon. Ear lobe capillary gases, which can be measured in many lung function laboratories, are also an acceptable substitute for arterial gases.

Maximal exercise testing adds little to the routine evaluation of SSc-ILD. However, in occasional patients with exertional dyspnoea that is disproportionate to the severity of SSc-ILD, maximal exercise testing is a useful means of excluding clinically significant interstitial lung disease. The absence of oxygen desaturation or widening of the alveolar-arterial oxygen gradient at end exercise may allow the clinician to conclude that exercise tolerance is limited by extra-pulmonary factors such as musculoskeletal disease or lack of fitness. The 6-min walk test is more useful as it more closely approximates daily activity. Major desaturation should prompt the clinician to exclude SSC-PH and to consider the potential benefits of ambulatory oxygen.

In routine monitoring, serial pulmonary function tests have a central role. The normal range is no longer a major confounder as significant change is indicative of disease progression, irrespective of premorbid pulmonary function levels. However, as in interstitial lung disease in general, measurement variation creates difficulties. Serial PFT trends are reliably indicative of disease progression only when FVC change exceeds 10% of baseline values (e.g. a change from 2.0 to 1.8 L). DLco trends may also be helpful but are less specific when there is concurrent pulmonary vascular limitation. Even when pulmonary function trends are significant, it is important that alternative explanations for functional decline are considered, including infection, pulmonary embolism and cardiac disease. It is important to remember that measurement variation can result equally in the understatement of change. Lesser changes (e.g. a 5–10% change in FVC) may be indicative of disease progression. Thus, functional trends should be reconciled with symptomatic change and, in selected cases, serial imaging data.

Imaging

High-resolution computed tomography (HRCT) can now be viewed as the reference standard for the detection of SSc-ILD. The chest radiograph is insensitive in the detection of SSc-ILD [39]. HRCT findings closely resemble those seen in idiopathic NSIP [15] typically consisting of a variable mixture of ground-glass attenuation and reticulation (Fig. 12.2). In a minority of patients with overt honeycomb change, a histological pattern of usual interstitial pneumonia can be suspected. The historical belief that ground-glass attenuation is indicative of reversible inflammatory disease has not stood the test of time. In occasional patients with prominent ground glass, without associated reticulation or traction bronchiectasis, disease is, indeed, likely to be reversible (Fig. 12.3a). However, in the great majority of cases, ground glass is admixed with reticulation, and there is traction bronchiectasis (Fig. 12.3b), a combination of HRCT signs that is reliably indicative of fine fibrosis [13, 40, 41].

Apart from the detection of disease, HRCT provides an alternative means of evaluating disease severity. Precise quantification of disease extent is arduous and insufficiently "user friendly" to be a part of routine evaluation. However, rapid semi-quantitative assessment of disease extent on HRCT helps the clinician to address the confounding effect of the normal range in the interpretation of pulmonary function tests. As discussed later, HRCT can also be used to stage disease as mild or extensive.

Serial HRCT evaluation tends to be over-used by clinicians, based on the supposition that a sensitive test must add to the accuracy of monitoring. In reality, HRCT is often **too** sensitive in the detection of change. No definition of "significant" HRCT change has been validated, and therefore, subtle regional HRCT change in patients with stable pulmonary function tests is difficult to interpret. In other patients with major pulmonary function trends, there may be little or no change on HRCT. Furthermore, the long-term risk of malignancy with excessive exposure to radiation should not be overlooked. Thus, the inclusion of HRCT in a routine-

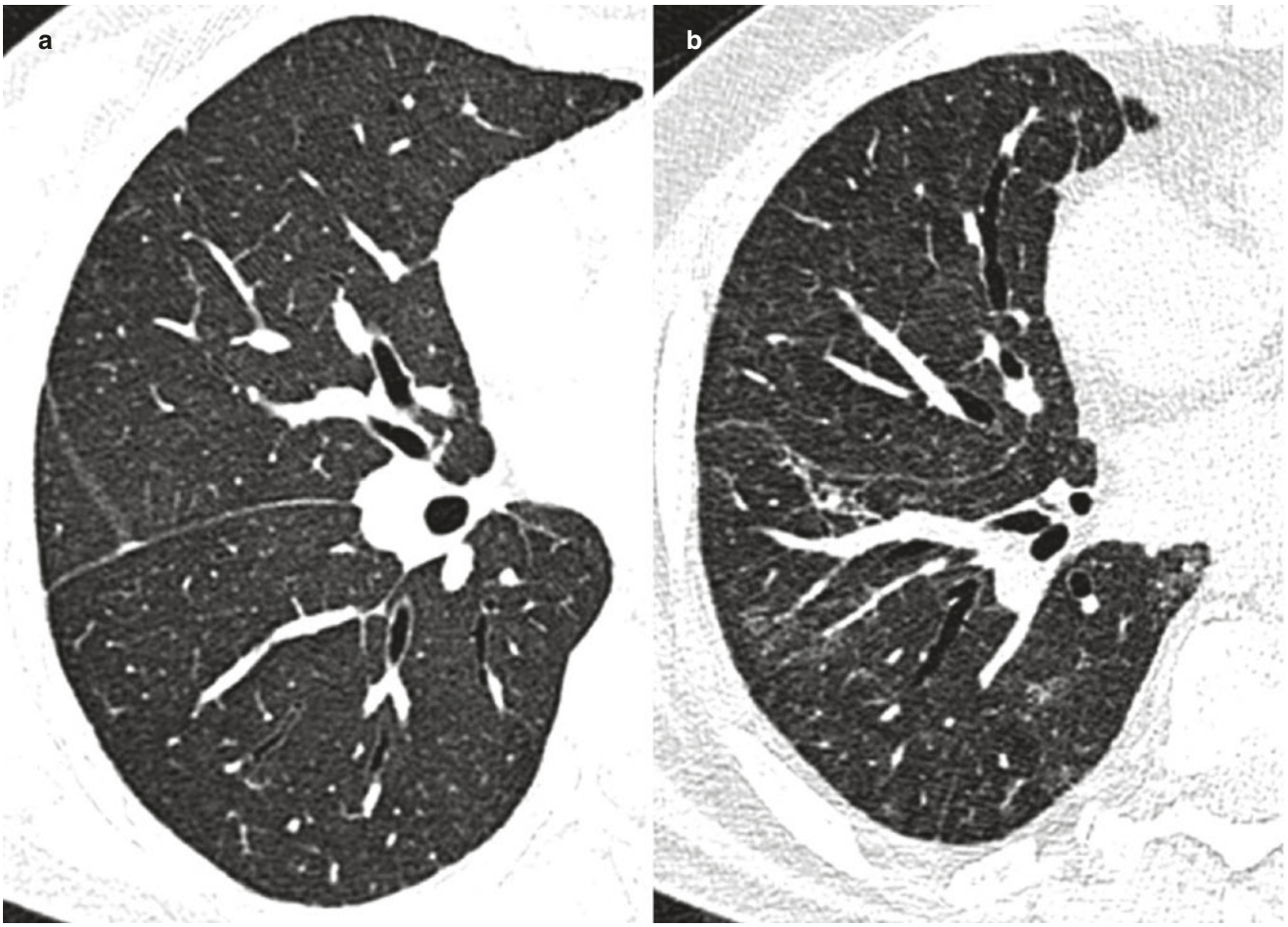


Fig. 12.3 (**a**) HRCT appearances in a patient with biopsy-proven cellular NSIP. There is a diffuse increase in lung attenuation without admixed reticulation or traction bronchiectasis. (**b**) HRCT appearances in a patient with biopsy-proven fibrotic NSIP. The diffuse increase in attenuation on HRCT represents fine fibrosis, with the presence of obvious traction bronchiectasis an important clue that interstitial disease was likely to be irreversible

monitoring protocol is difficult to justify. Serial HRCT should only be performed on a case-by-case basis to answer specific clinical questions, with the most frequent scenarios being discordance between symptomatic change and pulmonary function trends and disproportionate decline in measures of gas transfer, ascribable equally to progression of interstitial lung disease and worsening of pulmonary vascular disease.

Prognostic Evaluation of SSc-ILD: When Should Treatment Be Instituted?

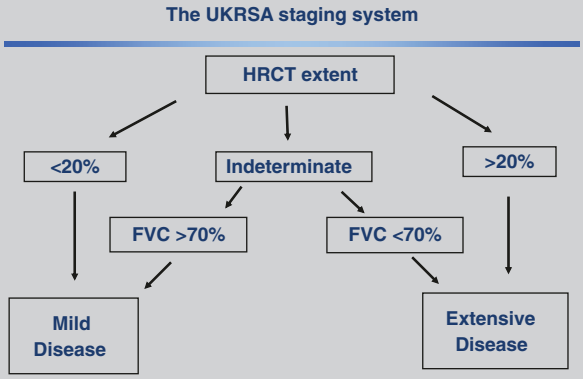
The routine use of HRCT in the initial evaluation of SSc often discloses limited interstitial abnormalities of uncertain significance. This creates a major dilemma for the clinician. It is axiomatic that early treatment is needed when disease is intrinsically progressive. However, when abnormalities are mild or "sub-clinical", overly aggressive intervention can result in major side effects without therapeutic gain. Intrinsically progressive disease cannot be identified reliably. However, based on accumulated clinical experience, the decision to institute therapy should be influenced by the severity of lung disease, the duration of systemic disease and evidence of ongoing disease progression.

It is widely accepted that the threshold for treatment is critically dependent on disease severity. Severe disease is a marker of repeated past disease progression and is, therefore, indicative of an increased likelihood of future disease progression. Furthermore, in severe disease, further progression is associated with major changes in exercise tolerance and quality of life. In a staging system centred on disease severity, Goh and co-workers evaluated the prognostic value of candidate FVC and HRCT disease extent thresholds [19]. Key prognostic thresholds consisted of a percent predicted FVC value of 70% and an HRCT extent threshold of 20%

(i.e. 20% of the total lung volume). In the staging system for SSc-ILD shown in Box 12.1, lung disease was classified as "mild" or "extensive", based on rapid semi-quantitative HRCT evaluation and in cases with an "indeterminate" disease extent, an FVC threshold of 70%. The Goh system has subsequently been validated in USA and Australian cohorts [42, 43]. These studies establish that the staging of severity using HRCT and FVC data is likely to be useful in informing treatment decisions in clinical practice.

Box 12.1

The mild/extensive severity staging system for prognostic evaluation in SSc-ILD. Extensive disease is associated with an increase in mortality of over threefold and a much higher likelihood of disease progression in the next year.



The duration of systemic disease is also an important consideration as the risk of progression of SSc-ILD is greater early in the course of systemic disease. Steen and colleagues observed that the risk of progression is highest in the first 4 years of systemic disease and especially in the first 2 years. The risk is even greater when the onset of lung disease precedes the cutaneous manifestations of SSc [4]. With regard to treatment decisions, interstitial lung disease that is detected early in the course of systemic disease can be viewed as intrinsically progressive, with a reduced threshold for introducing therapy. By contrast, in patients with minor pulmonary function impairment after more than 5 years of systemic disease, mild SSc-ILD is less likely to evolve to severe fibrotic lung disease.

Recent progression of disease, as judged by a variable combination of serial PFT tends, serial imaging data and symptomatic change, is, in itself, an indication for therapy. In SSc-ILD, decline in pulmonary function indices over 1 year or 2 years, including FVC, DLco and Kco levels, has been linked to mortality in two series, independently of baseline disease severity [44, 45]. Intervening to stabilize disease that is overtly progressive is warranted on simple commonsensical grounds.

Pleuroparenchymal fibroelastosis (PPFE), a clinical–pathological entity affecting the visceral pleura and the subpleural parenchyma with an upper-lobe predilection, was recently observed in 18% of patients in two large SSc cohorts [46]. The presence of PPFE was associated with increased mortality, independently of pulmonary disease severity and short-term pulmonary function trends. However, PPFE was only marginally associated with subsequent serial FVC decline and is not currently an accepted indication for earlier treatment of SSc-ILD, pending further research.

Thus, the severity of disease, the duration of systemic disease and evidence of recent progression should all be taken into account when treatment decisions are made. Currently, no validated algorithm exists to incorporate all these factors into management. Treatment decisions must be made on a case-by-case basis, acknowledging the wishes of the patient (which often become the key determinant when the grounds for introducing therapy are marginal). When immediate treatment is not warranted, rigorous monitoring is essential, primarily based on the performance of serial PFT, with an intention to treat if disease progression becomes evident. Based on accumulated clinical experience, both in SSc-ILD and idiopathic interstitial lung disease, three to six monthly repetition of PFT is recommended with the time interval between PFT prolonged after disease has been stable for at least 2 years.

As in interstitial lung disease in general, a biomarker in SSc-ILD that accurately predicted disease progression would greatly increase the accuracy of treatment decisions. Biomarkers evaluated in IPF and subsequently investigated in SSc-ILD include MMP-7, surfactant protein-D [SP-D], Krebs von den Lungen-6 [KL-6] and C-C motif chemokine ligand 18 [CCL18] [47]. Antibodies against CXCR3 and CXCR4 chemokine receptors have also been explored. Currently, serum KL-6 and CCL18 levels hold the most promise based on their association with pulmonary disease progression in a large cohort [48], in keeping with observations in smaller cohort studies. In another large cohort, serum interleukin 6 was predictive of lung function decline and mortality in SSc-ILD patients with limited disease but not in those with severe disease [49]. However, the prognostic utility of these biomarkers in individual patients remains uncertain: further validation is required to allow their use in routine practice.

Bronchoalveolar lavage (BAL) cellularity has been viewed historically as an invaluable aide to treatment decisions in patients with SSc-ILD. In a number of small cohorts, a BAL neutrophilia was linked to a worse outcome. However, these observations took no account of the now well-recognized association between the presence of a BAL neu-

trophilia and extensive SSc-ILD. Based on findings in two large patient cohorts, it appears that the link between disease progression and a BAL neutrophilia merely reflects the fact that more extensive SSc-ILD is more intrinsically progressive. In over 140 patients with SSc-ILD, BAL neutrophil levels were linked to global disease severity, as judged by PFTs and HRCT disease extent, and had no independent prognostic value with regard to disease progression or long-term mortality [50]. In the SLS, PFT follow-up was such shorter short in duration but was carried out at strictly standardized time intervals. BAL findings were predictive neither of a treatment effect nor of disease progression in the placebo arm [51]. Following these studies, BAL is no longer routinely performed in the prognostic evaluation of SSc-ILD. BAL continues to be performed in selected patients with disproportionate upper-lobe abnormalities (to exclude pulmonary tuberculosis) or when HRCT evaluation suggests a coexisting disease process such as smoking-related interstitial lung disease.

Management

Historically, the core principle in the management of SSc-ILD has been to suppress inflammation with corticosteroid or immunosuppressive therapy. This approach, based on a disease model in which inflammation precedes and leads to fibrosis, has been supported only by anecdotal reports and uncontrolled treatment effects in small groups of patients. The key limitation is the low prevalence of SSc-ILD in routine practice. For this reason, treatment statements were determined by clinical experience at single-referral centres for many years. However, since the millennium, multi-centre treatment studies in SSc-ILD (or in broader SSc populations with SSc-ILD evaluated using a key secondary endpoint), have proven to be possible. Pivotal data include placebo-controlled trials of oral cyclophosphamide [18], intravenous cyclophosphamide [52], bosentan [53], tocilizumab [54], nintedanib [55], a pivotal comparison between oral cyclophosphamide and mycophenolate mofetil [56], and a recent placebo-controlled trial of rituximab [57].

Cyclophosphamide was a logical trial therapy in the first controlled treatment trials in SSc-ILD because partial regression with treatment was seen in some patients in small pilot series. In the landmark placebo-controlled SLS-1 trial of oral cyclophosphamide, statistically significant treatment effects were apparent at 1 year on FVC levels, dyspnoea, skin thickening and quality of life [19]. The SLS-1 trial was followed by a UK placebo-controlled trial of intravenous cyclophosphamide (given once a month for 6 months, followed by maintenance therapy with oral azathioprine) [52]. The study was under-powered due to recruitment difficulties that are now regarded as inescapable in this field. The FVC treatment effect was similar to that seen in the SLS-1 trial, in spite of only marginally significant ($p = 0.08$) due to the small cohort sizes ($n = 45$) [50]. Taken together, the two studies prompted EULAR to conclude that cyclophosphamide was an appropriate therapy in SSc-ILD [58].

However, this conclusion has not been uniformly accepted, and at the least, it is clear that cyclophosphamide should not be introduced indiscriminately in all patients with SSc-ILD. In both trials, the average FVC treatment benefit was less than 5% of baseline values and in the SLS-1 trial, although not in the UK trial, the small gain in FVC came at the cost of a significant prevalence of adverse effects. Importantly, many patients with mild lung disease were enrolled in both studies. This is understandable: the risk that an individual patient may receive a placebo, when open therapy is available, is likely to be more acceptable to patients and referring physicians alike when lung disease was not overtly progressive or severe. In keeping with this limitation, it is salutary that after patients in the SLS-1 trial had completed treatment and returned to routine follow-up, less than 15% were prescribed open therapy by their primary physicians [59]. Crucially, there was no treatment effect in the SLS-1 trial in patients with mild disease on HRCT. By contrast, there was a striking treatment effect on FVC (>10%) in extensive fibrotic disease, providing a useful clue as to which patients are likely to benefit in clinical practice [18].

At the time, it came as a surprise that in both trials, the treatment effect mostly represented stabilization with active treatment, rather than improvement. Regression of disease had been seen more frequently in previous smaller retrospective reports and received more focus than disease stabilization though, in the largest case series, FVC levels increased by an average of 4% in 39 patients receiving cyclophosphamide but fell by 7% in 30 untreated patients [60]. Based on the reversibility of disease in these and other pilot series, BAL and HRCT findings considered to be indicative of "alveolitis" were inclusion criteria in the SLS study [18], although, as discussed earlier, reversible disease is identified reliably in SSc-ILD by neither test.

The SLS-1 and UK cyclophosphamide trials did not provide guidance on best longer-term management. Indeed, the SLS data underlined the need for maintenance therapy without providing any answers in this regard. Analyses of lung function trends in the SLS cohort showed that therapeutic benefits had entirely been lost 12 months after treatment cessation [59]. For many years, azathioprine or methotrexate was used empirically until mycophenolate mofetil has gained in popularity based on a perception of greater efficacy and lower toxicity. This anecdotal impression was evaluated formally in a meta-analysis of safety and efficacy drawn from six eligible studies: outcomes were evaluated using trends in

FVC and DLCO% [61]. Overall, mycophenolate was associated with stabilization of disease, with no significant improvement in either pulmonary function variables.

These and other data prompted a comparison of the efficacy and tolerability of mycophenolate and cyclophosphamide in SSc-ILD, the SLS-2 study, undertaken by the USA SLS group [56]. Treatment with mycophenolate for 2 years or cyclophosphamide for 1 year was associated with similar improvements in measures of lung function: mycophenolate was better tolerated and associated with less toxicity.

High-dose corticosteroid therapy is viewed by many as absolutely contraindicated in SSc-ILD, due to an association between renal crisis and the use of prednisolone doses in excess of 15 mg daily [62, 63].

Following the SLS-1 and SLS-2 studies, routine therapeutic intervention in SSc-ILD most commonly consisted of mycophenolate, preferred to cyclophosphamide based on tolerability, and variably given in combination with low-dose corticosteroid therapy. However, the therapeutic landscape has now changed in SSc-ILD with the recent trials of tocilizumab [54] and nintedanib [55].

The focuSSced trial of tocilizumab [54] in the treatment of patients with diffuse cutaneous SSc can be applied to routine SSc-ILD management with two caveats: the primary endpoint used and the study enrolment strategy. Active treatment was associated with significant attenuation of decline in FVC; however, FVC change was a secondary endpoint—the primary end-point (change in the modified Rodnan skin score) was not met. Reassuringly, in an earlier phase II trial of tocilizumab in SSc, the same pattern of endpoint responsiveness was observed: with active treatment, a change in skin score (the primary endpoint) was not seen, but there was a reduction in the frequency of pulmonary function decline [64]. Furthermore, the study did not selectively enrol patients with SSc-ILD, although the treatment effect was robust in the majority SSc-ILD subgroup. Pulmonary function tests at baseline were mostly normal or mildly reduced. From the nature of the study population, it can be argued that the treatment benefit applies to patients with diffuse cutaneous SSc and limited SSc-ILD, when pro-inflammatory pathways may be more prominent.

Nintedanib, a tyrosine kinase inhibitor with anti-fibrotic effects, was evaluated in the SENSCIS nintedanib SSc-ILD trial, in patients with fibrosis affecting at least 10% of the lungs. The annual rate of FVC decline, the primary endpoint, was 52.4 mL in the nintedanib arm and 93.3 mL in the placebo arm, a relative reduction in FVC decline of approximately 45%. No benefit of was observed for other manifestations of systemic sclerosis. Treatment was generally well tolerated with gastrointestinal adverse events, including diarrhoea, occurring more frequently with active treatment. Patients on mycophenolate for at least 6 months before randomization were able to participate and made up 49% of the total cohort. Importantly, the findings indicated that the combination of mycophenolate and nintedanib is a safe treatment option [65]. The benefits of mycophenolate and nintedanib in attenuating FVC decline appeared to be additive, but this requires further evaluation as the use of mycophenolate was not randomized.

Nintedanib was also evaluated in the INBUILD trial of non-IPF fibrotic lung disease, progressing despite management, including a subgroup of patients with SSc-ILD [66]. The treatment effect in attenuating FVC decline was highly statistically significant with a proportional reduction in decline of over 50% associated with active treatment. Taken together, the SENSCIS and INBUILD nintedanib data provide a basis for nintedanib therapy in SSc-ILD, both as initial treatment in selected patients and in patients with progressive lung disease despite immunosuppressive therapy.

Taken together, pivotal trials in SSc-ILD have validated the use of cyclophosphamide, mycophenolate, nintedanib and tocilizumab in patients at risk of ILD progression. Immunosuppressive therapy is likely to remain first-line treatment in the majority of SSc-ILD patients as neither tocilizumab nor nintedanib has had benefits in extrapulmonic disease. The optimal selection of patients to receive initial combination therapy with mycophenolate and nintedanib has yet to be defined.

Rituximab shows promise as an SSc-ILD intervention, despite yet to be subjected to controlled evaluation in a large patient cohort. In a pilot evaluation of anti-topoisomerase-positive SSc-ILD patients, there were improvements in pulmonary function data initially [67] and further improvements at 2 years [68]. Uncontrolled treatment benefits have also been reported in patients with polymyositis lung [69] and in a mixed group of patients with connective tissue disease and life-threatening lung disease [70]. In a small randomized control trial, comparing Rituximab with standard treatment, significant benefits were observed in the Rituximab arm in serial FVC and serial DLco [71]. The most compelling data come from a placebo-controlled evaluation of Rituximab, primarily focusing on skin disease, but supporting a significant benefit in SSc-ILD based on a key secondary endpoint [57].

Other interventions have not been studied in detail in SSc-ILD. Bone marrow transplantation has been used in small groups of patients with severe SSc, including in some

patients with severe SSc-ILD [72, 73]. Three randomized studies have shown that autologous hematopoietic stem cell transplantation is superior to conventional treatment in SSc, resulting in longer overall survival, longer disease-free survival and higher quality of life [72, 74, 75]. However, although significant improvements in pulmonary function tests have been documented, this treatment approach has yet to be widely viewed as standard therapy in severe SSc-ILD.

Clinical Vignette

A case of a 71-year-old man who presented with a 1-year history of Raynaud phenomenon, limiting dyspnoea and limited cutaneous scleroderma. He was a former smoker, stopping at age 30 with a five pack-year smoking dose. There was no other past medical history of note. At presentation, his exercise tolerance was unlimited on the flat, walking at his own pace, but he was compelled to rest on climbing two flats of stairs. On auscultation of his chest, crackles were audible to the mid-zones.

No abnormalities were present on routine blood tests. Initial autoimmune serology showed strongly positive anti-nuclear antibodies but no specific serological abnormalities and, in particular, he was anti-Scl70 antibody negative. Pulmonary function tests revealed FVC 60% of predicted, DLco 34% and Kco 68%. The calculated alveolar-arterial oxygen gradient was at the upper limit of normal (3.1 kPa). An echocardiogram was unremarkable. Representative HRCT sections (Fig. 12.4a–c) were in keeping with the overall conclusion, on rapid evaluation of all images between the main carina and the higher diaphragm that disease extent was "intermediate" overall (i.e. not clearly either <20% or >20% on rapid evaluation). Based on the FVC level of 60% of predicted, his lung disease was staged as extensive. There was also enlargement of the main pulmonary artery with the diameter greater than the aortic diameter (Fig. 12.4b).

His initial lung-specific therapy consisted of Prednisolone 10 mg daily, intravenous cyclophosphamide 650 mg/m squared at four weekly intervals. After six cycles of cyclophosphamide, he continued on low-dose prednisolone and mycophenolate for 6 years of follow-up with complete stability of FVC levels. However, there were major changes in measures of gas transfer and gas exchange (Fig. 12.5a–c). It is instructive to note that following a normal echocardiogram, serial Kco levels (Fig. 12.5b) provided the clearest signal of an increasing pulmonary vasculopathy whereas DLco change (Fig. 12.5a) was less clear cut, possibly due to the confounding effects of interstitial lung disease. Serial measures of pO2 and the A-a gradient were less useful in early progression of vasculopathy but changed strikingly prior to overt right ventricular decompensation. Even before pulmonary hypertension was diagnosed, the patient had received intermittent prostanoids for Raynaud phenomenon and warfarin was added follow right heart study. Following right ventricular decompensation, the patient was oxygen dependent and sildenafil was introduced.

The case is presented for several reasons. The use of the "mild/extensive" severity staging system, discussed in the text, is illustrated: a clear conclusion that the patient had extensive disease, despite a duration of disease of only 1 year, led to vigorous immunomodulation, with complete stabilization of interstitial lung disease during 6 years of follow-up. Had progression of interstitial lung disease occurred, possible treatment options, based on recent data, would have included nintedanib. The autoantibody profile was nonspecific, possibly in keeping with the parallel development of interstitial lung disease and a disproportionate pulmonary vasculopathy (in association with marginally extensive lung disease but no hypoxia until pulmonary hypertension was established). Overall, despite targeted therapy, there was an insidious downward in measures of gas transfer and gas exchange over 6 years, despite treatment. However, from our knowledge of the usual outcome in pulmonary hypertension in SSc, a worthwhile treatment benefit cannot be excluded. Finally, the case does illustrate the use of serial pulmonary function indices in helping to increase suspicion of worsening pulmonary vasculopathy, leading to earlier invasive evaluation in appropriate cases.

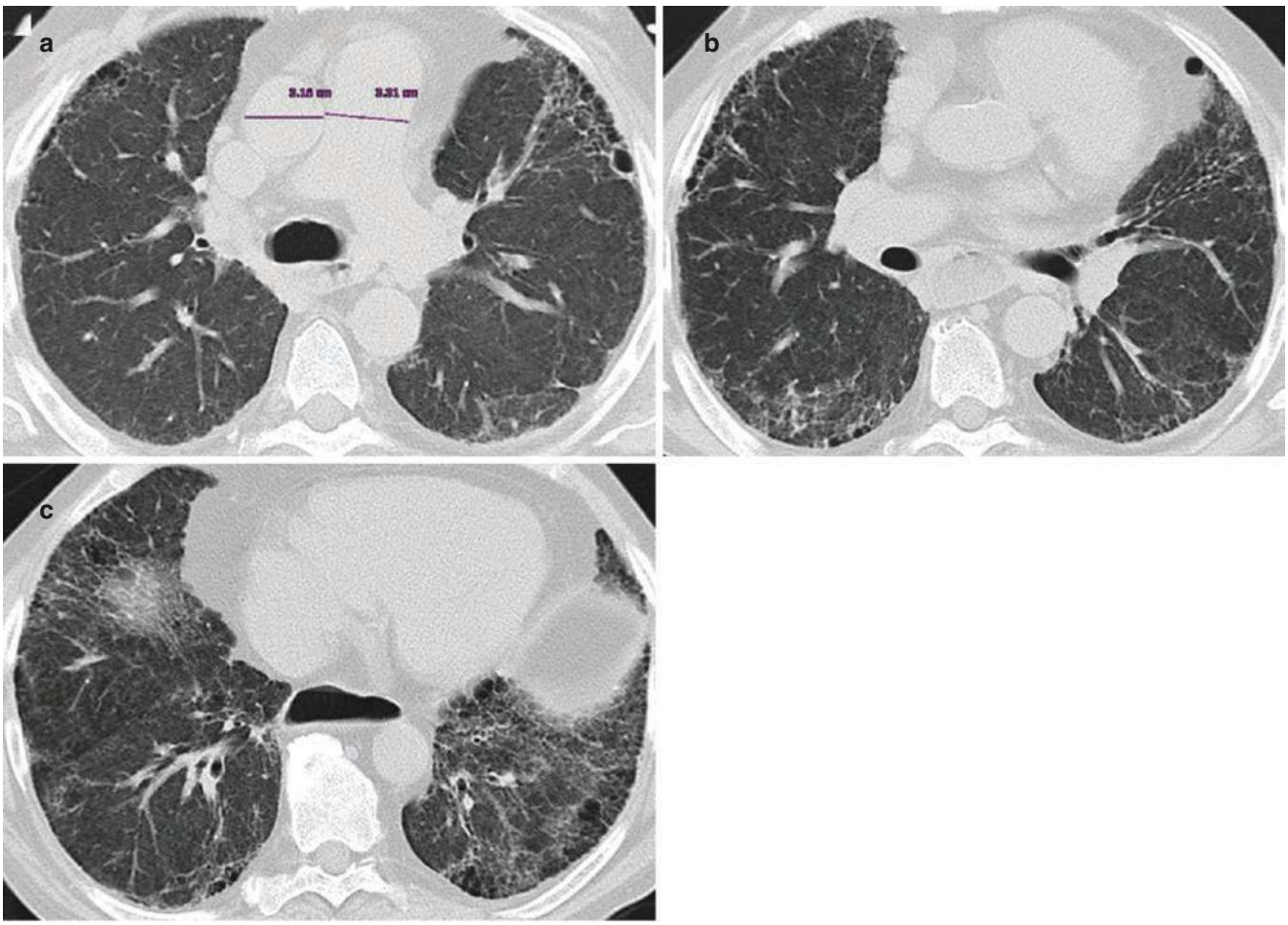


Fig. 12.4 (**a**–**c**) Representative HRCT sections in a patient who was staged as having extensive interstitial lung disease, based on an "indeterminate" disease extent and an FVC level of 60% of predicted. In basal sections, disease extent on HRCT was clearer greater than 20%, but this was counter-balanced by much less extensive disease between the main carina and the pulmonary venous confluence. Note also, in (**a**), that the ratio of the pulmonary artery to the aorta was increased, suggesting the presence of pulmonary vasculopathy

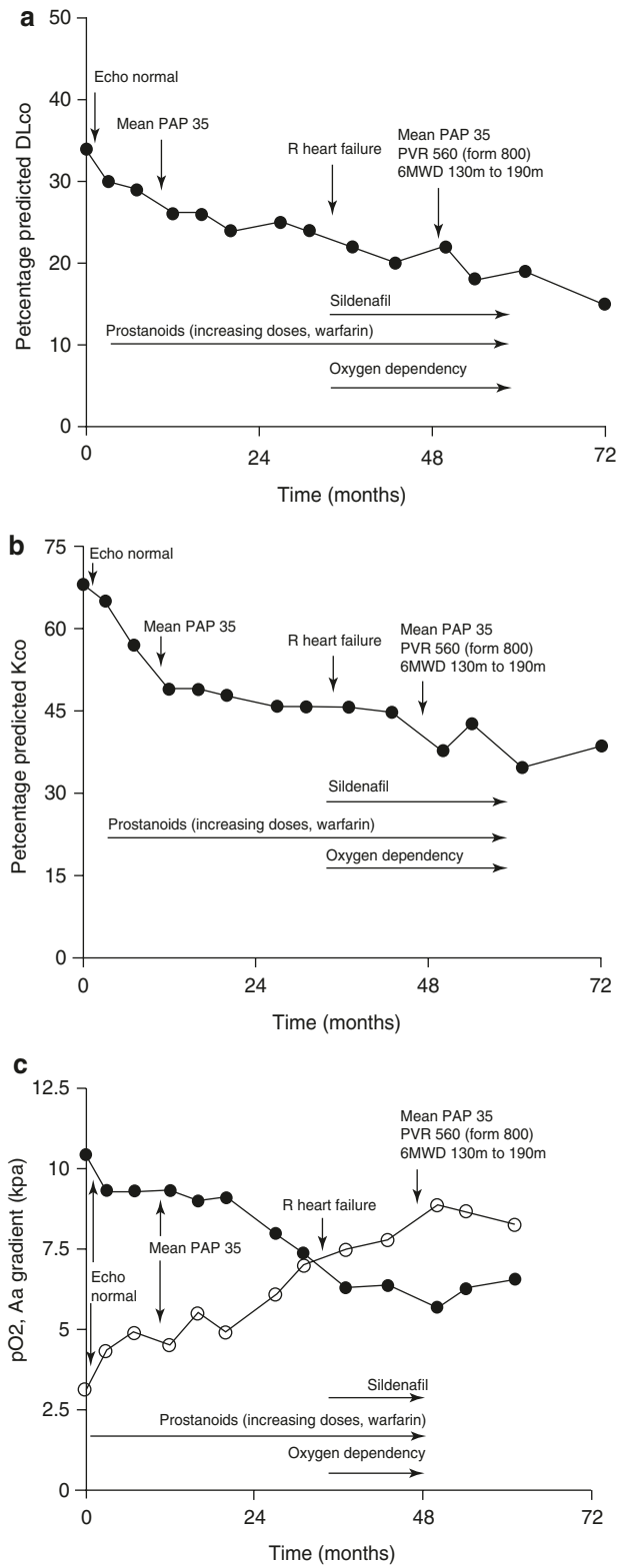


Fig. 12.5 Serial measures of gas exchange and gas transfer throughout follow-up are shown, including DLco (**a**), Kco (**b**) and pO2 and calculated alveolar-arterial oxygen gradient on air (**c**). Serial trends are shown in relation to relevant therapies and findings at echocardiography and right heart catheterization. Serial Kco trends were most discriminatory as pulmonary hypertension developed, whereas gas exchange trends were more predictive of right heart decompensation

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Rheumatoid Arthritis and the Lungs

13

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Introduction

Rheumatoid arthritis (RA) is the most common of the connective tissue diseases, with a global prevalence of 0.24–0.5% (more than 18 million people) [1, 2]. It is among the top 50 contributors to global disability [1] and leads to high healthcare related costs [3]. It has long been known that RA is not a disease isolated to the joints. Extra-thoracic manifestations (ExRA) are well described, reported in nearly every organ system, and lead to significant morbidity and mortality [4]. All compartments of the respiratory system can be involved (Table 13.1), with the interstitium, pleura, and airway most commonly affected. In addition to the direct pulmonary involvement, the lungs are at risk for secondary pulmonary complications such as drug-induced lung disease and opportunistic infections. Lung involvement of any kind is seen in 60–80% [5–7], though a significant number of these cases are either subclinical (no associated symptoms) or not clinically significant (not contributing to death or disability). Though the lung disease often follows the development of the articular disease, lung involvement may be first manifestation of RA in a subset of patients. In this chapter we will discuss the major lung manifestations of RA, namely interstitial lung disease, airways disease, and pleural disease.

Table 13.1 Pulmonary involvement in RA

Pleura
Pleural effusions
Pleural fibrosis
Airway
Cricoarytenoid arthritis
Bronchiectasis
Follicular bronchiolitis
Bronchiolitis obliterans
Diffuse panbronchiolitis
Chronic obstructive pulmonary disease
Mild airway inflammation
Interstitium
Usual interstitial pneumonia
Nonspecific interstitial pneumonia
Organizing pneumonia
Lymphocytic interstitial pneumonia
Diffuse alveolar damage
Acute eosinophilic pneumonia
Apical fibrobullous disease
Amyloid
Rheumatoid nodules
Vasculature
Pulmonary hypertension
Vasculitis
Diffuse alveolar hemorrhage with capillaritis
Secondary pulmonary complications
Opportunistic infections
Pulmonary tuberculosis
Atypical mycobacterial infections
Nocardiosis
Aspergillosis
Pneumocystis jiroveci pneumonia
Cytomegalovirus pneumonitis
Drug toxicity
Methotrexate
Gold
D-penicillamine
Sulfasalazine
Leflunomide
Biologic therapy

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Rheumatoid Arthritis-Associated Interstitial Lung Disease

Epidemiology

Interstitial lung disease (ILD), defined as varying degrees of inflammation or fibrosis in the interstitial compartment of the lung, is common in RA with a prevalence that varies with the population studied and the mode of detection (Table 13.2). Accurate prevalence estimates are further hindered by a lack of established diagnostic criteria, the absence of standard approaches to screening, and variations in the populations studied (i.e. age, presence of symptoms, modality of diagnosis). Studies that rely on health care databases are additionally subject to diagnostic coding and classification bias. When studying unselected RA patients, the prevalence ranges from 19% to 67% [6, 8–13]. Prevalence estimates for the general population range from 3.2 to 6.0 RA-ILD cases per 100,000 persons (with incidence rates from 2.7 to 3.8 per 100,000 persons) [14]. Studies of the US RA population have yielded cumulative incidence estimates of clinically significant RA-ILD in 5% of patients at 10 years [15], 6.3% at 15 years [16], and 6.8% over 30 years [17] of follow-up with an estimated lifetime risk of developing clinically significant ILD of 7.7% [18]. A large study of over 40 million US death certificates identified 160,000 records of decedents with RA; investigators found clinically significant ILD (defined as a contributor to death) in 6.8% of women and 9.8% of men [19]. Prevalence rates of RA-ILD have been reported for certain ethnic groups: 3.7% in a cohort of Hispanic and Asians [20], 3% in Koreans [21], 4.2% in Italians [22], 3.7% in Spaniards [23], and 4.8% in Turks [24]. Though the incidence of disease appears stable [14, 15], both the prevalence and the death from ILD among decedents with RA are on the rise [14, 15, 19, 25].

Healthcare costs among this patient population are significant. The total excess societal costs attributable to RA are estimated to be US $39.2 billion [3]. RA-ILD patients have an incurred annual healthcare cost of $30,000–$50,000 and a mean total 5-year healthcare cost of US $173,405 per patient [14].

Table 13.2 Prevalence and cumulative incidence of interstitial lung disease in rheumatoid arthritis

Cumulative incidence of RA-ILD	5% at 10 years [15]
	6.3% at 15 years [16]
	6.8% at 30 years [17]
Lifetime risk of RA-ILD	7.7% [18]
Clinically significant RA-ILD (defined as contributing to death)	6.8% in women [19]
	9.8% in men [19]
Prevalence of RA-ILD in ethnic subgroups	3% in Koreans [21]
	4.2% in Italians [22]
	3.7% in Spaniards [23]
	4.8% in Turks [24]
Prevalence of RA-ILD in "high risk" patients (symptoms or abnormalities on PFTs or CXR)	91% [26]
Prevalence of RA-ILD in unselected patients	19–67% [6, 8–13]
Prevalence of RA-ILD using a multi-modality approach	58% [9]

RA-ILD rheumatoid arthritis-associated interstitial lung disease, *PFTs* pulmonary function testing, *CXR* chest X-ray

Risk Factors for ILD (Table 13.3)

The presence of RA is a strong risk factor for the development of clinically significant ILD with an odds ratio of 8.96 [18]. In established RA, a number of risk factors for the development of ILD have been identified, though few have strong supporting data. Smoking, a documented risk factor for the development of RA in general [27], increases the risk of RA-ILD [28–30] and has been reported to do so in a dose-dependent manner [10]. Although RA is more common in women [31], male sex seems to be a risk factor for RA-ILD [9, 10, 12, 18, 32]. Age increases the risk [6, 16, 18], with a hazard ratio of 1.41 for every 10-year increase in age [16]. Higher RA disease activity, as measured by the Health Assessment Questionnaire [16], Disease Activity Score 28 [33], erythrocyte sedimentation rate [6, 16, 18], rheumatoid factor (RF) [6], erosions/destructive joint changes and rheumatoid nodules [18] have also been associated with the development of RA-ILD. Higher scores on the HAQ have also been associated with disease progression as measured by longitudinal declines in the forced vital capacity (FVC) and diffusing

Table 13.3 Possible risk factors for rheumatoid arthritis-associated interstitial lung disease

Stronger Evidence
Smoking
Male sex
Advanced age
Rheumatoid arthritis disease activity
Weaker Evidence
Methotrexate
Anti-TNF agents
Anti-cyclic citrullinated antibodies
Genetics

TNF tumor necrosis factor

capacity for carbon monoxide (DLCO) [10]. Many of the medications used to treat RA have been reported to be associated with the development of drug-induced ILD though evidence of causation is lacking. Methotrexate has long been speculated to contribute to ILD in a minority of RA patients [18] though recent data suggest no increased incidence in patients on long-standing treatment [34]. The anti-TNF agents infliximab [35], etanercept [36], and adalimumab [37] have all been associated with the development of ILD or exacerbation of pre-existing ILD in case reports, but large population-based studies have not supported an increased risk [38, 39].

In addition to clinical risk factors, genetic risk factors are being identified. The HLA shared epitope (SE) is known to be a risk factor for RA and, though older studies did not find an association between the presence of SE alleles and ILD [6, 16, 40], a recent study looking at 450 Japanese RA patients found associations between HLA-DR2 and ILD [41]. RA-ILD patients also appear to share gene variants linked to familial pulmonary fibrosis such as mutations in the *TERT*, *RTEL1*, *PARN*, and *SFTPC* genes [42]. Recently, a gain of function variant in the promoter region of a gene encoding mucin 5b (*MUC5B*), the strongest genetic risk factor for IPF, was found in up to 32% of patients with RA-ILD [43].

Pathogenesis

The pathogenesis of RA in general and in RA-ILD more specifically remains unknown. Genetics play a role, but they do not explain all of the risks. Environmental exposures resulting in a dysregulated immune response are also involved. A variety of environmental exposures are associated with RA-ILD risk, with tobacco smoking the strongest known. Smoking leads to increased citrullinated protein levels in the lung, as measured by bronchoalveolar lavage (BAL) fluid [44]. Because the RA-related anti-citrullinated protein antibodies target citrullinated proteins, it has been hypothesized that smoking-associated increases in citrullinated proteins may contribute to the pathogenesis of RA [45, 46], but further study is still needed. In general, it is well established that RA-related antibodies (e.g. RF and anti-citrullinated protein antibodies) can be elevated in the blood several years prior to the onset of joint inflammation [47]. This finding has led to the currently accepted model of RA development, in which the initial immune dysregulation starts at a mucosal site. Many of the data supporting this hypothesis suggest the lung as one of the main mucosal trigger sites [45, 46]. For example, studies have demonstrated RA-related antibody generation in the lung, using sputum or BAL, in individuals before and after RA onset in the joints [48, 49]. It is less clear what mechanisms lead to the development of RA-ILD, with more research clearly needed.

It has been speculated that RA-ILD may be the coincidental development of IPF in an individual with underlying RA. While there are some shared similarities between IPF and RA-ILD including shared clinical and genetic risk factors mentioned above, the prevalence of clinically significant RA-ILD within RA patients is markedly higher than the prevalence of IPF in the general population (5% vs. 0.2%), suggesting pathogenic features specific to RA are likely involved in the development of RA-ILD.

Clinical Features and Diagnosis

There are no established diagnostic criteria for RA-ILD (Box 13.1). Similar to other progressive ILDs, the onset of RA-ILD is often insidious and is characterized by progressive breathlessness with or without a dry cough. Unlike those with isolated ILD, patients with ILD and an inflammatory arthritis can have musculoskeletal limitations to physical activity leading to delayed recognition of respiratory symptoms. RA-ILD is more common in men [9, 10, 12, 18, 32] and the average age of ILD onset is in the seventh decade of life [50, 51] irrespective of the year of RA onset [52]. The duration of RA prior to the onset of ILD depends on the age of onset of RA (with earlier onset RA having a longer duration prior to ILD) and the subtype of ILD (with UIP having a shorter duration) [52]. The majority of patients with RA-ILD will present with RA first, though ILD can precede RA in up to 17% of cases [51, 52] and be diagnosed before or within a year of the diagnosis of RA in up to a third of cases [51–53]. In diagnosing RA-ILD, clinicians should consider the possibility of drug-induced lung disease and infection as a cause or contributor.

Box 13.1 Proposed Diagnostic Criteria for RA-ILD

Patient must have all of the following major criteria and at least one minor criterion:

Main Criteria

1. RA by 1987 ACR [54] and/or 2010 ACR/EULAR criteria [55]
2. Radiographic evidence of ILD
3. Exclusion of other known causes of ILD

Minor Criteria

1. Respiratory-related symptoms (i.e. rest or exercise-induced breathlessness and/or cough)
2. Physiologic evidence of restriction (i.e. FVC and/or TLC <80% predicted)
3. Gas-exchange abnormalities (exercise-induced desaturation of ≤89% and/or DLCO <80% predicted)

High-resolution computed tomography (HRCT) is the cornerstone of diagnosis and shows patterns similar to those in idiopathic interstitial pneumonias (IIPs). The most common pattern of RA-ILD is one of the usual interstitial pneumonia (UIP, Fig. 13.1), characterized by peripheral and basilar-predominate reticulations and honeycombing/traction bronchiectasis and a paucity or absence of other features such as ground glass opacities and nodules [56, 57]. The second most common pattern is nonspecific interstitial pneumonia (NSIP, Fig. 13.2), characterized by ground glass opacities and a paucity or absence of honeycombing. Organizing pneumonia is a rare manifestation of RA and can be secondary to medications or infection [58].

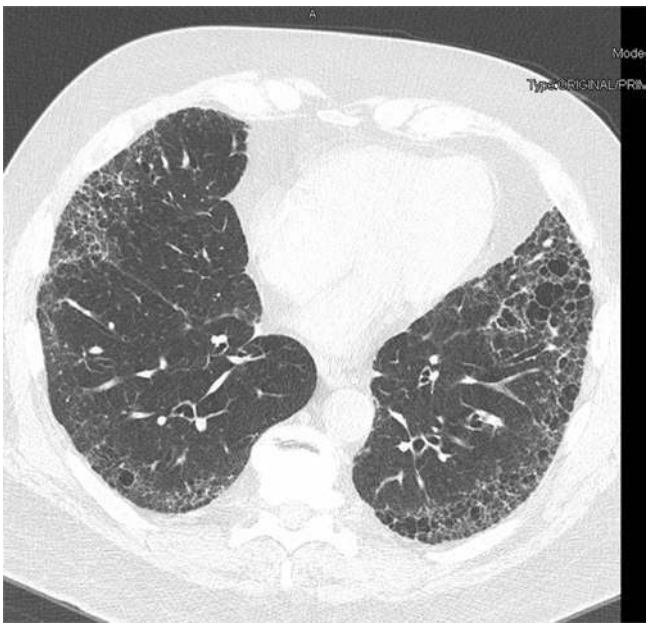

Fig. 13.1 High-resolution computed tomography (HRCT) findings in rheumatoid arthritis-associated usual interstitial pneumonia (RA-UIP)

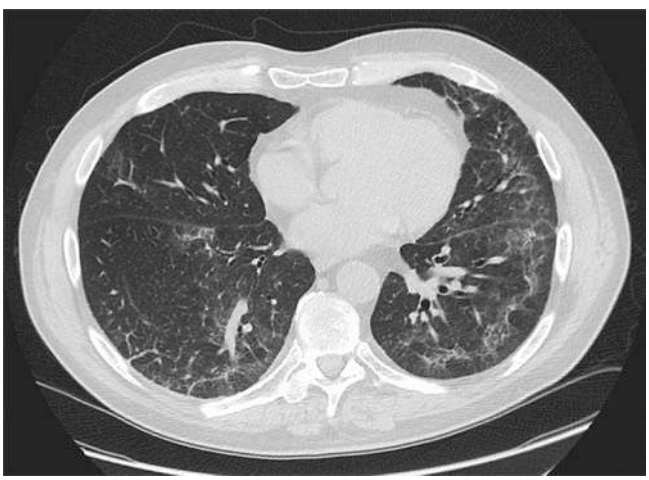

Fig. 13.2 High-resolution computed tomography (HRCT) findings in rheumatoid arthritis-associated nonspecific interstitial pneumonia (RA-NSIP)

Pulmonary function testing (PFT) shows a progressive restrictive ventilatory defect as the disease progresses, defined as reduced lung volumes (total lung capacity, FVC, and residual volume). Due to loss of surface area for gas exchange, the DLCO decreases and the reduced compliance of the lung leads to increased elastic recoil manifested by an increase in the forced expiratory volume in 1 s (FEV1)/FVC ratio. Gas-exchange abnormalities are present and correlate with the degree of parenchymal involvement. The correlations between the degree of interstitial involvement and PFTs can be affected by concomitant conditions such as emphysema (leading to a higher FVC and lower DLCO for any degree of interstitial involvement) and pulmonary hypertension (leading to a lower DLCO for any degree of interstitial involvement). Oxygen desaturation initially presents during activity and progresses to be present at rest and during sleep as the disease progresses.

BAL is not necessary for the diagnosis in the majority of cases. Patients with RA-ILD have an increase in the total cell numbers [59] with elevations in neutrophils, lymphocytes, and eosinophils [9, 26, 60]. BAL is also abnormal in subclinical ILD [61] and can help distinguish these patients from those with normal physiology and chest imaging [62]. BAL is particularly useful in excluding infection.

Surgical lung biopsy can help establish the diagnosis of RA-ILD and prognosticate. While histopathologic patterns may have prognostic significance [51, 56], chest imaging can often predict the underlying pathologic pattern, with an HRCT pattern of UIP highly specific for a pathologic pattern of UIP, thus precluding the need for a surgical lung biopsy [51, 63]. Pathologic findings vary, with UIP the most common pattern identified. It is characterized by temporal heterogeneity (i.e. areas of normal lung interspersed with areas containing fibroblast foci adjacent to areas of established fibrosis) subpleural accentuation and varying presence of microscopic honeycombing (Fig. 13.3) [51]. In comparison to the UIP pattern seen in IPF, UIP in RA has more lymphoid aggregates and germinal centers [64] and fewer fibroblast foci [65, 66]. NSIP has either patchy or, more commonly diffuse, fibrosis and inflammation that is temporally uniform (Fig. 13.4) [51].

Treatments

In spite of the prevalence and morbidity of RA-ILD, only one phase 2 randomized treatment trial has been completed (PMID: 36075242) and, there are no approved therapies specific for RA-ILD. There are limited reports of treatment with methotrexate [67], azathioprine [68], cyclosporine [69], mycophenolate mofetil [70], and TNF-α inhibitors [71, 72]. Mycophenolate mofetil has been evaluated in a retrospective cohort analysis of 125 patients with CTD-ILD and, in the 18

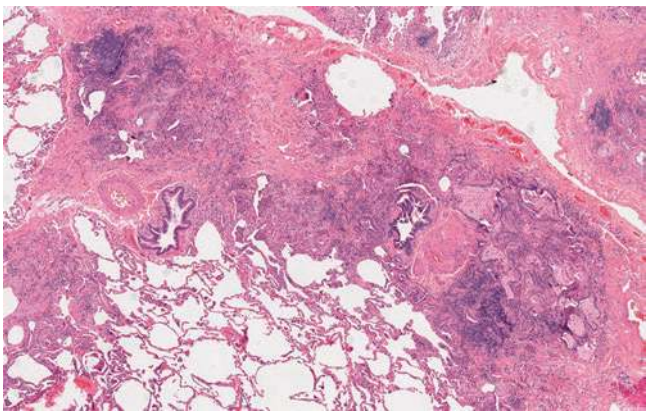

Fig. 13.3 Histopathology of rheumatoid arthritis-associated usual interstitial pneumonia (RA-UIP)

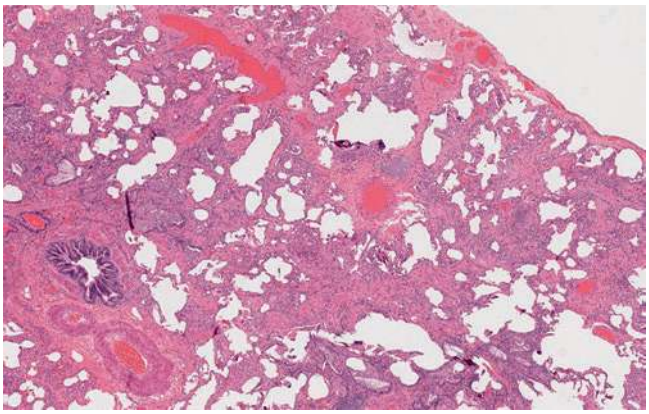

Fig. 13.4 Histopathology of rheumatoid arthritis-associated nonspecific interstitial pneumonia (RA-NSIP)

patients with RA-ILD, there was acceptable safety and tolerability and a trend toward an improvement in FVC [73]. In a recent open-label registry study of 63 patients with RA-ILD and a mean follow-up of 9.4 months, two-thirds of patients on abatacept, an antagonist of T-lymphocyte co-stimulation, had stable lung function and dyspnea as measured by the Modified Medical Research Council Dyspnea Scale [74].

Anti-CD20 therapy with rituximab has biological plausibility given the finding of CD20-positive B-cell hyperplasia in RA-ILD [75]. There are a number of case series showing rituximab stabilizing patients with RA-ILD when used as primary or salvage therapy [76–80]. A retrospective evaluation of 10 years of experience at a single center where rituximab was given for joint disease, 52% of patients with ILD were stable and 16% improved [78]. A prospective open-label study of rituximab for salvage therapy in progressive RA-ILD enrolled ten patients and found stabilization in six of seven patients who completed the study, three of whom had UIP [79].

Response to therapy appears to be dictated by the underlying pattern of ILD, with NSIP having a higher likelihood of response to immunosuppression compared to UIP [50, 51]. In treating patients with RA-ILD, it is important to remember that adequate control of joint disease does not correlate with adequate control of lung disease and vice versa. Any treatment plan should include input from the patient's rheumatologist.

Given the radiographic and pathologic similarities between RA-ILD and IPF, there is interest in evaluating the efficacy of the anti-fibrotics approved for use in IPF, nintedanib, and pirfenidone. RA-ILD was evaluated as a subgroup in the recently released INBUILD trial [81], finding that nintedanib resulted in a significantly slower rate of lung function decline compared to placebo for patients with fibrosing ILD, particularly in those with a UIP pattern of fibrosis. The only prospective randomized placebo-controlled treatment trial in RA-ILD is the TRAIL1 trial looking at pirfenidone in patients with RA and fibrotic ILD (PMID: 36075242). Though the primary endpoint wasn't met, pirfenidone slowed the progression of ILD as measure by decline in FVC in a magnitude similar to that seen in other trials of antifibrotics. In addition, the addition of pirfenidone was found to be safe and well-tolerated in the setting of RA-specific treatments.

In addition to pharmacologic therapy, RA-ILD patients should be vaccinated against common respiratory infections according to published guidelines [82]. Physical therapy should be considered for patients with deconditioning or limitations to physical activity from lung or joint disease. Clinicians should ensure normoxia at rest, with activity, and with sleep through formal oxygen titration and nocturnal oximetry. Given the prevalence of heart disease in subjects with RA [83], providers should have a low threshold to look for obstructing coronary disease in patients whose new or progressive dyspnea cannot be explained by their lung disease alone. Attention to bone health is crucial for any patient on corticosteroids. Smokers are overrepresented in the RA-ILD population and tobacco cessation for active smokers should be regularly stressed. Finally, RA-ILD has an impact on health-related quality of life [84] and attention should be paid to the patients mental health in addition to their physical health.

Lung transplant should be considered in all eligible patients with progressive lung disease. Outcomes in RA-ILD patients are similar to those with IPF and transplant results in significant improvement in quality of life [85].

Prognosis

ILD is a leading cause of death in patients with RA and worsens outcome [4, 14, 18]. The presence of ILD in RA increases mortality by two- to tenfold [53] and progression of disease is common—50% of patients with early asymptomatic RA-ILD and 60% of patients with established RA and a UIP pattern of fibrosis have radiographic progression over 1.5 years [86]. Large population-based medical database studies have found a median survival of 6.6–7.8 years and a 35–40% 5-year mortality for all-comers with RA-ILD (compared to 18% 5-year mortality in non-ILD RA) [14, 53].

Prediction of disease behavior over time in individual patients with RA-ILD is challenging and hindered by a limited understanding of the natural history of disease and no validated surrogate markers of progression [87]. It has long been known that HRCT and histopathologic pattern can predict outcome in ILDs. In RA-ILD, a UIP pattern on HRCT or histopathology carries a poor prognosis [50, 51, 80, 88–95], though radiologist-determined honeycombing (i.e. the distinction between "definite" and "probable" UIP based on the current international guidelines for the diagnosis and management of IPF [96]) does not seem to influence outcome [88]. Older studies found that outcomes in patients with RA and a UIP pattern of fibrosis were similar to that of IPF [50, 89–91] with median survival of 3.2–5.5 years [50, 89, 91] and 5-year survival rates of 36.6% [89] though more recent studies have found median survivals of 7.9–10.4 years [80, 88, 94]. A radiographic pattern of NSIP carries a more favorable diagnosis with 3- to 5-year survival rates ranging from 70% to 100% [51, 88, 89]. Semi-quantitative and quantitative HRCT assessments have been looked at in RA-ILD and both a radiologist-determined fibrosis score [97] and a CALIPER score vessel-related structure threshold of 4.4% [98] independently predict outcome. A risk prediction tool developed in IPF (the GAP (gender, age, physiology) model) has been shown to predict mortality in RA-ILD [99].

In addition to the chest imaging or histologic pattern of ILD, older age [16, 91, 92, 100], male gender [50], lower DLCO [50, 86, 92], and the presence of fibrosis on pathology [91] also predict mortality. Physiology at baseline and changes in physiology over time have been shown to be strong predictors of outcome [92], with a 10% decline in FVC at any point in follow-up more than doubling a patient's mortality [94].

Acute exacerbations (AE, defined as subacute worsening over 30 days without a precipitant) have an impact on progression and are a significant contributor to death in patients with RA-ILD [89]. Of all the CTDs, RA-ILD has the highest reported AE rate, estimated at 3–11% yearly and similar to that seen in the IIPs [101–106]. Exacerbations do not correlate with RA disease activity; quiescent extra-thoracic features do not preclude an AE in patients with RA-ILD. Whether from an AE or infection, patients with RA-ILD that are hospitalized for an acute respiratory worsening have a poor prognosis [106, 107], with one study reporting a median survival of 3.5 years after discharge [108].

Rheumatoid Arthritis-Associated Airways Disease

Airways disease in RA (RA-AD) can take on many forms including small airway disease (i.e. asthma, chronic obstructive pulmonary disease (COPD), constrictive bronchiolitis, and follicular bronchiolitis) and medium/large airway disease (bronchiectasis and arthritis of the cricoarytenoid joint). Similar to RA-ILD, the incidence of RA-AD depends on the population studied, the definition of airways disease, and the prevalence of smoking in the population studied. A significant number of patients with RA-AD will have physiologic or radiographic abnormalities without accompanying symptoms.

Epidemiology

The overall prevalence of RA-AD ranges from 15% to 44% [13, 109–112] in all-comers and 14–30% in non-smokers [109, 111]. The lifetime risk of developing airways disease (defined as a reduced FEV1/FVC ratio on spirometry and a physician-diagnosed airway or parenchymal lung disease) is 9.6% in all-comers with RA in comparison to 6.2% in the general population [113]. In a study of 100 consecutive RA patients who had normal CXRs, screening PFTs found 32% of patients had airflow obstruction as measured by decreased FEV1/FVC and/or forced expiratory flow 25–75 [111], a prevalence higher than in matched controls. Radiographic abnormalities suggestive of RA-AD are more common, with one study of early RA finding HRCT evidence of air trapping in 69% of patients [114]. A recent population-based study from the UK also found that airways disease, including COPD and asthma, is more prevalent in the years preceding the diagnosis of RA compared to controls (7% vs. 4% for COPD and 7% vs. 14% for asthma) [115], suggesting a potential link with RA pathogenesis. In this study, COPD preceded the diagnosis of RA by a median of 4.5 years and asthma preceded RA by a median of 12.5 years.

Risk Factors

Smoking is a well-documented risk factor for RA-AD with a hazard ratio for symptomatic AD of 4.38 in RA ever-smokers (95% CI 2.14–8.99) [113]. Other identified risk factors for AD in this population include advanced age [116], male gender [113], high titer RF and anti-citrullinated protein antibodies [116], more severe RA [113, 116], and a longer duration of RA [112, 116, 117].

Clinical Features, Diagnosis, and Outcome

RA-airways disease can be diagnosed with pulmonary physiology (i.e. reduced FEV1/FVC ratio [airflow obstruction] and elevated residual volume [gas trapping]) and HRCT (inflammation/structural changes in large and small airways

and indirectly with mosaicism and air trapping on expiratory imaging). Similar to RA-ILD, a subset of patients will have evidence of RA-airways disease on diagnostic testing without accompanying symptoms. Symptoms can range from a mild cough or wheeze with activity to profound exertional breathlessness, depending on the type of airway involvement. The presence of airway disease can lead to increased morbidity and even mortality [113, 118]. A study comparing mortality in RA patients with and without obstructive lung disease found a doubling in the risk of death in those with obstructive lung disease [113].

Subtypes or RA-AD

Obliterative Bronchiolitis

Obliterative bronchiolitis (OB) is a form of airway disease affecting the small airways (defined as airways ≤2 mm in diameter). Though first described in 1977 in six subjects (five of whom had RA [119]), there is a paucity of literature to guide clinicians in diagnosis and management. OB (also referred to as constrictive bronchiolitis) is identified by concentric narrowing of membranous and respiratory bronchioles caused by peribronchiolar inflammation and fibrosis without evidence of lymphoid hyperplasia [120]. RA has the highest incidence of bronchiolitis among the CTDs [121] though the cause is unknown and true estimates of prevalence are lacking. Studies looking at centrilobular nodules as a marker of bronchiolitis find these changes in 6% of patients [110, 122]. It is reported to be more common in women [123–126] and some case series report long-standing RA as a risk factor [124, 127]. Patients present with a nonspecific symptom complex of either abrupt or gradual onset of breathlessness and can have an accompanying cough with or without sputum production. Exam reveals squeaks and crackles on auscultation. HRCT imaging shows mosaic perfusion with or without concomitant bronchiectasis and air trapping on expiratory imaging [128] and lavage shows increases in neutrophils [129]. Up to a third of patients can have concomitant ILD [123]. There are conflicting results in the literature regarding prognosis. Older studies report declines often over months [119, 123, 127, 130–132]. In contrast, the largest case series of subjects with RA and OB found general stability with a slow decline in FEV1 over time and 27% all-cause mortality over a median follow-up of 5 years [124]. This stability over time was replicated in a study looking at all-comers with CTD-ILD (the majority of whom had RA) [121]. Female sex has been associated with better outcomes [121]. Treatment choices are based on case reports and anecdotal evidence and involve combinations of inhalers and systemic corticosteroids with or without other immunomodulatory agents. Corticosteroids are often tried though their effect may be limited [123, 126, 127, 129]. Other agents have been used in case reports such as azathioprine [127], cyclophosphamide [125], macrolide antibiotics [124, 129, 133], and etanercept [134].

Bronchiectasis

Though studies have found widely variable rates of bronchial dilatation or bronchiectasis in RA ranging from 16% to 62% [114, 135, 136], many studies find an overall prevalence around 30% [5, 29, 110, 122]. Bronchial dilatation is reported as one of the most common findings in both early and late RA [117] and, though studies have found cases where bronchiectasis precedes RA, it may be more prevalent in long-standing severe RA [137]. Recurrent infections and/or airway colonization likely play some role in its development in this population of patients treated with immunosuppression [138]. Secondary Sjögren in RA may also predispose to chronic or recurrent airway infection due to decreased and altered airway secretions. A higher prevalence of mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene has been noted in RA patients with bronchiectasis [139]. While bronchiectasis is often found as an incidental finding on chest imaging, it can cause cough with sputum, hemoptysis, dyspnea, and recurrent infections when severe [137]. The presence of early-onset bronchiectasis has been reported to increase mortality [140], up to fivefold in one study compared to patients with RA alone [141], and higher than bronchiectasis of other etiologies [142]. Treatments are similar to bronchiectasis of other etiologies and include strict management of respiratory infection, sputum mobilization, and consideration of scheduled oral/inhaled antibiotics in severe cases with recurrent infections. Severe bronchiectasis with recurrent respiratory infection in RA can be a management challenge, requiring providers to balance the use of immunosuppressive agents to control synovitis versus the risk of recurrent respiratory infection.

COPD

Though the incidence and prevalence of COPD appears to be increased in RA [113, 143–149], many studies did not control for smoking [143–145], a risk factor for both RA and COPD. Utilizing the Nurse's Health Study, investigators looked at 843 women with RA and a mean follow-up of 18.6 years and found that RA was associated with an increased risk for COPD after controlling for smoking (HR 1.68, 95% CI: 1.36–2.07) [148]. This increased risk in both smokers and non-smokers was also found in a population-based cohort study that included 603 RA patients from the Rochester Epidemiology Project [113]. These data suggest that RA patients may be more susceptible to the effects of tobacco smoke. Indeed there are possible

pathogenic links between RA and COPD that include smoking (increasing the risk of RA [27] and inducing the formation of ACPA [44, 150]) and occupational exposures [151]. Patients with RA and COPD have a 47% greater risk of COPD hospitalization compared to COPD patients without RA [152] and the 5-year mortality of patients with RA and COPD is double that of RA alone (41.9% vs. 20.5%) [153], similar to that found in ILD [14, 53]. In a study of mortality in women with RA over 36 years of follow-up, the majority of the deaths (57%) were from COPD [118]. Though a prospective trial of abatacept found a significant increase in adverse events in RA patients with COPD [154], a follow-up study utilizing US administrative databases found that biologic agents and targeted synthetic DMARDs were not associated with an increased risk of adverse respiratory events when compared to conventional synthetic DMARDs [155].

Cricoarytenoid Involvement

Cricoarytenoid involvement is common and occurs in as many as 75% of patients though many are asymptomatic [156]. Arthritis of the cricoarytenoid joints can lead to midline adduction of the vocal cords with resultant hoarseness and in some cases symptomatic inspiratory stridor.

Pleural Disease

Pleural disease is one of the most common intra-thoracic manifestations of RA with pleuritis and pleural effusion being the predominant subtypes. In post-mortem studies, pleural involvement is seen in up to 73% of patients with RA [157–159]. In a study looking at chest radiographs, pleural thickening and/or effusion was seen in 24% of men and 16% of women [160]. Pleural effusions have been associated with middle-aged men with rheumatoid nodules [161] and the presence of HLA-B8 antigen [162] and have a reported annual incidence of 1.54% in males and 0.34% in females [163]. Though the prevalence of pleural involvement is high, symptoms are less common. Pleurisy is reported in 20% of RA patients [164] and "clinical" pleural disease, including symptomatic effusions, is seen in less than 5% [161, 165, 166]. Pleural effusions in RA are exudative and sterile with low glucose (80%) and low pH 1 [167]. On cytology, they demonstrate features similar to that seen in rheumatoid nodules and synovitis, namely elongated macrophages and multinucleated giant cells alongside granulomatous debris [168]. They can rarely pre-date the onset of RA and RA-associated effusions often spontaneously resolve over time. When they are discovered, infection and malignancy need to be ruled out if appropriate.

Conclusion

RA can affect all pulmonary compartments but most commonly manifests as ILD, RA-AD, and pleural disease. RA-ILD is a prevalent and morbid condition with an increasing prevalence and a significant adverse impact on patients' quality of life. Its etiology is unknown, there are no FDA approved therapies and current treatment regimens are based on retrospective and open-label studies. RA-AD is also prevalent and can be clinically silent. The predominate types of airway involvement include bronchiolitis, bronchiectasis, and COPD and all can lead to excess morbidity and early mortality when severe. Treatment of RA-AD is based on case reports and case series and should be individualized. Finally, pleural disease is common, but often has minimal clinical impact and can show spontaneous resolution.

Clinical Vignette

A 65-year-old female presents with progressive breathlessness. She has had rheumatoid arthritis for 30 years and has been on various medications since her diagnosis such as prednisone, gold, penicillamine, and methotrexate. She recently has had good joint control on infliximab for the last 4 years. Six months ago, she had the gradual onset of breathlessness that started with activity and evolved to breathlessness at rest with a dry cough. She saw her primary care provider 3 months ago and had a workup that included a normal cardiac electrocardiograph, desaturation on a cardiac exercise treadmill, and a plain chest-radiograph showing basilar-predominate interstitial changes. A follow-up chest computed tomography showed a basilar and peripheral process consisting of reticulation and mild honeycombing without significant ground glass opacity in a usual interstitial pneumonia pattern. Her pulmonary physiology showed mild restriction with a total lung capacity of 78% predicted, a forced vital capacity (FVC) of 71% predicted, and a diffusing capacity for carbon monoxide (DLCO) of 63% predicted. She desaturated to 87% on a 6-min walk test. She has no other occupational or environmental causes for ILD and has no family history of ILD. In conjunction with her rheumatologist, she is changed from etanercept to rituximab every 6 months and an anti-fibrotic is added to her regimen. Follow-up after 6 months of therapy showed gradual progression of her lung disease as evidenced by mild reductions in both her FVC and DLCO. She had no evidence of active synovitis on follow-up. Her regimen was continued and she was referred for lung transplant evaluation.

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14 Lung Disease in Systemic Lupus Erythematosus, Myositis, Sjögren's Disease, and Mixed Connective Tissue Disease

Mada Ghanem, Eirini Vasarmidi, Lise Morer, Pierre Le Guen, and Bruno Crestani

Introduction

The lung is a frequent target of autoimmune-mediated injury in patients with connective tissue diseases (CTDs) [1, 2]. Myositis, Systemic Lupus Erythematosus (SLE), Sjögren's syndrome (SS), and Mixed Connective Tissue Disease (MCTD) can affect different levels of the respiratory tract, with a wide range of symptoms intensity, from asymptomatic to severe or life-threatening forms. Pleural disease is the most common lung manifestation in SLE and MCTD, while SS primarily affects the airways [3]. Myositis mostly affects the parenchyma, and interstitial lung disease (ILD) is the main lung manifestation of this disease [4]. However, ILD can also present in SLE, SS, and MCTD with different clinical presentations, ranging from minimal significant pulmonary restriction to severe progressive pulmonary fibrosis [5, 6].

Lung involvement in CTDs is associated with a poor prognosis, leading to increased morbidity and mortality, and an altered quality of life. Early recognition and treatment are imperative issues to limit morbidity and mortality. In addition, clinicians must be aware of non-specific pulmonary complications, such as infection, pulmonary embolism, and left heart failure, which may coexist with specific lung manifestations and contribute to increased morbidity.

Diagnosis of a pulmonary involvement can be easy when occurring in patients with a previously diagnosed CTD or can be helped by the presence of clinical features suggestive of CTD. The close collaboration of pneumologists and rheumatologists is central to the assessment of any patient with a suspicion of CTD, particularly in patients with ILD [7]. Besides clinical expertise, the use of new diagnostic tools, such as ultrasound imaging, where rheumatologists developed specific expertise, may be useful to identify and characterize CTD in patients with respiratory disorders [8] or to screen for lung involvement in patients with CTD [9]. However, respiratory symptoms might occur before any other symptom, and features of CTD can manifest later during follow-up. Homma et al. observed that 19% of the patients with ILD developed CTDs over a period of one to 11 years [10]. These manifestations could be a direct consequence of the inflammatory disease, such as ILD, or an indirect lung involvement such as infections or drug toxicity.

In this review, we aim to provide a short overview of lung involvement of these four CTDs; SLE, SS, MCTD, and myositis. We focus mostly on describing the pulmonary manifestations, the pathophysiology, and the treatment strategies based on current literature.

Clinical Vignette

A 56-year-old female with no medical history was evaluated for increasing dyspnea over 3 weeks with hands and ankles inflammatory pain. Physical examination revealed heliotrope facial edema (Fig. 14.1a) with hands and fingers swelling (Fig. 14.1b). Bibasal crackles were heard. Blood tests revealed elevated creatine kinase. A chest computed tomography showed bilateral consolidation with ground glass opacities and a localized pneumothorax (Fig. 14.1c, d). Serology detected anti-nuclear antibodies 1/600, with anti-MDA5 positivity. A diagnosis of dermatomyositis was given. The patient was treated with corticosteroids and intravenous cyclophosphamide.

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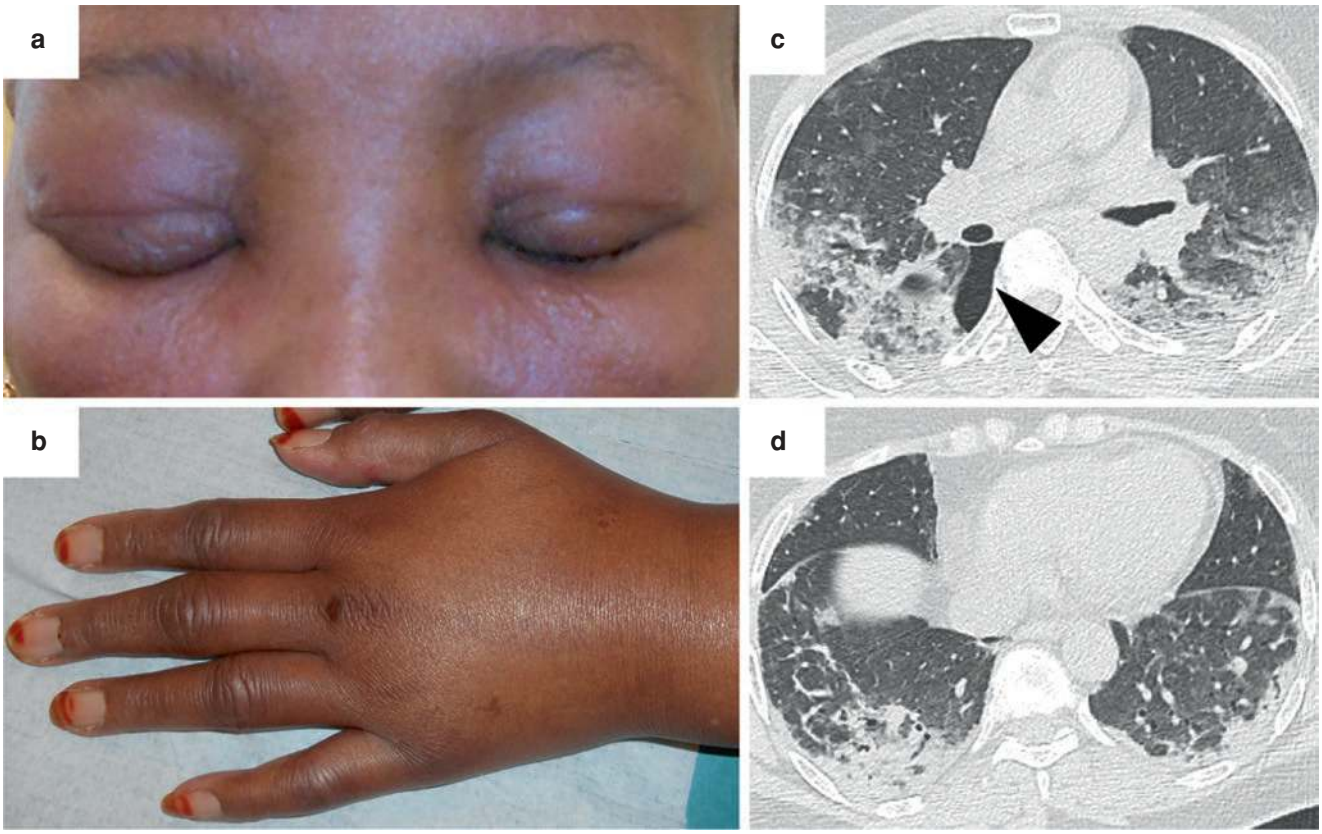


Fig. 14.1 (**a**) Heliotrope facial edema; (**b**) Fingers and Metacarpal swelling; (**c**) and (**d**): Chest computed tomography showing bilateral consolidations with ground glass opacities and a localized pneumothorax (arrowhead)

Systemic Lupus Erythematosus

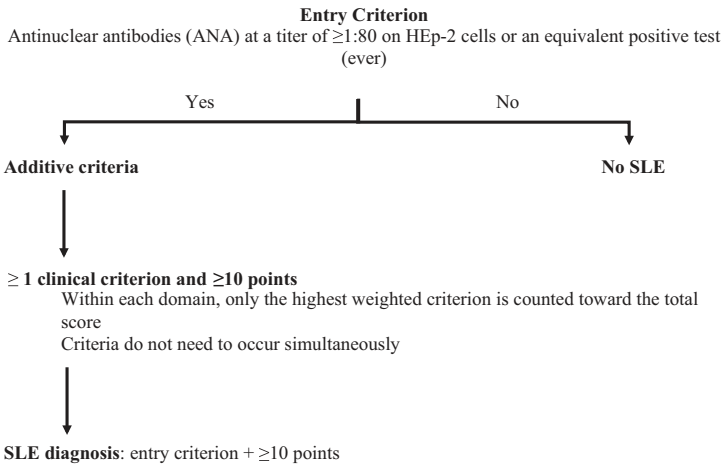
Epidemiology

Systemic Lupus Erythematosus (SLE) is a chronic, systemic autoimmune disease that mostly affects young women. Classification criteria for SLE are presented in Fig. 14.2 [11]. SLE can present with a large spectrum of clinical manifestations in several organs (skin, joints, kidney, respiratory system), with a relapsing-remitting course [12]. The prevalence of SLE is 24/100,000, with an incidence of 1–8 cases/100,000 persons/year [13]. SLE can affect all lung compartments (Table 14.1); the pleura, the parenchyma, the airways, the pulmonary vasculature, and the respiratory muscles [14] with the prevalence of respiratory involvement throughout the course of the disease ranging from 20 to 90% [15, 16].

Pathophysiology

Lupus pathophysiology)involves genetic and environmental factors, which lead to a break of immune tolerance, resulting in an aberrant immune response against endogenous nuclear antigens. Autoreactive B and T cells accumulate in secondary lymphoid organs and produce autoantibodies against multiple nuclear antigens, such as double-stranded DNA (dsDNA), RNP, Smith antigen, Ro, and La. These autoantibodies aggregate with the autoantigens and complement factors to form circulating immune complexes. The complexes deposit in target organs such as joints, skin, central nervous system, and/or kidneys to induce inflammation and tissue injury [17]. Lymphocytic and mononuclear interstitial and peribronchiolar infiltrates can be present in SLE-associated ILD. Pulmonary manifestations are generally associated with disease activity, hypocomplementemia, and increased levels of anti-dsDNA, while interstitial involvement has been associated with anti-Ro and anti-U1RNP antibodies, and with scleroderma traits [15, 18].

Antinuclear antibodies (ANAs) are positive in virtually all patients with SLE (usually 1:160 or higher), but are also often found in other autoimmune diseases, infections, neoplasia, drug exposure, and in healthy individuals, especially the elderly. Anti-dsDNA presents lower sensitivity (66–95%), but higher specificity, ranging from 75 to 100% and are linked to disease activity (Table 14.2). Anti-Smith (anti-Sm) are less sensitive (30%) but highly specific (over 95%). Anti-Ro (SSA), anti-La (SSB),)and anti-RNP antibodies are



Additive criteria:

Clinical Domains	Weight	Immunological Domains	Weight
Constitutional		**Antiphospholipid antibodies**	
Fever	2	Anti-cardiolipinantibodies or Anti-β2GP1 antobodies or Lupus anticoagulant.	2
Hematologic		**Complement proteins**	
Leucopenia	3	Low C3 or C4	3
Thrombocytopenia	4	**SLE-specific Antibodies**	
Autoimmune Hemolysis	4	Anti-dsDNA antibody or Anti-Smith antibody	6
Mucocutaneous			
Non-scarring alopecia	2		
Oral ulcers	2		
Subacute cutaneous or discoid lupus	4		
Acute cutaneous	4		
Serosal			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Musculoskeletal			
Joint Involvement	6		
Renal			
Proteinuria >0.5gr/24h	4		
Renal biopsy class II or V lupus nephritis.	8		
Renal biopsy III or IV lupus nephritis	10		

Fig. 14.2 2019 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) Classification Criteria for Systemic Lupus Erythematosus (SLE). (Modified from [11]). *Anti-β2GPI* anti–β2-glycoprotein I, *anti-dsDNA* anti–double-stranded DNA

Table 14.1 Pulmonary involvement in systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), mixed connective tissue disease (MCTD), and myositis

	SLE	Sjögren's	MCTD	Myositis
Parenchyma (ILD)	+	++	++	+++
Histology	NSIP > OP > UIP	NSIP > UIP > LIP > OP	NSIP	NSIP > OP > UIP > DAD
Vessels/PH	++	+	++	+++
DAH	+	_	_	+
Pleura	+++	+	+	+
Airways	+	++	+	

Table 14.2 Most common antibodies associated with each connective tissue disease

Antibodies	
SLE	ANAs (high sensitivity but low specificity) anti-dsDNA, anti- Sm, anti-Ro(SSA), anti-La(SSB)
Sjögren's	Anti-Ro(SSA), anti-La(SSB)
MCTD	Anti-U1snRNP
Myositis	• Myositis-specific autoantibodies, anti-tRNA synthetase; anti-Jo-1 (PL1), anti-PL7, anti-PL12, anti-KS, anti-OJ, anti-EJ, anti-SC, anti-JS, anti-YRS (ha), anti-zo • Dermatomyositis-specific autoantibodies; anti-Mi2, anti-NXP2 (MJ, p140), anti-MDA5 (CADM-140), anti-TIF-1γ (p155/140) • Other myositis-specific autoantibodies; anti-SRP, anti-HMGR (200–100), anti-SAE • Myositis-associated autoantibodies; anti-Ro/SSa, anti-U1RNP, anti-PM/Scl, anti-Ku

less specific markers, as they are positive in other autoimmune diseases [19]. Lupus-type circulating anticoagulants, anti-cardiolipin antibodies, and anti-B2GP1 antibodies are associated with antiphospholipid syndrome.

Pulmonary Manifestations

Pleural Disease

Pleural disease is the most common lung manifestation observed approximately in 60% of patients (50–83% in autopsy series) (Table 14.1) [20, 21].

Treatment choice for pleural disease depends on the severity of symptoms and the amount of liquid. Small asymptomatic effusions may not require specific treatment, while non-steroidal anti-inflammatory drugs and corticosteroids (prednisone dose 0.5 mg/kg) are mostly used when treatment is required [22]. In refractory cases, immunosuppressive and corticosteroid-sparing agents, such as azathioprine, mycophenolate mofetil, or methotrexate should be discussed. Chest tube drainage or pleurodesis are only rarely required for symptomatic relief of resistant disease.

Acute Lupus Pneumonitis and Diffuse Alveolar Hemorrhage

The most life-threatening lung manifestations are acute lupus pneumonitis and diffuse alveolar hemorrhage, which are observed only in a minority of patients (2–4%) [21]. A recent meta-analysis described potent risk factors correlated with increased risk of hemorrhage in SLE patients, such as neuropsychiatric involvement, nephritis, higher Systemic Lupus Erythematosus Disease Activity Index 2000 score, and low levels of C3 and C4 complement fractions, platelets, and hemoglobin [23].

Clinical data about treatment for acute immune-mediated lung injury associated with SLE are limited (no prospective controlled studies), and treatment strategies are based on other autoimmune conditions associated with pulmonary hemorrhage and acute pneumonitis. Corticosteroids are widely accepted as the first line of therapy, and intravenous pulses of corticosteroids are usually given (methylprednisolone 500 mg–1000 mg/day). Cyclophosphamide, rituximab, plasmapheresis, and intravenous immunoglobulins have been also used in critically ill patients [24].

Shrinking Lung Syndrome

The shrinking lung syndrome caused by diaphragmatic dysfunction, although well recognized, is a very rare manifestation [25].

There is no evidence for the optimal management of the shrinking lung syndrome. Corticosteroids and immunosuppressive agents, including azathioprine, mycophenolate mofetil, and rituximab, have been mainly used [26]. Individual cases have been improved with inhaled β-agonists [27], and theophylline [28].

Thrombotic Manifestations

Antiphospholipid syndrome is associated with SLE with a prevalence of 30% [29] and can be associated with thrombotic events, with or without pulmonary embolism in 35–42%, compared to 9% in patients with SLE alone [30]. Pulmonary embolism is an important entity to be considered in patients with SLE, and in that case, the initial management does not differ from the established guidelines. Thrombotic manifestations are mostly observed in patients who have secondary antiphospholipid syndrome [31]. Anticoagulant therapy, mainly with warfarin, is strongly recommended in antiphospholipid syndrome, due to the lack of evidence on novel oral anticoagulants. Pregnant women suffering from antiphospholipid syndrome require treatment with both aspirin and low molecular weight heparin throughout the pregnancy period.

Interstitial Lung Disease

Interstitial lung involvement has been found in about 15% of patients (Table 14.1). Non-specific interstitial pneumonia (NSIP), organizing pneumonia (OP), lymphocytic interstitial pneumonia (LIP), and less commonly, usual interstitial pneumonia (UIP) have been described [32]. Treatment of SLE-ILD is based on limited data and is mostly extrapolated from studies about other CTD-ILDs. The first-line treatment usually relies on corticosteroids, while mycophenolate mofetil or azathioprine are used as maintenance therapy. Rituximab and cyclophosphamide can be used in more severe cases [33].

Other Pulmonary Manifestations

Airways can be concerned in approximately 16% of the patients, mostly asymptomatic. Infection is the most common parenchymal disease observed in SLE, and it should always be excluded in patients with respiratory symptoms, particularly in patients under immunosuppressive therapy [34, 35]. Clinically significant pulmonary hypertension (PH) is a rare but severe complication of SLE, typically associated with scleroderma clinical features and anti-RNP antibodies [36–38].

Prognosis

SLE presents with a highly variable clinical course, while pulmonary infections and thrombotic events govern morbidity and mortality). PH also affects survival with two-year mortality just above 50%, but the most frequent causes of death are thromboses and infections [34, 38]. More rare causes associated with poor prognosis are acute lupus pneumonitis and diffuse alveolar hemorrhage, with mortality ranging from 50% to 90% despite treatment [39] (Table 14.3).

Table 14.3 Risk factors for interstitial lung disease (ILD) and pulmonary hypertension (PH) development and prognostic factors

Disease	Risk factors for ILD	Risk factors for PH	Poor prognosis
SLE	Longstanding disease older age overlapping clinical features with scleroderma; Raynaud's phenomenon, sclerodactyly SSB/La, Scl-70, and U1RNP antibodies	Antiphospholipid and anti-cardiolipin antibodies ILD shrinking lung syndrome	DAD acute lupus pneumonitis SSA/Ro antibodies
Sjögren's	Hypergammaglobulinemia Lymphopenia RF, SSA/Ro, and SSB/La antibodies	Raynaud's phenomenon pulmonary embolism RF, SSA/Ro, and SSB/La and anti-RNP antibodies	UIP pattern PH lymphoma
MCTD	Male gender high anti-RNP antibody titer anti-Ro-52 positivity no prior arthritis		PH
Myositis	Cutaneous manifestations; telangiectasias, Raynaud's phenomenon Anto-Ro52 positivity	Cutaneous manifestations peripheral microangiopathy SSA/Ro positivity severe ILD Polyarthralgia longstanding disease	Older age acute/subacute onset clinically amyopathic dermatomyositis rapidly progressive ILD; MDA5positivity PL7/PL12 positivity

Sjögren's Syndrome

Epidemiology

Sjögren's Syndrome is a systemic autoimmune disease, the second most common after rheumatoid arthritis. It is characterized by impairment of the exocrine glands (mainly lacrimal and salivary glands) due to lymphocytic infiltration, and also extraglandular, visceral involvement (Table 14.4) [40, 41]. It has a clear female predominance, and it occurs either as a primary disorder or in association with other CTDs as secondary SS. SS has a prevalence of 20–100/100,000 and an incidence of 3.9/100,000. The prevalence of lung involvement is between 10–20%, although up to 65% of asymptomatic patients may have abnormal lung imaging [42, 43].

Pathophysiology

SS pathophysiology involves a combination of environmental, genetic, and hormonal influences, leading to autoimmune epithelitis, deregulated immune responses, and infiltration of B and T lymphocytes into affected tissues [44]. Triggered B-cells favor the secretion of anti-SSA and anti-SSB autoantibodies directed to small cytoplasmic RNP-bound peptides [45]. T-cells are also activated and involved in cytotoxic procedures. Lung involvement is associated with higher levels of circulating immune complexes and autoantibodies [46]. The main serum markers indicative of SS are anti-SSA and anti-SSB (Table 14.2). High levels of these antibodies, and also ANA, rheumatoid factor, hyper-γ-globulinaemia, as well as older age and smoking history, have been considered risk factors for pulmonary involvement [47, 48].

Table 14.4 American College of Rheumatology/European league against Rheumatism classification criteria for primary Sjögren's syndrome (2016)

Item	Weight
AntiSSA(Ro) antibody positivity	3
Labial salivary gland with focal lymphocytic sialadenitis and a focus score ≥1 foci/mm^2	3
Abnormal ocular staining score ≥ 5 (or van Bijsterveld score ≥ 4) in at least one eye	1
Schirmer test ≤5 mm/5 min in at least one eye	1
An unstimulated salivary flow rate ≤ 0.1 mL/min	1

Individuals with signs and symptoms suggestive of Sjögren's syndrome who have a total score ≥ 4 for the items above, meet the criteria for primary Sjögren's syndrome
Reproduced and modified from [40]

Pulmonary Manifestations

Airway Disorders

Airway disorders are common manifestations of SS (Table 14.1). Apart from upper airway disorders due to mucosal dryness and impaired mucociliary clearance, bronchiolitis and bronchiectasis are also frequently described in patients with SS (more than 20%) (Fig. 14.3a, b) [49, 50]. SS should be included in the differential diagnosis in a patient presenting with airway disorder (chronic cough or small airway disease) or pulmonary lymphoproliferative disorder. However, clinicians should be careful as lymphoma and amyloidosis can present with a LIP pattern on HRCT, and so tissue biopsy should be discussed on a case-by-case base.

Lymphoproliferative Disease

Patients with SS display a high risk for both nonneoplastic (e.g., nodular lymphoid hyperplasia, follicular bronchiolitis,

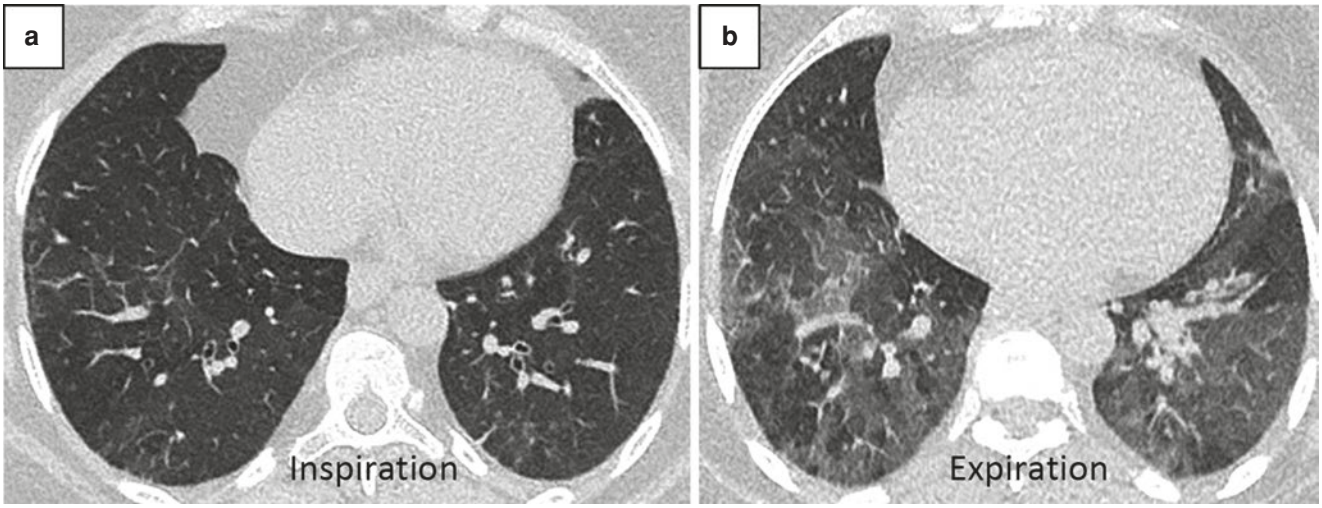


Fig. 14.3 Constrictive bronchiolitis in a patient with Sjögren's syndrome. A mosaic attenuation pattern is observed at full inspiration (Panel **a**), with air trapping revealed at end-expiration (Panel **b**)

lymphoid interstitial pneumonia), as well as neoplastic monoclonal lymphoproliferative disorders. The prevalence of lymphoma in SS ranges from 5% to 18% [51].

Approximately 6% of Sjögren-associated lymphomas involve the lungs and the most common types are the marginal zone B-cell lymphoma and mucosa-associated lymphoid tissue type [52, 53].

Such a lymphoproliferative involvement of the lungs in patients with SS can present as non-resolving consolidations, solitary or multiple nodules or masses, lymphadenopathy, and cystic lesions (Fig. 14.4). Given the increased risk for lymphoproliferative disorders, active clinical surveillance is recommended, especially for patients who are at high risk for lymphoma due to persistent salivary gland swelling, vasculitis and palpable purpura, lymphadenopathy, low C3 or C4 complement fraction, monoclonal gammopathy, cryoglobulins, anti-SSA and/or anti-SSB, rheumatoid factor, anemia, leukopenia, lymphopenia, neutropenia, thrombocytopenia, and elevated serum beta2-microglobulin [43, 54].

Lymphoma requires specific hematological treatment, and a multidisciplinary approach is suggested for diagnosis and management [43].

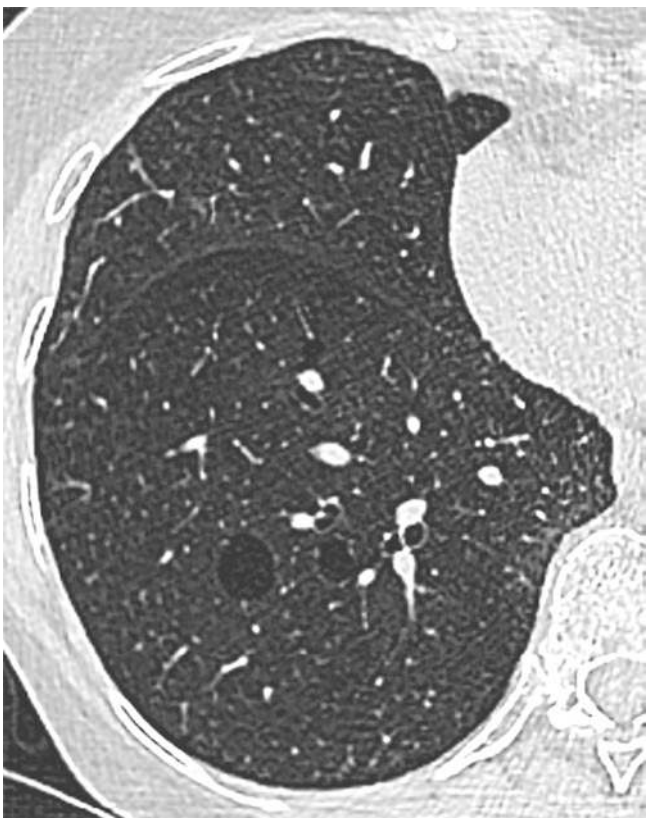


Fig. 14.4 Cystic lung disease in a patient with Sjögren's syndrome

Interstitial Lung Disease

ILD is mainly considered to be developed later in the course of Sjögren's syndrome, with a prevalence of 47% in 15 years; however, in 10–51% of patients, ILD may occur before other SS manifestations [42]. NSIP seems to be the prominent ILD pattern (45%), while UIP (16%), LIP (15%), and OP (7%) are less common, although a combined pattern is frequently described [55, 56]. The UIP pattern is associated with a progressive phenotype (Fig. 14.5a, b) [57].

With regard to the management of pulmonary disease in Sjögren's syndrome, recent consensus guidelines were published shedding light on the optimal way of evaluation and treatment of these patients [43]. For patients presenting a mild disease with preserved lung function and minimal symptoms, a serial follow-up is recommended. In symptomatic or moderate-severe lung function impairment or/and HRCT findings, the first-line treatment including corticoste-

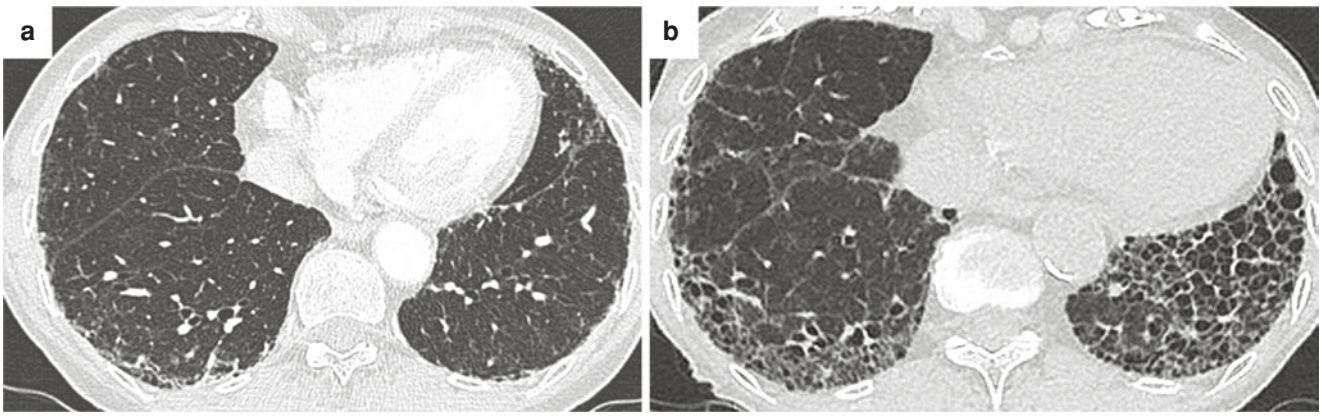


Fig. 14.5 Progression from mild fibrotic subpleural posterior abnormalities (Panel **a**) to massive honeycombing (Panel **b**) within 14 years in a patient with primary Sjögren's syndrome

roids, followed by azathioprine or mycophenolate mofetil as corticosteroids sparing or as add-on agents is the suggested treatment strategy. In refractory or rapidly progressive cases, high doses of steroids as well as rituximab or cyclophosphamide should be considered [43]. Regarding corticosteroids, which are suggested as a first-line treatment, an initial daily dose of 0.5–1 mg/kg of prednisone has been suggested [58, 59]. The HRCT pattern can help predict the efficacy of treatment, as NSIP, OP, and LIP have been associated with a better response than the UIP pattern [58, 60]. In the case of an established UIP pattern, it is doubtful whether immunosuppressive treatment ameliorates lung fibrosis [61]. The use of tocilizumab in SS-ILD has been reported in a case of steroid-resistant OP [62].

Prognosis

Pulmonary involvement in SS seems to compromise severely the mortality risk, and in particular, the UIP pattern has been associated with worse survival [42] (Table 14.3). A rare complication of SS as PH or lymphoma also worsens prognosis, with an average 5-year survival in case of lymphoma to be 65–90% [38, 63].

Mixed Connective Tissue Disease

Epidemiology

Mixed Connective Tissue Disease (MCTD) is an autoimmune disorder characterized by the detection of serum anti-RNP antibodies associated with features of systemic sclerosis (SSc), SLE, and inflammatory myopathies [64, 65].

The prevalence of MCTD is 3.8/100,000 adults [66] while the annual incidence was 1.9/100,000 in a recent study in the USA [67]. Serositis is common, with an estimated incidence varying from 6% to 50%. ILD occurs in about 36% to 50% of patients and is severe in 19% [68, 69]. PH is a major clinical feature in MCTD, with a prevalence of 10–50% [70–72].

Pathophysiology

Autoantibody production may be driven by distinct subsets of HLA-restricted T cells and HLA DRB1*04: 01 was confirmed to be a major risk allele for MCTD [73]. Anti-U1-small nuclear ribonucleoprotein particle autoantibodies (anti-U1-snRNP) may be pathogenic by different mechanisms of action. First, it could bind to endothelial cells, to U1-RNP peptides presented by the MHC class II, or/and recognize fragments of nucleosome RNP in endothelial cell apoptotic blebs. Anti-U1-snRNP may also contribute to immune complexes that may activate the complement. A recent study proposed that the basophil/IgE/IL-4/CCL11 axis could be involved in the pathogenesis of MCTD, as activated basophils and autoreactive IgE to U1-snRNP were found in MCTD patients [74]. However, further studies are needed to better understand the pathophysiology of MCTD.

Anti-U1-snRNP antibodies are a mandatory criteria for diagnosis of MCTD (Table 14.5) [75]. Although highly sensitive (almost 100%), this marker is characterized by its low specificity and can be found in SLE [70]. Two factors are considered highly indicative of MCTD: the positive IgG anti-U1-RNP with negative IgM anti-U1-RNP and the elevated 70 k anti-U1-RNP titers [76]. In MCTD, the anti-DNA positivity could predict drift to SLE, while rheumatoid factor and anti-CCP seem to associate with arthritis. Anti-U1RNP positivity may be a predictor of more aggressive erosive arthritis [70].

Table 14.5 Alarcón-Segovia and Villareal criteria for the classification of mixed connective tissue disease (MCTD) [75]

Serological	Anti-RNP (titer of ≥1:1.600)
Clinical	1. Raynaud's phenomenon 2. Swollen/"puffy" hands 3. Synovitis 4. Myositis 5. Acrosclerosis/peripheral sclerosis

MCTD diagnosis: Positive serology plus at least three clinical criteria
Reproduced table from [3] by permission

Pulmonary Manifestations

Pulmonary Hypertension

PH is frequently observed during the course of MCTD (Table 14.1) and can be classified into group 1, pulmonary arterial hypertension, or group 3, as a consequence of ILD according to the World Health Organization classification. Among CTDs, MCTD was found to be the most commonly associated with pulmonary arterial hypertension in a Japanese study [77]. In the national UK registry study, 8% of the pulmonary arterial hypertension-CTD patients presented MCTD compared to 74% presenting systemic scleroderma [78].

There are no specific guidelines for the treatment of PH associated with MCTD, and the treatment options are derived from studies of pulmonary arterial hypertension-specific therapies in idiopathic pulmonary arterial hypertension. In group 1 PH, endothelin receptor antagonists (bosentan, ambrisentan), phosphodiesterase 5 inhibitors (sildenafil, tadalafil), and prostanoids (intravenous epoprostenol, subcutaneous treprostinil, nebulized iloprost) could be discussed according to the prognostic risk calculation. Compared to idiopathic/heritable pulmonary arterial hypertension, patients with CTD respond poorly to treatment [79] and have a worse prognosis. Aggressive up-front combination therapy with ambrisentan and tadalafil has been shown to reduce the risk of clinical failure compared to monotherapy [80] and could be the ideal option in CTD-PH patients.

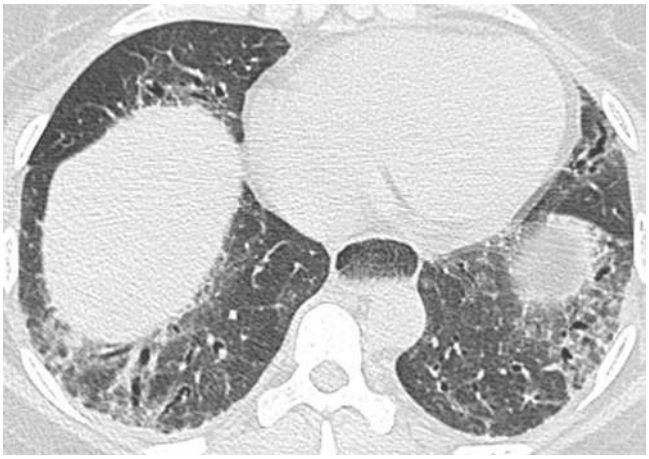


Fig. 14.6 Fibrotic NSIP pattern in a patient with mixed connective tissue disease. Note the esophageal dilation

Interstitial Lung Disease

MCTD-associated ILD affects up to 60% of patients, is usually slowly progressive, and is associated with increased mortality (Figs. 14.6 and 14.7). No controlled data are available, but immunosuppressive treatments are commonly suggested, including corticosteroids and immunosuppressive therapies, such as azathioprine, mycophenolate mofetil, cyclosporine, and methotrexate. Intravenous cyclophosphamide should be considered in severe ILD [69, 81, 82].

Prognosis

The most common cause of death is PH followed by severe infections due to immunosuppressive therapies [83]. Data on the course and outcome of ILD in MCTD are limited. A study has calculated the 5-year survival rates for <5% ILD extent to be 94%, compared to 82% for >5%. Common risk factors for ILD progression in MCTD is male gender, high

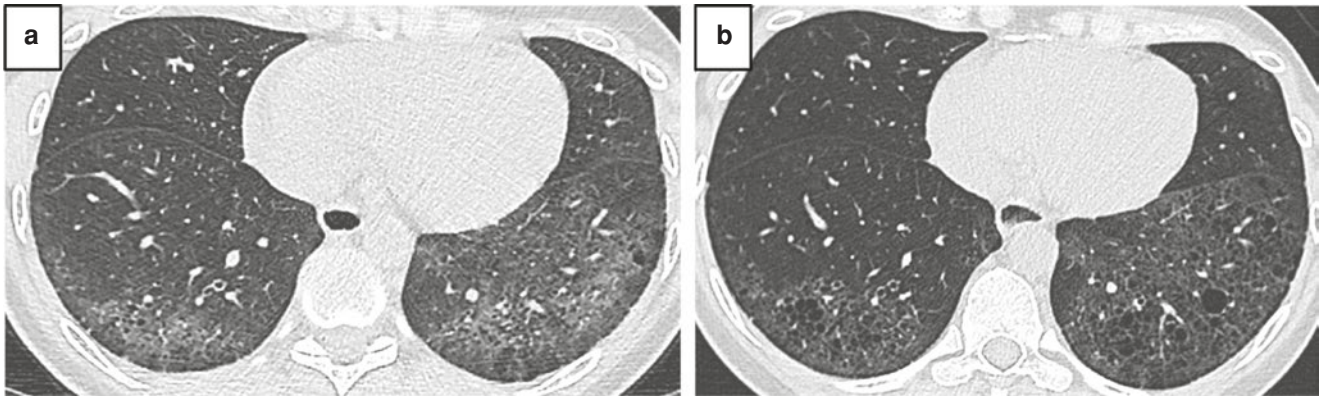


Fig. 14.7 NSIP pattern with ground glass opacities and cystic lesions in the lower lobes in a patient with mixed connective tissue disease (panel **a**). A progressive decrease of the ground glass and increase in the size and extent of cystic lesions was observed during follow-up (panel **b**)

anti-RNP antibody titer, presence of anti-Ro-52 antibodies, and no prior arthritis (Table 14.3) [68, 84].

Myositis

Epidemiology

Myositis, also known as idiopathic inflammatory myopathies, is a group of rare autoimmune diseases characterized by skeletal muscle inflammation, associated with frequent extramuscular signs such as arthritis, Raynaud's phenomenon, mechanic's hands, and interstitial lung disease (ILD) (Table 14.6) [85]. Myositis is a heterogenous group of CTDs composed of polymyositis (PM), dermatomyositis (DM), clinically amyopathic dermatomyositis and anti-synthetase syndrome [6, 86].

Due to this highly heterogeneous nature of myositis, along with the lack of clear diagnostic criteria, epidemiological data are scarce. Based on current data, myositis are rare, with a prevalence ranging from 2.4 to 33.8 per 100,000 inhabitants, and an annual incidence ranging from 1.16 to 19 per million worldwide [87].

Pathophysiology

Pathophysiology of anti-histidyl-tRNA synthetase, also known as an anti-Jo1 positive anti-synthetase syndrome, is best described. It can be favored by environmental exposure, such as tobacco, airborne contaminants and mineral particles, or by respiratory tract infections. These factors lead to aggression of lung tissue, and to a break of immune tolerance [88]. Innate immune cells such as NK lymphocytes are unspecifically activated and release proteolytic enzymes. The release of histidyl-tRNA-synthetase, an antigen that has immune properties, then leads to the recruitment of immune

Table 14.6 The 2017 EULAR/ACR classification criteria for adult and juvenile idiopathic inflammatory myopathies (IIM)

Variable	Score points	
	Without muscle biopsy	With muscle biopsy
Age of onset		
Age of onset of first symptom assumed to be related to the disease ≥18 years and < 40 years	1.3	1.5
Age of onset of first symptom assumed to be related to the disease ≥40 years	2.1	2.2
Muscle weakness		
Objective symmetric weakness, usually progressive, of the proximal upper extremities	0.7	0.7
Objective symmetric weakness, usually progressive, of the proximal lower extremities	0.8	0.5
Neck flexors are relatively weaker than neck extensors	1.9	1.6
In the legs proximal muscles are relatively weaker than distal muscles	0.9	1.2
Skin manifestations		
Heliotrope rash	3.1	3.2
Gottron's papules	2.1	2.7
Gottron's sign	3.3	3.7
Other clinical manifestations		
Dysphagia or esophageal dysmotility	0.7	0.6
Laboratory measurements		
Anti-Jo-1 (anti-histidyl-tRNA synthetase) autoantibody present	3.9	3.8
Elevated serum levels of creatine kinase or lactate dehydrogenase or aspartate aminotransferase or alanine aminotransferase	1.3	1.4
Muscle biopsy features-presence of		
Endomysial infiltration of mononuclear cells surrounding, but not invading, myofibres		1.7
Perimysial and/or perivascular infiltration of mononuclear cells		1.2
Perifascicular atrophy		1.9
Rimmed vacuoles		3.1

When no better explanation for the symptoms and signs exists, these classification criteria can be used. It is proposed that a patient may be diagnosed with IIM if the probability exceeds a predetermined cutoff of at least 55%, which corresponds to a score of ≥5.5, or ≥6.7 if biopsies are included

Modified table from [85]

cells, with CD8-T cell priming and CD4-T cell-B cell crosstalk, with the production of anti-histidyl-tRNA synthetase autoantibody. Genetic factors can also be involved, such as HLA-B*08.01. The propagation of the disease to other organs remains poorly explained [89].

Measurement of myositis-associated antibodies and myositis-specific antibodies levels is required in the initial evaluation of ILD, especially in the presence of skin or muscle clinical features (Table 14.2). The negativity of antinuclear autoantibodies does not rule out the presence of myositis-associated antibodies or myositis-specific antibodies [90].

Patients with the anti-synthetase syndrome are clinically characterized by arthritis, Raynaud's phenomenon, mechanics hands, and fever, but can also present with isolated ILD [91, 92].

The anti-synthetase antibodies (anti-Jo1, anti-PL7, anti-PL12, anti-KS, anti-OJ, anti-EJ, anti-SC, anti-JS, anti-YRS, anti-Zo) targeting the aminoacyl-tRNA synthetase enzyme are the most frequently found myositis-specific antibodies, occurring on average in 20% of PM patients and 29% of DM patients (Table 14.2). Anti-PL-7 appears to be associated with ILD preceding the diagnosis of myositis, and anti-PL12 patients have a higher rate of isolated ILD [92]. Anti-MDA5 antibody (previously known as anti-CADM-140) is a myositis-specific antibody associated with pulmonary involvement and is a risk factor for severe and rapidly progressive ILD, with increased mortality [93, 94]. Moreover, it is associated with a higher likelihood of having clinically amyopathic dermatomyositis [95]. Anti-MDA5 antibody detection identifies a subgroup of patients characterized by dermatomyositis skin rash, skin ulcers, calcinosis, mechanic's hands, ILD, arthralgia/arthritis, and a high mortality rate [96].

Anti-PM-Scl and anti-Ku are two myositis-associated antibodies associated with a high prevalence of ILD, ranging from 38 to 78% for anti-PM-Scl and 27% for anti-Ku [93].

Pulmonary Manifestations and Treatments

Interstitial Lung Disease

ILD is the most frequent and severe extramuscular involvement of myositis, leading to a significant increase in mortality [4, 97]. A prevalence varying between 19.9 and 86% was reported, representing one of the highest prevalence among CTDs (Table 14.1) [98–100]. ILD is particularly frequent in patients with anti-tRNA synthetase [101, 102], anti-MDA5 [49], and anti-PM-Scl antibodies [103–105].

ILD is responsible for estimated excess mortality of 50% in some series [4, 97] and may precede muscular manifestations in up to 20% of cases [106]. Muscular involvement can be subtle or even absent. Rapidly progressive ILD is associated with a poorer prognosis, with a 68% mortality at 3 months (Table 14.3) [107–110].

The most frequent pattern observed on HRCT is an association of consolidations, corresponding to areas of OP, and NSIP features, with bilateral ground-glass opacities, reticulation, and peribronchovascular thickening mostly affecting lower lobes (Fig. 14.8) [111–113]. These features correspond histologically to an overlap pattern of OP and NSIP patterns [114, 115]. HRCT features of ILD are usually unspecific to a subset of myositis.

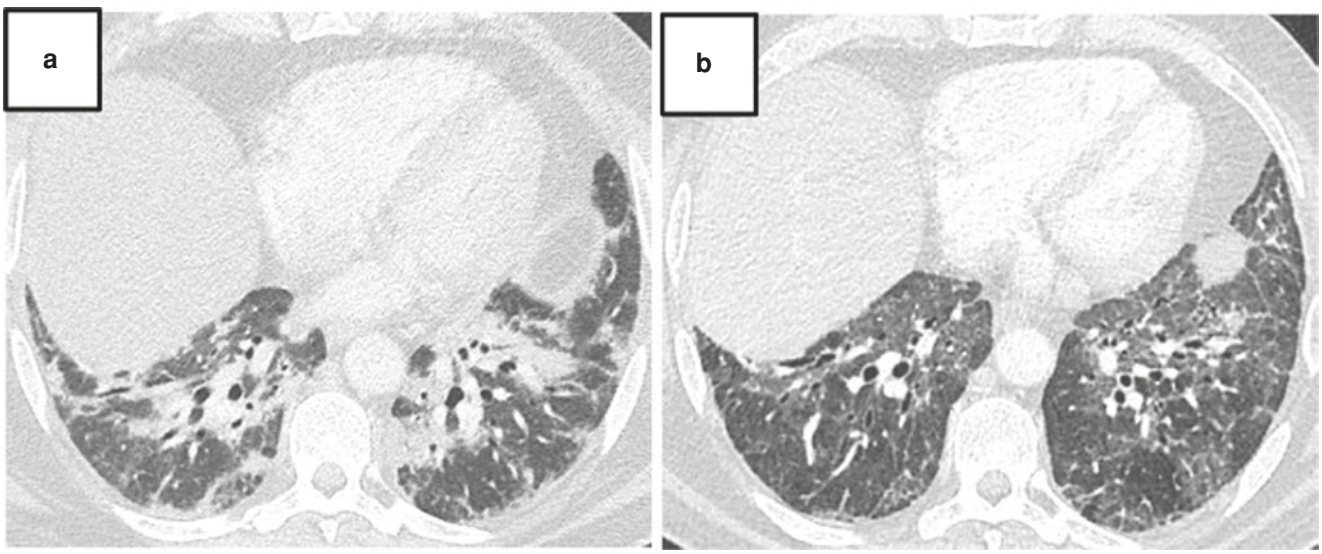


Fig. 14.8 Organizing pneumonia pattern with consolidation with a peribronchovascular predominance in both lower lobes (Panel **a**) in a patient with anti-glycyl-tRNA synthetase antibody (anti-EJ). With corticosteroids, there was a resolution of consolidation with residual ground glass opacities and bronchial distortions (panel **b**)

Due to the low prevalence of the disease and the high variability in clinical presentation, there is no guideline regarding the treatment of ILD associated with myositis. The choice of immunosuppressive therapy should distinguish between rapidly progressive forms or acute forms associated with respiratory failure, and slowly progressive forms. In rapidly progressive forms or in acute respiratory failure an aggressive treatment should be considered as a first-line treatment, associating high-dose corticosteroids with cyclophosphamide, rituximab, or a calcineurin inhibitor. In patients with mild disease or chronic presentation, corticosteroids alone or in association with mycophenolate mofetil or azathioprine could be proposed [99, 116].

Corticosteroids represent the cornerstone of the initial treatment of myositis-ILD and are generally used as a first-line strategy [4, 117]. An oral administration of 0.5–1 mg/kg of prednisone for 4–8 weeks is usually admitted, followed by progressive tapering with a duration of treatment that generally exceeds 24 months. In chronic presentations or slowly progressive forms of ILD, a recent meta-analysis reported an improvement rate of 89.2% (95%CI 89.2–93.6) with corticosteroids alone [107]. However, prednisone-resistance is frequent. Corticosteroids alone show a response rate of 50%, suggesting that combined use of immunosuppressive therapies should be preferred in rapidly progressive cases [118–120]. In a retrospective study, two treatment approaches were compared: an association of immunosuppressive treatment (cyclosporine, cyclophosphamide, azathioprine, or tacrolimus) and prednisone at the treatment initiation (intensive approach), or the adjunction of immunosuppressive therapy when prednisone alone had no favorable response (step-up approach). The intensive approach was associated with better survival [121]. In patients showing initially elevated serum levels of muscle enzymes (creatine phosphokinase), it has been suggested that tapering of corticosteroids should be initiated once enzymes return to normal levels.

Immunosuppressive therapies should be considered in relapsing diseases, or as corticosteroid-sparing agents. Data supporting the effectiveness of azathioprine and mycophenolate mofetil, as maintenance therapy after induction or for patients with mild ILD, are limited to small case series and case reports. Mira-Avendano et al., reported the same efficacy on clinical and functional stabilization and corticosteroids daily dose tapering, for oral cyclophosphamide, azathioprine, and mycophenolate mofetil in PM/DM-ILD and anti-synthetase syndrome-ILD [60]. In a recent retrospective study on 66 patients with myositis-associated ILD treated with azathioprine and 44 with mycophenolate mofetil, a significant improvement was observed in FVC (%) with both drugs, and DLCO (%) with azathioprine, allowing a tapering of corticosteroids daily dose [122].

Methotrexate is mostly used in case of rheumatic manifestations of myositis. It has been used for the treatment of myositis-associated ILD despite the absence of pulmonary-specific evidence, with a good safety profile.

Many retrospective studies, regarding both cyclosporine and tacrolimus, suggested that calcineurin-inhibitors may be useful in treating myositis-ILD. Tacrolimus might have an effect on functional and clinical improvement, as well as muscle strength improvement, especially in patients who did not respond to first-line corticosteroid treatment, with a decrease of prednisone daily dose [123, 124]. Cyclosporine could be suggested in chronic ILD associated with myositis, with a favorable outcome observed when associated with corticosteroids. In acute forms, cyclosporine is associated with a favorable outcome in polymyositis-ILD and in half of ILD associated with dermatomyositis patients, with a better survival rate when cyclosporine and prednisone were associated [125].

The use of cyclophosphamide is currently limited to the aggressive, rapidly progressive, or refractory forms of myositis-associated ILD with an improvement in survival. A systematic review of 12 studies published in 2015 supported the use of cyclophosphamide in myositis- ILD, with 58% (34 of 59) of patients showing an improvement in survival rate. In a recent meta-analysis, the global 3-month survival rate was 72.4% (95%CI 6.4–99.0) in rapidly progressive cases [107].

In myositis-ILD, rituximab was shown to have a role as a second-line treatment for refractory ILD in several retrospective studies, with a functional, imaging, and/or clinical improvement [126–129]. Overall, rituximab appears as a drug of choice in the management of refractory myositis-ILD and rapidly progressive ILD. Prospective randomized trials are ongoing to assess the efficacy and tolerability of rituximab in CTD-ILD [130, 131].

Intravenous immunoglobulin combined with steroids is effective in improving muscle strength and decreasing creatine kinase levels in patients with active muscle disease. Data suggesting a benefit in ILD are scarce [132, 133]. However, intravenous immunoglobulin could be discussed in patients with refractory disease associated with muscular involvement or with marked contraindications to immunosuppressive agents.

Respiratory Muscle Weakness

Respiratory muscle weakness is a rare but potentially life-threatening complication that can develop independently from skeletal muscle weakness. The management of respiratory muscle involvement is similar to that of peripheral muscle or extramuscular involvement and mostly relies on immunosuppressive therapies [134, 135]. In a retrospective

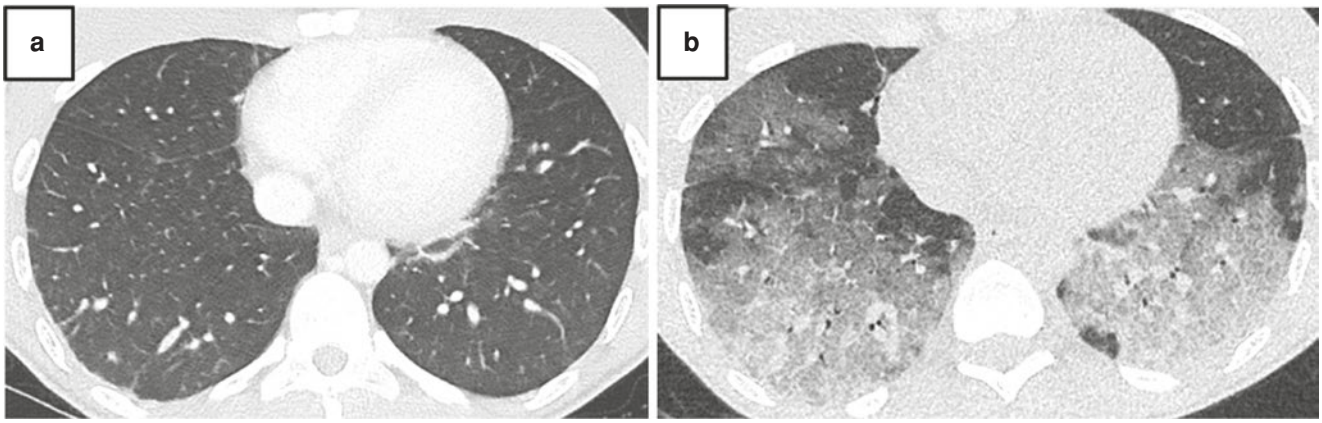


Fig. 14.9 Rapidly progressive pneumonitis in a 22 years-old patient with anti-MDA5 antibody. Very subtle ground glass opacities were observed at diagnosis (Panel **a**) which progressed to diffuse opacities and acute respiratory failure within 6 weeks, despite high dose corticosteroids and cyclophosphamide (panel **b**). The patient's condition required an emergency lung transplantation

series of 18 patients with respiratory muscle involvement leading to a restriction, an 83% remission rate was observed after treatment with corticosteroids or immunosuppressive therapies (azathioprine, cyclosporine) [136]. Intravenous immunoglobulin can also be rapidly effective in muscular involvement. In severe patients, close monitoring in the intensive care unit for possible noninvasive mechanical ventilation can be necessary.

Other Pulmonary Manifestations

Other pulmonary conditions can be observed during myositis, although with a lower frequency. PH can be observed with a low prevalence, as a consequence of ILD in most cases (group 3), although anecdotal cases of myositis-associated pulmonary arterial hypertension in the absence of ILD (group 1) were also reported [137]. Pleural effusion is also a rare complication of myositis, mostly observed in dermatomyositis.

Prognosis

Myositis-ILD is associated with significant morbidity and mortality. Mean overall mortality related to ILD is 14%, and retrospective studies have shown 10-year survival rates between 71 and 89%. Mortality is greatly increased in rapidly progressive ILD compared to chronic forms, with mortality at 3 months of 68% [138, 139].

The type of myositis and myositis-specific autoantibody is correlated with outcome (Table 14.3). Thus, patients with anti-PM/Scl autoantibodies tend to have less severe lung involvement than those with anti-synthetase antibodies and present relatively low mortality related to ILD (0–11%) [104].

A recent study identified acute/subacute presentations of ILD, older age, lower FVC, and clinically amyopathic dermatomyositis as predictors associated with higher mortality in myositis-ILD. In that study, more than 25% of patients died in the follow-up period [140]. HRCT pattern also seems to be related to outcome, with OP associated with a better prognosis than NSIP or UIP [141].

Moreover, treatment response and prognosis are variable among patients. Polymyositis-ILD is associated with a better response than dermatomyositis-ILD [123, 140]. An anti-MDA5 antibody is associated with corticosteroid resistance and poor prognosis (Fig. 14.9). Anti-aminoacyl tRNA synthetase antibodies are characterized by a greater response to corticosteroids, although associated with a greater risk of relapse (Table 14.3) [124, 142]. The use of JAK inhibitors for the treatment of myositis-ILD is of growing interest because of the potential anti-inflammatory and anti-fibrotic properties of these molecules [143], with small series and case reports suggesting that these molecules might be of interest in refractory cases and in rapidly progressive ILD [144], particularly when associated with an anti-MDA5 antibody [145].

Other Therapeutic Options in CTD-ILD

Antifibrotic Therapy

The currently available antifibrotic drugs are under investigation as promising candidates for the management of CTD-ILD patients, mainly focusing on progressive fibrotic phenotypes. Recently, the INBUILD trial assessed the efficacy and safety of nintedanib in non-IPF progressive fibrosing ILDs despite conventional therapies [146]. The use of nintedanib was associated with a slower decline of lung function in patients with progressive fibrotic ILDs, compared to placebo, with non-significant differences in the efficacy of nintedanib across ILD subgroups [146]. Additionally,

patients with unclassifiable ILD, including IPAF, were randomized to pirfenidone or placebo in a recent trial. The analysis of secondary endpoints suggested that pirfenidone may reduce lung function decline in unclassifiable progressive fibrotic ILD [147]. Similarly, pirfenidone was associated with a reduced decline of FVC in patients with progressive pulmonary fibrosis in the RELIEF trial which included some patients with CTD-ILD [148]. More data are needed to clarify the benefit of antifibrotic drugs and to investigate the optimal combination with immunosuppressive therapy.

Lung Transplantation

It remains controversial whether patients with CTD-ILD are eligible for lung transplantation [79]. It is generally believed that due to extrapulmonary disease and a higher risk for allograft rejection, these patients have increased mortality after transplantation [80, 81]. However, recently, several studies have shed light on the role of lung transplantation in scleroderma and non-scleroderma-associated ILD [149]. Selected patients should be considered eligible for transplantation when there is progressive pulmonary disease despite the appropriate immunosuppressive therapy when the systemic component of the disease is well controlled [150, 151]. A recent study suggested that adjusted survival was not significantly different among subgroups of myositis-associated ILD patients compared with IPF patients after lung transplantation [149]. There is emergent evidence to support emergency lung transplantation in patients with rapidly progressive ILD associated with anti-MDA5 antibody [152].

Conclusion

Myositis, SLE, SS, and MCTD can affect almost the entire respiratory tract. However, several differences exist mainly regarding the reversibility of lung disease and the prognosis. Pleural effusion in SLE, ILD in myositis, and airway disease in SS represent frequent lung-associated manifestations. ILD and pulmonary hypertension in all these diseases are mainly associated with morbidity and mortality. Diagnosis relies on pulmonary function tests, HRCT, and serological testing. Immunosuppressive agents and steroids are the main treatments to date although randomized trials are lacking. Data regarding long-term follow-up are lacking but it is of great importance to identify patients having a high risk for disease progression and initiate early treatment. Several factors and biomarkers have been proposed to be related to the severity and prognosis of ILD in CTDs, but further research should validate these data in order to evaluate possible pathogenetic associations [153, 154].

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Interstitial Pneumonia with Autoimmune Features

15

Amen Sergew, Aryeh Fischer, and Kevin Brown

Clinical Vignette

A 45-year-old woman, never smoker, presents with a slowly progressive dyspnea and also reports a dry cough that is worse with exertion. On symptom review, she reports several months of puffiness of the hands but denies any other features to suggest an autoimmune disease. On physical examination, she is noted to have digital edema and mild distal digital fissuring but no evidence of Raynaud phenomenon, sclerodactyly, or telangiectasia. Her musculoskeletal examination is otherwise normal; no synovitis or muscle weakness is detected. She has audible crackles on respiratory examination bilaterally. Her high-resolution computed tomography images reveal evidence of diffuse lung disease suggestive of nonspecific interstitial pneumonia (NSIP) pattern (Fig. 15.1). Laboratory testing is notable only for a positive anti-nuclear antibody at high titer (1:1280). All other serologies and lab tests are normal.

Does this patient have connective tissue disease-associated interstitial lung disease?

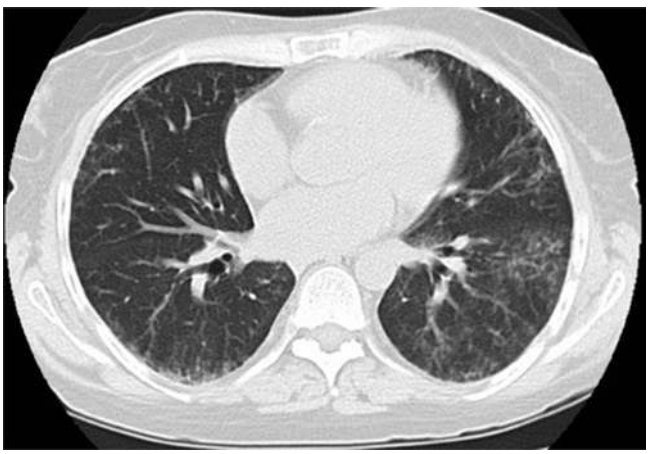

Fig. 15.1 High-resolution computed tomographic image demonstrating a pattern suggestive of nonspecific interstitial pneumonia

Introduction

The interstitial lung diseases (ILD) (also called interstitial pneumonias) are a heterogeneous group of pulmonary disorders that affect the pulmonary parenchyma and are classified together based on common clinical, radiological, and histopathological features [1]. Some occur in the absence of any known cause or association, the idiopathic interstitial pneumonias (IIP). Known causes and associations include environmental/occupational exposures, medications, specific genetic defects, and underlying connective tissue disease (discussed elsewhere). Connective tissue disease (CTD) refers to the spectrum of systemic diseases characterized by circulating autoantibodies and autoimmune-mediated organ damage. ILD in this setting is termed connective tissue disease-associated interstitial lung disease (CTD-ILD) [2], and accounts for 15–30% of new ILD diagnoses [3, 4]. In addition to characterized forms of CTD, it is not uncommon for individuals to have a variety of clinical features that suggest, but fall short of fulfilling existing classification criteria for a specific disease. When ILD occurs in a patient with

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autoimmune signs, symptoms, and/or serologies, one of the following scenarios may exist: (1) ILD is the presenting problem and further clinical evaluation reveals an underlying CTD, (2) ILD develops in a patient with a previously diagnosed CTD, (3) the ILD may occur within a clinical context suggestive, but not diagnostic of CTD, a scenario coined "interstitial pneumonia with autoimmune features" (IPAF). In this chapter, we review the third scenario, the clinical aspects of IPAF.

Diagnostic Criteria

An IIP is a diagnosis of exclusion, all other potential explanations for the presence of ILD have been considered and ruled out. However, within this group there is population of patients that have signs, symptoms and/or serologies suggestive of a CTD, but do not fit current CTD diagnostic criteria. Multiple definitions have been proposed for these patients, including "undifferentiated CTD associated ILD" (UCTD-ILD) [5], "lung-dominant CTD" [6] or "autoimmune-featured ILD" [7]. Each of these definitions differ slightly from each other and community acceptance has been variable. The European Respiratory Society/American Thoracic Society convened an international Task Force on Undifferentiated Forms of Connective Tissue Disease-associated Interstitial Lung Disease and in 2015 published a consensus statement that coined the term "interstitial pneumonia with autoimmune features" (IPAF) to describe patients who otherwise met criteria for an IIP, but also had findings suggestive, but not diagnostic of a CTD [8]. IPAF was established as a research classification to allow for a way to categorize and phenotype these patients and not as a clinical classification, though it has achieved wide-spread community acceptance.

The definition of IPAF requires the presence of an interstitial pneumonia based on chest imaging, with or without surgical histopathology, the exclusion of other causes of interstitial pneumonia, and findings suggestive but not diagnostic of an underlying CTD. More specifically, IPAF requires a combination of features from 2 or more domains: *clinical*, *serologic,* and *morphologic* (Table 15.1). The *clinical domain* includes Raynaud phenomenon, palmar telangiectasia, distal digital tip ulceration, and digital edema. These are findings are associated with (but not diagnostic of) systemic sclerosis (SSc) [9, 10]. When Raynaud phenomenon is present in a patient with an IIP, a chest imaging or histopathologic pattern of nonspecific interstitial pneumonia (NSIP) [11] is often seen. Besides SSc, the presence of Raynaud should raise one's suspicion for other underlying CTDs such as polymyositis/dermatomyositis (PM/DM), anti-synthetase syndrome, primary Sjögren syndrome, mixed connective tissue disease (MCTD), and systemic lupus erythematosus (SLE). Both "mechanic's hands" (cracking roughening of skin at the tips and sides of fingers) and Gottron sign (exanthem on the extensor surface of the digits) are associated with anti-synthetase syndrome or SSc-myositis overlap [12]. As more general clinical features such as alopecia, myalgias, dry eyes, weight loss, and photosensitivity are nonspecific, they are not included in the clinical domain, nor is the presence of joint pain alone, as it is nonspecific. However, symmetric joint swelling, morning stiffness, or synovitis on physical examination is more specific for an underlying CTD, and is part of the clinical domain. A patient with an IIP patient and any of these findings should be evaluated by a rheumatologist [8].

The *serology domain* includes: anti-nuclear antibodies (ANA), rheumatoid factor (RF), myositis panel, and anti-citrullinated peptide (CCP) antibodies [13]. Importantly, ANA and RF are poor screening tests: they have low specificity–particularly when present at low titer, and can be seen in otherwise healthy individuals [14, 15]. The IPAF criteria address this by requiring a high titer ANA and RF. An exception exists for low titer ANA if a nucleolar or centromere-staining pattern is present. Both of these suggest the SSc spectrum of disease [15].

The *morphologic domain* includes findings from both chest imaging and lung histopathology. Thoracic high-resolution computed tomography (HRCT) imaging plays a central role in the evaluation of ILD by providing detailed information on the presence of abnormal features and their distribution, as well as the pattern and extent of disease. The most common chest imaging patterns seen in CTD-ILD are NSIP, organizing pneumonia (OP), NSIP with OP, and lymphocytic interstitial pneumonia (LIP) [16–19]. Although usual interstitial pneumonia (UIP) and diffuse alveolar damage (DAD) patterns can be seen in CTD-ILD, they are not included in the IPAF morphologic domain as their presence alone does not suggest CTD. HRCT also allows for the identification of extra-parenchymal abnormalities, findings that include pleural disease, lymphadenopathy [16, 17], pleural effusions, and pericardial thickening/effusion [18].

When histopathology is available, it may also provide clues to the presence of an underlying CTD [20]. Suggestive histologic patterns include NSIP or LIP, as well as the presence of specific pathologic features including dense perivascular collagen, extensive pleuritis, lymphoid aggregates with germinal center formation, and prominent plasmacytic infiltration [20]. Furthermore, the presence of abnormalities in multiple anatomic compartments is common. In addition to parenchymal disease, small airway, pleural, pericardial, and pulmonary vascular involvement are frequently seen [20]. The presence of any of these histologic findings should raise the possibility of an underlying CTD.

Table 15.1 Characteristic features of Interstitial pneumonia with autoimmune features (IPAF)

	Number of patients who met IPAF criteria	Gender predominance	Mean Age	Never smokers	Most common clinical domain	Most common serologic domain	Most common morphological domain	UIP
Oldham et al. [35]	144	Female (52%)	63	45%	Raynaud phenomenon (28%)	ANA (78%)	HRCT: NSIP 45/144 Histology: 19/83	HRCT: 77/144 Histology: 61/83
Chartrand et al. [39]	56	Female (71%)	55	68%	Raynaud phenomenon (39%)	ANA (48%)	HRCT: NSIP 32/56 Histology: 13 /36	HRCT 5/56 Histology: 8/36
Ferri et al. [42]	35	Female (69%)	63	–	–	ANA (81%)	–	–
Ahmad et al. [44]	57	Male (51%)	64	66%	Raynaud phenomenon (74%)	ANA (82%)	HRCT: NSIP 24/57 Histology: 5/17	HRCT: 16/57 Histology: 3/17
Ito et al. [40]	98	Female (58%)	67.5	61%	–	RF (33%); ANA positive (33%)	HRCT: NSIP 63/98 Histology: 8/17	HRCT: Excluded Histology: 3/17
Collins et al. [46]	15	Male (53%)	55	53%	–	–	–	33%
Chung et al. [55]	136	Female (51%)	63.5	48%	–	–	HRCT: NSIP: 37/136 Histology:	HRCT: 89/136 UIP or possible UIP Histology: 57/74
Dai et al. [41]	177	Female (56%)	60	81%	Raynaud phenomenon (13%)	ANA (49%)	HRCT: NSIP 109/177 Histology: 1/18	HRCT: 8/177
Yoshimura et al. [45]	32	Male (59%)	63	44%	Inflammatory arthritis or morning stiffness ≥60 min (28%)	ANA (28%)	HRCT: NSIP 13/32 Histology: 19/32	Histology: 13/32
Kelly et al. [47]	101	Male (61%)	57	69%	Raynaud phenomenon (55%)	SSA (36%)	HRCT: NSIP 65/101 Histology: NSIP 7/51	HRCT: 12/101 Histology: 12/51
Yamakawa et al. [52]	58	Female (52%)	60	52%	Distal digital fissuring (12%)	Anti-tRNA synthetase (33%)	HRCT: NSIP 31/55 Histology: Fibrotic NSIP 18/55	HRCT: 2/58 Histology: 7/55
Biffi et al. [43]	41	Female (58%)	68	49%	–	–	–	–
Kim et al. [37]	109	Female (56%)	61	63%	–	–	–	HRCT: 40/109 Histology: 18/?
Lim et al. [50]	54	Female (65%)	68	72%	Inflammatory arthritis or morning stiffness ≥60 min (76.5%)	ANA (63%)	HRCT: NSIP 34/54 Histology: 0/34	HRCT: 14/54
Sambataro et al. [51]	45	Female (62%)	66	49%	Raynaud phenomenon (31%)	ANA (18%)	HRCT: NSIP 31/45	Possible UIP HRCT: 8/45 (0 with definite UIP)
Sebastiani et al. [48]	52	Female (56%)	68	48%	Inflammatory arthritis or morning stiffness ≥60 min (46.5%)	ANA (72%)	HRCT: NSIP 17/52	HRCT: 23/52 Histology: 2/2
Hernandez-Gonzalez [53]	24	Female (75%)	71	63%	Inflammatory arthritis (37.5%)	ANA ≥1:320 (42%)	HRCT: NSIP 15/24	HRCT: 1/24 Histology: 2

Controversies in the Diagnostic Criteria

The definition of IPAF was an effort to establish globally accepted criteria for those patients with clinical features that lie between CTD-ILD and IIP. These criteria have not been validated and reassessment of the three domains, as enlightened by further clinical expertise and practice, is needed. As with any new criteria generated by committee, time and further experience have led to calls to update them.

Modifications to each of the diagnostic domains have been proposed. In the *clinical domain*, the addition of esophageal hypomotility has been suggested [21]. In the *serologic domain*, concern has been raised about the inclusion of the anti-tRNA synthetase antibodies, as they are commonly seen in the setting of anti-synthetase syndrome [22–28]. In one study that followed 684 patients with anti-synthetase antibodies, 146 (21%) fulfilled IPAF criteria [26]. Within a median follow-up of 12 months, 42% had a definitive diagnosis of CTD suggesting IPAF as more transient in this population. Another study compared patients who met IPAF criteria with and without anti-tRNA synthetase antibodies; the former had an improved survival [28]. These two studies highlight that patients with IPAF and with anti-tRNA synthetase antibodies may have a different disease trajectories and prognoses. Additionally, in the serologic domain, the exclusion of anti-neutrophil cytoplasmic antibody (ANCA), myeloperoxidase (MPO), and proteinase-3 (PR-3) has been questioned. Patients with a fibrosing ILD and ANCA positivity, although rare, are regularly reported [29–31]. It is not uncommon for MPO ANCA positive patients and/or patients with microscopic polyangiitis to develop ILD [32, 33]. Within a few years of follow-up, one quarter of the patients with MPO ANCA serologies and IIP can develop vasculitis [32]. The clinical features and prognosis of PR-3 positive IIP patients appears to differ from IIP patients without these antibodies [32, 34] suggesting these patients, like those who met IPAF criteria, may benefit from further phenotyping.

In the *morphologic domain*, the exclusion of UIP has been questioned. IPAF with a UIP chest imaging or histologic pattern may represent a subset of patients with a uniquely poor prognosis [28, 35–37] as well as in those with leukocyte telomere length < tenth percentile [38]. Identifying IPAF with a UIP chest imaging or histologic pattern is important given its impact on prognosis and needs further study. A separate issue is the absence of a specific definition for the multi-compartment histopathologic involvement. Stricter definitions may lead to more uniformity of diagnosis.

The definition of IPAF will continue evolve, as we continue to study its longitudinal behavior, prognosis, and response to therapy.

Typical Clinical Features

Several studies from various countries have published on the common patterns and features seen. These characteristics are summarized on Table 15.1. Significant heterogeneity is seen, likely due to some combination of the inclusion criteria, referral bias, the small study size, and their retrospective study design. Overall, female predominance is common, with few studies showing a male predominance [35, 37, 39–53]. Age at the time of diagnosis is generally in the sixth or seventh decade. There is a higher prevalence of non-smokers. Most patients met IPAF criteria based on the serologic and morphologic domains. The most common clinical domain finding is Raynaud phenomenon, and the most common serologic domain finding is a positive ANA, with anti-SSA the next most common. The most common morphologic domain finding is the presence of an NSIP pattern on chest imaging. A UIP pattern, although not part of the criteria, was also present in a significant number of the patients, by both chest imaging and histology. Overall, multiple studies have demonstrated that a certain portion of patients who met IPAF criteria evolve into CTD-ILD [39, 40, 51, 54, 55]—and this highlights that in some cases, an IPAF "diagnosis" should remain provisional, and that longitudinal surveillance of evolution is a fundamental principle in the care of these patients.

Disease Progression and Prognosis

Recent studies have explored the question of whether patients who meet the IPAF criteria have outcomes more similar to well-characterized CTD-ILD or to non-IPAF IIP patients. Hernandez-Gonzalez et al. showed no difference in 1-year survival between CTD-ILD, IPAF and other forms of ILD [53]. This study also showed no significant differences in functional progression after 1 year as defined by ≥10% change in FVC and/or ≥ 15% decline in DLCO. Kim and colleagues followed 109 patients who met IPAF criteria for a mean period of 45 months [37]. Compared to those with non-IPAF IIP, patients who met IPAF criteria had a slower rate of decline in lung function and an increased propensity to develop a characterized CTD. Prognosis was comparable to CTD-ILD and better than an equivalent IIP. Those with UIP pattern, older age and lower DLCO had higher short-term mortality [37]. Kelly et al. studied 101 patients who met IPAF criteria. Compared to IPF, patients with IPAF and a UIP chest imaging or histologic pattern had similar survival; however, those with IPAF with a pattern other than UIP had longer survival [47]. Collins et al. studied 15 patients with IPAF, 36 patients with CTD-ILD, and 53

patients with IPF as well as 124 patients who were antibody positive that did not fit into one of these categories (non-IPF IIP subjects). After a year, there was no significant difference in FVC or DLCO between the groups [46]. Lim et al. followed 54 patients who met IPAF criteria, 175 IPF patients, and 76 patients with CTD-ILD [50]. Acute exacerbations were observed in 26% of the IPAF group, 35.4% of the IPF group, and 33% of the CTD-ILD ($p < 0.001$. Mean survival time was 73 months in IPAF, 104 months in CTD-ILD and was significantly worse in the IPF group as compared to both ($p < 0.001$) at 52 months in IPF. A multivariate analysis showed those with IPAF had a significantly better survival as compared to those with IPF [50].

Dai et al. recently reviewed 1429 IIP patients and found that 177 met the IPAF criteria [41]. Those who met the IPAF criteria survived longer than those with IPF ($n = 235$) ($p < 0.001$) but not as long as the non-IPAF, non-IPF cohort ($n = 996$) ($p < 0.001$). The mean survival time was 295.0 weeks in the IPAF group and 128 weeks in the IPF group [41]. Oldham et al. retrospectively studied 144 who met the IPAF criteria and were able to report on longitudinal behavior. Overall mortality was 40% during the follow-up period and 11% went on to lung transplantation [35]. There was a trend towards longer survival in patients who met IPAF criteria when compared to those with IPF ($p = 0.07$) but worse when patients who met IPAF were compared to those with CTD-ILD ($p < 0.001$). Similar to other studies, patients who met IPAF criteria with UIP on chest imaging or histologic patterns showed survival similar to IPF, while those categorized as IPAF without UIP had similar survival to CTD-ILD [35]. Sebastiani et al. prospectively enrolled 52 patients with IPAF and 104 IPF patients and followed them for 45 ± 32 months [48]. Over the follow-up period, seven patients who had previously met IPAF criteria evolved to a definite CTD. The 5-year survival in the IPAF group was estimated to be 69.5 ± 7.8%, higher than IPF. On univariate analysis, FVC and DLCO were the only factors found to be associated with mortality [48].

Markers of prognosis have been explored in many of these trials. As noted earlier, Kelly et al. findings suggest the finding of UIP on chest imaging or histology was associated with worse prognosis [47]. In Dai's study, univariate analysis showed age, history of tobacco use, presence of ANA ≥1:320, anti-RNP antibodies, as well as imaging findings of OP, pleural effusion or thickening were significantly associated with higher mortality. On multivariate analysis, age, history of tobacco, OP on chest imaging and presence of anti-RNP antibody predicted worsened survival [41]. Chung et al. followed 136 patients who met IPAF criteria and found that a significant majority of patients had a UIP pattern (57.4%), which was associated with smoking, male gender and older age. An NSIP pattern was noted in a quarter of patients. On multivariate analysis, the patients who met IPAF criteria with honeycombing and pulmonary artery enlargement on chest CT had a worse prognosis [55]. Oldham et al. noted worse prognosis on univariate analysis with older age, UIP pattern and hypothyroidism. A higher DLCO and the presence of the clinical domain were associated with better survival. IPAF that included features in the clinical domain had a significantly increased survival ($p = 0.03$) while those serological and morphological domains had worse survival. There was a significant risk of increased mortality especially in those with multi-compartment features. On multivariate analysis, age and DLCO were predictive of survival [35].

Ito et al. followed 98 patients who met IPAF criteria and reported a 5-year survival of 71% and a median survival of 12.5 years [40]. The 5-year survival rates were reported to be 100% in the OP pattern group, 87% in the NSIP + OP pattern group, and 59% in the NSIP pattern group. Markers of poor prognosis included NSIP pattern and SSc specific antibodies (ANA nucleolar pattern, ANA centromere pattern, anti-ribonucleoprotein, and anti-Scl-70). The presence of bronchoalveolar lavage fluid with lymphocytes >15% was associated with longer survival on univariate analysis. A total of 12 patients progressed to a characterized CTD (7 RA, 2 SSc, 1 SLE, 1 Sjögren and systemic sclerosis, and 1 dermatomyositis and systemic sclerosis) [40]. In a retrospective analysis of 156 IPF, 167 CTD-ILD, and 57 patients who met IPAF criteria, there was no statistically significant difference in the overall survival (median duration 16 months) between the IPF and IPAF group (probability of overall survival at 1 year was 95% and 84%, respectively, $p = 0.05$). In the IPAF group, the presence of a UIP pattern as compared to NSIP did not impact survival [44]. In a univariate analysis, history of smoking was associated with worsened survival.

Yoshimura et al. studied 194 patients with chronic fibrosing interstitial pneumonia out of which 32 were categorized as meeting criteria for IPAF [45]. The overall survival and incidence of acute exacerbations were better in the those who met the IPAF criteria as compared to those who did not meet IPAF criteria. IPAF with an NSIP pattern also resulted in improved survival when compared to those with NSIP without IPAF.

Yamakawa et al. compared fibrotic NSIP patients who met IPAF criteria ($n = 58$) with non-IPAF, idiopathic fibrotic NSIP ($n = 35$), and CTD-ILD with fibrotic NSIP ($n = 64$) [52]. The median follow-up ranged from 3.8 to 6.5 years and survival was better in IPAF than for idiopathic fibrotic NSIP ($p < 0.001$) but similar to CTD-ILD ($p = 0.920$). The cumulative 5-year survival rate was 65% and the 10-year survival rate was 37% in the idiopathic fibrotic NSIP group (non-IPAF), 95.4% and 70% in IPAF group, and 88.5% and 82% in the CT-ILD group. Univariate analysis suggested a worse prognosis with male gender, older age, history of smoking, diagnosis of idiopathic fibrotic NSIP, dyspnea on exertion, absence of findings in the clinical domain, lower FVC or

DLCO, and emphysema on HRCT. Biffi et al. showed no significant 3-year mortality difference between IPAF and idiopathic NSIP [43]. More patients with IPAF required oxygen compared with patients with idiopathic NSIP (22% versus 7%, $p = 0.034$). Patients who met IPAF criteria with and without anti-synthetase antibodies were compared and there was no significant difference in 3-year survival although there was a trend towards worse survival in the IPAF group with those antibodies.

In the only prospective study to date, 45 patients who met IPAF criteria were compared to 143 IPF patients [51]. At baseline, the IPAF group had higher FVC and DLCO values. The IPF group was older, more male, with more patients on oxygen. Of the 19 patients who met IPAF criteria who were followed for at least 1 year, two developed a UIP pattern on chest imaging and one developed PM. Several patients went on to develop additional antibodies and clinical features suggestive of a CTD but never met diagnostic criteria, although the authors note that a longer period of follow-up may result in more CTD diagnoses.

Taken together, our current knowledge is clearly incomplete, and does not allow definitive conclusions to be drawn from these cohorts. The above studies show us the variability of patients who meet IPAF criteria and this heterogeneity impacts our understanding of prognosis and longitudinal behavior. The available data do not allow definitive conclusions regarding prognosis when comparing IPAF with IIPs or CTD-ILD, however, the subset of patients who met IPAF criteria with UIP on chest imaging or histologic pattern likely has a survival time similar to IPF. The frequency of evolution to CTD-ILD is still uncertain, but clearly occurs. The available data do not provide specific guidance to help the practitioner predict prognosis or decide on treatment.

Management Considerations and Future Studies

Unfortunately, there are few studies to guide therapeutic decisions in IPAF. As such, in practice, we borrow from our knowledge of therapies utilized in CTD-ILD and IIP summarized elsewhere. This section focuses on published reports specifically in IPAF.

Cyclophosphamide (CYC) Wiertz et al. conducted a case series of 38 patients with IIP who were refractory to oral glucocorticoids, and were subsequently treated with intravenous CYC pulse therapy [56]. Of the 38 patients, 7 died during treatment, 4 had to discontinue due to drug toxicities, and 4 patients had missing data. Of the remaining patients, 13 met the criteria for IPAF and 10 had non-IPAF IIP. Before CYC, there was a mean decline of FVC of 15% in the total population and after treatment a mean increase of FVC by 3%. Compared to the patients with non-IPAF IIP, those who met IPAF criteria had more benefit with an FVC change of −12% before therapy and an improvement of +9% when evaluated after 6 months of therapy. In the IIP group, an FVC change of −18% prior to CYC therapy and −6% when evaluated 6 months after therapy.

Mycophenolate Mofetil (MMF) In a recent cohort study of 52 patients who met IPAF criteria, half received MMF and the other half did not receive MMF. After 22 months there was no difference in the FVC and DLCO between the treated and untreated group. However, in comparing the FVC and DLCO before and after MMF in the treated group, there was a trend towards a slowing of FVC and DLCO decline after treatment [54].

Anti-fibrotics Nintedanib is an intracellular tyrosine kinase inhibitor that has been shown to slow the decline in FVC and potentially prolong the time to acute exacerbation in IPF [57–60]. Nintedanib has also been shown to slow the adjusted annual rate of change in FVC in SSc-ILD, both alone and when combined with MMF [61]. The subsequent INBUILD trial studied the use of nintedanib in non-IPF progressing fibrotic ILDs over 52 weeks [62]. In this heterogeneous population of patients with a variety of fibrosing ILD who had shown clinical evidence of disease progression over the previous 24 months, despite appropriate therapy, the annual rate of decline in FVC was significantly reduced in the nintedanib group when compared to placebo. Studies are underway to further understand the role of nintedanib on progressive fibrosing ILD [62, 63]. Pirfenidone has shown a benefit in reducing the decline in FVC in patients with IPF [64, 65]. Pooled studies of pirfenidone in IPF show a significant reduction in mortality risk and progression-free survival [66, 67]. Pirfenidone was also studied in a Phase 2 multi-centered, double-blind study involving patients with progressive fibrosing unclassifiable interstitial pneumonia randomized to oral pirfenidone (n = 127) or placebo (n = 126) for 24 weeks [68]. There were 15 patients who met IPAF criteria in the pirfenidone group and 18 in the placebo group. The primary endpoint evaluated the mean change in FVC using a home spirometer, however, variability in the values made this assessment difficult. The median change in FVC using home spirometry after 24 weeks was −88 mL in the pirfenidone group and −157 mL in the placebo group. The placebo group was more likely to have a >10% ($p = 0.011$) decline in FVC than the pirfenidone group. The mean change in DLCO from baseline, mean change in 6MWD from baseline, cough and quality of life scores was also not statistically significant between the two groups.

Pirfenidone is also currently being evaluated in other fibrosing ILDs including CTD-ILD and IPAF in current trials in combination or in place of with immunosuppressants [63, 69–73].

Summary

The intersection of ILD and CTD is complex and commonly includes a well-documented CTD complicated by the presence of ILD, ILD as the presenting manifestation of a CTD, or arising within the context of IPAF. A consensus on characteristic criteria and phenotyping will lead to further prospective studies that will improve our understanding of the natural history and appropriate management. An interdisciplinary dialogue that includes pulmonologists, rheumatologists, radiologists, and pathologists will continue to advance our understanding of IPAF [2, 6]. Finally, as there is potential for evolution to defined forms of CTD, longitudinal assessment of these patients is required.

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Primary Histiocytic Disorders of the Lung

16

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Introduction

This chapter will review rare histiocytic disorders that affect the lungs of adults, focusing on Langerhans cell histiocytosis (LCH), Erdheim-Chester Disease (ECD), and Rosai-Dorfman Destombes Disease (RDD). The histiocytic syndromes are a heterogenous collection of rare diseases characterized by proliferative abnormalities of myeloid cell lineages that lead to organ infiltration [1–3], most commonly of the skin (Table 16.1). While historically considered to be benign, polyclonal, inflammatory processes [4], recent discoveries of mutations in the mitogen-activated protein kinase (MAPK) pathways have led to the reclassification of several histiocytoses as low-grade inflammatory neoplasms [1–3] (Fig. 16.1). Clinical manifestations range from asymptomatic and indolent to debilitating and life-threatening [6]. The annual incidence of all histiocytic neoplasms is likely less than five per million persons [4]. The best known and most common of these diseases is Langerhans cell histiocytosis (LCH), a disorder that primarily affects children. Pulmonary LCH (PLCH) is an adult variant of LCH that primarily affects smokers and results in cystic lung destruction. ECD and RDD can also affect the lung but are characterized by the absence of dendritic cells and a tendency to involve bone and lymph nodes, respectively (Table 16.1).

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Table 16.1 Summary of key findings of histiocytic disorders

	Histiocytic disorder		
	PLCH	ECD	RDD
Description	Infiltration of Langerhans' cells into organs; history of smoking	Xanthogranulomatous infiltration of multiple organ systems by foamy histiocytes	Benign proliferation of macrophages resulting in painless lymphadenopathy
Histopathology	S100+, **CD1a+, langerin+**	**CD68+**, CD163+, **CD1a−**, S100−, langerin−	CD68+, CD163+, CD11c+, **S100+**, CD1a−, langerin−, factor XIIIa−
Pathognomonic finding(s)	Birbeck granules on electron microscopy	Foamy (lipid-laden) histiocytes; bilateral symmetric cortical osteosclerosis of metadiaphyseal regions of long bones with sparing of epiphyses on plain films	**Emperipolesis** on histology
Genetic mutation(s)	BRAF V600E (30–50%)	BRAF V600E (50%)	KRAS and MAP2K1 mutations (~33%) phosphorylated ERK (90–100%)
	MAP2K1 (up to 50%)	NRAS	
		KRAS	
		PIK3CA	
Pulmonary/ mediastinal manifestations	Early: upper/mid lung pleural cysts (1–15 mm) and nodules sparing costophrenic angles, bullae	Thickening of interlobular septa and fissures, centrilobular nodular opacities, thin-walled cysts, ground-glass opacification, pleural thickening, mediastinal thickening	More common: polypoid masses of major airways, mediastinal and/or hilar adenopathy
	Middle: star-shaped nodules due to small airways dilation/ bronchial wall destruction		Less common: nodular parenchymal lesions, pleural nodules, diffuse interstitial thickening
	Late: fewer nodules; thin-walled irregularly-shaped cystic lesions (may mimic advanced emphysema)		
Treatment	Smoking cessation	Watchful waiting?	Watchful waiting?
	Watchful waiting appropriate?	Vemurafenib FDA-approved therapy	BRAF/MEK inhibitors
	Consider prednisone for nodular disease	Other BRAF/MEK inhibitor	Cladribine, cytarabine, methotrexate, vinblastine, prednisone
	BRAF/MEK inhibitors	IFN-α	Other: mTOR inhibitor
	Consider cladribine, cytarabine, vinblastine	Other: mTOR inhibitors, anikinra, imatinib, cladribine	Surgical excision
	Consider PH therapies	Lung transplantation	
	Lung transplantation		

Bolded = key pathologic findings

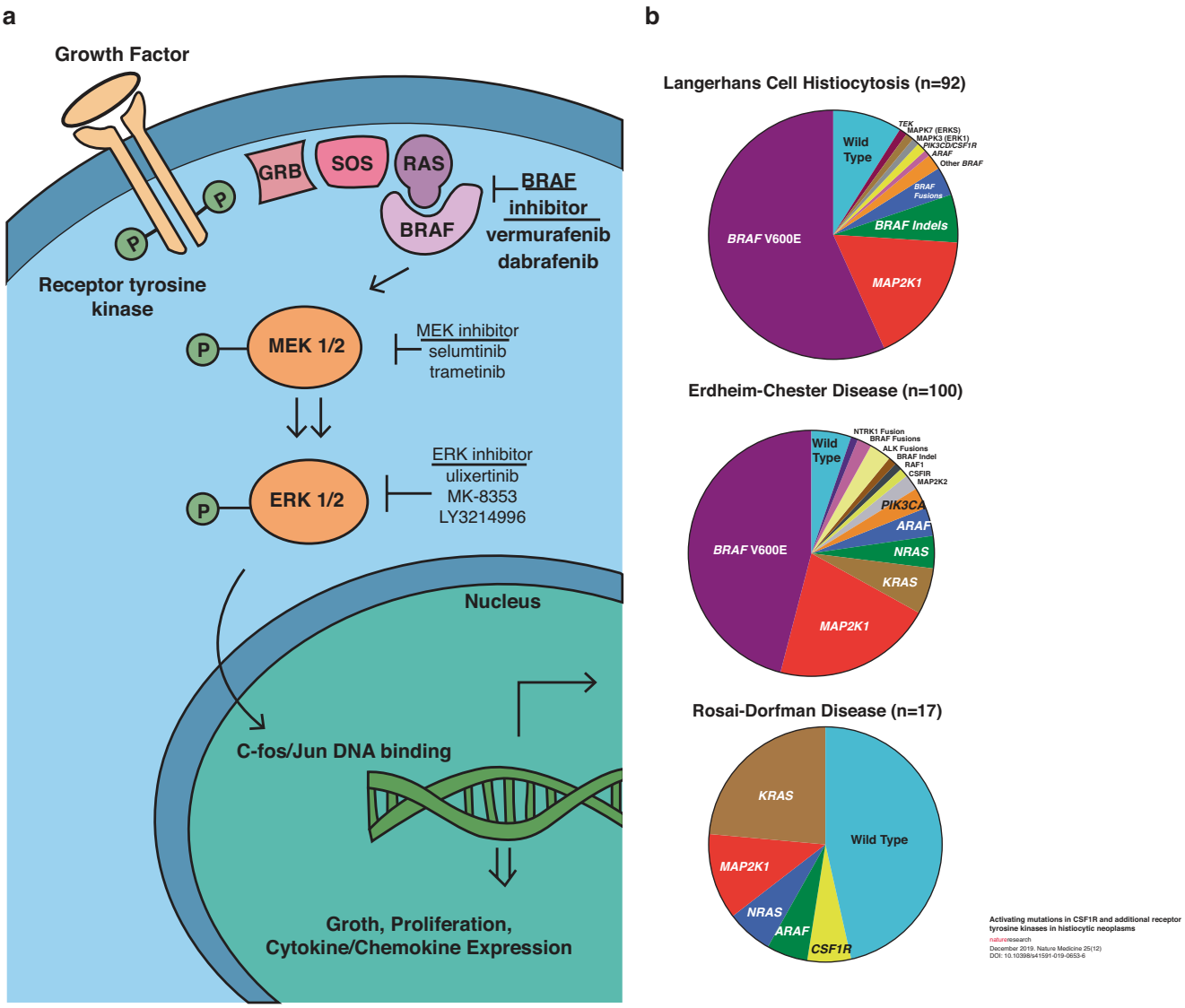

Fig. 16.1 (**a**) Mitogen-activated protein kinase (MAPK) pathways with common therapeutic targets for histiocytic neoplastic diseases, (**b**) Distribution of mutations found for LCH, ECD, and RDD. (Adapted from [5])

Histiocytes and Dendritic Cells

The term histiocyte is used to describe tissue-resident immune cells that arise from bone marrow-derived precursors of two myeloid lineages: macrophages, which play key roles in innate immune responses, and dendritic cells, which have important functions in antigen presentation and cell-mediated immunity. Monocytes originate in the bone marrow, migrate to the lung parenchyma and differentiate into macrophages, where they reside within alveoli and in the interstitium [7]. Dendritic cells are also derived from circulating monocytes and populate multiple compartments in the lungs including the airway mucosa and lung parenchyma. Langerhans cells are a specialized form of tissue-resident dendritic cells that are found primarily in the mucosa and submucosa of the airways. Immunohistochemical evaluation of macrophages reveals positivity for CD68 and CD163, while dendritic cells also express S100, and CD11c (Table 16.2). Langerhans cells also express S100, CD1a, and langerin and contain rod-shaped intracellular inclusions called Birbeck granules that are visible by electron microscopy [1, 4, 7, 11].

Table 16.2 Immunohistochemistry

Marker	Histiocyte
S100	Langerhans' dendritic cells[a]
CD1a	Langerhans' dendritic cells
CD68	Macrophages[b]
	Langerhans' dendritic cells
CD11c	Macrophages[b]
	Non-Langerhans' dendritic cells[c]
CD34	Macrophages[b]
	Dendritic cells[d]
	– Langerhans' cells[a]
	– Non-Langerhans' dendritic cells[c]
CD163	Macrophages[b]
	Non-Langerhans' dendritic cells[c]
Langerin	Langerhans' dendritic cells[a]

References in text [1, 5, 8–10]
[a] Derived from epidermal dendritic cells
[b] Found in mucous membranes throughout the body; roles in innate and specific immunity
[c] Interdigitating and follicular dendritic cells
[d] Found in skin, mucous membranes, bone marrow, reticuloendothelial organs (spleen, thymus, lymph nodes); important in the initiation of T-cell mediated immune response

While there are several similarities between these populations of myeloid cells, there are also several important differences. Langerhans dendritic cells, in contrast to non-Langerhans dendritic cells, are not terminally differentiated, exhibit continuous self-renewal, and are established in the skin before birth independent of bone marrow hematopoiesis [12]. Gene expression studies have also revealed that LCH cells are less mature in comparison to Langerhans dendritic cells and share gene expression profiles with myeloid dendritic cells [13–15]. Finally, the detection of MAPK pathway mutations in circulating myeloid precursors has identified early myeloid dendritic cells with Langerhans cell-like features as the pathognomonic cell in many of the histiocytic diseases [16] and suggests that the point in myeloid cell differentiation at which mutations occur may determine both the histiocytic disorder that results and the level of disease aggressiveness (Fig. 16.2).

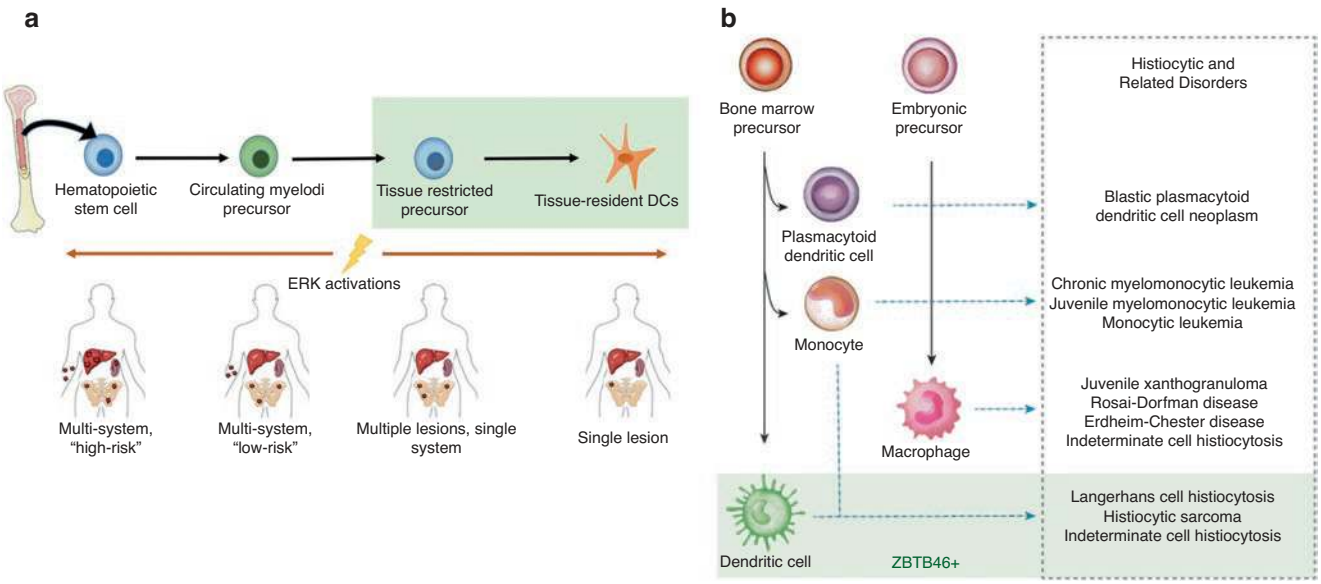

Fig. 16.2 Theory that the point along the differentiation pathway at which MAPK mutations occur determines both the (**a**) aggressiveness and systemic vs. localized nature of the disease, (**b**) the histiocytic disorder subtype (LCH, ECD, or RDD). (Used with permission from [17, 18])

PLCH: The Prototypical Adult Pulmonary Histiocytic Disorder

Introduction

PLCH typically occurs in younger adults, usually during the third or fourth decade of life, but can also affect older individuals [1]. PLCH is best characterized as a progressive lung disease of smokers that causes extensive inflammation and cystic and nodular remodeling in the lung. The disease has been reported to be more common in males, but the sex discrepancy has narrowed over time as the prevalence of smoking in males and females has declined in both groups and become more equal. It is important to note key similarities and differences between PLCH and LCH. Both LCH and PLCH are caused by the infiltration of tissues with mutant myeloid cells. LCH usually presents in childhood as localized or systemic disease, but it can also occur in adults. The disease has been reported to be more common in males in some series, but not all. LCH can result in lytic lesions in bones, mass lesions in subcutaneous tissues or lymph nodes, skin lesions, CNS involvement, and visceral infiltration, including the lung. The pulmonary involvement in children with LCH is usually in the form of nodules. The most striking epidemiological characteristic that distinguishes adult LCH from PLCH is the almost invariable association with smoking in the latter, usually with consumption rates of more than 20 cigarettes per day [19]. PLCH most commonly presents as a single-system disease, affecting only the lungs, but can also be associated with extrapulmonary manifestations, including bone lesions, pituitary infiltration resulting in diabetes insipidus, and skin lesions [19]. Occasionally, children with LCH who begin smoking as teenagers develop extensive cystic and nodular changes in the lung. Although we recognize that LCH is a spectrum of disorders with considerable overlap, the classification of LCH that we prefer includes LCH, adult LCH, and PLCH.

The nomenclature that has been used to describe PLCH has evolved over time. Abandoned names for PLCH include eosinophilic granuloma of the lung, pulmonary Langerhans cell granulomatosis, and pulmonary histiocytosis X. Even the term PLCH is a bit of a misnomer because the characteristic cells within the PLCH lesion do not have all the elements of a true Langerhans cell. Initial descriptions of 'Langerhans cells' in PLCH lesions were based on the presence of Birbeck granules but the neoplastic cells of PLCH do not share the same antigen-presenting functions of epidermal Langerhans cells and have features that suggest developmental arrest in an early state of cell activation [13].

Cellular and Molecular Pathogenesis

The pathophysiology of PLCH is incompletely understood, but likely involves an abnormal immune response to toxic substances present in cigarette smoke or to cells injured by smoke [20]. Dendritic cells normally reside in epithelial linings and submucosa and sample epithelial fluid for foreign antigens through the extension of dendritic-like projections between epithelial cells [1, 6]. When dendritic cells are exposed to antigens, toll-like receptors (TLR) and CD40 receptors are activated leading to maturation, activation, migration to lymphoid tissue, and co-stimulation of B and T cells [1, 6, 11, 20]. Accumulation of dendritic cells is more likely related to recruitment or enhanced survival than local proliferation, based on the low expression of proliferation markers in affected tissues [1, 8, 20]. Finally, when dendritic cells accumulate in a tissue, an inflammatory cascade is triggered that results in the recruitment of abundant stromal cells that cause destructive remodeling and varying degrees of organ dysfunction [6].

The identification of activating mutations in the MAPK pathway in LCH followed by PLCH has provided valuable insights into disease pathogenesis [11] (Fig. 16.1). The most common mutation identified to date has been in BRAF which, as part of the RAS signaling pathway, integrates signals from cell surface receptor tyrosine kinases. Activating mutations (such as the most common BRAF V600E) trigger a signaling cascade that culminates in the translocation of ERK (MAPK) to the nucleus, where it activates gene transcription regulating processes such as cell survival and pro-inflammatory mediator production. These signaling events play essential roles in mediating cellular differentiation, proliferation, senescence, and survival in response to diverse extracellular cues [8]. Additional studies have now identified many additional mutations in RAS/MAPK pathway proteins [4, 21]. Recent data suggests that disease pathogenesis depends in part on the stage of myeloid differentiation at which mutations occur (Fig. 16.2).

Pathology

Gross pathologic evaluation of the PLCH lung demonstrates cysts on the pleural and cut surfaces that can be small, 1–5 mm, or as large as 15 mm, and which can become increasingly profuse and coalescent in late disease evolving into large bullous and cystic lesions [1, 9]. PLCH can affect the bronchiolar, interstitial, alveolar, and vascular compartments of the lung, and is often associated with hyperinflation

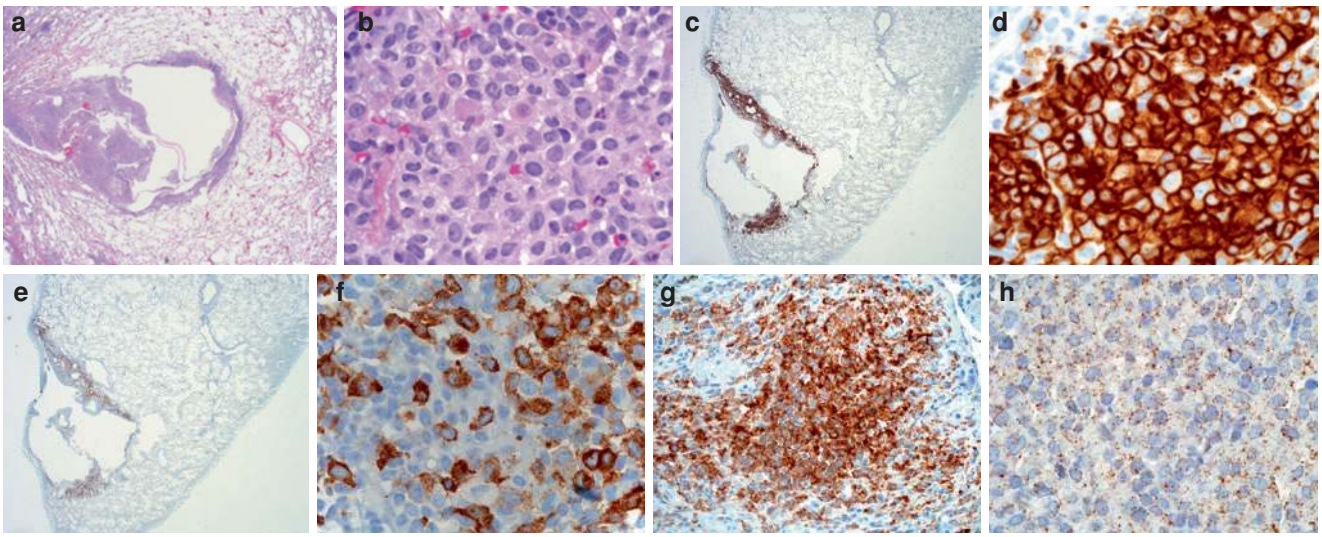

Fig. 16.3 Pathology of Langerhans cell histiocytosis (LCH). (**a**, **b**) Pulmonary-based LCH is a bronchocentric disease with nodular aggregates of lesional histiocytes destroying the airways and leading to cystic airspaces (**a**, H&E 2×). The LCH cells are composed of ovoid cells with indented nuclear contours and ample eosinophilic cytoplasm with a few admixed eosinophils (**b**, H&E 100×). The lesional cells are highlighted by CD1a (**c**, immunostain 20×, **d**, immunostain 100×) and Langerin/CD207, which highlights many but not all of the cells as it corresponds to the cytoplasmic Birbeck granules (**e**, immunostain 2×, **f**, immunostain 100×). Pulmonary LCH may harbor mutations in MAPK pathway for which the mutant-specific BRAF VE1 immunostain with strong expression (2–3+) correlates with the BRAF-V600E mutation (**g**, immunostain, 40×), whereas negative to weak (0–1+) punctate BRAF VE1 staining should be interpreted as negative (**h**, immunostain, 100×)

and advanced fibrosis [1]. Concomitant smoking-related pathologies including respiratory bronchiolitis or desquamative interstitial pneumonia are frequently encountered in histopathological evaluation [20].

In early PLCH, histopathologic evaluation reveals infiltration and proliferation of dendritic cells, macrophages, and eosinophils [10] around respiratory bronchioles and the adjacent interstitium in a symmetric, stellate pattern [1, 20] (Fig. 16.3). Dendritic cells in PLCH are identified by their pale cytoplasm and distinctive, convoluted and elongated nuclei with a "coffee bean" appearance [1, 20]. Adjacent pigmented alveolar macrophage accumulation ("pseudo-desquamative pneumonia") is often present [1]. The pathognomonic feature of Langerhans cells includes the presence of Birbeck granules [1, 11, 20] and surrogate positive staining for langerin, in addition to S100 and CD1a [1, 11, 20]. As infiltrative lesions evolve, the cellular infiltration characteristic of early disease gradually evolves to more collagenous, burnt-out lesions that form fibrotic stellate scars [11, 20] surrounding small airways with loss of typical immunohistochemical features [20]. Demonstration of the mutant-specific BRAF VE1 immunostain can serve as a surrogate for the BRAF-V600E mutation if there is strong and diffuse cytoplasmic staining (Fig. 16.3).

Clinical Presentation

The clinical presentation of PLCH is variable. Patients typically present with cough or dyspnea on exertion. Asymptomatic patients may be incidentally discovered to have abnormalities on radiographs obtained for another purpose. Chest CT typically reveals a mixed pattern of cysts and nodules in various stages of evolution, but predominantly nodular or predominantly cystic patterns on the initial scan are also common (Fig. 16.4). Enlargement of the main pulmonary artery may be indicative of associated pulmonary hypertension. Patients may present with chest pain or acute dyspnea secondary to a spontaneous pneumothorax which occurs in 10–20% of patients [1].

Treatment and Prognosis

Treatment approaches for LCH are outlined in Fig. 16.5, and those for PLCH are depicted in Fig. 16.6 and are more extensively covered in Chap. 30. The prognosis of PLCH is generally favorable, with some patients achieving spontaneous remission or durable stability. In those less fortunate, respiratory failure or major pulmonary hypertension due to PLCH may require lung transplantation, with outcomes similar to those found in patients with other patterns of diffuse infiltrative lung disease [1], or lead to death. The median duration of survival from the time of diagnosis of PLCH is 12.5 years [23]. Furthermore, PLCH has been reported to recur following radiological regression of nodular lung abnormalities up to 7.5 years after the patient's initial presentation, even in individuals who have stopped smoking [20]. There has been promising evidence supporting the use of MEK inhibitors to treat PLCH if progression occurs despite smoking cessation [24].

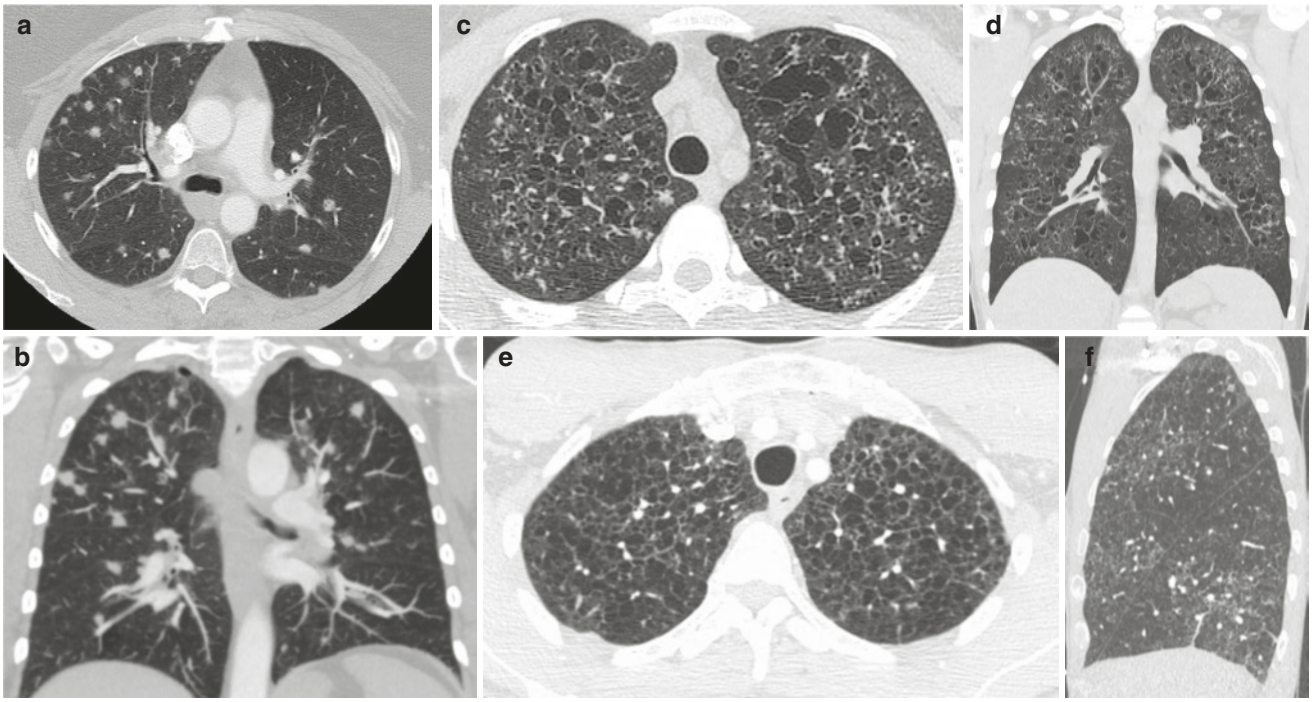

Fig. 16.4 Radiographic manifestations of PLCH. (**a**, **b**) 60 years old woman with 30 pack-year smoking history present with shortness of breath. (**a**) Contrast enhanced CT at the level of the carina reveals scattered centrilobular nodules. Lucency reflecting the bronchiolocentric nature of this process is seen on the left (white arrow). (**b**) Coronal multiplanar reformatting demonstrates the gradient of zonal involvement. The nodules are most severe in the apices with sparing at the bases. (**c**, **d**) 33 years old woman with severe tobacco abuse disorder presents with cough. (**c**) Noncontrast axial chest CT shows a combination of centrilobular nodules and bizarrely shaped lung cysts. (**d**) Coronal chest CT is notable for nodules and cysts with sparing of the costophrenic angles. (**e**, **f**) 47 years old man with a 90 pk yr smoking history and pulmonary arterial hypertension. (**e**) Contrast enhanced chest CT reveals confluent lung cysts in the apices. (**f**) Sagittal multiplanar reformat shows severe confluent cystic lung disease with sparing of the tip of the right middle lobe and anterior right lower lobe (arrow)

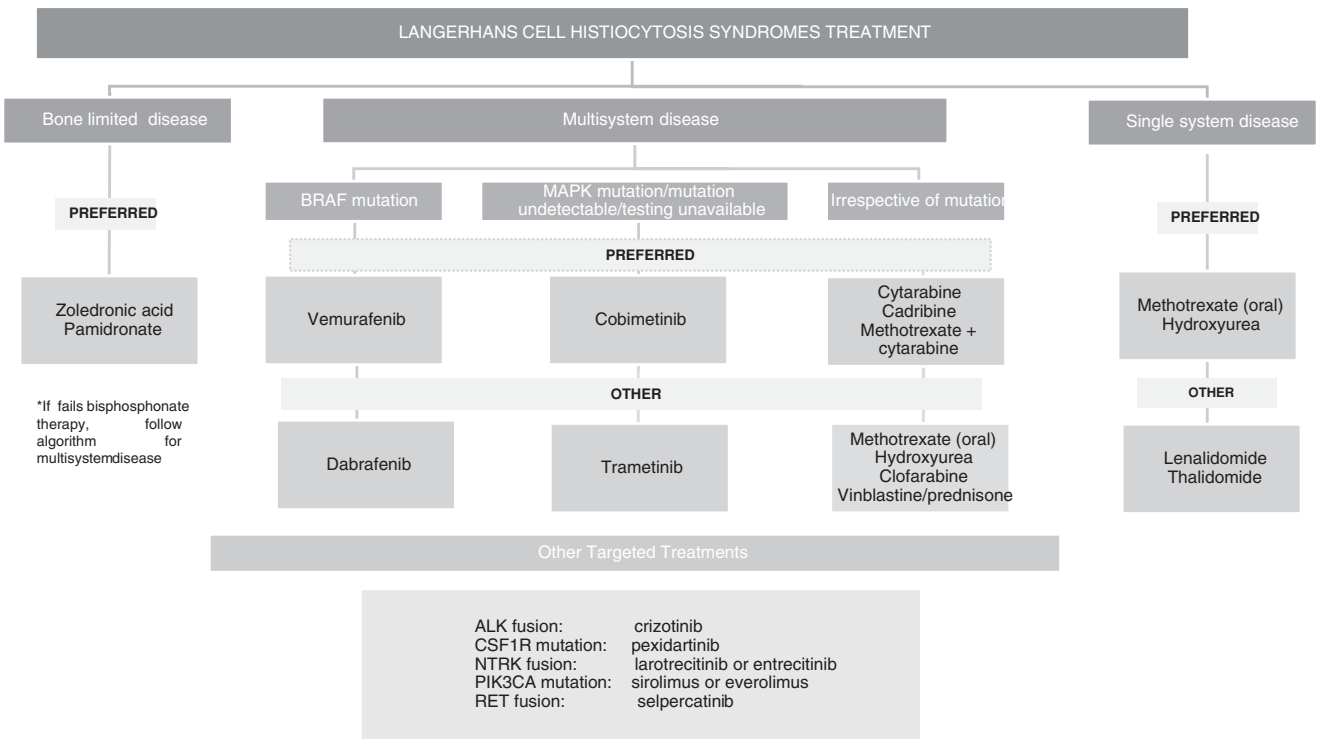

Fig. 16.5 Treatment algorithm for LCH. (Adapted from NCCN [22])

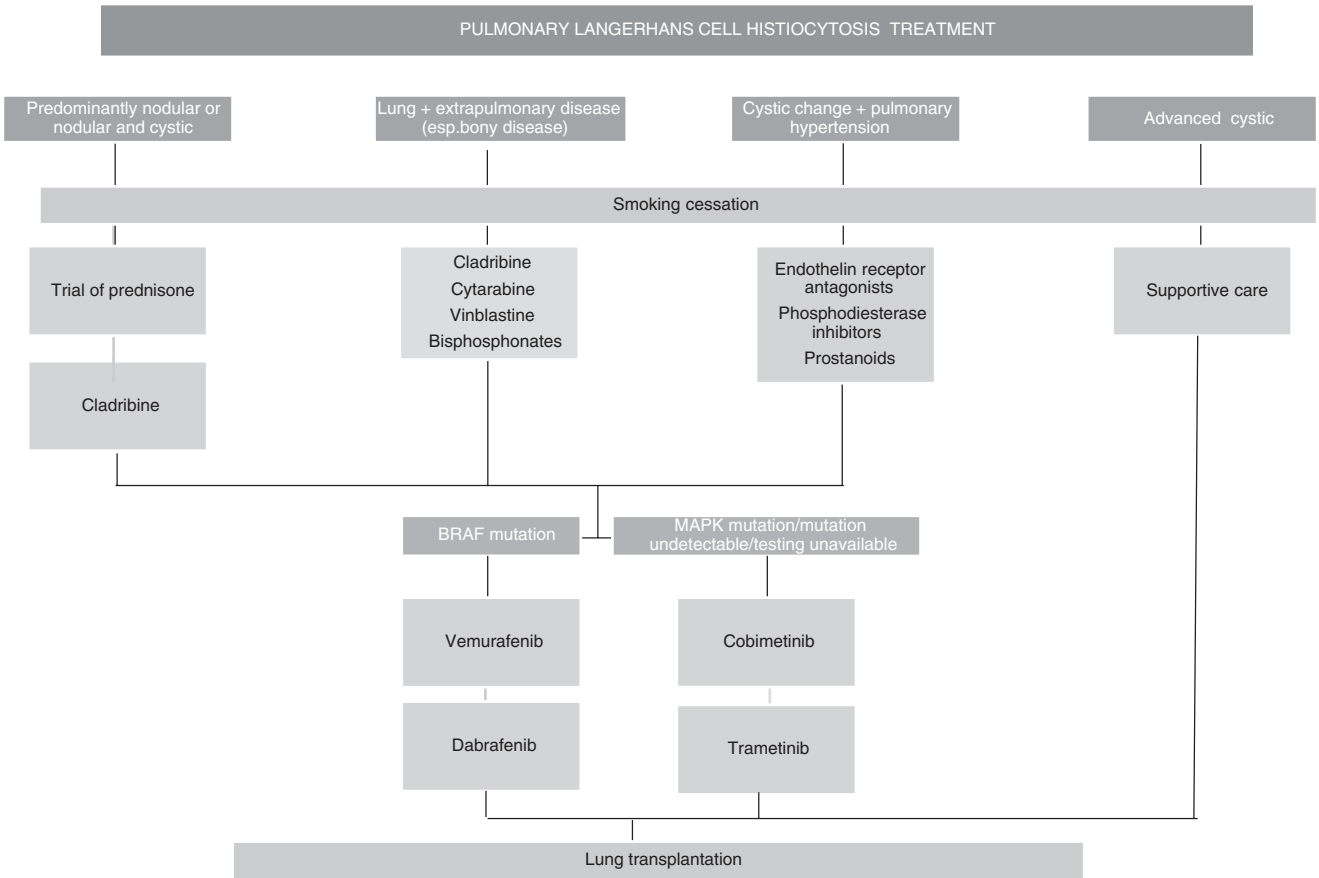

Fig. 16.6 Treatment algorithm for PLCH. (Adapted from NCCN [22])

Erdheim-Chester Disease

Definition

Erdheim-Chester disease (ECD) is a neoplastic disorder marked by hyperactivation of MAPK signaling in myeloid cells that results in xanthogranulomatous infiltration of multiple organ systems organs often by foamy (lipid-laden) histiocytes accompanied by T cells and B cells including plasma cells [25]. The diagnosis requires a multidisciplinary approach including correlative pathology (histology and molecular) and integration of key clinical and radiographic findings [25]. Pulmonary ECD is a rare disorder that is not often included in the initial differential of patients presenting with interstitial lung disease; it is generally first suspected when changes in diffuse lung infiltrates are accompanied by long bone pain [21, 26] (Fig. 16.7).

Epidemiology

There are limited epidemiological data available for ECD, with only ~800 cases reported in the literature through 2020 [1]. Most cases of ECD are diagnosed in middle age, between the fifth and seventh decades of life, although there have been reports of disease in children as young as 7 years old, and in adults up to 84 years [27]. A recent consensus statement by Goyal et al. [1] confirms the historic observation of a male preponderance of disease, with a median age of diagnosis of 46–56 years. Pediatric cases are rare, sometimes presenting as BRAFV600E positive juvenile xanthogranuloma mass lesions (JXG) in the CNS [28, 29].

Cellular and Molecular Pathogenesis

Similar to PLCH, ECD is a neoplastic disease arising from mutations in myeloid progenitor cells. The ECD cell of origin is believed to be a monocyte precursor as opposed to a dendritic cell precursor as is the case for PLCH; however, both likely have a common CD34+ bone marrow cell origins. Differences in the timing of mutation and local cytokine stimuli also play important roles in disease presentation and pathogenesis [30]. The paucity of mitotic figures within ECD lesions suggests that enhanced recruitment or cellular survival is a more likely mechanism of cellular accumula-

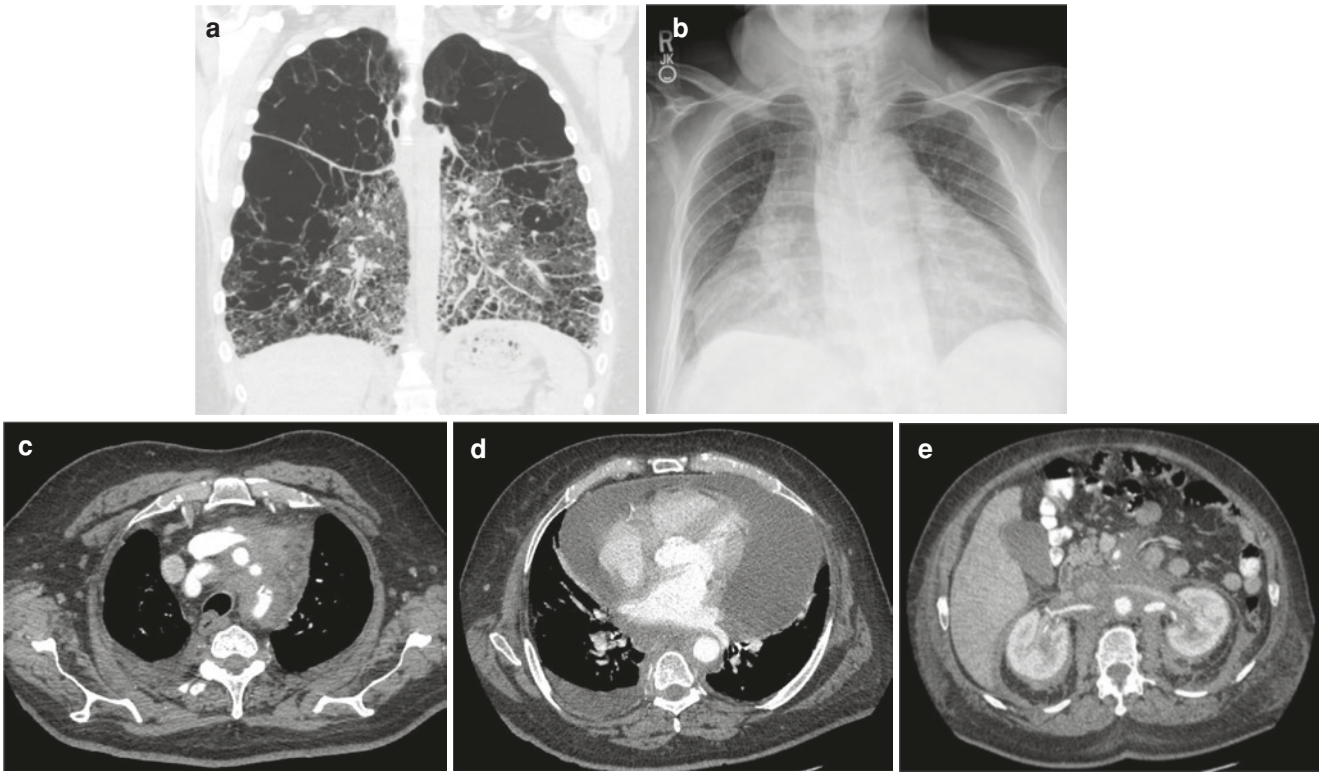

Fig. 16.7 Radiographic manifestations of pulmonary involvement of ECD. (**a**) 30 years old male smoker with ECD. Advanced destructive emphysema is present in the upper lobes. Diffuse fissural thickening (white arrow), bronchovascular thickening, and septal lines (black arrow) are present reflecting histiocyte infiltration. (Case courtesy of Seth Kligerman, M.D. San Francisco, CA). (**b**–**e**) 57 years old man presenting with cellulitis and exophthalmos. (**b**) Frontal chest radiograph is notable for a markedly enlarged cardiac silhouette consistent with the pericardial effusion identified at CT. (**c**) Contrast enhanced chest CT in soft tissue windows shows diffuse perivascular infiltration surrounding the great vessels (arrowheads). (**d**) Contrast enhanced chest CT in soft tissue windows at the level of the left atrium is notable for a large pericardial effusion (asterisk) and small right pleural effusion (white arrow). Periaortic soft tissue is also present (arrowhead). (**e**) At the level of the mid poles of the kidneys the perinephric halo sign can be seen with extensive retroperitoneal infiltrative soft tissue

tion than increased proliferation [27, 31]. ECD histiocytes are positive for CD68, CD163, CD14, CD4 (usually light staining), and often factor XIIIa, but not the characteristic immunohistochemical markers of Langerhans dendritic cells, S100, CD1a, and langerin [1, 4, 11, 20] (Table 16.2). There is mounting evidence of clonal derangements underlying ECD pathogenesis as more than 50% of patients have been found to have activating mutations in MEK/ERK pathways including BRAF, NRAS, KRAS, and phosphatidylinositol-3-kinase/protein kinase B (PIK3CA) [1, 4, 6, 21, 26, 32]. Genetic analysis of ECD lesions offers the potential for targeted treatment, such as the use of vemurafenib and other BRAF V600E inhibitors in patients who exhibit this mutation [21, 27, 32] or a MEK inhibitor such as cobimetinib or trametinib in patients found to have mutations elsewhere in the MAPK pathway. The observations that ECD and LCH pathologies are occasionally seen in the same individual suggests that they may share a common progenitor cell of origin [27].

ECD lesions exhibit a unique cytokine and chemokine signature that is consistent with Th1 polarization including increased levels of interferon-alpha, interferon-gamma, interleukin-6, interleukin-12, tumor necrosis factor-alpha, monocyte chemotactic protein-32, occasionally interleukin-1 beta, and decreased levels of interleukin-4, interleukin-7, and interleukin-10 [10, 27]. Several prior therapeutic approaches have been based on immunomodulatory agents (interferon-α), anti-cytokine therapies (IL1- and TNFα-blockers), and immunosuppressants (mTOR-inhibitors) [33].

Histopathology and Immunohistochemistry

ECD lesions characteristically demonstrate infiltration of non-LCH cells with either foamy (lipid-laden) and/or eosinophilic cytoplasm with or without multinucleate/Touton giant cells on an inflammatory background of polymorphic lymphocytes and plasma cells [1, 4], and varying degrees of fibrosis (Fig. 16.8). The dendritic cells within these lesions are distinct from LCH as they lack Birbeck granules and stain for light granular CD68, CD163, CD14, and often Factor XIIIa, but not for Langerin, CD1a or S100 [1, 10, 21,

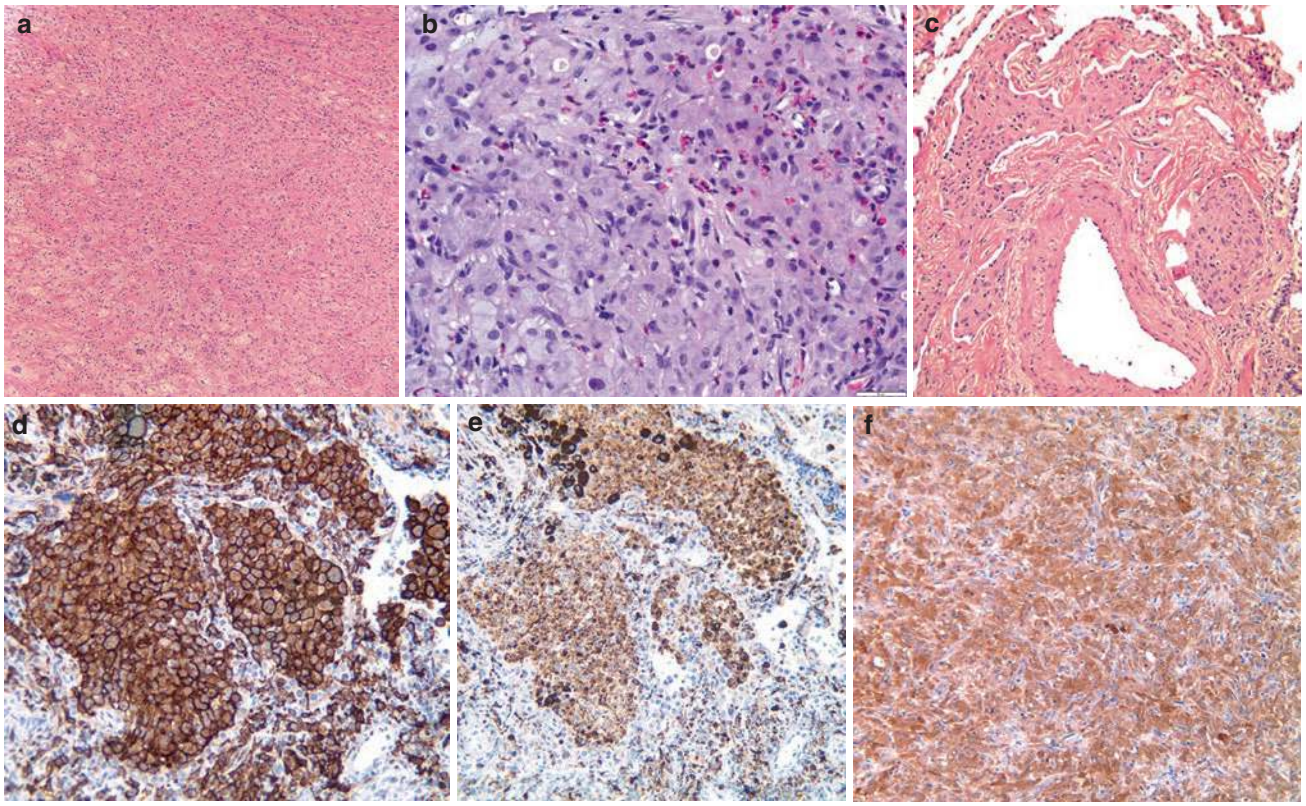

Fig. 16.8 Pathology of Erdheim Chester Disease (ECD) of the lung. (**a**, **b**) Epithelioid to foamy and xanthomatous histiocytes with occasional Touton Giant cells and a variable degree of fibrosis. Mixed inflammation including eosinophils can be noted in pulmonary nodular foci (**a**, H&E, 10×, **b**, H&E, 40×). Another more insidious pattern in pulmonary ECD is a lymphatic distribution of plump to spindled lesional histiocytes (**c**, H&E 20×). The histiocytes are diffusely positive for CD163 (**d**, immunostain, 20×), CD68 with a finely granular cytoplasmic staining as opposed to darkly stained alveolar macrophages (**e**, immunostain 20×), and are often lightly stained for Factor 13a (**f**, immunostain, 20×). Unlike high-grade malignant lesions, there is a very low Ki-67 proliferation rate index in ECD (not shown). Often the clonal histiocytes will express the mutant-specific BRAF VE1 immunostain with strong expression (2–3+) that correlates with the BRAF-V600E mutation (not shown)

26, 27]. As in LCH, demonstration of the mutant-specific BRAF VE1 immunostain can serve as a surrogate for the BRAF-V600E mutation if there is strong and diffuse cytoplasmic staining in >10% of lesional histiocytes. However, a notable staining pitfall in the lung for BRAF VE1 is strong staining of normal cilia which should not be interpreted as positive staining. Similarly, the normal anterior pituitary has dark BRAF VE1 staining in wild-type cells.

Clinical Presentation

Patient presentations are protean and range from incidental findings on imaging performed for unrelated reasons to multisystem dysfunction due to widespread histiocytic infiltration of multiple organ systems [1, 21]. Garcia-Gomez et al. described three prototypical presentations: disease confined to the skin which follows the most indolent course, multifocal involvement with central nervous system preservation, and systemic involvement with CNS infiltration, the most aggressive form with the worst prognosis. Bone involvement occurs in almost all (approximately 96%) of patients and bone pain typically manifests in the knees and ankles (approximately 50%) [1, 32] (Fig. 16.9). Bony involvement may be accompanied by constitutional symptoms such as fever, weakness, weight loss, night sweats, neurologic complaints, or polyuria [1, 32].

About 20–40% of those afflicted with ECD may have involvement in the pulmonary system [1, 11, 20], and in many cases is not associated with respiratory symptoms. CT findings include mediastinal infiltration, pleural thickening/effusion, reticular interstitial changes, centrilobular nodular opacities, ground glass opacities, or lung cysts. Common respiratory symptoms include chronic dry cough and dyspnea that progresses over months to years [27]. Cyanosis at the time of presentation is uncommon, however with increasing disease burden patients may develop hypoxic respiratory failure with or without hypercapnia [27]. If there

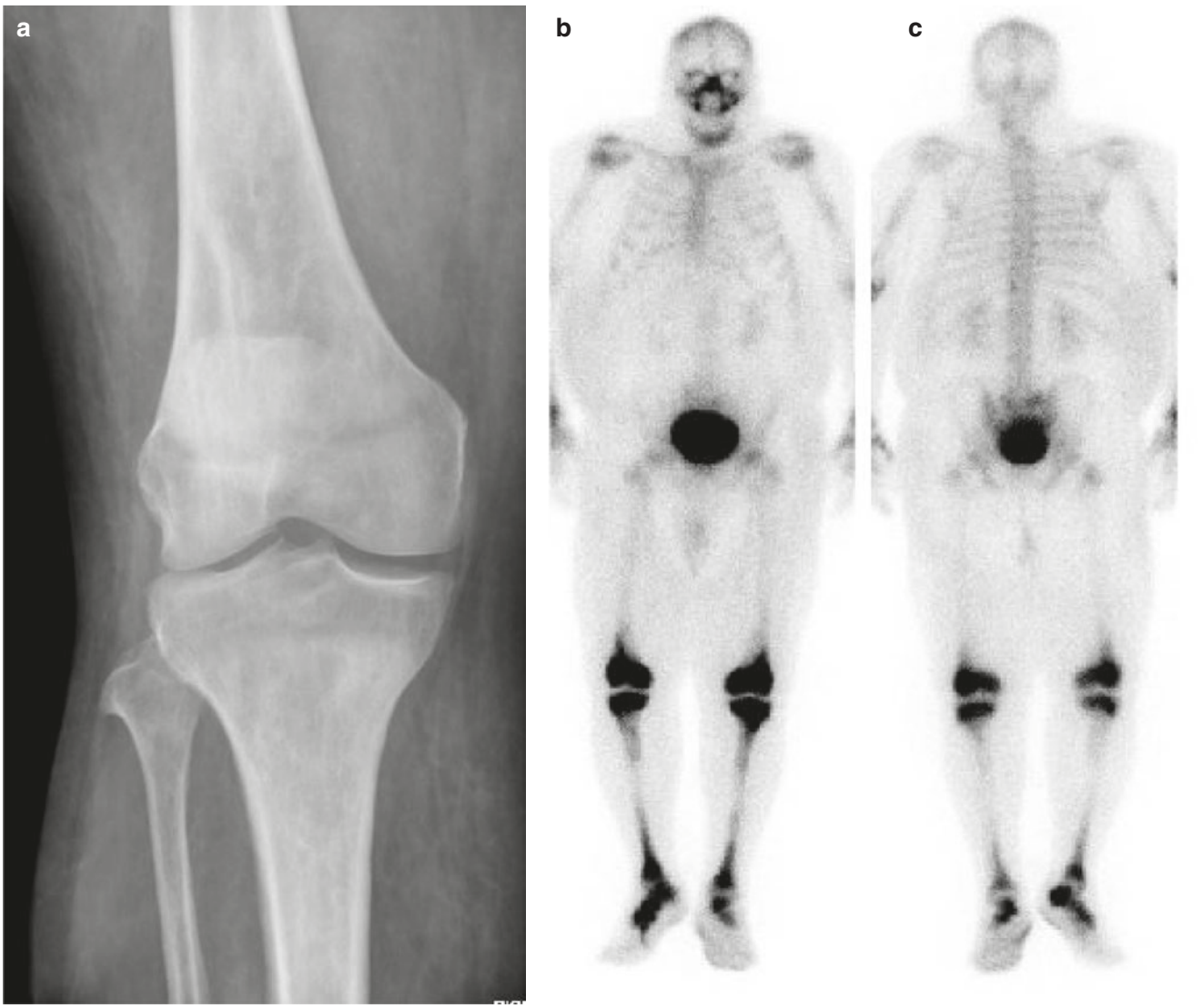

Fig. 16.9 Pathognomonic bony findings of ECD. (**a**) Mixed lytic and sclerotic density in the metadiaphyses of the distal femur and proximal tibia. (**b**, **c**) Technetium 99m MDP is notable for intensely increased radiotracer activity in the distal femurs, proximal and distal tibia

is cardiac involvement, the development of cardiogenic pulmonary edema may contribute to the sensation of breathlessness [27].

Clinical Presentation-Extrapulmonary/ Extraskeletal Involvement

An estimated 50% of patients will present with extra-skeletal and extrapulmonary involvement [27], including the central nervous system (CNS), cardiovascular system, retroperitoneal organs including the kidneys, and the skin [21, 27].

CNS involvement is associated with adverse prognostic implications (Fig. 16.10). Approximately 25% of ECD patients will have neurologic symptoms at the time of diagnosis, and 50% will develop neurologic complaints during the course of their disease. Deficits in cognitive function are less common.

Central nervous system infiltration typically occurs in the setting of widespread systemic involvement with ECD [21]. ECD histiocytes have been reported to infiltrate the midbrain, pons, cerebellar peduncles, pituitary, dura, and sinuses, as well as the orbits [4, 21, 32]. Clinical manifestations of CNS disease include central diabetes insipidus [10, 21], cerebellar syndromes like ataxia [4, 21], focal mass lesions causing seizures or radiculopathy [4, 21], and exophthalmos or other gaze disturbances [21].

Endocrine dysfunction usually results from direct CNS involvement, however adrenal, testicular, and thyroid involvement have been described. The most common endo-

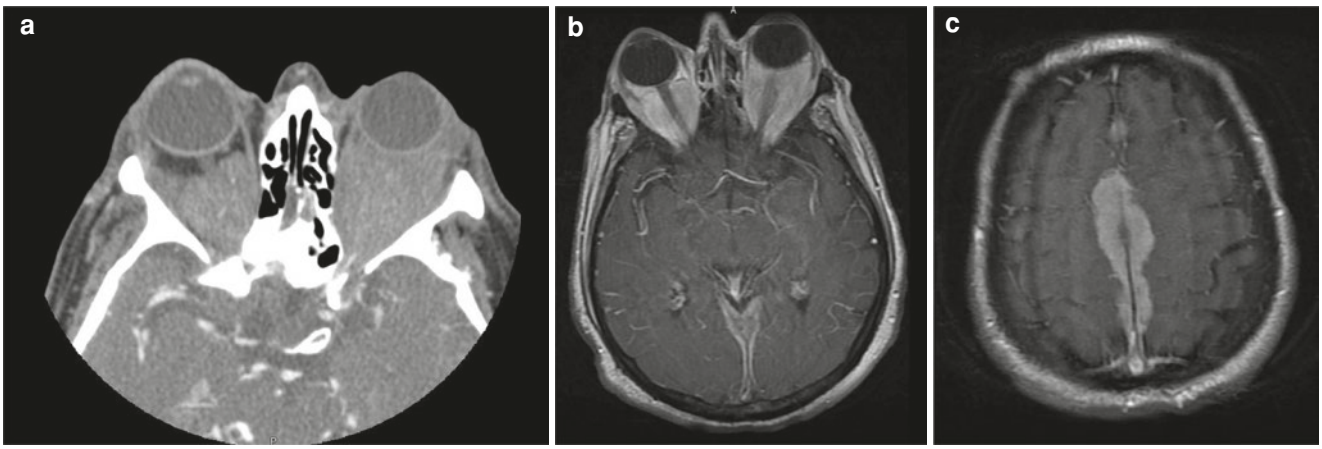

Fig. 16.10 Radiographic manifestations of ocular ECD involvement. (**a**) 57 years old man presents with cellulitis and exophthalmos. Contrast enhanced orbit CT shows bilateral retrobulbar soft tissue masses. (**b**, **c**) Axial T1 MRI with contrast confirms enhancing retrobulbar masses (arrows), and dural masses (arrowheads)

crine presentation is central diabetes insipidus [4, 32], followed by deficits in growth hormone [4], gonadotropins, thyrotropin [4], and rarely corticotropin [4, 32].

The heart is the most common extraskeletal site of ECD infiltration, which is rare in other non-Langerhans cell histiocytic diseases, and almost never occurs in Langerhans cell histiocytosis [4]. The histiocytes of ECD can infiltrate any cardiac layer, including the pericardium (up to 40%) [4]. Pericardial involvement can result in pericardial effusion [4, 26], although cardiac tamponade is rare [4]. There is a predilection for infiltration of the right atrium, which can present as a "pseudo-tumor" on cardiac imaging [1, 4, 10, 21], and can extend into the atrioventricular sulcus causing conduction blocks [4], and even direct valvular infiltration by histiocytes [10, 21, 27]. Vascular involvement can include periarterial infiltration [26, 27] and fibrosis [27] has been described to involve the coronary arteries in up to 55% (although the need for stent placement is uncommon), aorta, brachiocephalic trunk, subclavian arteries, pulmonary trunk, carotid arteries, celiac trunk, superior mesenteric trunk, and renal arteries [1, 4, 6]. Periarterial infiltration can lead to dire consequences if stenosis results in cerebral, myocardial, and/or mesenteric ischemia, and renovascular hypertension [27]. Additional clinical complications can include congestive heart failure, thromboembolic disease, and valvular dysfunction [27].

Retroperitoneal and kidney involvement is common [10, 21, 27, 32], with a higher frequency in males [21]. Histiocytes may infiltrate perinephric soft tissues leading to a "hairy kidney" appearance on imaging. Extension to the renal sinus, and the mid- and distal ureters can cause hydronephrosis necessitating stenting [4]. Mesenteric infiltration and fibrosis have also been described [32].

Other extra-pulmonary and extra-skeletal manifestations of ECD include skin nodules and soft tissue masses [21, 32], which increase in incidence with age [21]. ECD involvement in the reticuloendothelial and hematopoietic systems is rare [4].

Investigation/Diagnosis

The diagnosis of ECD can be extremely challenging, often requiring a multidisciplinary approach that includes the integration of clinical, radiographic, pathologic, and genetic data. There are no specific laboratory findings that are diagnostic or specific for ECD, but there are several that can offer insight into the extent or activity of the disease. Inflammatory markers such as erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), lactate dehydrogenase (LDH) [10], and alkaline phosphatase (ALP) may be elevated [27]. Hypothalamic-pituitary axis involvement may be detected by elevations of prolactin, or decreased levels of luteinizing hormone, follicle-stimulating hormone, adrenocorticotropic hormone, growth hormone, or thyroid stimulating hormone. Central diabetes insipidus can result in hypernatremia, and the diagnosis can be revealed by a doubling of urine osmolality after desmopressin administration or increased serum osmolality after water deprivation in a patient with polyuria [27]. Elevations in blood urea nitrogen and creatinine may point toward renal involvement [27].

Chest Studies

Imaging studies can offer aid in the initial diagnosis and provide important information for monitoring disease progression or treatment response. CXR may demonstrate prominent interstitial markings resembling Kerley B lines, due to lymphangitic involvement [20] (Fig. 16.7).

Computed tomography (CT) allows for the identification of lung, pleural, aortic, and skeletal lesions [26]. High-

resolution computed tomography (HRCT) is the gold standard for the identification of pulmonary manifestations of ECD. The changes seen on HRCT are due to histiocytic infiltration that typically manifests in a lymphangitic distribution involving the visceral pleura, interlobular septa, and bronchovascular bundles [27]. Other common findings include centrilobular nodular opacities, thin-walled cysts, ground-glass opacification, pleural effusion, and mediastinal involvement [1, 4, 11, 34]. Gallego et al. [11] described a common pattern of pleural thickening due to histiocytic infiltration of the right paravertebral basal area of the retrocrural space which creates a pseudotumor-like structure(Fig. 16.7).

When the lungs are involved, pulmonary function testing (PFT) should be completed. Findings may be normal early in the disease ranging to advanced obstructive or restrictive disease with reduced DLCO in more severely affected patients [4].

Cardiovascular Imaging

CT evaluation may also demonstrate an irregular appearance of the aortic intima, called "coated aorta," related to fibrous encasement of the aorta by histiocytic infiltration of the adventitia, a pattern that is pathognomonic of ECD [10, 21, 27]. Echocardiography can be used to assess degrees of cardiac involvement [27].

CNS Imaging

Magnetic resonance imaging is the modality of choice for CNS imaging and may demonstrate masses in the pituitary stalk, cerebellum, and brainstem, as well as retro-orbital masses with and without meningeal involvement [27] (Fig. 16.10).

Bone Radiography

Plain films demonstrating bilateral symmetric cortical osteosclerosis of the metadiaphyseal regions of long bones with sparing of the epiphyses is pathognomonic of ECD and seen in 96% of patients [1, 4, 10, 20]. The most commonly affected bones are the femur, tibia, and fibula, and less frequently affected are the ulna, radius, and humerus [27] (Fig. 16.9). The axial skeleton is typically spared [27].

99mTc Bone scintigraphy can be used as a screening test for bony involvement including the identification of pathognomonic features of parallel, symmetric uptake in long bones of both extremities [4, 21, 26] (Fig. 16.9).

Positron emission tomography/computed tomography (PET-CT) offers good sensitivity for the detection of bone lesions and can detect subtle vertebral lesions and aid in targeting for biopsy [4, 26]. PET-CT can also detect visceral and vascular infiltration as ECD lesions exhibit increased radiotracer uptake [26].

Other Imaging Findings and Considerations

Contrast-enhanced CT may show lymphadenopathy and diffuse bilateral infiltration of the perinephric soft tissue leading to thickening in a stellate pattern, often described as having a "hairy kidney" appearance [1, 4, 6, 10]. Combinations of imaging studies have important roles at the time of diagnosis, and as part of monitoring for disease progression and/or response to treatment. Mazor et al. [27] have outlined a strategy for imaging at the time of initial presentation and over time. Initial evaluation including plain films of the skeleton and whole-body bone scintigraphy may reveal pathognomonic symmetric osteosclerosis of the metadiaphyses of long bones. A whole-body PET-CT [1, 27] allows assessment of the extent of skeletal and extra-skeletal involvement, and identification of an optimal site for biopsy [1, 27]. Mazor et al. [1, 27] reported that PET-CT offers variable sensitivity, but excellent specificity for ECD lesions. A baseline MRI is the optimal study to evaluate patients for CNS involvement [1, 10, 26, 27], and baseline head CT aids investigation of skull and sinus involvement as well as guides biopsy site selection [1, 27]. HRCT screening is indicated at diagnosis and for patients who develop pulmonary symptoms [1, 27].

The gold standard for diagnosis of ECD is correlative tissue biopsy integrated with the clinical/radiographic findings [1, 4, 21]. Histological demonstration of xanthogranulomatous family histiocytic infiltration with appropriate staining in the right clinical/radiographic setting is diagnostic [1, 21, 26, 27]. In patients with pulmonary manifestations, extrapulmonary sites of involvement may be lower risk targets for biopsy [4, 11].

Disease Monitoring

Progression of the disease can be followed over time with serial PET-CT, annual low-dose CT of the chest, abdomen, and pelvis, and contrast CT of the chest if the patient develops symptoms concerning cardiac or mediastinal infiltration. Echocardiography should be obtained if cardiac involvement is suspected [27]. Lu et al. suggest serial MRI of the CNS and spine over time [21]. Pulmonary function tests are useful for following pulmonary disease progression.

Pathology

As shown in Fig. 16.8**,** pathologic evaluation of lung tissues reveals histiocytes with an abundance of pale, eosinophilic cytoplasm and bland appearing nuclei that infiltrate the pleura and lead to pleural thickening [20]. Histiocytic infiltration of the lung parenchyma in a peri-lymphatic distribution leads to thickening of the interlobular septa and bronchovascular bundles, often sparing the alveoli. The histological findings correlate with CT findings that often include ground glass opacities and interstitial changes in a lymphatic distribution [20].

Management/Treatment

Treatment recommendations are summarized in Fig. 16.11**.** The FDA has approved vemurafenib, a BRAF V600 inhibitor, and given cobimetinib, a MEK-inhibitor Breakthrough Therapy Designation for the treatment of ECD [1, 24] Current treatment recommendations for other agents are drawn from case reports, case-series, small open-label trials and retrospective studies [27]. In patients who are asymptomatic with indolent non-vital single organ disease, treatment may not be necessary for the short term, and adopting a "watch and wait" strategy with serial imaging may be reasonable [1, 10]. In patients who are symptomatic or progress with the disease that threatens to compromise major organs systems, (especially with pulmonary and CNS involvement), treatment should be initiated [1, 10].

The most thoroughly studied therapy for ECD is interferon-alpha (IFN-α) [10, 21, 26, 27, 32]. IFN-α has been reported to improve survival in multivariate retrospective studies [10, 32] but is often poorly tolerated [10, 21, 27, 32]. There is wide variability in reported dose ranges applied (from one million units three times weekly [10] to more than 18 million units total weekly [27]), with no consensus regarding the optimal regimen. Pegylated IFN-α has been reported to provide equal efficacy, better tolerance, and more convenient dosing with weekly once administration [10, 27]. Gianfreda et al. report an untreated mortality rate in ECD of 60%, which was reduced to 26% with administration of IFN-α. Although the mechanism of action is not entirely clear, IFN-α is thought to promote immune-mediated clearance of

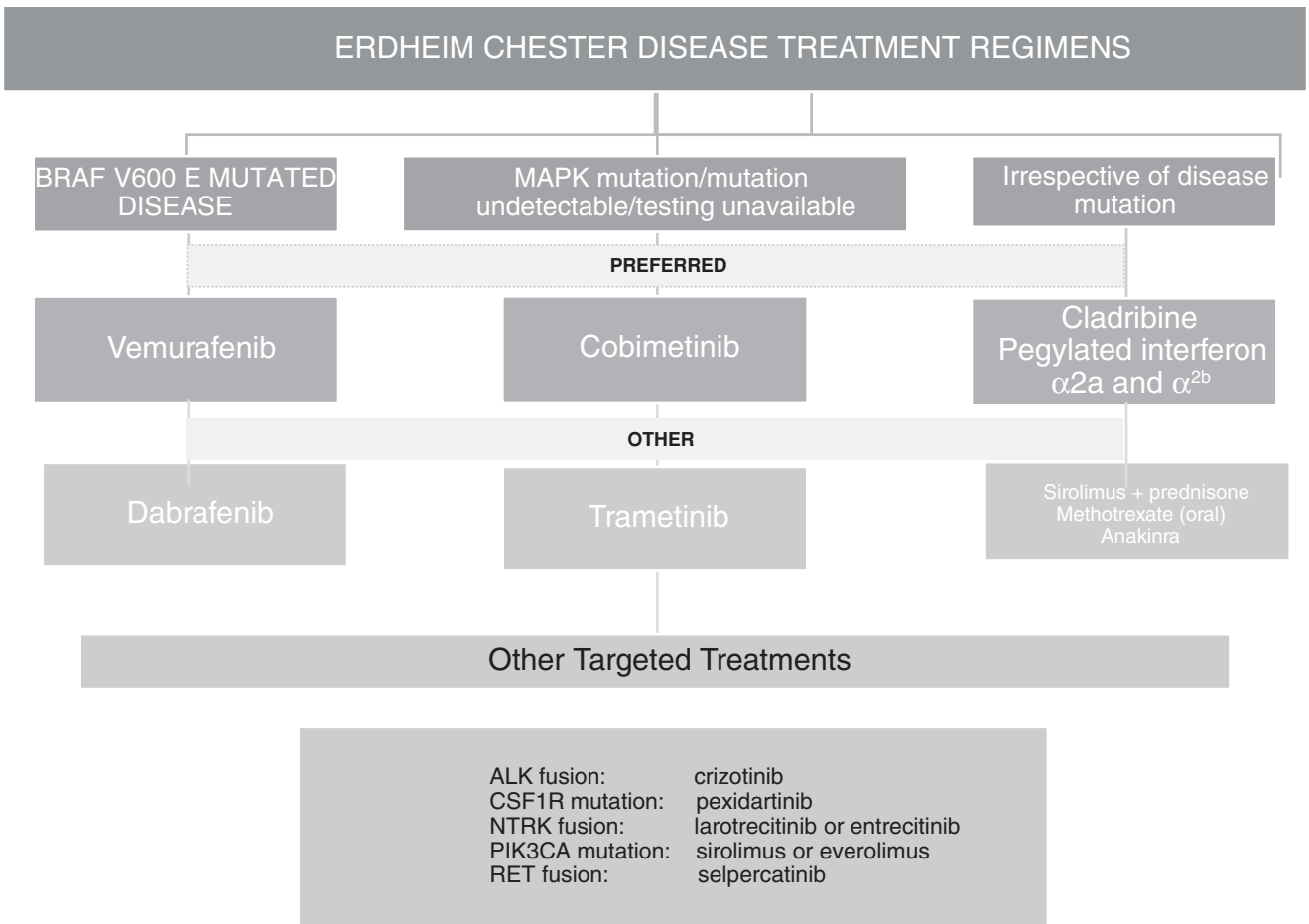

Fig. 16.11 Treatment algorithm for ECD. (Adapted from NCCN [22])

histiocytes and inhibit the terminal differentiation of immature histiocytes [27]. It is interesting to note that IFN-α levels are elevated in patients with untreated ECD [10, 32]. IFN-α results in durable regression of bone lesions and retro-orbital lesions, and reduction in pain and manifestations of diabetes insipidus [10, 27]. IFN-α does not appear to be effective for cardiac or central nervous system ECD lesions [10, 27, 32], and has a minor impact on pulmonary lesions [27]. There are currently no means to predict who will or will not respond to IFN-α therapy. Adverse effects of IFN-α include often intolerable fatigue (perhaps the most limiting adverse effect) [10], myalgia, pruritus, thrombocytopenia, and asthenia [27]. IFN-α should be used with caution in patients with a history of psychiatric disease as it can exacerbate these conditions [10], especially depression [10, 27]. As treatment is prolonged, often spanning more than 20 months, tolerance to treatment becomes a major limiting factor [27].

In patients who progress despite therapy, or cannot tolerate therapy with IFN-α, there are many other candidate therapies available. Many of these second-line therapies target key nodes in the pathogenic pathway outlined earlier.

Vemurafenib, a BRAF V600E inhibitor, has been shown to have efficacy in LCH and PLCH patients with this mutation [1, 21, 27, 32], and is an appropriate, FDA-approved consideration in the approximately 50% of ECD [10, 21, 27, 32] patients who harbor this mutation. Vemurafenib crosses the blood-brain barrier [21] suggesting potential efficacy for ECD CNS lesions. There have been reports of dramatic responses within a few weeks of initiation of vemurafenib [10, 21, 27], and the drug is usually well tolerated; the most common adverse effects in the literature include skin rash, fatigue, and diarrhea [10] which do not usually limit use. A recent phase II trial demonstrated a 62% response rate, with rapid and durable clinical responses in multiple disease sites with reversal of critical disease burden in some patients [1]. It was also noted during this phase II trial that about 2/3 of patients who discontinued vemurafenib relapsed within 6 months [1]. Additional risks that have since been identified include an increased risk of secondary neoplasia, sarcoidosis, and pancreatitis [1]. Goyal et al. [1] have suggested a management strategy that includes screening for BRAF mutations at the time of initial pathology review. In the BRAF V600E mutation-positive patients first-line therapy with vemurafenib should be offered [1]. If ECD is confirmed and no BRAF V600 mutation is found, a MEK inhibitor (targeting a downstream effector that will block signaling by other (undetected) activating mutations in the MAPK pathway) or therapy with IFN-α are reasonable next steps [1, 10, 24]. Furthermore, in patients who progress despite these therapies, or who cannot tolerate the drugs, a trial of second-line therapy with anakinra, imatinib, or cladribine is recommended [1, 6, 10].

Other mutations that have been identified in ECD include PIK3CA (approximately 13%) and NRAS mutations (approximately 4%), which cause activation of the mammalian target of rapamycin (mTOR) pathways [32]. mTOR inhibitors represent another attractive therapeutic option [32], offering anti-proliferative, anti-inflammatory, and anti-senescence properties [1, 32]. Gianfreda et al. performed an open-label trial utilizing the mTOR inhibitor, sirolimus, in combination with prednisone in patients with ECD who were not candidates for IFN-α therapy and did not express the BRAF V600E mutation. They reported a significant response with regression of peri-renal and peri-ureteral lesions, as well as improvement in pericarditis [32]. There were varied responses in CNS lesions and marginal or absent responses at other sites of disease [32]. They concluded that therapy with sirolimus and prednisone led to stabilization or improvement of disease and was generally well tolerated in patients with ECD [32].

The recombinant human interleukin-1 receptor (IL-1R) antagonist, anakinra [21, 27, 32] has been used in patients with ECD. Inhibition of the IL-1R blocks aberrant MAP kinase activation in histiocytes [10]. Munoz et al. [10] postulated that IL-1R antagonism may also downregulate the expression of IL-1 alpha receptors on the membranes of monocytes and the IL1 beta receptors of infiltrating histiocytes. Treatment with anikinra has been reported to reduce fever and bone pain, improve skin lesions, and result in weight gain. The drug is generally well tolerated [10, 27] with the most common adverse effect reported to be local skin reactions at the site of injection, and reactivation of previous infections, such as tuberculosis. Given the favorable safety profile, Munoz et al. [10] suggest that anikinra may be an appropriate therapy in elderly patients or patients with comorbidities.

Cladribine, also called chlorodeoxyadenosine, is an antineoplastic purine analog [32], often used for the treatment of LCH and PLCH, that represents another alternative for ECD therapy, although less data are available [10, 27]. Cladribine is toxic to monocytes [10] and has been reported to lead to partial regression of CNS lesions [27]. Adverse effects of bone marrow suppression and neurologic toxicity are dose-dependent [27].

The anti-tumor necrosis factor alpha (TNF-α) mononuclear antibody, infliximab, has been used to treat ECD [10, 21, 27]. TNF-α has been shown to play a role in regulating the recruitment of histiocytes [10]. Infliximab therapy has been reported to improve cardiac function and cause resolution of pericardial effusions [10] in ECD. The anti-IL-6 medication, tocilizumab, has also been utilized for the treatment of ECD [27].

Imatinib is a tyrosine kinase inhibitor that selectively targets cKIT, BCR-ABL, and platelet-derived growth factor

which has been shown to be effective for treating hairy cell leukemia and chronic myelogenous leukemia [10]. There are reports of response to imatinib therapy in ECD, and although the mechanism is unclear, it is well tolerated [10].

Other therapies that have been reported in the literature in case reports and small case series include immunosuppressants such as cyclophosphamide, methotrexate, azathioprine, cyclosporine, and various chemotherapeutic agents [21, 27]. Autologous bone marrow transplantation [10], radiation therapy and surgical intervention of brain or bone lesions [21, 27] have also been reported with variable results, and with mostly unsustained responses [21, 27]. Given the high prevalence of bony involvement, bisphosphonate therapies have been attempted with only partial success and their role remains unclear [10, 21, 27]. Glucocorticoids have been widely used for the treatment of ECD but have been shown to have little impact on disease [1, 10, 27] except in a few cases when used in high doses [10, 27, 32].

Prognosis

The prognosis of ECD is variable, with 5-year survival between 40 and 70% [1, 11, 21], depending on the degree of multisystem involvement [26]. While it is unclear if pulmonary involvement carries any prognostic weight [10, 27], CNS and cardiovascular involvement are well-established harbingers of a worse prognosis [4, 10, 21]. CNS involvement (especially with pituitary infiltration) accounts for approximately 30% of all deaths [1, 26, 32]. Cardiovascular complications, including heart failure from pericardial, myocardial, or aortic infiltration [1, 4, 10, 21], or myocardial infarction related to infiltration of coronary arteries [27], are responsible for about 61% of deaths [27]. Cardiac involvement is a late complication of ECD [21].

Clinical Vignette

A 63-year-old female presented with 2 years of progressive wheezing and daily cough that were worse when lying flat. These symptoms were associated with shortness of breath with ascending 1 flight of stairs, sneezing, bilateral eye pain, fatigue, and left upper extremity discomfort. Her history was remarkable for gastro-esophageal reflux disease controlled with daily proton pump inhibitor, and motor vehicle collision complicated by cervical spine trauma and right-sided hemothorax 5 years prior to presentation. Initial CXR was abnormal, and subsequent CT of the chest demonstrated mass-like subpleural consolidation in the right lower lobe (RLL), bilateral lower lobe ground glass opacification, and pleural and subpleural interstitial thickening consistent with fibrosis (see Clinical Vignette figure). A PET-CT was obtained revealing increased FDG uptake in several distributions, including the RLL subpleural consolidation, thickened pleura, scattered airspace disease of the right lung, and mediastinal lymph nodes. Biopsy of the RLL subpleural consolidation revealed marked inflammation and fibrosis but was nondiagnostic. She underwent a video-assisted thoracic surgery lung biopsy of her left lung, which revealed a fibroinflammatory process with a lymphangitic distribution, and a focal chronic interstitial infiltrate with abundant macrophage aggregates and non-necrotizing granulomatous inflammation of airspaces and interstitium. Immunohistochemistry was positive for CD34, which together with the histopathology was consistent with the diagnosis of ECD. A subsequent bone scan revealed pathognomonic changes of ECD with increased uptake within the distal diaphysis and metadiaphyseal regions of each femur. She completed initial evaluation with pulmonary function tests that showed a mild restrictive defect with reduced diffusion capacity, an MRI head which was negative, and a cardiac MRI which revealed cardiac involvement of her ECD.

During the course of the patient's evaluation, she was also found to have chronic myelomonocytic leukemia (CMML). Ultimately, it was discovered that the patient harbored a BRAF V600 E mutation leading to her ECD, with NRAS and ASXL1 mutations causing chronic myelomonocytic leukemia (CMML). Treatment was initiated with dabrafenib/trametinib (BRAF + MEK inhibitor) which resulted in remarkable improvement in pulmonary function testing, radiographic changes, and symptoms of dyspnea, cough, and wheezing (Fig. 16.12). Unfortunately, the patient's hematologic malignancy progressed and she passed away 4 years after her diagnosis of ECD due to complications of acute myeloid leukemia.

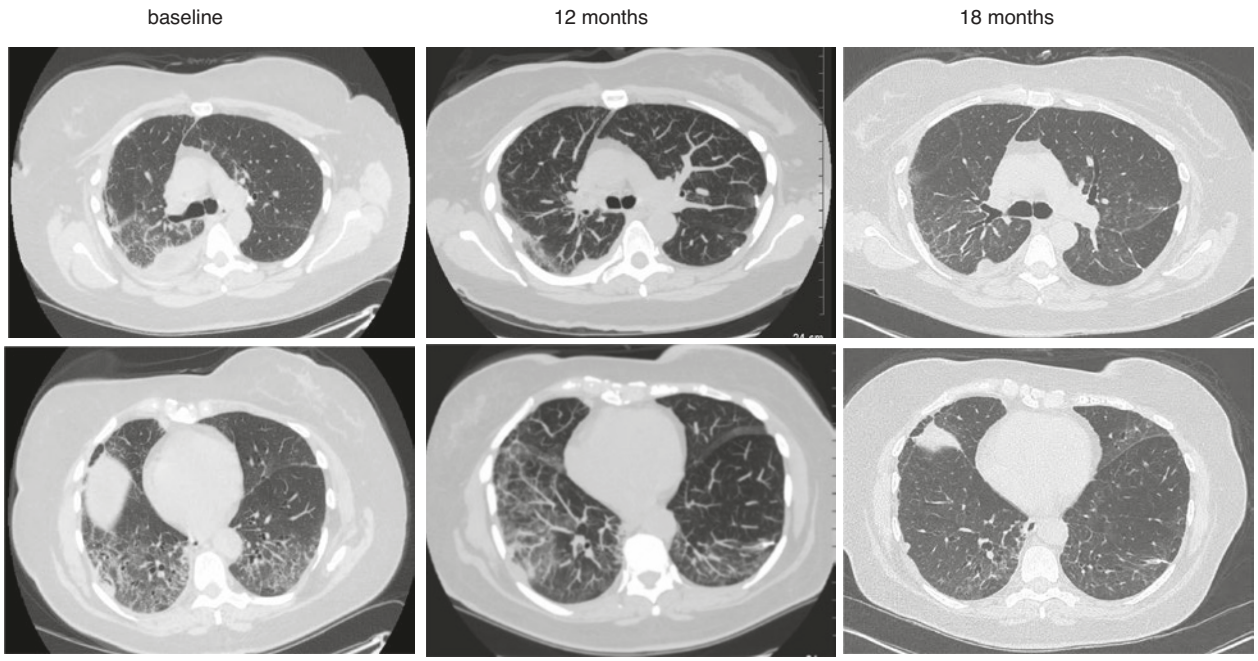

Fig. 16.12 HRCT at baseline, and 12 months and 18 months after therapy with dabrafenib/trametinib was initiated

Rosai-Dorfman Destombes Disease

Definition

Rosai-Dorfman Destombes disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy, is a very rare histiocytic disorder involving the proliferation of histiocytes with a macrophage-dendritic cell phenotype. RDD presents most commonly with painless lymphadenopathy and is characterized by emperipolesis on histology [1, 2, 11].

Epidemiology

RDD is a rare disorder with a prevalence ~1/200,000 that typically affects young adults and adolescents [4, 11], although it has been documented in all age groups [11]. A systematic review by Moyon et al. endorsed a median age at diagnosis of 45 years old [34]. There is limited evidence of a predilection for males and people of African descent, although epidemiologic data are sparse and not conclusive [11].

Etiology/Pathophysiology

The etiology of RDD is unknown and is thought to be multifactorial [11]. It has been suggested that viral infections such as herpes simplex virus and human immunodeficiency virus, lymphomas or other lymphoproliferative and autoimmune disorders, systemic lupus, IgG4 disease, amyloidosis, or polycythemia vera may be associated with the development of RDD [11]. Inherited conditions linked to RDD, include those due to mutations in *SLC29A3* and *TNFRSF*. Similar to PLCH and ECD, there is mounting evidence that RDD is a neoplastic histiocytic disease linked to mutations in the MAPK/ERK pathways. Studies have demonstrated mutually exclusive *ARAF*, *KRAS* and *MAP2K1* mutations in one-third of cases of RDD [5, 35] as well as positive staining for phosphorylated ERK (an indication of excess MAPK signaling) in 90–100% of cases examined [36, 37]. Detection of *BRAF-V600E* mutations may require very sensitive testing methods [2, 38].

Histopathology and Immunohistochemistry

The histopathologic features of RDD include tissue infiltration by large histiocytes that are characterized by extremely pale eosinophilic cytoplasm with a large hypochromatic nucleus and notable nucleolus with an inflammatory background comprised of numerous polytypic plasma cells, with or without lymphoid follicle formation and small neutrophilic infiltrates [1, 4, 11] (Fig. 16.13). The pathognomonic feature of RDD is emperipolesis; the finding of histiocytic

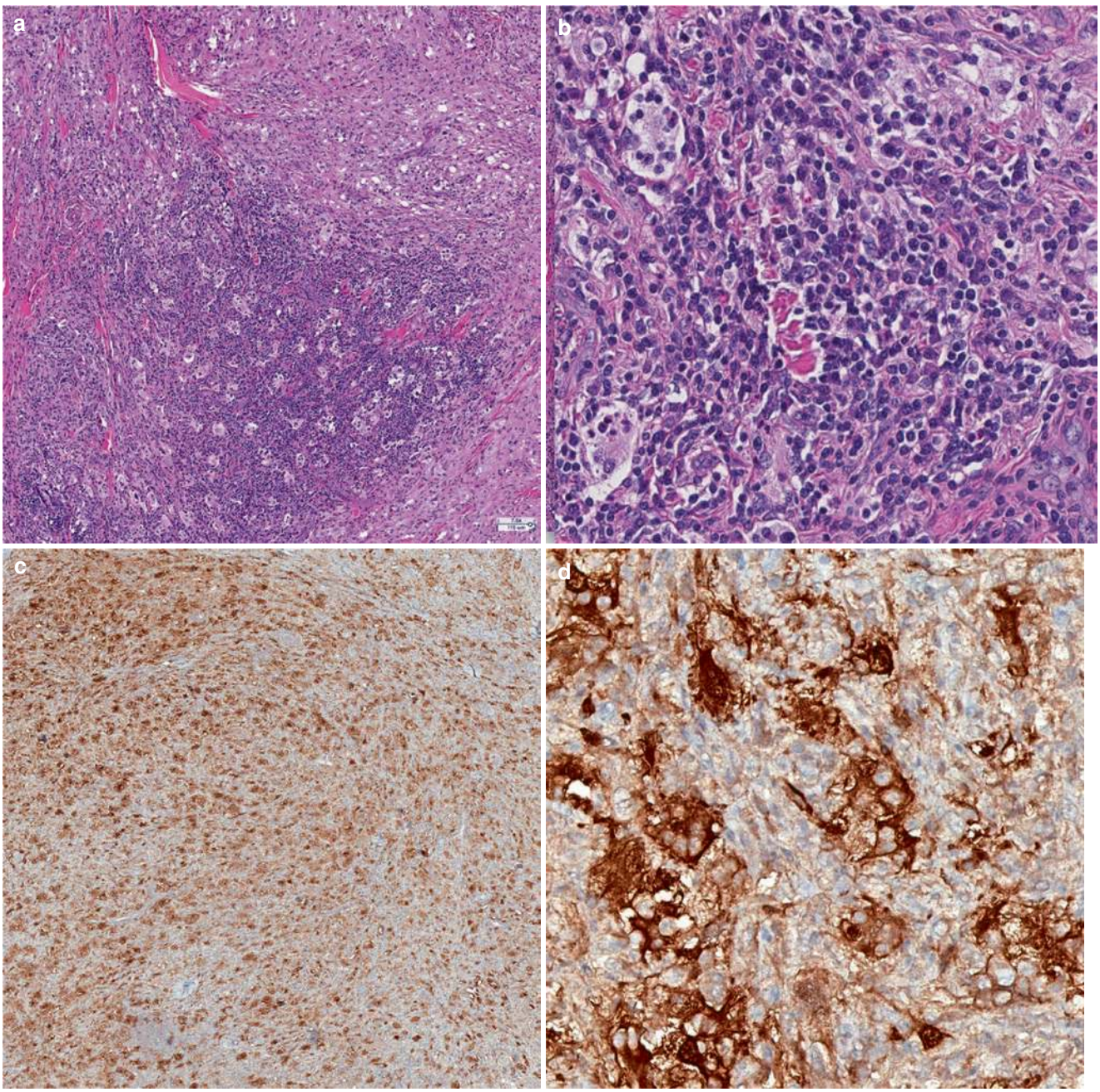

Fig. 16.13 Pathology of Rosai Dorfman Destombes Disease (RDD). (**a**) The lung is an uncommon location for RDD. Rather the lymph nodes may be more commonly involved with massive sinus expansion. When the disease progresses, the lesional cells may be obscured by a fibrotic stromal background that may mimic ECD in extranodal sites, as emperipolesis may be less pronounced in these locations (**a**, digital scanned H&E, 7.5×). The diagnostic RDD cell is a large histiocyte with ample pale lightly vacuolated cytoplasm and a large nucleus with hypochromatic chromatin and small but prominent nucleoli (**b**, digital scanned H&E, 40×). The S100 immunostain (**c**, **d** digital scanned immunostain, **c**, 5× and **d**, 40×) will best bring out the large cells with nuclear and cytoplasmic staining and evident negative staining reflection of the trafficking leukocytes (emperipolesis)

cells containing intact inflammatory and erythroid cells (leukocytes, erythrocytes, and plasma cells) within their cytoplasm; however, it is not mandatory for diagnosis and often scant in extranodal sites as compared to nodal sites [2, 4, 6, 11]. On the other hand, the degree of emperipolesis may be so great as to obscure the large hypochromatic nucleus of the RDD cells such that immunostains including S100 and fascin may better highlight the non-staining trafficking cells within the large stained RDD cells. Unlike PLCH and ECD, the histiocyte in RDD has a characteristic large-sized, unique monocyte/macrophage to dendritic cell type phenotype. Ranvindran et al. have recently identified OCT2 as a novel marker for the monocyte-macrophage phenotype of RDD as it was expressed in 97% of their tested RDD cases [39]; however, this is not specific to RDD and can be also seen in other histiocytic neoplasms, including malignant cases, and some LCH cases. Other markers useful in the diagnosis of RDD include S100, CD163, and cyclin D1. Like most histiocytic neoplasms, cyclin D1 is also often expressed with nuclear and cytoplasmic staining and phospho-ERK can show variable expression in the large RDD cells. RDD cells are negative for CD1a, langerin, and factor XIIIa [1, 4, 11, 20, 39].

Clinical Presentation

Patients typically present with painless bilateral lymphadenopathy, most commonly involving the cervical region, occasionally associated with constitutional symptoms including pyrexia and weight loss [4, 11]. While extranodal manifestation occurs in up to 40% of patients, pulmonary involvement is rare (less than 5% of cases) [2, 20], typically involving the large airways and sinuses, or the lung parenchyma [2, 4]. The most common pulmonary manifestation is that of polypoid masses involving the major airways with associated mediastinal or hilar adenopathy that can mimic sarcoidosis in radiographic appearance [20, 34]. Less commonly, interstitial expansion, parenchymal nodular lesions, pleural nodules, pleural effusion, or diffuse interstitial thickening may be seen [2, 4, 20] (Fig. 16.14). Lesional involvement of the airways produces the most common symptoms of chronic dyspnea, which can be severe dry cough, stridor, or hoarseness. Lesions within the airways may cause obstructive defects in spirometry [11, 34]. Although lower respiratory tract involvement can have an aggressive course, it is unusual for RDD to result in acute respiratory failure or cor pulmonale [2, 34].

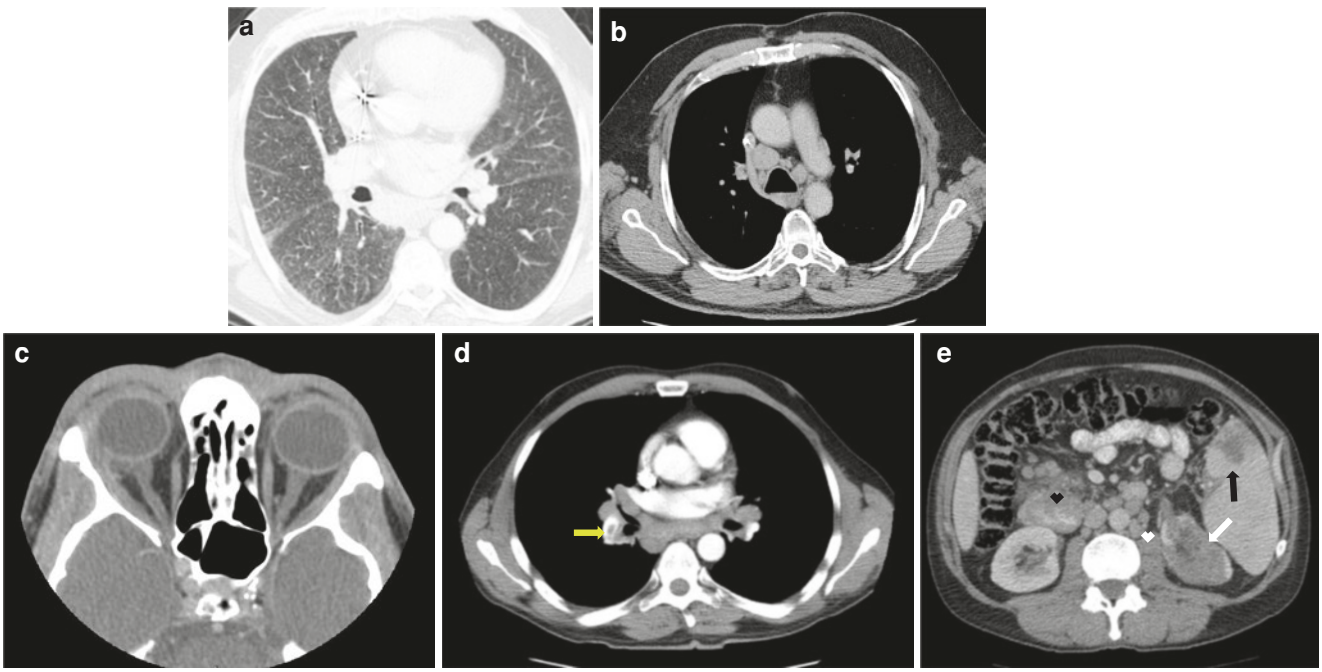

Fig. 16.14 Radiographic findings of pulmonary RDD. (**a**) Lung windows in a middle-aged man with Rosai-Dorfman Destombes disease. Contrast enhanced chest CT in lung windows reveals mild diffuse ground glass opacity, septal lines, and fissural thickening. (**b**). Mediastinal windows show paratracheal lymphadenopathy. (Case courtesy of Seth Kligerman, M.D. San Francisco, CA.). 53 years old man who presented with inguinal lymphadenopathy and periorbital eye swelling. (**c**) Contrast enhanced orbit CT periorbital and preseptal and right lacrimal gland soft tissue infiltration. (**d**) Contrast enhanced chest CT reveals bilateral hilar and subcarinal adenopathy. A right pulmonary artery pulmonary embolus (yellow arrow) is also present. (**e**) Contrast enhanced abdomen CT reveals low attenuation mass in the spleen (black arrow), left kidney (white arrow), duodenal infiltration (black arrowhead), and retroperitoneal adenopathy (white arrowhead). (Different images of this case were previously published in Ahuja J, Kanne JP, Meyer CA, et al. Histiocytic Disorders of the Chest: Imaging Findings. RadioGraphics 2015; 35: 357–370)

Pulmonary involvement is almost always accompanied by evidence of multisystem disease [34]. Other extranodal sites that can be involved in RDD in order of frequency include skin, nasal cavity, upper gastrointestinal tract, bone, orbits, central nervous system, genitourinary system, and rarely, (<5%) hepatic or pancreatic involvement [11]. A retrospective study of Mayo Clinic records performed in 2010 examined patients with histopathologic evidence of RDD on organ biopsy; 9 of 21 patients diagnosed with RDD had intrathoracic manifestations (43%) with the primary pulmonary symptoms being dyspnea and cough. Mediastinal lymphadenopathy (6 patients) was the most common radiographic manifestation while cystic change, interstitial lung disease, and airway disease were radiographically evident in 4 patients [40] (Fig. 16.14).

Investigation/Diagnosis

A high index of suspicion is necessary to diagnose RDD, as there is often very little physical examination (beyond lymphadenopathy) or on laboratory evaluation to suggest the diagnosis. Plain films obtained as part of the initial investigation are typically non-specific but may demonstrate mediastinal widening. CT of the chest may be helpful in evaluating lesions and guiding the optimal site for biopsy. The most common features of CT are mediastinal and hilar adenopathy [1]. Although less common, parenchymal nodules, interlobular septal thickening, thin-walled cysts, ground glass opacities, and poorly defined lung nodule(s) or masses may be seen [4, 11, 34]. There may be single or multiple nodular masses of the trachea and bronchi involving the adjacent fat and associated with varying degrees of airway obstruction [11]. PET-CT can be utilized as RDD lesions are metabolically active [11], and affected lymph nodes exhibit a halo appearance related to concentration of the most intense radiotracer uptake within their centers [4] (Fig. 16.14).

As with ECD and PLCH, pulmonary function tests in RDD may be normal or may demonstrate obstructive, restrictive, or diffusion defects depending on the nature of pulmonary involvement [34]. Bronchoscopy with endobronchial ultrasound and biopsy may be a useful diagnostic tool in RDD, given mediastinal adenopathy is often easily accessible with this technique. Bronchoalveolar lavage may demonstrate macrophage alveolitis [34], but this is non-specific. Transbronchial biopsy of lesions demonstrated on CT chest may be sent for pathologic examination and reveal histologic findings of RDD [34]. As with other histiocytic diseases, tissue sampling with histopathology and immunohistochemical evaluation is the gold standard for diagnosis, in the case of RDD demonstrating large cells that are S100 positive, and CD1a, langerin, and factor XIIIa negative [2, 4, 20].

In general, the diagnostic strategy for RDD is very similar to that of ECD and LCH. However, as RDD does not typically involve the endocrine system, evaluating for endocrinopathies as part of staging is usually unnecessary.

Management/Treatment

Treatment strategies for RDD are similar to the other histiocytic neoplasms and must be tailored to individual clinical circumstances as outlined in Fig. 16.15. Given that many patients remain asymptomatic with stable radiologic findings, or even experience spontaneous regression in 20–50% of cases, a conservative approach without intervention may be appropriate [1, 11]. In patients who are symptomatic, there are anecdotal reports of the use of the purine analog, cladribine [1], resulting in improvement in lung involvement on PET-CT [34], as well as reports of good responses to glucocorticoid therapy [11]. Moyon et al. described the use of cobimetinib, a MEK 1 and 2 inhibitor, in patients with RDD that exhibited KRAS mutations without detectable MAP kinase pathway mutations [24]. The only noted adverse effect was an acne-like rash.

There are reports of progression of RDD with the use of pegylated IFN-α [34], and limited or no responses with methotrexate, azathioprine, rituximab, vinblastine, cytarabine, infliximab, and/or combinations of these therapies [11, 34]. There are also reports of surgical, endoscopic, or laser debulking of adenopathy, together with adjuvant radiation therapy although efficacy is unclear [34].

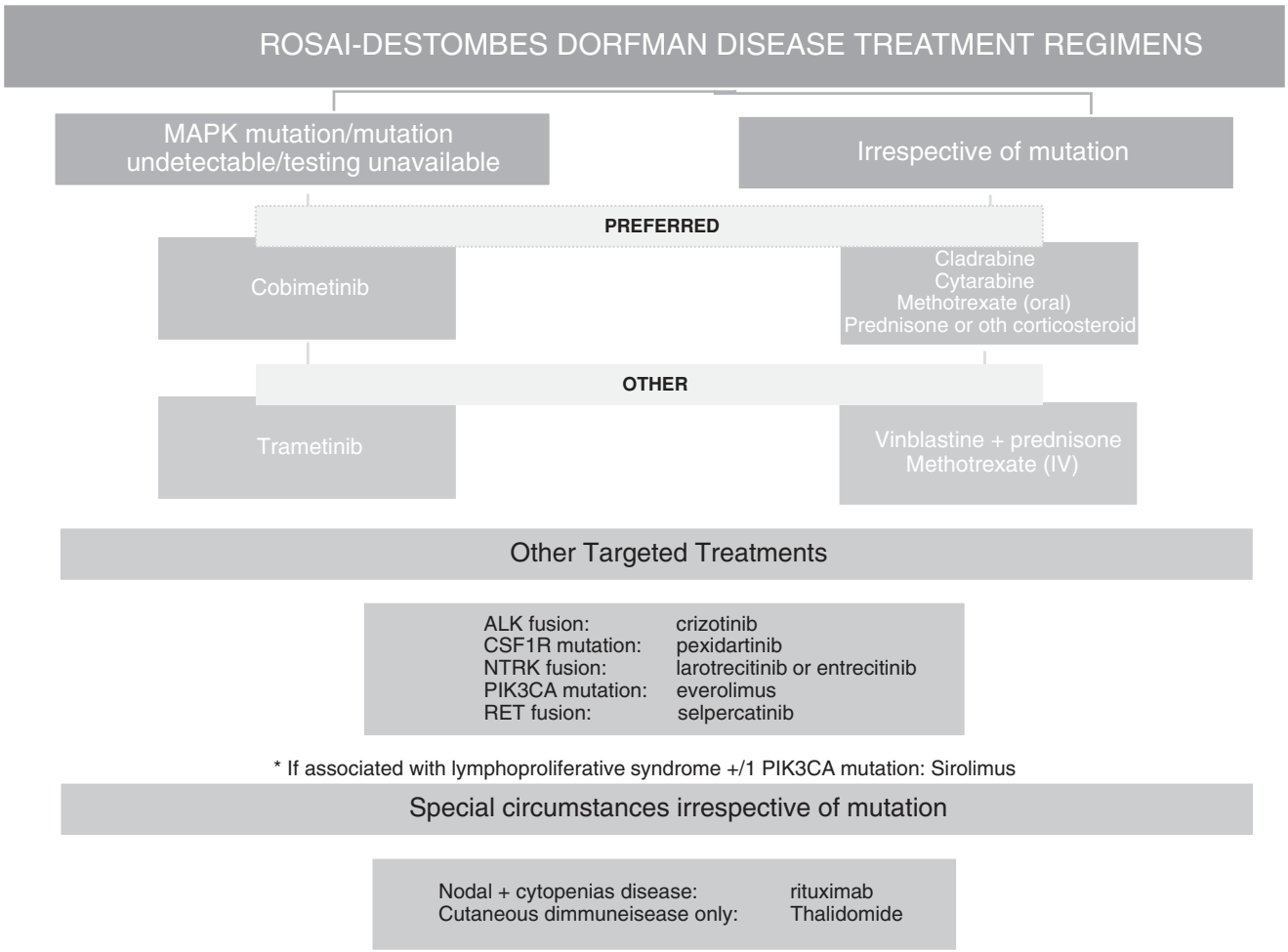

Fig. 16.15 Treatment algorithm for RDD. (Adapted from NCCN [22])

Prognosis

In general, the prognosis of RDD is good and nodal-limited disease typically has a benign course [1, 20, 34]. When RDD is extranodal and involving multiple systems, prognosis may be more guarded, although longitudinal studies are lacking [1, 34].

Conclusions

The histiocytic neoplasms that involve the lung are very rare diseases that can be a source of significant morbidity and mortality. The recent discoveries of mutations in the MAPK pathways have offered important insight into disease pathogenesis, allowing for the reclassification of histiocytic syndromes as inflammatory monomyelocytic neoplasms. The disease-driving mutant cells of the histiocytic syndromes appear to be most consistent with immature myeloid precursors with arrested development due to mutations that occur at different nodes in the RAS/MAPK/MEK/ERK and PI3K pathways. The identification of targetable mutations in PLCH, ECD, and RDD offers exciting new therapeutic options and genetic testing is now a key step in the evaluation of patients with these diseases.

Diagnostic Criteria for Primary Histiocytic Disorders of the Lung

(Adapted from NCCN Guidelines [22])

PLCH

- Even in the setting of highly suggestive clinical/radiological features, biopsy strongly recommended to confirm the diagnosis and to establish the mutational status
  - Histology showing histiocytes with grooved nuclei, eosinophilia
  - Immunohistochemistry reveals CD1a+, CD207 (Langerin)+, BRAF V600E(VE1)+/−
  - Electron microscopy reveals Birbeck granules
  - Genetic analysis may be useful in patients when pharmacotherapy is considered
    - No mutation identified
    - BRAFV600E mutation
    - Other MAPK gene mutation
  - Vigilance
    - VE1 IHC positivity should be confirmed with a second molecular assay
    - Negative BRAFV600E mutational testing should be confirmed with a second genetic modality or biopsy from more than one site
- Other recommended studies, as appropriate
  - Chest CT
  - Pulmonary function testing
  - Bone imaging if pain present
  - Echocardiogram/right heart catheterization
  - Endocrine studies for pituitary involvement
  - MRI brain/pituitary/sella turcica

ECD

- Even in the setting of highly suggestive clinical/radiological features, biopsy strongly recommended to confirm the diagnosis and to establish the mutational status
  - Histology reveals foamy histiocytes, giant cells, lymphoplasmacytic infiltrate
  - Immunohistochemistry reveals CD68+, CD163+, S100+/−, factor XIIIa+, CD1a−, Langerin−, BRAF (VE1) V600E+/−
  - Genetic analysis reveals
    - No mutation identified
    - BRAFV600E mutation
    - Other MAPK gene mutation
- Vigilance is required for atypical presentation
  - ECD can occur in the absence of bone disease
  - Characteristic xanthomatous histiocytes may be absent
  - VE1 IHC positivity should be confirmed with a second molecular assay
  - Negative BRAFV600E mutational testing should be confirmed with a second genetic modality or biopsy from more than one site
- Other recommended studies
  - Chest CT
  - Pulmonary function testing
  - Bone imaging
  - Whole body PET/CT including distal extremities
  - CBC, complete metabolic profile
  - Bone marrow aspiration/biopsy
  - Echocardiogram/right heart catheterization
  - Endocrine studies for pituitary involvement
  - MRI brain/pituitary/spine/sella turcica with contrast
  - CT sinuses with contrast

RDD

- Biopsy strongly recommended
  - Histology reveals histiocytes with round nuclei, central nucleoli, emperipolesis, plasmacytosis
  - Immunohistochemistry reveals S100+, CD68+, CD163+, cyclin D1+/−, CD1a−, Langerin−
- Other recommended studies, as appropriate
  - HRCT
  - Whole body PET/CT
  - CT sinuses, MRI orbit/brain/spine
  - CBC with differential
  - ALPS panel, ANA, RF, HLA-B27, IgG
  - Pulmonary function tests
  - Evaluation for anemia if present
  - NGS of lesional tissue for MAPK pathway mutations
  - If familial RDD is suspected, obtain SLC29A3
  - Bone marrow aspiration/biopsy should be considered

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Part IV

Lung-Dominant or -Limited Orphan Diseases

Eosinophilic Pneumonia

17

Vincent Cottin

Introduction

The eosinophilic lung diseases (Table 17.1) are characterized by the presence and presumed pathogenetic role of eosinophils in the lesional processes. Eosinophilic pneumonias are defined by a prominent infiltration of the lung parenchyma by eosinophils. The other eosinophilic lung diseases, mainly hypereosinophilic asthma (not discussed in this chapter), allergic bronchopulmonary aspergillosis, and the recently individualized hypereosinophilic obliterative bronchiolitis, mainly involve the airways.

Table 17.1 Definition of eosinophilia and hypereosinophilia

Term	Definition
Blood eosinophilia	>0.5 eosinophils × 10^9/L blood
Hypereosinophilia	>1.5 eosinophils × 10^9/L blood
Alveolar eosinophilia	>25% eosinophils at bronchoalveolar lavage
Tissue hypereosinophilia	• Percentage of eosinophils in bone marrow section exceeds 20% of all nucleated cells and/or
	• Pathologist is of the opinion that tissue infiltration by eosinophils is extensive and/or
	• Marked deposition of eosinophil granule proteins is found (in the absence or presence of major tissue infiltration by eosinophils)

Eosinophil Biology

Initially thought to be especially important in the defense against parasitic infestation, eosinophil leukocytes are now considered multifunctional cells implicated in the initial stage of innate and adaptive immunity, including but not restricted to numerous inflammatory reactions to parasitic helminth, bacterial, and viral infections [1]. Their broad role in homeostatic function, physiology, and pathophysiology is now well appreciated [2].

Eosinophil Differentiation and Recruitment

Eosinophil precursors differentiate and mature in the bone marrow under the action of cytokines and especially interleukin (IL)-5, IL-3, and granulocyte-macrophage colony-stimulating factor (GM-CSF) [1, 3]. Activation of the Ddbl-GATA-1 transcription factor is deemed critical in this process. Mature eosinophils then circulate in the blood for about 1 day before being attracted into tissues, through processes of chemotaxis, adhesion, and diapedesis that are primarily under the control of IL5 and eotaxin-1, itself regulated by the Th2 cell-derived IL-13 cytokine. In the tissues, they undergo apoptosis unless survival factors (mostly IL-5) are present.

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Physiologic and Immunologic Role of Eosinophils

Physiologic roles of eosinophils include their participation in host defense response, tissue regeneration, tissue repair after injury, metabolic homeostasis, immune homeostasis, angiogenesis, fibrosis, steady-state development of intestine and mammary gland, and tumor rejection [2, 4]. The eosinophil is involved in many allergic or inflammatory processes through its interaction not only with other cells, including especially T helper (Th) lymphocytes, but also with mast cells and basophils, endothelial cells, macrophages, platelets, and fibroblasts [2, 3]. Intercellular signaling is mediated by surface expression of adhesion molecules, apoptotic signaling molecules, chemokines, complement receptors, chemotactic factor receptors, cytokine receptors, and immunoglobulin receptors. For instance, eosinophils are capable of regulating mast cell function and histamine release. Eosinophils have further immune properties. They express the major histocompatibility complex II protein human leukocyte antigen (HLA)–DR, can present the antigen to T-helper lymphocytes, and secrete an array of cytokines, thereby promoting effector T-cell proliferation. They can synthesize IL-4 and promote IL-4, IL-5, and IL-13 secretion by $CD4^+$ T-cells (promoting Th2 lymphocyte activation), and secrete indoleamine 2,3-dioxygenase (indirectly promoting Th1 apoptosis), modulating the Th1/Th2 balance. Abnormalities in the T-cell receptor repertoire and T-cell clonotype of BAL lymphocytes and peripheral blood lymphocytes seem to contribute to the pathophysiology of eosinophilic lung diseases [5]. Overall, the paradigm of eosinophil function has changed from a terminal effector cell in allergic airway diseases to its being involved in the initial stages of pathophysiology.

Release of Mediators

The eosinophil contains two types of intracytoplasmic granules, the content of which can be released by exocytosis, piecemeal degranulation, or cytolysis, while other mediators are secreted (with the involvement of vesicle-associated membrane proteins in the regulation of granule fusion within the cell). Granule release through cytolysis is a rapid, stimulus-dependent process, and specific in terms of which cytokines are secreted.

The larger granules, identified by a dense crystalloid matrix at electron microscopy, contain the characteristic cationic proteins major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN), and the enzymatic protein eosinophil peroxidase (EPO) [1, 3, 4]. The smaller amorphous granules contain arylsulfatase and acid phosphatase. The process of degranulation by activated eosinophil releases cationic proteins into the extracellular space, with potential direct toxicity to the heart, brain, and bronchial epithelium. Degranulated eosinophils can be identified with electron microscopy by the presence of cytoplasmic vacuoles, and loss of electron density of the central core of the granules (inversion or disappearance of core density). Molecular and intracellular pathways regulating eosinophil differentiation, priming, activation, degranulation, and mediator secretion, and how the release of toxic substances contributes to the pathophysiology of eosinophilic disorders, have become better understood from a molecular standpoint [3].

In addition to cationic proteins, eosinophils release a number of preformed mediators including proinflammatory cytokines, lipid- and arachidonic acid-derived mediators, enzymes, reactive oxygen species, and matrix metalloproteases [4], all of which may contribute to the pathophysiology of eosinophilic lung diseases. Histopathologic lesions in eosinophilic pneumonias are formed by the recruitment of activated eosinophils and other inflammatory cells to tissues, and are largely reversible with treatment, especially with corticosteroids. However, tissue damage and remodeling with fibrosis may occur partly through the release by eosinophils of transforming growth factor-beta, especially in the bronchial mucosa, as in allergic bronchopulmonary aspergillosis (ABPA) and eosinophilic granulomatosis with polyangiitis (EGPA) (formerly Churg–Strauss syndrome).

Targeting the Eosinophil Cell Lineage

Corticosteroids shorten eosinophil survival in the blood and tissues and are among the most potent drugs to treat eosinophilic disorders, although lack of specificity can result in numerous adverse events. As the recruitment of eosinophils to the lung mostly implicates IL-5 and the eotaxin subfamily of chemokines (itself regulated by the Th2 cell-derived IL-13 cytokine), the IL-5 pathway is the target of several drugs, initially developed in asthma, and which have dramatically changed the therapeutic landscape of various eosinophilic disorders. Several other biologic therapies are already licensed to suppress type 2 inflammation via IgE and IL-4 receptor alpha [6]. Other targets for therapy more specific for eosinophils are being investigated including eotaxins, which drive eosinophil recruitment into tissues, CD2-binding protein, and eosinophil surface-expressed inhibitory receptors especially Siglec-8 [2, 4, 7] (Table 17.2).

Table 17.2 Main drugs targeting the eosinophil lineage

Drug	Target
Omalizumab	Immunoglobulin E
Mepolizumab	Interleukin-5
Reslizumab	Interleukin-5
Benralizumab	Interleukin-5 receptor-α
Dupilumab	Interleukin-4 receptor-α
Lebrikizumab	Interleukin-13
RPC4046	Interleukin-13
AK002	Siglec-8

General Features of Eosinophilic Pneumonias

Historical Perspective

Early descriptions of pulmonary "infiltration with eosinophilia" [8], "pulmonary eosinophilia" [9], and later of "cryptogenic pulmonary eosinophilias" [10] included cases now considered as probable idiopathic chronic eosinophilic pneumonia (ICEP), EGPA, and Löffler syndrome. Carrington and colleagues [11] described in 1969 the syndrome of ICEP.

Clinical Presentation

Eosinophilic pneumonia is pneumonia where the eosinophils are the most prominent inflammatory cells on histopathologic examination, whereas infiltration with lymphocytes and neutrophils does not predominate. Eosinophilic pneumonias are separated into two main etiologic categories: (1) those with a definite cause and (2) idiopathic eosinophilic pneumonias, either solitary or associated with extrathoracic manifestations that are a hallmark of EGPA, but can also be observed, to a lesser extent, in hypereosinophilic syndromes (HES), drug reactions, or infections, especially parasitic infections. It is therefore mandatory that the clinician take a full history and search thoroughly for a cause with potentially practical consequences, such as parasitic infection or drug or toxic exposures.

Most eosinophilic pneumonias can be classified within one of the well-characterized and individualized syndromes. They may manifest in different clinicoradiologic syndromes, namely Löffler syndrome, chronic eosinophilic pneumonia, or acute eosinophilic pneumonia, mostly differing from one another by the pattern of disease onset, severity, and evolution with or without corticosteroid treatment. The recent description of eosinophilic vasculitis, with systemic manifestations [12] or limited to the lung [13], has further drawn attention to vascular involvement that rarely may be present in eosinophilic pneumonias. The vast majority of cases of eosinophilic pneumonia respond dramatically to corticosteroid treatment [14] and heal without significant sequelae.

Pathology

Open lung biopsies that used to be performed for the diagnosis of ICEP have provided material for the few histopathologic studies published on eosinophilic pneumonia [10, 11, 15]. The pathologic features described in ICEP represent a common denominator of all categories of eosinophilic pneumonias, whatever their origin. Additional specific features may be observed depending on the etiological context (e.g., bronchocentric distribution of lesions in ABPA; the presence of parasites or fungal hyphae in eosinophilic pneumonia of parasitic origin; granulomas and eosinophilic vasculitis in EGPA; prominent eosinophilic vasculitis in idiopathic eosinophilic vasculitis).

In ICEP, the alveolar spaces are filled with eosinophils representing the predominant inflammatory cell, together with a proteinaceous and fibrinous exudate, respecting the global architecture of the lung. The distribution of eosinophilic pneumonia is generally diffuse. Macrophages are also present in the infiltrate, with scattered multinucleated giant cells occasionally containing eosinophilic granules or Charcot-Leyden crystals [11]. An associated interstitial inflammatory cellular infiltrate is invariably present, consisting of eosinophils, lymphocytes, plasma cells, and histiocytes. Some eosinophilic microabscesses may be observed (foci of necrotic intra-alveolar eosinophils surrounded by macrophages or epithelioid cells with a palisading arrangement). Degranulated eosinophils can be identified within the site of eosinophilic pneumonia by electron microscopic or immunohistochemical studies [16]. Areas of non-prominent organization of the alveolar inflammatory exudate are common [11]. Mucus plugs obstructing the small airways may be present in ICEP [11] and especially in ABPA. A mild *non-necrotizing* vasculitis involving both small arteries and venules is common; however, necrosis and fibrosis are absent.

In idiopathic acute eosinophilic pneumonia (IAEP), the pathologic pattern includes intra-alveolar and interstitial eosinophilic infiltrates, diffuse alveolar damage, and intra-alveolar fibrinous exudates, organizing pneumonia, and non-necrotizing vasculitis [17].

Diagnosis

The clinical diagnosis of eosinophilic pneumonia is suspected in patients with respiratory symptoms (dyspnea, cough, or wheezing), pulmonary opacities at chest imaging, and eosinophilia demonstrated in the peripheral blood and/or in the lung.

Bronchoalveolar lavage (BAL) is a good surrogate of lung biopsy to demonstrate lung eosinophilia, although no study has definitely established a correlation between increased eosinophils at differential cell count and eosinophilic pneu-

monia at lung pathology. In normal subjects, BAL eosinophilia is lower than 1% of cells at the differential count. In contrast, BAL eosinophilia greater than 40% is found mainly in patients with chronic eosinophilic pneumonia, whereas BAL eosinophilia between 3% and 40% (and especially between 3% and 9%) may be found in various interstitial lung diseases other than eosinophilic pneumonia. A conservative cutoff of 40% of eosinophils at BAL differential cell count has been adopted for the diagnosis of ICEP in clinical studies [18, 19], and a cutoff of 25% has been proposed for the diagnosis of IAEP [20]. We recommend that a clinical diagnosis of eosinophilic pneumonia be supported by alveolar eosinophilia when the eosinophils (1) are the predominant cell population of BAL cell count (macrophages excepted) and (2) represent more than 25% of differential cell count (acknowledging that the specificity is higher when the eosinophil cell count is greater than 40%). BAL is recommended to confirm the diagnosis of eosinophilic pneumonia in most cases.

Blood eosinophilia when present also contributes to the diagnosis of eosinophilic pneumonia in a patient with compatible HRCT features. It may be missing in patients who have already received systemic corticosteroids, and it is often absent at presentation in IAEP. Blood cell count must therefore be measured before starting corticosteroids. In normal subjects, however, blood eosinophil count is a continuous, rather than dichotomous, variable, and may be influenced by a variety of factors such as age, sex, atopy, and environmental exposure. Median eosinophil counts are typically between 100 and 160 cells/μL [21]. In the setting of eosinophilic lung diseases, *blood eosinophilia* has generally been defined by an eosinophil blood count greater than 0.5×10^9/L (500 cells/μL) (Table 17.3). It was further proposed to define *hypereosinophilia* as an eosinophil blood count greater than 1.5×10^9/L on two examinations over at least a 1-month interval, and/or tissue hypereosinophilia [22, 23]. Frank blood eosinophilia (e.g. greater than 1×10^9/L), and preferably hypereosinophilia, may obviate the need to perform BAL in the individual cases with typical presentation. For example, BAL may occasionally be omitted to confirm Löffler syndrome (as it occurs in ascariasis) in a patient with a mild cough, wheezes, transient pulmonary opacities at chest radiograph, and frank blood eosinophilia. However, BAL is generally useful to rule out alternative diagnoses (such as bacterial or parasitic pneumonia, or pulmonary infiltrates related to Hodgkin's disease), and is generally recommended.

Video-assisted thoracoscopic lung biopsy or transbronchial cryobiopsies are seldom necessary, especially if pulmonary eosinophilia has been demonstrated by BAL. Biopsies are therefore generally discouraged, and considered only in difficult cases where a differential diagnosis to eosinophilic pneumonia is contemplated (e.g. eosinophilic vasculitis, primary pulmonary lymphoma, etc.). Although they can show characteristic features of eosinophilic pneumonia, forceps transbronchial lung biopsies are generally not recommended either due to the small size of the specimens that allows only partial morphologic evaluation.

Table 17.3 Classification of the eosinophilic lung diseases

Eosinophilic lung disease of undetermined cause
Idiopathic eosinophilic pneumonias
Idiopathic chronic eosinophilic pneumonia
Idiopathic acute eosinophilic pneumonia
Eosinophilic granulomatosis with polyangiitis
Idiopathic systemic eosinophilic vasculitis
Hypereosinophilic syndrome
Idiopathic hypereosinophilic obliterative bronchiolitis
Eosinophilic lung disease of determined cause
Eosinophilic pneumonias of parasitic origin
Tropical eosinophilia
Ascaris pneumonia
Eosinophilic pneumonia in larva migrans syndrome
Strongyloides stercoralis infection
Eosinophilic pneumonias in other parasitic infections
Eosinophilic pneumonias of other infectious causes
Allergic bronchopulmonary aspergillosis and related syndromes
Allergic bronchopulmonary aspergillosis
Other allergic bronchopulmonary syndromes associated with fungi or yeasts
Bronchocentric granulomatosis
Drug, toxic agents, and radiation-induced eosinophilic pneumonias
Drugs (typical, occasional, or exceptional eosinophilic pneumonia)
Toxic agents (illicit drugs, vaping)
Eosinophilic pneumonia induced by radiation therapy to the breast
Miscellaneous lung diseases with possible associated eosinophilia
Organizing pneumonia
Asthma
Eosinophilic bronchitis
Idiopathic interstitial pneumonias
Pulmonary Langerhans cell histiocytosis
Malignancies
Other

Eosinophilic Lung Disease of Undetermined Cause

ICEP is characterized by a progressive onset of symptoms over a few weeks with cough, increasing dyspnea, malaise, and weight loss, whereas IAEP presents as acute pneumonia (similar to acute lung injury or acute respiratory distress syndrome [ARDS]) with frequent respiratory failure necessitating mechanical ventilation. Both conditions are idiopathic.

Idiopathic Chronic Eosinophilic Pneumonia

Chronic eosinophilic pneumonia was first described in detail by Carrington and colleagues [11], in a series of nine patients, and further confirmed and detailed by several and numerous case reports.

Clinical Features

ICEP predominates in women with a 2:1 female-to-male ratio [15, 19], with a peak of incidence in the fourth decade [15], and a mean age of 45 years at diagnosis [19]. A majority of patients with ICEP are nonsmokers [15, 19], suggesting that smoking might be protective. About half of the patients have a history of atopy [15, 19] and up to two-thirds have a history of asthma [15, 18, 19, 24, 25], with no particularities in the clinical presentation of ICEP with the exception of higher total immunoglobulin (Ig) E levels in asthmatics [18]. In addition, asthma may develop concomitantly with the diagnosis of ICEP (15% of patients) or develop after ICEP (about 15% of patients) [18]. Asthma in patients with ICEP often gets worse and requires long-term oral corticosteroid treatment [18].

ICEP is characterized by the progressive onset of cough, dyspnea, and chest pain [15, 19], with a mean interval between the onset of symptoms and the diagnosis of 4 months [19]. Mechanical ventilation may be required on exceptional occasions. Hemoptysis is rare but can occur in up to 10% of cases [15, 19]. Chronic rhinitis or sinusitis symptoms are present in about 20% of patients [19]. At lung auscultation, wheezes are found in one-third of patients [15] and crackle in 38% [19]. Systemic symptoms and signs are often prominent, with fever, weight loss (>10 kg in about 10%), and commonly asthenia, malaise, fatigue, anorexia, weakness, and night sweats.

Imaging

The imaging features of ICEP are characteristic, although they may overlap with those found in cryptogenic organizing pneumonia. Peripheral opacities at chest X-ray present in almost all cases [11, 15, 19, 26, 27] consist of alveolar opacities with ill-defined margins, with a density varying from ground-glass to consolidation (Fig. 17.1), and are migratory in 25% of patients [19]. The classic pattern of "photographic negative or reversal of the shadows usually seen in pulmonary edema," highly evocative of ICEP, is seen in only one-fourth of patients [15]; however, peripheral and upper zone predominance of abnormalities is usually present.

Whereas the opacities are bilateral in at least 50% of cases at chest X-ray [15], the proportion of bilateral opacities increases up to more than 95% at high-resolution computed tomography (HRCT) [19] (Fig. 17.2). Predominance of ground-glass attenuation and consolidation in the periphery and upper lobes of both lungs [15, 19] is very suggestive of

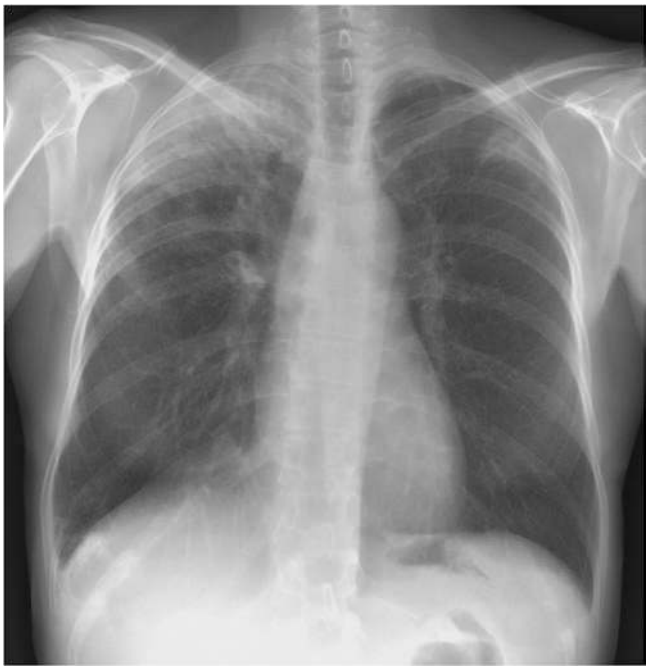

Fig. 17.1 Chest radiograph of a patient with idiopathic chronic eosinophilic pneumonia showing peripheral alveolar opacities predominating in the right upper lobe

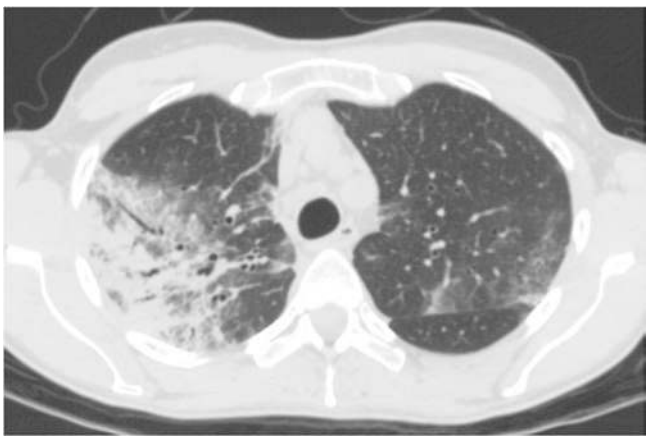

Fig. 17.2 Computed tomography (CT) scan of a patient with idiopathic chronic eosinophilic pneumonia showing bilateral asymmetric peripheral alveolar opacities with airspace consolidation and ground glass opacities

ICEP [19, 27, 28] (Fig. 17.3). Septal line thickening is common [28]. Centrilobular nodules (less than 20% of cases) [27], consolidation with segmental or lobar atelectasis, can also be seen. Upon corticosteroid treatment, consolidation rapidly decreases in extent and density, possibly evolving to ground-glass attenuation or inhomogeneous opacities, and later to streaky or bandlike opacities parallel to the chest wall. Cavitary lesions are extremely rare and should lead to reconsideration of the diagnosis. Reverse halo sign suggestive of organizing pneumonia is rare in ICEP. Pleural effu-

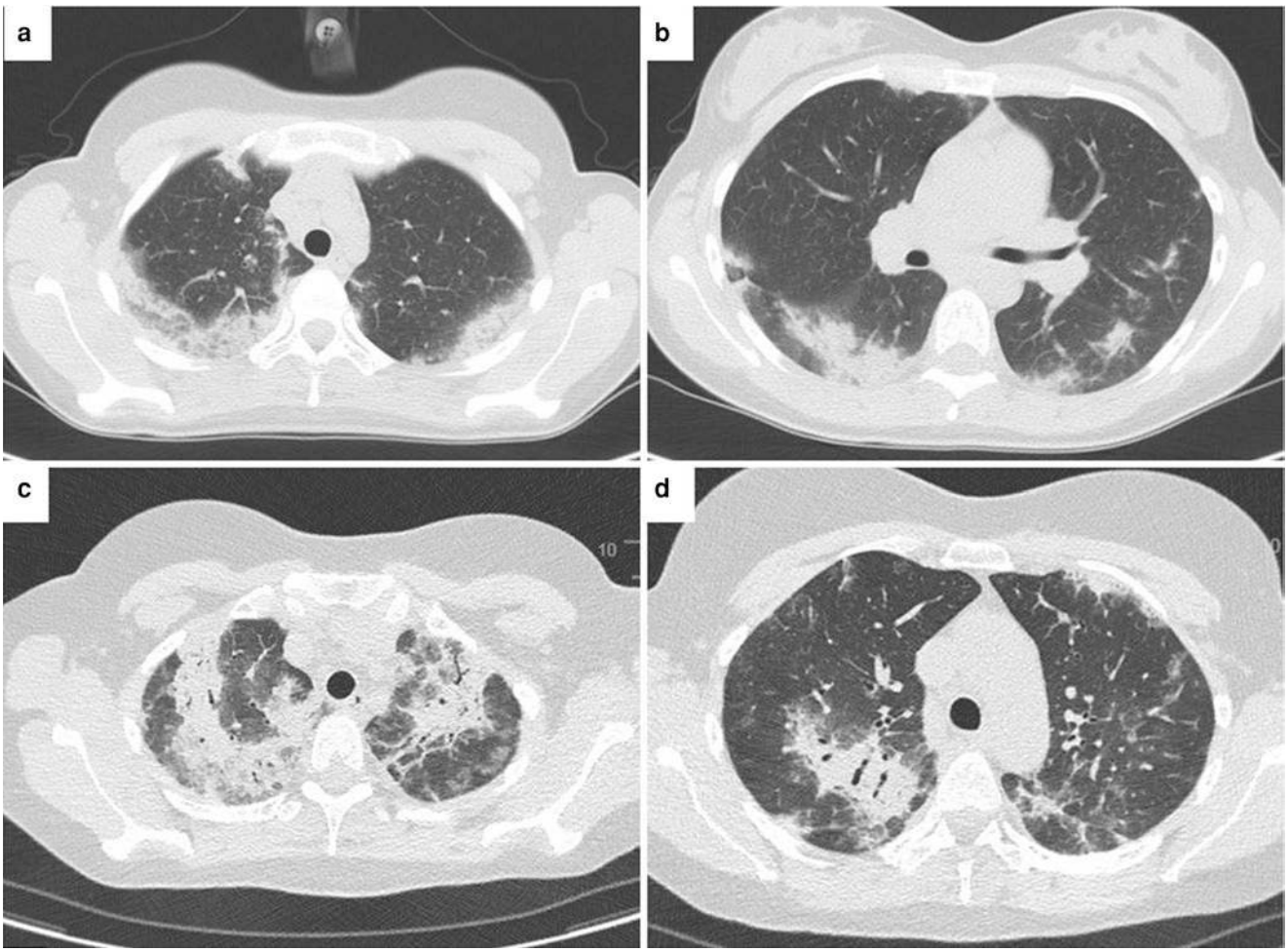

Fig. 17.3 Computed tomography (CT) scan of a patient with idiopathic chronic eosinophilic pneumonia at the time of diagnosis (**a**, **b**) and at the time of relapse 11 years later (**c**, **d**). Bilateral peripheral airspace consolidation predominates in the upper lobes

sions (which are common in IAEP) are rare and usually mild or moderate in ICEP. Mediastinal lymph node enlargement may be seen in 15–20% of cases [19].

Laboratory Studies

Peripheral blood eosinophilia is a diagnostic criterion of ICEP, and therefore the proportion of patients with ICEP and possible normal peripheral blood count is unknown. The mean blood eosinophilia was 5.5×10^9/L in the French series [19]. Eosinophils represent 26–32% of the total blood leukocyte count [15, 19]. C-reactive protein level is elevated [15, 19]. Total blood IgE level is increased in about half of the cases and greater than 1000 kU/L in 15% [19]. Antinuclear antibodies may occasionally be present [19]. Urinary EDN level indicating active eosinophil degranulation is markedly increased [29].

Bronchoalveolar Lavage

BAL eosinophilia is constant and key to the diagnosis of ICEP, obviating the need for lung biopsy (Table 17.4). The mean eosinophil percentage at BAL differential cell count was 58% at diagnosis in the French series [19]; however, the eosinophil count drops within a few days (or hours) upon corticosteroid treatment. The percentage of neutrophils, mast cells, and lymphocytes a BAL may be increased [19]. Sputum eosinophilia may also be present, although it is not a necessary tool for the diagnosis. Importantly, BAL contributes to rule out potential causes of eosinophilic pneumonia including infections, lymphoma, etc., and therefore must include both analyses of the differential cell count and microbiology.

Table 17.4 Diagnostic criteria for idiopathic chronic eosinophilic pneumonia

1.	Diffuse pulmonary alveolar consolidation with air bronchograms and/or ground glass opacities at chest imaging, especially with peripheral predominance
2.	Eosinophilia at BAL differential cell count ≥40% (or peripheral blood eosinophils $\geq 1.0 \times 10^9$/L)
3.	Respiratory symptoms present for at least 2–4 weeks
4.	Absence of other known causes of eosinophilic lung disease (especially exposure to a drug susceptible to induce pulmonary eosinophilia)

BAL eosinophils of patients with ICEP show features of cell activation and release eosinophil proteins, which are phagocytosed by macrophages. ECP and EDN levels are increased in the BAL fluid. Eosinophils are recruited to the lung through various chemokines and are resistant to Fas-induced apoptosis. Eosinophilic activation may be compartmentalized to the lung, as expressed by differential expression of HLA-DR molecules between alveolar and blood eosinophils. BAL lymphocytes include $CD4^+$ memory T-cells (expressing $CD45RO^+$, $CD45RA^-$, $CD62L^-$), and may present clonal rearrangement of the T-cell receptor repertoire [5].

Differential Diagnosis

Extrapulmonary manifestations when present challenge the diagnosis of ICEP and especially suggest the diagnosis of EGPA or overlap between ICEP and EGPA. Arthralgias, repolarization (ST-T) abnormalities on the electrocardiogram, pericarditis, altered liver biologic tests, eosinophilic lesions at liver biopsy, mononeuritis multiplex, diarrhea, skin nodules, immune complex vasculitis in the skin, and eosinophilic enteritis have been occasionally reported in ICEP [11, 19]; however, some cases would likely now be considered EGPA (e.g. eosinophilic pneumonia associated with mononeuritis multiplex). Furthermore, eosinophilic pneumonia may be a presenting feature of EGPA; corticosteroid treatment prescribed for ICEP may prevent the subsequent development of overt systemic vasculitis.

Lung Function Tests

An obstructive ventilatory defect is present in about half the patients [15, 19], and a restrictive ventilatory defect in the other half [19]. The carbon monoxide transfer factor (DLco) is decreased in half of the patients, and the transfer coefficient (DLco/unit alveolar volume, or Kco) is about one fourth. Hypoxemia ($PaO_2 < 75$ mmHg) present in two-thirds of patients [19] may be due to right-to-left shunting in consolidated areas of the lung, as suggested by increased alveolar-arterial oxygen gradient [15].

With treatment, the lung function tests rapidly return to normal in most patients [15]. However, a persistent ventilatory obstructive defect (not responsive to inhaled corticosteroids and bronchodilators) may develop over years in up to a third of patients, especially those with concurrent asthma and obstructive defects at diagnosis [30]. In one study, the persistence of a ventilatory obstructive defect was associated with a markedly increased BAL eosinophilia at initial evaluation [31].

Treatment

Because most patients receive corticosteroids, the natural course of untreated ICEP is not well known [15]. However, spontaneous resolution of ICEP may occur [15, 19]. The clinical and radiologic response to corticosteroids is dramatic, with the improvement of symptoms within 1 or 2 weeks and even within 48 h in about 80% [19] of cases, and rapid clearance of pulmonary opacities on chest X-ray. In one series, the chest radiograph was significantly improved at 1 week in 70% of patients, and almost all had a normal chest X-ray at their last follow-up visit [19]. Death directly resulting from ICEP is exceedingly rare.

The optimal dose of corticosteroids is not established, but treatment may be initiated with 0.5 mg/kg/day of prednisone, with slow tapering over 6–12 months based on clinical evaluation and blood eosinophil cell count. In an open-label, randomized study, no significant difference was found in the cumulative rate of relapse between patients with CEP randomized to receive oral prednisolone for either 3 or 6 months [32]. Treatment may therefore be initiated with 0.5 mg/kg/day of prednisone, with slow tapering down to 5–10 mg/day over 3 months based on clinical evaluation and blood eosinophil cell count.

Most patients require treatment for longer than 6–12 months because of relapse in more than half of patients while decreasing below a daily dose of 10–15 mg/day of prednisone, or after stopping oral corticosteroid treatment [15, 19]. Relapses respond very well to corticosteroid treatment, which usually can be resumed at a dose of about 20 mg/day of prednisone [19, 32].

Outcome and Perspectives

The clinical series in which long-term follow-up is available clearly show that most patients need very prolonged corticosteroid treatment: in a series with a mean follow-up of 6.2 years, only 31% were weaned at the last control visit [19]. In a series of 133 cases, relapse occurred in 56% of patients during a follow-up period of over 6 years [30]. Relapses of ICEP must be distinguished from asthma symptoms and may be less frequent in asthmatics, possibly because of inhaled corticosteroids prescribed after stopping oral corticosteroids [18, 19]. Alternate-day prescription of oral corticosteroids may reduce the adverse events of treatment. Inhaled corticosteroids might thus help in reducing the maintenance dose of oral corticosteroids, although they are not effective enough when given as monotherapy [33].

Long-term use of corticosteroids may lead to a variety of adverse events including osteoporosis and weight gain, which has to lead to consider steroid-sparing agents. Omalizumab, a recombinant humanized monoclonal antibody against IgE, was reported to prevent recurrence of ICEP and to spare oral corticosteroids in case reports; however, caution must be exerted given recent reports of omalizumab-associated EGPA [34, 35].

The anti-IL-5 monoclonal antibody mepolizumab and the IL-5-receptor antagonist benralizumab have been used in case reports of patients also suffering from severe eosinophilic asthma, but have not yet been evaluated properly in

patients with ICEP. Outside of the indication of severe eosinophilic asthma, and because of the exquisite sensitivity of ICEP to corticosteroids, the use of these agents should be restricted to exceptional cases of ICEP with frequent relapses of eosinophilic pneumonia preventing tapering of corticosteroids and/or intolerance or contraindications to oral corticosteroids. Cases considered refractory to corticosteroids should lead to reconsidering the diagnosis of ICEP.

Idiopathic and Smoking-Related Acute Eosinophilic Pneumonia

IAEP is often misdiagnosed as infectious pneumonia because of fever and bilateral opacities on chest X-ray present in all patients. However, IAEP [17, 20, 25, 36–41] markedly differs from ICEP by its acute onset, the severity of hypoxemia, the usual lack of increased blood eosinophils at presentation contrasting with highly increased eosinophil percentage at BAL, and the absence of relapse after clinical recovery. Because fever and bilateral opacities on chest radiograph are present in nearly all patients, IAEP is often misdiagnosed as infectious pneumonia [20]. Known causes of acute eosinophilic lung disease, particularly drug exposure, infection, or vaporized cannabis oil, must be excluded for the diagnosis of IAEP to be made (Table 17.5) [42, 43].

Clinical Features

IAEP may present at any age [44]; however, most patients are aged 20–40 years [20, 44, 45], with a very strong predominance in males [39]. Most patients have no prior asthma history [25]. However, taking a thorough exposure history is mandatory, as a causative role of cigarette smoke is established. Most patients have been recently exposed to dust or cigarette smoke within the days before the onset of disease, and often will have begun to smoke, restarted to smoke, or increased the number of cigarettes smoked daily, especially within 1 month before the onset of "idiopathic" AEP [39, 46]. The disease is therefore often not "idiopathic," being initiated or triggered by inhaled nonspecific causative agents in susceptible individuals; however, it can occur in the absence of any inhaled exogenous trigger. AEP may develop soon after the initiation of smoking, especially when starting with large quantities, and may relapse—not always—in patients who resume cigarette smoking [39, 46]. Flavoring components of smoked cigars have been suspected. In addition, the onset of IAEP seems to follow in some patients' outdoor activities or peculiar exposures, such as cave exploration, plant repotting, wood pile moving, smokehouse cleaning, motocross racing in dusty conditions, indoor renovation work, gasoline tank cleaning, explosion of a tear gas bomb, or exposure to World Trade Center dust [20, 44, 47]. Recently, cases of AEP caused by the use of electronic cigarettes [48–50] and inhalation of vaporized cannabis oil were also reported [51].

IAEP develops acutely or subacutely over less than 1 month in previously healthy individuals, with cough, dyspnea, fever, and chest pain at presentation [17, 44]. More than half of patients present with acute respiratory failure [39]. Abdominal complaints and also myalgias can occur [20]. Clinical signs include crackles or, less often, wheezes, tachypnea, and tachycardia.

Table 17.5 Diagnostic criteria for idiopathic acute eosinophilic pneumonia

1. Acute onset of febrile respiratory manifestations (≤1 month duration before consultation)
2. Bilateral diffuse opacities on chest radiography
3. Hypoxemia, with PaO_2 on room air <60 mmHg, and/or $PaO_2/FIO_2 \leq 300$ mmHg, and/or oxygen saturation on room air <90%
4. Lung eosinophilia, with >25% eosinophils on BAL differential cell count (or eosinophilic pneumonia at lung biopsy)
5. Absence of infection, or of other known causes of eosinophilic lung disease (especially exposure to a drug susceptible to induce pulmonary eosinophilia)

Imaging

Imaging of patients with IAEP is quite distinct from those with ICEP. In addition to bilateral alveolar and/or interstitial opacities (Fig. 17.4) [20, 37, 38, 44], the chest X-ray commonly shows bilateral pleural effusion and Kerley B lines [20]. The chest X-ray returns to normal within 3 weeks [20, 44], with pleural effusions being the last abnormality to disappear [20].

Typical computed tomography (CT) abnormalities include ground-glass attenuation and air space consolidation (Fig. 17.5), with poorly defined nodules. Interlobular septal thickening and bilateral pleural effusion seen in a majority of patients are highly suggestive of the diagnosis in the setting of eosinophilic pneumonia [20, 26, 37, 44, 52] (or in a patient spuriously suspected to have infectious pneumonia).

Laboratory Studies

In contrast with ICEP, peripheral blood eosinophilia is usually lacking at presentation, with white blood cell count showing increased leukocyte count with a predominance of neutrophils. However, the eosinophil count often rises within days during the course of the disease [20, 25, 44], a retrospective finding very suggestive of IAEP. When present at the presentation, peripheral eosinophilia may be associated with a milder disease status compared with those with normal eosinophil count [40, 53, 54]. Eosinophilia is also present at pleural fluid differential cell count [20] and in the sputum [25].

The IgE level may be elevated, while IgG levels may be reduced. Serum levels of thymus and activation-regulated

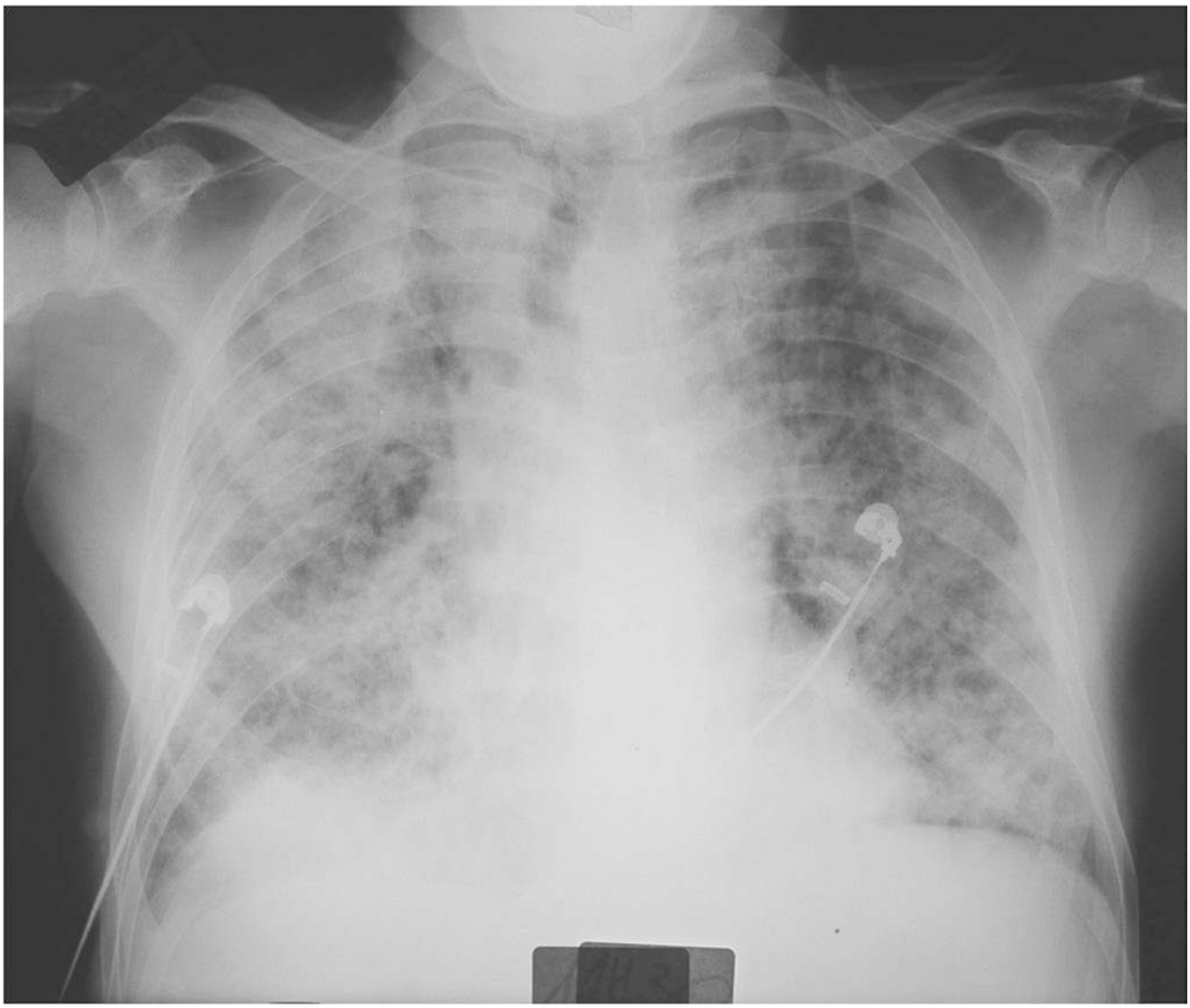

Fig. 17.4 Chest radiograph of a patient with idiopathic acute eosinophilic pneumonia and acute respiratory failure showing diffuse alveolar consolidation

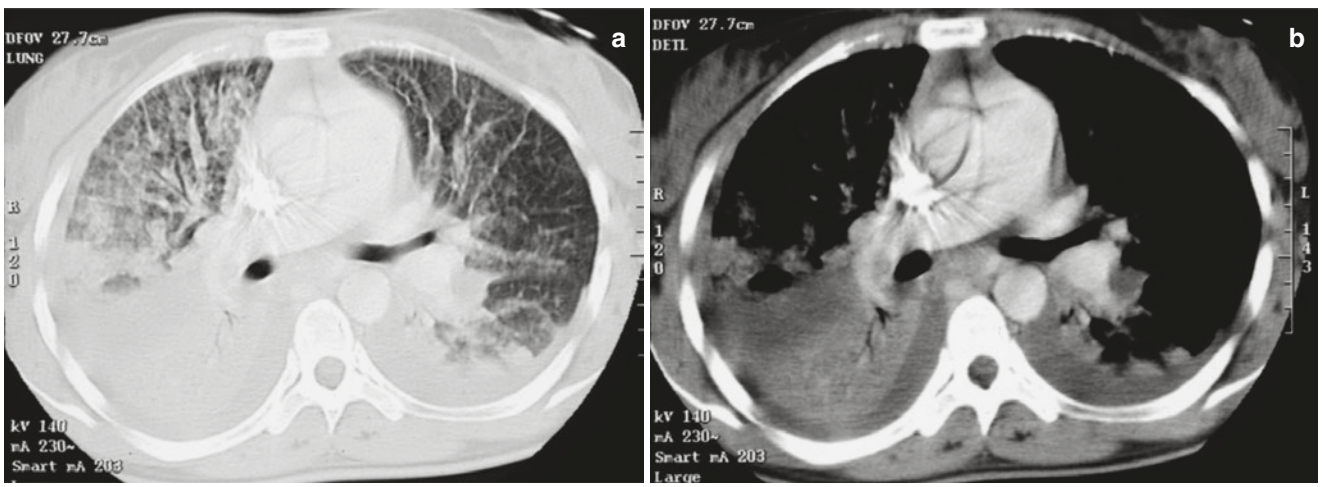

Fig. 17.5 CT scan of a patient with idiopathic acute eosinophilic pneumonia showing bilateral diffuse alveolar consolidation with air bronchograms, ground glass opacities (**a**, **parenchymal window**) and bilateral mild pleural effusion (**b**, **mediastinal window**)

chemokine (TARC/CCL17) [55] may be elevated, however, no biomarker other than eosinophil count has established clinical relevance in IAEP.

Bronchoalveolar Lavage

BAL is the key to the diagnosis of IAEP, especially in patients without blood eosinophilia at presentation. The finding of greater than 25% eosinophils at BAL obviates the need for lung biopsy, at least in immunocompetent patients. The average percentage of eosinophils at BAL differential count varies between series (37% [20] to 65% [55]), and lymphocyte and neutrophil counts can be moderately increased. Bronchoscopy may show inflamed mucosa of the trachea [56]. Importantly, systematic bacterial cultures of BAL fluid are sterile, and appropriate stainings are negative, ruling out infectious agents that can cause AEP. After recovery, eosinophilia at BAL may persist for several weeks.

Lung Function Tests

Hypoxemia may be severe in patients with IAEP, a majority of whom fit the definition of ARDS of various severity (except that there is no known clinical insult identified in IAEP) [57]. However, shock is exceptional and extrapulmonary organ failure does not occur in IAEP, in sharp contrast with ARDS.

Hypoxemia is associated with right-to-left shunting in areas with consolidation and may be refractory to breathing 100% oxygen in some patients [36, 44]. Alveolar-arterial oxygen gradient is increased [20]. Although mechanical ventilation was necessary for a majority of patients in earlier series [20, 44], more recent series have shown that the severity of IAEP is more varied than originally reported [39].

When performed in less severe cases, lung function tests show a mild restrictive ventilatory defect with normal forced expiratory volume in 1 s-to-forced vital capacity (FEV_1/FVC) ratio and reduced transfer factor. After recovery, lung function tests are generally normal, with possible ventilatory restriction in some of them [20].

Lung Biopsy

Lung biopsy or transbronchial lung biopsies are seldom necessary when BAL demonstrates alveolar eosinophilia. In older series of patients with IAEP, lung biopsy has shown acute and organizing diffuse alveolar damage together with interstitial alveolar and bronchiolar infiltration by eosinophils, intra-alveolar eosinophils, and interstitial edema [17, 20, 51, 58, 59].

Treatment and Prognosis

Exclusion of possible causes of AEP, especially infections and drugs, is key to the management of patients with AEP. Recovery of IAEP can occur without corticosteroid treatment [44, 55], and therefore improvement concomitant with corticosteroid treatment is not a diagnostic criterion of IAEP. In most patients diagnosed with IAEP, a course of corticosteroids is initiated with intravenous methyl prednisolone and later changed to oral prednisone or prednisolone that is tapered over 2–4 weeks [20]. FIO_2 may be decreased within a few hours of corticosteroid treatment in many patients initially requiring oxygen [20]; most patients are rapidly weaned from the ventilator. Clinical improvement generally begins within 3 days [39]. The chest X-ray is normalized within 1 week in 85% of patients, but mild pulmonary infiltrates and pleural effusion may still be present at CT at 2 weeks [39]. One recent study of 137 patients suggested that a treatment duration of 2 weeks may be sufficient, with an initial daily dose of 30 mg of prednisone (or 60 mg of intravenous methylprednisolone every 6 h in patients with respiratory failure) [39]. No relapse occurs after stopping corticosteroid treatment, in contrast with ICEP (Table 17.6). Because patients with peripheral blood eosinophilia at presentation tend to have milder disease, it was proposed to rapidly taper corticosteroid treatment after clinical improvement has been obtained in those subjects, leading to a very short treatment duration (median, 4 days) [60].

No significant clinical or imaging sequelae persist in the longer term. Mortality is rare despite the frequent initial presentation with acute respiratory failure. Identification of causative tobacco or environmental exposures is key to preventing rare recurrences, that in most cases are due to the resumption of cigarette smoking after a period of abstinence.

Table 17.6 Distinctive features between idiopathic chronic eosinophilic pneumonia (ICEP) and idiopathic acute eosinophilic pneumonia (IAEP)

	ICEP	IAEP
Onset	>2–4 weeks	<1 month
History of asthma	Yes	No
Smoking history	10%	2/3, with often recent initiation
Respiratory failure	No	Usual
Initial blood eosinophilia	Yes, on admission	No (delayed)
BAL eosinophilia	>25% (generally >40%)	>25%
Chest imaging	Homogeneous peripheral airspace consolidation	Bilateral patchy areas of ground glass attenuation, airspace consolidation, interlobular septal thickening, bilateral pleural effusion
	Predominance in upper lobes and lung periphery	
Relapse	Yes, possibly multiple	No

Eosinophilic Granulomatosis with Polyangiitis

History and Nomenclature

The first reliable case of EGPA (ex Churg-Strauss syndrome) was reported by Lamb in 1914 [61]. Churg and Strauss described in 1951 [62] the eponymous syndrome of "allergic granulomatosis, allergic angitis, and periarteritis nodosa," mainly from autopsied cases. In the 1992 Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis [63], CSS was included in the group of small vessel vasculitides. The nomenclature of the systemic vasculitides was revised in 2012 at the international Chapel Hill consensus conference [64], and the terminology of CSS was replaced by EGPA. As antineutrophil cytoplasmic antibodies (ANCA) are present in about 40% of the cases, EGPA belongs to the pulmonary ANCA-associated vasculitides, together with microscopic polyangiitis and granulomatosis with polyangiitis, and together with single organ ANCA-associated vasculitis.

EGPA is defined as an eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels and associated with asthma and eosinophilia [64]. The disease may be confined to a limited number of organs especially the upper or lower respiratory tract [64], with reported cases of histologically-confirmed EGPA localized to the lung [13]. The terminology of EGPA underscores that it is indeed a vasculitis, although not all patients have robust criteria of documented systemic vasculitis or ANCA [65]. Furthermore, some cases of pulmonary eosinophilic vasculitis are distinct from EGPA [66]. The current terminology and classification likely require further refinement.

Pathology

The pathologic lesions of EGPA (CSS) observed in series published over the last 20 years [67, 68] only rarely comprise all the characteristic features on biopsies from organs other than the lung, which is now rarely biopsied [13]. The diagnosis is made earlier in the course of the disease, often before overt vasculitis has developed, characterized histopathologically by eosinophilic infiltration of the tissues and often perivascular eosinophils but without vasculitis. In cases with overt EGPA, typical histopathologic features include vasculitis (necrotizing or not, involving mainly the medium-sized pulmonary arteries), granulomatous eosinophilic infiltration, and extravascular granuloma with palisading histiocytes and giant cells. When present, eosinophilic pneumonia in EGPA is similar to ICEP.

Clinical Features

EGPA is a very rare systemic disease, with no sex predominance, predominating in adults younger than 65 [65, 69–84], with cases occasionally reported in children and adolescents [85, 86]. Asthma occurs at a mean age of about 35 years [69] in patients with EGPA, preceding the onset of vasculitis by 3–9 years [69, 71, 72, 75, 82]; therefore the mean age at diagnosis of EGPA ranges from 38 to 49 years [69, 75]. The interval between asthma and the onset of vasculitis may be much longer in rare cases [71], or they may be contemporaneous [75]. Asthma is generally severe, and frequently requires oral corticosteroids; its severity typically increases progressively until the vasculitis develops, but it may attenuate when the vasculitis flourishes (possibly as a result of corticosteroids) and further increase once the vasculitis recedes [69, 71, 82, 87].

Chronic rhinitis (75% of cases) [69], relapsing paranasal sinusitis (60%) [72], and nasal polyposis with eosinophilic infiltration at histopathology are frequent [88, 89]. Crusty rhinitis may be present, however, it is much less severe in EGPA than in granulomatosis with polyangiitis. Septal nasal perforation and saddle nose deformation are exceedingly rare.

Asthenia, weight loss, fever, arthralgias, and myalgias often herald the onset of systemic vasculitis.

Heart damage in EGPA is undoubtedly a major source of morbidity and mortality, although its onset is often insidious and asymptomatic and diagnosed only when left ventricular failure and dilated cardiomyopathy have developed, possibly leading to cardiac failure or sudden death [69–72, 75, 90]. Heart involvement mostly results from eosinophilic myocarditis, and rarely from arteritis of the larger coronary arteries [91, 92]. Although marked improvement usually occurs with corticosteroid treatment, heart involvement in EGPA may require heart transplantation, with possible recurrence of eosinophilic vasculitis in the transplanted heart. A systematic cardiac evaluation is therefore warranted in any patient with suspected EGPA, generally including electrocardiogram, echocardiography, serum level of troponin, and N-terminal pro-brain natriuretic peptide. Magnetic resonance imaging (MRI) of the heart is the preferred method to confirm heart involvement, showing late enhancement of the myocardium [93–95]; however, it may be difficult to differentiate irreversible scar lesions from active inflammation requiring intense immunosuppression, and incidental findings from clinically relevant myocardial involvement. Treatment decisions are eventually based on critical clinical evaluation, taking into account results from several investigations, including electrocardiogram, echocardiography, troponin levels, and possibly a combination of cardiac MRI and Positron emission tomography. In addition to myocardial involvement, asymptomatic pericarditis with limited effusion at echocardiography is common, with rare cases of tamponade, and the risk of venous thromboembolic events [96] is increased in patients with EGPA. Endomyocardial involvement (typically seen in idiopathic HES) is uncommon in EGPA.

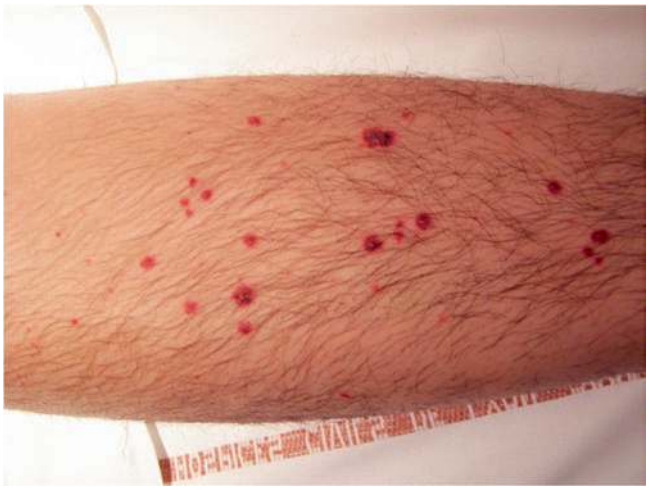

Fig. 17.6 Palpable purpura of the forearm in a patient with eosinophilic granulomatosis with polyangiitis

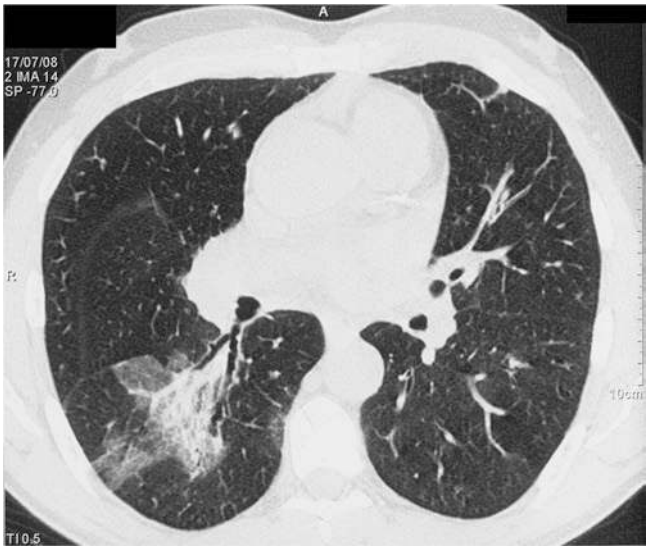

Fig. 17.7 CT scan of a patient with eosinophilic granulomatosis with polyangiitis showing airspace consolidation and ground glass opacity in the right lower lobe

Virtually all organs can be involved by EGPA. Mononeuritis multiplex, present in 77% of patients [72], is the most frequent and the most typical of peripheral neurologic involvement in EGPA, which may also consist of asymmetrical polyneuropathy in the lower extremities, or rarely cranial nerve palsies or central nervous system involvement [97]. Digestive tract involvement (31% of cases [72]) consists of isolated abdominal pain, and less frequently intestinal or biliary tract vasculitis, diarrhea, ulcerative colitis, gastroduodenal ulcerations, perforations (esophageal, gastric, intestinal), digestive hemorrhage, or cholecystitis. Cutaneous lesions (50% of patients [72]) mainly consist of palpable purpura of the extremities (Fig. 17.6), subcutaneous nodules (especially of the scalp and extremities), erythematous rashes, and urticaria. Renal involvement (about 25% of cases) may present as mild glomerulonephritis or glomerular hematuria [72]; however, renal failure is rare contrasting with the other ANCA-associated vasculitides [98].

Imaging

Pulmonary opacities corresponding to eosinophilic pneumonia are present on chest X-ray in a majority of patients with EGPA (37% [72] to 72% [69, 99]) and consist of ill-defined opacities, sometimes migratory, transient, and of varying density [69, 71, 100, 101]. In contrast to GPA, pulmonary cavitary lesions are exceptional. The chest X-ray may remain normal throughout the course of the disease. Mild pleural effusion and phrenic nerve palsy can be observed.

On thin-section chest CT, pulmonary abnormalities can schematically be separated according to whether they predominate in the airspaces corresponding to eosinophilic pneumonia, or in the airways corresponding to bronchiolar and bronchial involvement [101–103]. Airspace abnormalities or "infiltrates" consist of ill-defined opacities, with a density varying from ground glass attenuation to airspace consolidation (Fig. 17.7). They typically predominate in the lung periphery and upper zones of the lung, or have a random distribution, and can be migratory as in ICEP [26, 82, 100, 101]. Airway abnormalities include centrilobular nodules, bronchial wall thickening, and occasionally bronchiectasis or tree-in-bud pattern [26, 27, 82, 101]. Interlobular septal thickening, hilar or mediastinal lymphadenopathy, pleural effusion, and pericardial effusion [26, 100, 101] are less commonly found. In one study, centrilobular nodules were more frequent in EGPA than in patients with ICEP [27]. However, EGPA is difficult to differentiate from other causes of eosinophilic lung diseases on the basis of HRCT imaging [26]. Importantly, pleural effusion may arise due to either inflammatory eosinophilic exudate directly related to EGPA or a transudate caused by cardiomyopathy.

Laboratory Studies

Peripheral blood eosinophilia is a major feature of EGPA, with typical eosinophil counts between 5 and 20 × 10^9/L, although higher values are occasionally found [69, 71, 72, 82]. Blood eosinophilia usually parallels disease activity, and disappears within hours after the initiation of corticosteroid treatment [82]. Eosinophilia, sometimes greater than 60%, is also found on BAL differential cell count and in the pleural fluid when present.

Although EGPA belongs to the group of ANCA-associated vasculitides, ANCAs are present in only about 40% of patients. ANCAs in EGPA are mainly perinuclear (p-ANCA) with myeloperoxidase specificity, and more rarely are cytoplasmic ANCAs (c-ANCA) with proteinase 3 specificity [65,

Table 17.7 Distinct phenotypes of eosinophilic granulomatosis with polyangiitis

	Vasculitic phenotype	Tissular disease phenotype
Respective frequency	~40%	~60%
ANCA	Present (mostly p-ANCA with anti-MPO specificity)	Absent
Predominant clinical and histopathologic features	Glomerular renal disease	Cardiac involvement (eosinophilic myocarditis)
	Peripheral neuropathy	
	Purpura	Fever
Predominant histopathologic features	Biopsy-proven vasculitis	Eosinophilic pneumonia

ANCA antineutrophil cytoplasmic antibody, *MPO* myeloperoxidase, *p-ANCA* perinuclear antineutrophil cytoplasmic antibody
Adapted from references [77, 78]

72, 75, 77, 78, 80]. ANCA status characterizes two distinct clinical phenotypes in EGPA (Table 17.7), albeit with some overlap [65, 77–80, 104, 105]. Patients with ANCA have a vasculitic phenotype, with more frequent glomerular renal disease, peripheral neuropathy, palpable purpura, and biopsy-proven vasculitis. Patients without ANCA have a tissue phenotype of disease with more frequent eosinophilic myocarditis and eosinophilic pneumonia, which may correspond to a variant of the HES with systemic manifestations. Interestingly, genetic predisposition affects the phenotype of EGPA. The vasculitic phenotype of EGPA is more frequent in individuals carrying the major histopathology complex DRB4 allele, whereas the IL-10-3575/1082/592 TAC haplotype is associated with the ANCA-negative EGPA phenotype.

The serum IgE level, erythrocyte sedimentation rate, C-reactive protein level, and serum levels of IgG4, and other biomarkers are increased although none is validated as a diagnostic or prognostic EGPA biomarker. Anemia is common. High levels of urinary EDN may represent an activity index of disease. ANCAs are present in the sputum of patients with EGPA [106]; however, measurement of ANCAs in the sputum is not recommended in clinical practice.

Pathogenesis

EGPA is both a hypereosinophilic condition and an ANCA-associated systemic vasculitis, comprising two distinct yet overlapping pathogenic mechanisms [107]. ANCA-associated EGPA is considered an autoimmune process involving a Th2-mediated inflammatory response. A genetic predisposition within the major histopathology complex has been demonstrated in relation to EGPA, with the presence of ANCA, and with the clinical phenotype of the disease. Similarly, in patients without ANCA, another genetic predisposition was reported within the promoter of IL-10, an important anti-inflammatory cytokine. Familial EGPA has been reported, and the phenotype of EGPA may be affected by genetic predisposition.

EGPA is considered an autoimmune process involving T-cells, endothelial cells, and eosinophils. Defects have been identified in regulatory CD4+ CD25+ or CD4+ CD25− T-cell lymphocytes (producing IL-10 and IL-2) that may influence the progression of the disease, and support an immunological hypothesis of disease. Furthermore, clonal CD8+/Vβ+ T-cell expansions with effector memory phenotype and expressing markers of cytotoxic activity were found in peripheral blood lymphocytes, as well as T-cell receptor-Cβ gene rearrangement.

Contrary to common belief, evidence of allergy demonstrated by specific IgE together with a corresponding clinical history is present in less than one-third of patients [82]. When present in EGPA, allergy mainly consists of perennial allergies to Dermatophagoides, whereas seasonal allergies are less frequent than in the general asthmatic patient [108].

A variety of factors were historically reported to trigger or serve as adjuvant factors in the onset of EGPA, including some vaccines, desensitization protocols [109], fungal infections, smoked cocaine, and a variety of drugs (sulfonamides used together with antiserum, diflunisal, macrolides, diphenylhydantoin, mesalazine, propylthiouracil, masitinib, immune checkpoint inhibitors). Leukotriene-receptor antagonists (montelukast, zafirlukast, pranlukast) have been suspected to be involved in the development of EGPA, although their role is controversial [34, 75, 110–114]. The association between EGPA and leukotriene receptor antagonists may be coincidental, corresponding to EGPA flares related to reducing oral or inhaled corticosteroid doses in patients with smoldering EGPA; however, a direct causal relationship cannot be totally excluded [110, 112, 114, 115]. Many authors advocate for the avoidance of leukotriene receptor antagonists in patients with asthma, eosinophilia, and/or established or smoldering extrapulmonary manifestations. The onset of EGPA in asthmatic patients treated with inhaled corticosteroids [116], or with omalizumab, an anti-IgE antibody, is probably due to the reduction in corticosteroids [34, 117–122].

Diagnosis

The classical description of EGPA follows three stages: asthma and rhinitis; tissue eosinophilia (such as a pulmonary disease resembling ICEP); and extrapulmonary eosinophilic disease with vasculitis [65, 82]. Diagnosing EGPA may be challenging in patients with early disease corresponding to the so-called *formes frustes* [123], who often already receive oral corticosteroids for asthma, thereby masking the underlying smoldering vasculitis. The diagnosis is more straightforward at a later stage of disease with overt systemic

manifestations; however, it is extremely important that the diagnosis be established before severe organ involvement (especially cardiac) is present.

There are currently no established diagnostic criteria for EGPA. Lanham and associates [69] have proposed three diagnostic criteria including (1) asthma, (2) eosinophilia exceeding 1.5×10^9/L, and (3) systemic vasculitis of two or more extrapulmonary organs. These criteria do not include ANCAs, however, which when present certainly contribute to the diagnosis. Classification criteria (which are not *diagnostic* criteria) have been proposed by the American College of Rheumatology [124] and were recently updated by the American College of Rheumatology and the European Alliance of Associations for Rheumatology (Table 17.8) [128]. These criteria are validated for use in research for the classification as EGPA, in patients with a confirmed diagnosis of small- or medium-vessel vasculitis, and after excluding mimics of vasculitis, with excellent specificity. They are not validated, however, and cannot be readily used for the clinical diagnosis of EGPA in patients not yet diagnosed with systemic vasculitis. Inclusion criteria used in a recent trial may be used as diagnostic criteria [125]; however, they too need proper validation. Working diagnostic criteria including ANCA are shown in Table 17.8 [129].

Although a pathologic diagnosis is desirable and can be obtained from the skin, nerve, or muscle [72], it is not mandatory in patients with characteristic features of EGPA. Because cutaneous lesions are easy to access (when not involving the face), a skin biopsy is commonly performed to obtain pathologic evidence of vasculitis when they are present (Clinical Vignette). Conversely, lung biopsy either transbronchial or video-assisted is seldom necessary.

Table 17.8 Diagnostic and classification criteria of eosinophilic granulomatosis with polyangiitis

Reference	Criteria
Lanham and colleagues [69]	• Asthma
	• Eosinophilia
	• Evidence of vasculitis involving at least two organs
American College of Rheumatology[a] [124]	• Asthma
	• Eosinophilia >10%
	• Mononeuropathy, or polyneuropathy
	• Pulmonary infiltrates, nonfixed
	• Paranasal sinus abnormality
	• Extravascular eosinophil infiltration on biopsy findings
2012 Chapel Hill Consensus conference definition [64]	• Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract
	• Necrotizing vasculitis predominantly affecting small to medium vessels
	• Associated with asthma and eosinophilia
	• ANCA is more frequent when glomerulonephritis is present
Diagnostic criteria used in trial NCT02020889 [125]	• History or presence of: asthma plus eosinophilia (>1.0×10^9/L and/or >10% of leukocytes) plus at least two of the following additional features of EGPA
	• A biopsy showing histopathological evidence of eosinophilic vasculitis, or perivascular eosinophilic infiltration, or eosinophil-rich granulomatous inflammation
	• Neuropathy, mono or poly (motor deficit or nerve conduction abnormality)
	• Pulmonary infiltrates, non-fixed
	• Sino-nasal abnormality
	• Cardiomyopathy (established by echocardiography or MRI)
	• Glomerulonephritis (haematuria, red cell casts, proteinuria)
	• Alveolar hemorrhage (by bronchoalveolar lavage)
	• Palpable purpura
	• ANCA positive (MPO or PR3).
Diagnostic criteria used by these authors[b] [126, 127]	1. Asthma
	2. Peripheral blood eosinophilia >1500/mm^3 and/or alveolar eosinophilia >25%
	3. Extrapulmonary clinical manifestations of disease (other than rhinosinusitis), with at least one of the following:
	(a) systemic manifestation typical of the disease: mononeuritis multiplex; or cardiomyopathy confidently attributed to the eosinophilic disorder; or palpable purpura
	(b) any extrapulmonary manifestation with histopathological evidence of vasculitis as demonstrated especially by skin, muscle, or nerve biopsy
	(c) any extrapulmonary manifestation with evidence of ANCA with antimyeloperoxidase or antiproteinase 3 specificity

[a]Diagnosis is probable when four of the six criteria are present (sensitivity of 85%, specificity of 99.7%); these are classification criteria that may be used when the diagnosis of systemic vasculitis has been established by histopathology

[b]When a single extrapulmonary manifestation attributable to the systemic disease is present, disease may be called "forme fruste of EGPA"

Differential Diagnosis

Differentiating EGPA from the other ANCA-associated vasculitides and the other eosinophilic syndromes can be difficult. ANCA-negative EGPA without typical polyangiitis features and "formes frustes" (often consisting of cases in which the disease has been controlled to a greater or lesser extent by corticosteroids given for asthma) may overlap with unclassified systemic eosinophilic disease especially ICEP with minor extrathoracic symptoms. ICEP may also progress to EGPA. Furthermore, pathological features of mild non-necrotizing vasculitis are common in patients with ICEP [11]. Cases of EGPA strictly limited to the lung were reported and were established by lung biopsy performed due to atypical, corticosteroid-dependent, courses of eosinophilic pneumonia [13]. EGPA can also overlap with idiopathic HES. When present, ANCA or the finding of vasculitis and granulomas on biopsy contribute to the diagnosis of EGPA, whereas molecular biology or c-ANCA with proteinase-3 specificity may argue in favor of a diagnosis of idiopathic HES or GPA, respectively.

Idiopathic systemic eosinophilic vasculitis [12] is a recently described entity. Pathologically, the vasculitis, which may be necrotizing or not, differs from that of EGPA, without granulomas. By definition, patients do not have a history of asthma. Lung involvement may occur [66], although it has not yet been described in detail. Although idiopathic systemic eosinophilic vasculitis is distinct from EGPA, it may be part of a common spectrum [66].

Treatment and Prognosis

Treatment of EGPA is based on corticosteroids, which suffice in a large number of cases [69, 130–132]. In the most severe cases, treatment is initiated with methylprednisolone pulses, for 1–3 days, followed by oral corticosteroids, usually started with 1 mg/kg/day of prednisone, and continued for several months with progressive reduction of doses. Relapses are common as corticosteroids are tapered or after treatment has been discontinued, and may present as relapses of the systemic vasculitis (usually accompanied by increased peripheral blood eosinophilia greater than 1×10^9), or more frequently as remitting or persistent difficult asthma that may require long-term low-dose oral corticosteroids despite optimal inhaled asthma therapy [82, 87].

Patients with poor prognostic factors at the onset that could result in mortality or severe morbidity should receive intravenous pulses of cyclophosphamide therapy in addition to corticosteroids (three intravenous infusions of 0.6 g/m^2 intravenously each at Day 1, 15, 30; then three additional infusions of 0.7 g/m^2 every 3 weeks). Intravenous cyclophosphamide is preferred to oral administration as it is better tolerated. The dose of cyclophosphamide may be reduced to 0.5 g in individuals older than 65 years [133]. Although 12 cyclophosphamide pulses are better able to control the disease, a 6-pulse regimen is generally preferred when complete remission of the vasculitis is obtained. Four factors have been associated with a poor prognosis in patients with EGPA in a study of patients with either polyarteritis nodosa or EGPA, namely age >65 years, cardiac symptoms based on easily detectable clinical parameters, gastrointestinal involvement, and renal insufficiency with stabilized peak creatinine >150 μmol/L, whereas ear, nose and throat symptoms were associated with a lower risk of death from EGPA ("revisited five-factor score") [134]. Immunosuppressive therapy with cyclophosphamide is therefore warranted in patients with a five-factor score >1 and especially those with heart failure [135, 136]. Cardiomyopathy is indeed the main predictor of mortality [79], especially in the case of heart failure [135]. In addition, severe alveolar hemorrhage, eye involvement (e.g. scleritis), and/or fulminant mononeuritis multiplex also warrants the use of immunosuppressants. Disease control is improved by a combination of immunosuppressants with corticosteroids, with the caveat of a higher risk of infections.

Once remission has been achieved, prolonged maintenance therapy is necessary to prevent relapses. In the absence of criteria of poor prognosis, it generally consists of glucocorticoids alone, in tapering doses [137]. Immunosuppressive therapy, especially azathioprine or methotrexate, is occasionally used as a corticosteroid-sparing agent in this situation, particularly in subjects who require 10 mg/day of prednisone or more, however, it may now be less frequently used due to the availability of eosinophil targeted therapy. In patients with poor prognostic criteria, maintenance therapy is generally based on azathioprine for 18–24 months. Mycophenolate mofetil could be less effective than azathioprine to prevent relapses [138], but methotrexate 0.25 mg/kg/week is an alternative to azathioprine [139].

Mepolizumab, a human, a monoclonal antibody that binds to IL-5 and prevents its interaction with its receptor on the eosinophil surface, consistently reduces eosinophil cell counts in peripheral blood and improves severe eosinophilic asthma [140–144]. The efficacy and safety of mepolizumab were evaluated in a phase 3 randomized trial as add-on therapy versus placebo in subjects with relapsing or refractory EGPA [125], in many patients due to difficult to control asthma. As compared to placebo, mepolizumab (300 mg every 4 weeks) led to an increased proportion of patients achieving remission, an increased duration of remission, a lower rate of relapse, and a lower average daily dose of oral corticosteroids [125]. Mepolizumab is indicated as an adjunct therapy in subjects with relapsing or refractory EGPA, however many questions remain regarding its optimal use and timing in EGPA. Observational data confirm the efficacy of mepolizumab in EGPA [145, 146], and further suggest that mepolizumab (100 or 300 mg every 4 weeks)

may further be beneficial in cases with persistent severe asthma when the vasculitis is in remission [145, 147].

Reslizumab, another monoclonal antibody against IL-5, and benralizumab, a monoclonal antibody directed against the alpha subunit of IL-5 receptor, both have demonstrated a sparing effect of oral corticosteroids in prospective open-label pilot studies, each in ten patients with EGPA [148, 149]. The efficacy and safety of these drugs in EGPA warrant further study.

The optimal sequence and potential combinations of drugs for patients with EGPA remain to be determined. The 2021 guidelines of the American College of Rheumatology/Vasculitis Foundation recommend first-line treatment with pulse intravenous corticosteroids, high-dose corticosteroids, cyclophosphamide, or rituximab in patients with active severe EGPA, and oral corticosteroids combined with mepolizumab, methotrexate, azathioprine, mycophenolate mofetil, or rituximab, in patients with active non-severe EGPA [150]. Maintenance therapy once remission has been achieved may consist of methotrexate, azathioprine, or mycophenolate mofetil [150].

The anti-IL4/13 monoclonal antibody dupilumab may trigger hypereosinophilia with sudden deterioration of asthma, eosinophilic tissue infiltration, and EGPA-like symptoms in patients previously treated or not with anti-IL-5/IL-5R antibodies, and should therefore be used with caution when the diagnosis of EGPA is contemplated [151, 152].

The anti-IgE omalizumab has been used successfully to treat persistent asthma in patients with EGPA [153]; careful clinical monitoring is warranted because omalizumab does not control the systemic disease. Observational data suggest that rituximab may be useful [147]. In addition, some selected cases of severe EGPA refractory to corticosteroids and/or cyclophosphamide may respond to subcutaneous interferon-alfa, high-dose intravenous immunoglobulins, or cyclosporin A. The low level of evidence for these approaches is low, however.

Long-Term Outcome

Long-term follow-up is warranted due to the risk of relapse of the vasculitis, which is not prevented by cytotoxic agents, and is higher in patients with ANCA [79] and lower in those with baseline eosinophils >3.0 × 10^9/L [136]. The 5-year overall survival in EGPA is currently greater than 90% [65, 79, 81], and as high as 97% were alive in those without poor-prognosis factors [154]. Mortality is associated with disease severity. Most deaths during the first years of treatment are due to cardiac involvement [79, 155], gastrointestinal bleeding, renal insufficiency, or central nervous system involvement [130, 134].

Long-term morbidity is related to side effects of oral corticosteroids [81, 82, 154], and to frequent uncontrolled asthma with airflow obstruction (that in some cases may still be partly reversible with increased oral corticosteroid treatment [156]) despite corticosteroids and inhaled therapy [82, 87, 156–158].

Hypereosinophilic Syndrome

Definition

The "idiopathic" HES was historically defined in 1975 by Chusid and coworkers [159] as (1) a persistent eosinophilia greater than 1.5 × 10^9/L for longer than 6 months, or death before 6 months associated with the signs and symptoms of hypereosinophilic disease, (2) a lack of evidence for parasitic, allergic, or other known causes of eosinophilia, and (3) presumptive signs and symptoms of organ involvement, including hepatosplenomegaly, organic heart murmur, congestive heart failure, diffuse or focal central nervous system abnormalities, pulmonary fibrosis, fever, weight loss, or anemia.

The definition of HES was revised in a consensus statement [23], now requiring the following three criteria:

- Absolute blood eosinophil count ≥1500/μL on two examinations (with an interval of 1 month or more) and/or tissue hypereosinophilia defined by the following:
  - Percentage of eosinophils in the bone marrow section exceeds 20% of all nucleated cells and/or
  - Pathologist is of the opinion that tissue infiltration by eosinophils is extensive and/or
  - Marked deposition of eosinophil granule proteins is found (in the absence or presence of major tissue infiltration by eosinophils).
- Organ damage and/or dysfunction attributable to tissue hypereosinophilia, and
- Exclusion of other disorders or conditions as a major reason for organ damage.

HES is further divided into variants [23]: a hereditary (familial) HES variant, HES of undetermined significance, primary (clonal/neoplastic) HES produced by apparently clonal (neoplastic) eosinophils, and secondary (reactive) HES related to an underlying condition/disease in which eosinophils are considered non-clonal cells and HES is considered cytokine-driven in most cases.

Conditions such as ICEP and IAEP characterized by hypereosinophilia (as defined above) and clinical manifestations limited to a single organ are classified as an eosinophil-associated single-organ disease [23]. This section will mainly review pulmonary manifestations associated with clonal/neoplastic HES and reactive HES.

Pathogenesis

HES may result from clonal cell proliferation, involving either the lymphocyte lineage in the "lymphocytic variant"

of HES whereby clonal lymphocytes produce eosinophilopoetic chemokines, or the eosinophil cell lineage itself in chronic eosinophilic leukemia (the "myeloproliferative variant" of HES). In such cases, the HES may be considered a premalignant T-cell disorder [160, 161] or chronic leukemia, respectively. The term *idiopathic* is used to describe cases that cannot be classified in either category, and further innovative diagnostic tools will likely contribute in the future to differentiate these cases from other causes of eosinophilia of determined cause.

In the clonal/neoplastic HES variant, also called chronic eosinophilic leukemia (formerly, "myeloproliferative variant" of HES), an interstitial chromosomal deletion of a region in the long arm of chromosome 4 (q12) is causing a fusion protein by fusion of *FiplLl–PDGFR-α*, with the constitutive activation of the tyrosine kinase domain. Patients frequently present with hepatomegaly, splenomegaly, mucosal ulcerations, severe cardiac manifestations resistant to corticosteroid treatment, anemia, thrombocythemia, increased serum vitamin B_{12}, leukocyte alkaline phosphatase, and serum tryptase, circulating leukocyte precursors, and pronounced mastocytosis (lacking *KIT* mutations). Cutaneous manifestations are infrequent. Because the deletion is not detectable by karyotype analysis [162, 163], an analysis of chromosomal deletion using FISH probes to the gene *CHIC2* encompassed in the deleted sequence, and of the expression of the *FiplLl–PDGFR-α* fusion gene is required for the diagnosis. The tyrosine kinase activity of the fusion protein is inhibited by imatinib, which proved efficient in treating HES in patients refractory to corticosteroids, hydroxyurea, and/or interferon-α. Clonal eosinophilia in patients presenting with clinical features of HES can also be related to other uncommon, mutations in *PDGFRA*, *PDGFRB*, *KIT*, *BCR/ABL1*, *FGFR1*, or *JAK2* [164].

Patients with the reactive HES variant have an underlying inflammatory, neoplastic, or other disease or condition known to cause hypereosinophilia through the production of eosinophilopoietic cytokines. Specifically, chemokines (especially IL-5, but also IL-3) produced by clonal Th2 lymphocytes bearing clonal rearrangement of the TCR with an aberrant immunologic phenotype (such as $CD3^-$ $CD4^+$) promote the accumulation of eosinophils. An underlying hematopoietic neoplasm producing clonal eosinophils has to be excluded by means of histopathologic, cytogenetic, and molecular analyses. However, reactive HES can occur in hematopoietic neoplasms, such as in Hodgkin lymphoma, T-cell lymphoma, or B-lymphoblastic leukemia/lymphoma carrying certain molecular defects [23], a situation often referred to as the lymphoid variant of HES [23]. Lymphocyte phenotyping by flow cytometry to detect a phenotypically aberrant T-cell subset, and analysis of the rearrangement of the TCR genes in search of T-cell clonality in the peripheral blood (and possibly bone marrow), are therefore key to the diagnosis. Demonstration of increased IL-5 expression from cultured T-cells can also contribute to the diagnosis. Papules or urticarial plaques infiltrated by lymphocytes and eosinophils (and rarely, a cutaneous T-cell lymphoma or the Sezary syndrome) are frequently present. Serum levels of IL-5, TARC, and total IgE are increased but nonspecific.

Clinical and Imaging Features

The pulmonary involvement in patients with eosinophilia of clonal origin has not been studied specifically in the different variants of the HES. Most data available derive from older studies, in which the HES occurs much more commonly in men than in women (9:1), usually between 20 and 50 years, with insidious onset or incidental discovery of peripheral eosinophilia [165]. The mean eosinophil count at presentation was 20.1×10^9/L in one series [166], with occasionally extremely high values in excess of 100×10^9/L [159].

Lung or pleural involvement is uncommon in the reactive/lymphocytic variant of the HES [160, 161]. However, pulmonary involvement was reported at chest CT in about 40% of patients with clonal/neoplastic HES variant (formerly chronic eosinophilic leukemia) [159, 165].

Patients present with weakness and fatigue (26%), cough (24%), dyspnea (16%) [165], or asthmatic symptoms (25%) [167]. Morbidity and mortality in HES are driven by cardiovascular involvement, with characteristic endomyocardial fibrosis [165] (which differs from the eosinophilic myocarditis seen in EGPA), causing dyspnea, congestive heart failure, mitral regurgitation, cardiomegaly [165], and typical features at echocardiography [168]. The other manifestations of HES include neurologic manifestations (thromboembolic, central nervous system dysfunction, peripheral neuropathies), and cutaneous manifestations (erythematous pruritic papules and nodules, urticaria, and angioedema).

Respiratory manifestations are generally of mild severity, with rare eosinophilic pneumonia if any [167]. Chest CT may show pleural effusion, pulmonary emboli, small nodules, occasionally a halo of ground-glass attenuation, and focal areas of ground-glass attenuation mainly in the lung periphery [26, 169]. Notably, imaging features corresponding to eosinophilic lung involvement must be differentiated from those related to pulmonary edema resulting from cardiac involvement. Chronic dry cough can be remarkable and may be a presenting or the only feature [170–172].

Laboratory Studies

Blood eosinophilia is typically very high, exceeding $3–5 \times 10^9$/L, with higher values than in other eosinophilic lung diseases. Eosinophilia may be only mild at BAL, however suggesting that eosinophilia may be compartmentalized. Elevated serum levels of mast cell tryptase, and dysplastic mast cells may be present in the bone marrow, with some patients meeting minor criteria for systemic mastocytosis.

Treatment and Prognosis

In patients with the clonal/neoplastic HES variant (chronic eosinophilic leukemia), imatinib is the first-line therapy, with a more frequent response when the Fip1L1–PDGFR-α fusion protein is present [162–164, 173–175]. Imatinib should initially be associated with corticosteroids. Testing for the presence of FIP1L1-PDGFRA is recommended every 3–6 months in patients who require chronic imatinib therapy to avert relapses [176]. Long-term continuation of treatment is required in some patients to maintain remission, with possible tapering of the dose, whereas imatinib can be stopped without relapse in others [175]. Chemotherapeutic agents (hydroxyurea, vincristine, etoposide), cyclosporin A, and interferon-α either as monotherapy or in association with hydroxyurea, may be beneficial in some refractory cases.

In patients with the reactive "lymphocytic variant" of HES, corticosteroids remain the mainstay of treatment, although a response is obtained in only about half of them [164]. Mepolizumab, an anti-IL5 antibody, is beneficial as a corticosteroid-sparing agent in HES patients negative for the *FiplLl–PDGFR-α* fusion gene and requiring 20–60 mg/day of prednisone to maintain a stable clinical status and a blood eosinophil count of less than 1×10^9/L [177–179].

The long-term prognosis of HES has improved considerably, with a 3-year survival of only 12% in the first published series [159], to only one death in a recent series of 44 cases [175]. Further improvement in the long-term outcome and survival with this condition can be anticipated from recent advances in gene molecular biology that rapidly translate into innovative therapies.

Idiopathic Hypereosinophilic Obliterative Bronchiolitis

Hypereosinophilic obliterative bronchiolitis is a recently individualized entity [180], currently defined by provisional working criteria (Table 17.9), associating demonstration of bronchiolitis, of peripheral blood and/or alveolar eosinophilia, and persistent airflow obstruction despite high-dose inhaled bronchodilators and corticosteroids. Demonstration of bronchiolitis may be obtained by lung biopsy [180–182] and/or HRCT showing direct signs of bronchiolitis (e.g. centrilobular nodules and branching opacities) [180, 183] (Fig. 17.8). Hypereosinophilic obliterative bronchiolitis can be idiopathic, but may also occur in the setting of EGPA, ABPA, drug-induced eosinophilic lung disease (such as minocycline), and possibly in severe asthma [180].

Table 17.9 Working diagnostic criteria for hypereosinophilic obliterative bronchiolitis [180]. All three criteria are required. Hypereosinophilic obliterative bronchiolitis may be secondary to various conditions including EGPA, ABPA, or drug-induced eosinophilic lung disease

Peripheral blood and/or BAL	Blood eosinophil cell count >1 × 10^9/L and/or bronchoalveolar lavage eosinophil count >25%
Pulmonary function tests	Persistent airflow obstruction despite high-dose inhaled bronchodilators and corticosteroids
Demonstration of bronchiolitis	Eosinophilic bronchiolitis at lung biopsy and/or direct signs of bronchiolitis (centrilobular nodules and branching opacities) on computed tomography

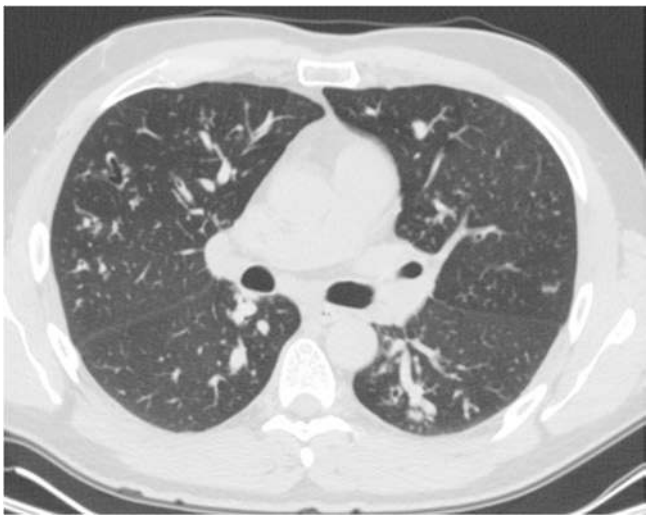

Fig. 17.8 CT scan of a patient with idiopathic hypereosinophilic bronchiolitis showing bronchiectasis in the right middle lobe and mucoid impaction in the left lower lobe

Patients report cough and exercise dyspnea but generally do not present with intermittent asthma symptoms or wheezes. The blood eosinophil cell count (with a mean value of 2.7×10^9/L), and the mean eosinophil differential percentage at BAL (with a mean value of 63%) are elevated [180]. Airflow obstruction is often severe but reversible in all cases with the initiation of oral corticosteroid therapy or increasing its daily dose, however, clinical and functional manifestations often recur when the daily dose of oral prednisone is tapered to less than 10–15 mg. Mepolizumab or benralizumab may be beneficial [184–187] however experience in this indication is very limited.

Unrecognized untreated hypereosinophilic obliterative bronchiolitis might be a cause of irreversible airflow obstruction in chronic eosinophilic respiratory diseases. Notably, whitish tracheal and bronchial granulations or bronchial ulcerative lesions can be present with prominent eosinophilia on bronchial biopsy [180].

Eosinophilic Lung Disease of Determined Cause

Once the diagnosis of eosinophilic pneumonia has been made, a thorough evaluation is necessary to investigate possible causes. A more comprehensive description of eosinophilic pneumonia related to fungi or parasites can be found elsewhere [188–190].

Eosinophilic Pneumonias of Parasitic Origin

The most common cause of eosinophilic pneumonia in the world, eosinophilic pneumonias related to parasite infestation arises mainly in humans infected by helminths and especially nematodes (roundworms).

Tropical Eosinophilia [191]

Tropical eosinophilia caused by the filarial nematodes *Wuchereria bancrofti* and *Brugia malayi* is endemic in tropical and subtropical areas of Asia, Pacific, Africa, and less commonly in South and Central America. It has been reported mostly in Indians, and occasionally in patients originating from India or Asia and living in western countries. It is characterized by severe spasmodic bronchitis or chronic dry cough (exacerbated at night), often associated with expiratory dyspnea and wheezing, fever, loss of weight, anorexia, leukocytosis, and high blood eosinophilia, and disseminated bilateral opacities at a chest X-ray. Eosinophilic pneumonia is generally seen 1–3 months after infestation. Blood eosinophilia is prominent, with more than 2×10^9 eosinophils/L in all cases, and up to 60×10^9/L in some cases. BAL shows intense alveolitis with a mean percentage of 54% of eosinophils with marked degranulation. Because the circulating microfilariae are trapped in the lung vasculature, they are usually not found in the blood or the lung. BAL eosinophils drop within 2 weeks upon anti-parasitic treatment. Lung function tests show a restrictive ventilatory defect, with a reversible obstructive ventilatory defect and hypoxemia in about a quarter of the patients. Nonspecific opacities are present on chest X-ray and CT in a majority of patients; irregular basilar opacities may persist for longer than 1 year. The diagnosis is made by the combination of cough worse at night; residence in a filarial endemic area; eosinophil count greater than 3300 cells/mm^3; and clinical and hematologic response to diethylcarbamazine. The latter is the only effective drug for tropical eosinophilia. Association of corticosteroids to diethylcarbamazine may be beneficial.

Ascaris Pneumonia

The most common helminth infecting humans, *Ascaris lumbricoides* is transmitted through food or water contaminated by human feces. Transient pulmonary infiltrates with blood eosinophilia (Löffler syndrome) may develop during the migration of the larvae of the parasite through the lung, with usually mild pulmonary symptoms (cough and wheezing), transient fever, a possible pruritic eruption at the time of respiratory symptoms. Blood eosinophilia may be as high as 22×10^9/L. Symptoms spontaneously resolve in a few days, whereas blood eosinophilia may remain elevated for several weeks. The diagnosis is made by the delayed finding of the worm or ovae in the stool within 3 months of the pulmonary manifestations. Intestinal ascariasis is treated with oral mebendazole.

Eosinophilic Pneumonia in *Larva Migrans* Syndrome

Visceral larva migrans is caused by *Toxocara canis*, and occurs mainly in children infected by eggs contaminating the soil of public playgrounds in urban areas. Whereas the majority of patients remain asymptomatic and undiagnosed, some present with fever, cough, dyspnea, seizures, fatigue, wheezes or crackles at pulmonary auscultation, and pulmonary opacities at a chest X-ray. Corticosteroids may be beneficial in rare severe cases in adults necessitating mechanical ventilation. Blood eosinophilia may be present initially, or may develop only in the following days. The diagnosis is difficult, as both IgG and IgM antibodies may reflect residual immunity rather than recent infection and do not have diagnostic significance [192]. Only symptomatic treatment is generally required. The use of anthelmintics is controversial. Corticosteroids seem beneficial in cases with severe pulmonary involvement.

Strongyloides Stercoralis Infection

Prevalent in the tropical and subtropical areas, infection with the intestinal nematode *Strongyloides stercoralis* is acquired through the skin by contact with the soil of beaches or mud and may persist for years, often without peripheral eosinophilia that is mostly present in recently infected patients [160, 193]. Löffler syndrome occurs when larvae migrate through the lungs after acute infection. Immunocompromised patients or those receiving immunosuppressive therapy are at risk of severe disseminated strongyloidiasis, which may affect all organs (hyperinfection syndrome). The diagnosis depends on the demonstration of larvae in the feces or sputum and BAL fluid. Immuno-diagnostic assays by ELISA methods may be useful for diagnosis and screening. All infected patients should be treated using ivermectin.

Eosinophilic Pneumonias in Other Infections

Löffler syndrome can also be caused by the human hookworms *Ancylostoma duodenale* and *Necator americanus*. Simple pulmonary eosinophilia may be due to cutaneous

helminthiasis (creeping eruption) related to the dog hookworm *Ancylostoma braziliense*. Transient multiple small pulmonary nodules at chest imaging and eosinophilia may occur in early acute schistosomiasis due to *Schistosoma haematobium* or *S. mansoni*, whereas post-treatment eosinophilic pneumonitis (also called reactionary Löffler-like pneumonitis) may develop in chronic schistosomiasis (in addition to the risk of portopulmonary hypertension) [194]. Other parasites causing rare pulmonary manifestations with eosinophilia include the filarial parasite of dog *Dirofilaria immitis* (the pulmonary fluke), *Paragonimus westermani*, *Trichomonas tenax*, *Capillaria aerophila*, and *Clonorchis sinensis*.

Pulmonary infection with eosinophilia has been reported occasionally with *Pneumocystis jirovecii*, fungi (*Coccidioides immitis*, *Bipolaris australiensis*, *Aspergillus niger* and *Bipolaris spicifera*), *bacteria* (tuberculosis, brucellosis), and viruses (respiratory syncytial virus, influenza infection).

Allergic Bronchopulmonary Aspergillosis

ABPA is a distinct condition characterized by asthma, eosinophilia, and bronchopulmonary manifestations with bronchiectasis due to the fungus *Aspergillus fumigatus*, and differing from invasive pulmonary aspergillosis, aspergilloma, *Aspergillus*-associated asthma, or chronic necrotizing aspergillosis, although it may be associated to the latter. ABPA is related to a complex allergic and immune reaction to *Aspergillus* colonizing the airways in susceptible hosts, namely 1–2% of adults with previous asthma and 7–10% [195, 196] of patients with cystic fibrosis. In addition, rare cases have been recently reported in patients with chronic obstructive pulmonary disease. Five stages have been described (acute, remission, recurrent exacerbations, corticosteroid-dependent asthma, and fibrotic end stage), although they do not reflect the natural course of disease in many patients, and alternative staging systems have been proposed [197]. Allergic *Aspergillus* sinusitis, a sinus equivalent of ABPA [198], can be associated with ABPA in a syndrome called *sinobronchial allergic aspergillosis*.

Pathogenesis

ABPA results from the persistence of *A. fumigatus* in the airways, and the skewing of adaptive immune responses to type 2 [199]. Damage to the bronchial epithelium, submucosa, and adjacent pulmonary parenchyma is caused by a chronic inflammatory reaction in the bronchi and the surrounding parenchyma. ABPA is mediated by type I and type III immunologic response of the host (mediated by IgE, and IgG and IgA antibodies, respectively), together with a Th2 $CD4^+$ T-cell mediated immune response and sustained IL-17 expression [200] to antigens from *Aspergillus* growing in mucous plugs in the airways. Cytolytic eosinophils release filamentous chromatin fibers and create extracellular traps, composed of condensed chromatin fibers and contribute to the high viscosity of eosinophilic mucus [201]. Eosinophils accumulated in the airways also release toxic cationic proteins [202], causing epithelial damage and leading to airways mucus plugging. The chronic inflammatory reaction, with the secretion of a variety of inflammatory cytokines and recruitment of inflammatory cells, results in damage to the bronchial epithelium, submucosa, and adjacent pulmonary parenchyma.

In addition to mechanisms associated with innate and acquired immunity, ABPA can occur preferentially in genetically susceptible hosts [197], as suggested by the increased prevalence of heterozygotic cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations [203, 204], and association with a polymorphism within the IL-4 receptor α-chain gene and HLA DR subtypes. Genetic susceptibility likely explains why not all patients with asthma develop ABPA despite the environment. Infection with nontuberculous mycobacteria [205], infliximab therapy for sarcoidosis [206], Kartagener syndrome, and occupational exposures (in workers in the bagasse-containing sites in sugar cane mills) [207] may also contribute to the pathogenesis of ABPA. In addition to *Aspergillosis*, other fungi or yeasts can cause a similar syndrome of allergic bronchopulmonary disease (reviewed in [208]), with difficulties in assessing the sensitization to the specific fungi probably accounting for part of the low frequency of recognition of these conditions as compared to ABPA.

Diagnostic Criteria

The diagnosis of ABPA is made on a combination of clinical, immunologic (microbiological), and thoracic imaging findings [199]. Several sets of criteria have recently been proposed (Table 17.10) [197, 209–211], as the diagnosis is generally made on the combination of clinical and biologic features. The classical diagnostic criteria include asthma, history of pulmonary infiltrates, proximal bronchiectasis, elevated serum IgE, and immunologic hypersensitivity to *A. fumigatus* (immediate reaction to prick test for *Aspergillus* antigen, precipitating antibodies against *A. fumigatus*, elevated specific IgE against *A. fumigatus* [209, 212]). The expectoration of mucous plugs, the presence of *Aspergillus* in sputum, and late skin reactivity to *Aspergillus* antigen [209] are also frequent findings that contribute to the diagnosis when present. Typical proximal bronchiectasis may be absent in cases designated ABPA-seropositive [213]. New diagnostic criteria consisting of ten components showed high sensitivity and specificity for the diagnosis of ABPA in patients without cystic fibrosis [211]; they are also useful for the diagnosis of allergic bronchopulmonary disease due to fungi other than *Aspergillus*.

Table 17.10 Diagnostic criteria of ABPA

Minimal essential diagnostic criteria of ABPA	
Rosenberg–Patterson criteria for diagnosis of ABPA in patients with asthma (1977) [209]	*Primary criteria*[a]
	1. Episodic bronchial obstruction (asthma)
	2. Peripheral blood eosinophilia
	3. Immediate skin reactivity to Aspergillus antigen
	4. Precipitating antibodies against Aspergillus antigen
	5. Elevated serum IgE concentrations
	6. History of pulmonary infiltrates (transient or fixed)
	7. Central bronchiectasis
	Secondary criteria
	• *A. fumigatus* in sputum (detected by repeated culture or microscopic examination)
	• History of expectoration of brown plugs or flecks
	• Arthus reactivity (late skin reactivity) to Aspergillus antigen
ISHAM criteria for diagnosis of ABPA (2013) [197]	Predisposing conditions: asthma, cystic fibrosis
	Obligatory
	• Positive type 1 *Aspergillus* skin test result or elevated IgE antibody levels
	• Total IgE level >1000 IU/mL
	And >2 of the following:
	• Precipitating or IgG serum antibodies to *A. fumigatus*
	• Radiographic pulmonary opacities consistent with ABPA
	• Eosinophil count >500 cells/mL in steroid-naive patients (may be historical)
Modified ISHAM criteria for diagnosis of ABPA in asthma (2020) [210]	Presence of the following:
	1. Asthma
	2. *A fumigatus*-specific IgE level >0.35 kU A/L
	3. Serum total IgE levels >500 IU/mL and >2 of the following:
	(a) *A fumigatus*-specific IgG level >27 mg A/L
	(b) Bronchiectasis on chest CT scan
	(c) Eosinophil count >500 cells/mL
	(d) Mucus impaction on chest CT scan
Asano criteria for diagnosis of ABPM in patients without cystic fibrosis (2021) [211]	Presence of >6 of the following:
	1. Current or previous history of asthma or asthmatic symptoms
	2. Peripheral eosinophilia >500 cells/mm^3
	3. Total IgE level >417 IU/mL
	4. Positive result of immediate skin test or specific IgE level for filamentous fungi[b]
	5. Presence of precipitins or specific IgE for filamentous fungi
	6. Positive filamentous fungal sputum test or bronchial lavage culture result
	7. Fungal hyphae in bronchial mucus plugs
	8. Central bronchiectasis on CT scan
	9. Mucus plugs detected by CT, bronchoscopy, or expectoration
	10. High-attenuation bronchial mucus on CT scan

ISHAM International Society of Animal and Human Mycology, *ABPM* allergic bronchopulmonary mycosis

[a]The diagnosis "likely" if primary criteria 1–6 are present and "certain" if all primary criteria are present

[b]Filamentous fungi in criteria 4–6 should be identical

Of note, patients who are negative for *Aspergillus fumigatus*-specific IgE are unlikely to have ABPA, a feature that is helpful to rule out the disease in severe asthmatics [197]. Similarly, a normal serum total IgE level excludes active ABPA disease [199]. The yield of sputum cultures for *A. fumigatus* is only about 40–60% in ABPA, therefore negative sputum cultures do not exclude ABPA [199]. However, since manifestations of ABPA are nonspecific, a high index of suspicion should be exerted in any asthmatic patient.

Biology

Pulmonary infiltrates with alveolar eosinophilia and/or peripheral blood eosinophilia may be present only during the acute phase or recurrent exacerbations of the disease. Blood eosinophilia is generally greater than 1×10^9/L. Sputum and expectorated plugs contain eosinophils and Charcot-Leyden crystals. Serum levels of TARC are elevated and might be used as a marker for the identification and monitoring of ABPA.

Demonstration of immediate and/or late immunologic hypersensitivity to *A. fumigatus* is key to the diagnosis of ABPA. Out of about 40 antigenic components of *Aspergillus* that can bind with IgE antibodies [213], two seem to be the most helpful for diagnostic purposes (e.g. specific antibodies to recombinant *rAsp f1* and *rAsp f2*) [199, 214–216].

Imaging

Proximal bronchiectasis on CT (in the medial half of the lung from the hilum to the chest wall) predominating in the upper lobes [217] is considered a hallmark of ABPA, albeit one with low sensitivity and specificity, and the finding may be absent especially in early disease [197]. It has been suggested that serological ABPA (without bronchiectasis) may correspond to a variant rather than an early stage of disease [218]. Bronchiectasis represents the ultimate consequence of damage to the large bronchi by chronic inflammation. Mucoid impaction of high attenuation on CT represents mucous plugs containing *Aspergillus* obstructing the airways with subsequent atelectasis [219]. Mosaic attenuation, centrilobular nodules, and tree-in-bud opacities are also commonly seen. The presence of bronchiectasis, centrilobular nodules, and mucoid impaction on CT scans are highly suggestive of ABPA in an asthmatic (Figs. 17.9, 17.10, and 17.11) [220]. Agarwal et al. have suggested a classification based on CT imaging patterns between serological ABPA (without bronchiectasis), ABPA with bronchiectasis, ABPA with high-attenuation mucus, and ABPA with pleuropulmonary fibrosis [197].

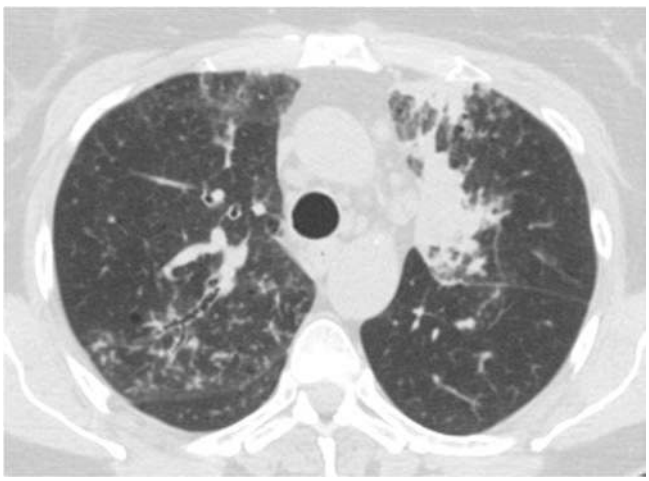

Fig. 17.9 CT scan of a patient with allergic bronchopulmonary aspergillosis showing central bronchiectasis and tree-in-bud pattern in the right upper lobe, with alveolar consolidation corresponding to eosinophilic pneumonia in the left upper lobe

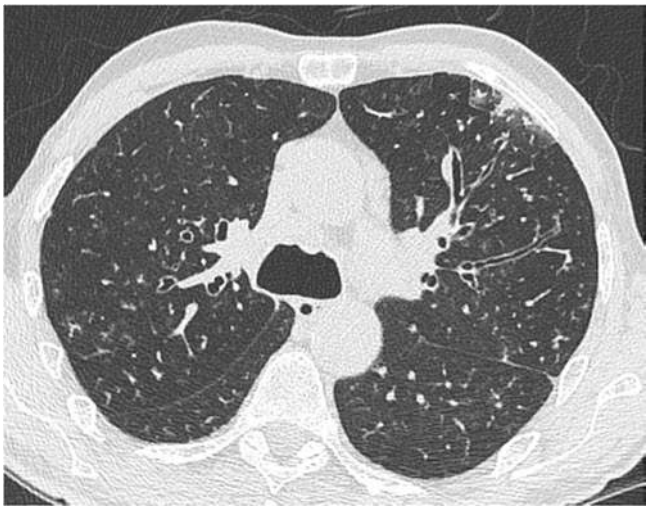

Fig. 17.10 CT scan of a patient with allergic bronchopulmonary aspergillosis showing central bronchiectasis predominating in the left upper lobe, with mild subpleural alveolar consolidation

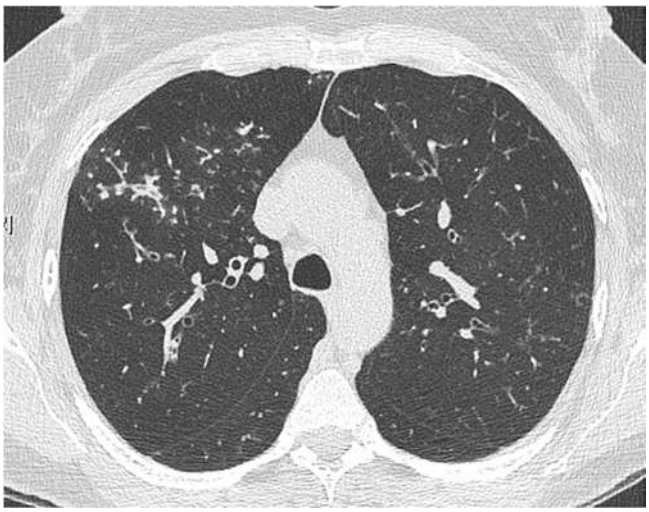

Fig. 17.11 CT scan of a patient with allergic bronchopulmonary aspergillosis showing peripheral tree-in-bud and branching pattern in the right upper lobe

On imaging, fleeting infiltrates due to eosinophilic pneumonia or mucus plugging with ensuing segmental or lobar atelectasis are frequent during the initial stage of the disease, however, the diagnosis is rarely made at this stage. A V-shaped lesion with the vertex pointing toward the hilum suggests mucoid bronchial impaction, which may be associated with atelectasis.

Treatment

Management of asthma is of primary importance in ABPA, often requiring high-dose inhaled corticosteroids (which may reduce the need for long-term oral corticosteroids) and long-acting bronchodilators. In addition, oral corticosteroids are used during acute exacerbations, with rapid tapering. Treatment is initiated at 0.5 mg/kg/day of prednisone for 1 or 2 weeks, then tapered over a total duration of about 12 weeks (short regimen) [213], a protocol which is now preferred to a longer regimen with higher doses of corticosteroids (0.75 mg/kg/day for 6 weeks, then tapered over a total duration of 6–12 months) [221–223]. Oral corticosteroids are maintained in the long-term only in patients with frequent symptomatic attacks or chronic symptoms, with the objective of preventing the progression to the fibrotic end stage, albeit with low-level evidence.

Antifungal therapy to attenuate the fungal load in the airways is an alternative to corticosteroids, or can be combined with corticosteroids [199]. Several randomized, placebo-controlled studies [224, 225] demonstrated that oral itraconazole allowed reduction of the doses of corticosteroids, a decrease in the number of exacerbations [225], and improvement of biologic (sputum eosinophils, sputum ECP levels, serum IgE levels, and serum IgG levels to *A. fumigatus*) and physiologic criteria. A clinical benefit accrued in approximatively 60% of patients with ABPA [226], especially those with corticosteroid-dependent ABPA, although no significant effect was observed on pulmonary infiltrates [227]. Itraconazole is therefore recommended in ABPA in asthmatics [228]. It can also be used as an alternative to oral corticosteroids [229]. Itraconazole may also be useful in ABPA patients with cystic fibrosis [226, 230]. Itraconazole therapy is generally continued for a minimum of 4–6 months. Monitoring total serum IgE level may be helpful, with the objective of reducing the serum total IgE level by ≥25% with therapy [197]. Itraconazole interacts with many medications, with a risk of adrenal insufficiency. Due to frequent drug interactions, the use of oral prednisone, and inhaled beclomethasone or ciclesonide, should be preferred to that of oral methylprednisolone and inhaled budesonide or fluticasone [226]. Voriconazole has been used in patients with acute-stage ABPA, however without proven benefit as compared to itraconazole [231].

In spite of total IgE levels that frequently exceed 1000 IU/mL, the anti-IgE recombinant antibody omalizumab may be useful in some cases to reduce the number of episodes of exacerbation and the steroid dose [232, 233], especially in subjects with treatment-refractory ABPA or those who are intolerant to first-line treatment [199]. In difficult cases, some clinical benefit was suggested with pulses of intravenous corticosteroids (to treat exacerbations), voriconazole, posaconazole, or nebulized liposomal amphotericin B [234]. More recently, mepolizumab, benralizumab, reslizumab, and dupilumab have been used successfully in isolated cases.

Bronchocentric Granulomatosis

Bronchocentric granulomatosis [235] is a chronic inflammatory granulomatous and destructive process extending from the bronchiolar walls into the surrounding peribronchiolar lung parenchyma [236]. Pathology demonstrates destruction and necrosis of the mucosa and walls of bronchioles, often surrounded by palisading histiocytes and dense peribronchial inflammatory infiltrate, with occasionally scattered fungal hyphae stained by Grocott, and possible vascular inflammation and mucoid impaction [236]. In asthmatics, eosinophils are prominent within the inflammatory infiltrate of bronchocentric granulomatosis, whereas they are less conspicuous in nonasthmatics. Patients with bronchocentric granulomatosis often present clinically as asthmatics who have a fever, chronic cough, and peripheral blood eosinophilia greater than 1×10^9 eosinophils/L [236]. Imaging features consist of masses, alveolar opacities, consolidation, and possible reticulonodular opacities. Abnormalities all predominate in the upper lung zones and are generally unilateral [237]. Management is based on oral corticosteroids. As most of these patients also fulfill the criteria for ABPA, this condition may be underdiagnosed. Although the prognosis is excellent, recurrences are common.

Drug, Toxic Agents, and Radiation-Induced Eosinophilic Pneumonias

Eosinophilic pulmonary infiltrates can be caused by a number of drugs (Table 17.11, see www.pneumotox.com), with a demonstration of causality for only a few of them. The typical patient will present with acute (or chronic) onset of eosinophilic pneumonia following the recent initiation of treatment with nonsteroidal anti-inflammatory drugs or antibiotics. Simple pulmonary eosinophilia (Löffler syndrome with transient pulmonary infiltrates), or chronic eosinophilic pneumonia, can also be induced by drugs. Associated extrapulmonary iatrogenic manifestations, especially cutaneous rashes, fever, or nausea, may be present.

Table 17.11 Drugs that may commonly cause acute eosinophilic pneumonia. A more extensive list of drugs reported to cause eosinophilic pneumonia may be found at www.pneumotox.com

Anti-inflammatory drugs and related drugs	Acetylsalicylic acid, diclofenac, ibuprofen, naproxen, phenylbutazone, piroxicam, sulindac, tolfenamic acid
Antibiotics	Ethambutol, fenbufen, minocycline, nitrofurantoin, penicillins, pyrimethamine, sulfamides, sulfonamides, trimethoprim-sulfamethoxazole
Other drugs	Captopril, carbamazepine, Granulocyte monocyte-colony stimulating factor (GM-CSF)

Pleural effusion is possible. Systemic eosinophilic vasculitis involving the lung and closely resembling EGPA has been reported. Cases with severe pulmonary involvement may require mechanical ventilation, or present with systemic manifestations (drug reaction with eosinophilia and systemic symptoms, DRESS) [238, 239]. Up to 75% of cases are associated with an antiviral immune response to reactivated human herpesvirus-6 [240].

A thorough history is required to suspect drug-induced eosinophilic lung disease, as the offending drug may have been taken in the weeks or months preceding the clinical syndrome, or may be denied by the patient as in the case of illicit drugs (cocaine, heroin, crack, marijuana/cannabis). Eosinophilic pneumonia can also be caused by non-cigarette smoking products including vaping, waterpipe smoking, and marijuana [241–243]. Pulmonary manifestations may regress after withdrawal of the suspected drug, confirming the diagnosis, however, this may take a long time, and therefore corticosteroids are also frequently given. Reintroduction of the suspected drug can be dangerous and should generally be avoided, although it may be carefully considered on rare occasions.

Historically, the toxic oil syndrome and the eosinophilia-myalgia syndrome related to preparations of L-tryptophan caused eosinophilic lung disease in Spain in 1981 and the United States in 1989, respectively.

A syndrome similar to ICEP can develop up to 10 months after radiotherapy for breast cancer in women [244]. Patients often have a history of asthma or allergy, presumably with a Th2-oriented lymphocyte response. Pulmonary opacities at imaging may be unilateral (irradiated lung) or bilateral, and occasionally migrate. Peripheral blood eosinophilia greater than 1.0×10^9/L and/or eosinophilia greater than 40% on the BAL differential cell count distinguish this syndrome from organizing pneumonia primed by radiation therapy to the breast. Rapid improvement is obtained with oral corticosteroids, with possible relapse after treatment withdrawal. Similar cases have also been reported following radiation therapy for lung cancer.

Miscellaneous Lung Diseases with Associated Eosinophilia

Eosinophilia in blood and/or in BAL has been found in several conditions not associated with typical eosinophilic pneumonia. For example, some overlap can occur between organizing pneumonia and ICEP, with BAL eosinophilia (that is typically moderate in organizing pneumonia), foci of organizing pneumonia in ICEP or conspicuous eosinophils in organizing pneumonia at pathology, or evolution of untreated CEP to organizing pneumonia.

The eosinophilic inflammation of the airways that is typical of asthma plays a direct role in disease pathogenesis [245] and correlates with the severity of the disease [246]. Asthma is frequent in eosinophilic lung diseases, especially ABPA, ICEP, and EGPA. BAL has shown mildly increased levels of eosinophils (usually <5%) on differential cell count in asthmatics. The eosinophilic phenotype of asthma, with eosinophilic airway inflammation and often little or no increase in the peripheral blood eosinophil counts, is a marker of steroid-responsive disease and elevated exacerbation risk and may respond to anti-IL5 monoclonal antibodies [247]. Patients with asthma and high-level blood hypereosinophilia (i.e., >1.0 and especially $>1.5 \times 10^{-9}$) or alveolar eosinophilia (>25% and especially >40%), are considered to have "hypereosinophilic asthma" [248, 249]. These patients frequently require high-dose inhaled or even oral corticosteroids and should be monitored closely as they may progress to EGPA, ABPA, hypereosinophilic obliterative bronchiolitis, or ICEP.

Eosinophilic bronchitis (without asthma) is defined by a high percentage of eosinophils in the sputum with normal lung function and absence of bronchial hyperreactivity [250]; eosinophilic bronchitis is clearly distinct from asthma and from hypereosinophilic obliterative bronchiolitis, however it can cause chronic cough responsive to inhaled corticosteroid treatment [251], and rarely may evolve to irreversible airflow obstruction [252, 253]. Treatment with an antagonist of the eotaxin tissue receptor CCR3, the receptor for eotaxin and other chemokines, may be beneficial [254]. Eosinophilic bronchitis is distinct from bronchial asthma, although it may in rare cases.

Mildly increased levels of eosinophils may be found at BAL differential cell count or may be focally present histopathologically in the idiopathic interstitial pneumonias. In pulmonary Langerhans cell histiocytosis, the pathologic lesions consist of nodules with a bronchiolocentric stellate shape composed of Langerhans cells with variable numbers of eosinophils, especially in the initial active stage and at the periphery of the lesions. Eosinophilic alveolitis in lung transplant recipients may be indicative of acute rejection (tissue eosinophilia is involved in rejection after renal, cardiac, hepatic, and pancreatic transplantation). BAL eosinophilia of 2% or greater is associated with a poor outcome in lung transplantation [255], or may result from infection.

Clinical Vignette

A 32-year-old female, never-smoker, with an 8-year history of chronic rhinosinusitis with nasal polyposis and asthma for the last 4 years, was admitted for acute onset of dyspnea and skin manifestations. She had no history of allergic manifestations. The severity of asthma had increased over the past year, and montelukast had been prescribed 4 months ago by her general physician in addition to her long-term treatment with inhaled long-acting corticosteroids and bronchodilators. On admission, she presented with acute exacerbation of asthma, nasal obstruction with nasal crusts, asthenia, arthralgia, palpable purpura of the lower extremities, and neuropathy consistent with mononeuritis multiplex. The chest radiograph showed areas of ground glass opacity, with patchy peripheral bilateral alveolar consolidation on chest CT. The peripheral blood eosinophil count was 5.6×10^9/L. The differential cell count of bronchoalveolar lavage demonstrated 65% eosinophils, 4% neutrophils, 7% lymphocytes, and 24% macrophages. Skin biopsy showed leukocytoclastic vasculitis. Antineutrophil cytoplasmic antibodies were negative. Electrocardiogram, echocardiography, and serum troponine level were normal. Pulmonary function tests showed airflow obstruction, with marginal improvement with inhaled bronchodilators. The patient was diagnosed with eosinophilic granulomatosis with polyangiitis and was treated with oral prednisolone (1 mg/kg/day for 1 month then progressively tapered). Montelukast was discontinued. Complete remission was obtained. Three years later, the patient now complains of chronic rhinosinusitis, dyspnea on exertion with nonreversible moderate airflow obstruction despite high-dose inhaled anti-asthmatic therapy and 5 mg/day of oral prednisolone. There are no apparent systemic sequelae of her vasculitis. Peripheral blood eosinophils are 0.6×10^9/L despite oral prednisolone. Benralizumab is initiated, allowing rapid discontinuation of prednisolone and improvement in lung function tests.

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Langerhans Cell Granulomatosis and Smoking-Related Interstitial Lung Diseases

18

Carlo Vancheri and Silvia Puglisi

Introduction

Cigarette smoke contains a mixture of thousands of chemicals, including nicotine, chemical poisons, toxic gases, small particles, and carcinogens. This complex mixture of substances is a leading cause of preventable deaths, causing approximately 650,000 premature deaths each year in the European Union [1]. Inhalation of the toxic particles associated with cigarette smoking and the subsequent immune response leads to a variety of pathological manifestations. Cardiovascular diseases, Chronic Obstructive Pulmonary Disease (COPD), and lung cancer are the most frequent causes of smoking-related deaths [2]. Cigarette smoking has also been implicated as a major cause of interstitial lung diseases (ILDs). ILDs such as respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) and desquamative interstitial pneumonia (DIP), although considered by the current ATS/ERS classification to be idiopathic forms of ILD [3], are clearly associated with cigarette smoking and may be more appropriately defined as "smoking-related interstitial lung diseases" (SR-ILD). Another clinical entity causatively associated with smoking is Pulmonary Langerhans Cell Histiocytosis (PLCH) [4]. More than 90% of all PLCH reported cases and 85–90% of RB-ILD and DIP patients are smokers [4, 5]. In addition, several epidemiological studies have shown evidence for disease remission when smoking ceases [6]. In spite of that, the pathogenic mechanism(s) explaining the association between these diseases and tobacco smoke exposure have not been completely elucidated. Respiratory Bronchiolitis (RB) is a common histopathological finding in smokers, characterized by the accumulation of pigmented macrophages in respiratory bronchioles and alveoli. It has been postulated that a small proportion of smokers may develop an excessive response to smoke provoking interstitial and airspace inflammation as well as fibrotic thickening of the alveoli. These events can eventually lead to symptoms such as cough and dyspnea and to impaired lung function. RB-ILD is usually associated with a good prognosis with radiological and clinical resolution often occurring after smoking cessation; some cases with severe clinical involvement are often treated with corticosteroid therapy, albeit with unknown benefits. Similarly, DIP is characterized by macrophage accumulation in bronchioles and alveoli, although it is much more diffuse than seen in RB-ILD. DIP has a worse prognosis than RB-ILD, and is more often treated with corticosteroid therapy, despite the absence of controlled studies evaluating the efficacy of this approach. PLCH is characterized by the presence of bronchiolocentric interstitial lesions which form nodules that ultimately cavitate and evolve to form cysts, the predominant feature of the disease. PLCH has a good prognosis with smoking cessation alone, though chronic progressive disease or rapid clinical deterioration may sometimes require the use of chemotherapeutic agents. Although SR-ILDs have several distinctive histopathological and radiological features, mixed patterns of SR-ILDs may frequently coexist in the same patient. These observations support the concept that RB-ILD, DIP, and PLCH form a spectrum of interstitial patterns of lung injury related to cigarette smoke [7].

Acute Eosinophilic Pneumonia (AEP) has also been included in the SR-ILD group. Smoking may precipitate AEP in young adults with a recent onset of heavy tobacco use, as occurred among US military personnel deployed in Iraq. AEP is considered a rare disorder with only a few cases reported in the medical literature. It is a severe acute illness usually found in younger adults, although patients of any age can be affected. It is characterized by acute febrile respiratory failure, diffuse bilateral lung infiltrates on chest X-rays,

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and pulmonary eosinophilia. AEP mimics pulmonary edema on chest radiographs, with reticular opacities and interlobular septal thickening appearing in the earlier stages of the disease. These changes are apparent on HRCT, and patchy ground glass and consolidation appear as the disease progresses [8]. Idiopathic pulmonary fibrosis (IPF) and combined pulmonary fibrosis with emphysema (CPFE) are other diseases with a strong association with cigarette smoking. Of 607 patients with CPFE observed in different studies, 592 (98%) were either current or former smokers, whereas in IPF the prevalence of smokers or former smokers varies from 41% to 83% [9]. Although new studies are needed to better clarify the role of smoking in AEP, CPFE, and IPF, it is reasonable to list these diseases among those with a common etiologic factor, cigarette smoke.

Pulmonary Langerhans' Cell Histiocytosis

History and Classification

Langerhans' cells (LCs) belong to the family of dendritic cells but can be distinguished from other myeloid cells in this lineage by their tissue location, morphological features, and functional properties [10]. A medical student, Paul Langerhans, was the first to describe these cells in 1868 during his studies of tactile corpuscles in human skin [11]. Almost 100 years after Langerhans' original observations, LCs were linked to a heterogeneous group of disorders and clinical syndromes currently known as Langerhans' cell histiocytosis (LCH). In 1941, Farber recognized histologic similarities in three different diseases: Hand–Schuller–Christian disease, characterized by the triad of skeletal lesions, exophthalmos, and diabetes insipidus, Letterer–Siwe disease, a multiorgan disease of children affecting the liver, spleen, lymph nodes, lungs, and bones and eosinophilic granuloma defined as a solitary or multiple histiocytoses of bone [12]. In 1953, Lichtenstein gathered these three conditions under the term histiocytosis X, where "X" was referred to the unknown cause and pathogenesis of these diseases [13]. Many terms have been used to define histiocytosis X and its related conditions beyond the three above, including Hashimoto–Pritzker syndrome, self-healing histiocytosis, pure cutaneous histiocytosis, Langerhans' cell granulomatosis, Langerhans' cell granulomatosis, type II histiocytosis, and non-lipid reticuloendotheliosis. In 1961, Birbeck et al. studying the electron microscopic features of basal melanocytes and LCs in patients with vitiligo observed distinctive granules (Birbeck granules) in the cytoplasm of epidermal LCs, which remain among the most specific markers for these cells [11]. Langerhans cell histiocytosis (LCH) is part of a spectrum of other histiocytic disorders, characterized by aberrant accumulation of cells thought to be derived from dendritic cells or macrophages of different organs, often involved in granuloma formation.

The first classification of histiocytosis, published in 1987 by the Working Group of the Histiocyte Society, consisted of three categories: Langerhans cell (LC), non-LC-related, and malignant histiocytoses [14]. In light of recent insights, a new classification has been proposed for histiocytic disorders, dividing them into five groups based on clinical, radiographic, pathological, genetic, and/or molecular features [15]. These include: (1) the Langerhans family of Langerhans cells histiocytosis, Erdheim–Chester Disease and extracutaneous juvenile xanthogranuloma; (2) cutaneous and mucocutaneous histiocytoses, such as xanthogranuloma family, characterized by the presence of non-LCH localized to skin and/or mucosal surfaces; (3) the malignant histiocytoses, tumors with anaplastic histology and negativity for specific differentiation markers such as keratins, EMA, Melan-A, HMB45, B, and T lymphocyte markers; (4) Rosai–Dorfman disease and miscellaneous noncutaneous non-Langerhans cell histiocytoses; (5) hemophagocytic lymphohistiocytosis, a rare, often-fatal syndrome of intense immune activation characterized by fever, cytopenias, hepatosplenomegaly, and hyperferritinemia and macrophage activation syndrome, which often occurs in the setting of an underlying rheumatic condition. The first classification of the histiocytoses, published in 1987 by the Working Group of the Histiocyte Society, endorsed the term "Langerhans cell histiocytosis" to replace the term histiocytosis X and presented a new classification of histiocytic disorders divided into groups according to organ involvement [14]. This classification was made possible by the advent of high-resolution computed tomography (HRCT) that improved imaging and characterization of histiocytic lesions. Depending on the organs involved, LCHs may be categorized into a localized form, defined as "single-system disease," and a disseminated form known as "multisystem disease." Single-system disease is characterized by isolated involvement of lung, bone, or skin. Multisystem disease is subdivided into low-risk and high-risk groups, according to clinical course and response to treatment. This distinction is made because prognosis and treatment are closely linked to the extent of disease at presentation and whether or not "risk" organs (liver, spleen, lung, bone marrow) are involved. Isolated Pulmonary Langerhans' cell histiocytosis that primarily affects adult smokers, was categorized as an LCH variant, different from the severe and lethal pulmonary involvement seen in multisystem disease [16, 17].

Epidemiology

Precise data regarding the prevalence of PLCH are not available. Alston et al. estimated an incidence of five cases per

1,000,000 children aged 0–14 [18]. In a 5-year prospective study in 20 pulmonology centers in Belgium, 360 patients with interstitial pneumonia were identified, of whom 3% had PLCH [19]. During a 6-year period, Colby et al., identified 15 cases of PLCH compared with 274 cases of sarcoidosis among patients evaluated at a referral center [20]. A large epidemiological study was conducted by Aricò et al. with the aim to detect the incidence of LCH in a 1-year period among 13 countries. They found 274 adult patients with an LCH diagnosis: 31.4% (86 patients) were single-system LCH, including isolated pulmonary involvement in 44 patients; and 68.6% (188 patients) had multisystem disease [16]. A Japanese study of discharge diagnoses from a group of hospitals with more than 200 beds found 160 cases of PLCH over a 1-year period, with the prevalence of the disease estimated at 0.27 and 0.07 per 100,000 persons in males and females, respectively [21]. The widespread use of HRCT is increasingly identifying incidental cases of PLCH in asymptomatic patients, suggesting the prevalence of the disease is likely underestimated. The fact that many patients experience spontaneous remission and that histological findings are not always entirely diagnostic for PLCH also contribute to under-recognition. Accurate epidemiological data are not currently available regarding racial differences [17]. PLCH predominantly affects young adults, with a peak frequency between 20 and 40 years of age [22]. Although a marked male predominance was initially reported, more recent studies reveal similar proportions of males and females, or even a slight predominance of females, particularly in series from the USA. These differences probably reflect changing smoking habits over time. Abundant data support a causal relationship between cigarette smoke and PLCH in adults, revealing that at least 90% of adult patients who develop PLCH smoke tobacco or marijuana or were exposed to substantial second-hand smoke exposure. In addition, there is clear evidence of partial or complete resolution of the disease after smoking cessation [17, 23]. In current smokers, cigarette smoke induces macrophage recruitment and accumulation around small airways, interstitium, and distal airspaces in the lungs. One unresolved question relates to the observation that only a very small proportion of smokers develop PLCH, thus implying an involvement of endogenous host factors or additional exogenous factors. It is tempting to speculate that PLCH develops due to an amplified inflammatory response caused by tobacco smoke that induces activation of multiple inflammatory cells in the lung, resulting in a vicious cycle of inflammation, tissue injury, and tissue remodeling. It is still unknown whether failure of endogenous anti-inflammatory mechanisms or additional exogenous insults like viral infections plays a role in promoting smoking-induced PLCH and this continues to be an important area for future investigation [24]. It is important to note that PLCH has been reported in adult nonsmokers. In addition, epidemiological data reveal interesting differences in the incidence of isolated PLCH in children and adults. Isolated PLCH is less frequent in children than multisystem disease suggesting it is a different form of PLCH with no obvious correlation to cigarette smoke.

Pathogenesis

Despite decades of study, the pathogenesis of PLCH remains poorly understood and may be different from that of other LCHs. A central question concerning LCH is whether it represents a neoplastic process or is reactive process due to an as yet unidentified stimulus. According to Wilman et al., LCH has been shown to be a monoclonal proliferation of histiocytes, supporting a neoplastic origin [25]. However, another study suggests polyclonal expansion of LCs in the lungs of patients with PLCH. Yousem et al. [26] state that PLCH, in contrast to other forms of LCH, is characterized by a nonmalignant clonal evolution of LCs after being stimulated by smoking. In order to investigate clonality in PLCH, the X-linked polymorphic human androgen receptor assay (HUMARA) was applied in lung biopsies from female PLCH patients. LCs from pulmonary nodules were studied for differential methylation patterns at the HUMARA locus: 29% were clonal and 71% were non-clonal. The authors concluded that the smoking-induced form of PLCH is a biologically distinct histiocytosis variant that is more consistent with a reactive rather than a clonal proliferative process initiated by cigarette smoking in certain predisposed individuals [24]. In this model, the primary event induced by cigarette smoke is probably the recruitment and activation of LCs in the small airways. LCs are dendritic cells produced in the bone marrow, whose main function is antigen presentation to T-cells. LCs are morphologically different from other dendritic cells due to the presence in their cytoplasm of specific organelles involved in the internalization of exogenous substances, the Birbeck granules, which are visible by electron microscopy. In the normal lung, LCs are confined to the tracheobronchial epithelium and are only activated by danger signals. Their function is antigen presentation and migration to regional lymphoid tissues where adaptive immune responses are induced. They also play an important role in mediating tolerance toward inhaled antigens and in preventing unnecessary inflammation of the airways by innocuous antigens. It is important to note that increased numbers of LCs are found in other smoking-related lung diseases such as chronic obstructive pulmonary disease (COPD), other interstitial lung diseases, and lung cancer. These observations suggest that cigarette smoke may alter the physiologic turnover of dendritic cells in the lung, or may facilitate recruitment of LCs precursors. Cigarette smoke is also known to induce the production of a number of cytokines involved in

the recruitment and activation of LCs. One of the most important cytokines induced by cigarette smoke and studied in PLCH lesions is transforming growth factor-beta (TGF-β). This cytokine is produced by epithelial cells and macrophages and is involved in the processes that lead to tissue remodeling, fibrosis, and scar formation. Immunohistochemical studies show that TGF-β is overexpressed in PLCH lung biopsies. Tumor necrosis factor-alpha (TNFα) is also produced by epithelial cells and macrophages and has a critical role in activating LCs [24]. Granulocyte macrophage colony stimulating factor (GM-CSF) is another cytokine produced by epithelial cells and fibroblasts that modulates the distribution and differentiation of LCs. Tazi et al. showed that GM-CSF is abundantly expressed in the epithelium of bronchioles of patients affected by PLCH [27]. It is plausible that smoking-induced production of the three above-mentioned cytokines, in proximity to lung dendritic and LCs, results in continuous stimulation of these cells and their precursors, facilitating their local expansion in peribronchiolar regions. The relationship between smoking and PLCH was recently confirmed by gene expression studies on LCs obtained from tissues and bronchoalveolar lavage cells (BAL) of PLCH patients that spontaneously produce increased amounts of osteopontin. Osteopontin is a glycoprotein involved in cell-mediated immunity and pro-chemotactic activity for macrophages, monocytes, LCs, and dendritic cells. Prasse et al. demonstrated an augmented production of osteopontin in BAL cells from SR-ILD patients and not from other ILDs such as sarcoidosis or IPF, with the highest levels in PLCH and DIP. On the contrary, very low or undetectable osteopontin levels were observed in healthy smokers and healthy nonsmoking volunteers, suggesting that an increase in osteopontin production is not common to all inflammatory lung diseases but may instead be an indicator of a specific form of macrophage activation due to cigarette smoke. Cigarette smoke constituents may in fact stimulate the epithelium, increase the production of proinflammatory cytokines, including osteopontin, hence inducing the recruitment of alveolar macrophages and the differentiation of LCs. Differences in the concentration of cytokines and osteopontin in BAL cells from DIP-PLCH patients and healthy smokers remain incompletely understood [28]. Taken together, these data suggest that cigarette smoke acts as a direct stimulant of airway factors that promote the differentiation, activation, and survival of dendritic and LCs, supporting the hypothesis that cigarette smoke may directly promote pro-survival dendritic/LCs pathways [24].

The recent identification of an oncogenic BRAF-V600E mutation in more than half of all LCH cases represented a major advance in our understanding of the pathogenesis of LCH lesions [29], including PLCH lesions. BRAF-V600E mutations have been detected in circulating cell-free DNA extracted from peripheral blood plasma of PLCH patients using allele-specific real-time PCR or digital droplet PCR [30], a procedure called "liquid biopsy." Many other BRAF mutations, other than V600E, have more recently been identified in patients with PLCH [31–33].

The BRAF protein is a member of the serine/threonine kinase RAF family, and is a key component of the MAPK (RAS-RAF-MEK-ERK) signaling pathway that leads to the activation of transcription factors involved in cell growth and proliferation. BRAF V600E, the most common mutation in PLCH, is a major driver of human malignancies that result from downstream constitutive activation of MEK and ERK, including malignant melanomas and hairy cell leukemia [34]. However, BRAFV600E somatic mutation does not necessarily mean that LCH is a malignant disease because this mutation has also been observed in benign nevi [35]. Recent studies demonstrated BRAF V600E mutation in 38–57% of extrapulmonary LCH cases [29, 36]. Some studies have reported that BRAF-V600E mutation is more commonly observed in multisystem disease than in isolated disease. The presence of this mutation in children with LCH is associated with an increased risk of recurrence of systemic LCH, a high-risk disease (with risk organs) with increased resistance to first-line therapy [36, 37]. The second-most common mutated gene in LCH is MAP2K1, a member of the MAPK pathway, identified in ~50% of LCH patients with wild-type BRAF [38, 39]. Recently, activating NRASQ61K/R mutations have been described in PLCH, in some cases occurring concurrently with BRAFV600E mutations in different cell clones from the same patient [40]. A significant expression of the programmed cell death PD-1/PDL-1 immune checkpoint inhibitors and T-regulatory cells was shown to be present in the microenvironment of LCH lesions, and these markers were correlated with the presence of the BRAFV600E mutation [41].

In conclusion, it is possible to consider LCH as an inflammatory myeloid neoplasm with a variable clinical expression. Smoking probably plays a role in recruitment of circulating mutant myeloid cells and/or a triggering role in the development of lung inflammation by these cells.

Diagnosis

Clinical Features

Establishing a diagnosis of PLCH requires a high index of clinical suspicion. Physical examination findings are generally nonspecific and despite widespread involvement of the lung, symptoms can be relatively minor or absent, and patients often attribute their symptoms to smoking. In up to 25% of cases, the disease causes no symptoms and is only detected on routine chest radiography [42]. The most common respiratory symptoms are dry cough and, less frequently, dyspnea on exertion, that can be associated with

constitutional manifestations such as asthenia, fever, night sweats, and weight loss. Spontaneous pneumothorax resulting in chest pain leads to diagnosis in 10–20% of cases [43]. Pneumothorax is more common in young males, occurs at any time during the course of the disease, and may be bilateral and recurrent [17]. Hemoptysis is uncommon and should not be attributed to PLCH until other causes such as bronchogenic carcinoma or aspergilloma within a cystic cavity have been ruled out. Physical examination of the chest is usually normal, except in patients with pneumothorax, rib lesions, or advanced disease. Rales and/or digital clubbing are rarely present [24].

Extrathoracic Lesions

Although PLCH in adults generally presents as a single-system disease, symptoms due to extra-pulmonary localizations may be present in up 10–15% of patients. According to Tazi et al., bone lesions (20% of patients), diabetes insipidus with polyuria and polydipsia, resulting from infiltration of the posterior pituitary (5% of patients), and skin lesions are the most common extrapulmonary manifestations in PCLH (Fig. 18.1) [17]. History and physical examinations are essential to search for extrathoracic LCH involvement, as are skeletal radiographs including a dental panoramic, complete blood chemistry analysis to detect liver involvement and morning urine osmolality to screen for diabetes insipidus. Adult LCH commonly involves bones and may occur as a bone-limited disease (38%) or as a component of a multisystem disease (66%) [44]. Bone lesions manifest as pain or as a "mass" or "swelling" of the involved site.

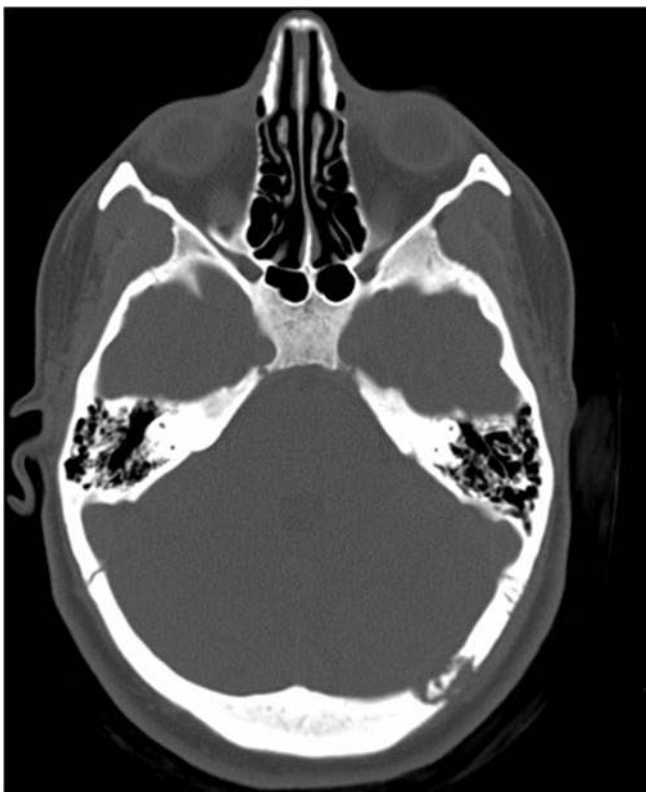

Fig. 18.1 Skull CT scan of a patient affected by PLCH. It shows two osteolytic bone lesions in the parietal bones and a bigger one in the occipital bone

Islinger et al. reviewed a series of LCH patients with bone lesions over a 58-year period which included 211 LCH adults. It was estimated that in adults, lesions of the skull occurred in 28% of cases, of the rib in 25%, of the pelvis in 8%, and of the spine in 3%. However, other sites can be involved in long bones and mandible [45]. The radiological appearance of bone lesions and clinical manifestations depends on the site involved and on the disease stage. Typically bone lesions are lytic or may have poorly defined borders, and in early stages are characterized by a more aggressive pattern of osteolysis. Chronic lesions may resolve completely with or without therapy, or develop a sclerotic appearance due to periosteal new bone formation. Bone lesions of the skull are lytic, round with defined margins and sometimes may contain a residual bone fragment. They may extend across suture lines, increase in number, or extend into adjacent soft tissue. Osseous lesions may evolve into epidural or epicranial soft tissue masses. Skull lesions can be asymptomatic or can cause headache and tenderness in the skull region involved while those of the mandible can destroy alveolar bone producing the radiological appearance of "floating teeth." Rib involvement is demonstrated by osteolytic areas, periostitis, and fractures. Sometimes, it is possible to find an extrapleural mass resulting from soft tissue extension, which causes pain. Pelvic involvement is characterized by poorly defined areas of osteolysis that develop well-defined sclerotic margins over time. Spine lesions are osteolytic and can cause the collapse of the vertebral body. In long bones, lesions are frequently intramedullary and diaphyseal and may appear aggressive. Treatment regimens differ widely and are often based on empiric observations. Surgical interventions such as curettage or total excision, radiotherapy, and chemotherapy have all been reported. Although treatment options for adults have never been validated by a clinical trial, studies in the literature compare the efficacy of different chemotherapeutic treatments. Cantu et al. studied 58 adult LCH patients with bone lesions at a site or as a component of a multisystem disease and described improvement or resolution of bone lesions in a majority of patients treated with radiotherapy, surgery, or chemotherapy (vinblastine/prednisone, 2-chlorodeoxyadenosine, and cytosine arabinoside) in comparison with corticosteroids alone [46]. Lair et al. also reported that radiotherapy is a safe and effective means for providing local control of LCH involving bones [47].

Another important extrapulmonary complication of LCH is pulmonary hypertension. It tends to be more severe in

PLCH than in other interstitial lung diseases, often characterized in later stages by dyspnea at rest and features of right-ventricular circulatory failure. Histopathologically, PH in PLCH is associated with intimal fibrosis and remodeling of both venous and arterial systems [48]. Dauriat et al. estimated that pulmonary hypertension is present in 92% of 36 patients evaluated for lung transplantation [49]. Because pulmonary hypertension is a poor prognostic indicator in PLCH, it is important to screen all patients, especially those with excessive dyspnea and normal lung function tests, by echocardiography [48]. In selected cases, cardiac catheterization is necessary to confirm PH. Once the diagnosis is made, therapy with vasodilators including phosphodiesterase inhibitors or endothelin receptor antagonists may be considered. Improved exercise capacity can be achieved with these agents, often with an objective reduction in pulmonary pressures, but arterial oxygenation can also worsen as a result of a greater imbalance in ventilation/perfusion due to the inhibition of hypoxic pulmonary vasoconstriction. Prostacyclin can cause severe pulmonary edema and should be used very cautiously in these patients because of the venous involvement. Le Pavec et al. reported their experiences with a group of 29 PH-PLCH patients treated with the usual pulmonary hypertension therapies: endothelin receptor antagonists, phosphodiesterase 5 inhibitors, or prostanoids demonstrating improvement in hemodynamics without oxygen worsening or pulmonary edema in most patients. Supplemental oxygen should be administered to maintain saturations greater than 90% with rest, exercise, and sleep, based on extrapolation from other diseases where the benefits of the therapy have been demonstrated. However, more studies are needed to evaluate safety and efficacy of all pulmonary hypertension treatments and management approaches in PH-PLCH [50].

The reported prevalence of central nervous system (CNS) complications ranges widely from 3.4% to 57% [51, 52] and can be subdivided clinically into two groups: the "mass lesion" forms presenting as space occupying lesions anywhere in the CNS; the "neurodegenerative" forms which are characterized by neural cell loss and pyramidal syndrome.

Typical LCH mass lesions may contain CD1a+ LCH cells, lymphocytes, and macrophages with histology similar to extracranial lesions, and usually involve the anterior and posterior hypothalamic pituitary regions, resulting in diabetes insipidus, growth hormone deficiency, and thyroid function abnormalities. Radiological findings include thickening and enhancement of the pituitary stalk with loss of the posterior pituitary bright spot; enlargement and enhancement of the pineal gland; thickening and enhancement of the choroid plexus; and intraparenchymal masses, usually characterized by a nodular pattern after contrast administration. A variable degree of atrophy of the cerebellum and midbrain has also been described [51]. Magnetic resonance imaging (MRI) may show tissue expansion or cystic changes in either the pituitary stalk or the pineal gland in up to 63% of patients [53].

"Neurodegenerative CNS LCH" is a syndrome of variable severity characterized by progressive clinical and radiological abnormalities that can occur at any point in the LCH disease course from the initial diagnosis to greater than 5 years later. The only histopathologic study available reported the absence of CD1a+ histiocytes, an inflammatory collection of CD8+ lymphocytes associated with neuronal and axonal degeneration [54]. Magnetic resonance imaging (MRI) may show increased T2-weighted MRI signal in the dentate nucleus of the cerebellum, basal ganglia, and pons and PET scanning may reveal decreased or increased FDG uptake in affected regions of the brain [55]. Clinically, ataxia, and tremors may be a consequence of cerebellar involvement. Rarely, patients may develop a progressive cerebellar syndrome, with spastic tetraparesis, pseudobulbar palsy, and cognitive deterioration [56].

LCH patients should be carefully evaluated for cerebellar, pyramidal, and bulbar deficits. Several rating scales have been proposed but not yet broadly approved for LCH patients, such as the Brief Ataxia Rating Scale (BARS) which includes a subset of five tests focusing primarily on coordination of gait, arm, leg, speech, and eye movements [57].

Very few studies are present in the medical literature and an optimal treatment for CNS localization of the disease has not been defined. Tin et al. have described a good response to vinblastine, used in other aggressive forms of LCH, in patients with CNS mass lesions with response rates of up to 70%. No effect of this therapy has been described on neurodegenerative lesions [58].

Pulmonary Function Tests

Pulmonary function test findings are variable in PLCH and the disease can be associated with a restrictive, obstructive, or mixed pattern. According to Tazi et al., the obstructive pattern is the most common. In this study, flow–volume curve alterations were present in 50% of patients, and the ratio of forced expiratory volume in 1 s (FEV1) to vital capacity (VC) was diminished in 20–30% of patients with recent onset of PLCH [17]. This pattern may be related to the bronchial involvement characteristic of smokers, or to bronchiolar obstruction due to peribronchiolar fibrosis or inflammatory infiltrates [17]. On the contrary, Crausman et al. described a restrictive pattern in 11 patients of a cohort of 23 patients with an early PLCH diagnosis. However, in advanced stages, a restrictive pattern usually predominates as lung fibrosis progresses [18, 59]. At the time of diagnosis, up to 20% of patients may have normal pulmonary function tests, while approximately 60–90% of patients have low diffusing capacity for carbon monoxide (DLCO). Blood gas values at rest may remain normal even in advanced disease, although increased A-a gradient and hypoxemia can occur in early

stages [17]. Canuet et al. correlated lung function with HRCT findings and found that the extent of cysts was closely associated with the impairment of both lung function and gas exchange. Interestingly, a predominantly nodular pattern, suggestive of an active inflammatory disease, has only moderate functional consequences [60].

Tazi et al. similarly described the correlation between lung function and HRCT lesions. They studied a group of 49 PLCH patients who experienced a deterioration of lung function in 60% of cases, including a decline of FEV1 in 40% of patients and a decline of DLCO in 50% of the patients. The DLCO reduction can herald the presence of pulmonary hypertension. However, according to other studies, the main lung function defect is airway obstruction and this finding is consistent with the bronchiolar localization of pulmonary LCH lesions. Increased profusion of cysts on HRCT scans correlated with a deterioration in lung function parameters. Serial lung function tests are the preferred method to monitor progression of disease to limit exposure to radiation [61].

Chest Radiography

Most patients with PLCH exhibit chest radiographic abnormalities. In the earlier stages of the disease, it is common to find small nodules that typically range from 1 to 10 mm in diameter and have a bilateral and symmetric distribution on chest radiography. These nodules are characterized by irregular borders and may be single or coalescent. The distribution of nodules is typically limited to upper/middle lung zones with sparing of the lung bases, especially in the costophrenic sulci. As the disease progresses, reticulonodular abnormalities and cystic changes may predominate. As cysts become more numerous, nodules tend to diminish in number [11]. End-stage PLCH is characterized by reticular areas of opacity that may progress to honeycomb lung and contiguous cystic cavities up to 2 cm diameter resulting in patterns that can mimic the radiographic appearance of advanced emphysema or LAM. LAM and end-stage PLCH are the two forms of ILD that can produce hyperinflation rather than reduced lung volumes on CXR and PFTs [62]. Pneumothorax is known to be a complication of PLCH and may occur in the absence of other radiographic pulmonary abnormalities. Chest radiography has limited sensitivity and specificity for the detection and characterization of interstitial lung diseases, and in some cases of PLCH, chest X-ray may even appear to be normal. Khoor et al. reported a rare presentation of PLCH in a 45-year-old male cigarette smoker on chest radiography as a solitary pulmonary nodule. Biopsy showed the histologic and immunophenotypic characteristics of PLCH [63]. Twenty-one years after excision of the sentinel nodule, a new contralateral lung nodule appeared which remained unchanged during 36 months of observation. Another notable radiographic finding in PLCH is pulmonary artery prominence, due to pulmonary hypertension that may occasionally complicate PLCH [63].

High-Resolution Computed Tomography (HRCT)

HRCT is superior to routine chest radiography in demonstrating the morphology and distribution of lung abnormalities. Patterns differ widely based on the stage of PLCH. In the early stages of the disease, a pattern defined by the presence of multiple nodular opacities measuring 1–5 mm in diameter or larger is often found [64]. Nodule sizes greater than 10 mm in diameter are unusual [65]. These small nodules, which are not typically apparent on chest X-rays, are characterized by irregular margins surrounded by normal lung parenchyma (Fig. 18.2). They may be profuse and are generally solid, although cavitation may occur over time.

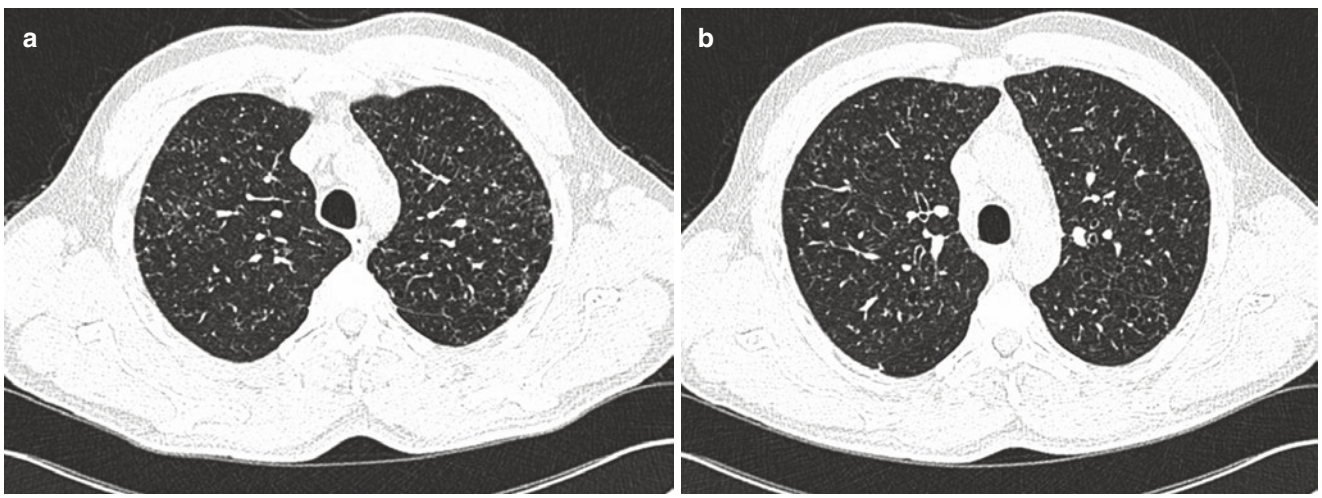

Fig. 18.2 HRCT of the lungs of a patient affected by PLCH, showing a predominant nodular pattern. Centrilobular and peribronchiolar nodules and present (**a**), some of which are cavitated (**b**)

However, the predominant characteristic of lung nodules is their distribution, with a topographical predominance in the upper and middle lung zones with relative sparing of the lung bases. Most nodules show a centrilobular or peribronchial distribution, reflecting the bronchiole-centered localization of PLCH lesions in histopathologic studies. Brauner et al. has proposed a temporal progression of these pulmonary nodules into cavitary nodules and then into cysts [64], with serial scans revealing a decreasing preponderance of nodules and an increasing number of thin-walled cysts. Cystic lesions tend to be small and thick walled initially, with diameters of less than 10 mm, and then become larger and thinner walled, with diameters up to 20 mm. Conceptually, cyst formation can develop due to cavitation within a centrilobular nodular lesion or to increasing bronchiolar dilatation from granulomas destruction and fibrosis at the lesion margin. Cyst distribution is most prevalent in upper lung zones where they can appear as round or ovoid spherical spaces or with bizarre shapes that result from coalescence of adjacent cysts (Fig. 18.3a–c). Some of these cystic spaces reach diameters of up to 80 mm. Advanced disease is characterized by architectural distortion by cysts with few nodules [66], while late-stage disease is marked by the presence of large areas of honeycombing, predominantly in the upper lung zones. Some studies have described full or partial resolution of lesions occurring in patients with nodular lesions, indicative of reversibility, while cystic lesions remain unchanged or worsen with time [67]. Soler et al. compared the nature of the findings on CT scans with those of lesions on biopsy samples in PLCH patients. They found that early-stage PLCH histopathological lesions consisted of florid granulomas that were composed of typical LCs associated with macrophages and inflammatory cells, particularly lymphocytes and eosinophils. In more advanced disease, necrotic granulomas were found in pulmonary samples, characterized by a prominent central cavity and few fibrotic changes, but still numerous LCs and inflammatory cells in their walls. In these cases, few cavitated nodules or thin-walled cysts were seen on CT scans. In late-stage PLCH, fibrous cysts of variable size, demarcated by a

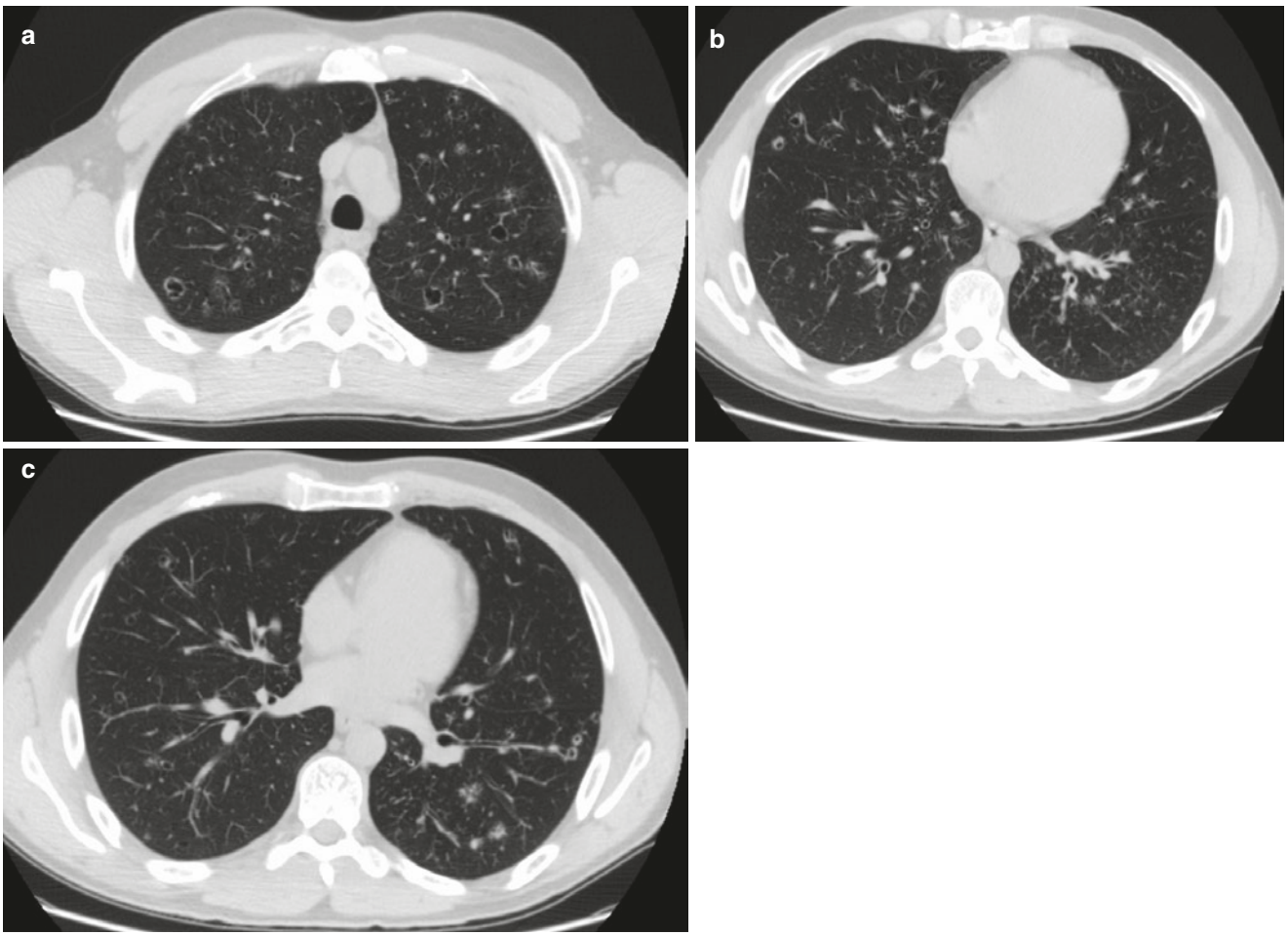

Fig. 18.3 HRCT of the lungs of a patient affected by PLCH showing a predominant cystic pattern. The cysts are characterized by variable wall thickness and bizarre shapes (**a**). Centrilobular and bronchiolocentric nodules are present, some of which are starting to cavitate (**b**, **c**)

fibrous ring of variable thickness, and containing no LCs and few or no inflammatory cells, were usually found [68]. Kim et al. studied a cohort of 27 PLCH biopsy-proven patients, evaluating HRCT and histopathological findings at the time of surgical lung biopsy. The predominant CT pattern was represented by centrilobular nodules (ten patients) corresponding to peribronchiolar granulomas with LCs on biopsy. Nodules were typically present on upper lung zones with a random distribution. Thick- and thin-walled cysts and bizarre-shaped cysts were present in four, eight, and five patients, respectively, most with a predominant distribution in the upper lung zones and characterized by a central cavity surrounded by a thin wall of LCs and eosinophils. These studies suggest that while it is possible to conclude that a nodular pattern on CT scans reflects histopathologically active PLCH disease, no correlation is possible between histological and radiological findings in cyst predominant disease because HRCT cannot differentiate between fibrous cysts and cavitary granulomas [67]. Canuet et al. reported that the distribution of cysts was closely associated with an impairment of both lung function and gas exchange. A dominant nodular pattern suggestive of active inflammatory disease has only moderate functional consequences, while a cyst predominant pattern was strongly correlated with lung function parameters [60]. Nodular changes may be present in several other lung diseases including sarcoidosis, silicosis, tuberculosis, RB-ILD, hypersensitivity pneumonitis, or metastatic disease [68], which can represent a dilemma. Although all of these conditions are associated with a centrilobular nodular pattern on CT scans, the relationship of nodules to other pulmonary structures and their distribution can be an aid to a correct diagnosis. A perilymphatic distribution with nodules in interlobular septa, peribronchovascular and subpleural spaces is typical of sarcoidosis. A random distribution of nodules within secondary pulmonary nodules is characteristic of miliary tuberculosis and hematogenous metastases. In some cases, a halo of ground glass attenuation characteristic of metastatic nodules can be useful to differentiate them from PLCH nodules. In other cases, only lung biopsy can discriminate between them [69]. When only cysts are seen on the CT scan, the differential diagnosis includes idiopathic pulmonary fibrosis (IPF), emphysema, bronchiectasis, and lymphangioleiomyomatosis (LAM). When honeycombing is present, defined as the presence of air-filled cystic spaces that often predominate in a peripheral subpleural location, the primary differential is between IPF and PLCH. These cysts can be of different sizes with wall thicknesses between 1 and 3 mm, consisting of fibrous tissue lined by bronchiolar epithelium, which is shared by adjacent cysts. This radiographic pattern is most typical for honeycombing and is not seen in cysts that are found in PLCH. In addition, honeycombing is often associated with other findings of pulmonary fibrosis such as reticular opacities, irregular subpleural and peribronchovascular thickening, and traction bronchiectasis, while PLCH cysts are surrounded by normal lung zones. The most important difference between the two entities remains the sparing of lower lung zones in PLCH, while IPF is characterized by a predominantly basilar distribution of the cysts. Pulmonary emphysema is defined as a permanent, abnormal enlargement of airspaces distal to the terminal bronchiole accompanied by the destruction of the alveolar walls. It is usually easy to differentiate PLCH from emphysema by the walled off focal areas of low attenuation that are found in PLCH, contrasting with hyperlucent regions without walls surrounded by normal lung parenchyma in emphysema [64]. Bronchiectasis is localized, irreversible bronchial dilatation, bordered by a thickened bronchial wall that may be mistaken for cystic airspace disease when viewed in cross-section. It can be differentiated from cystic lung disease by the presence of an adjacent blood vessel suggesting a bronchovascular unit rather than a cystic air space, and by stepping through adjacent HRCT sections that demonstrate continuity of the cystic space with an airway [70]. LAM is characterized by the presence of thin-walled cysts of variable size from 2 to 40 mm diameter on HRCT. Vessels can be seen at the periphery of the cysts, unlike emphysema where vessels may be found in the center of the lesion. The most important difference between LAM and PLCH lies in the distribution of cysts, with LAM cysts involving all regions of the lungs in a uniform pattern without sparing the costophrenic angles [70, 71].

Positron emission tomography with ^{18}F-fluorodeoxyglucose has a limited value in the assessment of patients with PLCH. Only 20–25% of patients show higher ^{18}F-fluorodeoxyglucose uptake in the lungs, particularly in thick-walled cysts and nodular lesions. Krjicek et al. reported in a small series that PET scan imaging cannot reliably distinguish between the benign inflammatory nodular lesions of PLCH and malignant lesions [72–74].

Bronchoscopy and Bronchoalveolar Lavage (BAL)

Bronchoscopy is a well-tolerated procedure that can provide useful information for the correct diagnosis of PLCH. In PLCH, the bronchial tree is usually either normal on gross examination or reveals signs of nonspecific inflammation due to smoking and the bronchoalveolar lavage fluid of may exhibit an increased number of cells with a marked predominance of alveolar macrophages, a decreased CD4/CD8 ratio or increased levels of eosinophil cells. These features are also often present in the BAL fluid of smokers where there is no evidence of interstitial lung disease. LCs identified by staining with antibodies against CD1a and S-100 antigens on the cell surface have been proposed as PLCH markers. Casolaro et al. have demonstrated the presence of LCs in the bronchoalveolar lavage of smokers without interstitial lung

diseases, concluding that cigarette smoking is associated with an expansion in the population of LCs on the epithelial surface of the lower respiratory tract [75]. In addition, Tazikawa et al. have described the presence of LCs in patients affected by idiopathic pulmonary fibrosis, sarcoidosis, and other fibrotic lung disorders so it would seem that LCs in bronchoalveolar lavage are not specific for diagnosing PLCH [48]. However, Tazi et al. demonstrated that even if an increased level of LCs may be present in other pulmonary diseases, a threshold of 5% LCs ensures adequate specificity, although the sensitivity remains quite low (<25%) [17]. Smetana et al. demonstrated the presence of another cell surface marker in the BAL fluid of PLCH patients named Langerin (CD207), which is specific for LCs present in the skin and in the epithelia of small airways and bronchioles. They compared the percentage of CD1a and Langerin positive cells in PLCH with other fibrotic lung disorders such as sarcoidosis and IPF, and found they were almost identical in all the tested cases. This result highlights the potential utility of Langerin for improving the usefulness of BAL in the diagnosis of PLCH [76], although the true diagnostic potential has yet to be assessed in clinical studies. Bronchoalveolar lavage rarely establishes a definitive diagnosis of PLCH in adults with ILD, but can be helpful in the differential diagnosis of infectious diseases characterized by the presence of excavated nodules, such as *Pneumocystis jiroveci* pneumonia.

Lung Biopsy

Transbronchial lung biopsy has a limited role in the diagnostic workup for PLCH as confirmed by Vassallo et al. in a study of 102 patients with histological diagnoses of PLCH. Among 29 patients who underwent transbronchial lung biopsy, the findings were diagnostic only in six patients [77]. However, transbronchial lung biopsy remains useful for differential diagnosis by excluding other disorders, such as sarcoidosis. Even if the HRCT is suggestive of PLCH in the great majority of patients with typical clinical manifestations, some cases are difficult to interpret. In patients with systemic symptoms and cavitated pulmonary nodules, patients with suspected pulmonary metastases or in female patients in differential diagnosis with LAM, a definitive diagnosis often requires pulmonary biopsy. In cases in which the diagnosis is uncertain, surgical biopsy may permit a diagnosis of PLCH demonstrating the presence of the characteristic lesions. However, lung biopsy should not be performed in patients with extensive destructive lesions given the increased procedural risk in patients with limited pulmonary reserve [17]. In a patient with suspected PLCH and an extrapulmonary lesion with compatible HRCT findings, a diagnosis may be provided by a biopsy of the lesion. However, a majority of adults have isolated PLCH, which requires a surgical lung biopsy using video-assisted thoracoscopy or open thoracotomy for a definitive diagnosis. Since the lesions are focal, the specimens should be sufficiently large to avoid sampling error, preferably from 2 to 3 different areas of the lung. Lung biopsy is not considered necessary when HRCT findings are characteristic and concordant with the clinical history [68]. With the discovery of BRAF mutations and their evolving role in the prognosis and treatment of LCH, the importance of lung biopsy is now being reconsidered, even for those for whom a confident clinical diagnosis is possible through noninvasive means.

Pathology

Gross lung tissue specimens in PLCH may exhibit different features according to the stage of the disease at the time of biopsy. In the earlier stages, nodules appear as focal lesions with irregular and stellate borders. In advanced disease phases, the predominant finding is a hyperinflated lung with cysts and honeycomb formation [68]. On microscopic examination, the characteristic early lesions in PLCH are localized to terminal and respiratory bronchioles and are composed of activated LCs organized into loose granulomas containing lymphocytes and inflammatory cells including eosinophils and macrophages (Fig. 18.4a, b) [10]. The morphology of LCs found in these inflammatory nodular lesions is generally similar to that of LCs in normal tissues: they are medium sized cells with elongated nuclei, and display multiple cytoplasmic extensions and pale cytoplasm which contains few phagocytic vacuoles. A definitive identification of LCs in these inflammatory lesions is possible by immunohistochemical staining with monoclonal antibodies directed against the membrane antigen, CD1a (Fig. 18.5), or by the identification of Birbeck granules, identifiable through electron microscopic visualization. Birbeck granules are intracytoplasmic organelles that may be involved in the intracytoplasmic transport of antigens captured by LCs. The histology of PLCH granulomas varies according to the particular stage of the disease, even if lesions of different ages can be found in the same lung biopsy specimen. The lesions are focal, poorly demarcated, and separated by apparently normal lung parenchyma. They are centered on the terminal and respiratory bronchioles and destroy the airway walls, giving the impression that PLCH pathogenesis is more closely aligned with a bronchiolitis than a diffuse infiltrative lung disease. At this stage, LCs form a compact central granuloma surrounded by variable numbers of lymphocytes, eosinophils, and macrophages, which extend to adjacent alveolar structures. This lesion may evolve forming a cavity

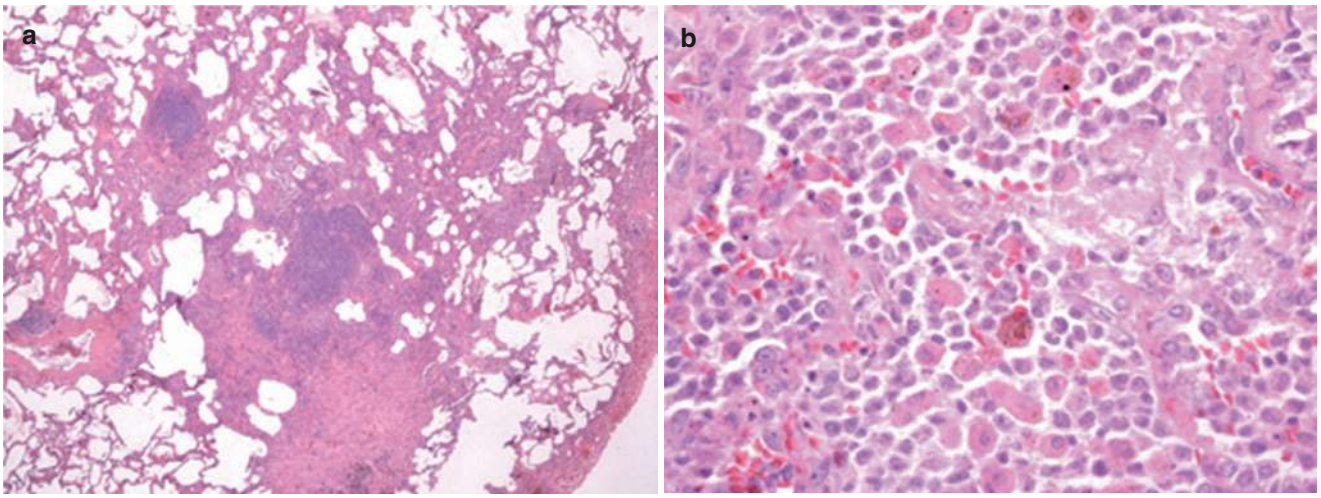

Fig. 18.4 LCH with centrilobular nodules with irregular margins (**a**) and aggregates of Langerhans cells together with golden macrophages and eosinophils (**b**). (Courtesy of Professor G. Rossi. University of Modena-Reggio Emilia, Italy)

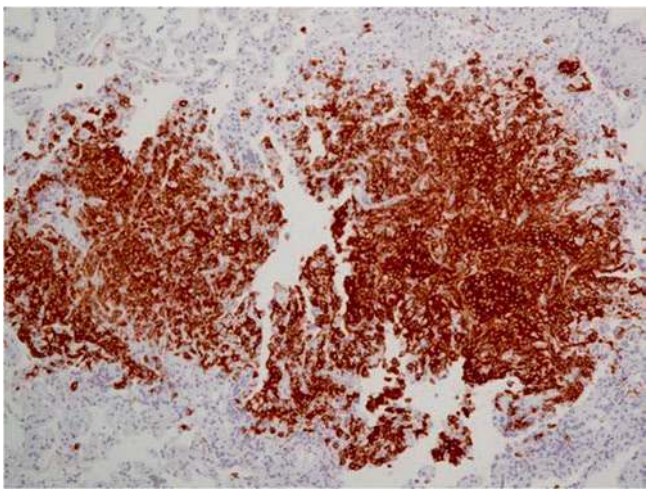

Fig. 18.5 Immunohistochemistry for CD1a highlights Langerhans cells. (Courtesy of Professor G. Rossi. University of Modena-Reggio Emilia, Italy)

that results from the expansion of the lumen of a bronchiole damaged by granulomatous reaction. PLCH granulomas are poorly demarcated and extend in adjacent alveolar structures that often contain pigmented macrophages, producing RB-ILD-like changes or a desquamative interstitial pneumonia-like pattern. In lesions of intermediate age, there are few LCs, while lymphocytes, macrophages, and neutrophils are still present in LCH granulomas. In late-stage lesions, LCs are almost absent and there are more macrophages containing pigment or lipid inclusions [10]. The lesions are then replaced by stellar fibrotic scars or by confluent adjacent cysts. Interestingly, in uninvolved areas, the lung structure seems to be normal or characterized by common smoking-related abnormalities, such as respiratory bronchiolitis and increased levels of pigmented macrophages infiltrating the bronchiole walls [17].

Treatment

The recruitment of a sufficient number of patients for controlled therapeutic trials has been hampered by the low incidence of PLCH and its relative clinical stability. To date, no randomized trials of therapy for adult PLCH have been reported. All data regarding the effectiveness of PLCH treatment are derived from observational studies, case reports, and expert opinions. The association between PLCH and smoking suggests that cigarette smoke plays a role in the pathogenesis of the disease. Therefore, it is imperative that patients stop smoking and this should be encouraged by clinicians, especially in heavy smokers, through smoking cessation programs, tobacco replacement therapy, and other means [17]. Some case reports have shown that interventions that eliminate smoke exposure can lead to an improvement in the clinical and radiographic findings or even in the resolution of the disease [50]. Mogulkoc et al. described two cases of PLCH in smokers characterized by the presence of nodules, some of which were cavitated or formed small cysts on CT scans and by a reduced DLCO. After smoking cessation, there was an objective radiological improvement with reduction of nodules and functional improvement with an increase in DLCO [23]. Similarly, Negrin-Dastis [78] described a PLCH case with total regression of radiological lesions after 12 years of smoking cessation. Because of the rarity of PLCH and the unpredictable course of the disease, there are

no reliable data regarding the efficacy of smoking cessation on disease resolution. Tazi et al. [79] reported four smokers with biopsy-proven PLCH who experienced disease regression after smoking cessation but who subsequently developed reactivation with the appearance of new nodules on CT scans that were empirically treated with corticosteroid therapy. However, other studies provide contrasting data, describing cases where the disease has worsened despite smoking cessation [79, 80] and recently Tazi et al. have reported that smoking cessation did not modify the pulmonary LCH outcomes in a group of 49 LCH adult patients [61]. Finally, it is well established that the disease can improve spontaneously and there is, as yet, no definitive proof that smoking cessation affects the outcome of the disease. Nonetheless, smoking cessation is considered as a first step in the treatment of PLCH. Failure to prevent the progression of the disease by this means is generally followed by a trial of steroid treatment. The rationale of using corticosteroids, especially in the early stages of the disease in which nodular lesions are the predominant features, is based on the possibility of accelerating the resolution of the associated granulomatous and inflammatory processes. In advanced stages, the presence of fibrosis may explain the lack of response to therapy that is often observed with steroids. On this basis, it has been suggested that corticosteroid therapy is promising for treatment of symptomatic PLCH with a predominant nodular pattern on HRCT scans. Usually prednisone or prednisolone are administered at a starting dose of 0.5–1 mg/kg/day tapered over 6–12 months [17]. In a group of 42 PLCH patients treated with corticosteroids, Schonfeld and coworkers demonstrated clinical and radiographic improvements, although they did not observe any significant changes in respiratory function [81]. If disease progression occurs in spite of a 6-month period of steroid treatment, chemotherapy may be considered. The cytotoxic agents that have been used for treatment of PLCH include vinblastine, mercaptopurine, cyclophosphamide, or more recently, cladribine (2-chlorodeoxyadenosine).

In the 1960s, chemotherapy was used to treat LCH in children because it was thought to be a malignant process. Single agents such as methotrexate, 6-mercaptopurine, vinblastine, and vincristine were initially and successfully used in pediatric patients and these encouraging results led to new trials. Different perspectives were explored in randomized trials conducted by the Histiocyte Society: in the first study, the efficacy of vinblastine or etoposide in combination with prednisolone was compared. For 24 weeks, patients were treated vinblastine (6 mg/m^2) intravenously every week, or etoposide (150 mg/m^2/day) intravenously for 3 days every 3 weeks, followed by a single initial dose of corticosteroids. There was no difference in survival or disease reactivation rates with this regimen, but the absence of response after 6 weeks of treatment was presumed to be related to poor prognosis with increased mortality. The second trial conducted by the Histiocyte Society was carried out on 193 randomized LCH children divided into two groups, the first group receiving vinblastine, prednisolone, and mercaptopurine, the second receiving the same therapy with the addition of etoposide. The dosage was as follows: first group, initial treatment of continuous oral prednisone (40 mg/m^2 daily in 3 doses for 4 weeks tapering over 2 weeks) and vinblastine (6 mg/m^2 intravenous bolus weekly for 6 weeks); while the second group received the same therapy with the addition of etoposide (150 mg/m^2/day, 1-h infusion weekly for 6 weeks). At the sixth week, the maintenance therapy was 6-mercaptopurine (50 mg/m^2 daily orally) and pulses of oral prednisone (40 mg/m^2 daily in 3 doses, Days 1–5) and vinblastine (6 mg/m^2/day once every 3 weeks) in the first group, while the second group received vinblastine in addition every 3 weeks. The total duration of treatment was 24 weeks. This trial demonstrated that more intensive treatment increases response rates and reduces mortality from LCH [82]. The Histiocyte Society conduced its third clinical trial with the aim of assessing whether the addition of methotrexate to prednisolone and vinblastine and increasing treatment duration to 12 months could reduce relapse rates. Even though all of these studies were performed on pediatric populations, they suggest that these agents may have a role in the treatment of LCH in adults with pulmonary and/or multisystemic involvement (considering PLCH as a single-system disease with a "risk organ" involvement) [83]. In multisystem LCH, which is often refractory to treatment and characterized by frequent relapse, there is no standard salvage regimen. Recently, however, cladribine has been used as a second-line treatment for both children and adults with good response. Cladribine is a purine nucleoside analogue with selective toxicity to lymphocytes and monocytes, which acts by interfering with single-stranded DNA repair and synthesis in lymphocytes and monocytes. Aerni et al. described a case of LCH with pulmonary involvement that responded well to cladribine treatment, suggesting the possibility of its use in selected cases [84].

Similarly, Grobost et al., in a small series of five patients reported cladribine efficacy, as a single agent, in the treatment of PLCH patients with nodular lung lesions and/or thick-walled cysts providing that a diffuse hypermetabolism on positron emission tomography (PET)-scan was observed [85].

Other therapies have been proposed for LCHs, including oral acitretin, which is a Vitamin A analogue. Derenzini et al. treated a group of seven patients, three suffering from multisystem and four from single-system LCH, with MACOP-B. This chemotherapy regimen is used for non-

Hodgkin lymphoma and consists of a combination of prednisolone, vincristine, bleomycin, methotrexate, doxorubicin, and cyclophosphamide. A 100% response rate in all seven adult patients was reported [86].

Bisphosphonate therapy can also be effective for treating LCH bone lesions [87, 88]. A nationwide survey from Japan described 16 children treated with bisphosphonates for bone LCH. All children had bone disease; none had risk-organ disease. Most patients received six cycles of pamidronate at 1 mg/kg per course given at 4-week intervals. In 12 of 16 patients, all active lesions including skin and soft tissues resolved. Although bisphosphonates are used for bone LCH, some publications report response in other organs, such as skin [29]. The discovery of BRAF and MAP2K1 mutations in LCH has led to targeted therapies acting upon the RAS/RAF/MEK/ERK pathway. Approximately, 60% of LCH cases harbor the somatic mutation that produces the oncogenic BRAF V600E variant [29]. Most of the 40% of cases not expressing BRAF V600E have other genetic alterations including those that result in structural rearrangements of BRAF, and mutations in other components of the pathway, such as MAP2K1 [38]. The pathogenetic role played by these alterations in LCH is confirmed by the clinical responses to targeted inhibitors of BRAF or MEK1 (the product of the MAP2K1 gene) seen in LCH cases carrying activated mutations of those targets [89].

Resistance to BRAF inhibitors has been reported commonly in malignancies in adults but only very rarely in the histiocytoses. The approach of combining a BRAF inhibitor with a MEK inhibitor has been investigated in adult malignancies and may be a future consideration for treatment of LCH. An ongoing international trial is addressing this by testing the combination of dabrafenib and a MEK inhibitor, trametinib, in adults and children with refractory or relapsed LCH. *BRAF* V600E mutations can be targeted in different ways by BRAF inhibitors (vemurafenib and dabrafenib) or by the combination of BRAF inhibitors plus MEK inhibitors (dabrafenib/trametinib and vemurafenib/cobimetinib). These combinations are already approved in different contexts such as melanoma [90, 91].

Small series and anecdotal case reports of refractory and relapsed BRAFV600E-mutated LCH have shown responses to the BRAF inhibitors, vemurafenib, and dabrafenib [92].

Vemurafenib (VMF), a BRAF (v-RAF murine sarcoma viral oncogene homolog B) inhibitor originally approved for metastatic melanoma [93], was approved by the European Medicines Agency as an orphan drug for refractory LCH [94]. VMF monotherapy is administered orally (10 mg/kg twice a day) for at least 8 weeks. The main adverse events include severe cutaneous toxicity, cardiac toxicity, squamous cell carcinoma and, more rarely, secondary pancreatic cancer.

Bhatia reported about 11 patients with Erdheim–Chester disease (ECD) or ECD/LCH harboring the *BRAF*V600E mutation treated with the single-agent dabrafenib following the failure of chemotherapy or radiation, or following discontinuation of vemurafenib therapy because of toxicity or intolerance. Surprisingly, responses were observed in the central nervous system, a site of disease often refractory to other treatments [95].

It is important to note that PLCH treatment is not yet standardized, and to date the data regarding the effectiveness of treatment are derived from observational studies, case reports, and expert opinions. More studies are needed regarding more effective and less toxic treatments.

Another important treatment to be considered is pleurodesis in cases of recurrent pneumothorax due to rupture of cystic lesions. Mendez et al., demonstrated the superiority of pleurodesis to tube thoracostomy alone in preventing ipsilateral recurrence of pneumothorax [96].

Lung transplantation is performed in selected patients with progressive disease that is refractory to other forms of treatment, including patients with severe pulmonary hypertension unresponsive to vasodilator therapy, and when severe respiratory failure develops. Etienne et al. performed lung transplantation in seven adult LCH patients and observed resolution in five of these patients, while the other two have suffered recurrence of LCH in the grafted lung. These two patients resumed smoking after transplantation and had extrapulmonary localization of the disease at baseline [97]. A retrospective multicenter study of 39 patients who underwent lung transplantation for end-stage PLCH described a recurrence rate in the allograft as high as 20.5%. The presence of extrapulmonary disease before transplantation and a resumption of smoking post transplantation have been described as risk factors for recurrent disease. These risk factors for recurrence should be considered in evaluating candidacy for transplant [49].

Course and Prognosis

PLCH is has an unpredictable natural history in the individual patient ranging from an asymptomatic and stable course to a progressive debilitating disease that leads to respiratory failure and death over a period of months. The ability to identify patients with poor prognosis would facilitate difficult decisions regarding the benefit of aggressive treatment early in the course of disease.

Established prognostic factors in LCH include disease extent at diagnosis, the presence of risk organ dysfunction, and early response to therapy. According to Delobbe et al., older age, lower FEV1/FVC ratio at diagnosis and prolonged corticosteroid therapy suggest an adverse prognosis [98]. However, in this study, the diagnosis of PLCH was not

confirmed by lung biopsy and some patients included were children. Other studies in literature suggest that PLCH patients are at increased risk of developing bronchogenic carcinoma and hematological malignancies, although such occurrences may be merely coincidental [99]. In a more recent study, Vassallo et al. studied a cohort of 102 PLCH patients and reported a median survival of 12.5 years, demonstrating that adult patients affected by PLCH have a shortened survival compared to the general population. Reduced DLCO or severe COPD due to concomitant cigarette smoking were considered as possible negative prognostic factors [77]. Pulmonary hypertension is an unrecognized complication of PLCH that is associated with poor prognosis [100]. Thus, it is important to estimate pulmonary hypertension by echocardiography at the time of diagnosis and afterwards in follow-up controls. When pulmonary hypertension is suspected on the basis of echocardiography, and especially when the estimated PAP is higher than 40 mmHg, a cardiac catheterization is warranted to confirm and define the severity of pulmonary hypertension [24]. Multiorgan involvement may be characterized by poor prognosis and for correct management of PLCH is necessary to investigate other possible organs involvement. The diagnostic approach to these patients should include skeletal X-rays to show possible bone disease and gadolinium-enhanced magnetic resonance imaging of the brain to identify potential involvement of the hypothalamic region. In recent years, fluorodeoxyglucose (FDG) PET scan imaging has been proposed to differentiate malignant pulmonary nodular lesions from benign ones. However, false-positive FDG-PET scan has been demonstrated in other conditions such as active infections, noninfectious inflammatory processes, benign neoplasms, and interstitial lung diseases such as sarcoidosis. In a cohort of 11 patients with PLCH diagnosis, PET-scan-positive patients had predominantly nodular lung disease, while PET-scan-negative patients had mainly cystic lung changes. However, it was not possible to distinguish between the benign inflammatory nodular lesions of PLCH and malignant lesions because the pulmonary nodules, and some cystic lesions, can demonstrate standardized uptake value (SUV > 2.5) similar to malignant lesions [72]. Phillips et al. compared both the capacity of different imaging techniques to determinate the extent of LCH and the effectiveness of therapy. A decreased FDG uptake following therapy suggested a role for FDG-PET in detecting disease activity and early response to therapy with greater accuracy than other imaging modalities in patients with LCH affecting bones and soft tissues [101]. However, it is necessary to have more prospective data to guide the clinical use of FDG-PET in the diagnosis and follow-up of LCH. After PLCH diagnosis is made, it is important to follow the course of the disease carefully, evaluating clinical parameters, chest radiography or (better yet) HRCT, and pulmonary function, initially at intervals of no more than 6 months. HRCT scanning has proven to be useful in understanding the evolution of the pathological lesions, as confirmed by the study of Soler et al. in which a correlation between the extent of nodular abnormalities and the density of florid granulomatous lesions in lung tissue was demonstrated. Long-term follow-up of PLCH patients is recommended because even after years of apparent quiescence, lung function can deteriorate and new nodular lesions can occur, due to reactivation of the disease [68]. Case reports of PLCH in pregnant women have been reported. Pregnancy does not seem to influence the course of the disease, except for the appearance of exacerbations of LCH-related diabetes insipidus. Pregnancy is not contraindicated in PLCH women unless there is a severe respiratory failure [10].

Case Report I

An 18-year-old woman with a 2-year history of tobacco smoking went to her doctor complaining of chest pain for 2 months. The patient was previously healthy and was not taking regular medication of any kind. She denied a prior history of dyspnea on exertion, cough, or fever. A chest radiograph revealed a right pneumothorax, and an HRCT revealed evidence of nodules, some of which were cavitary, and cysts that extended throughout the lungs sparing only the costophrenic angles (Fig. 18.6a–c). Pulmonary function tests showed normal spirometric values, normal walking test, and a decreased DLCO value (56% of predicted). A bronchoscopy with BAL was performed showing that CD1a+ cells were 8% of total cells. Nevertheless, a lung biopsy was performed and the histological diagnosis was compatible with PLCH. CD1a and S100 positive cells were found. No extra-pulmonary manifestations of the disease were found. The patient quit smoking soon after the diagnosis was made and was monitored with clinic visits every 3 months that demonstrated stability of disease based on symptoms. Thanks to the frequent follow-up, assessment of the clinical-radiological and functional trajectory of disease was possible at the 1 year visit. On CT scans many new cysts were found, some formed by the confluence of smaller cysts, ranging in size up to 6–7 cm of diameter. Total parenchymal loss was estimated at 30% in 1 year. The patient, began to complain of dyspnea on exertion and coughing. Considering the progression of the disease and the patient's young age, therapeutic intervention was felt to be indicated. In line with the Histiocyte Society study, the patient was treated with prednisolone + vinblastine + 6mercaptopurine for 6 months. Since completion of the therapy, functional and clinical improvement have been observed. Symptoms gradually disappeared and DLCO increased to 70%. Six years after therapy lung function is back to normal, symptoms are absent and CT scan shows stability of the disease.

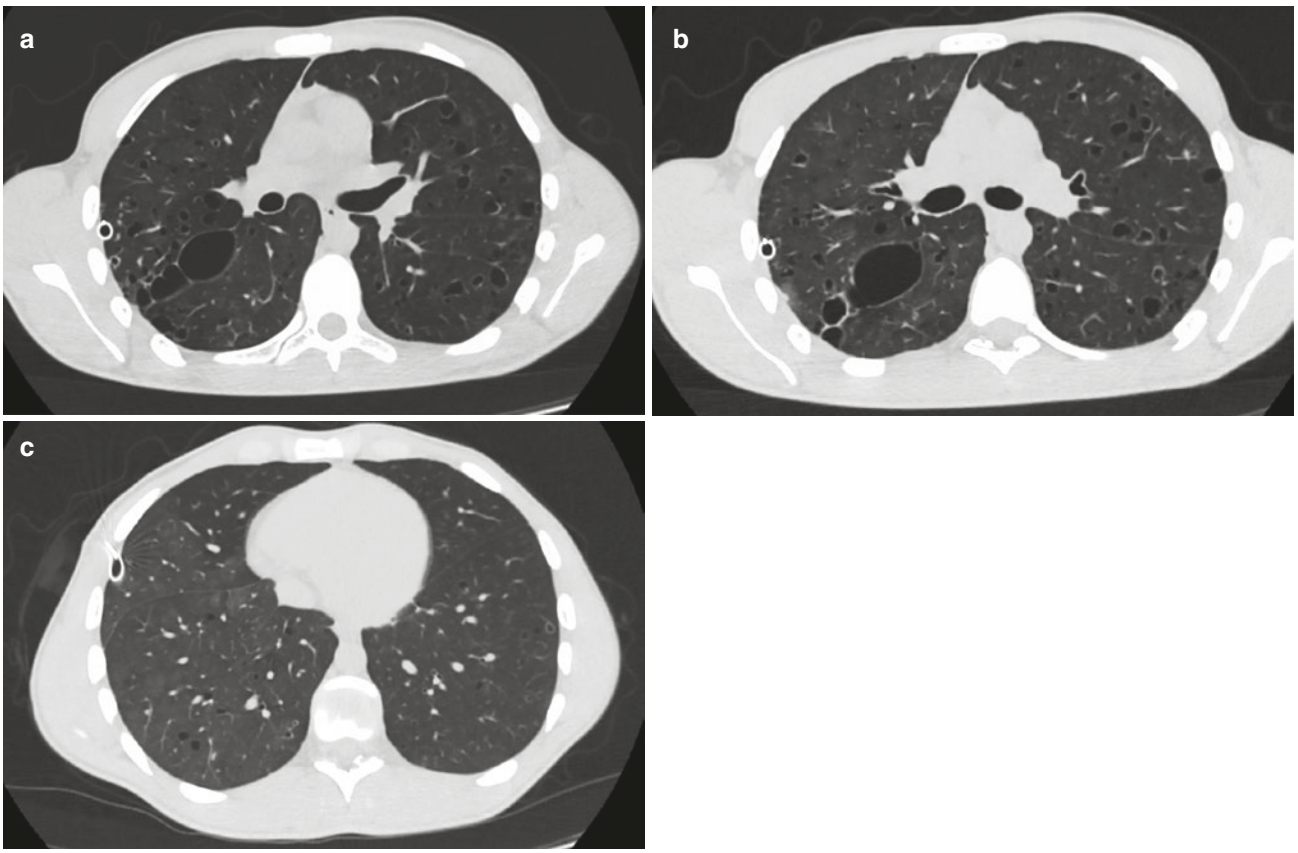

Fig. 18.6 (**a**) High-resolution CT scan demonstrates a small left pneumothorax with chest drainage and bilateral irregular cysts, with thin walls. (**b**) Some of these cysts appear to coalesce into larger and irregular structures with bizarre shapes. (**c**) Image depicting the typical lesion distribution with relative sparing of lower lobes

Respiratory Bronchiolitis-associated Interstitial Lung Disease (RB-ILD)

Introduction

Bronchiolitis is a generic term used to describe an inflammatory process involving the small airways that may be the consequence of cigarette smoke exposure, infections, aspiration, environmental agents, drugs or underlying systemic disorders such as connective tissue diseases and transplantation rejection [102]. In 1974, Niewoehner described the presence of inflammatory changes in the peripheral airways of a group of young smokers who had died of sudden death. The postmortem findings showed the presence of clusters of pigmented macrophages in respiratory bronchioles and neighboring alveoli [103]. These changes, termed respiratory bronchiolitis (RB), is used to describe this form small airways inflammation that occurs in virtually all smokers. In 1987, Myers et al. studied six smokers with clinical, functional, and radiological features suggestive of interstitial lung disease who underwent lung biopsy. The major pathologic findings were the presence of respiratory bronchiolitis, characterized by clusters of pigmented alveolar macrophages within respiratory bronchioles, and, in addition, a mild chronic interstitial inflammatory infiltrate of bronchiolar walls associated with hyperplasia of alveolar epithelial cells [104]. These were the first cases described in literature of respiratory bronchiolitis associated with an inflammatory and fibrotic involvement of the interstitium. The term "respiratory bronchiolitis with associated interstitial lung disease" (RB-ILD) appeared in 1989 in a study by Yousem et al. describing the histopathological differences between this new entity and other interstitial lung diseases. These and other studies, looking at the histopathological differences between RB and RB-ILD, have concluded that RB-ILD is usually associated with a greater extension of fibrosis, even though lungs of smokers affected by RB may also show mild alveolar fibrosis. The result is that differential diagnosis between RB and RB-ILD, exclusively based on histopathological and/or radiological findings, can be very difficult [105], and should also be based on clinical presentation. RB is usually asymptomatic while in RB-ILD symptoms such as dry cough and dyspnea are more often present [103].

Cottin et al. studied a population of 79 smokers affected by spontaneous pneumothorax who underwent surgical biopsy. RB and RB-ILD were found in 88.6% and 67.1% of patients, respectively [106]. Emphysematous lesions were also present in a third of patients, collectively demonstrating the high incidence of these three pathologies in patients with spontaneous pneumothorax. However, explaining the mechanism by which tobacco induces change in small airways and the development of emphysema and bullae, remains an ongoing challenge.

The occurrence of RB is uncommon in the absence of smoke exposure. Fraig et al. studied a population of 109 patients affected by RB of whom 98% were smokers (current or former smokers). and only 2% were nonsmokers [107]. Woo et al. described a case of a nonsmoking woman with radiological and histological features of RB–ILD, who was continuously exposed to cigarette smoke because of her job. This study highlights the limitation of focusing on the incidence of RB in smokers and nonsmokers, as second-hand smoke and environmental exposure can also result in respiratory bronchiolitis [108].

BAL findings in RB-ILD patients usually do not differ from those seen in normal "healthy" smokers and include an increased total number of cells or an increase in the percentage of macrophages that contain black tobacco pigment inclusions. A modest increase in neutrophils may also be present [109, 110].

Epidemiology

In a study performed on lung biopsy of smokers, Fraig et al. described the presence of RB in all smokers and about 50% of former smokers [107]. They also found an interesting correlation between the degree of pigmentation of macrophages and peribronchial fibrosis with the number of pack-years of cigarettes. In other studies, the relationship between RB and total smoke exposure is less obvious, although the percentage of smokers developing RB is consistently very high, ranging from 70% to 90%. RB-ILD is also closely related to smoking; different studies have shown that more than 90% of patients affected by RB-ILD are current smokers. RB-ILD typically affects smokers of 40–50 years of age with a slight male predominance and a history of cigarette smoking of 30 or more pack-year [5].

Clinical Features

The most common symptoms of RB-ILD are cough and dyspnea, and the typical physical exam findings include inspiratory crackles and, more rarely, digital clubbing. Lung function tests are nonspecific, and they can even be normal, but more commonly will reveal obstructive, restrictive, or mixed obstructive/restrictive patterns. An obstructive pattern is a typical sign of smoking exposure and RB, while mixed patterns suggest a diagnosis of RB with interstitial lung disease. Diffusing capacity is usually decreased and may be a useful guide of severity of disease. DLCO values are not diagnostically useful, however, since they may be affected by other conditions related to cigarette smoking such as emphysema [42].

Histopathological Findings

According to Myers et al., who first described the disease, RB-ILD and RB share many histological similarities [104]. The histological hallmark of both disorders is the accumulation of pigmented alveolar macrophages within respiratory bronchioles. RB macrophages are identified by abundant eosinophilic cytoplasm, with brown granular pigmentation representing constituents of cigarette smoke. A chronic inflammatory cell infiltrate within bronchiolar walls is seen in RB-ILD, without honeycomb change or fibroblastic foci (Fig. 18.7). Myers and colleagues suggested that the main difference between RB and RB-ILD is based on the extent of the fibrosing and inflammatory process, which in RB-ILD also involves adjacent alveolar walls in addition to airways [104]. Nakanishi et al. correlated the histopathological findings of RB-ILD patients with radiological features. Accumulation of macrophages within bronchioles was associated with centrilobular micronodules (<3 mm), while the association of peribronchiolar inflammation, fibrosis, and amassment of macrophages within the alveolar spaces corresponded to larger nodules (>3 mm). Ground glass opacities were the result of mild alveolar fibrosis accompanied by inflammation and accumulation of macrophages. In more advanced stages of the disease, HRCT showed areas of linear and reticular opacity that histologically corresponded to alveolar and subpleural microcystic fibrosis [111]. Craig et al. compared the histological features of DIP and RB-ILD, studying their clinical and radiological correlation [112]. They studied 24 patients with RB-ILD and 25 with DIP. The typical histological feature of the two entities is the presence of intra-alveolar macrophages characterized by pigmented cytoplasm and associated with variable interstitial fibrosis and chronic inflammation. RB-ILD lesions usually have a bronchiolocentric distribution, while DIP lesions are diffuse involving the entire pulmonary acinus. They also described a significantly greater extent of interstitial fibrosis, eosinophilic infiltration, and lymphoid follicle formation in DIP compared to RB-ILD. Yousem and coworkers examined nine cases of smokers with dyspnea, a mixed obstructive/restrictive pattern on lung function, reduced DLCO, and radiographic features of RB-ILD showing centrilobular nodules,

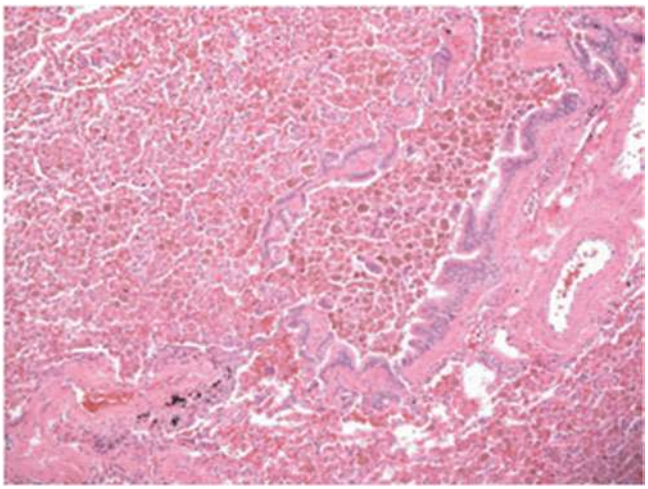

Fig. 18.7 RB consisting of distorted bronchioles with aggregates of "golden" macrophages into and around the bronchioles. (Courtesy of Professor G. Rossi. University of Modena-Reggio Emilia, Italy)

ground glass opacities, and emphysema. Surprisingly, lung biopsy revealed an extensive collagenous thickening of the alveolar septa with a patchy and subpleural distribution characteristic of nonspecific interstitial pneumonia (NSIP). This study confirms how difficult the differential diagnosis of these diseases may be, and highlights the critical role that smoking plays in fibrotic lung diseases [113].

Radiologic Findings

Chest X-ray is normal in up to 20–30% of cases of RB-ILD, and in other cases may show nonspecific thickening of the central and peripheral bronchial walls, bilateral reticular-nodular opacities with diffuse distribution or upper lobe predominance [42]. The most common HRCT findings are thickening of the bronchial walls, centrilobular nodules in the upper lung zones, and ground glass opacities (Fig. 18.8). Heyneman et al. compared the predominant HRCT features in a cohort of patients affected by RB, RB-ILD, and DIP, observing that in all of these conditions centrilobular nodules and ground glass opacities represent the most common radiological pattern [114]. In RB-ILD, these abnormalities are more profuse compared to RB and are characterized by the presence of areas of reticulation suggesting underlying interstitial fibrosis, albeit in the absence of honeycombing or traction bronchiectasis. There is no radiological cutoff that defines the boundary between RB and RB-ILD. The radiological differential diagnosis may become even more complicated considering that HRCT findings of RB-ILD may be very similar to those described for DIP [2]. DIP is characterized on CT scans by the presence of large areas of ground glass attenuation, which are usually bilateral, largely symmetrical, and peripheral and lower zone predominant. Basal,

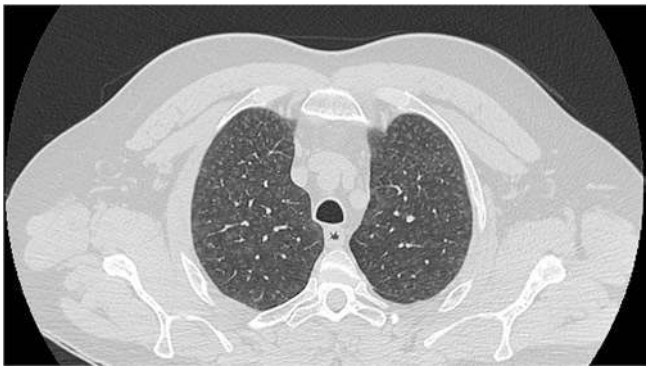

Fig. 18.8 HRCT of a patient affected by RB-ILD showing poorly defined centrilobular nodules

interlobular opacities can be associated with small peripheral cystic spaces with traction bronchiectasis. NSIP is marked by ground glass opacities, with irregular linear or reticular opacities and scattered micronodules in a subpleural distribution. In advanced disease, the presence of traction bronchiectasis and subpleural small cysts defined as "microcystic honeycombing" may be helpful in making the correct diagnosis of NSIP [115].

Prognosis and Therapy

A number of studies that have linked smoking with the development of RB-ILD have demonstrated a clear improvement of the disease after smoking cessation. Nakanishi et al. have shown that smoking cessation alone, without any other treatment, leads to clinical, functional, and radiographic improvement. Symptoms and DLCO values were both improved after smoking cessation, as were ground glass opacities and centrilobular nodules on CT scans. A significant correlation between the change in DLCO and the reduction of centrilobular nodules and ground glass opacities was observed [111]. Sadikot et al., described two patients with biopsy-proven RB-ILD with dyspnea, severe lung function involvement, and respiratory failure who had significant clinical and functional improvement after smoking cessation [116]. Mavridou et al. reported a case of acute RB-ILD in which smoking cessation alone was not adequate, requiring steroid treatment. Gradual clinical, functional, and radiological improvement was reported, although it was necessary to continue high dose of corticosteroids for a longer period of time because of clinical deterioration following corticosteroid tapering [117]. Similarly, Woo et al. described a case of RB-ILD occurring in a patient exposed to second-hand cigarette smoke. The patient was treated with high dose of corticosteroids which resulted in improvement of ground glass opacities and centrilobular nodules on HRCT [108]. However, some other studies have not confirmed the effectiveness of smoking cessation and

have also questioned the role of steroid treatment. Moon et al. retrospectively studied a group of ten patients with pathological features typical of RB-ILD. All patients were smokers except one, who was instead exposed to solder smoke. Most of them were symptomatic and nine patients had quit smoking either before or at the time of the diagnosis. Lung function tests showed both restrictive and obstructive patterns and severe DLCO reduction. Seven patients were treated with steroids, together with cyclophosphamide or azathioprine in six cases. The patients who received only steroids reported DLCO and FVC improvement, while in the six patients treated with corticosteroids and cyclophosphamide, FVC was unchanged in five cases and worsened in one. DLCO improved just in one patient, deteriorated in two, and remained unchanged in three cases. The three patients who quit smoking without any additional treatment reported unchanged FVC and DLCO values in the follow-up period [5]. In another study of RB-ILD patients, Portnoy et al. described clinical and functional decline in 32 patients in spite of smoking cessation and steroid treatment. These studies suggest that the prognosis of RB-ILD is not as good as usually believed. Even though mortality secondary to smoking-related interstitial lung disease is quite rare [109]. Due to the lack of clinical trials, the choice of treatment in RB-ILD is often based on expert opinions or case series. While some studies have shown disease improvement following corticosteroid treatment, the benefit of this therapy is unproven, and patients with RB-ILD should be strongly encouraged to enroll in a smoking cessation program and stop smoking. However, the true effectiveness of smoking cessation, corticosteroids or immunosuppressants in the treatment of RB-ILD remain unanswered clinical question that require further studies.

Desquamative Interstitial Pneumonia

The term "desquamative interstitial pneumonia" was originally coined by Liebow et al. who believed that intra-alveolar cells, typical of this disease, were reactive alveolar pneumocytes that had "desquamated" from the alveolar surface [118]. Later, electron microscopy demonstrated that these cells were alveolar macrophages. Early studies proposed that DIP was the cellular phase of usual interstitial pneumonia (UIP), because of some similarities in histopathological features [119]. This idea was not sustained by Carrington et al., who highlighted the poor prognosis for UIP and the absence of response to corticosteroid therapy in comparison with DIP. It has since been concluded that the pathogenesis and natural history of DIP and UIP are distinct [120]. Currently, DIP is included in the American Thoracic Society/European Respiratory Society classification as a form of idiopathic interstitial pneumonia characterized by the presence of diffuse exudation of pigmented macrophages in the alveolar spaces [3].

Epidemiologic and Clinical Features

Although classified as idiopathic, DIP has a number of radiological and histopathological similarities to RB-ILD and is also related to cigarette smoking. Different studies have supported this correlation, showing that almost 90% of patients affected by DIP are current or former smokers. Based on a comprehensive evaluation of HRCT findings, Heyneman et al., hypothesized that DIP and RB-ILD may be considered different degrees of severity of reaction of small airways and lung parenchyma to cigarette smoke [113]. In another study, Craig et al. showed that only 60% of DIP patients have a history of cigarette smoking [114]. It is in fact important to note that DIP has been also associated with a variety of other conditions including drug reactions and connective tissue diseases. Schartz et al. described a case of scleroderma with pulmonary involvement where a lung biopsy confirmed a diagnosis of DIP [121]. Similarly, Esmaeilbeigi et al. reported a case of lupus, with interstitial lung disease on CT scans, suggestive of NSIP pattern, while lung biopsy confirmed the diagnosis of DIP [122]. Ishii et al. reported the association between rheumatoid arthritis and interstitial lung disease with DIP pattern, supporting the possible correlation between autoimmune diseases and DIP [123]. It has been also reported one case of DIP characterized by increased serum levels of angiotensin-converting enzyme (ACE) and lysozyme that are known to be elevated in sarcoidosis. These findings are likely related to the involvement of macrophages and neutrophils in the pathogenesis of DIP and may suggest a possible role for ACE as a diagnostic tool for DIP. Obviously, more studies are necessary to prove the correlation between ACE serum levels and DIP [124]. Very few epidemiological data regarding DIP are present in literature. According to Carrington et al., DIP accounts for less than 3% of interstitial lung diseases. Its low incidence is probably linked to the poor knowledge of the disease and to the objective difficulties in making a correct diagnosis. It commonly affects patients in their third to fifth decade, with a preference for males who are affected nearly twice as often as females [120]. Patients usually complain of dyspnea on exertion and productive or dry cough. It is also possible to observe a variety of nonspecific symptoms such as weight loss, fatigue, and fever. Digital clubbing may be present while on chest auscultation it is possible to identify crackles. In the two largest case series reported in literature [114, 120] almost 90% of DIP patients were smokers or had a cigarette smoke exposition, even if, as described above, DIP can be the radiological and histological pattern of presentation in autoimmune disorders or in drug reactions. Lung function tests can show restrictive, obstructive, or mixed patterns together with a marked reduction in DLCO that is common and typical of DIP [42]. In any case, DIP is characterized by a more marked reduction

of DLCO in comparison to RB-ILD and by a more serious impairment of gas exchange [125].

Histopathological Findings

Histopathological diagnosis of DIP can be difficult to distinguish from RB-ILD. According to Wells, DIP is histologically characterized by hyperplasia of type II pneumocytes, accumulation of dusty macrophages within alveoli and diffuse alveolar septa thickening. These features are very similar to those observed in RB-ILD [126]. Nonetheless, the criteria to differentiate histological patterns of DIP from RB-ILD are well defined by consensus in the ATS/ERS classification for idiopathic interstitial pneumonias [3]. According to this classification, DIP is characterized by macrophage accumulation in the distal airspaces with alveolar pneumocyte proliferation along the alveolar septa. The alveolar septa thickening is also due to a chronic inflammatory infiltrate that includes plasma cells, occasional eosinophils, and lymphoid aggregates (Fig. 18.9). However, histological differential diagnosis between DIP and RB-ILD is based not only on the typology of lesions but also on their extent: DIP affects the lung in a more uniform, diffuse manner and rather than the more limited bronchiolocentric distribution observed in RB and RBILD. Despite these differences, it has been hypothesized that RBILD and DIP represent extremes of a spectrum of reactions of small airways and alveoli to cigarette smoking [114]. Other authors, consider DIP and RBILD as distinct entities, characterized by different presenting features and clinical courses. Wells et al. maintained that DIP and RB-ILD are separate entities that can be distinguished by radiological features (predominance of centrilobular nodules in RB-ILD and ground glass opacities with fibrosis in DIP); prognosis (better in RB-ILD than in DIP) and therapeutic indication (marginal in RB-ILD and necessary in DIP) [126]. However, in the differential diagnosis of DIP, other ILDs should be considered because many ILD patients are current smokers and often show, on lung biopsy, intra-alveolar macrophage accumulation as a consequence of smoking. In these cases, clinical and anamnestic information may be helpful for the diagnosis.

Radiological Findings

The radiologic pattern is nonspecific and includes ground glass areas and reticular or nodular opacities with a basal predominance as described by Liebow [118]. The prevailing abnormality at HRCT is represented by ground glass attenuation that may be peripheral, patchy, or diffuse and often with a basal subpleural predominance (Fig. 18.10) [42]. Hartman et al. studied a cohort of patients with biopsy-proven diagnosis of DIP, and described the presence of ground glass attenuation as the predominant finding. These lesions involved mainly the middle and lower lung zones with a peripheral distribution in 60% of patients, a patchy distribution in 25% of patients, and a diffuse distribution in 15%. The distribution of lesions on CT scans is very similar to that seen in usual interstitial pneumonia, but differential diagnosis should be easy because of the prevalence of ground glass opacities in DIP [127]. Craig et al. reported that HRCT appearances were suggestive for DIP just in 4 of 13 DIP patients, while the most prevalent appearance (7–13 cases) was represented by NSIP pattern. Also CT scans performed in follow-up period were characterized by a NSIP pattern

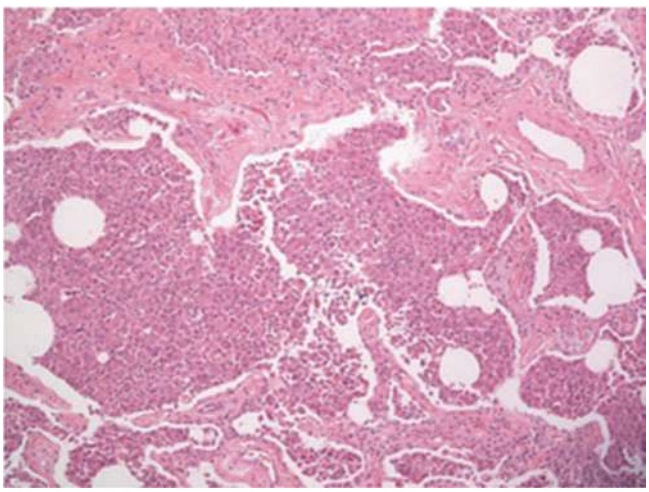

Fig. 18.9 DIP is characterized by homogeneous interstitial fibrosis with pools of golden histiocytes in dilated alveolar spaces. (Courtesy of Professor G. Rossi. University of Modena-Reggio Emilia, Italy)

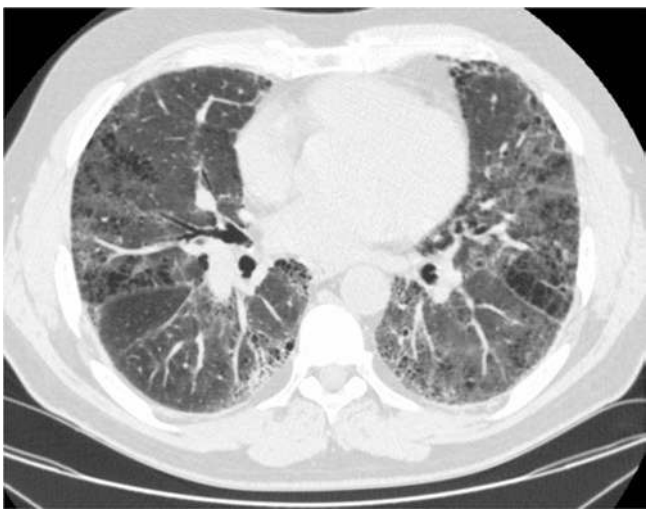

Fig. 18.10 High-resolution CT image obtained through the mid lungs showing peripheral reticulation and bilateral patchy ground glass in a patient with DIP

suggesting a possible evolution of DIP in NSIP [112]. Ground glass opacities described on CT scans of DIP patients are also present in RB-ILD, although in this disease centrilobular nodules are the predominant feature. The distribution of ground glass opacities is diffuse, symmetrical, and patchy in DIP, while peribronchiolar distribution prevails in RBILD [128]. Heyneman et al. also confirmed that ground glass opacities represent the predominant pattern in 100% of DIP patients, localized in mid to lower lung zones and with a subpleural distribution. They also described the presence of fibrosis with intralobular lines and honeycombing associated to traction bronchiectasis. Minor findings revealed on CT scans were subpleural nodules, emphysema, and areas of consolidation [114].

Prognosis and Therapy

The objective difficulties in making the correct diagnosis of DIP and the low incidence of the disease have contributed to the absence of studies large enough to obtain reliable data concerning the course of the disease. Carrington et al. compared mortality in UIP and DIP in a 1-year follow-up period, showing 87% of mortality in UIP and 16% in DIP [120]. Baloira et al. estimated a 10-year survival rate of 70%, while no death occurred in RB-ILD patients in the same period of follow-up [125]. A 27.5% mortality rate has been described in a group of 40 patients with DIP who had been followed up for a mean duration of 9 years. Similarly, Yousem et al. reported a 32% mortality rate in 36 patients with DIP, while no deaths were observed in 18 patients with RB-ILD [105]. Although the correlation between DIP and cigarette smoke has not been conclusively demonstrated, spontaneous remission has been reported after smoking cessation with no recurrence of disease in up to 4 years of follow-up [129, 130]. In those cases where smoking cessation alone does not stop disease progression, empiric steroid treatment has been attempted. The dose of prednisone used is 40–60 mg daily with a gradual tapering over a 6- to 9-month period [131]. Akira et al. reported a case series of DIP patients treated with prednisolone at the initial daily dose of 40–60 mg and described CT changes in a 12-month follow-up period. All DIP patients presented with ground glass opacities in mid and lower lobes with a subpleural distribution on the initial CT. After stopping smoking and following corticosteroid therapy, a decrease in the extent of ground glass opacities was described in the majority of patients. When DIP does not respond to corticosteroids immunosuppressive agents are often considered, although data supporting this approach are limited [132]. Unfortunately, DIP can progress to end-stage disease and lung transplantation may become necessary because of severe functional and clinical decline. DIP recurrence has been reported after lung transplantation.

Conclusion

It is widely known that tobacco smoke may cause pulmonary diseases such as COPD or cancer, but its role in causing smoking-related interstitial lung diseases, including RB-ILD, DIP, and PLCH, is under-recognized. The correlation between cigarette smoke and these diseases is supported by solid epidemiological data demonstrating a preponderance of smokers in cases of SR-ILD. It has been also been shown that smoking cessation may represent an effective therapy, even if pulmonary abnormalities can persist for long periods after smoking cessation. The pathogenic mechanisms underlying the relationship between smoke and SR-ILD have not been elucidated, but it has been postulated that cigarette smoke in susceptible individuals may cause an excessive inflammatory and/or fibrotic response at the bronchiolar and alveolar level. Because of the common etiologic agent, SR-ILDs share many clinical and functional aspects and, to some extent, radiological and histopathological patterns. DIP and RB-ILD, for instance, are both characterized by poorly defined centrilobular nodules and ground glass opacities; in these circumstances, only the extent of the lesions may help to discriminate the two diseases. In PLCH, the presence of nodules, cysts, and the characteristic sparing of lower lung lobes may greatly simplify the diagnostic process. It is obvious that radiological findings should be interpreted in an appropriate clinical context that must account for smoking history, symptoms, signs, and pulmonary function tests. Nevertheless, in some cases, where all these elements are nonspecific and diagnosis remains vague, a lung biopsy should be considered. Sometimes not even the histological features allow the correct diagnosis because DIP and RB-ILD may have very similar histopathological patterns. The incidence of SR-ILDs is probably underestimated because of the problematic diagnostic approach that requires integration of complex pulmonary, radiological, and pathological features. Furthermore, many issues regarding pathogenesis, clinical evolution, and treatment strategies remain unresolved. New and larger studies are needed to better define the factors that define susceptibility and the clinical course of SR-ILDs and their responses to smoking cessation, corticosteroid, and immunosuppressant treatment.

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Lymphangioleiomyomatosis

19

Simon R. Johnson

Introduction

Lymphangioleiomyomatosis (LAM) is a disease characterised by lung cysts, enlargement and obstruction of the axial lymphatics, and in many cases angiomyolipomas, benign tumours occurring mainly in the kidneys. LAM almost exclusively affects women and can occur as a sporadic disease but is also common in adults with tuberous sclerosis complex (TSC) [1]. Although the clinical course can vary, many patients lose lung function at an accelerated rate and eventually develop respiratory failure.

The prevalence in the populations studied varies between 3.4 and 7.8/million women with an incidence of 0.23–0.31/million women/per year [2]. As the symptoms of LAM are similar to a number of more common respiratory diseases, the condition is under-recognised and there is often a period of years between the initial symptoms and the correct diagnosis. LAM has been described in most racial groups: TSC and female sex are the only known risk factors for developing LAM.

Pathogenesis

The association between LAM and TSC has been a key factor in understanding the molecular basis of LAM. Both sporadic and TSC-LAM are associated with loss of function of either *TSC-1* or more commonly *TSC-2*, the genes abnormal in TSC [3]. Hamartin and tuberin, the protein products of *TSC-1* and *-2*, respectively, form a complex with multiple functions, including as a guanosine triphosphatase accelerating protein (GAP) which inactivates Rheb, a small GTPase [4]. Rheb in turn activates the mammalian target of rapamycin (mTOR). mTOR associates with raptor and other proteins in complex 1 (mTORC1) which regulates cell growth, gene translation autophagy and metabolism, and with rictor and other proteins in the mTORC2 pathway which has other less well-defined functions but has a role in control of cytoskeletal arrangement and migration via the GTPase Rho [5] (Fig. 19.1. For a detailed description see [6, 7]). Loss of TSC-1/2 function by a combination of genetic or possibly epigenetic modifications results in constitutive activation of mTORC1 and hence uncontrolled proliferation, abnormal migration and a dependence on glycolytic metabolism within a clonal population of 'LAM' cells [8]. Drugs which block the activity of mTORC1 have transformed the treatment of the disease [9, 10]. Identical genetic abnormalities in *TSC-2* have been identified in LAM cells from different sites (lung, lymph nodes, angiomyolipoma) within the same patient, suggesting LAM cells are clonal and migrate throughout the body [11] leading to the 'benign metastasis model' of LAM pathogenesis [12]. LAM cells express receptors for oestrogen and progesterone, possibly in keeping with the female preponderance of the disease [13]. In model systems, oestrogen promotes LAM cell growth and metastasis; however, anti-oestrogen therapies have not proven effective for patients [14, 15]. The hallmark of LAM is the presence of lung cysts. Lined by nodular proliferations of LAM cells, it is thought that cysts may develop as a consequence of extra-cellular matrix proteolysis resulting from the secretion of proteases by LAM cells. Consistent with this idea, it has been shown that LAM cells produce a number of proteases, including cathepsin K [16] plasmin [17] and matrix metalloproteinases-1, -2, -9 and -14 [18, 19]. These proteases are capable of degrading extra-cellular matrix proteins, including collagens, elastin and proteoglycans. They may also contribute to the disease by activating growth factors, modulating cell surface receptor activity, inflammatory cell trafficking, angiogenesis and cellular invasion. LAM nodules are complex structures composed of multiple cell types, including LAM cells, LAM-associated fibroblasts and lymphatic endothelial cells forming central lym-

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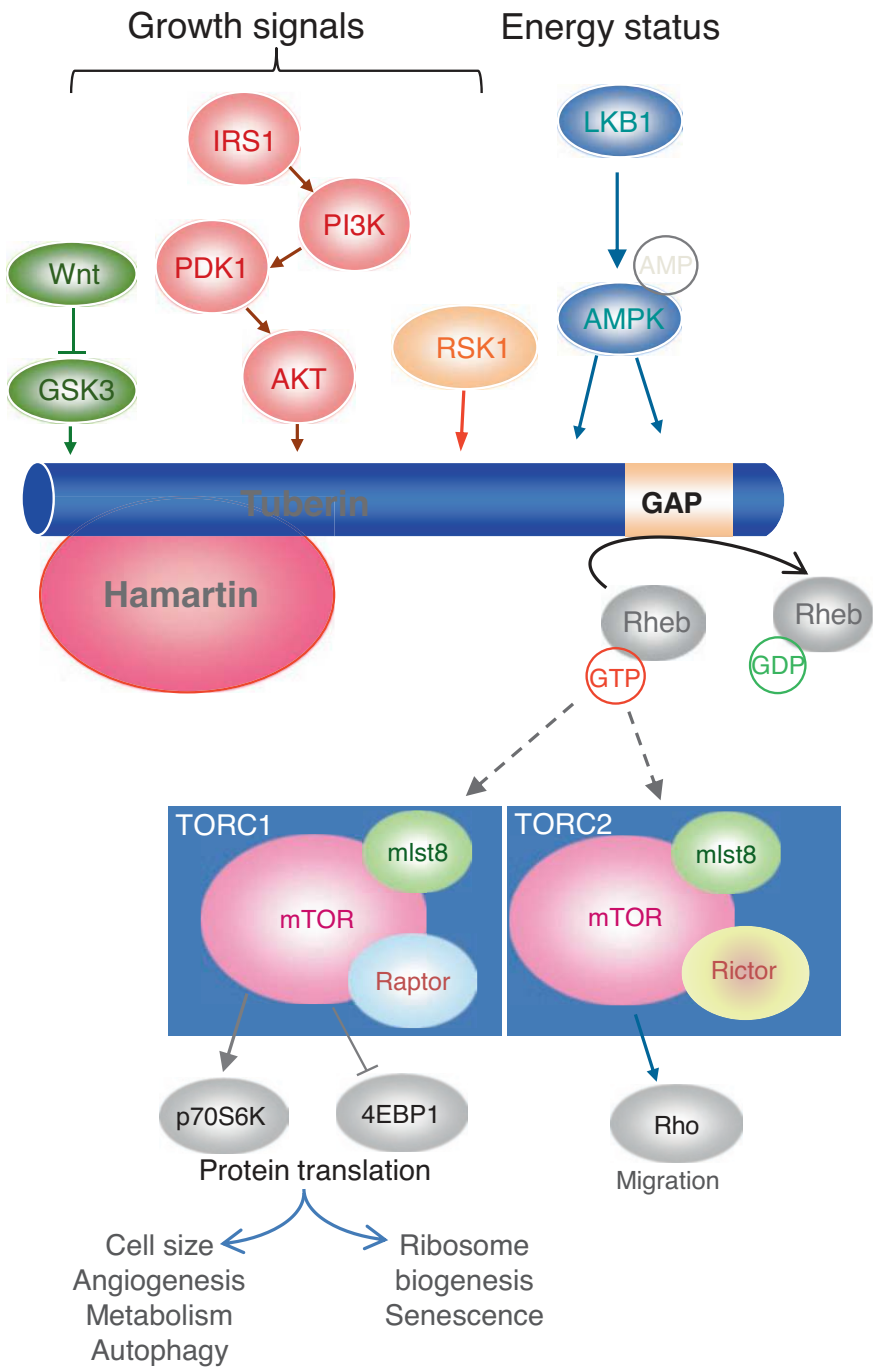


Fig. 19.1 Schematic representation of the mTOR pathway. Tuberin is phosphorylated by multiple inputs from growth signals via growth factors or as a consequence of change in cellular energy status. Phosphorylation of tuberin leads to increased guanine nucleotide hydrolysis via tuberin's GAP domain. Conversion of guanine triphosphate (GTP) to guanine diphosphate (GDP) inhibits Rheb (Ras homologue enriched in brain) activity, an activator of both mTOR complexes. Activation of the two multiprotein complexes results in differing downstream functions: for TORC1, including the translation of a selection of mRNA species changes in cell size, metabolism, proliferation, autophagy and other functions via the serine/threonine kinase p70S6K and 4EBP1, a component of the protein translation machinery. TORC2 is less well understood but functions include cell migration via the small GTPase Rho

phatic clefts, and covered by hyperplastic type 2 pneumocytes [20, 21]. Very recently, inflammatory cells have been described within LAM nodules, have been associated with disease activity and may represent future therapeutic targets [22, 23]. Many aspects of the disease mimic cancer biology and despite the benign appearance of the LAM cell, due to their uncontrolled growth, metastatic behaviour, interactions with host cells and their metabolic signature, LAM is viewed by some as a slow growing neoplasm or cancer-like disease [24]. The processes contributing towards the pathogenesis of LAM are summarised in Fig. 19.2.

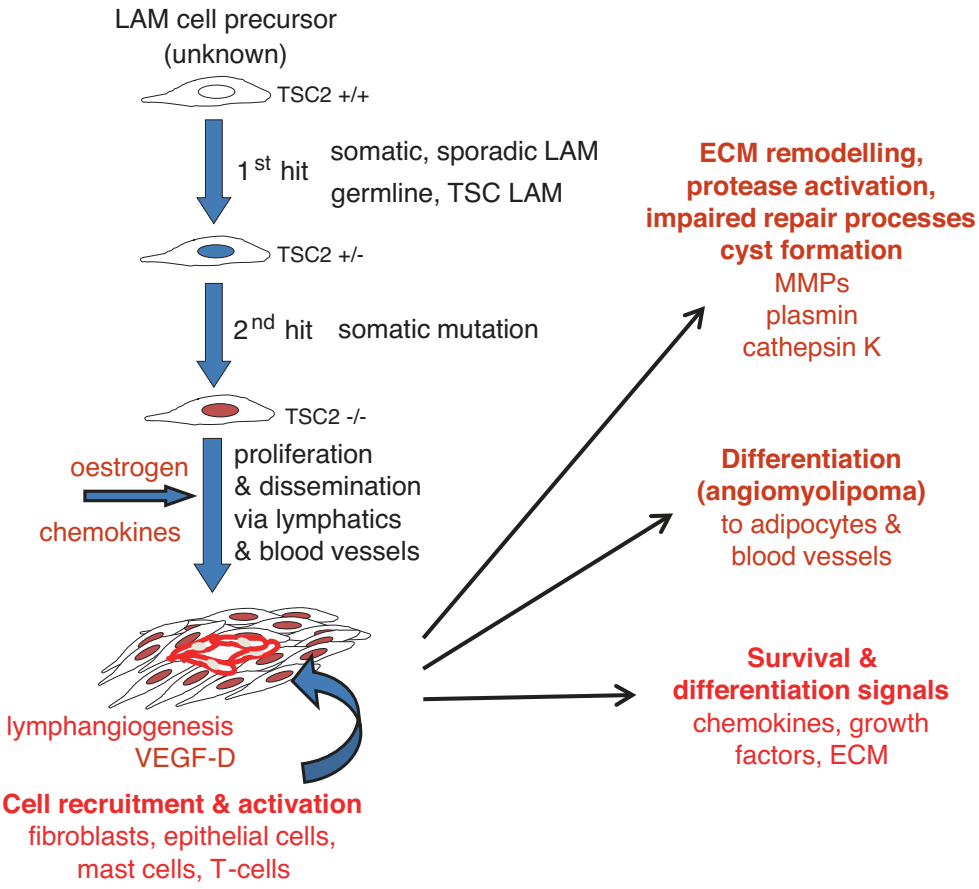


Fig. 19.2 Cellular and pathologic events contributing to the development of LAM. Biallelic inactivation of TSC-2 results in loss of functional tuberin protein in the LAM precursor cell. This confers a survival advantage and metastatic capability which is likely to be oestrogen dependent. LAM cells disseminate and form nodules acting as foci for lymphangiogenesis. The LAM nodule provides a supportive environment for LAM cell growth possibly allowing differentiation into the other components of angiomyolipoma, including blood vessels and adipocytes. LAM cells recruit stromal cells, including LAM-associated fibroblasts and inflammatory cells. The production of proteases is likely to result in cyst formation and support further LAM cell dissemination

Presentation

LAM most commonly presents with respiratory symptoms, but abdominal disease, LAM detected as a consequence of TSC and identification in asymptomatic individuals undergoing CT scanning for other problems also occur.

Cysts replace the lung parenchyma to cause breathlessness and symptoms of airway narrowing, including cough and wheezing. This collection of symptoms is the presenting feature in over 40% of patients and frequently leads to treatment for asthma: a poor response to treatment or other features not typical of asthma may then prompt further investigation. Lung cysts also cause pneumothorax which may be recurrent and difficult to treat. Dyspnoea or pneumothorax are the presenting problem in the majority of patients. Around 5% of patients present with chylous pleural effusions due to obstruction of the thoracic duct by LAM cells [1]. The combination of chylous effusions and lung cysts in women is pathognomonic of LAM. Some patients expectorate chylous secretions due to intrapulmonary lymphatic stasis, whilst others may develop haemoptysis. Onset of respiratory symptoms may occur during pregnancy particularly with refractory pneumothorax, including bilateral pneumothorax or chylopneumothorax. Symptoms may persist until surgical correction can be performed, often after delivery [25].

Abdominal disease may be the first symptom of LAM. Most commonly this is with symptomatic renal angiomyolipoma, in some patients, preceding lung symptoms by many years [26]. Sometimes large tumours present with abdominal fullness but more commonly haemorrhage causes acute flank pain with or without haematuria. The use of CT scanning to evaluate renal tumours in these situations may coincidentally reveal lung cysts. Up to 20% of patients have cystic lymphatic masses caused by occlusion of abdominal, retroperitoneal or pelvic lymphatics by LAM cells. Termed lymphangioleiomyomas, these can give rise to abdominal bloating, swelling or peripheral oedema [27]. In a small number of cases, discovery of these masses may lead to a biopsy for suspected malignant disease often resulting in persistent chylous leakage. The tissue obtained reveals characteristic histology usually leading to the correct diagnosis. In rare cases, symptoms from chylous ascites can be the presenting problem although chylous ascites is generally associated with more advanced disease.

Table 19.1 Clinical scenarios suggestive of LAM

'Asthma' with poor response to treatment, especially with fixed airway obstruction
Early onset 'emphysema', especially in non-smokers
Recurrent or bilateral pneumothorax in women
Pneumothorax in pregnancy
Chylothorax or chylous ascites
Respiratory symptoms in TSC
Angiomyolipoma in women
Asymptomatic lung cysts identified during medical imaging

The prevalence of LAM in TSC increases with age: at 40 years cysts are present in up to 80% of women [28]. Although respiratory symptoms occur in many, only a minority of these women develop severe respiratory disease [29–31]. The presenting symptoms in TSC-LAM are similar to sporadic LAM with dyspnoea and pneumothorax. Treatment guidelines for TSC recommend screening adult women for TSC at 18 years [32]. This, as well as CT performed for non-respiratory problems in both TSC and sporadic LAM, inevitably results in the detection of patients with early and asymptomatic disease. Occasionally, patients with severe learning difficulties may present with advanced disease and even cyanosis or behavioural change due to pneumothorax. The majority of patients with TSC-LAM have renal angiomyolipomas which may be very large, multiple and bilateral and may be the presenting feature [33]. Lymphatic disease appears less common in TSC-LAM than sporadic disease [34]. Clinical presentations suggestive of LAM are listed in Table 19.1.

Diagnosis and Workup

Interstitial changes and preserved lung volumes may be present on chest radiograph (Fig. 19.3) although plain X-rays are often normal at diagnosis. In patients with suspected LAM, high-resolution CT scanning is the investigation of choice. The characteristic features are of thin-walled cysts. Cysts are evenly distributed throughout the lung fields, are generally round and vary in diameter between 0.5 and 5 cm. The intervening lung parenchyma is normal although occasionally small areas of airspace shadowing representing haemorrhage or chyle may be present [35] (Fig. 19.4). Widespread alveolar shadowing, however, is not typical of LAM. Chylous pleural effusions and pneumothorax may also be present (Fig. 19.5). In patients with TSC, nodules of proliferating type 2 pneumocytes, termed multifocal micronodular pneumocyte hyperplasia, may coexist with LAM or occur without LAM [36]. The presence of interstitial abnormalities, thick-walled cysts or unevenly distributed cysts is not typical of LAM. CT alone is not diagnostic of LAM and once LAM is suspected, confirmatory features are required to make a definite diagnosis, including either the presence of renal angiomyolipomas, chylous pleural or abdominal effusions, lymphatics involved by LAM or the presence of TSC. Current diagnostic criteria are summarised in Box 19.1 [37]. A previous history of renal tumours and symptoms of TSC should be sought. A careful clinical examination should be made for signs of TSC, including facial angiofibromas, periungual fibromas, hypomelanotic macules and shagreen patches. In some patients, skin abnormalities are subtle and where there is no history of epilepsy or learning difficulties the diagnosis can be difficult to make and evaluation by a TSC specialist or dermatologist may be helpful. Diagnostic criteria for TSC have been clearly defined [38] but where doubt exists referral to a clinical geneticist is advised. To detect the abdominopelvic manifestations to aid diagnosis and management, once LAM is suspected, contrast CT scanning of the abdomen and pelvis is recommended to detect angiomyolipoma, lymphangioleiomyoma, lymphadenopathy or ascites which are collectively present in over half of patients [39].

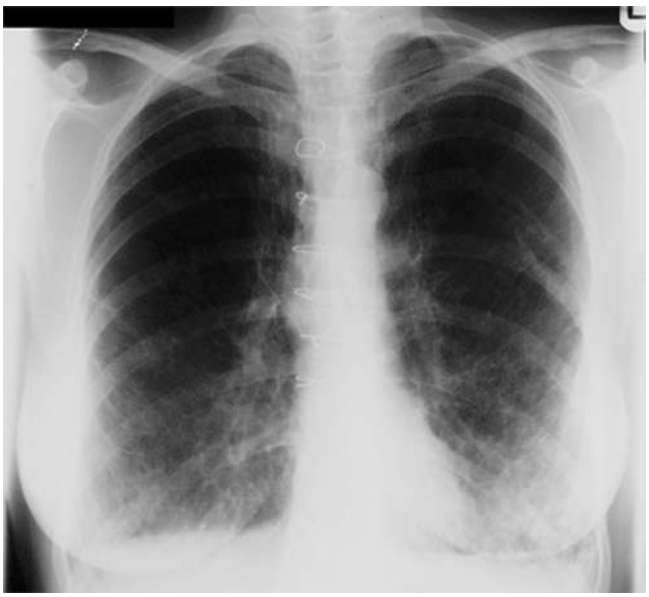


Fig. 19.3 Chest radiograph of a patient with advanced LAM. Reticular shadowing with preserved lung volumes, sternal wires from pleural surgery are visible

Pulmonary function testing may be normal in early disease, but DL_{CO} is often reduced even in early disease [40]. As the disease progresses, airflow obstruction develops. Lung volumes are generally preserved [41]. Cardiopulmonary exercise testing (CPET) provides more information on physiological derangement in early disease although is seldom performed [42]. The 6 min walk test is more practical than CPET and provides useful information about disability and exertional hypoxaemia.

Women with both sporadic and TSC-LAM are at increased risk of meningioma being present in 8 of 250 patients

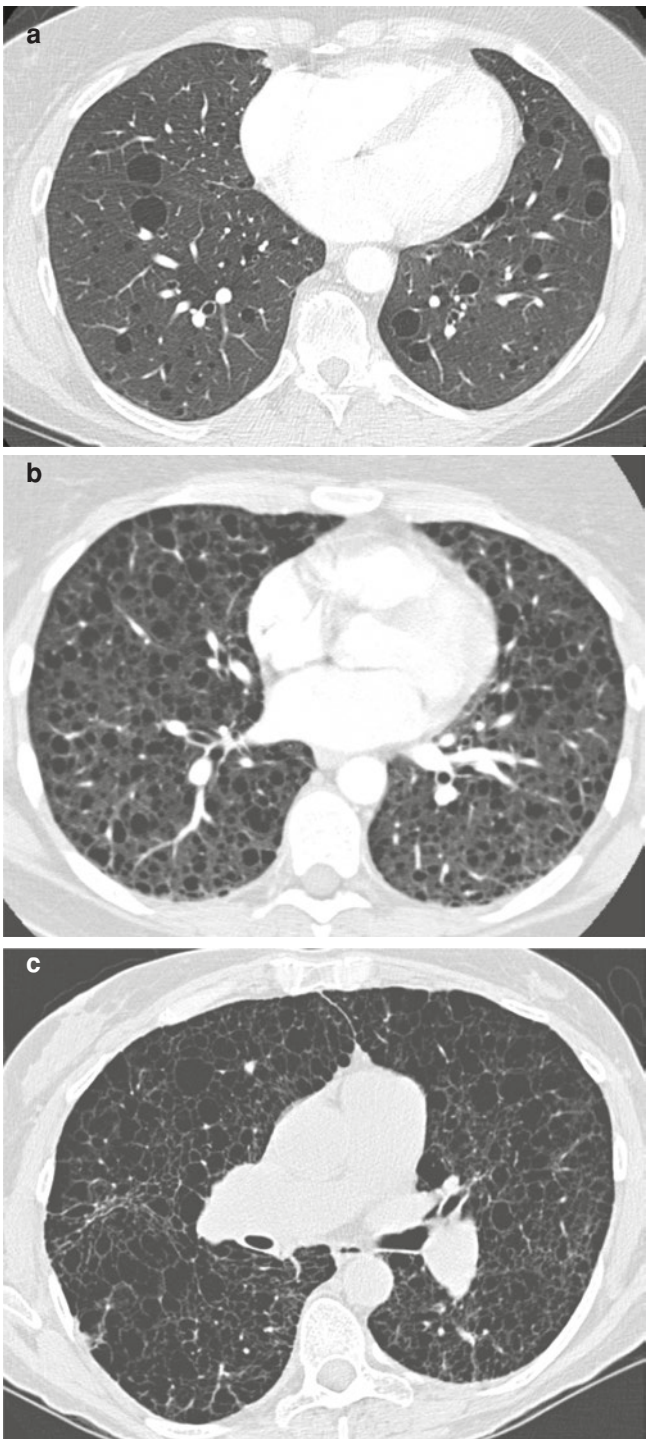


Fig. 19.4 High-resolution CT appearances in LAM. (**a**) A patient with very slowly progressive disease who has normal spirometry and mildly reduced gas transfer. (**b**) A patient with progressive LAM with significant airflow obstruction and impaired gas transfer. (**c**) Advanced lung disease with very little lung parenchyma visible

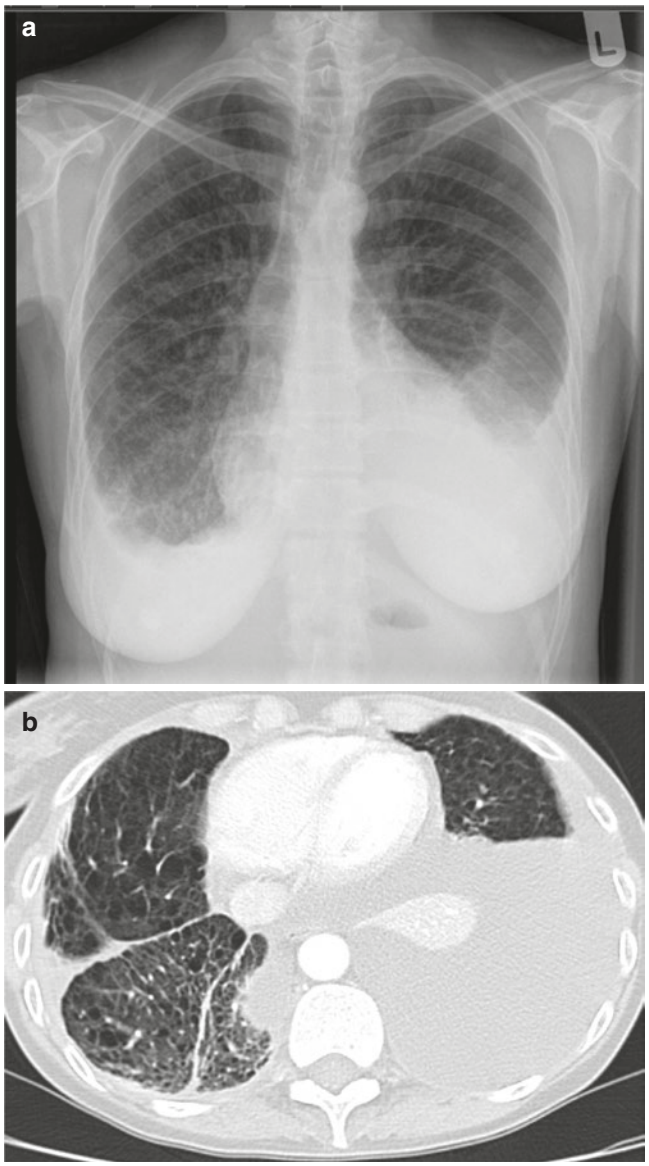


Fig. 19.5 Chylous complications. (**a**) Chest X-ray and (**b**) CT from the same patient showing bilateral pleural effusions and parenchymal changes due to LAM

screened by MRI scanning in one series [43]. Some meningiomas can cause symptoms and require surgery. MRI of the brain may be performed at baseline especially in the presence of headache, seizures or other neurological symptoms. In patients with TSC-LAM and those presenting with LAM who are suspected of having TSC, brain MRI scanning should also be performed where subependymal giant cell astrocytoma (SEGA), subependymal nodules and white matter abnormalities may be present [39].

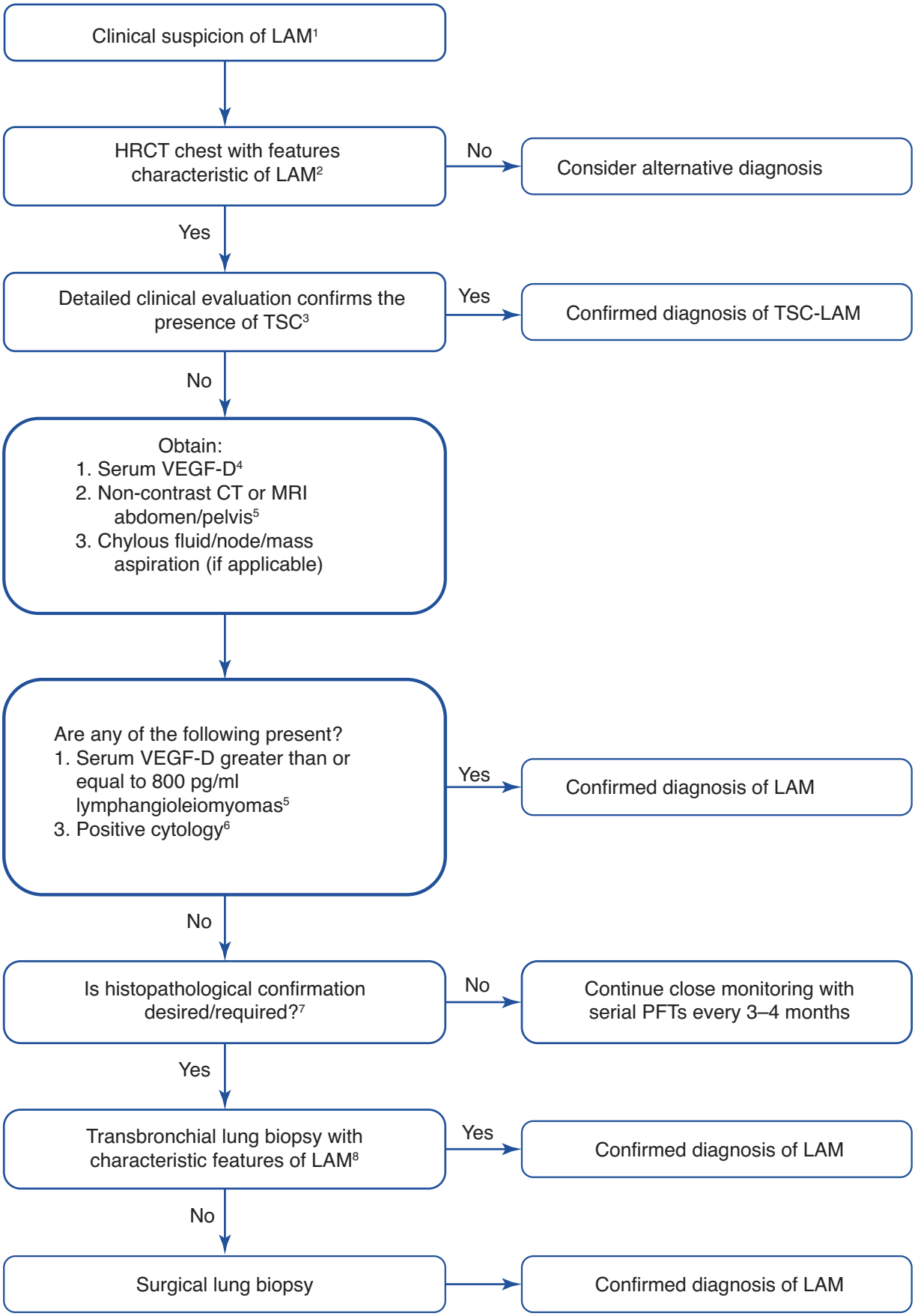
A definite diagnosis of LAM can be made without lung biopsy in around 2/3 of patients [44]. The lymphangiogenic growth factor, vascular endothelial growth factor-D (VEGF-D), is elevated in around 2/3 of patients with LAM, particularly those with lymphatic involvement [45]. A serum VEGF-D level of greater than 800 pg/mL has been shown to differentiate LAM from other cystic lung diseases when used

in combination with other clinical features, avoiding the need for lung biopsy [44, 46]. VEGF-D has also been correlated with disease severity and response to treatment with mTOR inhibitors [47]. At the time of writing, the test is not routinely available in all centres.

In those with suspected LAM and low VEGF-D levels, a lung biopsy is required to make a firm diagnosis. Whether to perform a lung biopsy or not should be discussed with the patient. In general terms, it is important to obtain a definite diagnosis in patients with progressive disease who require (or may require in the future) specific treatment for LAM. Those with few symptoms and stable lung function may be observed with biopsy being performed if the disease progresses [39]. Lung biopsy may be hazardous for patients with advanced disease and should only be considered if essential to management. Lung tissue may be obtained by transbronchial biopsy and when combined with immunostaining with the monoclonal antibody HMB45 can be diagnostic in some cases and avoid the need for a surgical biopsy [48, 49]. Video-assisted thoracoscopic biopsy is performed more often, gives a better indication of the tissue architecture which provides some prognostic information and has better sensitivity and specificity. The American Thoracic Society and Japanese Respiratory Society LAM Guidelines outline the diagnostic strategy and workup for those with suspected LAM (Fig. 19.6) [37].

In most cases the appearance of cysts surrounded by nodular proliferations of mesenchymal cells is sufficient to make the diagnosis in the correct clinical context. In early disease, LAM cells may be sparse and their detection can be improved by immunostaining for the smooth muscle markers α-smooth muscle actin and desmin, oestrogen and progesterone receptors [50, 51] (Fig. 19.7). HMB45 stains 30–70% of LAM cells in biopsy tissue. HMB45 is particularly useful diagnostically, not being expressed in normal lung.

Fig. 19.6 ATS/JRS diagnostic algorithm. The proposed strategy aims to confirm the diagnosis of LAM using the least invasive approach. (1) Suspect LAM in women presenting with worsening dyspnoea and/or pneumothorax/chylothorax. Most patients with LAM will have an obstructive defect on PFTs. Some patients, especially early in their disease course, may be asymptomatic and have normal PFTs. (2) Characteristic HRCT features are the presence of multiple, bilateral, round, well-defined, relatively uniform, thin-walled cysts in a diffuse distribution. The intervening lung parenchyma often appears normal. Other features sometimes present on CT scanning are chylous pleural effusions, pneumothorax, ground-glass opacities suggestive of chylous congestion, or multiple tiny nodules characteristic of multifocal micronodular pneumocyte hyperplasia in TSC-LAM. (3) Features suggestive of TSC include subungual fibromas, facial angiofibromas, hypomelanotic macules, confetti lesions, shagreen patches, positive family history of TSC, history of seizures or cognitive impairment, or presence of cortical dysplasias, subependymal nodules and/or subependymal giant cell astrocytomas on brain imaging. (4) Serum VEGF-D is currently available in a limited number of Centres including Cincinnati Children's Hospital Medical Center: www.cincinnatichildrens.org/ttdsl. (5) The diagnosis of angiomyolipoma can usually be made radiographically on the basis of the presence of fat in the tumours. Lymphangioleiomyomas can typically be diagnosed on the basis of characteristic radiographic appearance. (6) Cytological analysis of pleural fluid for the diagnosis of LAM is only available at select centres. (7) The decision to obtain tissue confirmation via invasive means should be made on a case by case basis. For some patients with mild disease and few symptoms, a clinical diagnosis of probable LAM with serial monitoring may be sufficient if a definitive diagnosis of LAM would not change management and some level of diagnostic uncertainty is acceptable to the patient and clinician. Every attempt should be made to establish the diagnosis of LAM with certainty before initiation of pharmacologic therapy with mTOR inhibitors. (8) Transbronchial biopsy has an estimated yield of greater than 50% for the diagnosis of LAM. Consultation with an expert centre is recommended in cases where transbronchial biopsy is being considered, including for the interpretation of the biopsy. *AML* angiomyolipoma, *CT* computed tomography, DI_{CO} diffusion capacity of the lung for carbon monoxide, *HRCT* high-resolution computed tomography, *MRI* magnetic resonance imaging, *mTOR* mechanistic target of rapamycin, *PFTs* pulmonary function tests, *TSC* tuberous sclerosis complex, *VEGF-D* vascular endothelial growth factor-D. (Adapted and reprinted with permission of the American Thoracic Society. Copyright © 2019 American Thoracic Society. Gupta, N., et al. (2017). "Lymphangioleiomyomatosis Diagnosis and Management: High-Resolution Chest Computed Tomography, Transbronchial Lung Biopsy, and Pleural Disease Management. An Official American Thoracic Society/Japanese Respiratory Society Clinical Practice Guideline." American Journal of Respiratory and Critical Care Medicine 196 (10): 1337–1348. The *American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society)


Clinical suspicion of LAM[1]
HRCT chest with features characteristic of LAM[2]
No
Consider alternative diagnosis
Yes
Detailed clinical evaluation confirms the presence of TSC[3]
Yes
Confirmed diagnosis of TSC-LAM
No
Obtain:
1. Serum VEGF-D[4]
2. Non-contrast CT or MRI abdomen/pelvis[5]
3. Chylous fluid/node/mass aspiration (if applicable)
Are any of the following present?
1. Serum VEGF-D greater than or equal to 800 pg/ml lymphangioleiomyomas[5]
3. Positive cytology[6]
Yes
Confirmed diagnosis of LAM
No
Is histopathological confirmation desired/required?[7]
No
Continue close monitoring with serial PFTs every 3–4 months
Yes
Transbronchial lung biopsy with characteristic features of LAM[8]
Yes
Confirmed diagnosis of LAM
No
Surgical lung biopsy
Confirmed diagnosis of LAM

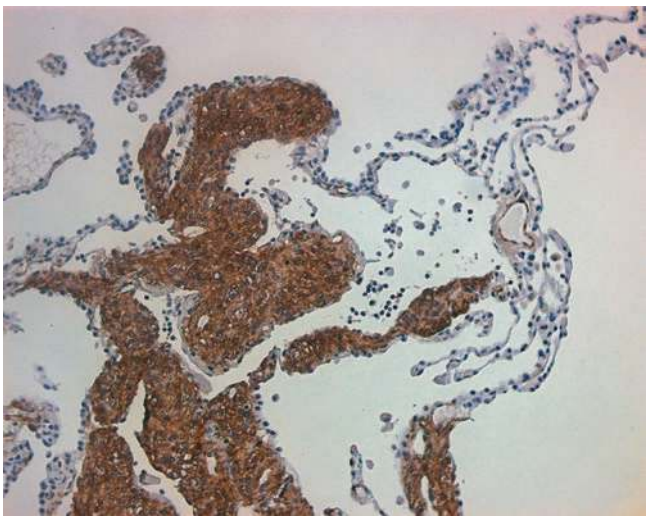


Fig. 19.7 Histological appearance of LAM. Lung section showing lung infiltrated by nodular proliferations of LAM cells which stain strongly for the smooth muscle marker, α-smooth muscle actin (brown)

Prognosis

It is currently difficult to predict prognosis accurately at diagnosis in individual patients. Various studies have associated clinical and pathologic features with outcome and it is reported that pre-menopausal status, presentation with breathlessness rather than pneumothorax, low K_{CO} at presentation, extensive LAM involvement of the lung biopsy and the presence of bronchodilator reversibility have been associated with more rapid disease progression in cohort studies [52–57]. However, these factors lack predictive power in individuals and in practice, calculation of the disease trajectory by estimating the change in lung function from the onset of symptoms or over a period of observation is probably the most reliable approach but risks an irreversible fall in lung function. Estimating survival for women with LAM is difficult as older studies have tended to over-represent patients with severe disease and worse outcome and it is important to put these studies into context for patients. Recent studies based on larger patient cohorts have estimated median transplant-free survival to be between 20 and 30 years [2, 58]. Improvements in lung transplant outcome and the impact of mTOR inhibitors mean that the prognosis for many patients with a recent diagnosis of LAM should continue to improve.

Management

General Measures

Women with definite or probable LAM are likely to benefit from general measures applicable to other chronic respiratory diseases and should be advised to maintain a normal weight, refrain from smoking, receive prophylactic vaccinations against influenza, pneumococcus and COVID19 and in those limited by dyspnoea undertake pulmonary rehabilitation [59]. Patients with LAM should receive advice on the symptoms of pneumothorax and what to do should these occur. Where relevant, symptoms of bleeding angiomyolipoma should also be discussed. Patients should avoid supplemental oestrogen, particularly in the form of the combined oral contraceptive and post-menopausal hormone replacement therapy [39].

The diagnosis of a rare or orphan disease can lead to a feeling of isolation and helplessness. This may be compounded if incorrect information is given about the disease at diagnosis or the patient is left to find out about the disease themselves. At this time, support from other patients through patient organisations can be very helpful. Strong patient groups exist in many countries, including the UK (www.LAMaction.org), the USA (www.thelamfoundation.org), France (http://asso.orpha.net/FLAM/) and others. In addition rare disease organisations, such as Orphanet (http://www.orpha.net/consor/cgi-bin/index.php), provide disease specific information.

Parenchymal Lung Disease

Longer-term management should be aimed at determining rate of disease progression and avoiding complications. During the course of the disease, lung function, particularly rate of decline of FEV_1, DL_{CO} and exercise tolerance should be assessed regularly. Routine follow-up, including spirometry and gas transfer, is generally scheduled between one to four times a year, with the interval between follow-up dependent upon the individual patient's previous rate of disease progression. On average patients lose FEV_1 by around 60–120 mL/year [41, 60], with loss most rapid in pre-menopausal women [57].

Pleural Disease

Patients with LAM are at high risk of pneumothorax. Pneumothorax occurs in 70% of patients and is recurrent in the majority of these. On average, patients have four pneumothoraces with each episode requiring 7 days in hospital [61]. Surgical intervention reduces recurrence rates and should be considered after the patient's first pneumothorax [37]. Evidence is only available from case series but suggests that surgical approaches may be more effective than pleurodesis via chest tube [25, 61]. In a significant number of cases, more than one surgical procedure is required. There is no clear evidence to suggest one procedure is superior to

another in patients with LAM. It is therefore appropriate to perform the minimal degree of pleural intervention which will prevent recurrence. Although pleural surgery results in increased peri-operative bleeding during transplant procedures, it does not seem to affect overall survival [62] and patients with pneumothorax should be treated with the most appropriate surgical procedure to treat pneumothorax [37].

Clinically significant chylous pleural effusions affect around one in ten patients. Occasionally these are stable and can merely be observed. Simple drainage usually results in rapid re-accumulation of the fluid [63]. Rates of fluid formation may be reduced by a low fat diet. Supplementation of medium chain triglycerides, that are not absorbed through the lymphatic system, has been used to avoid insufficient intake of lipids and the lipid soluble vitamins A, D, E and K. The use of the mTOR inhibitor rapamycin has been shown to reduce the volume of chylous pleural effusions and reduce the need for thoracentesis and other surgical interventions in these patients and is now the first-line treatment for these complications [64].

Renal Angiomyolipoma

Patients with angiomyolipomas should have their renal tumours monitored regularly. Once initial cross-sectional imaging using either CT or MRI has been performed, follow-up imaging in uncomplicated cases, where a straight forward measurement of growth is required, may be performed by ultrasound (Fig. 19.8). For small tumours with a low risk of bleeding, renal imaging once a year is recommended. For tumours at higher risk of bleeding, specifically, those greater than 4–5 cm in their longest axis, those with aneurysmal blood vessels and symptomatic tumours should be evaluated by a urologist, ideally with expertise in conservative management of these lesions [65]. As angiomyolipomas are frequently bilateral, treatment of large and symptomatic lesions should aim to conserve healthy renal tissue where possible. Those with TSC-LAM almost always have renal angiomyolipomas which tend to be bigger and more likely to bleed than those in patients with sporadic LAM [33] (Fig. 19.9). Current guidelines for those with TSC now suggest the consideration of mTOR inhibitor therapy for angiomyolipomas greater than 3 cm [32]. Physical approaches can be used particularly where risk of haemorrhage is high and include selective transcatheter embolisation or conservative nephron sparing surgery. Outcomes are similar between techniques although embolisation may be performed without the use of

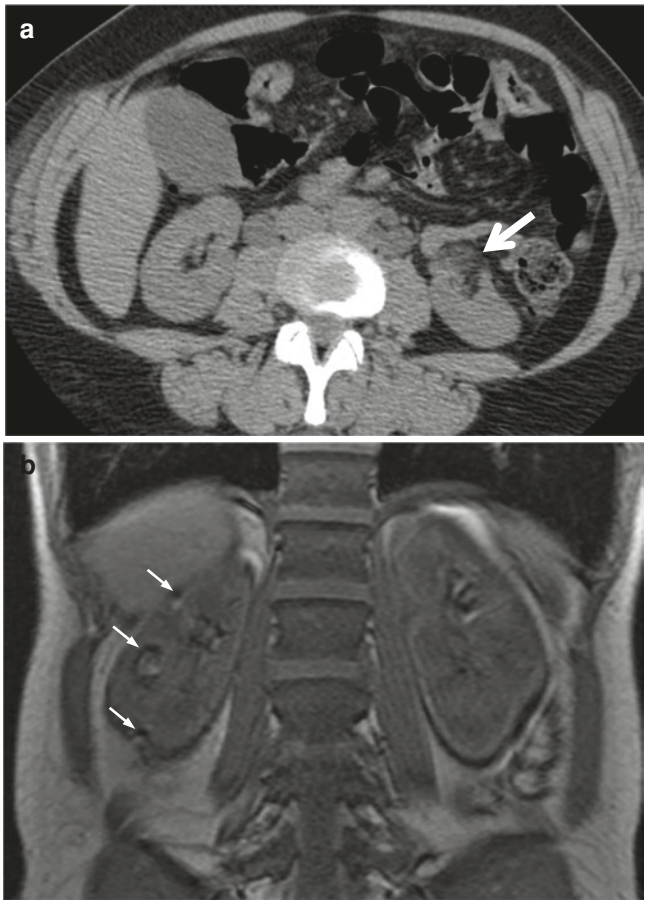


Fig. 19.8 CT appearances of angiomyolipoma in patients with sporadic LAM. (**a**) A characteristic small asymptomatic lesion in the anterolateral aspect of the left kidney (arrow). The low density areas containing fat are characteristic of angiomyolipoma. (**b**) Coronal section of a T1-weighted MRI image showing multiple small angiomyolipomas in the right kidney (arrows)

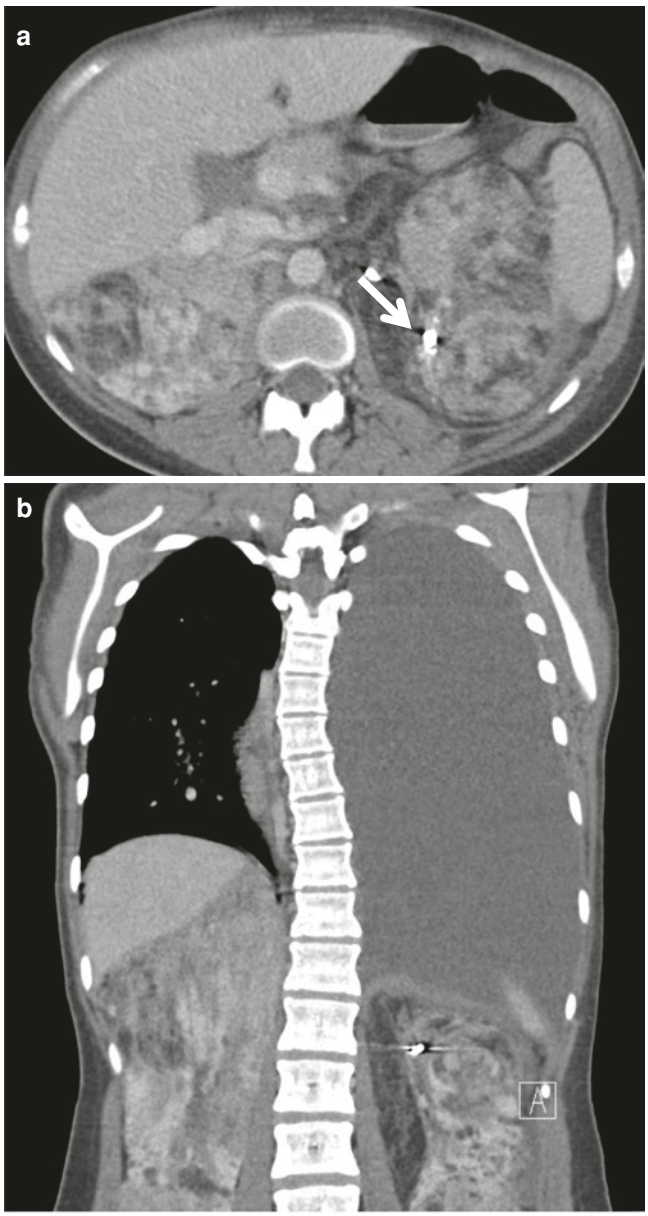


Fig. 19.9 Angiomyolipomas in TSC-LAM. (**a**) A cross-sectional image of a patient with TSC-LAM and multiple, bilateral angiomyolipomas greatly enlarging both kidneys. The arrow highlights an embolisation coil, used to treat a bleeding lesion. (**b**) A coronal CT of the same patient who presented with dyspnoea due to a large left chylous effusion

a general anaesthetic, including during episodes of haemorrhage and pregnancy [66].

Abdominopelvic Lymphatic Disease

Occlusion of the axial lymphatics by LAM cells can result in retroperitoneal cystic structures termed lymphangioleiomyomas. Although often asymptomatic, these lesions can be associated with abdominal distension and bloating [67] and characteristically enlarge throughout the day, which can be associated with worsening symptoms in the afternoon [68]. Rarely, larger lesions can cause pressure symptoms on other organs including the bladder. Abdominal lymphatic disease may be associated with chylous ascites which can also cause abdominal symptoms (Fig. 19.10). Surgical treatment of abdominal lymphatic masses can be followed by prolonged chylous leakage and is best avoided. A number of case reports and series have suggested that treatment with mTOR inhibitors is effective for symptomatic abdominopelvic lymphatic disease resulting in resolution of symptomatic chy-

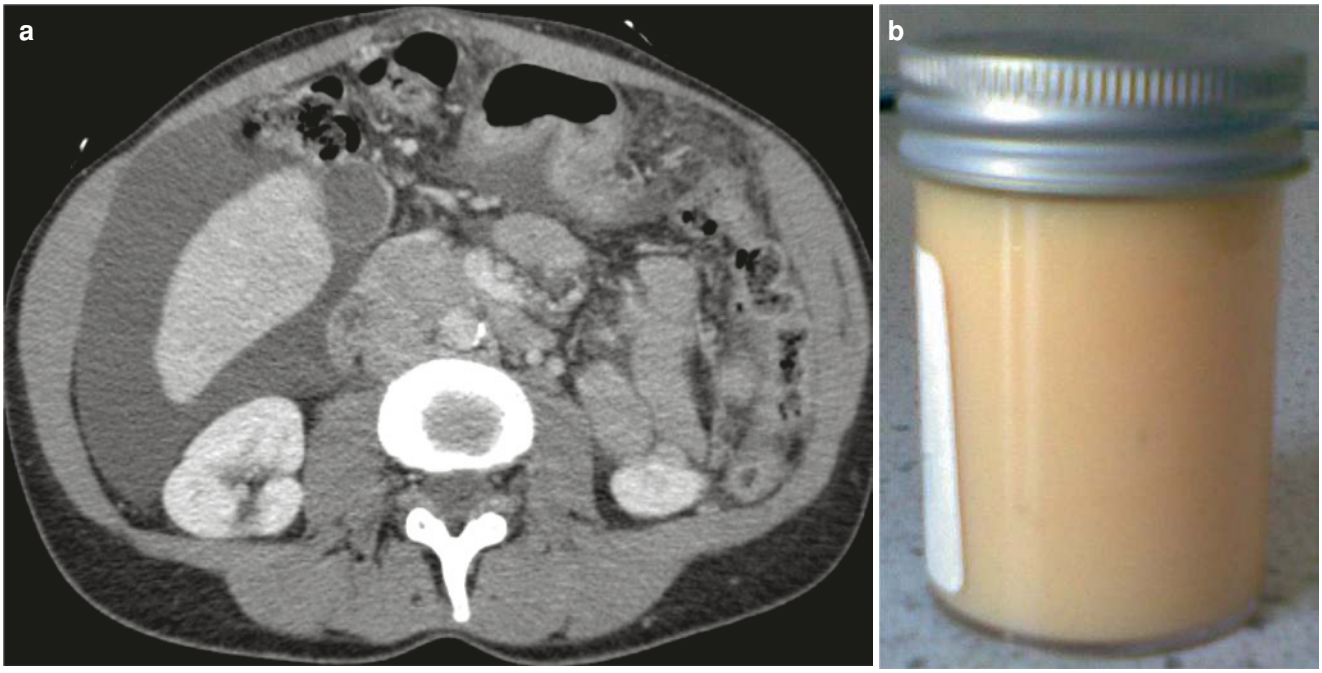


Fig. 19.10 Abdominal lymphatic disease. (**a**) CT showing dilated retroperitoneal lymphatics and chylous ascites. (**b**) The appearance of chylous fluid from a patient with LAM

lous ascites and lymphangioleiomyomas [64]. In resistant cases, imaging of the lymphatic circulation with a view to selective embolization rather than a 'blind approach' is essential.

Pregnancy

During pregnancy, women with LAM have an increased risk of pneumothorax, chylous effusion and possibly bleeding angiomyolipoma [25]. Patients with TSC-LAM have a 50% chance of having a child with TSC and these risks should all be discussed prior to pregnancy. The risks of pregnancy to the mother are likely to depend upon her lung function. At present it is unknown if pregnancy influences the course of LAM in the long term although one retrospective study suggests that pregnancy does not significantly accelerate the disease in most cases [69].

Tuberous Sclerosis

Patients with LAM presenting to chest physicians may have TSC, including previously undiagnosed disease. It is now recognised that LAM and angiomyolipoma are two of the leading causes of morbidity and mortality in adults with TSC [70, 71]. Although some patients with TSC may be under a TSC specialist, those with LAM as their main clinical manifestation of TSC may not. The main screening investigations for patients with TSC have been described in consensus statements and are summarised in Table 19.2 [32]. Those requiring genetic counselling, those with symptomatic epilepsy,

Table 19.2 Baseline investigations for patients with TSC

Clinical feature	Timing of assessment	Initial testing
Cognitive function	At diagnosis and at school entry	Neurodevelopmental testing
Retinal hamartomas	At diagnosis	Fundoscopy
Epilepsy	If seizures occur	Electroencephalography
Cardiac rhabdomyomas	At diagnosis or if cardiac dysfunction occurs	Electrocardiography Echocardiography
Renal angiomyolipomas and cysts	At diagnosis	Renal MRI
LAM	Women in adulthood and if pulmonary dysfunction occurs	High-resolution CT and baseline pulmonary function
Cerebral hamartomas and tumours	At diagnosis	Cranial MRI

Adapted from [32]

brain tumours, cognitive and other neurologic disorders, including autism, disfiguring skin lesions and renal disease, including polycystic kidneys, are all likely to benefit from specific interventions and monitoring by specialists in these areas. TSC patients with mutations in either *TSC-1* or *TSC-2* may develop LAM and those with mutations in *TSC-2* tend to have more lung cysts, worse lung function and are more likely to develop severe lung disease. *TSC-2* patients are also more likely to have large and symptomatic angiomyolipomas. *TSC-2* is located on chromosome 16 adjacent to *PKD1,* the gene associated with adult polycystic kidney disease. In some patients with large deletions in *TSC-2* there is also disruption of *PKD1* and these patients have a syndrome comprising TSC (including LAM and angiomyolipomas) and renal cysts with a high prevalence of renal failure [72, 73].

Lung disease in those with TSC may be as severe as in patients with sporadic LAM, presenting at a similar age with the same symptoms and resulting in respiratory failure and death [70]. However, this is not the case for the majority of those with TSC-LAM for whom the disease is mild and may not progress. Although over one-third of women with TSC will have lung cysts compatible with LAM, only a small minority of these patients will have significant pulmonary symptoms and a progressive fall in lung function. The increased use of CT screening in adult women with TSC has identified many of these patients with mild disease and their management should involve general measures for LAM, such as advice about pneumothorax and oestrogen avoidance [32]. Lung cysts also occur in men with TSC, but cysts tend to be few in number and very seldom cause symptoms or progressive disease [74, 75] and screening for LAM with thoracic CT scanning is only recommended for men with respiratory symptoms [32]. Whilst LAM can be the major health problem in adult women with TSC, for the majority of patients, LAM may be only one of their medical problems possibly with epilepsy, autism and learning difficulties being their major clinical issues with non-respiratory clinicians being their main care providers.

Drug Treatment

Bronchodilators

Around 25% of patients have a positive bronchodilator response according to American Thoracic Society criteria, particularly those with airflow obstruction [25, 53]. One recent study evidence suggests beta agonists might also alter disease progression in LAM, although this needs confirmation [76]. Although anti-muscarinic drugs are untested in LAM, long-acting beta agonist and anti-muscarinic combinations are frequently used in LAM [77].

mTOR Inhibitors

LAM cells have constitutive activation of the mTORC1 complex and in a randomised placebo controlled trial the mTOR inhibitor rapamycin (sirolimus) reduced the decline in FEV_1 of patients with impaired lung function [60]. Rapamycin also reduces the volume of angiomyolipomas [78, 79] and subependymal giant cell astrocytoma (SEGA) in patients with TSC [80]. Randomised controlled trials of other mTOR inhibitors, including everolimus, show good efficacy in other indications in patients with TSC, including angiomyolipoma [81], SEGA [82] and epilepsy [83]. Although evidence in pulmonary LAM is not as strong, everolimus appears effective for pulmonary [84] and extra-pulmonary disease [85]. mTOR inhibitors cause side effects in the majority of patients treated, particularly mouth ulcers, hyperlipidaemia, nausea, diarrhoea, proteinuria and peripheral oedema. Pneumonitis may also occur less commonly. An increased susceptibility to infections was an initial concern although this has not emerged as a significant problem [86]. For LAM, rapamycin is generally dosed to achieve a serum level of 5–10 ng/mL although some case series have suggested serum levels of 2–5 ng/mL might be equally efficacious and reduce side effects [87, 88]. Serum levels should be monitored at the start of therapy after 14 days, and at routine clinical review at least twice annually or if toxicity is suspected [89]. Current indications for use of mTOR inhibitors in LAM include an FEV_1 of less than 70% predicted [10], or decline in FEV_1 of 90 mL/year or greater [10, 60], chylous collections unresponsive to other therapies [64] and angiomyolipoma endangering renal function which are not suitable for surgical therapy [79]. In current practice the decision to use an mTOR inhibitor may also be influenced by the patient's likely future course, with those with younger, pre-menopausal subjects tending to have more active disease than post-menopausal women [57].

Anti-Oestrogen Therapy

Although LAM appears to be an oestrogen-dependent disease, observational and retrospective studies have suggested that blocking oestrogen production by oophorectomy, GnRH agonists [90], progesterone [41, 91] or oestrogen receptor binding drugs, such as tamoxifen, does not affect disease progression in the majority with established disease. Moreover, as these drugs are commonly associated with adverse effects, including increased growth of meningioma [92] and reduced bone density [90], they are not recommended for routine use [10, 39]. A small study has examined aromatase inhibition in post-menopausal women with LAM suggesting it was safe and worthy of further study [93].

Experimental Therapies

Studies of the molecular pathology of LAM have suggested a number of potential candidate drugs for LAM, both as stand-alone agents and as adjuncts to mTOR inhibition. Initial safety studies have been performed for simvastatin, chloroquine [94] with studies of resveratrol and tyrosine kinase inhibitors in progress.

Interventions for Advanced Disease

Those with severe disease are likely to develop hypoxaemia and secondary pulmonary hypertension and seem particularly prone to respiratory infections.

Oxygen Therapy

Hypoxaemia at rest, on exertion and overnight are common in patients with moderate to advanced disease. As patients with LAM are relatively young and may have few comorbidities they are frequently keen to keep active. It is therefore important to assess exercise-induced hypoxaemia and consider ambulatory oxygen therapy. At present there are no evidence-based guidelines for the use of oxygen therapy in LAM and not unreasonably, patients with LAM are often prescribed oxygen as for other patients with obstructive lung diseases.

Pulmonary Hypertension

A small proportion of patients with LAM develop pulmonary hypertension secondary to advanced lung disease and hypoxaemia [95]. LAM cells can infiltrate small pulmonary arteries to involve the pulmonary vasculature and rarely patients can develop pulmonary hypertension earlier in the course of the disease [96]. Screening for pulmonary hypertension by echocardiography may be useful for those with advanced disease, but is only likely to be helpful in patients with early disease if dyspnoea is out of proportion to their lung function defect.

Although not well described or studied, it is apparent that patients with advanced disease often suffer respiratory infections, both with typical organisms but also *Pseudomonas* and atypical mycobacteria. Aggressive investigation and treatment of infections in these patients can improve quality of life.

Patients with LAM and advanced disease may be treated by lung transplantation, including those with TSC-LAM. Patients with LAM represent around 1% of lung transplantees and the overall survival for these patients is favourable when compared with lung transplantation for other lung diseases [97, 98]. At the time of transplant, patients generally have limited exercise tolerance with New York Heart Association functional class III or IV and severe impairment in lung function with resting hypoxaemia [62, 97]. Particular aspects of the pre-transplant assessment for these patients should include a thorough assessment of renal angiomyolipomas. Although angiomyolipomas are not associated with post-transplant renal failure, pre-transplant embolisation may be needed to prevent renal haemorrhage postoperatively. Women with LAM tend to be at risk of low bone density due to chronic lung disease and anti-oestrogen therapies [99]. As many of these patients require transplantation close to the menopause, bone mineral density should be assessed and where necessary treated with bisphosphonates as appropriate. Prior pleural interventions, particularly surgical treatment of pneumothorax and pleural effusions increases the incidence of peri-operative bleeding and operative duration but not overall survival [62]. The effect of mTOR inhibitors on wound healing post-transplantation has been a concern for transplant centres [100]. This must be balanced against the risk that withdrawal of mTOR inhibitors results in accelerated lung function decline. The evidence in this area is still evolving and currently varies with the individual transplant centre. Currently, many centres require cessation of mTOR inhibitors when patients are listed for transplant although some will continue sirolimus until the day of transplant, whilst others recommend the use of everolimus in pre-transplant patients as the shorter half-life is considered to reduce the risk of post-transplant wound dehiscence [101]. Although studies have suggested there is no overall differ-

Box 19.1 ATS/JRS Diagnostic Criteria for LAM

A definite diagnosis of LAM can be established when there is a compatible clinical history and characteristic HRCT *plus* one or more of the following:

- TSC
- Renal angiomyolipoma*
- Serum VEGF-D ≥ 800 pg/mL
- Chylous pleural effusion or ascites (confirmed by biochemical fluid analysis)
- Lymphangioleiomyomas*
- Cytology showing LAM cells or LAM cell clusters in chylous effusions or lymph nodes
- Lung or extra-pulmonary biopsy confirming LAM

*Angiomyolipoma and lymphangioleiomyomas can normally be diagnosed by a characteristic radiographic appearance. Adapted from [37].

Case Vignette

A 41-year-old woman developed exertional dyspnoea at the age of 18 and was treated for asthma. Breathlessness worsened over years and was poorly responsive to treatment. Over this period she worked as a technician and gave birth to five children. Some years later she developed abdominal discomfort and became aware of a fullness in her abdomen: irritable bowel syndrome was diagnosed. Four years later, following severe flank pain, she was admitted to hospital. A CT scan showed an 18-cm bleeding angiomyolipoma arising from the right kidney: the tumour was treated successfully by two-stage embolisation. The abdominal CT scan also revealed multiple lung cysts in the lung bases and a high-resolution chest CT was performed which showed changes consistent with advanced LAM. There were no signs of TSC and *TSC* gene analysis was normal. Sporadic LAM with renal angiomyolipoma was diagnosed. Lung function showed irreversible airflow obstruction with an FEV_1/FVC ratio of 34% and a gas transfer of 49% predicted. The history suggests LAM that has been present for over 20 years during which time her FEV_1 has deteriorated by >100 mL/year. Due to advanced and progressive lung disease she was treated with bronchodilators and sirolimus.

ence in survival between those treated with single or double lung transplant, occasionally over-inflation of the native lung can impair the function of the graft after single lung transplantation. Post-transplant, normal practice is to use tacrolimus-based regimens rather than sirolimus as this is likely to be optimal for graft function long term [102]. The outcome for women with LAM is at least as good as other lung diseases [103], and whilst recurrent LAM post-transplant has been reported, this is seldom clinically relevant and not a contraindication to transplant.

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Diffuse Cystic Lung Disease

20

Francis X. McCormack and Brian M. Shaw

Introduction

Diffuse cystic lung diseases (DCLDs) are a group of disorders with a broad differential that are defined by the presence of multiple, thin-walled, air-filled parenchymal lucencies, typically without other diffuse parenchymal changes. The most common DCLDs seen in pulmonary clinics are lymphangioleiomyomatosis (LAM), pulmonary Langerhans cell histiocytosis (PLCH), Sjogren cystic lung disease, and Birt-Hogg-Dubé (BHD) syndrome. However, the differential also includes metastatic neoplasms, smoking-related disorders, infections, congenital anomalies, hypersensitivity pneumonitis, and many other disorders. To remain focused on true ("primary") DCLDs, we will not discuss forms of thin-walled cystic change that can accompany diseases in which interstitial lung disease or other parenchymal change is present, such as in sarcoidosis or idiopathic pulmonary fibrosis.

The most common presentations of DCLDs are chronic dyspnea on exertion, pneumothorax, or incidental discovery of cystic changes on a HRCT. As with all diseases, the first step in establishing the correct diagnosis is a detailed history and physical examination. Classical findings are outlined in Table 20.1.

High-resolution computed tomography (HRCT) scanning can substantially narrow the differential, and in some cases can provide a diagnosis. For HRCT to be useful to the physician, it is essential to understand the radiographic definition of a cyst, and to be able to distinguish it from other structures, such as emphysematous air space dilation, cavities, blebs, bullae, and pneumatoceles (Table 20.2). Review of the HRCT by a pulmonary radiologist familiar with the DCLDs is critical as the radiographic characteristics of cysts can be diagnostically useful (Table 20.3).

Table 20.1 History and gender predilection of common DCLDs

Disease	History of present illness associations	Gender predilection
LAM	Dyspnea on exertion, spontaneous pneumothorax, renal AML	Much more common in women than men
PLCH	Spontaneous pneumothorax, skin lesions, osteolytic lesions, diabetes insipidus, smoking/exposure to smoke	Historically more common in men, now more equal
BHD	Spontaneous pneumothorax, renal tumors	Equal in men and women
LIP/FB	Rheumatological problems such as sicca syndrome, arthralgias, Raynaud's, immunodeficiencies, viral infections such as HIV or EBV	Slightly more common in women than in men

LAM lymphangioleiomyomatosis, *PLCH* pulmonary Langerhans cell histiocytosis, *BHD* Birt-Hogg-Dubé, *LIP* lymphocytic interstitial pneumonia, *FB* follicular bronchiolitis, *AML* angiomyolipoma, *HIV* human immunodeficiency virus, *EBV* Epstein-Barr virus

Table 20.2 Radiographic definitions

Lesion	Radiographic definition
Cyst	A thin-walled (<2 mm), air-filled, spherical lucency with a well-defined lung/air space interface [169]
Cavity	A thick-walled lesion (>2 mm) filled with air or fluid that is more irregularly shaped than a cyst and is located within a consolidation, mass, or nodule [170]
Bullae	A sharply demarcated region of emphysema that is 1 cm or more in diameter that has a wall thickness of less than 1 mm [170, 171]
Bleb	A gas containing space that is located within the visceral pleura of the lung [170]
Pneumatocele	A thin-walled air-filled space within the lung that is typically the result of trauma or an infection [171]

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Table 20.3 Characteristic chest CT findings of selected DCLDs

Disease	Characteristic chest CT findings
Lymphangioleiomyomatosis	Smooth, round cysts with a diffuse and random distribution that are typically 2 mm to 2 cm in size. Rarely contain internal structures
Pulmonary Langerhans cell histiocytosis	Bilateral and symmetric lesions characterized by upper- and mid-lobe predominant nodules and cysts with sparing of the costophrenic sulci. Cysts often irregularly shaped and of varying size. Rarely contain internal structures
Birt-Hogg-Dubé syndrome	Round and lentiform cysts with a basilar, mid-lobe, and subpleural distribution that are elliptical or lentiform in shape and typically less than 1 cm in size. Some contain internal structures
Amyloidosis	Round cysts with a random distribution, often associated with nodular consolidations
Lymphoid interstitial pneumonia/Follicular bronchiolitis	Diffuse and randomly distributed cysts that are variable in size and may contain internal structures

Several pathophysiologic mechanisms have been proposed to explain cyst formation within the lung, including ball valve obstruction with distal over-inflation, ischemia, or remodeling secondary to matrix-degrading enzymes [1]. Unfortunately, there is a paucity of good animals models addressing this question and the quality of evidence supporting these pathogenic mechanisms is weak.

Common Diffuse Cystic Lung Diseases

Lymphangioleiomyomatosis

LAM is a rare cystic lung disease that primarily affects females and is caused by infiltration of the lung by smooth muscle cells that contain growth-activating mutations in tuberous sclerosis genes. The origin of these neoplastic cells remains unclear, but it is apparent that they arise from an extrapulmonary source and spread to the lungs via the blood and lymphatics [2, 3]. Recent single-cell RNA sequencing data of LAM cells suggests a possible uterine primary [4], but other candidates include kidney, bone marrow, genitourinary tract, and lymphatic system.

LAM occurs in patients with tuberous sclerosis complex (TSC-LAM) and in a "sporadic" form in patients who do not have tuberous sclerosis (S-LAM) [5]. In TSC-LAM, tuberous sclerosis mutations are found in the germ line, while in S-LAM, tuberous sclerosis mutations are found only within the neoplastic lesions [6, 7]. TSC-LAM occurs in >30% of women with TSC [8–10] and in 10–15% of men with TSC [11, 12]. S-LAM appears to be almost entirely restricted to women, with one possible exception in the literature, mentioned with the caveat that mutational analysis is not perfectly sensitive and low-level mosaicism for TSC mutations is difficult to exclude [13].

The average age at diagnosis is about 35 years, but cases have been seen in teenagers [14] and octagenarians [15]. The prevalence is reported to be about 3.4–7.8 per million women in the US and Europe [16], but as with all rare diseases is likely underestimated [17].

Pathogenesis

To date, S-LAM has been associated with only *TSC2* mutations, while TSC-LAM is caused by mutations within *TSC1* or *TSC2,* with TSC1 disease being less common and less severe. In patients with TSC-LAM, mutations in TSC genes are present in all cells, and neoplasms and dysplasias arise in various organs when "second hit" somatic TSC mutations occur. In patients with S-LAM, mutations in both copies of the parental *TSC2* alleles occur post-conception and within somatic tissues and tend to be confined to lesions in the lung, kidney, and lymph nodes [6, 18]. In both cases, the cells that comprise the pulmonary lesions are thought to arise from extrapulmonary sources.

TSC1 and *TSC2* encode for proteins called hamartin and tuberin, respectively, which form a complex that maintains mTOR in an inactive state. Deficiency or dysfunction in either protein results in upregulated activity of mTOR, which increases protein translation and leads to inappropriate cellular proliferation, migration, and invasion. In LAM cells, this results in suppression of autophagy and expression of the metastasis promoting lymphangiogenic vascular endothelial growth factors, VEGF-C and VEGF-D [2]. Genetic analysis of blood [19], lymphatic fluid, and recurrent LAM lesions in donor allografts after lung transplantation [20–22] have revealed that LAM cells circulate and metastasize [23]. Serum levels of VEGF-D are elevated in 50–70% of patients with LAM, and are both diagnostically and prognostically useful [24–26].

Several studies have reported increased LAM symptoms and/or progression when estrogen levels are high, such as during pregnancy [27, 28] or when exogenous estrogen is taken [29, 30], and disease progression slows after menopause when estrogen levels fall [31]. A recent survey-based study of 307 premenopausal women with LAM revealed that about one-third of women have cyclic worsening of their chest symptoms, including shortness of breath and chest tightness during menstruation [32]. Analysis of the MILES cohort showed that there was a greater rate of decline of FEV_1 in patients who were premenopausal versus those that

were postmenopausal [33]. The role of estrogen in LAM is not completely understood and is currently a key focus of LAM research.

Pathologic and Radiographic Characteristics

Histopathological evaluation shows smooth muscle cell invasion of the lung parenchyma, airways, lymphatics, and blood vessels associated with nodular accumulation and thin-walled cysts [34]. LAM lesions express VEGF-C and VEGF-D and contain lymphatic channels lined by endothelial cells that express their cognate receptor, VEGFR-3 [35, 36]. LAM cells classically spare tissue planes as they expand the interstitium but can invade and destroy surrounding vessels, airways, and other tissue [37, 38].

Radiographically, pulmonary cysts in LAM are diffusely distributed throughout the lung, vary in size from 2 mm to 2 cm, and are well-defined, round, and thin-walled (Fig. 20.1) [39].

Diagnostic Approach

The diagnosis of LAM should be considered in any young to middle-aged nonsmoking female with a pneumothorax [40], asymptomatic women with TSC after age 18 [41, 42], patients with an angiomyolipoma [43] or a lymphangiomyoma, cysts in the lung bases on abdominal CT, unexplained chylous ascites or chylous effusions, and progressive dyspnea in females with presentations that are atypical for COPD or asthma.

Per the European Respiratory Society Guidelines, the diagnosis of LAM can be made with characteristic cystic changes on CT in a patient with tuberous sclerosis, angiomyolipoma, lymphadenopathy, or chylothorax [44]. The ATS/JRC extended the diagnostic criterion to include serum VEGF-D level ≥800 pg/mL in a patient with typical HRCT findings [26]. If these associated clinical and serologic features are not present, and diagnostic certainty is required or desired, a biopsy or cytologic evaluation is indicated for diagnosis. Transbronchial biopsy (which has a yield of about 60%) [45, 46], transbronchial cryobiopsy [47], or cytological examination of pleural fluid, lymph nodes, or masses [48] represent appealing, nonsurgical approaches to obtaining a diagnosis. Video-assisted thoracoscopic surgery (VATS) lung biopsy is an option when the diagnosis remains elusive despite deployment of all less invasive approaches. In all cases in which tissue is obtained, evaluation by an expert pathologist who is familiar with LAM is essential. LAM is normally negative on fluoro-deoxyglucose positron emission tomography (FDG-PET), which helps distinguish it from other conditions associated with abdominal and pelvic masses, such as malignant PEComa, lymphoma, or ovarian cancer [49].

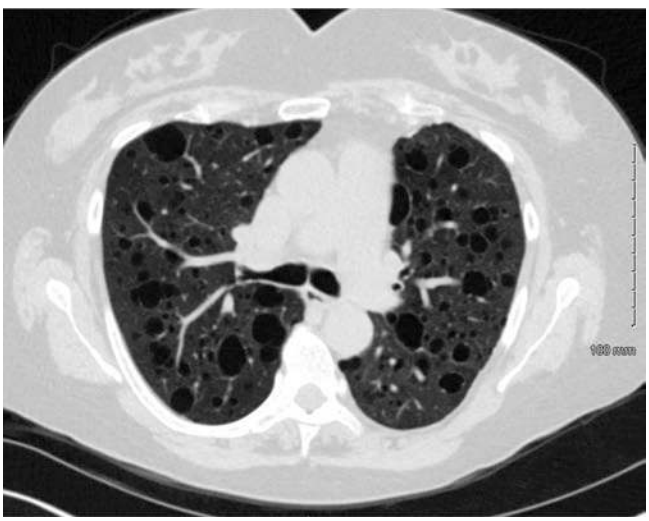

Fig. 20.1 Patient with lymphangioleiomyomatosis. CT imaging demonstrating small round cysts that are diffusely distributed

Prognosis and Management

LAM is characterized by progressive dyspnea on exertion, recurrent pneumothoraces, and, less frequently, chylous pleural effusions and chylous ascites [50]. In the pre-sirolimus era, 55% of LAM patients had dyspnea with activities of daily living (ADLs), 20% required supplemental oxygen, and 10% died within 10 years of diagnosis [51, 52]. A longitudinal analysis of 217 patients enrolled in the National Heart, Lung, and Blood Institute LAM Registry revealed transplant-free survival at 5, 10, 15, and 20 years to be 94%, 85%, 75%, and 64%, respectively, with a median survival of greater than 20 years (also pre-sirolimus era data) [53]. Poor baseline pulmonary function and premenopausal status at diagnosis were associated with elevated risk of progression and need for transplant [53]. Airflow obstruction and hyperinflation are the most common PFT alterations and forced expiratory volume in 1 s (FEV_1) typically declines at a rate of 50–250 cm^3 per year [28, 31, 54–56]. In patients with S-LAM, premenopausal status, and elevated VEGF-D levels [24] are associated with a more rapid decline in lung function. All of these prognostic and outcome measures need to be reevaluated to determine the impact that mTOR inhibitor therapy on the natural history of disease.

Angiomyolipomas that are greater than 4 cm in size have an elevated risk for spontaneous bleeding [57] and treatment with an mTOR inhibitor is considered the first line approach [58]. Embolization is an alternative for large tumors, especially in cases where bleeding has occurred or aneurysmal content is high. Air travel is safe for most patients with LAM [59, 60]. For patients with reversible airflow obstruction on pulmonary function testing or in patients who report symptomatic benefit, bronchodilators are indicated [61]. Pleurodesis should be performed following the first pneumothorax as the rate of recurrence is about 70% [62].

The Multicenter International LAM Efficacy of Sirolimus (MILES) Trial was a double blind, randomized, parallel group trial of 1 year of treatment with sirolimus or placebo followed by 1 year of observation [63]. Patients who were treated with placebo lost about 10% of their lung function over the course of the treatment year, while patients who received sirolimus had stable lung function, improved functional performance, and improved quality of life. Patients with increased VEGF-D levels responded better to treatment with sirolimus and declined faster without treatment [24]. During the observation year, lung function decline resumed in the sirolimus group and paralleled that of the placebo group. The ATS/JRS LAM Clinical Practice Guidelines recommendations are that sirolimus be used for LAM patients who have an FEV_1 that is less than or equal to 70% predicted, problematic chylous effusions, rapidly progressive disease, or a substantial disease burden based on other lung function parameters, such as DLCO [64].

The median survival after transplant in LAM is 12 years [65], which is greater than most lung disorders, most likely because LAM patients with end-stage lung disease typically have few prior co-morbidities. Although several cases of recurrence of LAM in the allograft have been reported [20, 22, 66–68], graft failure due to recurrence is unusual and is not considered a contraindication in most centers [69]. Lung transplantation can be safely performed in most patients despite prior pleurodesis [66, 67, 70]. Sirolimus has been associated with bronchial dehiscence post-transplantation, so discontinuation is recommended on the date that transplant is performed [71, 72].

Pulmonary Langerhans Cell Histiocytosis (PLCH)

PLCH is a DCLD that is characterized by centrilobular lesions composed of CD1a positive dendritic cells (DCs) and other inflammatory cells with surrounding fibrosis. Approximately 90% of adult PLCH patients smoke cigarettes or marijuana or have a history of substantial second-hand smoke exposure [73–75]. Dyspnea and/or cough are present in many PLCH patients, but some patients have minimal or no symptoms [74]. Constitutional symptoms, such as weight loss and fever, occur in up to 20% of patients [74]. Pneumothorax is the presenting symptom in about 15% of patients [76] and a similar proportion of patients have extra-pulmonary involvement, such as lytic bone lesions, diabetes insipidus, or skin lesions [74, 77–80]. Disease course is variable and unpredictable, ranging from spontaneous resolution, to complete remission with smoking cessation, to rapid progression despite abstinence from tobacco.

Pathogenesis

Through advances in research, driven largely by discoveries in the form of LCH that occurs primarily in pediatric patients and has no association with smoking [81–83], PLCH is understood to be an inflammatory myeloid neoplasm. In PLCH, abnormal dendritic cells (DCs) with activating *MAPK* mutations accumulate within the pulmonary parenchyma in response to cigarette (or marijuana) smoke exposure [75] and recruit inflammatory and stromal cells. Data from human studies and mouse models indicate that the mutant DCs and accumulated inflammatory cells release cytokines, cytotoxic mediators, and matrix-degrading enzymes, which leads to nodule formation and cystic destruction [84].

Mutations in *BRAF*, *ARAF,* and *MAP2K1* genes have been found in myeloid lineages in children and adults with LCH, and in patients with PLCH [85–87]. The most commonly identified *BRAF* mutation in PLCH is V600E. The *MAPK* mutations found in the PLCH lesions are similar to mutations found in melanoma [88], hairy cell leukemia [89], papillary thyroid cancer [90], as well as other histiocytic disorders, such as Erdheim-Chester disease (ECD) [91].

Pathological and Radiographic Characteristics

Histologically, PLCH lesions are nodular, patchy, peribronchiolar infiltrates that are composed of dendritic cells, lymphocytes, macrophages, and eosinophils. DCs can be identified within the lesions by their unique morphological and immunohistochemical features, including staining for S-100 and CD1a.

The underlying mechanisms responsible for lung destruction in PLCH are not well understood. The CD1a positive cells in the nodules of PLCH express membrane maturation markers that are similar to those on the surface of DCs after being activated by cytokines or pathogens [92]. Direct cytotoxic damage by pulmonary macrophages, natural killer cells and cytotoxic CD8 T cells that have been aberrantly activated by the abnormal DCs likely contribute to destructive remodeling [84]. Expression of the BRAF V600E mutation in CD11c myeloid cells was recently shown to result in secretion of CCL7, increased responsiveness to CCL20, and enhanced cellular survival and recruitment [93]. There are several different metalloproteinases in PLCH nodules that are thought to participate in tissue destruction [75, 94, 95].

Radiographically, PLCH lesions are typically bilateral, symmetric, upper-lobe predominant nodules and cysts that spare the bases, especially the costophrenic sulci (Fig. 20.2) [96–98]. In the early stages of disease, small and irregular nodules can predominate [74]. As disease progresses, the nodules form, cavitate, and evolve into thin-walled, irregular, bilobed, clover leafed, or branched cystic structures [98]. Longitudinal studies have shown that the nodules can completely resolve without obvious sequela, but the cysts tend to persist or enlarge [99]. Ground-glass opacities, linear densities, and emphysematous bullae can also be seen as part of the known spectrum of cigarette smoke-induced lung injury [100].

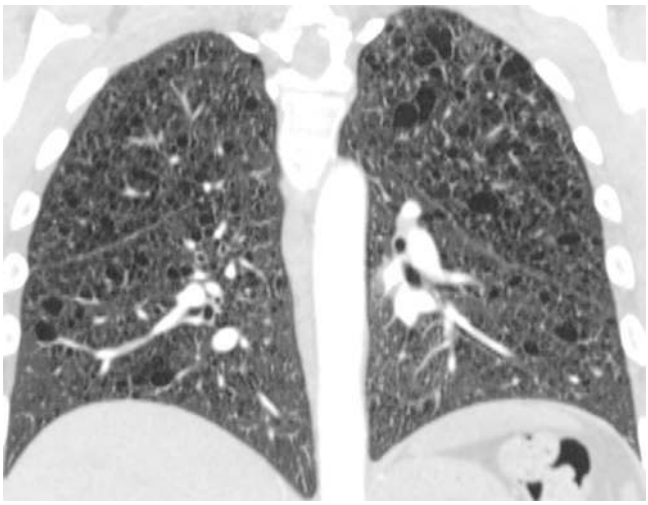

Fig. 20.2 Patient with pulmonary Langerhans cell histiocytosis. CT imaging showing symmetric lesions that are predominantly located in the upper and mid-lung zones with sparing of the costophrenic angles

Diagnostic Approach

PLCH should be considered in individuals with cystic or nodular upper-lobe predominant infiltrates on chest imaging, in current or former cigarette smokers with or without a history of spontaneous or recurrent pneumothorax, and in any patient with lung infiltrates and a history of skin rash, bone lesions, or diabetes insipidus. Pulmonary function testing may be normal, or may reveal obstructive, restrictive, or mixed abnormalities [74]. Normal lung function or mild restrictive impairment is typically present in earlier phases of disease, while obstructive defects with air trapping and reduced diffusing capacity for carbon monoxide can predominate in advanced stages [74, 101]. In patients with advanced PLCH, hypoxemia with rest, exercise and sleep may develop, resulting in a requirement for supplemental oxygen.

It is possible to make the diagnosis of PLCH with CT alone in patients with classical imaging and a history of smoke exposure. In cases where uncertainty remains, bronchoscopy with transbronchial lung biopsy can be diagnostic in about 30% of cases [45, 102]. Surgical lung biopsy may be required for definitive diagnosis in some cases. PLCH lesions are often FDG avid and PET scanning may be helpful to detect occult extrapulmonary disease or to follow the response to therapy [103].

Prognosis and Management

Smoking cessation and avoidance of second-hand smoke are the cornerstones of PLCH management. Stabilization and even regression following these interventions are well established in the literature [73, 104]. The recent discovery of *MAPK* mutations in PLCH has suggested the possibility that targeted therapeutic interventions could be effective, similar to other histiocytic disorders and malignancies harboring activating mutations in key signaling pathways. Pharmacotherapy with MAPK pathway inhibitors is effective in children with LCH, but there have been no trials in adults, and it should only be considered in patients with potentially reversible disease. Assessment and treatment of complications, including pneumothorax, hypoxemic respiratory failure, diabetes insipidus, and secondary pulmonary hypertension, apply to important subsets of PLCH patients.

Some patients experience very little decline in lung function, while others develop progressive lung disease, even after smoking cessation [101]. Serial PFTs at 3–6-month intervals are useful for tracking disease trajectory in new patients and in those with disease that is evolving [101]. Oral corticosteroid therapy is often attempted but is rarely efficacious. Case reports and small series suggest that chlorodeoxyadenosine (cladribine) may induce stabilization or even improvement of nodular lesions [105–107] and in some cases has been shown to improve lung function, CT findings, and pulmonary hemodynamics when smoking cessation has failed to halt disease progression [108–110].

Patients should be screened for pulmonary hypertension by echocardiography at the time of diagnosis and if there are any changes in exercise tolerance. Spontaneous pneumothorax tends to recur frequently, with rates approaching 60% [76, 111]. Surgical pleurodesis can substantially reduce the risk of recurrence to 0–20% [76, 111]. Lung transplantation outcomes for PLCH is similar to other advanced pulmonary diseases, although recurrence in the transplanted lung has been reported [112–115]. In a study of 39 patients from France, there was a recurrence rate of about 20% in the transplanted lung [116].

Birt-Hogg-Dubé Syndrome (BHD)

BHD is a rare, autosomal dominant disorder that is characterized by renal neoplasms, hair follicle tumors, and pulmonary cysts. Cystic lung lesions in BHD are typically discovered in the fourth or fifth decade of life [117, 118], but rarely can been seen in teenagers and octogenarians [119]. Although pneumothorax has been described in BHD in the absence of detectable cysts by HRCT, by age 50, there is >80% penetrance of pulmonary cysts [120, 121].

Approximately 24% of patients with BHD develop a pneumothorax, and there is a very high (75%) rate of recurrence, so pleurodesis is recommended with the first event [122]. In an epidemiological study of 312 patients with BHD, the median age of initial pneumothorax was 38 years old (range 15–69) [123].

Pathogenesis

BHD is caused by mutations in the folliculin (*FLCN*) gene, which encodes the tumor suppressor protein folliculin, a sig-

naling protein that impacts the mTOR, E-cadherin, LKBP1, and AMPK signaling pathways [124–127]. A proposed mechanisms of cyst formation is decreased structural integrity along the alveolar septal junctions due to dysregulation of key intercellular adhesion pathways, which renders them susceptible to mechanical damage during the respiratory cycle [124, 125].

Pathological and Radiographic Characteristics

Cysts in BHD are typically thin-walled, often with elliptical or oblong shape, and are predominantly located within the basilar segments (Fig. 20.3) [128]. Cysts tend to abut the pleura and pulmonary vessels [128]. In a study of 229 cysts from 50 patients with BHD, 88% involved interlobular septa and 14% contained intra-cystic structures [125]. On histological evaluation, the cysts are lined by pneumocytes, and surrounded by normal lung parenchyma, without evidence for cellular infiltration or inflammation [125], which distinguishes them from LAM and PLCH, but not from the air-filled, histologically bland structures that are characteristic of emphysema.

Diagnostic Approach

A spontaneous pneumothorax in a young patient should raise the suspicion of BHD. A thorough skin examination is important, as many (but not all) patients with BHD will have characteristic papular, waxy skin lesions of the face, neck, or upper trunk. Skin biopsy can be useful in patients with skin lesions and a spontaneous pneumothorax, as the finding of the characteristic hair follicle tumors, fibrofolliculomas or trichodiscomas, is diagnostic for BHD in the right clinical context [122].

HRCT is highly useful in the initial evaluation of a patient with suspected pulmonary BHD. Approximately 80–100% of patients with BHD have pulmonary cysts [121, 122, 124], and their characteristic features and distribution can strongly suggest the diagnosis. A definitive diagnosis typically requires a family history of a confirmed case, tissue confirmation from kidney or skin biopsy, or genetic testing.

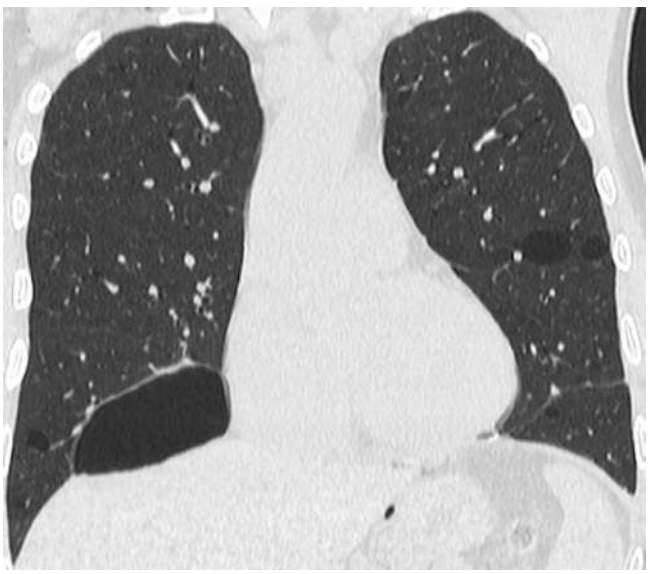

Fig. 20.3 Patient with Birt-Hogg-Dubé. CT imaging showing discrete cysts that are located in the middle and lower lung zones

Abdominal imaging of the kidneys is useful for identifying BHD-associated renal masses and tracking their growth trajectory. The most common renal neoplasms in BHD are chromophobe adenomas and oncocytomas, and they are bilateral and multifocal in more than half of patients [129]. Approximately 20–30% of patients with BHD will develop renal cell carcinoma [121, 130, 131] at a mean age of 46 years (range 20–83 years) [132]. Other renal malignancies such as clear cell, papillary, and mixed pattern carcinomas can also occur [129, 133, 134]. In patients who develop early onset (<50 years old) multifocal or bilateral renal cancer, the diagnosis of BHD should be strongly considered [130].

Not all patients with pulmonary manifestations of BHD will have a positive family history or classical skin or renal findings [117, 135, 136]. Genetic counseling and testing for *FLCN* mutations should be recommended to patients suspected to have BHD to confirm the diagnosis and to facilitate screening of family members.

Prognosis and Management

BHD does not commonly progress to respiratory failure. In a study of patients with BHD, pulmonary function tests revealed a mild reduction in diffusion capacity for carbon monoxide, but there was little evidence of lung function decline over time [137]. Due to frequent recurrences, pleurodesis after the first pneumothorax should be considered [121]. Air travel is generally safe [138], although reports of delayed pneumothorax have emerged [139], and patients with a prior pneumothorax, extensive cystic changes, or new/worsening chest symptoms should be evaluated by a pulmonologist prior to travel [140].

Patients with a diagnosis of BHD should be screened for the presence of renal tumors beginning at 20 years of age [130, 141]. Ultrasonography is not recommended for screening as it lacks sensitivity for detecting small lesions [142]. MRI is superior to CT for serial screening to avoid the cumulative radiation from CT scans [141]. If there are no abnormalities on the initial scan, imaging should be repeated within 3 years [141]. Renal cancer associated with BHD is indolent and with proper screening and early diagnosis, development of metastases is rare [130]. Resection is recommended for tumors >3 cm as the risk of metastasis increases with tumor size [130, 141].

Lymphoproliferative Disorders

Lymphocytic Interstitial Pneumonia/Follicular Bronchiolitis

Lymphocytic interstitial pneumonia (LIP) is characterized by lymphocytic infiltration of the lung parenchyma, airways, vessels, and other structures [143]. Follicular bronchiolitis (FB) is a form of LIP in which there is lymphoid follicular hyperplasia that is centered on airways, vessels, and interlobular septa in a lymphatic distribution [144]. LIP can be idiopathic or associated with an underlying condition. Autoimmune/rheumatological disorders, such as Sjögren syndrome (SjS), rheumatoid arthritis (RA), or systemic lupus erythematosus (SLE), viral infections due to human immunodeficiency virus (HIV) or Epstein-Barr virus, or immunodeficiencies, such as common variable immune deficiency (CVID), are the most common conditions associated with LIP [145]. Among rheumatological disorders, SjS has the highest association with both LIP and FB.

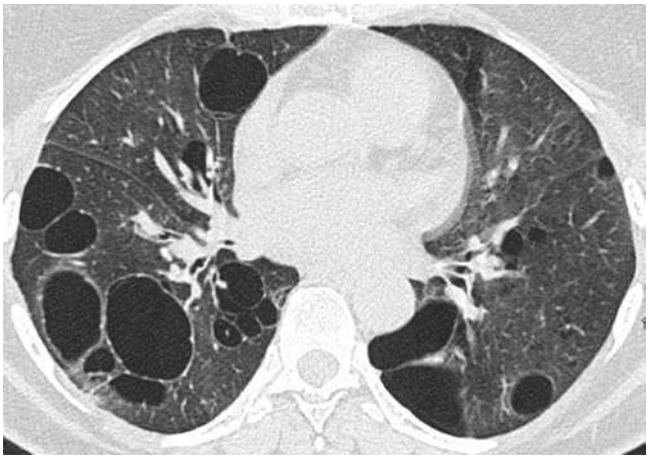

Fig. 20.4 Patient with Sjogren syndrome and follicular bronchiolitis. CT imaging showing multiple cysts, some with internal structures and associated ground-glass opacities

Pathogenesis

FB and LIP represent a spectrum of lymphocytic infiltration from a concentration in bronchus-associated lymphoid compartments to extensive cellular expansion of the interstitium with fibrosis. The factors that lead to recruitment and targeting of lymphocytes to the lung are unknown, as are those that lead to destructive lung remodeling. Post-obstructive bronchiolar ectasia, ischemia from vascular obstruction, and bronchiolar compression by lymphoid tissues resulting in subsegmental inflation due to ball valve physiology have all been suggested as the mechanisms for the cystic changes found in LIP and FB [146].

Pathological and Radiographic Characteristics

LIP is characterized by expansion of all pulmonary structures with lymphocytes (both T and B cells) mixed with variable numbers of plasma cells, while the defining histological feature in FB is peribronchial and peribronchiolar lymphoid follicles with reactive germinal centers [147]. Classically, LIP presents as a diffuse interstitial lung disease, with or without FB and cystic changes. This review is focused on the diffuse cystic changes that occur with little or no interstitial change in LIP and FB. Pathologically the cysts associated with FB are of varying size, contain internal septations, and can be associated with eccentric vessels [148].

Radiographically, the cysts in both LIP and FB are randomly distributed, variable in size, and often contain internal structures [149]. The internal cystic structures can assume the appearance of disappearing lung [150] and can be useful for distinguishing LIP and FB from other forms of DCLD. In addition to cysts, it is not uncommon to find ground-glass opacities, reticular changes, and centrilobular nodules on HRCT (Fig. 20.4) [151].

Diagnostic Approach

Patients with LIP and FB can be asymptomatic but typically present with nonspecific symptoms, such as cough, dyspnea, weight loss, fever, and fatigue. Pulmonary function tests in LIP that presents as diffuse ILD commonly show a restrictive defect with a reduced DLCO [145], while the PFT pattern in FB with diffuse cystic change is characterized by an obstructive pattern with a reduced DLCO [152].

Characteristic diffuse cystic change on CT in nonsmoking patients with a known rheumatologic disease, such as RA, SLE, or SjS (or even in patients who do not meet strict criteria for these diseases but who have convincing sicca complex or positive serologic studies), is considered to be diagnostic for FB, and biopsy is not recommended. To establish the diagnosis of LIP/FB in patients who do not have the features required for a confident clinical diagnosis, a biopsy may be required. Transbronchial biopsy in LIP/FB has a low yield and surgical lung biopsy is typically required [145]. Bronchoscopic cryobiopsy is an emerging technique that has future promise as a nonsurgical approach to diagnosis in diseases that have a bronchovascular distribution, like FB. Evaluation of the specimen by an expert pathologist is required to rule out malignant lymphoproliferative disorders [146].

Prognosis and Management

Improvement or stabilization of nodules and ground-glass opacities with corticosteroid treatment and/or immunosuppressive medications has been reported in patients with LIP; however, the effect of these treatments on progressive cystic change is less clear [145, 153]. In patients with HIV, treatment with anti-retroviral medications has resulted in clinical and radiological resolution in some cases of LIP [153].

Cystic lung disease in the presence of SjS may be associated with low grade malignancies such as MALT lymphoma [154]. In general, malignant transformation to lymphoma

from LIP is a rare phenomenon [143]; however, these patients are at an increased risk when compared to the general population. The prognosis of patients with LIP is variable in the literature with reported median survival times ranging from 5 years [146] to 11.5 years [145], but it is unclear how these statistics apply to patients with FB-related DCLD and there is a general sense they fare much better.

Amyloidosis

Pulmonary amyloidosis is characterized by abnormal deposition of extracellular proteins in a fibrillary fashion (amyloid fibrils) within the lung interstitium, vessels, or airways. Amyloidosis can be an isolated process within the lung, but it is more commonly a manifestation of systemic disease. Pulmonary amyloidosis classically presents with multiple pulmonary nodules that may cavitate over time. Occasionally, pulmonary amyloidosis can present as diffuse cystic lung disease [155], either alone or in the setting of SjS [156].

While the mechanism of cyst formation in pulmonary amyloidosis is unclear, the most likely explanation is that deposition of proteins in the lung interstitium triggers inflammation and matrix degradation, which results is lung destruction. Other proposed mechanisms include narrowing of the airways by inflammation, amyloid protein deposits leading to development of a ball valve phenomenon with distal overdistension [157, 158], or ischemic destruction from disruption of capillaries [156].

The characteristic histologic features of pulmonary amyloidosis include fibrillar deposits displaying apple-green birefringence when Congo red stained sections are examined under polarizing microscopy. Examination with immunohistochemistry can also reveal immunoglobulin light chain protein deposition within tissue samples [154].

Light Chain Deposition Disease (LCDD)

LCDD presents as a DCLD with deposition of a nonfibrillary amorphous material in the alveolar walls and small airways that does not bind Congo red or exhibit apple-green birefringence under polarized light [159]. It is rare for LCDD to present as an isolated pulmonary process; patients typically have multiple myeloma or another lymphoproliferative disorder, with concurrent renal involvement [160]. HRCT findings of LCDD can vary from diffuse, small round cysts (mimicking LAM) to large cysts associated with reticulonodular opacities (mimicking PLCH) or bronchiectases [161]. Management involves identifying and treating the underlying lymphoproliferative disorder, but it is not clear that decline in lung function is affected by pharmacologic interventions [162]. Lung transplantation is an option for advanced cases with chronic respiratory failure [161].

Smoking-Related Diffuse Cystic Lung Disease

Exposure to cigarette smoke can result in DCLDs other than PLCH, including desquamative interstitial pneumonia (DIP) and respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) [163, 164]. RB is characterized by the accumulation of pigmented macrophages in the distal airways and bronchial metaplasia and is nearly ubiquitous in smokers [163]. DIP and RB are part of a spectrum, with DIP being the more extreme, characterized by dense infiltration of distal airspaces with pigmented macrophages [165]. RB-ILD and DIP have significant radiographic overlap with common abnormalities, including bronchial wall thickening, centrilobular nodules, and ground-glass attenuation [166]. Cysts in DIP and RB are less common, typically involve a small fraction of the parenchyma, and appear within areas of ground-glass opacities [167]. Given that emphysema and smoking-related DCLDs can mimic other cystic disease processes [168], it is essential to obtain a detailed history of exposures to smoke and dust.

Conclusion

DCLDs are uncommon diseases that have a broad differential diagnosis (see Table 20.4 and Fig. 20.5). LAM, PLCH, and FB are the most common DCLDs seen in clinical practice. HRCT remains the diagnostic modality of choice and can establish the diagnosis in some cases. The use of serum biomarkers has reduced the need for a tissue biopsy in some DCLDs, especially VEGF-D in LAM, and ANA antibodies in autoimmune disease, and SPEP and UPEP in LCDD. Bronchoscopy with transbronchial biopsy and/or cryobiopsy can establish the diagnosis in some cases, especially when the clinical context is compelling, but surgical lung biopsy may be required. Establishing the correct diagnosis is critical for implementation of lifestyle interventions (e.g., avoidance of smoke in PLCH, estrogen containing meds in LAM, etc.), prognostication, and to establish candidacy for established (e.g., sirolimus in LAM) and future effective treatments.

Table 20.4 Summary of clinical and diagnostic features of selected diffuse cystic lung diseases

	LAM	PLCH	BHD	LIP/FB	Amyloid	LCDD
Personal history	Pneumothorax, angiomyolipomas, chylous effusions, and cortical tubers, seizures, skin lesions if TSC	Pneumothorax, smoking	Pneumothorax, skin lesions, renal tumors	HIV, autoimmune diseases, sicca symptoms, Raynaud's phenomenon	Sicca symptoms, autoimmune diseases	Lymphoproliferative disorders
Family history	TSC	Not relevant	Pneumothoraces, skin lesions, renal cancers	Not relevant	Not relevant	Not relevant
Extrapulmonary manifestations and other associations	Renal angiomyolipomas, chylous effusions, TSC manifestations	Diabetes insipidus, cutaneous and osteolytic bone lesions	Renal tumors, skin fibrofolliculomas	SS and other CTDs, HIV, EBV, CVID	SS and other CTDs, systemic amyloidosis	Lymphoproliferative disorders, renal failure
Laboratory testing	Serum VEGF-D	Serum and urine studies for diabetes insipidus	Genetic testing for *FLCN* mutations	Polyclonal dysproteinemia	Monoclonal dysproteinemia	Lymphoproliferative disorders, renal failure
Diagnostic yield of bronchoscopy (BAL, TBBx)	>50%	30–50%	0	Low yield	Low yield	Low yield
Consider surgical lung biopsy	Yes	Yes	No	Yes	Yes	Yes
Genetic testing	TSC mutations, but usually not clinically indicated	BRAF mutation	*FLCN* gene mutation	No	No	No
Treatment	Sirolimus	Smoking cessation, immunosuppression, cladribine	None available	Corticosteroids and other immunosuppressive agents for LIP	None available	None available

BAL bronchioalveolar lavage, *BHD* Birt-Hogg-Dubé syndrome, *BRAF* v-Raf murine sarcoma viral oncogene homolog B, *CTD* connective tissue disease, *CVID* common variable immune deficiency, *EBV* Epstein-Barr virus, *FB* follicular bronchiolitis, *FLCN* folliculin, *LAM* lymphangioleiomyomatosis, *LCDD* light-chain deposition disease, *LIP* lymphoid interstitial pneumonia, *PLCH* pulmonary langerhans cell histiocytosis, *SS* sjögren syndrome, *TBBx* transbronchial biopsy, *TSC* tuberous sclerosis complex, *VEGF-D* vascular endothelial growth factor-D
(From Am J Respir Crit Care Med Vol 192, Iss 1, pp. 17–29, Jul 1, 2015, permission requested)

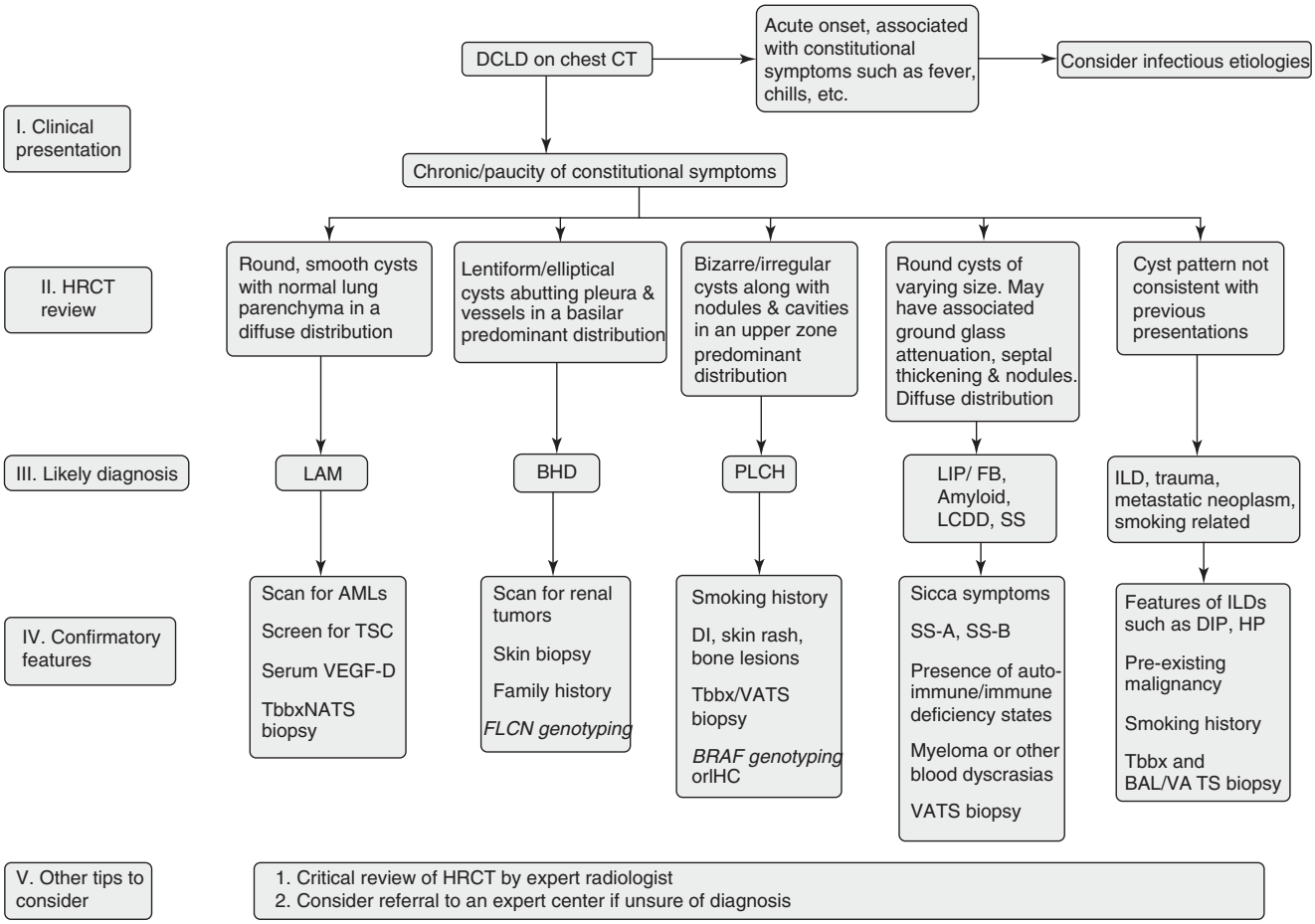

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Fig. 20.5 Algorithm to guide approach to the diagnosis of diffuse cystic lung diseases. *AML* angiomyolipoma, *BAL* bronchoalveolar lavage, *BHD* Birt-Hogg-Dubé syndrome, *BRAF* v-*Raf* murine sarcoma viral oncogene homologue, *DI* diabetes insipidus, *DIP* desquamative interstitial pneumonia, *DCLD* diffuse cystic lung disease, *FB* follicular bronchiolitis, *FLCN* folliculin, *HRCT* high-resolution computed tomography, *HP* hypersensitivity pneumonitis, *IHC* immunohistochemistry, *ILD* interstitial lung disease, *LAM* lymphangioleiomyomatosis, *LCDD* light chain deposition disease, *LIP* lymphoid interstitial pneumonia, *PLCH* pulmonary Langerhans cell histiocytosis, *SS* Sjögren syndrome, *Tbbx* transbronchial biopsy, *TSC* tuberous sclerosis complex, *VATS* video-assisted thoracoscopic surgery, *VEGF-D* vascular endothelial growth factor D

Box 20.1

LAM

Based on ATS/JRS Diagnostic criteria, a diagnosis of LAM can be established when there is a compatible clinical history and characteristic HRCT **plus** one or more of the following:

- TSC.
- Renal angiomyolipoma*.
- Serum VEGF-D ≥ 800 pg/mL.
- Chylous pleural effusion or ascites (confirmed by biochemical fluid analysis).
- Lymphangioleiomyomas*.
- Cytology showing LAM cells or LAM cell clusters in chylous effusions or lymph nodes.
- Lung or extra pulmonary biopsy confirming LAM.

*Angiomyolipoma and lymphangioleiomyomas can normally be diagnosed by a characteristic radiographic appearance. Adapted from reference.

PLCH

A diagnosis of PLCH can be established entirely on clinical grounds when there is a compatible clinical history that includes exposure to particulates and characteristic HRCT that exhibits upper-lobe predominant nodules and/or cysts. When doubts remain, any one of the following additional elements can establish the diagnosis:

- CD1a positive cells >5% on BAL.
- Lung or extrapulmonary biopsy confirming PLCH.

FB/LIP

A diagnosis of FB/LIP can established entirely on clinical grounds when there is a compatible clinical history that includes autoimmune disease and characteristic HRCT. When doubts remain, any one of the following additional elements can establish the diagnosis:

- Lung biopsy confirming FB or LIP.

LCDD

A diagnosis of LCDD can be strongly suspected on clinical grounds when there is a compatible clinical history that includes a monoclonal gammopathy or plasma cell dyscrasia and a characteristic HRCT. The diagnosis generally requires the following:

- Lung biopsy confirming FB or LIP.

Clinical Anecdote

A nonsmoking 28-year-old woman who had a CT of the abdomen obtained as part of a trauma evaluation after a traffic accident is found to an incidental finding of scattered thin-walled cysts in the lung bases and a fat containing 2 cm angiomyolipoma on her left kidney. She runs daily for exercise and has no respiratory symptoms, but is referred to a pulmonary physician for further evaluation. A high-resolution chest CT is obtained, which reveals a mild profusion of scattered thin-walled cysts. Her pulmonary function tests are normal, with an FEV1 and DLCO of 90% of predicted, but she has gas trapping with an RV of 120% predicted. Her VEGF-D is 590 pg/mL. A diagnosis of LAM is made based on the presence of typical cystic changes on HRCT and an angiomyolipoma on her abdominal CT. The VEGF-D is in the normal range and is uninformative. Since the patient is asymptomatic, the pulmonary physician and patient make a joint decision to follow along conservatively with spirometry every 3 months. Over the course of a year, she has a steady downward trend in FEV1, with an overall annual loss of 250 cc, but she remains asymptomatic without exercise limitation and her FEV1 remains greater than 85% of predicted. Based on ATS/ERS Guidelines, she qualifies for treatment with sirolimus given that her FEV1 is declining at a rapid rate. She is started on 1 mg sirolimus per day, with a plan to adjust the dose based on lung function trajectory over time.

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Complex Thoracic Lymphatic Disorders of Adults

21

Hassan Mujahid, Anita Gupta, Adrienne Hammill, Christopher T. Towe, and Francis X. McCormack

Introduction

Complex lymphatic anomalies (CLAs) not only comprise a diverse set of congenital disorders that usually come to medical attention early in life, either in utero or during early childhood, but can also manifest in adulthood [1]. The major members of this family include generalized lymphatic anomaly (GLA), Gorham-Stout disease (GSD), kaposiform lymphangiomatosis (KLA), and central collecting lymphatic anomaly (CCLA). Depending on the anomaly, these manifestations can be systemic or isolated to a single site or organ system. Lung involvement with CLAs is not uncommon, and can be the primary manifestation [2]. Lymphangioleiomyomatosis, which can present with lymphatic masses, cystic lung disease, and chylous effusions, is the subject of another chapter and will not be addressed here. Although not considered a CLA, Yellow Nail Syndrome is an acquired lymphatic disorder that typically presents in adulthood with some combination of discolored nails, lymphedema, sinusitis, bronchiectasis, and pleural effusion that is occasionally chylous [3]. This chapter will focus on these five lymphatic disorders that may present to an adult pulmonologist (Table 21.1).

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Table 21.1 Complex lymphatic anomalies (CTA)–clinical manifestations, diagnosis, and treatments

Disease	Clinical manifestation	Diagnosis	Known mutations	Treatment
Generalized lymphatic anomaly (GLA)	– Multifocal lymphatic malformations can involve liver and spleen – Bone involvement medullary, non-contiguous, and without cortical destruction – Pleural effusions	MRI, CT and bone scintigraphy	*PIK3CA* [27]	– Sirolimus – Interferon 2b – Zoledronic acid – Embolization/ sclerosis – Surgical
Kaposiform Lymphangiomatosis (KLA)	– All of the above and hematologic abnormalities – Hemorrhagic effusions (pleural, pericardial)	Spindle cells on biopsy	*NRAS* [47] *CBL* [48]	All of the above and Steroids Vincristine MEK inhibitor[a]
Gorham stout disease (GSD)	– Multifocal lymphatic proliferations with cortical bone destruction – Predilection for axial skeleton	Cortical destruction on bone imaging	*KRAS* [111]	– Sirolimus – Interferon 2b – Zoledronic acid – Surgical stabilization – Radiation MEK inhibitor[a]
Central conducting lymphatic anomaly (CCLA)	Chylous effusions Protein-losing enteropathy Chylous leaks	– Lymphangiography – Dynamic magnetic resonance lymphangiography	*ARAF* [73] *EPHB4* [72]	Sirolimus MEK inhibitor[a] Surgical correction
Yellow nail syndrome (YNS)	Sinusitis Bronchiectasis Lymphedema Yellow nails Pleural effusion	2/3 symptoms		Vitamin E/antifungal Symptomatic

[a]When underlying genetic cause has been identified as RAS/RAF/MAPK pathway

The Pulmonary Lymphatic System: Structure and Function

Lymphatics are a blind-ended organ system of interconnected vessels, lymph nodes and lymphatic tissues that transport 2–4 L per day of a clear fluid called lymph from peripheral tissues toward the heart [4] (Fig. 21.1). They play an essential role in the circulatory system by returning extravasated cells, plasma, macromolecules, and interstitial components to the bloodstream. Chylomicrons are triglyceride rich lipoprotein particles that are generated in the endoplasmic reticulum of enterocytes and secreted into gut lacteals where they enter the lymphatic stream to become chyle. They ultimately flow into the venous circulation to transport lipid to adipose tissue and skeletal and cardiac muscle. As an integral component of the immune system, the lymphatics are responsible for transporting antigen-loaded dendritic cells and memory/effector T cells to draining lymph nodes, providing a platform for initiation of adaptive immune responses. Lymphatic capillaries are present in all tissues, with the exception of the bone marrow and cartilage. Lymphatic networks were recently discovered in the brain [5], an organ that was thought to be devoid of these structures.

Below the diaphragm, the lymphatic system consists of three major components: the soft tissue lymphatic system, the intestinal lymphatic system, and the hepatic lymphatic system (Fig. 21.1) [4]. These organ systems drain into cisterna chyli and ultimately into the thoracic duct (TD) which courses through the thorax and inserts into the left innominate vein at the junction with the internal jugular vein. The pulmonary lymphatic system primarily drains into the thoracic duct. A smaller lymphatic network comprises the right upper lobe, right head and neck, and right

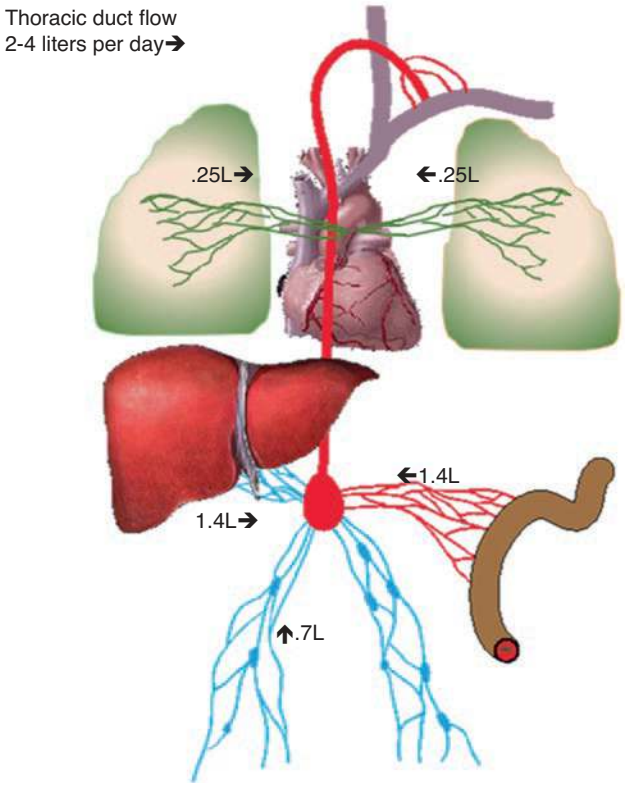

Fig. 21.1 Lymphatic fluid courses through the soft tissue, hepatic and intestinal lymphatic networks, and converges on the cisterna chyli in the abdomen. The approximately daily volume of fluid generated from each source is shown. Chylomicrons generated in the lacteals of the gut impart a milky white appearance to the lymphatic fluid as it flows cephalad via the thoracic duct to the junction between the left innominate and left internal jugular vein [113]

arm drains into right thoracic duct, which inserts into the right subclavian vein [2, 4]. It is important to note that chyle is generated in the abdomen and can only enter the lung or pleural space through abnormal abdominal pulmonary lymphatic communications with the airways or pleural space, or via reflux from the thoracic duct into the pulmonary lymphatic network when the pressure gradient for flow is reversed [6].

On microscopy, lymphatics capillaries are characterized by thin walled vessels with a mostly round/irregular lumen lined by a single layer of endothelium resting on a discontinuous basement membrane [7]. Smooth muscle cells or pericytes may be absent or only partially surround the vessel [4, 8] (Fig. 21.2). These lymphatics drain into pre-collecting vessels and then into contractile collecting vessels with a continuous muscular layer made up of intima, media, and adventitia layers that propel lymph forward, augmented by skeletal muscle contraction and arterial pulsations, with one-way valves to prevent backflow. Afferent collecting vessels deliver soluble and antigen presenting cell-associated antigens to lymph nodes, and efferent vessels directly processed lymph to the venous system via the thoracic duct or the right lymphatic duct.

The pulmonary lymphatics transport cells and fluids from the peripheral lung to the venous system via central lymphatic conduits, to regulate tissue pressure, keep the alveolus dry for optimal gas exchange, and to facilitate regional immune responses (Fig. 21.3a) [8, 9]. There are two major lymphatic networks in the lung; the subpleural superficial plexus located within the connective tissues of the visceral pleura and the deep peribronchovascular

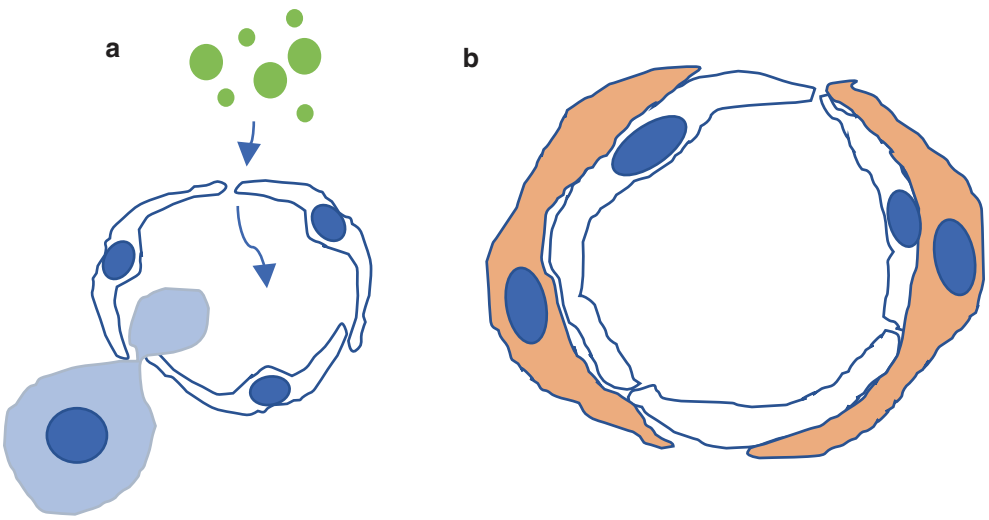

Fig. 21.2 (**a**) Lymphatic capillary showing single layer of lymphatic endothelial cells allowing access for cells (blue dumbbell-shaped structure and small molecules (green dots)). (**b**) Central lymphatic vessel composed of lymphatic endothelial cells surrounded by smooth muscle cells (orange cells)

plexus comprised of inter- and of intra-lobular lymphatics located in the connective tissues lining vascular structures and airways. The subpleural lymphatics are most abundant in the lower lobes and join with the lymphatics of the deep plexus near the hilum, or more rarely drain directly into the mediastinum. The more distal, smaller lymphatics associated with arterioles are involved in absorption and propulsion of lymph with the help of arterial, respiratory, and cardiac movements, with the peribronchovascular plexus providing most of the drainage (Fig. 21.3b).

Lymphatic Development

A comprehensive discussion of lymphatic development is beyond the scope of this review, but a basic awareness of the process of lymphangiogenesis provides a platform for understanding adult lymphatic disorders, including biomarkers and molecular targets. Florence Sabin is credited with recognizing that the lymphatic system arises from the cardinal vein [10]. Endothelial cells differentiate from angioblasts, and undergo arterial or venous specification [11–13]. Embryonic venous endothelial cells express high levels of VEGFR3, LYVE-1 (in a lateralizing subpopulation), and SOX18, which in turn upregulates PROX-1, the first step in lymphatic endothelial cell specification. As VEGFR3 expression is diminishing in blood vessels, neuropilin 1 expression is induced in LECs making them more responsive to VEGF-C signals arising from the lateral mesenchyme, which promotes sprouting of lymphatic sacs from central veins. LECs express podoplanin (D2–40), which through Clec-2 promotes platelet aggregation to form a barrier between the vein and the budding lymphatic sac, separating the blood and lymphatic vascular systems. Further maturation of the differentiating lymphatic collecting vessels follows, including the formation of intraluminal valves, recruitment of smooth muscle, and assembly of a basement membrane.

Clinical Presentation of Lymphatic Disorders

Patients with pulmonary lymphatic disorders may develop chylous complications, including chyloptysis, chylous pulmonary congestion or lymph collections in the pleural space or pericardium [2, 6]. Chyloptysis presents with expectoration of milky white material and can occur when chylous lymphatic fluid gains access to airways by direct communication through abnormal or fistulous tracks, rup-

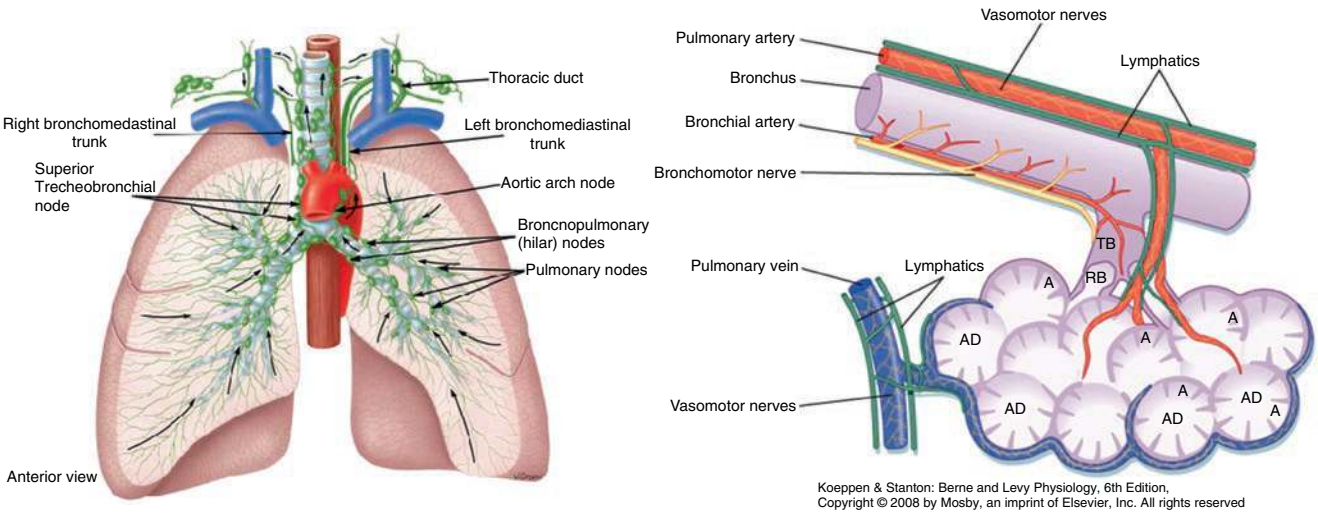

Fig. 21.3 The pulmonary lymphatics transport cells and fluids from the periphery of the lung via central lymphatic conduits to the venous system, to regulate tissue pressure, facilitate regional immune responses, and to provide a mechanism for antigens and infectious pathogens to interact with immune cells within lymph nodes. Flow is propelled forward by arterial pulsations and respiratory motion, and backflow is prevented by one way valves. (Used with permission from [112])

ture of airway lymphatics, or flooding of alveoli with lymphatic fluid due to reflux of chyle via retrograde flow through pulmonary lymphatics in a condition known as chylous pulmonary congestion (CPC) or lymphatic pulmonary edema [14]. CPC not only was originally described in lymphangioleiomyomatosis (LAM) but also occurs in other lymphatic disorders (Fig. 21.4). In the case of LAM, CPC is usually accompanied by thickened alveolar septa and often by chylous pleural effusion and tends to respond to sirolimus treatment [15]. Occasionally, chylous material that fills the airway can solidify and be expectorated as branching multi-antennary structures that represent molds of the bronchial tree (Fig. 21.5) [6, 16]. This condition, known as plastic bronchitis, has also been described in non-lymphatic disorders, including *Mycobacteria* infections, allergic bronchopulmonary disorders, and post-Fontan repair [17]. Chylopericardium is a rare manifestation of thoracic lymphatic disorders [18]. In addition to the CLAs, chylous pleural effusions can occur in patients with LAM, lymphoma, other neoplasms, or infectious diseases that obstruct or violate the thoracic duct [19]. The hallmarks of chylous pleural effusions are a milky white appearance with lymphocyte predominance and excess triglycerides on laboratory evaluation.

Pulmonary lymphatic disorders, such as GLA, may present with malformed lymphatic channels within the pleura, bronchovascular bundles, and interstitium (Fig. 21.6). Similarly, the bronchiectasis that occurs in patients with Yellow Nail Syndrome may be a consequence of lymphatic dysregulation (Fig. 21.7). Finally, in the CLAs, solid or cystic lymphangiomas can occur in the chest or abdomen (Fig. 21.8), as well as hepatic, splenic, or bony involvement.

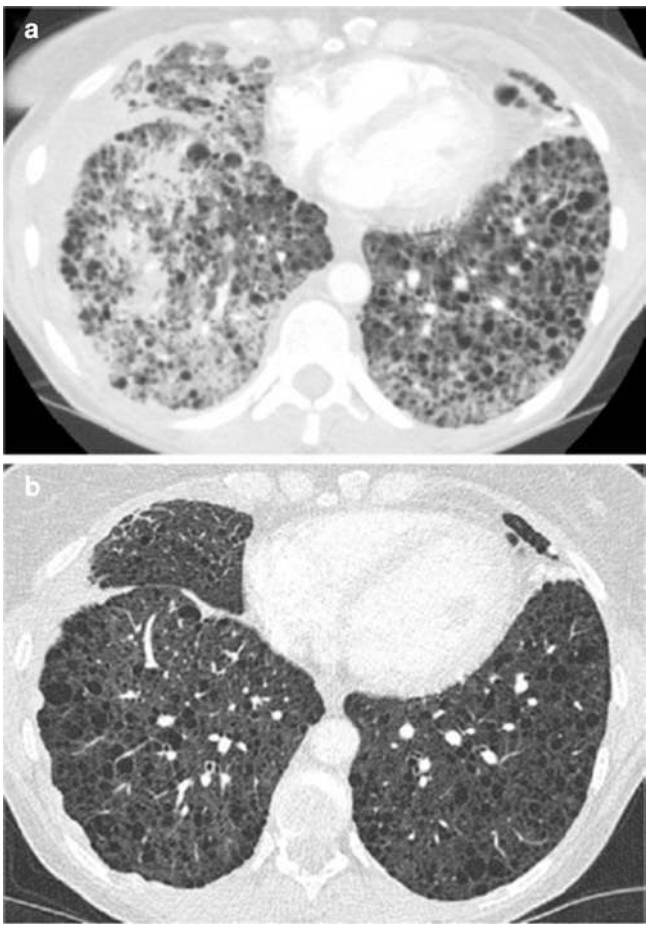

Fig. 21.4 (**a**) chylous pulmonary congestion associated with interlobular septa thickening, patchy consolidation, and pleural effusion on a background of cystic parenchymal lung disease due to LAM. (**b**) Near complete resolution after treatment with sirolimus. (Used with permission from [15])

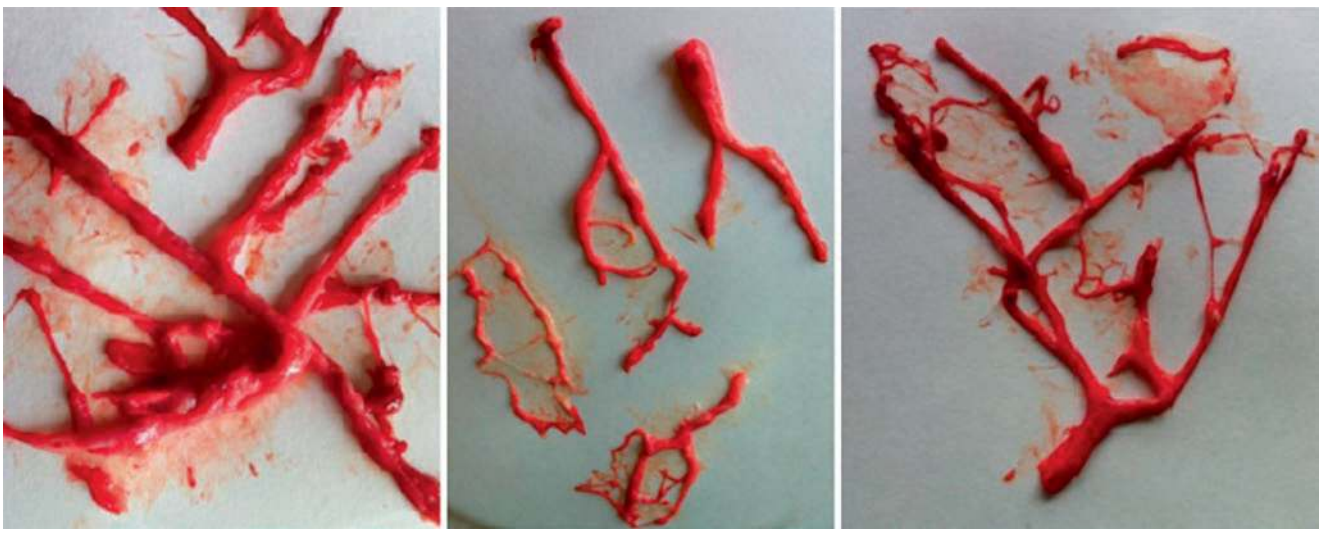

Fig. 21.5 Branching multi-antennary bronchial casts from a patient with plastic bronchitis due to a lymphatic anomaly

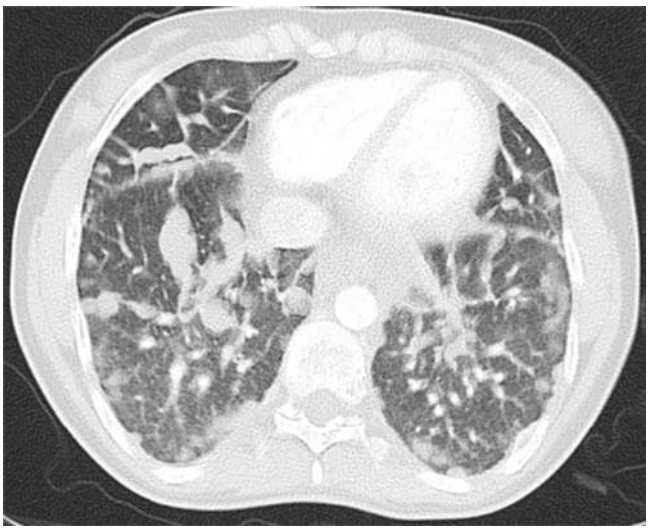

Fig. 21.6 Dilated pulmonary lymphatics in a patient with GLA

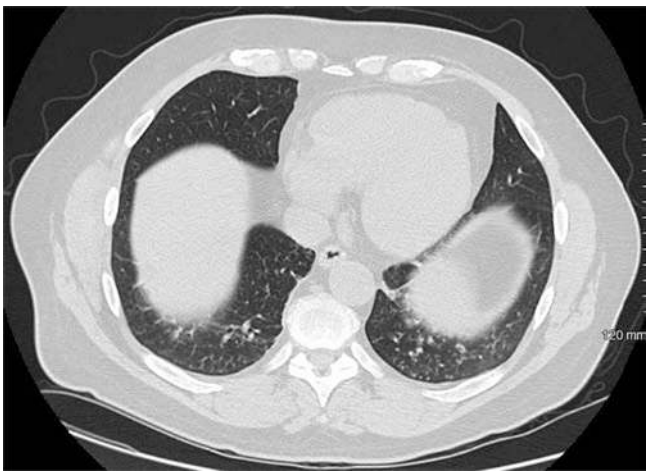

Fig. 21.7 Basilar mucous plugging and bronchiectasis in a patient with Yellow Nail Syndrome

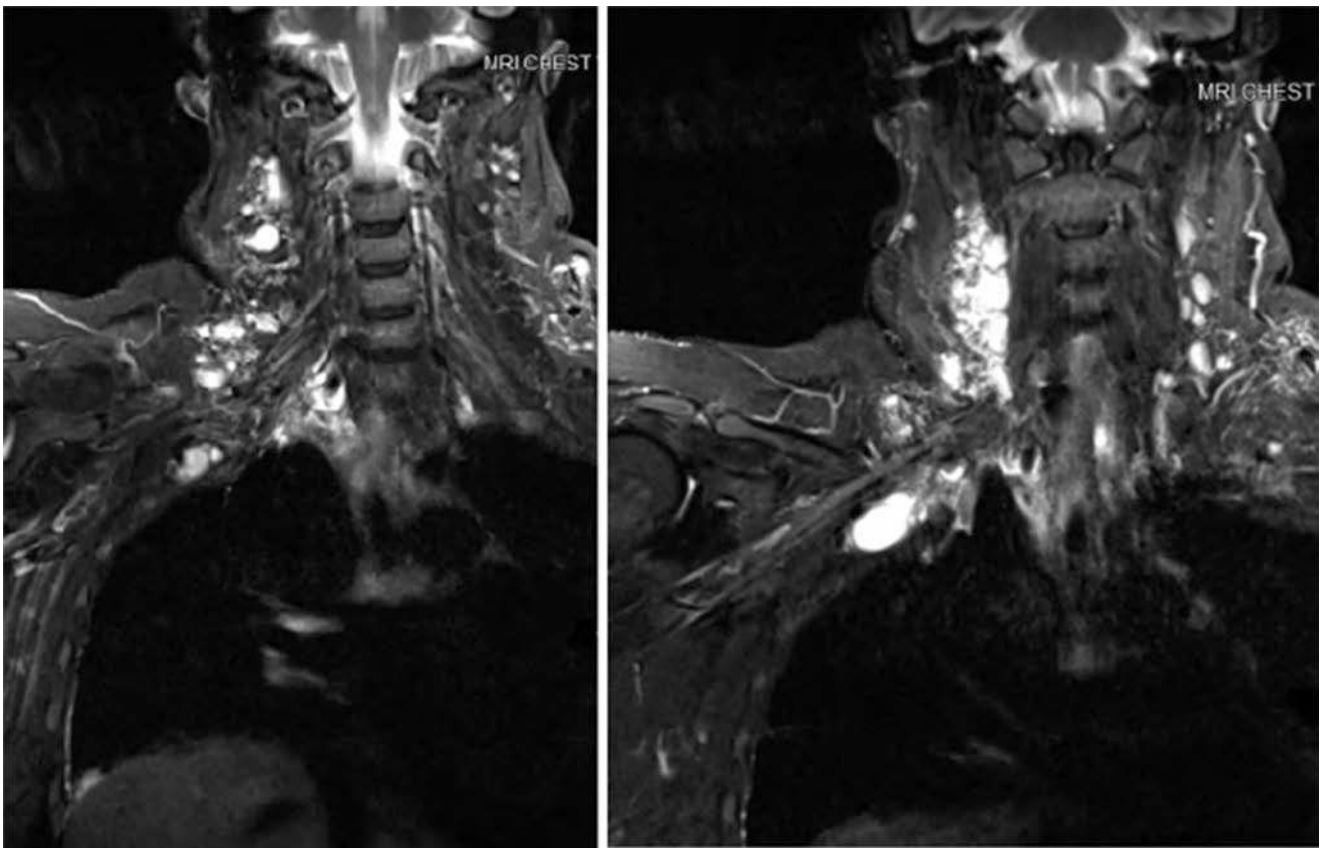

Fig. 21.8 T2-weighted MRI demonstrating a lymphangioma involving the neck and upper thorax

Approaches to Diagnosis and Management of Congenital Lymphatic Anomalies

Problematic chylous leaks must be imaged to understand the anatomy and physiology of the leak. T2-weighted MRI can be used to identify abnormal lymphatic tissue. Dynamic contrast-enhanced MR and intranodal lymphangiography provides greater anatomical detail [2, 6]. Thoracic duct cannulation and lymphangiography are useful methods for identifying the source of the leak, and for transthoracic duct delivery of lipiodol, glues, and coils to obstruct flow [20]. Thoracic duct cannulation also provides opportunities to obtain axial lymphatic system samples for research. Caution should be exercised when considering biopsy of lymphatic lesions, since persistent leaks can result. Most of these disorders are caused by somatic mutations, so genetic mutations may only be present in the lesion.

Overview of Complex Lymphatic Anomalies Multiple disease processes with individual but overlapping pathophysiology and genetics are collectively called complex lymphatic anomalies (CLA) [21]. This array of diseases is believed to stem from embryological errors due to distinct gene mutations [22]. The classification of the major CLAs was refined by the International Society for Study of Vascular Anomalies (ISSVA) in 2018 (https://www.issva.org/classification) and an update incorporating genetic analysis has been recently published [23, 24]. A schematic of some of the mutants known to cause CLAs mapped onto the RAS/MAPK and PI3K/Akt/mTOR pathways is shown in Fig. 21.9.

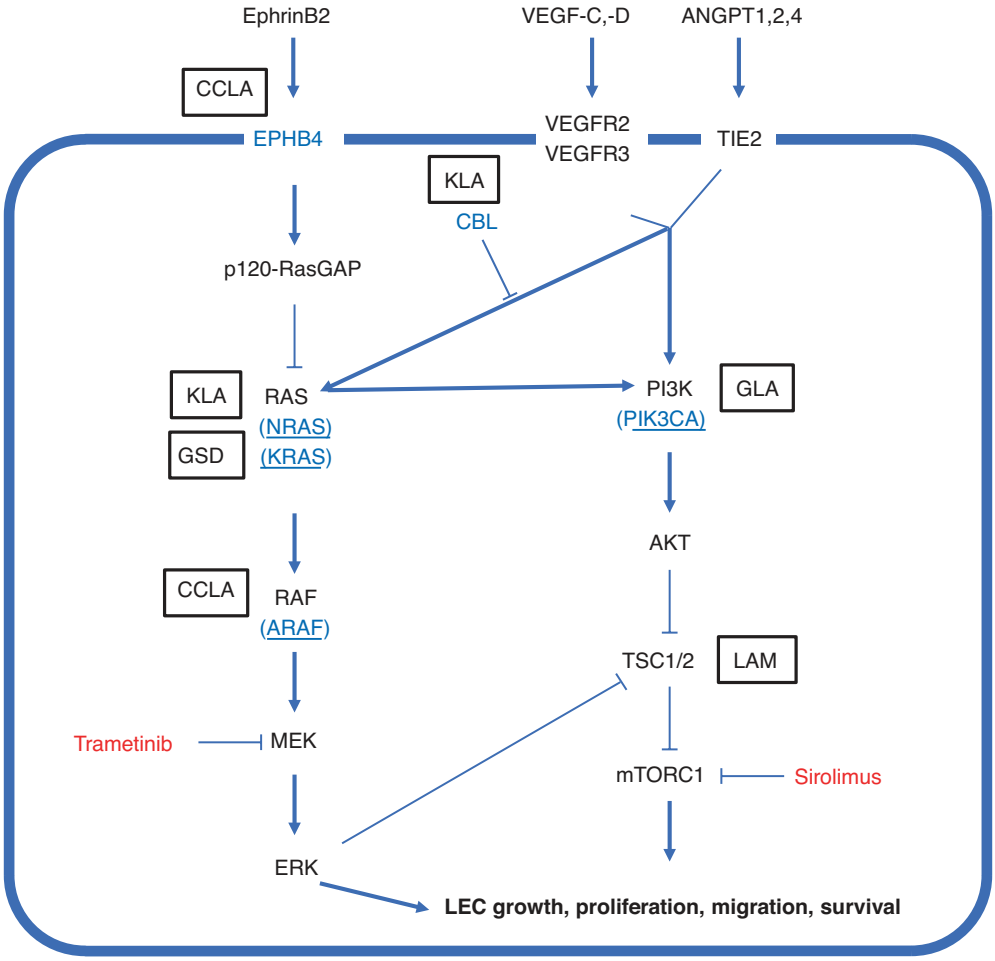

Fig. 21.9 Signaling pathway mutations implicated in complex lymphatic disorders in adults. Schematic overview of PI3K-AKT and RAS-MAPK pathways is shown. Disease-causing mutations are shown in blue, potential therapeutic options in red. *AKT* protein kinase B, *ANGPT* angiopoietin, *CBL* casitas B-lineage lymphoma, *CCLA* central conducting lymphatic disorder, *ERK* extracellular signal-regulated kinase, *GLA* generalized lymphatic anomaly, *GSD* Gorham Stout disease, *KLA* kaposiform lymphangiomatosis, *MAPK* mitogen-activated protein kinase, *MEK* mitogen-activated protein kinase kinase, *mTORC1* mammalian target of rapamycin complex 1, *RAF* rapidly accelerated fibrosarcoma, *RAS* rat sarcoma, *TIE2* tyrosine kinase with immunoglobulin-like and epidermal growth factor homology domains-2, *TSC* tuberous sclerosis, *VEGF* vascular endothelial growth factor, *VEGFR* vascular endothelial growth factor receptor, *LEC* lymphatic endothelial cell

Generalized Lymphatic Anomaly

Generalized lymphatic anomaly (GLA) (formerly known as lymphangiomatosis) is a rare multisystem disorder characterized by diffuse or multifocal lymphatic malformations, often associated with osseus involvement [25]. Lung involvement is not uncommon, and can include chylous effusions, peribronchovascular pulmonary infiltrates, and pleural disease. GLA is present at birth but occasionally is recognized later in young adults or even middle-aged patients.

Etiopathogenesis

GLA can arise from somatic mutations in *PIK3CA* (similar to Klippel-Trenaunay Syndrome (KTS)) and is associated with congenital lipomatous overgrowth, vascular malformations, epidermal nevi and spinal (scoliosis), and/or skeletal anomalies (CLOVES), vascular malformations (VM) and lymphangiomas [26, 27]. GLAs are characterized by multifocal, well-circumscribed lesions within the lung, pleura, pericardium, spleen, soft tissue, bone, peritoneum, and other visceral organs. The malformed lymphatic channels are microcystic (<1 cm), lined by a single layer of bland endothelial cells, with no atypia (Fig. 21.10). These channels may lack smooth muscle investment or show partial muscularization of the vessel wall. The endothelial cells are immunoreactive to vascular and lymphatic markers. Organizing thrombi can be seen. Bone may show osteopenia and secondary fracture changes. Staining of PROX-1 and D2–40 reveals dilated lymphatic lumens containing pink proteinaceous material consistent with lymphatic fluid [25, 28–30]. GLA has recently been found to be associated with sporadic somatic activating mutations in *PIK3CA* gene [27], which interestingly have also been also detected in isolated LMs and several overgrowth syndromes.

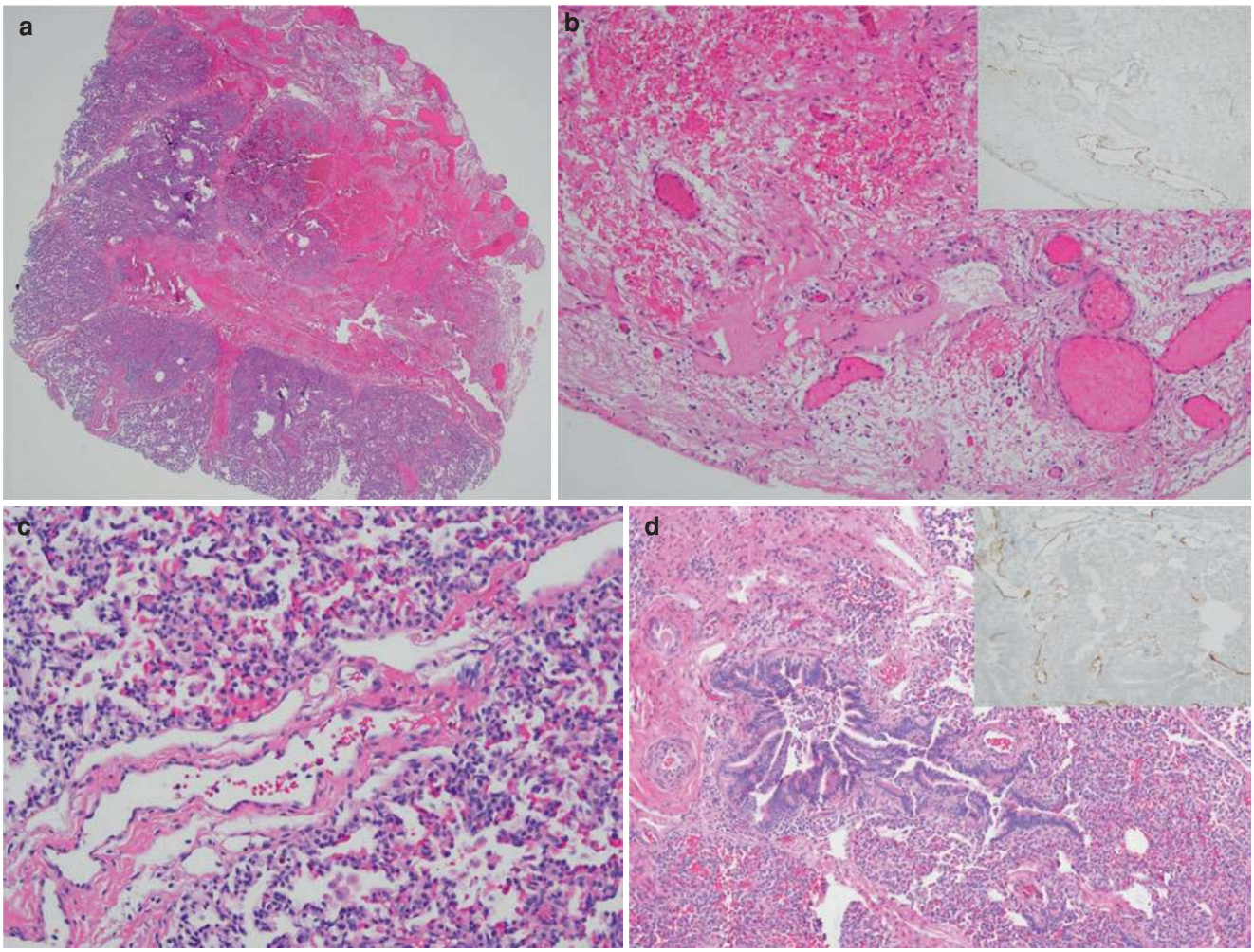

Fig. 21.10 Generalized Lymphatic Anomaly (GLA). (**a**) H&E section of mature lung tissue demonstrates excessive, irregular thin-walled vascular channels within the septa, pleura, and bronchoalveolar bundles. (**b**) H&E of the pleural, (**c**) septa, and (**d**) bronchoalveolar bundles at higher magnification highlight irregular vascular channels which are immunoreactive to an anti-podoplanin antibody, D2–40 (**b** and **d**, insert), a lymphatic marker

Clinical Presentation and Diagnosis

Patients can present with cystic lymphatic malformations of the thorax or abdomen, effusions (pericardial, pleural, or peritoneal), chyloptysis or plastic bronchitis, chyluria, or protein losing enteropathy [31]. Pulmonary parenchymal disease is not uncommon and presents with thickened bronchovascular bundles and pleural surfaces. Bony lymphatic lesions can cause pain and impaired mobility [28, 32].

LMs in GLA share several radiological findings with common cystic lymphatic malformations, although splenic and hepatic involvement appears to be more common [28, 33]. Bone lesions can be characterized by plain radiographs, CT, MRI, or bone scintigraphy. CT is more sensitive than radiographs at identifying and characterizing bony lesions associated with GLA, and MRI is the most sensitive; in addition, MRI is preferred for its ability to demonstrate soft tissue components, such as lymphatic malformations. Typically, on MRI the bone marrow is hypointense on T1 in affected areas with hyperintense T2 signal noted in osseous lesions. GLA may be associated with multiple lytic abnormalities in the medullary compartment of bone. In contrast to GSD, however, GLA does not cause cortical destruction, although pathologic fractures can still occur. Lesions in GLA more commonly involve a greater number of bones than GSD and are non-contiguous. They can include the appendicular skeleton though are most frequently identified as multiple lesions throughout the pelvis and vertebrae [25, 28, 32, 33].

In patients with GLA, CT scan of the chest can demonstrate bilateral interstitial infiltrates with diffuse smooth thickening of interlobular septa and bronchovascular bundles, with extensive involvement of mediastinal connective tissue and perihilar regions (Fig. 21.6) [25, 28–30, 32, 33].

Course/Prognosis

GLA diagnosed earlier in life carries a worse prognosis with mortality of up to 39% described in a review of patients under 16 years of age [34]. Thoracic involvement in GLA is generally associated with a worse prognosis. Bone fractures and recurrent effusion in the pleural or pericardial spaces add to morbidity. There are few data available regarding prognosis in adults, but a recent study of 35 patients with GLA that included adults (median age 18 years) showed >60% survival over 10 years [32].

Management

Recent advances in therapy, including the use of mTOR inhibitors with addition of bisphosphonates for symptomatic or high-risk bony disease, can provide significant improvement in morbidity and mortality.

Sirolimus is a direct inhibitor of mTOR complex 1 and blocks downstream signaling and protein synthesis [29, 30, 35, 36]. Adams et al. reported an 85% response rate in complicated vascular anomalies at the end of approximately 12 months [37]. All seven patients with GLA reported partial responses. The most common adverse event was bone marrow suppression (27%). Many physicians prescribe prophylaxis for PJP for patients with GLA on sirolimus, particularly if there is hypogammaglobulinemia or lymphopenia from lymph or chyle losses [28, 38]. Notably the heterogeneity in GLA disease manifestations in these populations can confound interpretation of many of these studies. A phase 3 study of sirolimus is currently underway and will provide valuable information regarding the topic (NCT02638389).

Newer therapies with more targeted agents, such as inhibitors of PI3K-alpha (the product of the PIK3CA gene), have the potential to improve disease control in cases where a specific genetic mutation is identified [39].

Interferon alpha 2b was one of the first treatments reported to be effective for GLA. The mechanism of action is thought to be regulation of VEGF expression. Administration can be associated with a flu-like syndrome [40, 41]. In addition, side effects, including severe depression and mood issues, can limit is use in adults.

Zoledronic acid is a potent bisphosphonate that inhibits osteoclast-mediated bone resorption and induces osteoclast apoptosis. There are several reports of improvement in bone pain in patients with GLA [28, 40]. It is often used in combination with sirolimus when bony disease is present, particularly when patients report pain or pathologic fracture [42].

Sclerosis and surgical resection have been used to debulk large LMs associated with GLA. Sclerotherapy is usually guided by direct real-time imaging to help differentiate healthy lymphatic tissue from diseased tissue. Pleurectomy, pleurodesis, and ligation of the thoracic duct can be performed to address recurrent pleural effusions.

Successful treatment with irradiation for unresectable LMs causing significant symptoms has been reported but carries risk of malignant conversion to angiosarcoma (or lymphangiosarcoma).

Kaposiform Lymphangiomatosis

Kaposiform Lymphangiomatosis (KLA) is an aggressive subtype of GLA that was first identified by Croteau et al. at Boston Children's Hospital in 2015 [43]. They reported histopathological characteristics of spindled lymphatic endothelial cells accompanying malformed lymphatic channels in 20 patients with lymphatic anomalies. Although the clinical presentations of GLA and KLA can be similar, hematologic

and coagulation abnormalities should raise suspicion for KLA and biopsy confirmation should be sought [44]. While KLA shares some histological features with kaposiform hemangioendothelioma (KHE), its clinical features are distinct [45]. The finding that multiple different genetic mutations can cause KLA, including RAS mutations, favor classification as a neoplasm rather than a malformation.

Etiopathogenesis

Similar to many vascular anomalies with somatic activating variants in the RAS/PI3K/mTOR signaling pathways, Barclay et al. found an activating NRAS mutation (p.Q61R) in KLA [46, 47]. Recently a mutation in the Casitas B lineage lymphoma (CBL) gene, an inhibitor of the RAS pathway, was also identified in a patient with KLA [48]. NRAS is a proto-oncogene that regulates proliferation via the MAPK and PI3k/AKT pathway. The finding that KLA can also be caused by mutations in the MAPK pathway could explain the non-responses or insufficient responses to mTOR and PI3K targeted therapy in KLA patients who were initially diagnosed with GLA and treated with sirolimus or other Akt pathway inhibitors [1, 22, 28, 32, 36, 43, 46, 48–51]. One case of human papilloma virus RNA identified by PCR from tissue sampling of a KLA patient has also been reported [52].

Grossly, KLA demonstrates a pattern similar to primary diffuse lymphangiomatosis in the lung with the addition of hemorrhage. KLA morphology is dominated by malformed lymphatic channels within the pleura, pulmonary septa, and bronchoalveolar bundles. In addition, there are foci of intravascular and perivascular, spindle shaped to flat "kaposiform" endothelial cells which are occasionally hemosiderin laden and show platelet microthrombi (Fig. 21.11). Although

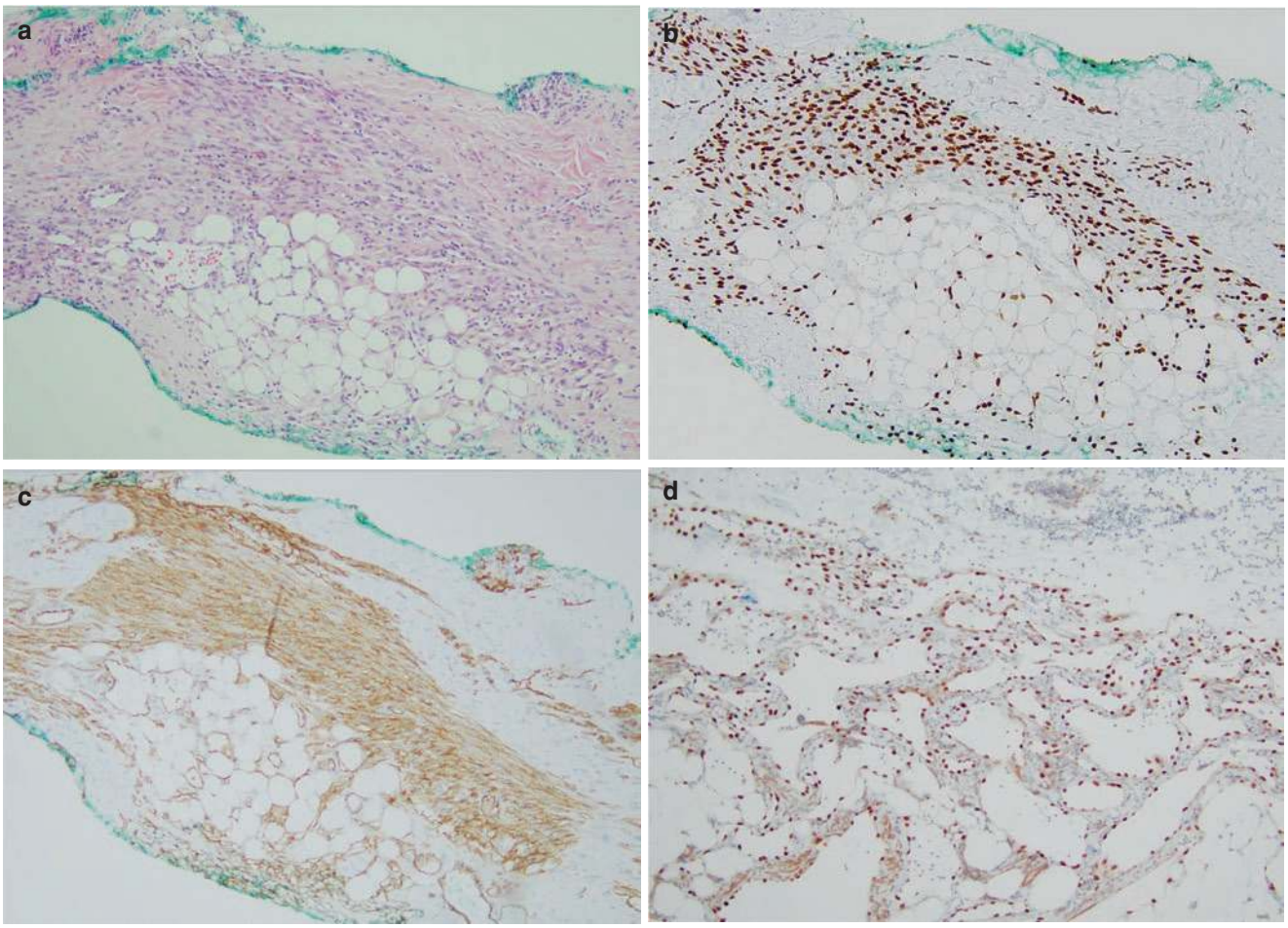

Fig. 21.11 Kaposiform Lymphangiomatosis (KLA). (**a**) Biopsy demonstrates H&E section of fibrocollagenous tissue with excessive, irregular slit-like vessels lined by a single layer of endothelial cells. Scattered foci of perivascular and intravascular spindles cells are present. (**b**) These spindle cells are admixed with lymphocytes, extravasated red blood cells, and occasionally hemosiderin laden macrophages. (**c**) These spindle cells are diffusely immunoreactive to CD34, an endothelial cell marker, and (**d**) PROX-1, a lymphatic marker (insert)

the clinical presentations of GLA and KLA can be similar, hematologic abnormalities should raise suspicion for KLA and biopsy confirmation should be sought. While KLA shares some histological features with kaposiform hemangioendothelioma, its clinical features are distinct and the latter has a prominent spindled endothelial cell component. The endothelial cells in KLA are immunoreactive to vascular markers, including CD31, CD34, and ERG, and lymphatic markers Podoplanin (D2–40) and PROX-1.

Clinical Presentation and Diagnosis

Although KLA is typically diagnosed in the pediatric population at a mean age of 6 years, the original cohort included patients as old as 44 years of age [43], and the disease is increasingly recognized in adults [53]. KLA is associated with coagulopathy, including hypofibrinogenemia, thrombocytopenia and bleeding that are not present in GLA [44]. Bleeding can often be the presenting complaint. In addition, serum angiopoietin-2 is markedly elevated in cases of KLA (and KHE), allowing differentiation from GLA [54]. Angiopoietin-2 levels can also be used to follow response to therapy [55]. KLA has a stronger predilection than GLA for the thoracic cavity and on presentation most patients have pleural, posterior mediastinal and hilar disease. A typical pattern on imaging in KLA is contrast enhancing, infiltrative soft tissue thickening, and lung parenchymal involvement along the bronchovascular bundles (Fig. 21.12). Patients often have an associated pleural/pericardial effusion with both a chylous and hemorrhagic component. Lytic osseous lesions are typically similar to those in GLA with cortical sparing, and pathologic fractures have been noted as in GLA. The anatomic distribution often resembles that of central conducting lymphatic anomalies (CCLAs), and it can be difficult to differentiate the two on lymphangiography. Findings can include dilated and tortuous lymphatics with reflux into different channels. This may explain why effusions, which are commonly seen and are often the presenting complaint, are associated with an aggressive course. The overall mortality rate for KLA in 43 patients with well-characterized pathology was approximately 21% [56].

Management

Sirolimus has been used with some benefit in many patients with KLA, although it is often not sufficient as a single agent. Zhou et al. report a partial response in 58.3% of their cohort with sirolimus [57]. Adams et al. reported good response in six of seven sirolimus treated patients [37]. As KLA was only recently identified as a distinct entity, it is likely that some patients classified as GLA in past studies actually had KLA [37, 55, 57].

When response to sirolimus is suboptimal, courses of vincristine and/or corticosteroids have often been added to treatment regimens during flares in an attempt to stabilize disease. Vincristine has been used for the coagulopathy in KLA based on shared pathophysiologic elements with Kasabach-Merritt phenomenon, which has been shown to be responsive to that therapy [28, 43, 58].

Bisphosphonates such as zoledronic acid are often added when there is significant bony involvement, similar to their use in GLA and GSD [42].

More recently, with the identification of activating *NRAS* or *CBL* mutations in affected tissues, therapies have been used to target the RAS/MAPK pathway. MEK inhibitors block signals in the distal elements of the RAS pathway, and are therefore useful for targeting most mutations in this signaling network. Foster et al. report resolution of pleural effu-

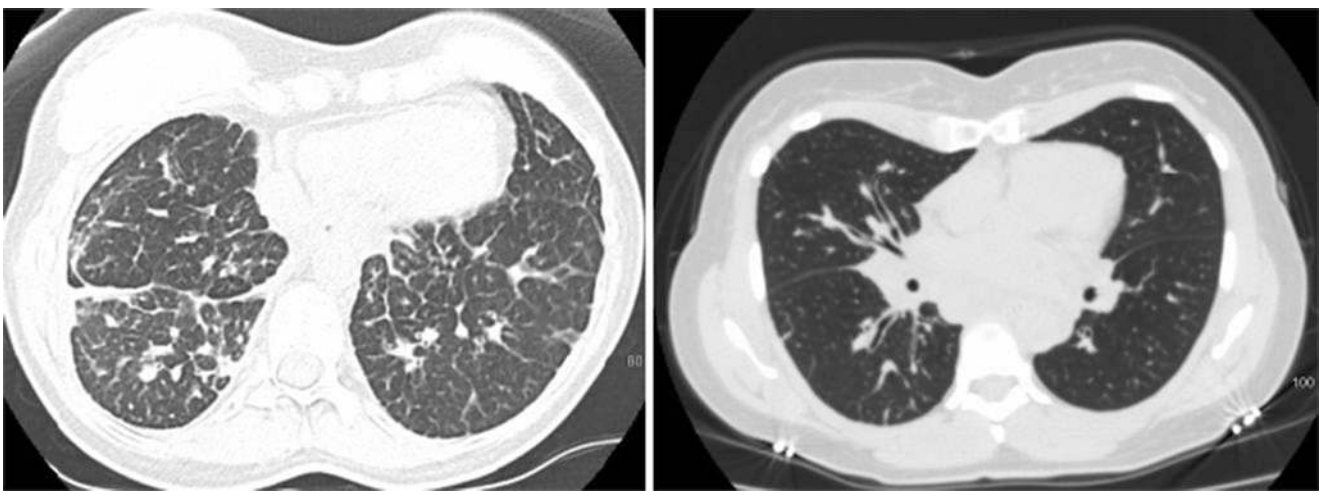

Fig. 21.12 Right hilar fullness and thickening of interlobular septa and bronchovascular bundles in a patient with KLA

sions, improvement in pulmonary function tests, and symptoms in a KLA patient with a CBL mutation treated with trametinib [48, 49].

Thoracic duct embolization has been reported to be effective for controlling chylous complications when there appears to be a component of CCLA [59].

Course/Prognosis

KLA is an aggressive disease with variable response to treatment and often poor outcomes [59]. In the original study of 20 patients describing KLA, the 5-year survival was 51% with an overall survival of 34% [43]. The most common cause of death is cardiorespiratory failure and disseminated intravascular coagulation (DIC). A second study with six patients and a mean follow-up of 4.5 years reported 4 failures of treatment with 2 deaths [45]. Although KLA has continued to carry a poor prognosis, the ability to identify a causative mutation and choose a targeted therapy may change outcomes for these patients in the future [49]. It is important to note that these data were derived from pediatric cohorts, and that response to treatment, outcomes, and survival for adult populations is not clear [2].

Gorham Stout Disease

Gorham Stout disease (GSD) is a rare condition that was first described in 1838 by Jackson [60], and further characterized in a review of 16 cases by Drs. Gorham and Stout in 1954 [61]. It is a disease of young adults and children with no gender predilection. Approximately 400 cases have been reported to date [32, 62]. A hallmark feature that differentiates GSD from GLA is progressive destruction of flat and/or long bones, a feature that has spawned the alternative designation of "vanishing bone disease" [63]. The most common sites affected include ribs, scapula, vertebrae, humerus, femur, skull, and maxillofacial bones.

Etiopathogenesis

No genetic mutations that are definitely responsible for the clinical manifestations of GSD have been identified to date. Recently, two groups identified KRAS mutations at known hotspots (G12D, Q61R) within GSD lesions [27, 64]. Their work has suggested that either increased PI3K signaling in lymphatic endothelial cells or overexpression of VEGF-C by bone cells can stimulate aberrant formation of lymphatics in bone. These lymphatics recruited from regional networks infiltrate the periosteum and eventually invade bone [65]. Increased VEGF-A levels in local tissues may play a role in angiogenesis and bone resorption through RANK-mediated osteoclastic activity [66, 67]. Increased IL-6 levels have also been noted.

Histology demonstrates progressive osteolysis of the cortex or lytic lesions in the bone characterized by thin reactive bony trabeculae with increased osteoclast activity. Intraosseous lymphatic malformations characterized by thin, irregular, occasionally dilated vascular channels stain that positive for PROX-1 and D2–40 replace the marrow cavity.

It can be challenging to differentiate from GSD from GLA histologically. GSD typically produces contiguous lesions in the ribs, cranium, clavicle, and cervical spine, and can be associated with pleural/pericardiac effusions and CSF leak [1, 25, 28, 32, 33, 42, 68].

Clinical Presentation and Diagnosis

GSD usually presents in the third decade of life although onset in younger and older patients has been reported [32, 62]. Two types of GSD include focal/progressive type with spontaneous stabilization and arrest after years of bony destruction, and diffuse involvement that includes pleura or/and visceral organs.

Symptoms vary, but pain, weakness, and functional impairment are common, with specific manifestations depending on the location of lesion. Pathologic fractures are often among the presenting manifestations. Spinal involvement can result in CSF leak, and cervical spine involvement is particularly worrisome given high risk for severe morbidity or even mortality with pathologic fracture. Pulmonary parenchymal disease and pleural or pericardial effusions can present with respiratory symptoms. Chylothorax occurs in up to 17% of patients, thought to be due to lymphatic leak from affected bone.

There is no single diagnostic test for GSD, although imaging and/or biopsy demonstrating evidence of cortical bone destruction is commonly used. It is important to avoid biopsy of an affected rib if at all possible, as this could introduce leak of chyle into the chest resulting in new pleural effusion. Cortical bone destruction is often present in contiguous lesions with a predilection for the axial skeleton. On MRI, soft tissue masses of GSD usually generate low T1 and high T2 signals. When there is a suspicion for GSD, imaging should cover the axial skeleton which is more commonly involved compared to GLA.

Management

Treatment is usually individualized based on lesions and symptoms. Medical management includes bisphosphonates to limit bone resorption and alleviate pain. Pegylated interferon has also been shown to improve symptoms. More recently, sirolimus has shown promise, as has been the case for GLA. In some cases, pleural effusions respond to treatment with mTOR inhibitors, but the pulmonary parenchymal disease rarely improves with therapy [69, 70].

Surgical resection with bone grafting for GSD can also be performed; however, it carries considerable morbidity and is often complicated by recurrence and graft failure when medical therapy for disease control is not also instituted [40]. The same caveat applies to surgical intervention for CSF leak.

Radiation has historically been used in the treatment of the highest risk GSD cases(often cervical spine). The dose used is typically in the range 25–45 Gy. The side effects including risk of malignancies limit its usefulness, especially in the young. It may be useful as a palliative option especially for intractable pain associated with bone destruction [40, 68].

Course/Prognosis

GSD has the most favorable outcomes compared to GLA and KLA. A systematic review of 89 publications showed 5 deaths, however, suggested half of patients with GSD have persistent disease despite treatment [71]. A separate cohort out of Japan demonstrated a mortality of 28.6% (10/35 patients) [32].

Due to the rarity of the disease, only limited longitudinal follow-up data are available, making it difficult to compare different interventions. In addition, the disease course is often unpredictable and can be remitting/relapsing with some reports of spontaneous resolution or long-term stability after an initial aggressive course. Intrathoracic involvement, particularly pleural effusion, is associated with worse outcomes. There is anecdotal evidence that exacerbations can occur with puberty and pregnancy.

Channel-Type LM/Central Conducting LM

The central conducting lymphatic anomalies (CCLA) are a family of lymphatic anomalies, encompassing many disorders that cause dysfunction of the paraxial lymphatic system including the lumbar trunks, cisterna chyli, thoracic duct, and their major tributaries. Failure of the conducting lymphatics results in reflux and leakage of the lymphatic fluid into pleural, pericardial and peritoneal spaces [21].

Etiopathogenesis

The etiology is poorly understood and likely varies within the umbrella term of CCLA. Genetic mutations in EPHB4 [72]and ARAF mutations [73] have been identified and more recently the JAG-1 gene has also been implicated [72, 74].

Clinical Presentation and Diagnosis

Patients present with chylothorax, chylous pulmonary congestion, chyloptysis and plastic bronchitis, chylous ascites, protein-losing enteropathy, chyluria, chylorrhea, fistulous communications with abdominal viscera (Fig. 21.13), cutaneous vesicles, or superficial chylous leaks. A definitive diagnosis can be made with lymphangiography and dynamic magnetic resonance lymphangiography. As presentations vary widely, an individualized approach is needed for diagnosis and treatment.

Management

Traditionally, supportive therapy with albumin and immunoglobulin therapy and surgical correction have been utilized. Mutations in EPHB4 and ARAF suggest a role for mTOR or MAPK/MEK inhibition, and several groups have reported responses with the use of sirolimus and trametinib [73]. Other groups [75, 76], however, report a lack of success with sirolimus in CCLA; some of these differences in responses may be related to the genotypically heterogeneous nature of this disorder. Surgical interventions, including lymphaticovenous bypass of the thoracic duct, have not been consistently successful [39]. Mapping of sites of lymphatic leak followed by embolization have been reported to control lymphatic leak by some centers with particular expertise [2, 6].

Course/Prognosis

Long-term follow-up studies are lacking, particularly with different interventions. Common clinical complications include chronic edema and recurrent infections.

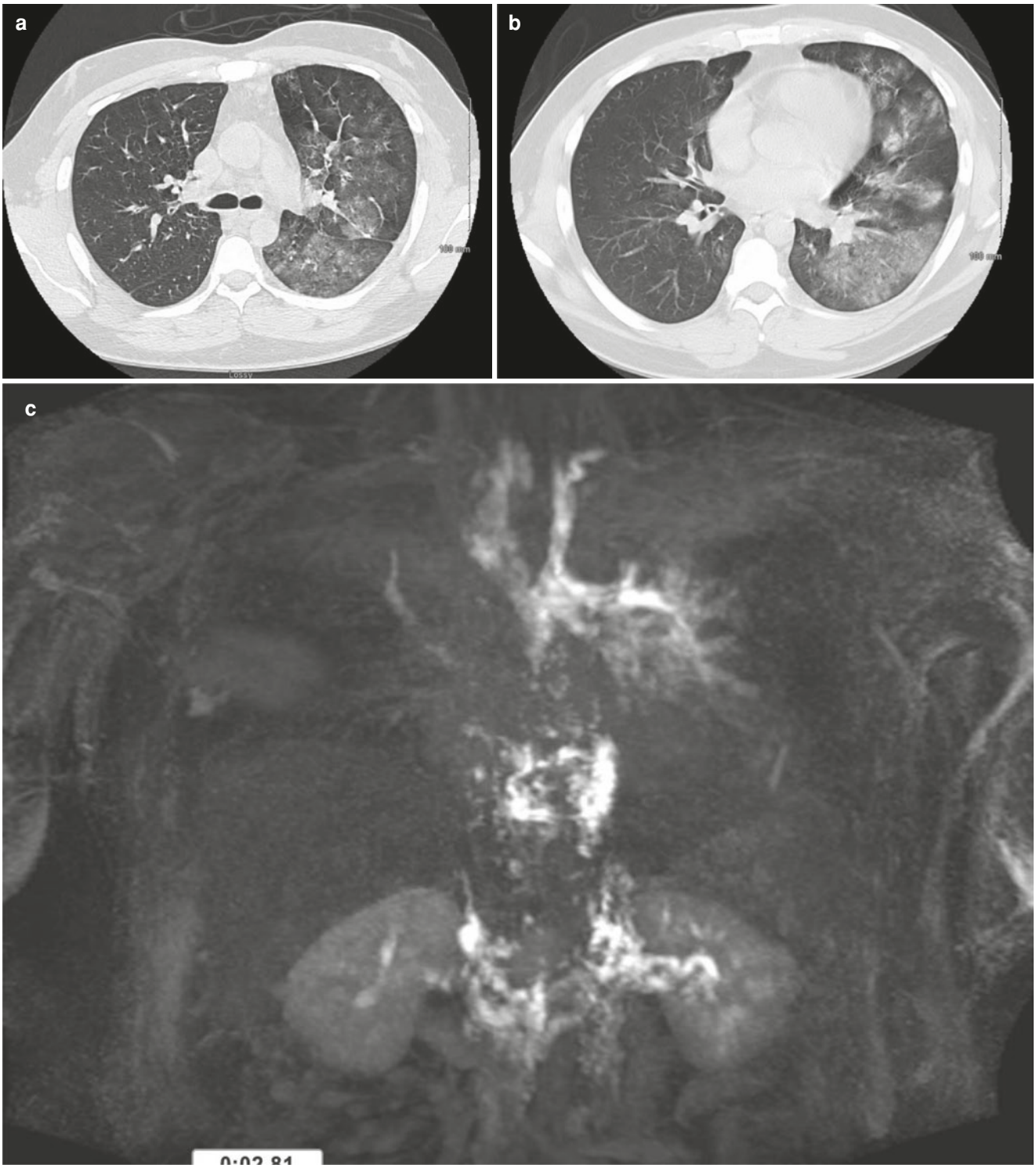

Fig. 21.13 Flooding of airways and alveolar spaces and kidneys with chylous fluid due to abnormal communications between of lymphatics and bronchi (**a**, **b**, **c**) and kidneys (**c**) in a patient with CCLA

Yellow Nail Syndrome

Yellow nail syndrome (YNS) is a rare acquired lymphatic disorder with estimated prevalence less than 1/1,000,000 [2, 3, 77] that was first described by Samman and White in 1964 [78]. The classic triad of yellow nail discoloration, idiopathic lymphedema, and respiratory tract manifestations, such as sinusitis, pleural effusions, and bronchiectasis, are rarely all present simultaneously [79]. Most patients present in the fourth or fifth decade of life. The disease

tends to be slowly progressive, but in some cases it can spontaneously remit.

Etiopathogenesis

The exact etiology of YNS is unknown; however, impaired lymphatic transport has been implicated in several studies [80]. Lymphoscintigraphy has demonstrated impaired functional lymphatic activity in patients with YNS rather than hypoplasia or aplasia [81]. There have reports of infants born with non-immune hydrops fetalis as well as a familial form of YNS affecting siblings suggesting an inheritable cause in some cases [82] [83, 84]. YNS has been reported in patients with autoimmune diseases [85–87], malignancies [88], and immunodeficiencies [89, 90]. Reports of onset of YNS after major surgery have also been reported, such as after mitral valve replacement or coronary bypass [91–95].

Exposure to titanium has been implicated as a possible cause, supported by high titanium levels in the nails of YNS patients [84, 96]. Sources of titanium are thought to include implants and food.

Clinical Presentation and Diagnosis

YNS is a clinical diagnosis, usually based on documentation of two of the three classical symptoms (yellow nails, lymphedema, and pleural effusion). Ruling out other common causes of lymphedema is important, however. While a diagnosis can be made without nail discoloration, it is challenging to do so due to overlap with other lymphedema syndromes. Nail discoloration varies from pale yellow to dark green and is associated with markedly thickened, hard and excessively curved nails (side to side) that grow very slowly [97]. There is also loss of the lunula and cuticles with detachment from the nail bed [98].

Pulmonary manifestations occur in 50–70% percent of patients, with chronic cough being the most common, followed by pleural effusions [99, 100]. The effusions tend to be recurrent, bilateral, lymphocytic exudates. A common misconception in YNS is that chylothorax is the most common type of effusion, although only 20% have triglyceride levels consistent with that diagnosis [100]. Bronchiectasis is present in 44% of cases, typically with a bilateral lower lobe distribution [101] (Fig. 21.7). Pulmonary symptoms often precede nail discoloration.

Lymphedema occurs in 30–80% of the cases and is usually bilateral and below the knee, but can also occur in other distributions, such as the face or result in ascites or chylopericardium. Acute or chronic rhinosinusitis is common and is reported in up to 83% of the patients and may precede nail changes by up to a few years [102]. Hard ear wax and keratosis obturans have been reported in YNS as well [103, 104].

Although YNS is not known to be due to genetic mutations, some cases of YNS have been reported in individuals with mutations in the FOXC*2* gene, which also causes a similar disorder called lymphedema-distichiasis syndrome [105].

Management

Pleural effusions may require symptomatic management with drainage; however, they tend to re-occur. Pleurodesis and decortication are effective treatments for recurrent clinically significant effusions. Octreotide has been used in some cases and appears to be more efficacious in patients with chylous effusions [106]. Spontaneous remission of nail changes is noted in up to 30% of the cases. Oral antifungals have also been used, sometimes in conjunction with Vitamin E, with inconsistent benefit [107–109]. It is important to exclude fungal infection with Wood's lamp testing and other means in patients with YNS since onychomycoses can mimic the disorder. Lymphedema can be treated with compressive stockings or wraps, elevation of the extremities, manual lymphatic drainage, or a comprehensive approach called Complete Decompressive Physiotherapy.

In a few isolated case reports, major surgery or use of bucillamine have been found to be associated with YNS [110], while sinus surgery [102], removal of titanium implants [96], or other sources of exposure have occasionally been reported to result in clinical improvement. It is admittedly difficult to distinguish spontaneous remission from a clinical effect of the intervention in these cases, however.

Course/Prognosis

There is no cure for YNS at this time and current treatment is focused on relieving symptoms. Prognosis varies depending on the severity of manifestations, but the disease has a relatively benign course in most patients. Recurrent thoracenteses are sometimes required, with risk of procedural complications and can sometimes lead to hypoalbuminemia.

Summary

Thoracic lymphatic disorders are uncommon conditions that can present with protean manifestations in adults. A high index of suspicion should be maintained in patients with chylous effusion, plastic bronchitis, or low density mediastinal masses or lymphatic parenchymal patterns on CT, such as interlobular septal thickening. Submission of tissue for genetic analysis and referral to specialized centers is strongly advised, as many of these conditions have been shown to be driven by targetable mutations in cell growth and proliferation pathways.

Clinical Vignette

A 50-year-old non-smoking South American woman presented with a 20-year history of recurrent cough productive of milky fluid, intermittent hemoptysis, and pleuritic chest pain. She carried a diagnosis of LAM based on a lung biopsy obtained 6 years earlier. She had no history of pneumothorax, tuberous sclerosis, or exercise limitation. Laboratory evaluation demonstrated normal hemoglobin and prothrombin time (PT), a low normal platelet count (109,000/mL (100,000–400,000/mL)), elevated d-dimer (10.10 mg/mL (0.01–0.49 mg/mL)), normal fibrinogen (250 mg/dL (150–425 mg/dL)), and elevated fibrin split products (FSPs) at more than 20 mg/mL (>5 mg/mL). A chest radiograph showed a prominent right hilum with a perihilar interstitial infiltrate. Chest computerized tomography (CT) imaging showed multiple enlarged hypodense lymph nodes in the mediastinum and both hila, and prominent peribronchovascular and interlobular septal thickening, especially in the right lower lobe (Fig. 21.12). There were no cystic parenchymal lesions suggestive of LAM or no bony or splenic involvement. MRI of the chest showed a cystic, septated appearance of the mediastinal lymph nodes with heterogeneously increased T2 and decreased T1 signal intensity. Pulmonary function tests were normal. The right lower-lobe lung biopsy specimen from 6 years earlier was reviewed, and revealed mature lung parenchyma with dilated, malformed lymphatic vascular channels within the pulmonary septa, bronchoalveolar bundles, and fibrotic pleura that stained with anti-CD4. There were foci of PROX-1-positive intralymphatic and perilymphatic spindle cells, hemosiderin deposits, and extravasated blood cells. There was no evidence of pulmonary cysts or smooth muscle cell infiltrates suggestive of LAM, and immunostains for Human Melanoma Black (HMB-45), estrogen receptor, and progesterone receptor were negative. The clinical and pathological findings were felt to be most consistent with KLA. The patient presented before genetic testing was widely available for KLA, but treatment with sirolimus was recommended.

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Pulmonary Alveolar Proteinosis Syndrome

22

Marissa O'Callaghan, Cormac McCarthy, and Bruce C. Trapnell

Clinical Vignette

A 37-year-old male ex-smoker had a 1-year history of progressive exertional dyspnea, three episodes of streaking hemoptysis, but no other medical history, and was taking no medications. He worked as an accountant and had no occupational or household pulmonary exposures. His peripheral blood oxygen saturation (SpO_2) was 94% while breathing room air and he did not experience serious respiratory distress. Lung auscultation was remarkable for fine inspiratory crackles at both lung bases. Laboratory investigation showed no increase in serum markers of inflammation. Pulmonary function testing demonstrated normal spirometry and a reduced diffusing capacity corrected for hemoglobin (DLCO) of 45% predicted. Chest radiograph showed bilateral patchy infiltrates. Computed tomography (CT) of the thorax reveal bilateral ground-glass opacities and superimposed septal thickening (the crazy paving sign) with sparing of the lung bases and costophrenic angles (Fig. 22.1). Bronchoscopy with bronchoalveolar lavage (BAL) was performed. Microbiology was negative and the cell differential included 75% macrophages, 10% lymphocytes, 12% neutrophils, and 3% eosinophils, and lipid-laden macrophages were observed. A serum GM-CSF autoantibody test was abnormal (44 μg/mL; normal <3) and a diagnosis of autoimmune PAP was established.

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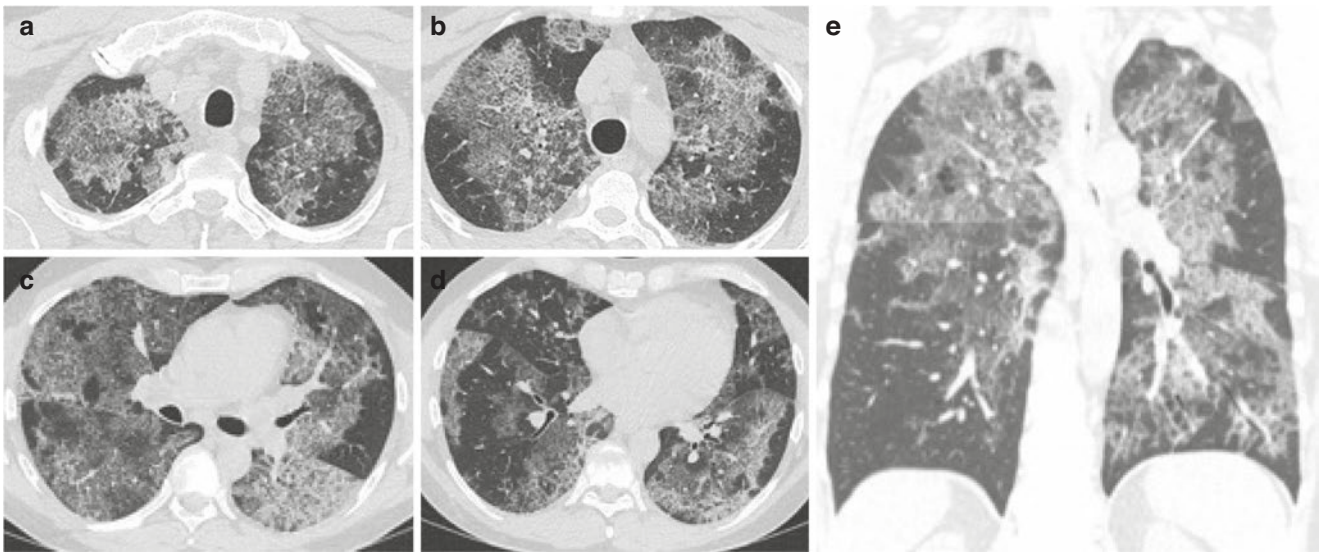

Fig. 22.1 Imaging of a PAP. Computed tomography of the chest showing the radiographic findings in autoimmune PAP in a 59-year-old man. (**a**–**d**) Cross-sectional CT chest images showing ground-glass opacification involving some but not all secondary lobules resulting in a distinctive "geographic" pattern. Also, note the distinctive pattern of interlobular septal thickening superimposed on ground-glass opacification, often referred to as "crazy paving." There is relative sparing of the lower lobes of the lung. (**e**) Sagittal CT chest image revealing ground-glass opacification in a patchy distribution with relative sparing of subpleural space and the costophrenic angles

Introduction

Pulmonary alveolar proteinosis (PAP) is a rare syndrome defined by abnormal accumulation of surfactant in pulmonary alveoli and can result in hypoxemic respiratory failure. It comprises a heterogeneous group of mechanistically distinct diseases, which are usefully considered to be disorders of surfactant production or clearance [1–3]. The latter can be subdivided into primary PAP and secondary PAP. Primary PAP is caused by disrupted GM-CSF signaling, which causes dysfunction of alveolar macrophages and neutrophils and includes two diseases, autoimmune (caused by GM-CSF autoantibodies) and hereditary PAP (caused by genetic mutations in CSF2RA or CSF2RB, encoding the alpha and beta chain of the GM-CSF receptor, respectively). Secondary PAP is caused by a reduction in the number and/or function of alveolar macrophages due the presence of another underlying disease, exposure to environmental inhaled toxins, or pharmaceutical agents. Congenital PAP includes multiple diseases caused by genetic mutations in the genes required for normal surfactant production that also referred to as pulmonary surfactant metabolic dysfunction (PSMD) disorders. Rarely, the etiology of PAP cannot be determined, resulting in a diagnosis of unclassified PAP. Recent advances have improved our understanding of PAP pathogenesis, epidemiology, [4–6] and have resulted in new methods to diagnose, evaluate, and treat patients [7]. Because of the numerous advances, this chapter will specifically focus to the pathogenesis, classification, clinical presentation, and management of autoimmune PAP except where otherwise noted.

Historical Note

The physical properties of surfactant were described in the early 1950s [8] and shortly afterward PAP was first described, a disease caused by excessive pulmonary surfactant accumulation [9]. Enlarged, foamy alveolar macrophages filled with lipids were later identified with dysfunctional chemotaxis, adhesion, and microbial killing in addition to reduced survival, suggesting that the alveolar microenvironment was abnormal [10]. BAL from patients with PAP were consistently abnormal with increased levels of a 40-kDa protein which altered macrophage function and numbers [11] supporting the concept of an abnormal protein-led pathogenesis [12]. Interestingly, whole-lung lavage (WLL) therapy improved alveolar macrophage functions [13]. Further studies discovered that PAP spontaneously developed in GM-CSF-deficient mice [14, 15]. Subsequently, the macrophage function-inhibiting protein of concern in the BAL fluid (and serum) of patients with PAP was found to be an immunoglobulin that bound and neutralized GM-CSF [16, 17]. The identification

of these pathognomonic GM-CSF targeting antibodies led to a nomenclature change from "Idiopathic" PAP to the more appropriately named autoimmune PAP [1, 18–21]. These studies identified the critical role that GM-CSF plays in maintaining surfactant homeostasis, alveolar stability, and host defense [22].

Epidemiology

While disorders of surfactant homeostasis are rare, they occur in worldwide distribution. More than 1000 cases of PAP have been reported in the medical literature since it was first reported in 1958 [2, 4, 5, 9, 23–26]. Autoimmune PAP accounts for 90% of all patients with PAP [2, 4–6, 23]. A national PAP registry study that identified 248 patients with PAP syndrome in Japan reported the incidence and prevalence of autoimmune PAP to be 0.49 ± 0.13 and 6.7 per million, respectively [23]. Another study conducted the United States based on analysis of comprehensive health insurance claims data reported the prevalence of PAP syndrome to be 6.87 per million [27]. Interestingly, 31% of the patients in the Japanese national registry were identified through mandatory health screening and were asymptomatic at diagnosis suggesting these prevalence values may be underestimates. Indeed, a third more recent study from Japan based on Poisson analysis of annual incidence data reported a prevalence of 26.

Male gender and smoking have been described as risk factors for PAP [2]. However, an analysis of several large case studies found that 21–43% of PAP patients were never smokers, indicating that PAP is not simply a smoking-related disease [2, 4–6, 23]. Furthermore, while a comprehensive meta-analysis of 410 separate cases of PAP found that patients were more likely to be male (male: female ratio = 2.65:1.0), the gender balance was reversed when non-smoking patients were taken in isolation (male: female ratio = 0.69:1.0). This led to the conclusion that the male dominance among patients with PAP may be explained by their higher frequency of tobacco use. The median age at diagnosis in this study was 39 years (39 in men and 35 in women) [2]. Finally, several studies have searched for a genetic predisposition to the development of autoimmune PAP [28, 29]; one evaluating 198 autoimmune PAP patients and 395 controls of Japanese ancestry identified two major histocompatibility complex alleles as independent risk factors (HLA-DRB1*08:03 and HLA-DPb1) [17].

In summary, PAP syndrome is caused by autoimmune PAP in 90% of cases and has a prevalence of 7–10 (possibly up to 26) per million in the general population. It affects men, women, and children independent of ethnicity, gender, and socioeconomic status [22].

Pathogenesis

Surfactant Homeostasis in PAP

A primary function of surfactant is to reduce surface tension at the air–liquid–alveolar wall interface, thereby preventing alveolar collapse during the breath cycle. It is composed of ~80% polar phospholipids, ~10% neutral lipids (mostly cholesterol), and ~10% surfactant proteins. Surfactant is synthesized in type II alveolar epithelial cells (AEC-2) and secreted into the alveolar space. Surfactant is cleared from the lung surface by recycling and catabolism in AEC-2 cells and by catabolism and export by alveolar macrophages [7]. Studies in animals and humans identified a critical role for GM-CSF in surfactant homeostasis; alveolar macrophages require GM-CSF in order to clear surfactant (Fig. 22.2). GM-CSF is a 23-kDa cytokine identified in the 1970s [30, 31], which is expressed by a variety of cell types, including lung epithelial cells [32, 33]. It is, perhaps, best known its role in inflammation, host defense, and autoimmune diseases [34, 35]. Specifically, pulmonary GM-CSF stimulates survival, proliferation, differentiation, and the functions of alveolar macrophages [36–39].

GM-CSF Signaling Disruption

GM-CSF signaling occurs via cell surface receptors composed of a low affinity GM-CSF-binding α chain (CDw116) and an affinity-converting β chain (CD131) [40, 41] which constitutively binds Janus activating kinase (JAK) [42]. Ligand binding results in the assembly of αβJAK2 multimers and activation of JAK2, phosphorylation of α [43] and β chains, and initiation of signaling via multiple pathways, [42, 44] including the signal transducer of activation and transcription-5 (STAT5) [45].

Disruption of GM-CSF signaling causes the development of PAP (Fig. 22.3). Mice deficient in GM-CSF (*Csf2*^{KO}) or the GMC-CSF receptor α chain (*Csf2ra*^{KO}) or β chain (*Csf2rb*^{KO}) develop PAP with similar physiological, histopathological, and immunological features to autoimmune PAP [14, 15, 46]. PAP was corrected by transplantation of wild-type bone marrow in *Csf2rb*^{KO} mice identifying myeloid cells and not lung epithelial cells as the cellular site of pathogenesis [47]. Reversal of PAP was achieved in *Csf2*^{KO} mice by expression of GM-CSF in the lungs [48–50] and in

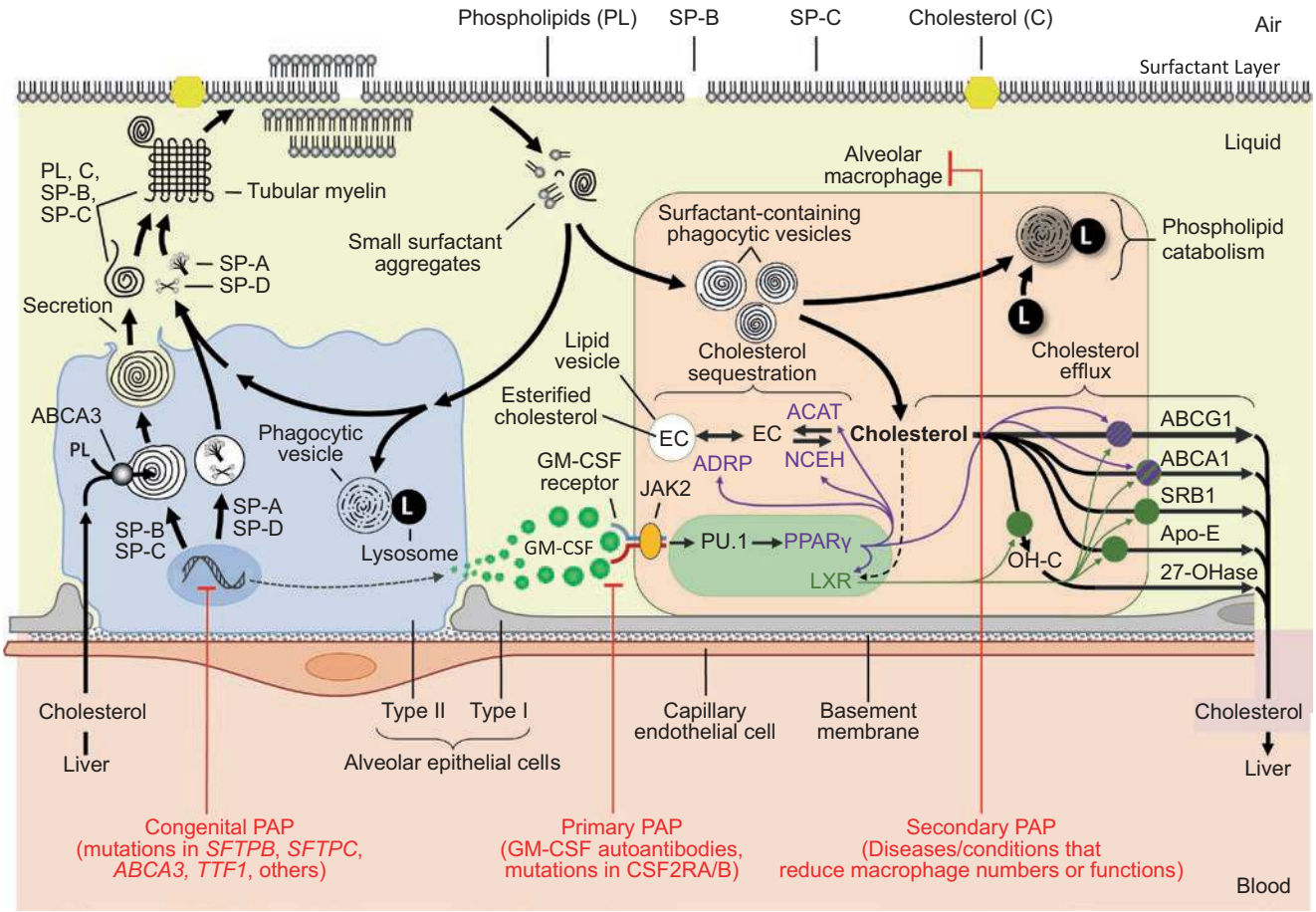

Fig. 22.2 Normal alveolar surfactant homeostasis. A portion of a pulmonary alveolus is shown. Pulmonary surfactant normally comprises a thin layer of polar lipids (mostly phospholipids), neutral lipids (mostly cholesterol), and surfactant proteins (**A**–**D**) located at the alveolar air–liquid interface that reduces surface tension on the alveolar wall and is critical to alveolar stability and lung function. Surfactant homeostasis is tightly regulated by balanced secretion of surfactant lipids and proteins by type II alveolar epithelial cells and removal by these cells (through recycling and catabolism) and by alveolar macrophages (through catabolism and excretion). Alveolar macrophages require GM-CSF constitutively to an adequate rate of cholesterol clearance, which occurs through multiple pathways

Csf2rb^{KO} and *Csf2ra*^{KO} mice by pulmonary macrophage transplantation [51, 52]. GM-CSF is detectable at low but non-zero levels in normal human lung [37]. While the absence of GM-CSF causes PAP, excessive GM-CSF causes accumulation of alveolar macrophages within the distal airspaces of the lung; a phenotype resembling desquamative interstitial pneumonia in humans [53]. In summary, pulmonary GM-CSF is a low abundance cytokine regulator of surfactant homeostasis, alveolar structure, lung function, and host defense [22].

Myeloid Cell Dysfunction

We have established that pulmonary GM-CSF plays a critical role in surfactant homeostasis, alveolar structure, and lung function via its regulation of myeloid cells—particularly alveolar macrophages [22]. Constitutive GM-CSF signaling occurs via PU.1, the master macrophage transcription factor purine box binding protein 1 [37], and peroxisome proliferator-activated receptor gamma (PPARγ) [54, 55], the lipid metabolism-related transcription factor. The transcription factor PU.1 is a required component of the GM-CSF signaling pathway, [37] and both PU.1 and PPARγ are needed for alveolar macrophage specification and to enable cholesterol exportation, surfactant clearance, and other important macrophage functions [30]. Furthermore, macrophages from *Csf2*^{KO} mice have reduced expression of PPARγ and its target gene ATP binding cassette transporter G1 (ABCG1), a transmembrane lipid transporter protein important in cholesterol efflux from macrophages [56–58]. And mice deficient in ABCG1 (ABCG1^{KO}) develop a PAP-like pulmonary phenotype with foamy macrophage formation, implicating ABCG1 specifically in pulmonary surfactant homeostasis [59, 60].

Similar observations have been made in human studies. Alveolar macrophages from patients with PAP are foamy in appearance due to reduced expression of PU.1, PPARγ, and ABCG1, associated with accumulation of esterified choles-

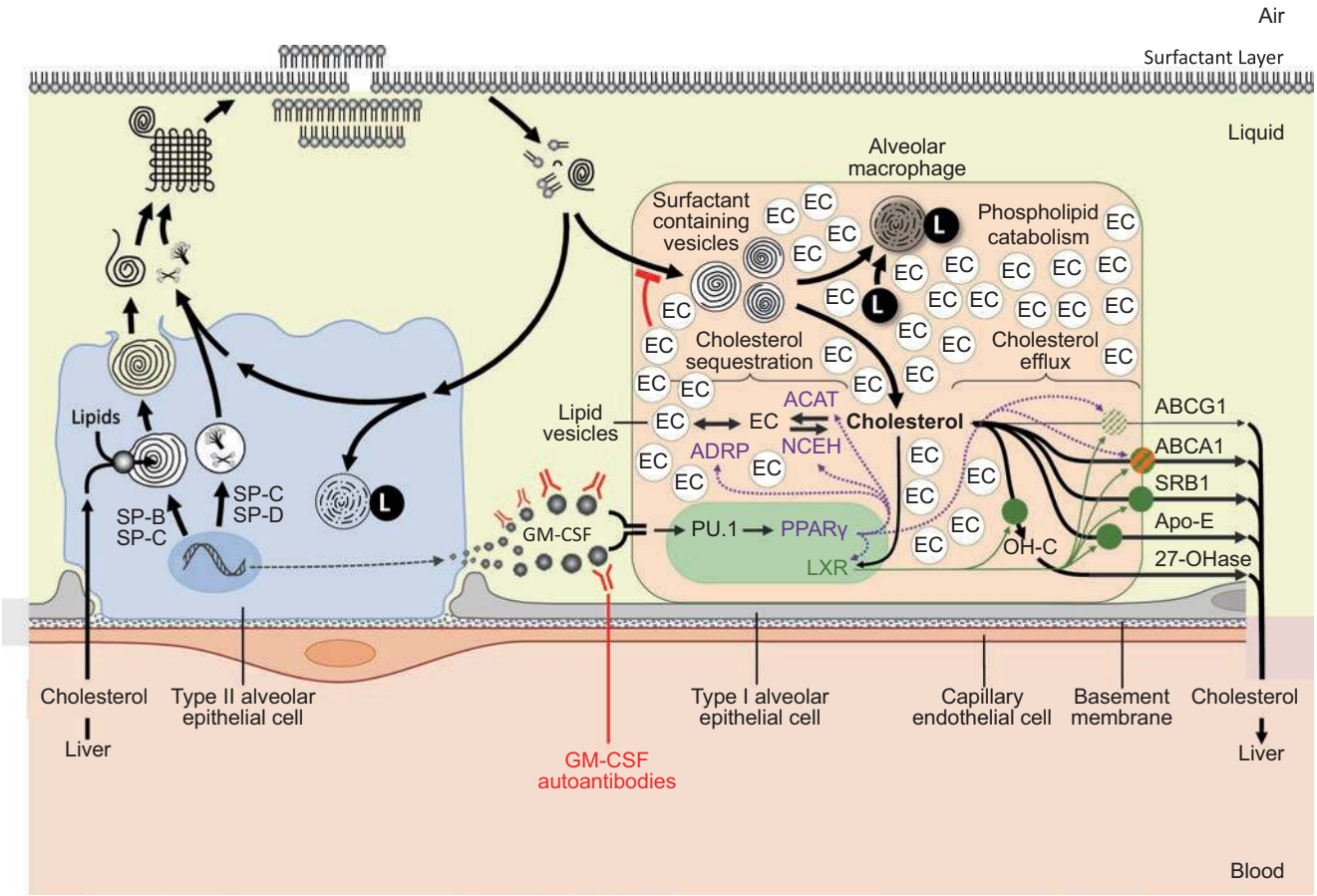

Fig. 22.3 Pathogenesis of autoimmune PAP. An increase in polyclonal, neutralizing GM-CSF autoantibodies blocks GM-CSF signaling in the blood and tissues, which impairs multiple functions by altering expression of multiple genes including expression of the macrophage cholesterol transporter, ABCG1, resulting in a primary reduction in cholesterol clearance and a secondary reduction surfactant clearance from the alveolar surface. Increased intracellular cholesterol stimulates increases in ABCA1 and other LXR-mediated cholesterol clearance pathways that attempt albeit unsuccessfully to compensate for the loss of ABCG1-mediated clearance. In response to reduced cholesterol efflux, alveolar macrophages esterify and store cholesterol in lipid droplets, which accumulate inside the cells resulting in the formation of foam cells

terol in intracytoplasmic droplets [55, 58]. While surfactant from PAP patients contains increased amounts of phospholipids, the increase in cholesterol is even greater, resulting in an increase in the ratio of cholesterol to phospholipid [30, 31]. This has important implications for the surface tension-lowering biophysical properties of surfactant [61–63]. GM-CSF via its downstream pathways involving PU.1, PPARγ, and ABCG1 in alveolar macrophages regulates cholesterol efflux as well as fatty acid catabolism but has no apparent effect on the initial steps involved in catabolism of phospholipids. In both human and murine studies this results in cholesterol ester-filled intracytoplasmic droplets accumulating with alveolar macrophages or the so-called foamy macrophages [64]. Finally, this is further supported by the increase in alveolar macrophage surfactant cholesterol: phospholipid ratio when there is a loss of GM-CSF signaling, which impairs surfactant function [7].

Neutrophils from patients with autoimmune PAP and *Csf2*^{KO} mice also have impaired host defense functions but appear to be fully differentiated with normal morphology and phenotypic marker expression but reduced capacity for bacterial killing, phagocytosis, reactive oxidase species production, and cell adhesion [18]. Ex vivo exposure of normal human neutrophils to GM-CSF autoantibodies reproduces the functional impairments observed in PAP neutrophils [18]. It is likely that GM-CSF constitutively regulates the basal functional capacity of neutrophils in vivo in a rheostatic manner based on studies in humans, mice, and non-human primates [18]. The dysfunctional neutrophils in autoimmune PAP contribute to impaired innate immunity, thus providing a molecular and cellular explanation the increased infection risk in these patients [18].

GM-CSF Autoantibodies

Following the discovery in *Csf2*^{KO} mice, elevated levels of GM-CSF autoantibodies were noted in the serum and BAL

fluid of patients with "idiopathic" PAP. Interestingly they were not identified in secondary or congenital PAP [16, 17]. When healthy non-human primates were exposed to GM-CSF autoantibodies purified from patients with PAP, they developed lung disease and had abnormal GM-CSF signaling [19, 20]. It was subsequently demonstrated that the presence of GM-CSF autoantibodies was pathognomonic for "idiopathic" PAP which prompted a nomenclature change from idiopathic to the more accurate term autoimmune PAP which accounts for the majority of cases of PAP syndrome [21]. GM-CSF autoantibodies are also found at low levels in healthy individuals so there appears to be a critical threshold at which antibody concentration impairs GM-CSF signaling resulting in disease [21]. Furthermore, the absolute level of GM-CSF autoantibodies does not correlate with disease severity [7, 65].

Lymphocytosis

Lung pathology in autoimmune PAP includes pulmonary lymphocytosis, although this has not been well studied. Interestingly, GM-CSF also has regulatory effects on lymphocytes [66–68]. The BAL cell differential count reveals increased pulmonary lymphocytes composed of increases in both CD4+ and CD8+ cells [69]. Furthermore, variable infiltration of B and T cell lymphocytes is typically present where pathological specimens are available [9, 70, 71]. While increased pulmonary levels of monocyte chemoattractant protein-1 (MCP-1) may contribute to pulmonary lymphocyte accumulation, the precise mechanism(s) responsible have not been defined [67].

Clinical Manifestations

Clinical Presentation

Patients with PAP syndrome usually present with subacute onset of progressive dyspnea with or without cough, fatigue, scant production of whitish frothy sputum, and occasionally weight loss. The presence of fever and/or hemoptysis suggests the presence of secondary pulmonary infection. More than 30% of patients are asymptomatic. Diagnosis is often delayed by months or years due to the non-specific symptoms and physical exam findings; many patients are initially misdiagnosed with pneumonia or asthma. Physical exam findings occasionally include crackles, or cyanosis however; digital clubbing is not a feature of autoimmune PAP but is occasionally seen in other PAP-causing diseases. The clinical presentation can be surprisingly benign compared to the severe presentation expected from the extent of the radiographic abnormalities typically seen in PAP, a finding that should raise the suspicion of PAP; a heightened awareness is an important aspect of the timely diagnosis of PAP.

Secondary Infections

PAP patients have an increased risk of infection by both common or opportunistic pathogens, including Nocardia spp., Mycobacteria, Aspergillus, and others [2, 18]. Secondary infections can occur at the initial clinical presentation or in the first year or so and are associated with a higher mortality rate [72]. An increased infection risk is seen in mice in which the GM-CSF gene has been knocked out ($Csf2^{KO}$), and these mice have increased susceptibility to a range of bacterial, fungal, parasitic, and mycobacterial pathogens. This increased infection risk can be explained in humans and mice with GM-CSF signaling deficiency based on the observation that macrophages and neutrophils exhibit numerous innate immune defects [18, 27, 37, 73–75].

Pulmonary Fibrosis

Pulmonary fibrosis occurs to varying degrees among PAP-causing diseases; it is a less-common manifestation of autoimmune PAP, variably present in secondary PAP, and the predominant manifestation in congenital PAP although this manifestation appears to present later in life [76]. The pattern of fibrosis varies considerably and can present as non-specific interstitial pneumonia (NSIP), usual interstitial fibrosis, and can progress to end-stage fibrosis with honeycombing and/or traction bronchiectasis [76]. Thus, evaluation for the presence of fibrosis should be part of the routine follow-up of all patients with PAP [7]. While anti-fibrotic agents are widely used in idiopathic pulmonary fibrosis [77, 78], they have only recently been licensed for progressive fibrosing interstitial lung disease and thus could be used in patients with PAP if fibrosis is identified [79]. Lung transplantation remains the only viable treatment option for patients with significant fibrotic lung disease.

Diagnosis

Pulmonary Function Testing

Routine spirometry and lung volumes may be normal in patients with mild PAP or may show varying degrees of restrictive lung impairment that varies in proportion to lung disease severity. In contrast, the DLCO is a sensitive measure of PAP disease severity and is reduced in proportion to disease severity [2, 23]. The 6-min walk test is often normal in PAP patients with mild or even moderate disease. Arterial blood gases show a varying degree of reduction in the arterial PaO_2 and increase in the alveolar-arterial difference in oxygen concentration ($A\text{-}aDO_2$) both of which correlate with disease severity and thus are useful indicators of the need for treatment [2].

Radiographic Assessment

The chest radiograph in PAP can be similar in appearance to that of pulmonary edema (diffuse bilateral symmetrical perihilar infiltrates) but without other radiographic features of heart failure [80, 81]. A high-resolution computed tomography of the chest should be performed as the plain chest radiograph lacks sensitivity and specificity. Radiographic findings on the HRCT include ground-glass opacification superimposed on septal thickening with abnormal regions sharply demarcated from more normal-appearing regions resulting in what is often referred to as "geographic" appearance. These regions appearing as polygonal shapes and sharply marginated areas of involvement correspond to secondary lobules, interlobular, and lobar boundaries and give an appearance often referred to as "crazy paving" [81, 82]. While this geographic, "crazy paving" pattern is commonly seen in autoimmune PAP, is not diagnostic but, rather, can also be seen in various other idiopathic, infectious, neoplastic and inhalational lung disorders [82]. Neither the chest radiograph nor chest CT is capable of identifying any specific PAP-causing disease [83].

Bronchoscopy and Bronchoalveolar Lavage

Bronchoalveolar lavage can be useful in diagnosing PAP syndrome and for assessment of secondary lung infection, which should typically be done when performing bronchoscopy in these patients because of the increased infection risk. BAL fluid has a characteristic milky or waxy appearance and can contain large amounts of surfactant sediment that settles if left standing. Microscopic examination of BAL specimens stained with Periodic acid–Schiff reagent or Papanicolaou reveals a "dirty appearing" cytology with acellular eosinophilic globules, large foamy alveolar macrophages (that also appear red after staining with oil-red-O), and significant amounts of cell debris (that stains only weakly with PAS) [2, 23, 84, 85]. Biochemical analysis of BAL fluid from patients with PAP shows increased phospholipids, a greater increase in cholesterol (and cholesterol ester) resulting in a markedly increased cholesterol to phospholipid ratio, an increase in surfactant proteins, and increased cytokine biomarkers of PAP (macrophage colony stimulating factor and monocyte chemoattractant protein) [86].

Laboratory Studies and Biomarkers

Routine laboratory studies are usually normal in PAP except for serum lactate dehydrogenase (LDH) levels, which are typically elevated in proportion to lung disease severity and A-a$D0_2$ [2, 87]. In secondary PAP associated with hematological conditions, other laboratory abnormalities may be present. Other serum biomarkers of PAP include tumor antigens CEA [88], CYFRA 21 [5, 89], and NSE [90], lung epithelium derived proteins (KL-6 [91], SP-A, SP-B, and SP-D [92, 93]), MCP-1 [94] and the chitinase-like protein, YKL-40 variably correlate with disease severity but none of these are diagnostic of PAP syndrome or any of the PAP-causing diseases [7].

GM-CSF Autoantibodies

An abnormal serum GM-CSF autoantibody test is the most well-established and useful biomarker, partly because an abnormal (increased) level is very specific for autoimmune PAP [1, 18, 74, 95–97]. While serum GM-CSF autoantibodies are present at non-zero levels in healthy people [73], a high serum level is diagnostic of autoimmune PAP and has a reported sensitivity and specificity of 100% [97, 98].

GM-CSF Signaling Deficiency Test

Serum GM-CSF signaling tests are useful in the evaluation of PAP patients and are abnormal in primary (autoimmune and hereditary) PAP but not in secondary or congenital PAP [25, 99–104]. In autoimmune PAP both the serum GM-CSF autoantibody test and a serum GM-CSF signaling test are abnormal. In hereditary PAP, the autoantibody test is normal (negative for a high level of antibodies), but the GM-CSF signaling test is abnormal. In other PAP-causing diseases, both these tests are typically normal.

Genetic Testing

When the GM-CSF autoantibody test is normal and the GM-CSF signaling test is abnormal, screening for mutations in either CSF2RA or CSF2RB can be useful.(REFS) When the GM-CSF autoantibody and GM-CSF signaling tests are normal in a patient with PAP, screening for mutations in genes required for surfactant production-related genetic mutations should be pursued including for the genes encoding *SFTPB* [105–107], *SFTPC* [107–109],, *ABCA3* [110, 111], or *NKX2.1* [112]. Testing for mutations of *SLC7A7* and *MARS* should be considered if there is suspicion of secondary PAP [113–116].

Lung Pathology

Traditionally transbronchial or surgical lung biopsy were considered necessary to make a diagnosis of PAP syndrome. However, a lung biopsy can have a significant false negative rate due to the patchy distribution of disease [117] and usually provides little to no information of use in identifying the specific PAP-causing disease present and, consequently, is no longer recommended for use in routine cases. However, if the diagnosis is unclear after the above tests have been successfully completed, a lung biopsy may be helpful in identifying other conditions with radiological, cytological, or pathological features similar to PAP. The classical histological findings of PAP include preserved architecture of lung parenchyma with alveoli and terminal airways filled with PAS-positive eosinophilic material, abundant alveolar macrophages, and positive immunohistochemistry for surfactant proteins [1].

Diagnostic Approach to the Patient with PAP

Multiple conditions can present with clinical and/or radiological findings similar to PAP and should be considered in the differential diagnosis including pneumonia, pulmonary edema, hypersensitivity pneumonitis, and a range of interstitial lung diseases. PAP patients typically present with exertional dyspnea, cough, and fatigue and undergo chest radiographic investigations and pulmonary function testing and both these tests are useful and recommended. Characteristic HRCT findings and a reduced DLCO with or without restrictive pulmonary physiology should prompt the consideration of PAP syndrome. The observation of BAL with a milk appearance strongly supports a diagnosis of PAP syndrome. A GM-CSF autoantibody test should be performed in all patients because it is highly accurate for a diagnosis of autoimmune PAP, which is responsible for 90% of all patients with PAP syndrome. No other available clinical or genetic tests are available to specifically diagnose autoimmune PAP. Genetic testing should be pursued in patients with a normal GM-CSF autoantibody levels and a detailed history to determine any possible causes of secondary PAP (Fig. 22.4). The criteria for diagnosis of autoimmune PAP are listed (Table 22.1).

Table 22.1 Criteria for diagnosis of autoimmune pulmonary alveolar proteinosis[a]

Essential criterion
Abnormal serum GM-CSF autoantibody test result[b]
Supporting criteria (at least one is required)
• Chest HRCT scan showing diffuse ground-glass opacification and superimposed septal thickening[c] • Bronchoalveolar lavage cytopathology showing extensive, mostly extracellular, amorphous PAS-positive cell fragments/debris, ghost cells, large foamy (PAS-positive, oil-red-O-positive) macrophages[d]
• Lung biopsy histopathology showing alveoli filled with eosinophilic (PAS-positive) granular sediment, enlarged foamy-appearing alveolar macrophages, cholesterol crystals (clefts)[e]

HRCT high-resolution computed tomography, *GM-CSF* granulocyte/macrophage colony-stimulating factor, *PAS* periodic acid–Schiff

[a]Diagnosis requires the presence of the essential criterion and (any) one of the supporting criteria

[b]Usually determined quantitatively by enzyme linked immunosorbent assay (ELISA). The (laboratory specific) cutoff value for an abnormal test depends on the nature of the GM-CSF autoantibody reference standard and the assay protocol (see text for details)

[c]Ground-glass opacification may occur without superimposed septal thickening in mild disease, usually but not always involves multiple lobes, with or without subpleural sparing

[d]Bronchoalveolar lavage fluid usually appears opalescent, milky white (or brown in smokers) and contains a waxy sediment, which appears quickly upon standing at room temperature or in the cold

[e]A lung biopsy is often unnecessary and should only be obtained if clinically indicated (see text for details)

Natural History and Prognosis

While no longitudinal studies have reported on the clinical course of autoimmune PAP, a comprehensive meta-analysis of 343 patients with PAP reported a survival rate of 75% at 5 years and 68% at 10 years. Over 80% of the deaths attributable to PAP occurred within 12 months of diagnosis, with respiratory failure (72% of deaths) and uncontrolled infection (20% of deaths) as the most common causes of death. A cross-sectional cohort study of 223 patients with autoimmune PAP in Japan reported no deaths over the course of a 5-year study period [23]. Spontaneous improvement of PAP has been reported in 7.9% of patients in a large meta-analysis [9]. Autoimmune PAP typically follows one of three patterns: progressive deterioration, stable disease, or spontaneous resolution [2]. Prognosis for patients with secondary PAP is significantly worse with a median survival of less than 20 months reported in a study of 40 patients [118]. Congenital PAP is associated with significant progressive pulmonary fibrosis in adolescents and adults.

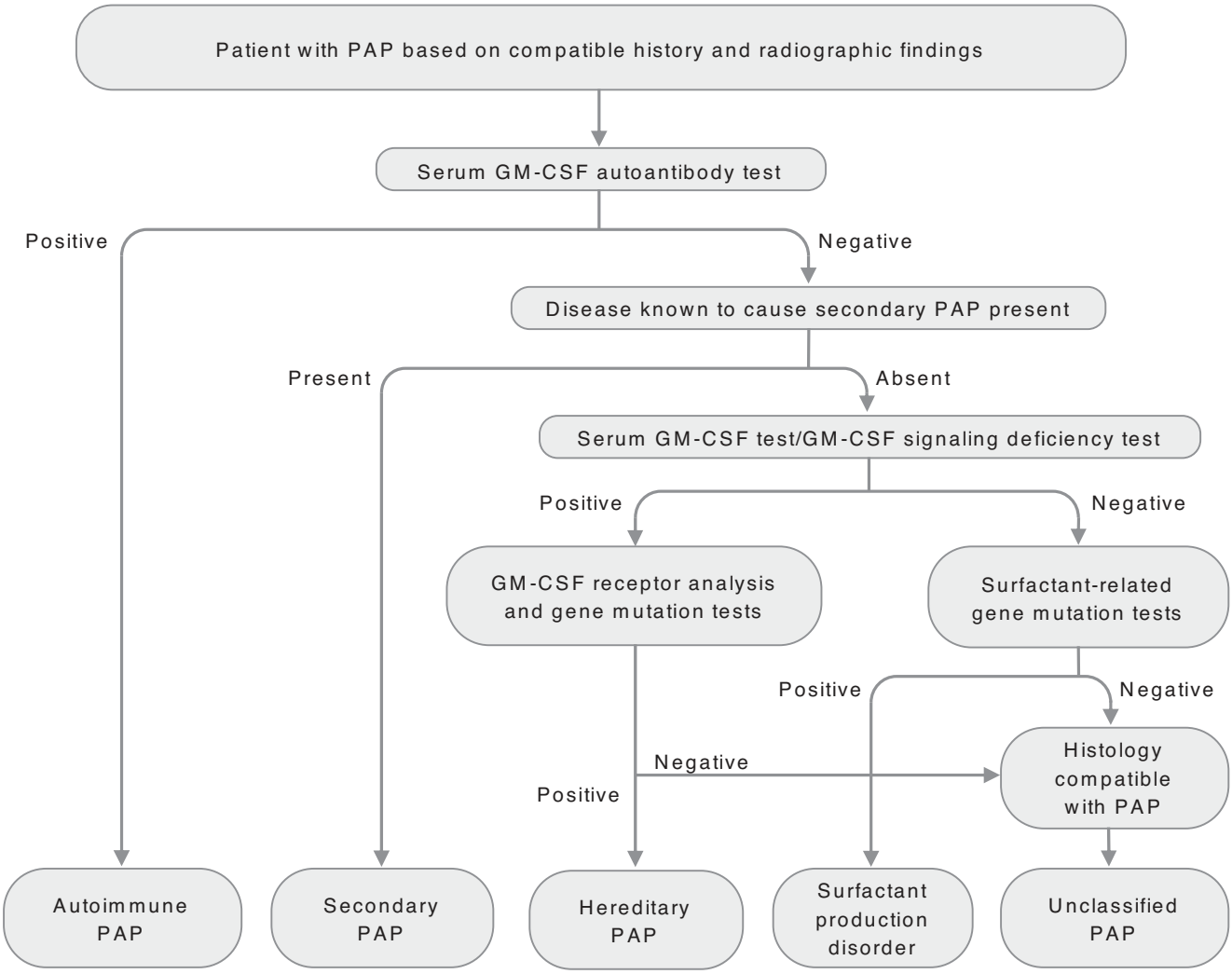

Fig. 22.4 Algorithm used for diagnosis of PAP syndrome. The presence of PAP is suspected based on a compatible history, typical radiologic findings, and bronchoalveolar lavage cytology findings. GM-CSF autoantibody test should be performed initially when PAP is suspected: a positive test confirms the diagnosis of autoimmune PAP. Patients with a negative GM-CSF autoantibody test that have a disease known to cause PAP are diagnosed with secondary PAP. Those with a negative GM-CSF autoantibody test and no underlying PAP-causing disease should undergo a blood-based GM-CSF signaling test and serum GM-CSF test: individuals with positive tests should undergo further tests for GM-CSF receptor gene (CSF2RA or CSF2RB) mutations to identify hereditary PAP. Patients with a negative GM-CSF signaling test should undergo further tests for other gene mutations (e.g., in SFTPB, SFTPC, ABCA3, or NKX2.1) to diagnose surfactant production disorders. If no PAP-causing disease can be found, a transbronchial or surgical lung biopsy for lung parenchymal histopathological examination may be needed. (Adapted from Trapnell et al. Pulmonary alveolar proteinosis. *Nat Rev Dis Primers*. 2019 Mar 7;5(1):16. doi: 10.1038/s41572-019-0066-3. PMID: 30846703)

Treatment

Shortly after PAP was first reported, a number of therapeutic strategies were tested in case studies, including administration of antibiotics, corticosteroids, and acetylcysteine among others [119]. Whole-lung lavage (WLL) emerged early and has remained the standard treatment. The serendipitous discovery of a PAP in *Csf2*^{KO} mice and the subsequent discovery of GM-CSF neutralizing antibodies in patients with (then) idiopathic PAP shifted the focus toward evaluation of GM-CSF augmentation therapy and others, including plasmapheresis and anti-B lymphocyte immunotherapy. We focus on WLL and GM-CSF augmentation therapy.

Whole-Lung Lavage

WLL is widely considered to be appropriate first-line therapy of autoimmune PAP. Ramirez introduced the use of pulmonary saline instillation as therapy of PAP in the early

1960s with a procedure in which a transtracheal catheter was used to drip saline into the trachea multiple times per day for several weeks to induce cough-mediated surfactant clearance. However, the approach was not well tolerated or accepted into general practice. Subsequently, the procedure for instilling saline into the lungs underwent refinements, such as use of a double-lumen endotracheal tube and use of large volumes of saline that allowed the lungs to be more effectively and safely removed in a single session—a procedure now referred to as WLL. Briefly, saline is administered via a double-lumen endotracheal tube under general anesthesia, thereby allowing one lung to be "washed" to physically remove the excess surfactant while the other lung is mechanically ventilated [120–122]. Notwithstanding improvements, WLL is not been standardized across institutions with respect to the method, indications for its use, evaluation of treatment responses, or the timing of repeated procedures.

The WLL procedure is dependent on operator experience and, ideally, should be performed by an experienced team including an interventional pulmonologist or surgeon, anesthesiologist, a nurse, and a respiratory therapist [123]. Briefly, general anesthesia is induced and the patient is intubated with a double-lumen endotracheal tube to isolate each lung, and positioned for the procedure. Various body positions are used at different centers, including treated side up or down, supine, lateral decubitus; however, little supporting evidence has been reporting to identify the optimal approach [124]. The non-treated lung is ventilated with 100% oxygen to optimize oxygenation. Lung isolation is confirmed and then saline pre-warmed to 37 °C is instilled under a small (30 cm) hydrostatic head in infused in volumes of 500–1000 mL aliquots and drained under gravity via a closed system [22]. Chest percussion is used to loosen the surfactant sediment and emulsify it with the saline—either by manual percussion or using a wrap-around, pulsating vest [125, 126]. Each cycle of saline infusion, chest percussion, and drainage typically required 3–5 mins to complete (or longer if asthma is present). This process is repeated until the milky/turbid effluent clears, which can require up to 50 L of saline per lung in adults although most patients clear with about 30 L and smaller volumes in children. Patient monitoring during the procedure includes continuous measurement of peripheral blood oxygen saturation (SpO_2) and vital signs, serial measurement of $Pa0_2$, tracking infusion and effluent volumes, observation for leakage of saline into the non-treated (ventilated) lung, and monitoring for adverse events, such as leakage of saline into the pleural space. Upon completion of infusion/drainage cycles, the lungs are examined bronchoscopically and residual saline is aspirated, ventilation with 100% oxygen is resumed, and the double-lumen tube is replaced with a single-lumen tube until extubation can be performed safely. In high risk adults, the use of extracorporeal membrane oxygen [127], hyperbaric conditions [127, 128], or bronchoscopic segmental and lobar lavage can be used to reduce intraoperative risk [129].

The indications for WLL therapy are not standardized among institutions but exertional dyspnea-limiting physical activity is a common primary indication [125, 126]. WLL should be considered in patients with declining lung function, PaO_2 or SpO_2, a shunt fraction >10–12%, or radiographic evidence of disease progression [122]. The most severely affected lung or lung segment is usually treated first and the less affected lung is treated several days to weeks later. Active bacterial lung infection, sepsis, and shock are contraindications for WLL [125, 126].

While no randomized controlled trials evaluating the safety and efficacy of WLL have been reported in the medical literature, WLL it is widely regarded as capable of improving patients' symptoms, radiographic abnormalities, and oxygenation [130, 131]. One study described the WLL outcomes for 231 individuals with PAP, reporting an overall 5-year survival of 94% with lavage versus 85% without lavage [2]. This study reported WLL was typically performed within 5 years of diagnosis (70% of patients) and the median number of lavages required was two per patient. In one subgroup analysis (n = 55), only 20% of patients remained recurrence free at 3 years and the median duration of benefit was 15 months. A demonstrable improvement in arterial PaO_2 of 20.1 mmHg was noted among 41 patients for whom data were available with less impressive improvements in other pulmonary physiology parameters. Overall, WLL was an effective intervention with a response in over 95% of patients with pulmonary fibrosis noted with greater prevalence in the remaining 5% who failed to respond. Treatment-related improvements are often noted within hours or days after the procedure. WLL is generally well tolerated and safe but nonetheless carries a risk of several uncommon complications, including persistent hypoxemia, pneumonia, sepsis, hydropneumothorax, and acute respiratory distress syndrome.

Subcutaneous GM-CSF

In 1996 (shortly after the discovery of PAP in GM-CSF-deficient mice), recombinant GM-CSF therapy was reported in a patient with (then) idiopathic PAP who experienced a treatment-related reduction in PAP-related symptoms and improvement in PaO_2 [132]. Subsequently two small open-label studies evaluated subcutaneous GM-CSF administered in autoimmune PAP in escalating doses over a period of 3 months or 6–12 months, respectively. The overall treatment response rates (defined as a 10 mmHg improvement in room air A-a$D0_2$) in the two studies were 43% and 48%, respectively [93, 133]. Improvement was also observed in DLCO, radiographic abnormalities, and the distance walked in a 6MWT (in the second study). Subsequent case studies and small series reported similar findings with objective

improvement noted in lung disease severity in approximately 50% of patients. The treatment result varied depending on the dose and duration of administration. Injection site irritation occurred in 85% of patients in one study [133], but there was no significant treatment-associated adverse events reported in any of the referenced studies.

Inhaled GM-CSF

In 2005, aerosolized GM-CSF therapy was first reported in three patients with autoimmune PAP in whom treatment-related improvements were observed in A-a$D0_2$, and microscopic abnormalities seen in BAL cytology [89, 134, 135]. Subsequently, other small studies reported similar positive results [136]. In a 64-week retrospective study in which 12 autoimmune PAP patients received inhaled GM-CSF in escalating doses (250–500 μg, twice daily every other week), 11 had improvements in a$D0_2$ and DLCO [137]. In a subsequent prospective open-label study, 39 patients with unremitting or progressive autoimmune PAP were administered inhaled GM-CSF in two phases: a high-dose induction phase (250 μg daily on days 1–8, every 2 weeks for 3 months) followed (in 35 of the 39 patients) by a low-dose maintenance phase (125 μg, days 1–4, every 2 weeks for 3 months) [138]. Of the 35 patients receiving both induction and maintenance therapy, 24 (62%) experienced improvement in A-a$D0_2$ (the primary endpoint) and the treatment was found to be safe and well tolerated. A follow-up study found 23 of 35 patients had a durable treatment response [139]. A randomized, placebo controlled open-label study of inhaled GM-CSF therapy (150 μg twice daily, alternate weeks, 24 weeks) in 36 patients with mild–moderate autoimmune PAP conducted in China reported improvement in DLCO and St George Respiratory Questionnaire score but not in A-a$D0_2$, radiographic abnormalities, or WLL requirement [140].

Recently, two randomized, placebo-controlled, double-blind studies have evaluated the safety and efficacy of inhaled GM-CSF in autoimmune PAP, the PAGE, and IMPALA trials. The PAGE trial was conducted in Japan in 64 patients with mild–moderate disease (PaO_2 <75 mmHg and >50 mmHg) [141]. The blinded treatment group (GM-CSF 125 μg twice daily on alternate weeks, for 6 months) demonstrated improvement in a$D0_2$, radiographic lung densitometry scores (based on chest CT scan evaluations), and reduction in levels of PAP biomarkers in the treatment group compared to the control group but no improvement in clinical or patient-reported outcomes. [141] No safety concerns were identified. The IMPALA study evaluated 138 autoimmune PAP patients and compared three intervention groups during a 24-week blinded treatment period: (1) continuous GM-CSF (300 μg daily), (2) intermittent GM-CSF (300 μg daily on alternate weeks with placebo on alternate weeks to maintain the blind), and (3) placebo (inhaled daily). [142] Compared to placebo, significant improvement was observed in the continuous GM-CSF group as measured by change in a$D0_2$, DLCO, radiographic ground-glass opacification score (based on chest CT scan evaluations), Saint George's Respiratory Questionnaire Total Score, and PAP biomarkers. Further improvements were seen in an open-label treatment extension period of 48 or 72 weeks.

Inhaled GM-CSF was well tolerated and without any treatment-related serious adverse events. This study demonstrated inhaled GM-CSF resulted in improvement in clinical, radiographic, physiologic measures, quality of life, and was safe and well tolerated, and that continuous administration was more effective than daily administration on alternating weeks [142]. A subsequent study, IMPALA-2, was designed as a global phase 3 trial to evaluated the long-term efficacy and safety of continuous daily inhaled GM-CSF therapy in patients with autoimmune PAP is currently underway. [22].

A small randomized open-label study in Italy reported marked reduction in the requirement for subsequent WLL therapy when WLL was combined with inhaled GM-CSF in 18 patients with autoimmune PAP [143]. Several case reports describe improved treatment responses when WLL is performed prior to administration of inhaled GM-CSF [144, 145].

In summary, results from numerous case reports, small patient series, and two randomized, placebo-controlled, double-blind trials have repeatedly demonstrated the safety and efficacy of inhaled GM-CSF, while still off-label, is a promising pharmacotherapeutic of autoimmune PAP. Treatment efficacy is greater when administered by aerosol compared to subcutaneously, and when administered continuously compared to daily on alternating weeks. A starting dosing of 250–300 μg/day appears to be effective in half–two-thirds of patients and no safety concerns have been identified in any study. Further research is needed to determine if a dose-dependent response exists as suggested by anecdotal clinical observations, and to determine the optimal dose, duration of treatment required for a maximal treatment response, and whether an induction–maintenance treatment strategy will be useful to maintain the treatment response [22].

Other Approaches

As previously mentioned, a number of other treatment approaches have been tested in small numbers of autoimmune PAP patients. The observation that GM-CSF was required for normal cholesterol metabolism by alveolar macrophages led to studies targeting cholesterol homeostasis.

The PPARγ agonist (pioglitazone) showed promising results in a mice studies [30] and human case reports [146] with results pending from a phase I/II trial of pioglitazone in autoimmune PAP. Furthermore, administration of statins

(HMG-CoA reductase inhibitors) to mouse models of PAP has been shown to increase alveolar macrophage cholesterol efflux [31]. This finding was replicated in a case series of patients with autoimmune PAP; patients were treated with rosuvastatin with resultant resolution of PAP lung disease, better lung function, oxygenation, and improvements in radiological findings [31].

Other strategies targeting GM-CSF autoantibodies include plasmapheresis and B-lymphocyte depletion. Plasmapheresis to remove autoantibodies is challenging because it must be repeated daily for several weeks to lower the GM-CSF autoantibody levels to sufficiently low levels, which limits the practical utility of this approach in clinical practice [147]. The use of rituximab anti-B lymphocyte therapy in autoimmune PAP has been described in case reports and small studies [148–150]. Results suggested initial improvements in $AaD0_2$ but benefits were not sustained over the follow-up period. Thus, the role for rituximab in autoimmune PAP is unclear and it should be reserved for patients who are refractory to other therapies [22]. Corticosteroids are often considered or used in clinical practice despite a lack of convincing evidence. A recent retrospective study demonstrated a worsening in lung disease and increased risk of infection in a cohort of 31 patients with autoimmune PAP [151].

Ultimately, lung transplantation is the only option for patients with autoimmune PAP patients who develop pulmonary fibrosis as other therapies such as WLL become ineffective. Such measures should be taken with caution as the autoimmune PAP lung disease returns in the donor lung(s) and thus must be treated [152].

Conclusions and Future Directions

Considerable advances have occurred in our knowledge of autoimmune PAP pathogenesis, diagnosis, clinical course, and treatment. Notwithstanding, important questions remain. Although a serum GM-CSF autoantibody test is 100% sensitive and specific for a diagnosis of autoimmune PAP, antibody levels do not reflect disease severity. Thus, robust markers of autoimmune PAP disease severity are needed. Radiographic assessment is promising as such a measure for a several lung diseases, including PAP with promising reports from semi-quantitative approaches [153, 154] and more interestingly a parenchymal pattern analysis method which has been previously used in idiopathic pulmonary fibrosis [155–157]. This minimally invasive biomarker has potential as an outcome measure in both clinical and academic practice, with utility already demonstrated as a measure of treatment response to inhaled GM-CSF and cholesterol targeted therapy [31, 158].

Disruption of lipid homeostasis is central to autoimmune PAP (and other PAP-causing diseases) and disrupt the normal cholesterol to phospholipid ratio of surfactant [31, 159], which is expected to alter the biophysical properties of surfactant in PAP. In addition to improving our understanding of the pathogenic mechanisms involved, these observations but may identify additional molecular targets for therapeutic or diagnostic development. Future data may indicate whether the alveolar lipidome correlates with clinical profile or alters in response to targeted therapies [157, 160].

Internationally agreed clinical practice guidelines for diagnosis and management of PAP are lacking and are needed to help guide physicians and patients so that optimal care can be provided.

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Gastroesophageal Reflux: Idiopathic Pulmonary Fibrosis and Lung Transplantation

23

Ciaran Scallan and Ganesh Raghu

Introduction

Many co-morbidities have been identified in patients with idiopathic pulmonary fibrosis (IPF) and there is growing interest in their impact on disease pathogenesis and outcomes. The importance of the relationship between the upper GI tract and the respiratory system has been long appreciated. In as early as 1927 Vinson reported the development of a pulmonary abscess in a patient with achalasia [1]. Bartlett and Gorbach described the "triple threat" of aspiration syndromes according to the inhaled substance which they categorized as toxic fluids (including gastric acid), bacterial pathogens, and inert substances (fluids or particulates) [2]. Later, in 1976 Mays et al. first described the presence of gastric secretions in the tracheobronchial aspirates of patients with pulmonary fibrosis and suggested a possible causative link [3].

Under normal conditions gastric contents are prevented from entering the esophagus by a number of mechanisms at the level of the gastroesophageal junction (GEJ). The lower esophageal sphincter is a segment of continuously contracted smooth muscle that is primarily responsible for maintaining the integrity of the GEJ in addition to the diaphragmatic hiatus and the gastric cardia. The neurologic control of this region is complex to facilitate appropriate anterograde flow of food while preventing reflux of gastric contents. With disruption of any of these mechanisms reflux can occur and ultimately enter the lower respiratory tract [4].

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Definitions (GER/GERD/Microaspiration)

Several different terms for the description of these processes exist in the literature. For clarity, we will define the terms used in this chapter below.

Gastroesophageal Reflux (GER) is defined as the reflux of gastric contents into the esophagus. These contents can be either acidic (esophageal pH < 4.0) or non-acidic (esophageal pH > 7.0) and can occur with or without symptoms.

Gastroesophageal Reflux Disease (GERD) is a condition that develops when the reflux of gastric contents causes symptoms, macroscopic changes with or without microscopic features at the level of the GE junction, and complications [5]. These have been divided into esophageal and extraesophageal syndromes.

Microaspiration is the entry of small particles of oropharyngeal or gastric contents into the lower respiratory tract. It is subclinical and separate from the other conditions associated with aspiration (i.e., aspiration pneumonitis or aspiration pneumonia). This could be silent or overt; it is often silent and hence called "silent aspiration." Microaspiration is the common pathway by which the lung is affected and there are several proposed mechanisms contributing to the pathogenesis of IPF which will be explored later in this chapter.

Epidemiology/Anatomy and Physiology/Pathobiology

Epidemiology

Multiple co-morbidities are often present in patients with IPF and there has been a high reported prevalence of GER and GERD. Estimates vary widely (0–94%) which is largely due to the significant variation in how patients are evaluated and the presence or absence of GER specific symptoms [6–9]. When rigorous and systematic testing is used to evaluate for the presence of acid reflux in patients with IPF it is clear that there is an extremely high prevalence [9]. Hiatal hernia

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has been shown to have a high prevalence in IPF patients (up to 53%) and its presence has been associated with increased respiratory associated mortality [3, 10].

Anatomy/Embryogenesis of the Upper GI and Respiratory Tracts

The respiratory and upper gastrointestinal systems are closely linked beginning in the stages of early human development (Fig. 23.1). During gastrulation the three germ layers are formed and as the endoderm is folded into a tube the foregut is established. On day 22 the respiratory diverticulum arises from the ventral portion of the foregut and eventually develops into the lower respiratory system. A layer of mesoderm surrounds the developing trachea preventing the development of peripheral airway structures and the tracheoesophageal ridges separate it from the developing esophagus. The dorsal portion of the foregut tube develops into the esophagus and the most caudal portion develops into the pharyngeal clefts and eventual pharynx [11].

The close relationship between these two systems persists into adult life given the proximity of the openings of larynx and proximal esophagus. The transit of esophageal and gastric contents into the respiratory tract allows them to influence the biology of the respiratory epithelium and alveoli.

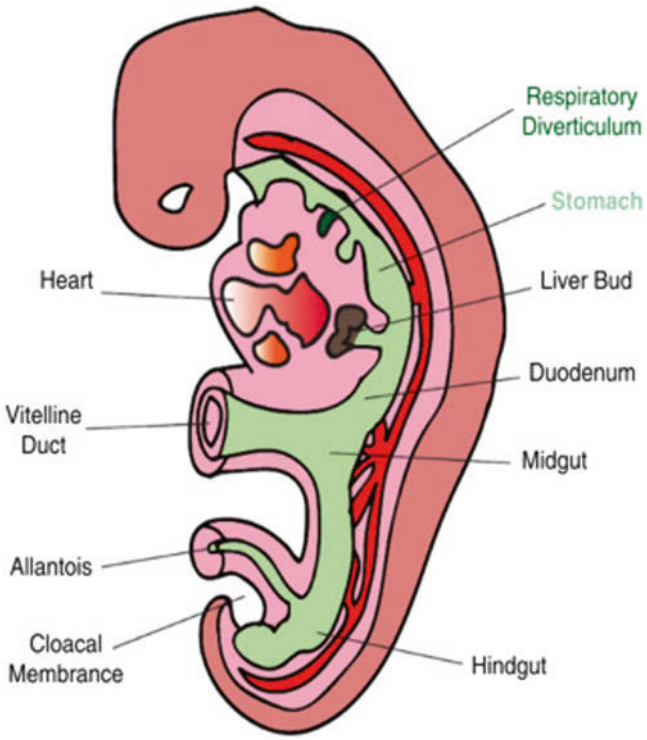


Fig. 23.1 Outpouching of foregut endoderm and respiratory tract tissues during human embryogenesis. The respiratory diverticula that form the pulmonary system and the stomach are in green

Gastric Contents

The stomach secretes approximately 2 L of gastric fluid per day and has several constituents: water, hydrochloric acid (HCl), mucous, intrinsic factor, growth, and immune factors. Other components found in gastric fluid include bile acids and salts, food particles, and endotoxins from bacteria lysed in the stomach. HCl is produced by parietal cells and functions to decrease the pH of gastric fluid, kill pathogens in the stomach, and activate pepsin from pepsinogen.

Several mechanisms exist to protect the gastric mucosa from both the low pH environment created by the secretion of HCl and the proteolytic action of pepsin. These include the secretion of protective mucous and bicarbonate by surface epithelial cells. The lung epithelium lacks these protective mechanisms and while playing an integral role in the digestion of food and destruction of pathogenic bacteria the reflux and microaspiration of gastric contents has several deleterious effects in the respiratory system.

Pathobiology of GER/Microaspirate in the Lungs of Patients with IPF

The entry of gastric contents into the respiratory system has long been understood to have negative consequences (Fig. 23.2). Mendelson first described the clinical phenomenon of aspiration pneumonia in obstetrical anesthesia cases in 1941 [12]. There have been several studies in both animal models and humans that support the model of microaspiration as a contributor to the development of pulmonary fibrosis. In animal models, instillation of acid solutions into the lung promote increased cell membrane permeability, an inflammatory and immune response, and increased fibroblast proliferation leading to fibrosis [13–15]. Other components of gastric juice have also been postulated to contribute to progressive fibrosis. Perng et al. cultured primary human alveolar epithelial cells and exposed them to chenodeoxycholic acid (CD) a component of human biliary secretions. CD exposure was associated with increased expression and release of TGF-beta in addition to increased activity of co-cultured fibroblasts [16]. Pepsin, another major component of gastric juice, has been identified in the bronchoalveolar lavage (BAL) samples of IPF patients with acute exacerbations [17]. Several models have identified pepsin as a potent regulator of epithelial cell biology by affecting cytokine secretion, inflammation, and cell turnover [18, 19].

Sleep is a particularly vulnerable time for the respiratory system with regard to exposure to reflux and microaspiration. Several physiologic changes occur with sleep including a decrease in upper esophageal pressure [20]. In normal subjects, Gleeson et al. identified that nearly half had objective evidence of aspiration after a night's sleep [21]. Obstructive

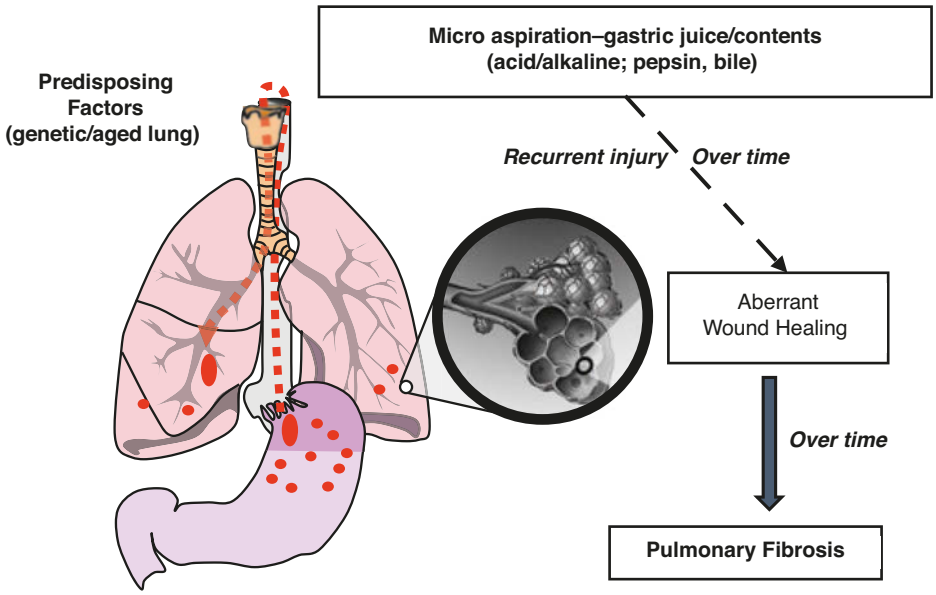


Fig. 23.2 Concepts of gastroesophageal reflux and microaspiration in the pathogenesis of IPF. Note the transit of gastric juice from the stomach to the pulmonary system via reflux and microaspiration (red dots). Recurrent injury caused by the contents of gastric juice leads to aberrant wound healing and eventual pulmonary fibrosis

sleep apnea (OSA) is another co-morbid disorder that has been identified in as many as 88% of patients undergoing prospective evaluation [22]. While the presence of OSA and nocturnal hypoxia alone have been associated with accelerated lung function decline and increased mortality there is a strong body of evidence supporting a link between nocturnal apnea and abnormal gastroesophageal reflux [23]. Several hypotheses exists regarding the link between OSA and GER including periodic decreases in intrathoracic pressure caused by inspiratory efforts against an obstructed upper airway or lower esophageal sphincter dysfunction [24].

GER and the Microbiome

The epithelial tract of the lung is populated with a diverse array of microbes with new bacterial rRNA sequencing techniques allowing for better characterization of these populations compared to traditional culture techniques [25]. The lung microbiome has been an area of increased interest as a possible contributor to the pathogenesis of IPF and a potential therapeutic target [26]. Animal studies have suggested that the presence of gut specific bacteria in the respiratory tract can potentiate inflammation and lung injury [27]. Interestingly, the use of proton pump inhibitors has been shown to have a significant effect on both gastric and lung microbiota [28]. Whether the changes in the gut microbiome which have been identified in patients with abnormal GER and IPF or the microaspiration of gastric contents have a direct effect on the lung microbiome need further study.

Diagnosis

Clinical History/Physical Exam

When assessing patients for possible GER it is important to determine the presence of any of the typical esophageal symptoms including heartburn, regurgitation, or chest pain. There are also extraesophageal symptoms including cough or laryngitis. However, the presence of symptoms is an unreliable indicator of the presence of GER as a significant number of patients with IPF can have significant reflux without typical symptoms. In a prospective evaluation of 65 IPF patients Raghu et al. found that while 87% had significant GER based on 24-h pH testing only 47% experienced classic symptoms [9]. Allaix et al. demonstrated in patients with IPF the prevalence of esophageal symptoms such as heartburn are less common while extraesophageal symptoms such as cough are more prevalent [29].

Investigations

Esophageal Physiology

Upper Esophageal Sphincter

After mastication and formation of a food bolus the swallowing mechanism is initiated, and the bolus is rapidly moved by the tongue via the pharynx to the esophagus. The upper esophageal sphincter (UES) is a region of predominantly striated muscle that begins at the distal pharynx. At rest, it is normally closed and tonically contracted generating a resting

pressure separating atmospheric and intrathoracic pressures that reduces air entry from the pharynx and prevents retrograde movement of esophageal contents. This pressure varies significantly during normal daily activities (ex. respiration, sleep, and coughing) and adaptive changes in pressure are controlled by afferent signaling from the vagus nerve. A number of reflexes increase UES tone and play a key role in preventing the reflux of gastric contents into the lung. For example, UES tone increases in response to slow dilation of the esophagus or in response to increase in intrathoracic pressure (i.e., gagging or the Valsalva maneuver).

Esophagus and Peristalsis

The esophagus is a 22–24 cm tube in adults that terminates at the gastroesophageal junction (GEJ). Primary peristalsis is triggered by the swallowing mechanism which results in a sequence of contractile events through four distinct segments. Secondary peristalsis can also occur at any segment of the esophagus and occurs in response to luminal distension. These actions propel the esophageal contents distally towards the stomach. Esophageal motility can be abnormal with decreased contractions (hypocontracting esophagus), increased contractions (nutcracker esophagus), or be affected by systemic disorders such as scleroderma (fibrosis of esophageal smooth muscle) [30]. Esophageal function is best assessed by high resolution manometry which is discussed in detail in a later section.

Lower Esophageal Sphincter and Diaphragm

The lower esophageal sphincter (LES) is a specialized section of smooth muscle at the junction of the esophagus and stomach. Similar to the UES tonic contraction of this region creates a resting pressure that is 15–30 mmHg higher than intra-abdominal pressure. The most distal portion of the LES lies distal to the diaphragm and is exposed to intra-abdominal pressures which has a valve-like effect. The portions of the diaphragm adjacent to the LES are the crura, fibromuscular structures that originate from the vertebra wrapping around the esophageal hiatus and inserting into the central tendon (Fig. 23.3). The crural diaphragm plays a key role in maintaining LES pressure during dynamic events such as respiration or increased intra-abdominal pressure. Several studies have demonstrated that even in the absence of lower esophageal sphincter tone the activity of the crural diaphragm can prevent reflux of gastric contents. In addition to relaxation during swallowing and peristalsis the LES undergoes transient episodes of relaxation to allow for events such as belching. It is thought that during these episodes of relaxation the majority of GER occurs [31].

A hiatal hernia is the translocation of abdominal contents through the esophageal hiatus into the thoracic cavity (Fig. 23.4). There are three recognized types with Type I being the most common (>90% of cases) and describes the

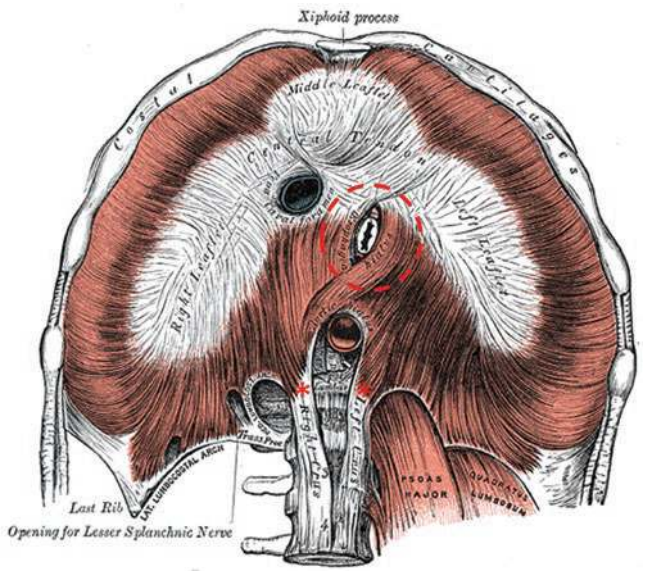


Fig. 23.3 The undersurface of the diaphragm. The esophageal hiatus is marked by the dashed circle. The origins of the left and right crus are marked by (*) originating from the vertebra wrapping around the esophageal hiatus to insert into the central tendon. These structures are essential to maintaining lower esophageal sphincter pressure

herniation of the gastric cardia upwards due to widening of the aperture of the esophageal hiatus [32]. The presence of a hiatal hernia increases the risk of GER through several mechanisms including: decreased LES pressure and length, impaired diaphragmatic sphincter activity, and delayed esophageal acid clearance [33]. Numerous studies have demonstrated that the presence of a hiatal hernia is associated with more frequent GER, increased severity, and a poorer response to pharmacologic therapy [34, 35].

One theory has proposed a causative link between IPF and abnormal GER as a result of decreased compliance of the pulmonary system and distortion of mediastinal structures as fibrosis progresses. This distortion effect could impact the pressure and behavior of the esophageal sphincter causing increased reflux. Furthermore, the presence of pulmonary fibrosis could lead to increased transdiaphragmatic pressure gradients. This has not been rigorously tested and several studies have not shown any positive correlation between severity of lung function impairment and the presence of GER [9, 36, 37].

Esophageal pH and Impedance Testing

The direct measurement of acid GER is facilitated by the use of a catheter which can measure the pH of the esophageal contents in the area of the sensor. A transnasal catheter is advanced through the esophagus with the end resting at 5 cm above the lower esophageal sphincter (to allow for shifting with head movement). Some catheters have a second sensor at the proximal esophagus to allow for measurements in this

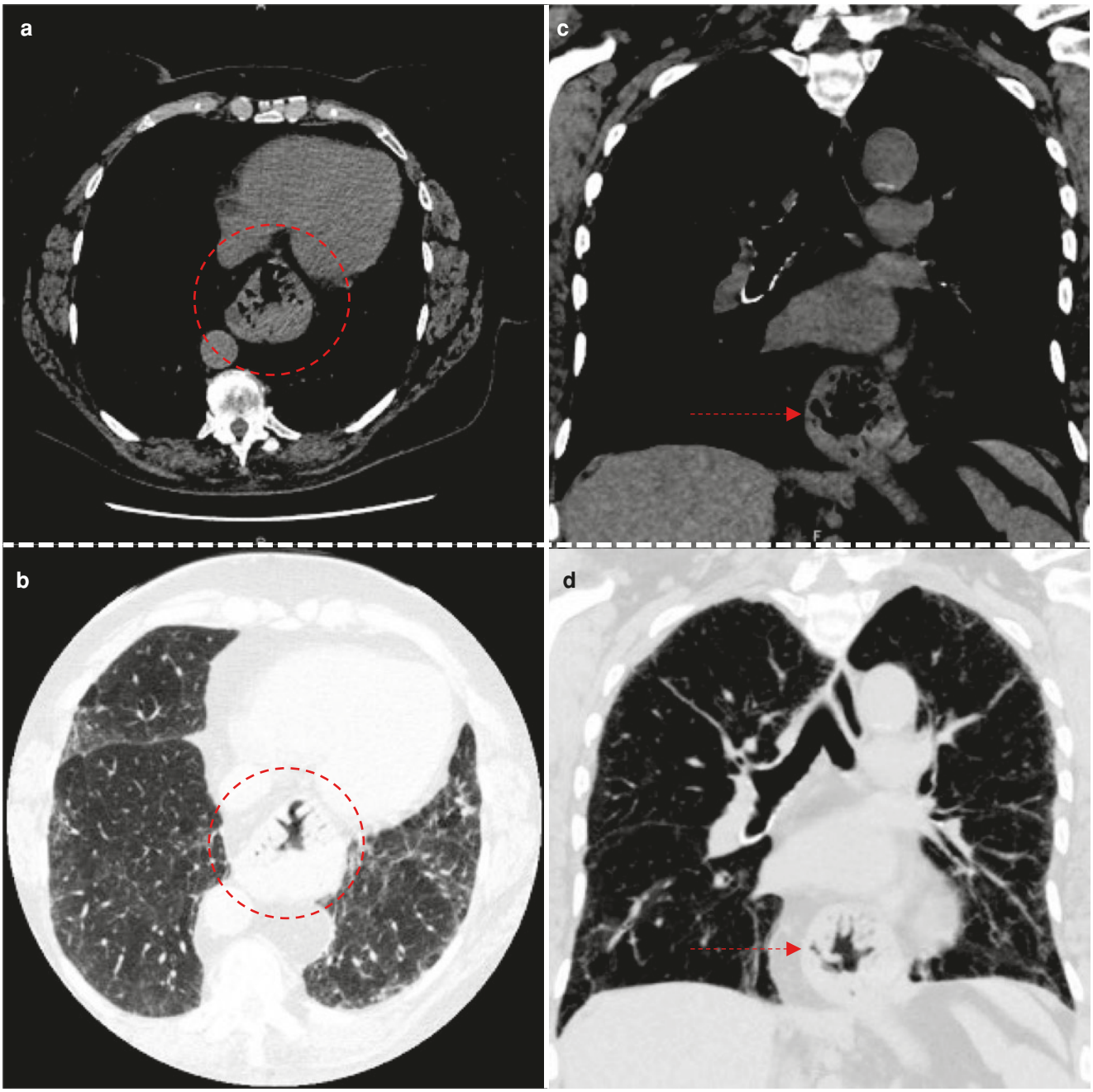


Fig. 23.4 High resolution computed tomography (HRCT) images with sagittal and coronal sections. Panels **a** and **b** demonstrate in the sagittal plane a moderate sized hiatal hernia in the thoracic cavity (red circle and arrows). Panels **c** and **d** demonstrate the same finding in a coronal plane. In addition, there are basal predominant subpleural reticular markings and interlobular septal thickening

area. Less commonly, a wireless pH sensor can be placed via endoscopy in the distal esophageal mucosa. The catheter is left in position and takes repeated measurements over a period of 24 h. This duration is chosen to capture and entire circadian cycle with a variety of activities and postures including eating (upright) and sleeping (recumbent). Most reports are provided with tracings showing the pH at both the proximal and distal probes over the duration of the study (Fig. 23.5).

A reflux event is defined as a decrease in the esophageal pH to less than 4. The acid exposure time (AET) can be calculated by determining the percent of time of the total study with a pH < 4. **The DeMeester score** is a composite of six parameters from the 24-h test including: total AET, upright AET, supine AET, number of reflux episodes (of any length), number of reflux episodes >5 mins, and the duration of the longest reflux episode. A 24-h pH score (DeMeester Score) is

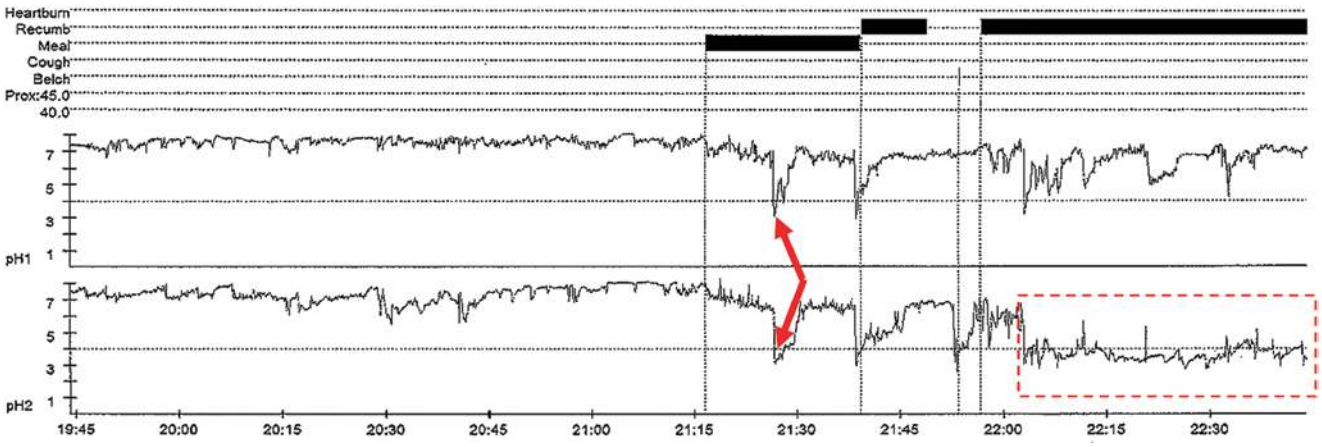


Fig. 23.5 Sample tracing from a 24-h pH monitor study. Time is displayed along the *X*-axis in 15-min intervals and both the proximal (pH1) and distal (pH2) probes are displayed. The pH measured at each probe is displayed on the *Y*-axis. Patient-reported events including meals, and symptoms are reported above the pH tracings. In this example an early period of normal pH is demonstrated with periodic episodes of decreased pH at both the distal and proximal probes associated with a meal (red arrows). A subsequent period in the recumbent position is associated with a prolonged episode of reflux (pH < 4) at the distal probe (red box). This example highlights an episode of prolonged reflux after eating a meal and lying recumbent shortly thereafter

Table 23.1 Components of the DeMeester score [39]

Parameters	Normal values (mean control values +/− 1 SD)
Total AET	<4.2% (1.47% ± 1.38)
Upright AET	<6.3% (2.33% ± 1.97)
Supine AET	<1.2% (0.286% ± 0.467)
Number of reflux episodes	<50 (18.93 ± 13.78)
Number of reflux episodes >5 mins	≤3 (0.64 ± 1.28)
Duration of longest reflux episode	<9.2 min (3.83 min ± 2.78)

AET acid exposure time

determined by calculating the number of standard deviation equivalents in each measured value of the six components. The normal values for these measurements are displayed in Table 23.1 and a normal total score is <14.7 [38, 39].

A major disadvantage of pH testing is the inability to measure weakly acidic or non-acidic reflux episodes which contain other gastric contents that can be introduced to the lower respiratory system. Impedance testing provides the ability to measure and characterize the movement of liquid in the esophagus. Several pairs of electrodes are placed along the esophageal catheter and the electrical resistance between these pairs is measured (as impedance). Impedance is low with liquid present between the electrodes and high when air is present. This allows for anterograde and retrograde movement of esophageal fluid to be quantified and characterized. When added to pH testing this increases the specificity and sensitivity of detecting reflux episodes [40].

High Resolution Esophageal Manometry

The evaluation of esophageal function is a critical part of the investigation of patients with IPF and suspected GER or microaspiration. High resolution manometry is the recommended test for identifying major or minor disorders of peristalsis and outflow obstruction of the distal esophagus. A standardized approach to test performance and interpretation has been published in the Chicago Classification [41].

A manometry catheter is introduced into the esophagus and in the supine position the patient ingests 10 separate boluses of 5 mL of saline. An additional set of swallowed boluses can be performed with a viscous gel to better simulate the consistency of food. Sensors distributed along the catheter measure pressure along the esophagus and allows for the assessment of peristalsis and sphincter function (Fig. 23.6).

Peristalsis is critical for the propulsion of a food bolus through the esophagus and coordinated function of the upper and lower esophageal sphincters prevent retrograde movement. Impaired esophageal motility can increase the prevalence and severity of GER [42, 43]. Gao et al. compared patients with IPF and matched controls (both groups had GERD) and performed high resolution esophageal manometry, pH, and impedance testing. When compared to controls IPF patients with GER (confirmed with pH testing) had lower upper esophageal sphincter pressures and increased food bolus transit times [44].

While some disagreement exists over whether any specific findings on manometry studies correlate with GERD [45, 46] identifying abnormal esophageal motility can iden-

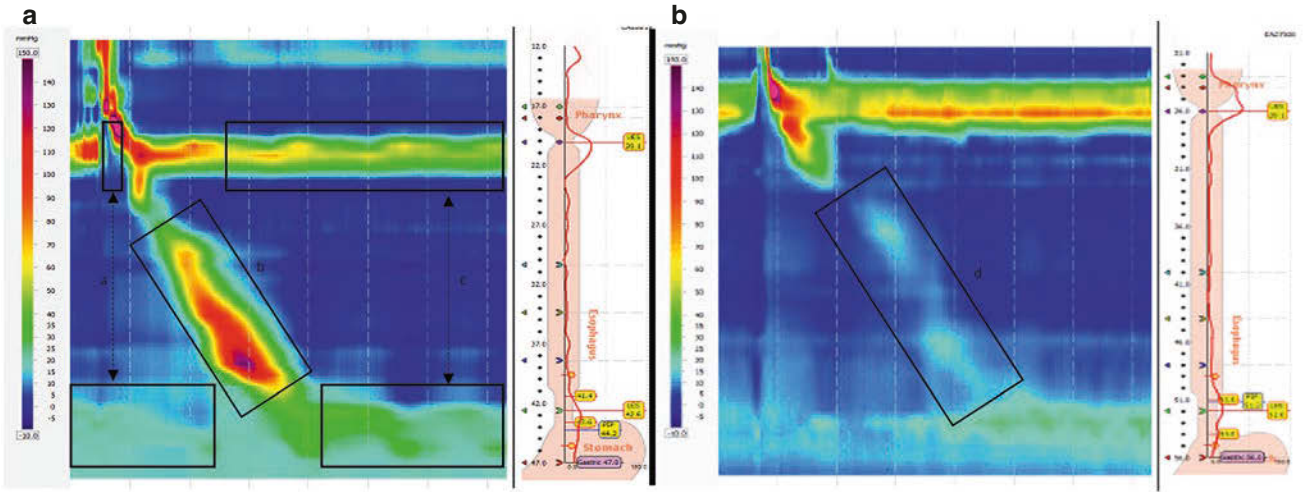


Fig. 23.6 High resolution manometry with esophageal pressure topography. These are composite images of ten consecutive swallows. The *y*-axis represents distance along the catheter from the pharynx at the top to the stomach at the bottom. Pressure is displayed as a heat map with blue representing lower pressures and red to purple representing higher pressures. The *x*-axis represents time. The left panel (**a**) represents a *normal swallow* with relaxation of the upper and lower esophageal sphincters (UES/LES) (*a*) with subsequent contraction along the length of the esophagus (*b*). The swallow ends with resumption of normal basal tone of the UES/LES (*c*). The right panel (**b**) represents an esophagus with 90% failed peristalsis (*d*) or *severely impaired esophageal motility* with normal resting UES/LES tone

tify patients who are at increased risk for reflux of gastric and esophageal contents. Additionally, many surgeons incorporate manometry findings as part of planning for any fundoplication procedures.

Esophagram/Barium Swallow

A barium swallow or esophagram is an inexpensive and readily available method of assessing swallowing function, esophageal motility, GER, and structural abnormalities of the esophagus and stomach [47]. Specific protocols for performing the test are center specific but generally involve a pharyngeal phase where a bolus of barium is swallowed with dynamic recordings to assess the swallowing mechanism and detect entry of barium into the pharynx and trachea. Next, additional boluses of barium are swallowed in the supine and upright positions to assess esophageal motility and the presence of any structural abnormalities including hiatal hernias.

Bronchoalveolar Lavage/Sputum: Biomarkers

Another area of interest has been the detection of biomarkers of microaspiration in samples from the distal airways. Both pepsin and bile acids have been quantified in bronchoalveolar lavage (BAL) samples as potential markers of gastric contents in the respiratory system [48, 49]. Starosta et al. demonstrated in a pediatric population the BAL pepsin level correlated with the degree of reflux as measured by 24-h pH monitoring [50]. There was no significant correlation with the BAL concentration of bile acids. Examination of expectorated sputum of subjects with suspected GER and microaspiration has also been identified as a potential clinical tool. Parameswaran et al. examined the sputum of 33 subjects with 24-h pH testing for the presence of intracellular lipids in macrophages. A higher concentration of intracellular lipids, calculated as a "lipid index," was found to be both sensitive and specific for the presence of GER [51]. While sputum and BAL biomarkers represent a promising avenue for confirming the occurrence of microaspiration additional work is needed to develop standardized methods of measurement and the relationship between the concentrations of the biomarkers and the risks of disease progression.

Treatment

The recommended approach to the management of GER in patients with IPF includes non-pharmacological, pharmacologic, and lifestyle modifications. In patients with progressive disease without contraindications for general anesthesia, anti-reflux surgical interventions are considerations for intractable GER/D despite strict adherence of conservative measures to decrease risks of GER. Most clinical practice guidelines suggest a stepwise approach to therapy which should be individualized based on the severity of symptoms and any esophageal or extraesophageal complications. Lifestyle modifications are the cornerstone to the conservative treatment of GER and suggestions include weight loss in overweight or obese patients, smaller meals, avoidance of late meals, avoidance of precipitating factors, use of a sleep positioning device or elevating the head of the bed with sleep [52]. While these interventions are often proposed to patients

in a clinical setting only elevating the head of the bed and weight loss have been shown to be effective in reducing GER symptoms.

Anti-Acid Therapy (PPI/H2 Blocker)

From a pharmacologic perspective the treatment of GER is focused on the use of proton pump inhibitors (PPI) and histamine 2 receptor antagonists (H2RA). It is important to note, however, that while both PPIs and H2RAs are effective at reducing the acidity of the refluxate they do not decrease the overall number or severity of reflux events [53]. This highlights the need to consider the non-acid components of reflux and their deleterious effects on the respiratory system.

The use of anti-acid medications in IPF has been extensively studied and has been shown in multiple studies to improve outcomes (Table 23.2). The most recent ERS/ATS/JRS/ALAT Clinical Guidelines for the Treatment of IPF give a conditional recommendation for the use of PPIs in patients with IPF (with a very low confidence in effect estimates) [54]. A large number of both prospective and retrospective studies have been completed investigating the relationship between GER and disease outcomes in IPF (summarized in Table 23.2). The results of these studies have been mixed and suffer from methodological limitations. In particular, the use of post-hoc, subgroup, and exploratory analyses is limited by a lack of pre-specified study design. This is important in determining the dosing of and compliance with anti-reflux medications, adjudication of side effects, the influence of confounding factors, and the impact of immortal time bias. While these studies have generated hypotheses for further testing only one randomized control trial has been performed to date which demonstrated safety with PPI use and a larger trial is currently underway [55].

Other Effects of PPI Therapy (Pleiotropic)

Aside from their anti-acid properties several studies have demonstrated PPIs have effects extending beyond the proton pump in the gastrointestinal system. These include an anti-oxidant effect by scavenging reactive oxygen species and promoting the activity of anti-oxidant enzymes and proteins [69]. PPIs have also been shown to have a pleiotropic effect in regulating processes that are involved in pulmonary inflammatory and fibrotic cascades. Ghebremariam et al. have demonstrated in both in vitro and in vivo studies that esomeprazole suppresses the transcription of inflammatory cytokines, adhesion molecules, and matrix metalloproteinases which attenuates inflammation and fibrosis in a bleomycin mouse model [64].

Laparoscopic Anti-Reflux Surgery (LARS)

In addition to the use of antacid therapy for the treatment of GER, surgical interventions are another option that have generated significant interest. Nissen laparoscopic fundoplication was first performed in 1955 and has evolved to be considered the gold standard approach for the surgical management of GER and the repair of hiatal hernias. While techniques vary from center to center the procedure essentially involves reduction of the hiatal hernia (if present), plicating the gastric fundus 360° around the distal esophagus to mechanically reinforce the LES, and repair of the diaphragmatic hiatus. The procedure is generally well tolerated with the most common complications being dysphagia and abdominal bloating [70]. Other approaches have been developed including the Toupet fundoplication (a posterior 270° wrap) and the Dor fundoplication (an anterior 180° wrap). Recent studies have suggested that these techniques have similar efficacy to the Nissen fundoplication and may have lower rates of post-operative dysphagia and bloating [71, 72].

A large retrospective cohort study suggested improved survival in those patients who underwent reflux surgery compared to those on antacid therapy alone [66]. A single center case series demonstrated an excellent safety profile and stabilization of lung function in patients who underwent reflux surgery [73]. The WRAP-IPF trial was a Phase II randomized, non-blinded, multicenter trial of laparoscopic anti-reflux surgery. A total of 58 patients with a consensus diagnosis of IPF and GER confirmed with 24-h pH testing were randomized to surgery or medical management alone. Fundoplication was shown to be a safe procedure in patients with IPF and while no significant difference in rate of change of FVC was found between groups there was a signal for decreased rates of acute exacerbations and hospitalizations in the surgery group [74].

GER and Acute Exacerbations of IPF

While the typical natural history of IPF is described as a gradual and progressive decline in lung function, the disease course can be significantly affected by episodes of sudden deterioration which have been characterized as acute exacerbations (AE-IPF). These episodes are defined as an acute worsening in clinical condition with associated radiographic changes and the absence of an alternative explanation [75]. The occurrence of AE-IPF have a marked impact on prognosis with median survival after an event being 3–4 months [76]. While the etiology of these events are most likely multifactorial, GER and microaspiration have been suggested to play an integral role in the development of acute lung injury. This hypothesis is supported indirectly by post-hoc analysis of the placebo arms from three separate clinical trials which

Table 23.2 Summary of antacid therapies in IPF

Study	Year	Study approach	Outcome
Prospective studies			
Jo et al. B*MC Pulmonary Medicine* [56]	2019	Prospectively collected data from the Australian IPF Registry to assess the impact of antacid therapy on survival and disease progression	No difference in survival or disease progression, regardless of antacid treatment
Kreuter et al. *Lancet Respir Med* [57]	2016	Post-hoc analysis of the *placebo groups* of three trials (CAPACITY 004, CAPACITY 006, and ASCEND) to assess the effects of antacid therapy	No significant difference between groups for disease progression, survival, or hospitalizations. Pulmonary infections were higher in patients with advanced IPF (FVC < 70%) who were treated with antacids (14% vs. 6%; $p = 0.0214$)
Lee et al. *Lancet Respir Med* [58]	2013	Prospectively collected data from three IPFnet clinical trials. Patients receiving placebo had data collected about reflux diagnosis and treatment over a period of 12 months	Patients taking anti-acid treatment at baseline had a smaller decrease in FVC at 30 weeks (difference 0.07 L, 95% CI 0–0.14; $p = 0.05$). Patients taking anti-acid therapy at baseline had fewer acute exacerbations (0 events versus 9 events, $p < 0.01$)
Post-hoc analysis			
Kreuter et al. *Respiration* [59]	2017	Post-hoc analysis of the *Pirfenidone treatment groups* of three trials (CAPACITY 004, CAPACITY 006, and ASCEND) to assess the effects of antacid therapy	No significant differences between groups for disease progression all-cause or IPF related mortality, or hospitalizations. Severe gastrointestinal adverse events (3.7 vs. 0.9%; $p = 0.015$) and severe pulmonary infections (3.7 vs. 1.1%; $p = 0.035$) were more frequent with antacid therapy
Raghu et al. *ERJ* [60]	2015	Post-hoc analysis of patients receiving vs. not receiving anti-acid medication and nintedanib	No significant treatment-by-subgroup interaction for change in FVC
Retrospective studies			
Liu et al. *Int J Clin Exp Med* [61]	2017	Retrospective, observational study of 69 patients with IPF and GER	Use of anti-reflux mediations was significantly associated with prolonged survival and was an independent predictor of longer survival time
Kreuter et al. *PLOS One* [62]	2016	Retrospective, observational study of 272 patients reviewed for co-morbidities and their treatments	The use of proton pump inhibitors at baseline was not associated with a survival benefit
Raghu et al. *ERJ* [60]	2016	Retrospective single center study of patients with disease progression despite anti-acid therapy undergoing anti-reflux surgery	Surgery was well tolerated with no significant difference in lung function decline pre- and post-surgery
Lee et al. *J Neurogastroenterol Motil* [63]	2016	Retrospective, observational study of 786 consecutive patients with IPF	Patients with PPI use for at least 4 months had a lower IPF-related mortality rate
Ghebremariam et al. *J Transl Med* [64]	2015	Retrospective analysis of two IPF databases	Patients taking PPI therapy had greater transplant free survival when compared to controls (3.4 vs. 2.0 years; $p = 0.001$)
Noth et al. *ERJ* [65]	2012	Retrospective, observational study of 100 patients with IPF and hiatal hernias	Patients with hiatal hernia demonstrated better lung function with anti-reflux treatment than those without
Lee et al. *AJRCCM* [66]	2011	Retrospective, observational study of 204 patients with a history of GER, anti-acid use, or anti-acid surgery	Reported use of anti-acid medications was associated with decreased radiologic fibrosis and an independent predictor of longer survival
Raghu et al. *Chest* [67]	2006	Retrospective review of four patients diagnosed with GER and treated with anti-acid therapy	Stabilization or improvement in pulmonary function in all treated patients
Linden et al. *J Thorac Cardiovasc Surg* [68]	2006	Retrospective, observational study of 149 patients on lung transplant waiting list. 19 with severe GER (based on pH monitoring) underwent laparoscopic anti-reflux surgery	Patients who underwent anti-reflux surgery demonstrated stable lung function post-operatively and when compared to controls had stable oxygen requirements

showed that AE-IPF only occurred in those patients not taking anti-acid medications [58].

In a small case-control study, Lee et al. found increased bronchoalveolar lavage (BAL) pepsin levels in the group of patients with AE-IPF. However, there was no survival advantaged noted and a small subgroup of patients had markedly elevated pepsin levels driving the difference between groups [17]. This hypothesis is also supported by changes in the microbiome of patients diagnosed with AE-IPF. Molyneaux et al. discovered a significant increase in *Campylobacter* species, a well-established gastrointestinal pathogen, on bronchoalveolar lavage samples suggesting translocation of these bacteria as a result of the microaspiration of gastric contents [77].

Reflux/GER/Microaspiration in Lung Transplant

While the prevention of disease progression and improved survival is the principal goal in the management of patients with IPF many continue to decline and ultimately are considered for lung transplantation. The most significant limitation to long-term survival after lung transplant is chronic lung allograft dysfunction (CLAD) with bronchiolitis obliterans syndrome (BOS) being the most common subtype. While many possible causative factors of CLAD have been considered, the occurrence of GER and microaspiration have been proposed as significant contributors. Many of the proposed mechanisms of epithelial injury, inflammation, and fibrosis are similar to those discussed in a previous section. Animal models have suggested that repeated exposure of the allograft to gastric contents may enhance allorecognition and accelerate the development of graft dysfunction/rejection [78]. The prevalence of abnormal GER in lung transplant recipients is very high and it has been proposed that the process of lung transplantation itself can worsen pre-existing reflux disease [79, 80].

The data regarding the detection of microaspiration in the respiratory system of lung transplant recipients is more robust than for patients with IPF; both the detection of bile acids and the use of oil red O stains have been proposed as effective screening tests [49, 81, 82]. While these biomarkers are useful in identifying those patients with abnormal GER and microaspiration, further research is needed to identify those patients at risk for development of CLAD that would benefit from more aggressive management of their GER.

As in patients with IPF there has been significant interest in anti-reflux surgery in this patient population with regard to safety and the efficacy of preventing CLAD. Overall existing data suggests that laparoscopic anti-reflux surgery is safe in patients who are post-lung transplant with complication rates ranging from 5 to 14% comparable to those patients who have not undergone transplant with the most common complication being dysphagia [83, 84]. Several retrospective and prospective studies have been conducted to evaluate the efficacy of anti-reflux surgery with a strong signal that suggests early surgery in patients with documented reflux can reduce the risk of developing CLAD/BOS. For example, Hartwig et al. prospectively collected data on 297 LTX recipients and reported that early fundoplication appeared to preserve allograft function in those patients with abnormal 24-h pH testing [85].

Clinical Vignette

A 65-year-old former smoker presents for evaluation of a 2-year history of progressive dyspnea on exertion associated with a non-productive cough. He has no history of environmental or occupational exposures and no clinical findings of a connective tissue disease. Pulmonary function testing reveals a moderate impairment in both forced vital capacity (FVC) and the diffusing capacity for carbon monoxide (DLCO). The time course of pulmonary function changes is illustrated in Fig. 23.7. Computed tomographic imaging of the chest reveals subpleural reticular markings in a basal distribution with areas of traction bronchiectasis in the bilateral lower lobes in addition to a moderate sized hiatal hernia. Based on the clinical and radiographic criteria a diagnosis of idiopathic pulmonary fibrosis is made consistent with the updated 2018 ATS/ERS/JRS/ALAT criteria. He is started on anti-fibrotic therapy and undergoes rigorous evaluation for abnormal GER with a barium esophagram, esophageal manometry, and 24-h pH monitoring. These reveal normal esophageal motility and sphincter function with a DeMeester score of 40.8 confirming the presence of abnormal reflux. He is started on PPI therapy and counseled extensively about lifestyle modifications and weight loss.

He returns to the clinic 18 months later with a 15% decrease in FVC despite regular adherence to his medications and lifestyle modifications. Given this change he is referred and eventually undergoes a successful laparoscopic Nissen fundoplication. He is now 2 years post-fundoplication and has demonstrated stability of lung function and exercise tolerance.

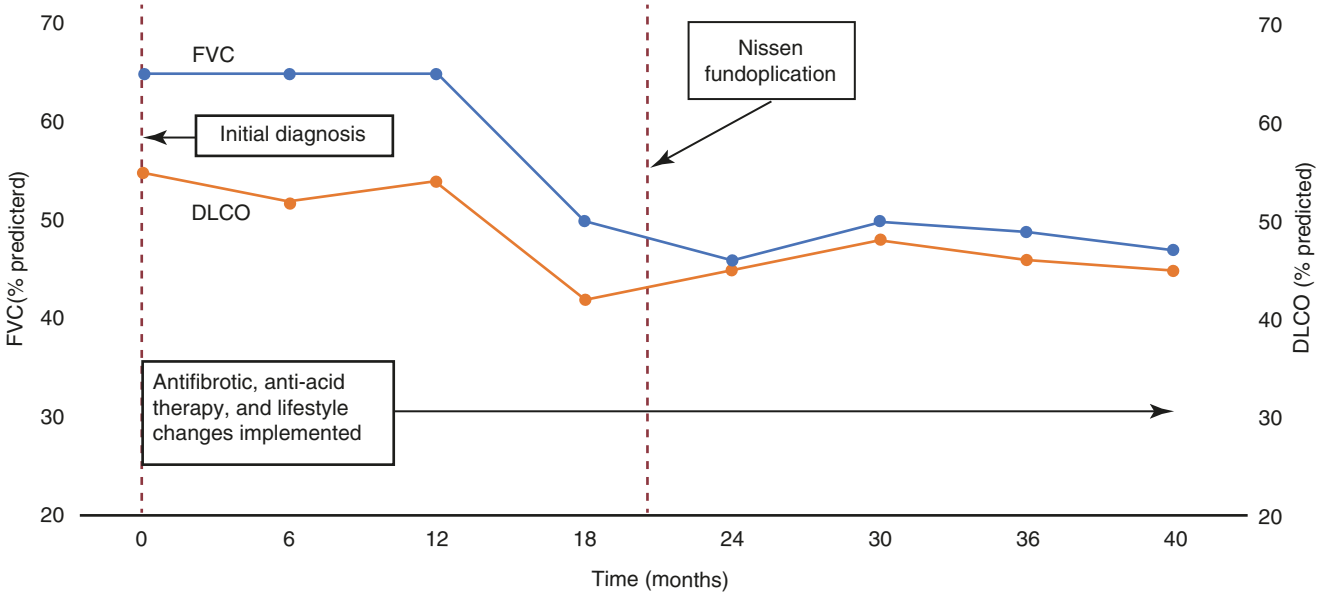
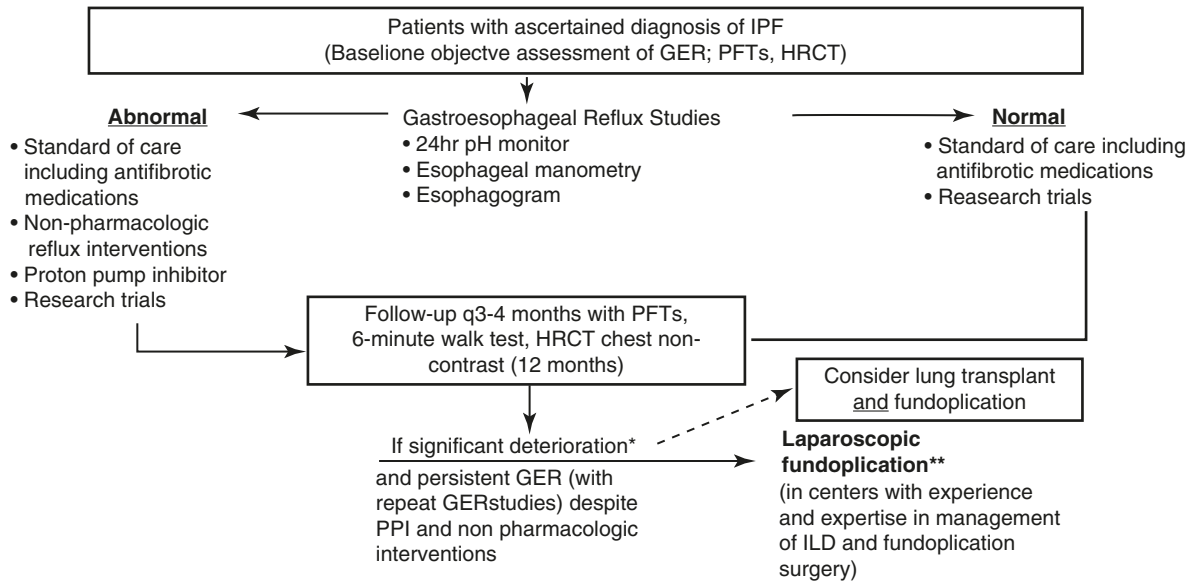


Fig. 23.7 Change in forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO) over time from initial diagnosis of idiopathic pulmonary fibrosis. After a significant drop in lung function at 18 months after diagnosis, Nissen fundoplication was performed with stabilization of lung function and ongoing non-surgical interventions

Suggested Approach

Below we have outlined a suggested approach to the diagnosis and management of GER in patients with an established diagnosis of IPF (Fig. 23.8).



*Significant deterioration as defined in ATS/ERS/JRS/ALAT 2011 guidelines by one of : progressive dyspnea; progressive sustained decrease from baseline in absolute change in FVC of 10% and/or DLCO (corrected to hemoglobin) of 15%; progression of fibrosis from baseline on HRCT; acute exacerbation and new need for oxygen supplementation or increased oxygen requirements

**Contraindications for laparosopic fundoplication include any of the following : Body mass index > 35; Severe pulmonary hypertension (mPAP>35mmHg); FVC< 50% predicted; 6MWD <50 meters; significant hypoxic respiratory failure

Fig. 23.8 Suggested management of GER in patients diagnosed with IPF Approach followed at the Center for ILD, University of Washington Medical Center based on evolved knowledge with evidence and experience : Patients with confirmed diagnosis of IPF [87] and willing to undergo a formal and thorough evaluation for the detection of abnormal GER are subjected to esophageal manometry and barium esophagogram immediately following 24 h pH monitoring at baseline. Those patients with abnormal testing are offered treatment with a combination of proton pump inhibitors and non-pharmacologic interventions (described in detail in chapter text). Patients are followed up at regular intervals to monitor lung functional status with pulmonary function testing, 6-min walk test at 3–4-month intervals and chest imaging (every 12 months). Patients with significant deterioration* and previously documented abnormal reflux are re-evaluated for the persistence of abnormal GER and if present are considered for laparoscopic anti-reflux surgery in the absence of contraindications**. Such patients if considered for lung transplantation are also considered for anti-reflux surgery in discussion with the lung transplant team

Summary and Future Directions

A close relationship between the pulmonary and gastrointestinal system exists beginning from the early stages of embryogenesis. This relationship is particularly important in individuals diagnosed with IPF because of the impact of gastroesophageal reflux and microaspiration on disease pathogenesis and behavior. We have outlined the key mechanisms involved in the impact of gastric contents on the respiratory epithelium and their contributions to the development of pulmonary fibrosis. Several testing modalities are available to evaluate patients with IPF for clinically significant reflux and should be implemented in a systematic, stepwise fashion. Several treatment options are available including anti-reflux surgery which has been shown to be a safe intervention in carefully selected patients.

Further research is needed to better clarify the role of GER and microaspiration in the pathogenesis and progression of IPF. Changes in esophageal physiology have been associated with increased age including decreased UES and LES pressures and impaired esophageal motility [86]. While many older individuals have significant reflux, not all develop IPF. Are GER and microaspiration a contributing factor to fibrosis development in genetically predisposed individuals? Additionally, the impact of microaspiration on the lung microbiome and its effect on disease pathogenesis is an area needing further exploration. As identified in one of the previous sections there remains a need for carefully designed, prospective, randomized controlled trials that examine the effects of PPI use in patients with IPF. A large, multicenter clinical trial –TIPAL (ISRCTN13526307; the EudraCT number 2020–000041-14) is underway in the UK examining the therapeutic potential of omeperazole (PPI0 in patients with IPF).

As the understanding of IPF and its pathomechanisms continues to expand, the role of reflux and microaspiration will be further clarified allowing for individualized approaches to disease management.

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Part V

Genetic Rare Lung Diseases

Genetic and Familial Pulmonary Fibrosis Related to Monogenic Diseases

24

Raphael Borie, Caroline Kannengiesser, and Bruno Crestani

Clinical Vignette (CV)

A 53-year-old man was evaluated for lung fibrosis. He was a past smoker. His medical history revealed asymptomatic thrombocytopenia (between 50,000 and 100,000/mm^3), red cell macrocytosis (103 µm^3) without anemia, liver cirrhosis, and a premature graying of his hair at the age of 25. He also had a familial history of lung fibrosis (in red, Fig. 24.1) and premature appearance of white hair (in blue, Fig. 24.1a). The CT scan showed a definite usual interstitial pneumonia (UIP) pattern (Fig. 24.1b). The pulmonary function tests showed reduced forced vital capacity (FVC) at 61% and diffusing lung capacity for CO (DLCO) at 46% of the predicted values.

A diagnosis of idiopathic pulmonary fibrosis was made and the patient received pirfenidone for 3 months but developed a skin rash.

He refused to take nintedanib and subsequently presented with an increase in shortness of breath. The pulmonary function tests showed a rapid decline of FVC at 43% and DLCO at 41% of the predicted values, 1 year after initial diagnosis. The CT scan showed a progression of the lung fibrosis without evidence of an acute exacerbation.

Genetic analysis revealed a pathogenic *RTEL1* mutation (c.2869C > T. p.Arg957Trp). Following discussion in multidisciplinary team, recommendations were made to offer genetic counseling to the family, and to discuss lung transplantation with the patient. The patient opted for lung transplantation evaluation and is currently on the waiting list.

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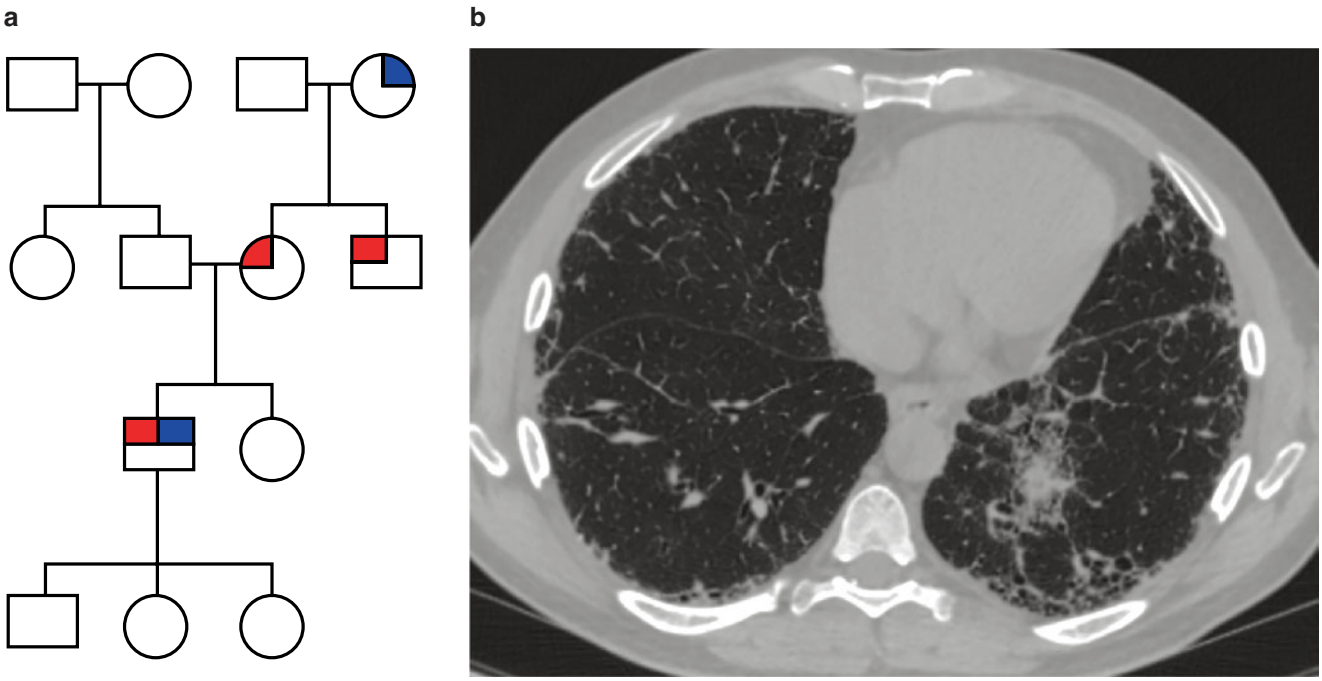

Fig. 24.1 Clinical vignette. (**a**) Pedigree of the patient (arrowhead); in red, patients with history of lung fibrosis and in blue relatives with known premature occurrence of white hair. (**b**) CT scan with usual interstitial pneumonia (UIP) pattern

Introduction

Interstitial lung disease (ILD) encompasses a set of heterogeneous lung diseases characterized by inflammation and/or fibrosis of the lung parenchyma. Idiopathic pulmonary fibrosis (**IPF**) is the most frequent idiopathic **ILD** after the age of 50. Evidence of a familial aggregation of ILD (i.e., **familial interstitial pneumonia or familial pulmonary fibrosis** (FPF)) suggests a role for genetic factors in the development of ILD. Over the past three decades, genetic discoveries in monogenic familial forms of FPF have led to significant insights into the role of inherited risk mutations in disease pathogenesis, and in the understanding of the intimate mechanisms of lung fibrosis, either idiopathic or non-idiopathic.

This chapter will focus on the main monogenic diseases associated with ILD with a particular focus on telomere-related genes and surfactant-associated protein gene mutations, the most frequent Mendelian disorders associated with ILD (Table 24.1, Fig. 24.2).

Table 24.1 Rare variants associated with interstitial lung disease

Pathway	Main phenotypes	Main genes
Telomerase	Pulmonary fibrosis, dyskeratosis congenita, cirrhosis, myelodysplasia	*TERT-TERC-TINF2- PARN-NAF1-RTEL1-DKC1*
Surfactant production	ILD-lung cancer- pulmonary cysts-brain lung thyroid syndrome	*SFTPA1-SFTPA2-SFTPC-ABCA3- NKX2.1*
Interferon production	ILD, vasculitis, arthralgia	*TMEM173/ COPA*
Surfactant clearance	Alveolar proteinosis, opportunistic infections, hepatomegaly, splenomegaly, Lysinuric protein intolerance	*CSF2RA-CSF2RB GATA2-MARS-SLC7A7*
Lysosomal diseases	Hermansky-Pudlak syndrome, Gaucher, Acid sphingomyelinase deficiency or Fabry diseases	*HPS-1 to 8-AP-3B1- GBA-SMPD1-GLA*
Miscellaneous	Poikiloderma Lung fibrosis	*FAM111B*
	Acadian variant of Fanconi syndrome	*NDUFAF6*

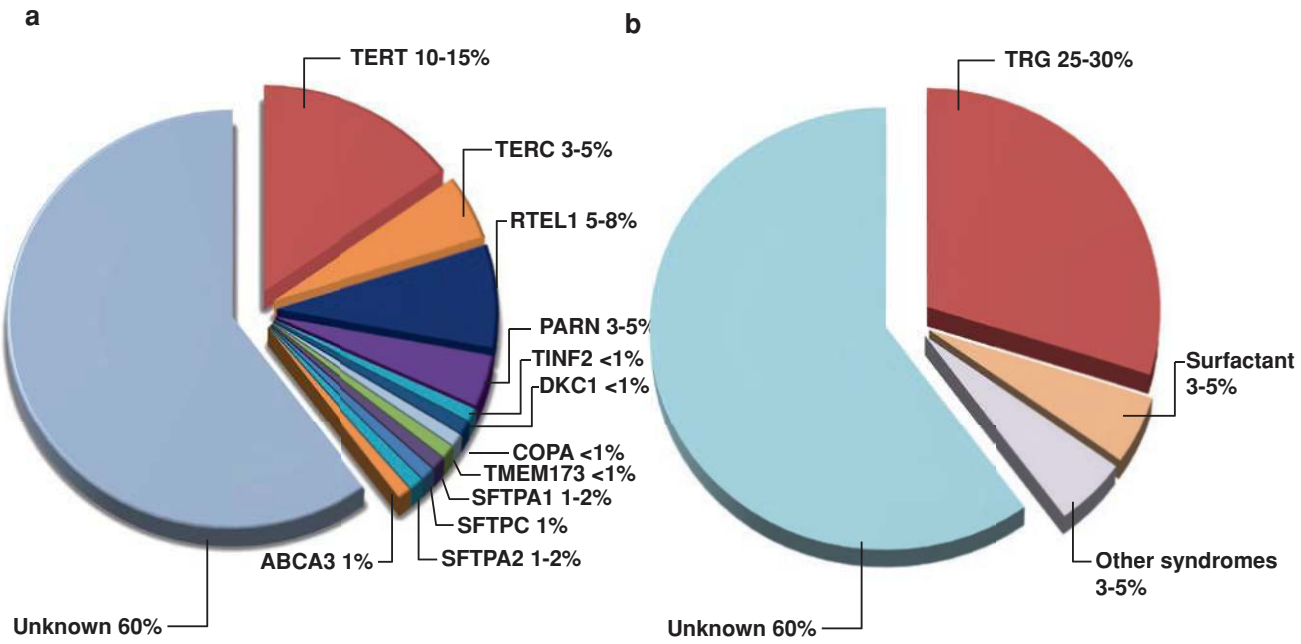

Fig. 24.2 Prevalence of (**a**) main genes and (**b**) corresponding pathways: TRG (telomeres related genes: *TERT, TERC, RTEL1,* etc.), surfactant (SFTPA, ABCA3, NKX2.1, etc.) and other miscellaneous syndrome (*COPA, TMEM173*, etc.) with mutations associated with monogenic pulmonary fibrosis in adults

Familial Interstitial Pneumonia

Although there is no consensus definition, FPF is usually defined as a case of ILD in which the patient also has a family history of one or more relatives with ILD [1, 2]. Current studies report that familial forms of the disease account for 5–10% of IPF [3–5]. Adults with FPF are essentially indistinguishable from patients with sporadic IPF except that those with FPF tend to present earlier in life [6].

Male gender (55.7% vs. 37.2%, $p < 0.0001$), age (68.3 vs. 53.1 years, $p < 0.0001$), and cigarette smoking history (67.3% vs. 34.1%, $p < 0.0001$) were reported to be risk factors for developing ILD in a study of 111 FPF families, including 309 individuals with ILD and 360 unaffected relatives. Among ILD patients, a UIP pattern was identified in 85% patients; however, 45% of the families had two or more pathologic patterns identified, such as evidence of both UIP and NSIP histopathology [6]. Indeed several cohorts reported heterogeneity within families suggesting that distinct ILD categorizations may share similar pathogenesis pathways [7, 8]. The identification of cigarette smoking as a FPF risk factor also suggests that interaction between genetic predisposition and environmental exposures is central to the pathophysiology of ILD [6]. Many analyses of FPF families have suggested an autosomal dominant mode of inheritance with incomplete penetrance [6, 9, 10].

A single nucleotide polymorphism (SNP) rs35705950 located in the promoter region of the *MUC5B* gene is associated with an increased risk of FPF or sporadic IPF, with odds ratios (ORs) for disease of 6.8 (95% confidence interval [CI], 3.9–12.0) and 20.8 (95% CI, 3.8–113.7) for FPF and 9.0 (95% CI, 6.2–13.1) and 21.8 (95% CI, 5.1–93.5) for IPF, respectively [2]. This rs35705950 T risk allele is common in the Caucasian population, since it is detected in 9% of control individuals, but it is much less frequent in people of Asian origin [11, 12]. The rs35705950 variant is neither necessary nor sufficient to cause disease, suggesting a causative role for other genetic or environmental factors in disease development, but may explain 30% of the risk of developing lung fibrosis [13]. GWAS studies identified other polymorphisms associated with an increased risk of developing lung fibrosis (Table 24.2) [14].

Table 24.2 Common variants associated with idiopathic pulmonary fibrosis

Gene	Single nucleotide polymorphism (SNP)
AKAP13	rs62025270
ATP11A	rs1278769
CDKN1A	rs2395655 rs733590
DPP9	rs12610495
DSP	rs2076295
ELMOD2	Unknown
FAM13A	rs2609255
HLA-DRB1	rs2395655
IL1RN	rs408392 rs419598 rs2637988
IL8	rs4073 rs2227307
MAPT	rs1981997
MDGA2	rs7144383
MUC2	rs7934606
MUC5B	rs35705950
OBFC1	rs11191865
SPPL2C	rs17690703
TERC	rs6793295
TERT	rs2736100
TGFB1	rs1800470
TLR3	rs3775291
TOLLIP	rs111521887 rs5743894 rs2743890
TP53	rs12951053 rs12602273

Telomere Related Genes

Genetic

Telomeres are regions of non-coding repetitive nucleotide repeats (TTAGGG) at the ends of chromosomes that protect them from deterioration during mitosis or fusion with neighboring chromosomes. The telomerase complex is a group of proteins and RNA that catalyzes the addition of these nucleotide repeats to the ends of chromosomes. There are numerous components to the telomerase complex, including telomerase reverse transcriptase (**TERT**) and the telomerase RNA component (TERC, encoded by the *TERC* gene, also known as *TR or hTR*), which are essential for normal operation and telomere integrity. The telomerase complex also requires the activity of other proteins, such as the regulator of telomere elongation 1 (**RTEL1**), the poly(A)-specific ribonuclease (**PARN**), and the nuclear assembly factor 1 (*NAF1*). All have been involved in in pulmonary fibrosis [15, 16]. Numerous other genes have been implicated in telomere maintenance beyond telomerase complex, and they have been grouped in telomere related genes (TRG) group.

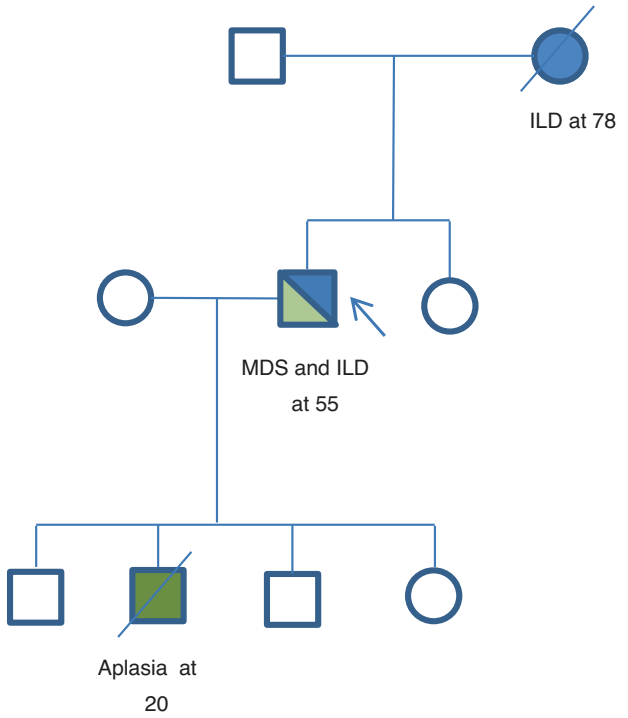

Fig. 24.3 Pedigree suggestive of a telomere-related genes (TRG) mutation. Filled in blue, patients with interstitial lung disease (ILD), filled in green patients with hematological disease (MDS, myelodysplastic syndrome)

Heterozygous mutations of *TERT* (≈15%), *RTEL1* (5–10%), *PARN* (≈5%), and *TERC* (≈3%) have been implicated in familial forms of pulmonary fibrosis. Mutations in *DKC1*, *NAF1*, and *TINF2* have more rarely been reported (Fig. 24.2) [15, 17–25]. Mutations of *TERT* and *TERC* were initially found in only about 1–3% of sporadic IPF cases [26, 27]. However, rare variants within *TERT, TERC, PARN, and RTEL1* have been reported in 149 (9%) of 1739 IPF patients included in 4 clinical trials (INSPIRE, CAPACITY, ASCEND, and RIFF), 29 (11.3%) of 262 IPF patients evaluated in one center before lung transplantation, 33 (9.3%) of 353 patients with chronic *hypersensitivity pneumonitis* (HP), and in 11 of 101 patients with rheumatoid arthritis-ILD [28–31]. However, for the most part, conformation of the pathogenicity of the genetic variants in these disorders will require further study.

There are no frequent mutations nor hotspots reported in the TRG. Environmental exposure modifies the risk of pulmonary fibrosis developing in a carrier of *TERT*, *TERC,* or *RTEL1* mutations (also known as penetrance) [19, 32, 33].

Telomere Length

Telomere length can be measured on circulating leucocytes by Flow-FISH, qPCR, or Southern blot and compared with

age-matched controls [34, 35]. Telomere length can also be measured at a single cell level in tissues.

When evaluated in blood cells (granulocytes monocytes or lymphocytes) from patients with FPF, mutations in TRG show shortened telomeres in 80–90% of the cases [19, 36]. Patients with *TERT* mutations have the shortest telomere among patients with FPF [36]. However, 15% of the *TERT* mutation carriers presented with normal telomere length in one study, and half of the patients with pulmonary fibrosis older than 60 years with *TERT*, *TERC,* or *RTEL1* mutations had a telomere length > tenth percentile in another [19, 37].

Patients with *TRG* mutations transmit their short telomeres independently of transmission of the mutation and telomeres shorten at a younger age in subsequent generations [17, 19], consistent with the phenomenon of genetic anticipation (Fig. 24.3) [17, 38, 39].

Some experts suggest analyzing telomere length before genetic analysis of TRG [37, 40, 41]. A reduced telomere length in the recipient has been uniformly associated with reduced overall survival or post-lung transplantation survival in pulmonary fibrosis patients [28, 42].

Pulmonary Involvement

Interstitial Lung Disease

The prevalence of ILD in TRG mutation carriers increases in older patients [19]. In a North American cohort of *TERT* mutation carriers, none of the subjects younger than 40 years had ILD, although after the age of 60, the prevalence of ILD was more than 60% [19]. Among TRG mutation carriers, patients with *TERC* mutations may present with an ILD diagnosis at a younger age [17]. In a cohort of 114 patients with ILD carriers of a TRG mutation, ILD was diagnosed at a mean age of 51 years ($n = 7$) for *TERC*, 58 years ($n = 75$) for *TERT*, 60 years ($n = 14$) for *RTEL1*, and 65 years ($n = 19$) for *PARN* ($p = 0.03$) [17, 32]. The male/female ratio was reported to vary from 0.5 to 0.7. Tobacco smoking and other respiratory exposures are frequently reported in patients with ILD and TRG mutations in sporadic IPF cohorts (40–96%) [17, 19, 32].

The CT pattern is considered typical of UIP in 46–74% of cases (Fig. 24.4) [17, 19, 32]. It is considered indeterminate for UIP in 13–20% of cases because of atypical features:

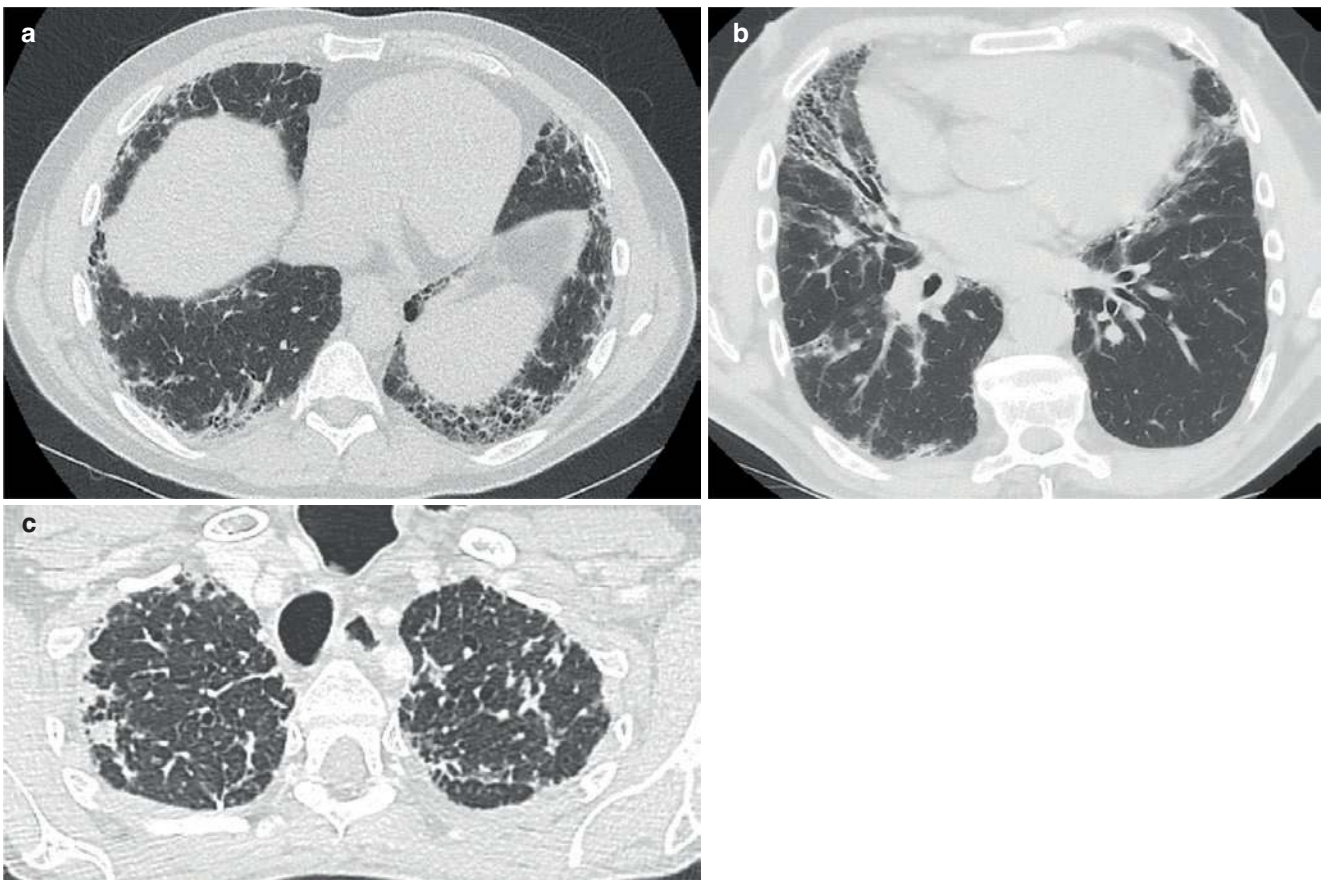

Fig. 24.4 High-Resolution Computed Tomography Imaging of different manifestations of TRG mutations, including patterns that are (**a**) consistent with usual interstitial pneumonia (UIP), (**b**) indeterminate for UIP and (**c**) suggestive of pleuroparenchymal fibroelastosis (PPFE)

fibrosis with upper lung predominance, centrilobular fibrosis, or a **pleuroparenchymal fibroelastosis** (PPFE) pattern [17, 19, 32]. In patients with TRG mutation, IPF is the most frequent ILD diagnosis (45–86%) [9, 30, 38], but other ILD diagnoses are frequent: PPFE (up to 10%), chronic HP (7–11%), and unclassifiable fibrosis (19–30%) [17, 19, 32, 33]. Alternative diagnosis, such as pneumoconiosis, rheumatoid arthritis associated ILD, and alveolar lipoproteinosis are very rare in patients with FPF due to TRG mutations.

Carriers of rare TRG variants have a more rapid decline in forced vital capacity (FVC) than patients without TRG variants [17, 43]. Newton et al. reported a 300 mL/year decline in FVC independent of the type of TRG (*TERC*, *TERT*, *RTEL1,* or *PARN*), or of the ILD diagnosis (IPF vs. non-IPF) [17].

The mean survival after ILD diagnosis is 2.8–5.2 years [44] in TRG-related FPF. However, disease progression varies and the ILD histopathology may modify the prognosis [33, 45].

Other Lung Disease

Hepatopulmonary Syndrome

Hepatopulmonary syndrome (HPS) should be suspected in patients carriers of a TRG mutation presenting with hypoxemia, especially when the ILD is mild [46]. Liver involvement must be actively searched for, because blood liver abnormalities can be subtle or absent. In a series of 42 patients with telomere syndrome who complained of dyspnea, nine patients had a hepatopulmonary syndrome, defined as the combination of liver disease, evidence of intrapulmonary vascular dilatation, and hypoxemia. TRG mutations implicated in HPS include *TERT* (n = 4), *RTEL1* (n = 1), or *DKC1* (n = 1) [46].

Emphysema

Several lines of evidence suggest an increased risk of **emphysema** in TRG mutation carriers. The KO *TERC* mice with short telomeres develop emphysema when exposed to tobacco smoke, but no lung fibrosis [47]. In female smokers with severe chronic obstructive pulmonary disease and emphysema, *TERT* and *NAF1* mutations have been found [15, 48, 49]. The prevalence of *combined pulmonary fibrosis and emphysema* (CPFE) in cohorts of TRG mutation carriers is reported to be 13–15%, in line with the usual prevalence of emphysema in IPF cohorts [17, 32, 33, 50].

Immunodeficiency

Immunodeficiency and opportunistic infections have been mainly been described in children. A *Pneumocystis jirovecii infection* has been reported in an adult carrying a *TERC* mutation without any immunosuppressive therapy [51, 52]. Although the exact prevalence of immunodeficiency and its impact for lung transplantation need to be evaluated, patients with TRG mutations appear to be at an increased risk of CMV infection after lung transplantation [53].

Extrapulmonary Manifestations

Pulmonary and extrapulmonary manifestations associated with TRG mutations lack a consensus definition and have been variably reported as "telomere syndrome," "telomeropathy," or "short telomere syndrome."

Mucocutaneous Involvement

Dyskeratosis congenita (DKC) was the first telomeropathy associated with TRG mutations [54, 55]. DKC is defined by the mucocutaneous triad: reticular skin pigmentation, nail dystrophy, and oral mucosal leukoplakia [56]. Mucocutaneous involvement appears in childhood, and bone marrow failure usually appears after the age of 10 [56]. Lung fibrosis may spontaneously appear in DKC, although after **hematopoietic stem cell transplantation**, patients with DKC may develop severe pulmonary complications, including lung fibrosis [57].

Adult patients with TRG mutation and pulmonary fibrosis usually do not present the mucocutaneous triad, but 15–40% present premature hair graying (before the age of 30) [32, 58]. The same gene mutation can be associated with different phenotypes, likely as a consequence of genetic anticipation and telomere shortening. For instance, descendants of patients with pulmonary fibrosis without DKC features may present with typical DKC [17].

Hematological Involvement

TRG mutations have been associated with **bone marrow failure, myelodysplasia**, or **acute leukemia** [59–61]. The coexistence of pulmonary fibrosis and bone marrow failure, particularly in a young patient, increases the probability of an underlying TRG mutation (Table 24.3) [62, 63]. The coexistence of myelodysplasia and lung fibrosis in older patients is probably more coincidental [62].

Table 24.3 French Proposal for Indication of a Genetic Testing (RESPIFIL)

Idiopathic or non-idiopathic ILD with at least one of the following:
– Familial ILD.
– Idiopathic ILD < 50 years old.
– Personal or familial history of:
– Bone marrow failure, thrombocytopenia, or myelodysplasia.
– Dyskeratosis congenita.
– Cryptogenic cirrhosis.

Blood abnormalities are frequent in patients with TRG mutations: 17–27%, of the patients with TRG mutations and pulmonary fibrosis present with anemia, 24–41% with macrocytosis, and 8–54% with thrombocytopenia [17, 32]. *DKC1*, *TINF2,* and *TERC* mutations may be more frequently associated with hematological involvement than *TERT* or *RTEL1* mutations [17, 33].

Liver Involvement

Elevated liver enzyme levels or overt liver involvement are detected in 5%–27% of patients with ILD and TRG mutations [17, 32]. Carriers of TRG mutations may present with cryptogenic or secondary liver **cirrhosis**. In a series of 86 patients who received **liver transplantation**, 17(20%) had probably deleterious variants of one TRG (based on in silico *analyses)*, though the pathogenicity of the variants was not confirmed. The presence of any TRG variant was associated with an increased number of readmissions within 1 year after liver transplantation (OR = 3.15; 95% CI, 1.22–8.57), but no association with survival was observed [64].

Hepatic manifestations may vary in relatives with the same mutation, from normal to isolated elevation of liver enzyme serum levels, to variable degrees of necrosis, inflammation, fibrosis, and regeneration on liver histology [65]. Among six patients with hepatopulmonary syndrome, the most common histological diagnosis was nodular regenerative hyperplasia ($n = 4/6$). From the same series, two patients received liver transplantation, but lung fibrosis developed 18 months and 12 years later, respectively [46].

Other Manifestations

Other manifestations that have been associated with TRG mutations include exudative retinopathies, central neurological disease and cerebral calcifications, gastrointestinal bleeding, radiation sensitivity, infertility, osteoporosis, or renal insufficiency [54]. With respect to the latter, whole exome sequencing in a cohort of 92 patients with chronic kidney disease of unknown cause identified loss-of-function mutations in *PARN* in 2 probands with tubulointerstitial fibrosis [66].

Treatment

Antifibrotic Therapy

One post hoc analysis and one retrospective study have been reported on safety and efficacy of pirfenidone in patients with TRG mutations [28, 67]. A European multicentric retrospective study of 33 patients did not show a beneficial effect of *pirfenidone* on lung function decline. In fact, decline of FVC was 161.8 ± 31.2 mL/year before treatment and 235.0 ± 49.7 mL/year after pirfenidone initiation [67]. A post hoc analysis of two prospective phase 3 clinical trials (CAPACITY, ASCEND) identified 102 patients carriers of rare TRG variants in the IPF cohorts. Those TRG variant positive patients had a more rapid decline in FVC than patients without a rare variant (1.66% vs. 0.83% per month), and pirfenidone reduced the decline of FVC in this subgroup with severe disease [28]. A recent retrospective study confirmed safety and efficacy of pirfenidone and nintedanib in patients with TRG mutations [68]. In linear mixed effects model, the mean FVC decline was 39 mL per month (95% CI 23–55 mL per month) before treatment, and 22 mL per month (95% CI 17–28 mL per month) in the next 30 months after treatment initiation ($p = 0.026$) [68].

Telomerase Complex Agonists

Danazol is a synthetic sex hormone with androgenic properties that induces telomerase complex activation in laboratory studies. In a 2-year prospective study of 10 patients with "overt" pulmonary fibrosis and 15 patients with "subclinical" pulmonary fibrosis, danazol therapy was associated with a stabilization of diffusing capacity of the lung for CO (DLCO), FVC and CT scan findings [16]. Moreover, treatment with danazol was associated with telomere elongation and a beneficial hematological response in 79% of the patients (19/24). However, danazol therapy is associated with liver adverse effects and an increased risk of venous thrombosis. A phase I/II trial (ANDROTELO, NCT03710356) with danazol is ongoing in France, including carriers of a TRG mutation with lung fibrosis and/or severe hematologic involvement.

Lung Transplantation

Lung transplantation is often discussed in FPF because of the young age of ILD onset in many patients. Five retrospective series reported the outcome of lung transplantation in TRG mutation carriers [53, 69–72]. Hematologic toxicity is a significant concern and requires an adjustment of immunosuppression in most patients. Myelodysplastic syndrome or bone marrow failure occurred in some patients and thrombocytopenia requiring platelet transfusion was frequent [69, 70]. In a cohort of 262 lung transplant patients, patients with *TERT*, *RTEL*, *or PARN* mutation ($n = 31$, 11.8%) were recently reported to have a reduced post-transplantation survival (HR = 1.82: 95%CI [1.07–3.08], $p = 0.03$]) and higher risk of CLAD (HR = 2.88; 95%CI [1.42–5.87], $p = 0.004$) [72], though this retrospective study did not reveal a higher risk of hematological complication or renal insufficiency in TRG mutation carriers [72]. Interestingly short telomeres and mutations of TRG have been associated with increased prevalence of CMV infection after lung transplantation [53].

Moreover, in an independent cohort, patients with telomere length less than the tenth percentile before transplant were reported to have a worse survival and also a shorter

time to onset of chronic lung allograft dysfunction [42]. Comparison of the <tenth percentile telomere length group with the >tenth percentile group showed a higher rate of primary graft dysfunction, but there were no differences in the incidence of acute rejection, cytopenia, infection, or renal dysfunction [42].

Interestingly, among the patients included in the PANTHER-IPF trial (prednisone/azathioprine/N-acetylcysteine), patients with the shorter telomere length (<tenth percentile) had the worse outcome (death, lung transplantation, hospitalization, or FVC decline) and a post hoc analysis showed an interaction between immunosuppression and telomere length [73], suggesting that azathioprine and prednisone are particularly harmful for patients with short telomeres and probably also for TRG mutations carriers.

Surfactant Pathway

Surfactant functions to alter surface tension to prevent alveolar collapse. Surfactant is secreted by type II epithelial alveolar cells and is composed of 90% lipids and 10% proteins. The main surfactant proteins are SP-A, SP-B, SP-C, and SP-D and the corresponding genes are called *SFTPA, SFTPB, SFTPC,* and *SFTPD* [7]. **ABCA3** transporter (ATB Binding Cassette family A, member 3) encoded by *ABCA3* is critical for pulmonary surfactant synthesis and processing [74]. Among surfactant gene mutations, *SFTPA1, SFTPA2,* and *SFTPC* mutations have been implicated in FPF.

Surfactant Protein Genes

Although *SFTPC* mutations were first linked to pediatric cases of ILD, the contribution of *SFTPC* mutations in adult FPF has been also established in 1–5% of FPF cohorts [8, 75, 76]. De novo mutations are frequent in children and may explain as much as 50% of cases [77].

Heterozygous mutation in *SFTPA2*, or *SFTPA1,* has been identified in subjects with FPF and/or lung **adenocarcinoma** [78, 79].

ABCA3 is expressed in Type II AEC lamellar bodies and is important in surfactant processing. Although homozygous *ABCA3* mutations are usually associated with respiratory failure in newborns [80], several adult patients carriers of mutations of *ABCA3* with pulmonary fibrosis and emphysema have been reported [81].

NKX2.1 encodes a transcription factor closely related to surfactant protein transcription [82]. Heterozygous mutations are classically associated with the triad of ILD, **hypothyroidism**, and neurologic anomalies (hypotonia, delayed development, **chorea**) [83]. However, thyroid abnormalities and neurologic anomalies may be subtle and easily overlooked, or even absent, in up to 1/3 of cases, including adult cases [83].

Pulmonary Involvement

Biallelic *ABCA3* mutations and heterozygous *NKX2.1*, *SFTPA1 SFTPA2*, and *SFTPC* mutations in adults may share similar clinical and radiological presentation (Fig. 24.5). The most frequent radiological pattern associates diffuse ground-glass opacities, septal thickening, and cysts of variable size with a preferential distribution in the upper lobes and in subpleural areas (Fig. 24.3). Differentiating emphysema from **cysts** is sometimes difficult, so *SFTPC* mutations should be considered in any young patient with what appears to be combined pulmonary fibrosis and emphysema [84]. At later stages of disease, honeycombing can predominate.

Histologically, the most frequently related pattern in adults is UIP, but NSIP, organizing pneumonia, or desquamative interstitial pneumonia have also been reported. Moderate inflammation and centrilobular fibrosis can be observed [76].

Treatment

In children, treatments that have been reported to be successful in case reports or short series include **methylprednisolone, hydroxychloroquine, and azithromycin** [81, 85–87]. No treatment appears to reduce disease in a patient with prominent honeycombing. The effectiveness of antifibrotic drugs, such as pirfenidone or nintedanib, is unknown. The disease does not appear to recur after pulmonary transplantation [85].

Because lung fibrosis may alter spine growth during childhood, acquired scoliosis and pectus excavatum are frequent and may require corrective surgery (Fig. 24.5).

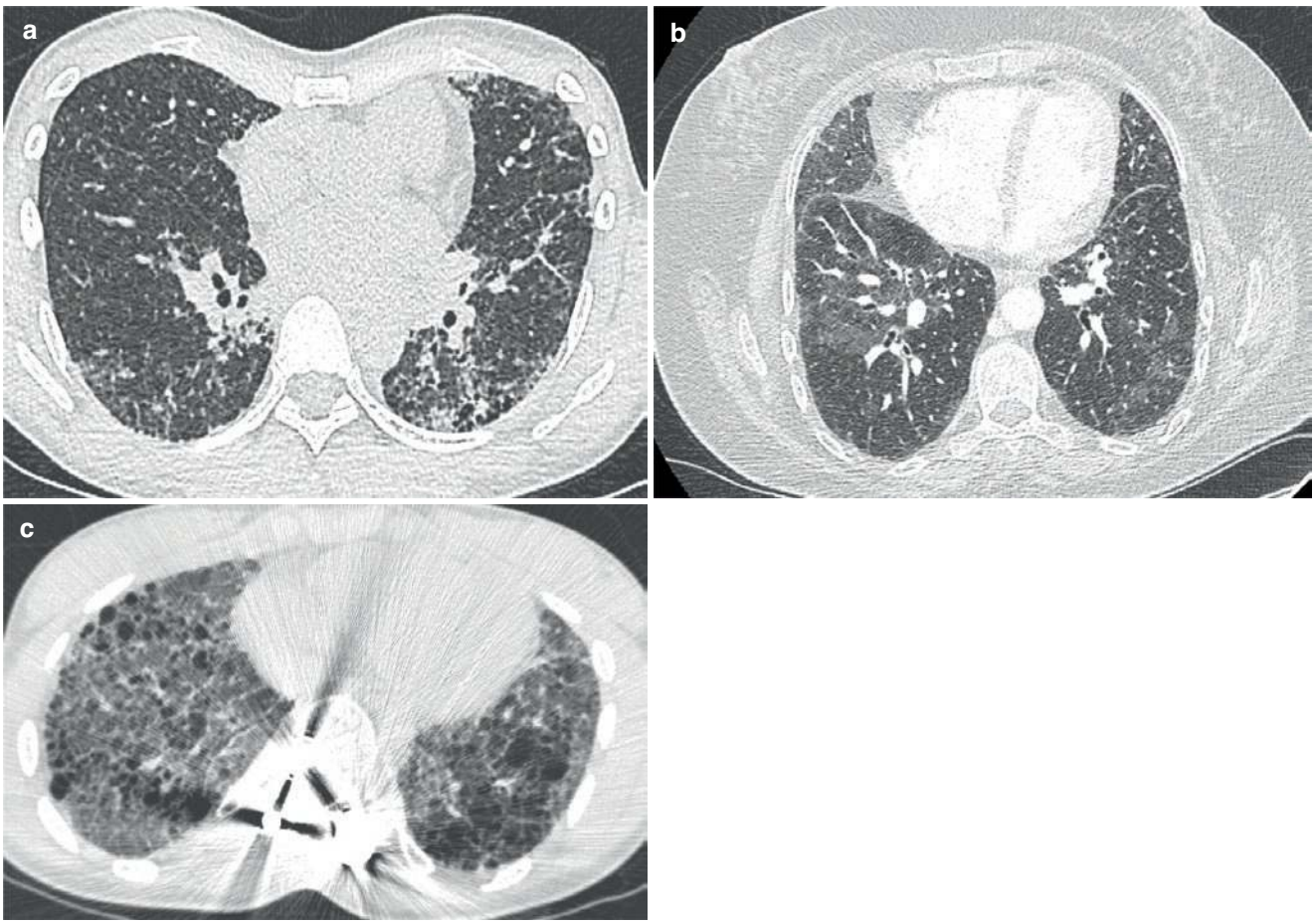

Fig. 24.5 High-Resolution Computed Tomography of (**a**) non-UIP pattern (indeterminate) with ground-glass opacities and reticulation associated with (**a**) *SFTPA1* mutation, (**b**) compound heterozygous *ABCA3* mutation and with (**c**) end-stage lung fibrosis associated with *SFTPC* mutation (note the artifact due orthopedic hardware in the spine)

Other Genetic Diseases That Can Cause Fibrosing ILD

Heritable Forms of Pulmonary Fibrosis with Autoimmune Features

TMEM173

Ten initial pediatric and young adult patients with systemic inflammation, peripheral vascular inflammation with skin involvement and ILD, were associated with gain-of-function *TMEM173* gene mutations [88, 89]. The *TMEM173* gene encodes the stimulator of interferon gene (**STING**). The mutations are associated with a strong **interferon** signature in blood monocytes with increased interferon-induced cytokine levels in the serum that could be used as a screening test before genetic analysis. Screening for autoantibodies shows variable lupus-like positivity (antinuclear or antiphospholipid antibodies) and ANCA positivity has also been reported [88, 89]. Pulmonary fibrosis may lead to respiratory insufficiency, lung transplantation, or death [89]. Janus kinase inhibitors (**tofacitinib** or **ruxolitinib**) have shown promising results for systemic inflammation but appear to have less of an effect on ILD [90, 91].

COPA

Twenty-one patients from five families were initially reported with arthritis, renal disease, and ILD that were associated with heterozygous *COPA* mutations, impairing endoplasmic–Golgi transport [92]. Similarly to patients carriers of *TMEM173* gene mutations, *COPA* mutations induce a strong upregulation of interferon-stimulated genes [93]. Most of the patients (76%) were under 5 years of age, 95% had joint pain, and all had ILD or **alveolar hemorrhage** [92]. Screening for **autoantibodies** showed positivity for ANCA (71%), antinuclear antibodies (67%), and rheumatoid factor (43%). The nature of ANCA, such as anti-MPO or anti-PR3 positivity, is most often not specified.

Alveolar hemorrhage generally occurs before the age of 5 years and may be life threatening. After the second decade of life, patients develop ILD. Chest CT scans initially show diffuse ground-glass opacities with septal thickening and honeycomb cysts. The number of cysts tend to increase through time as the ground-glass opacities decrease, with an ultimate pattern that is most consistent with NSIP or lymphocytic interstitial pneumonia [93]. Histopathological evaluation shows alveolar hemorrhage and pulmonary capillaritis with vascular infiltration by neutrophils and necrosis of the capillary walls, as well as lymphoid aggregates around airways [94]. Lung biopsies of older patients show NSIP and follicular bronchiolitis or diffuse interstitial pulmonary neuroendocrine cell hyperplasia [94, 95].

Most patients have at least a partial response to immunosuppression particularly in the case of alveolar hemorrhage but death or need for lung transplantation can occur with disease progression and during acute exacerbation of the disease [94].

Pulmonary Alveolar Proteinosis

GMCSF Receptor Mutations

Pulmonary alveolar proteinosis (PAP) is a syndrome that is characterized by alveolar accumulation of surfactant due to autoimmune, hereditary, and environmental etiologies. Autoimmune PAP caused by an autoantibody to GM-CSF is the most frequent form of PAP, representing 90% of cases. PAP may not only result from several heritable genetic mutations, especially in the GM-CSF receptor gene, but also from surfactant gene mutations [77, 96]. The **GM-CSF receptor** is composed of an α chain, encoded by *CSF2RA*, and a β chain, encoded by *CSF2RB*. Homozygous mutations of *CSF2RA* and heterozygous mutations of *CSF2RB* have been associated with PAP. Patients with PAP associated with *CSF2RA* mutation are usually below 5 years, while mean age of patient with autoimmune PAP is 50 years. However, *CSF2RA* PAP is very similar to autoimmune PAP and may lead to pulmonary fibrosis. Features of *CSF2RA* PAP that are unlike autoimmune PAP include that interstitial cell infiltration is generally absent, alveolar and serum concentration of GM-CSF are increased due to compensatory mechanisms, and anti-GM-CSF antibodies are absent. **Whole-lung lavage** is generally effective, but GM-CSF therapy does not seem to provide benefit [97–99]. Studies are underway to determine if GM-CSF receptor mutations can be corrected by hematopoietic stem cell transplantation or pulmonary macrophage transplantation [100, 101].

GATA2

GATA2 is a transcriptional factor that plays a key role in the functionality of hematopoietic stem cells. *GATA2* mutations were initially associated with **MonoMAC syndrome** (monocytopenia, lymphopenia, mycobacterial infection) and were further associated with numerous hematological disorders [102]. *GATA2* mutation has also been associated with PAP syndrome, but pulmonary fibrosis has also been reported [103, 104]. Hematopoietic stem cell transplantation may improve lung disease in patients with GATAs deficiency [102].

MARS

Homozygous mutations of **methionyl-tRNA synthetase** *(MARS)*, an enzyme that catalyzes the binding of methionine to tRNA and plays a critical role in protein synthesis, have been described in a cohort of 34 children with ILD from La Réunion Island belonging to the same family [105]. Most of them presented with PAP, and a similar mutation was detected in two independent families (of Comorian and Tunisian origin) [105]. The mean age at diagnosis is almost 9 months. All patients have respiratory failure and failure to thrive, half have hepatomegaly related to steatosis and one-third have splenomegaly. CT scanning shows a crazy paving pattern and consolidations (76%). In addition to accumulation of surfactant consistent with a PAP pattern, pulmonary histology shows **lipoid pneumonia** (42%), fibrosis (42%), and interstitial inflammation (84%). Overall survival at the age of 5 years is 65%. Despite temporary improvement after pulmonary lavage, survival is not different between patients receiving and not receiving therapeutic pulmonary lavage [106]. MARS activity is restored in vitro by methionine supplementation suggesting a possible targeted therapy [105]. The pathophysiology of the lung disease has yet to be understood and the risk of recurrence after pulmonary transplantation has not been evaluated.

Lysinuric Protein Intolerance

Lysinuric protein intolerance (LPI) is an autosomal recessive disease caused by mutations of *SLC7A7* that result in defective transport of cationic amino acids across epithelial cell membranes in the intestine and kidney [107]. The disease is usually diagnosed in children who present with failure to thrive and gastrointestinal symptoms. The most frequent chronic manifestations are related to renal and pancreatic insufficiency. Lysinuric protein intolerance is diagnosed by the presence of excessive amounts of dibasic amino acids (argi`, lysine, ornithine) in the urine, particularly after protein ingestion, and/or mutation of *SLC7A7* [107]. Pulmonary manifestations are variable and range from subclinical ILD to respiratory insufficiency. PAP is frequently present and patients may develop lung fibrosis out of proportion to the severity of PAP [107]. The treatment is based on a low protein diet and oral supplementation with citrulline. Whole-lung lavage and nebulized GM-CSF therapy seem to be effective. However, recurrent PAP may lead to death and

relapse after lung transplantation [107]. Indeed PAP and ILD may be related to a macrophage dysfunction, not treated by lung transplantation though the exact pathophysiology of PAP is unknown [100].

Lysosomal Diseases

Hermansky-Pudlak Syndrome

Hermansky-Pudlak Syndrome (HPS) refers to a heterogeneous group of autosomal recessive disorders of intracellular trafficking that result in oculocutaneous albinism, clotting dysfunction secondary to defective platelets, and, in some subtypes that affect alveolar type II cells, ILD. To date, eight different subtypes have been described in humans associated with different genetic abnormalities that lead to abnormal protein trafficking associated with dysfunction of lysosome-related organelles [108]. The disease is most prevalent in Puerto Rico due to a founder effect.

Among HPS subtypes, ILD and pulmonary fibrosis occur in HPS-1 and HPS-4. HPS-1 is the most common subtype of this disease, accounting for approximately 50% of HPS cases outside the Puerto Rican population.

In most individuals with HPS-1 or HPS-4 who survive to adulthood, ILD can be found, with many patients having severe progressive pulmonary fibrosis resulting in respiratory failure [109, 110]. Patients who present with lung fibrosis have a mean age of onset of symptoms of 35 and an average age of death related to respiratory failure of 37, consistent with very rapidly progressive disease [110].

Lung biopsy in HPS can not only reveal a pathologic pattern similar to UIP but can also show hyperplastic AECs filled with phospholipid-rich droplets and enlarged lamellar bodies, suggestive of possible defects in the surfactant secretory pathway [111]. Compared to HPS-1, HPS-4 is much less common, but lung manifestations occur in the same pattern as noted in HPS-1 [112]. Two small trials evaluated the effect of pirfenidone vs. placebo in these patients and contradictory results were reported. One report, including 35 patients, did not find a difference between the two groups, while the other study of 21 patients reported decreased lung function decline in treated patients [113].

Lysosomal Storage Disorders

Gaucher disease is an autosomal recessive disease secondary to mutations in the glucocerebrosidase gene resulting in deficiency of the lysosomal hydrolase acid β-glucosidase and in accumulation of its substrate, glucosylceramide [114]. The most frequent manifestations of type 1 Gaucher disease are related to the infiltration of bone marrow, liver, spleen, and lung by lipid-engorged macrophages (Gaucher cells). Type 2 and 3 Gaucher disease manifests with primary central nervous system (CNS) involvement expressed as spasticity, oculomotor apraxia, and seizures with onset in infancy and premature death [114]. In the few cases of lung involvement of Gaucher disease that have been specifically reported, the chest CT showed a predominant ground-glass pattern with superimposed thickening of interlobular septa [115]. The natural history of Gaucher disease has been dramatically modified by the development of enzyme replacement therapy [116].

Acid sphingomyelinase deficiency (ASMD, ex-Niemann-Pick disease) is an autosomal recessive disease secondary to acid sphingomyelinase deficiency. The most frequent clinical presentation is a neurovisceral infantile form in type A, but a chronic visceral form presenting with hepatosplenomegaly and pulmonary involvement may also encountered in adults in type B disease [117]. ASMD-B Niemann-Pick disease is a autosomal recessive inherited condition related to mutation within *SMPD1* [117]. The most frequent CT patterns are interlobular septal thickening and ground-glass opacities, and bronchoalveolar lavage shows characteristic Niemann-Pick cells (Fig. 24.6) [118, 119]. Although pulmonary manifestations eventually worsen, the results of a clinical trial with enzyme replacement therapy should soon be available (NCT02004691).

Fabry disease is an X-linked lysosomal storage disorder caused by mutation of the α-galactosidase gene (*GLA*) causing deficiency of α-galactosidase A activity [120]. This enzymatic defect leads to the progressive accumulation of glycosphingolipids resulting in neurological, ocular, skin, renal, and cardiac manifestations in classical type of the disease [120]. Respiratory symptoms are most frequently related to cardiac involvement. A few cases of ILD and ground-glass pulmonary infiltrations on CT scan in patients with Fabry disease have been reported [121]. Enzyme replacement therapy may improve or stabilize respiratory manifestations [121].

FAM111B, NDUFAF6, PEPD

At least five families with **poikiloderma** associated with tendon contractures and pulmonary fibrosis were found to have *FAM111B* mutations [122]. In this series, CT seems to be inconsistent with UIP.

Acadian variant of Fanconi syndrome refers to a specific condition characterized by proximal tubular dysfunction in newborns, resulting in chronic kidney disease and pulmonary interstitial fibrosis. It has been associated with biallelic intronic variants of *NDUFAF6* encoding a **mitochondrial** enzyme. Pulmonary data are sparse, but the age of

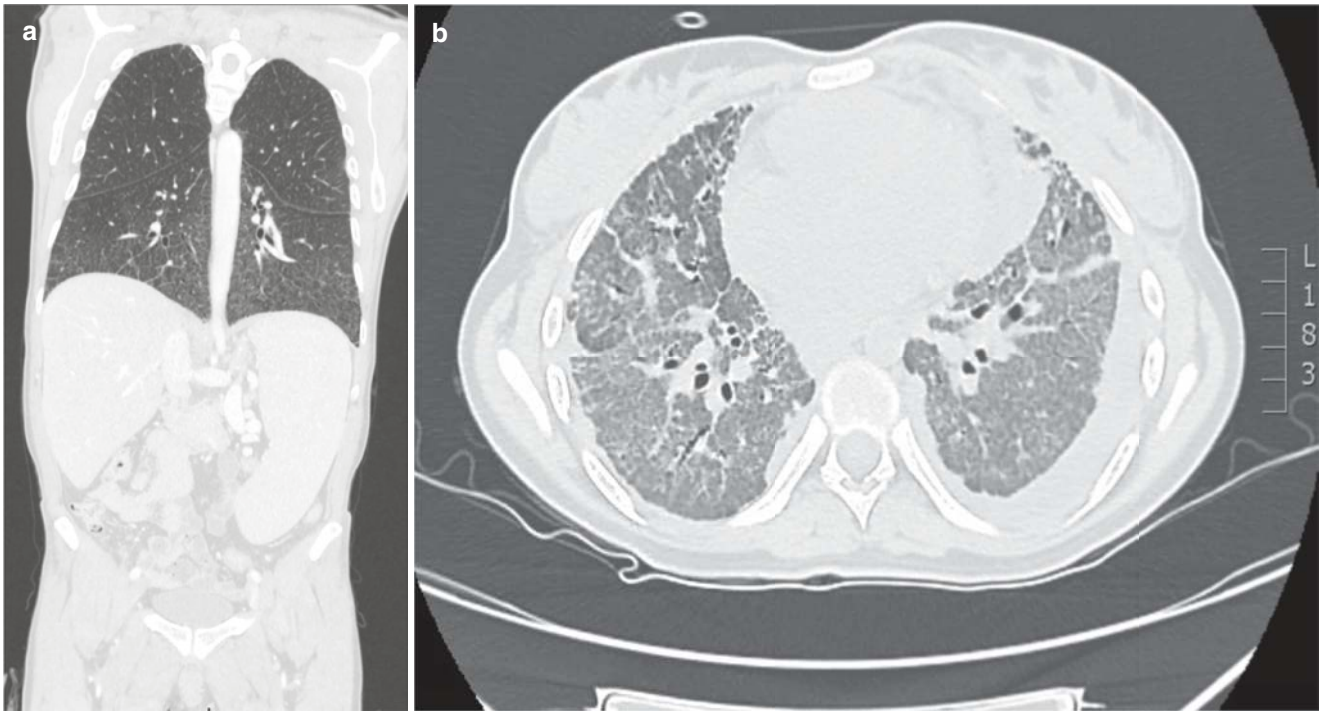

Fig. 24.6 High-Resolution Computed Tomography of (**a**) non-UIP pattern (indeterminate) with ground-glass opacities and reticulation associated with splenomegaly in a Niemann-Pick patient, (**b**) ground-glass opacities and reticulation associated with a *MARS* mutation

the patients varied from 19 to 50 and patients presented with lung fibrosis [123].

Conclusion

ILD and pulmonary fibrosis may be present in diverse monogenic diseases. The most frequent in adults are related to TRG mutations and the most frequent ILD diagnosis is IPF. Other diseases are usually not associated with an IPF diagnosis. Although extrapulmonary manifestations may be at the forefront, ILD is often the most life threatening. Clinical trials are urgently needed to evaluate therapies that are effective in other forms of pulmonary fibrosis, such antifibrotic therapy for IPF and progressive, fibrotic NSIP. Lung transplantation remains the intervention of last resort but for several of the genetic familial pulmonary fibrosis disorders special consideration must be given to liver, renal, marrow, and hematopoietic complications. Mendelian transmission raises specific issues requiring genetic counseling for the relatives with coordination by the caregivers. In order to offer the best possible care to these patients, they should be referred to an expert center and benefit from multidisciplinary team discussion that includes participants with pulmonary, radiologic, pathologic, and genetic expertise.

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Diffuse Bronchiectasis of Genetic or Idiopathic Origin

25

Jane S. Lucas, Katharine C. Pike, Woolf T. Walker, and Amelia Shoemark

Introduction

Bronchiectasis is a disorder of cough, sputum production and persistent or recurrent bronchial infection associated with damaged and dilated bronchi. Although historically considered irreversible, increased use of high-resolution computed tomography (HRCT) scanning has identified 'mild bronchiectasis' which is reversible if treated aggressively at an early stage. Moreover, the radiological disease can be present in some asymptomatic patients, particularly the elderly. European Respiratory Society (ERS) Guidelines for the management of adult bronchiectasis specifically define the disorder as a permanent dilatation of the bronchi with associated chronic symptoms [1]. In recent years, the international prevalence of bronchiectasis has markedly increased in both children and adults [2–4].

Reported causes of bronchiectasis vary depending on health care infrastructure. Diffuse bronchiectasis in countries with good diagnostic resources is typically attributed to cystic fibrosis (CF), primary ciliary dyskinesia (PCD), immune deficiency or abnormal bronchial anatomy. Bronchiectasis is more likely to be termed 'idiopathic' or post-infectious in settings where exploration of an underlying diagnosis is limited. Post-infectious bronchiectasis is an imprecise diagnosis, and it is usually difficult to confirm causality. However, it is recognised that infections such as pulmonary tuberculosis or severe adenovirus infection predispose individuals to bronchiectasis. In older patients, coexistence of bronchiectasis is commonly reported with COPD or asthma. The relationship of these different airway conditions is poorly understood, and is perhaps partially explained by misdiagnoses due to overlapping symptoms.

Importantly, bronchiectasis is the end-point of a heterogeneous group of diseases and pathological mechanisms [5]. Identifying bronchiectasis is just the starting point to diagnosing the underlying cause. Although some management strategies are shared (e.g. airway clearance therapy), some diseases require specific therapies. The failure of most clinical trials to show positive outcomes possibly reflects the need for future trials targeting specific diseases [6]. Moreover, knowledge of the underlying cause is necessary to provide personalised counselling regarding prognosis, associated morbidities and genetic counselling.

Pathophysiology

Bronchiectasis is a description of permanent airway dilatation associated with cough, sputum production and bronchial infection; bronchiectasis is usually divided into cystic fibrosis and non-cystic fibrosis related disease. A number of diseases including cystic fibrosis, primary ciliary dyskinesia and immunodeficiency disorders predispose patients to recurrent or chronic infection. Bronchiectasis can also be triggered by tuberculosis or following a severe respiratory infection. These triggers can result in airway plugging, recruitment of inflammatory cells and release of inflammatory mediators and cytokines. In turn, this can lead to the destruction of the elastic and muscular elements of the bronchial walls, causing airway dilatation, and damage to the motile cilia which line the airways [7, 8]. Accumulation of purulent viscous secretions ensues, resulting in the persistence of infection and inflammation. In the 1980s Cole pro-

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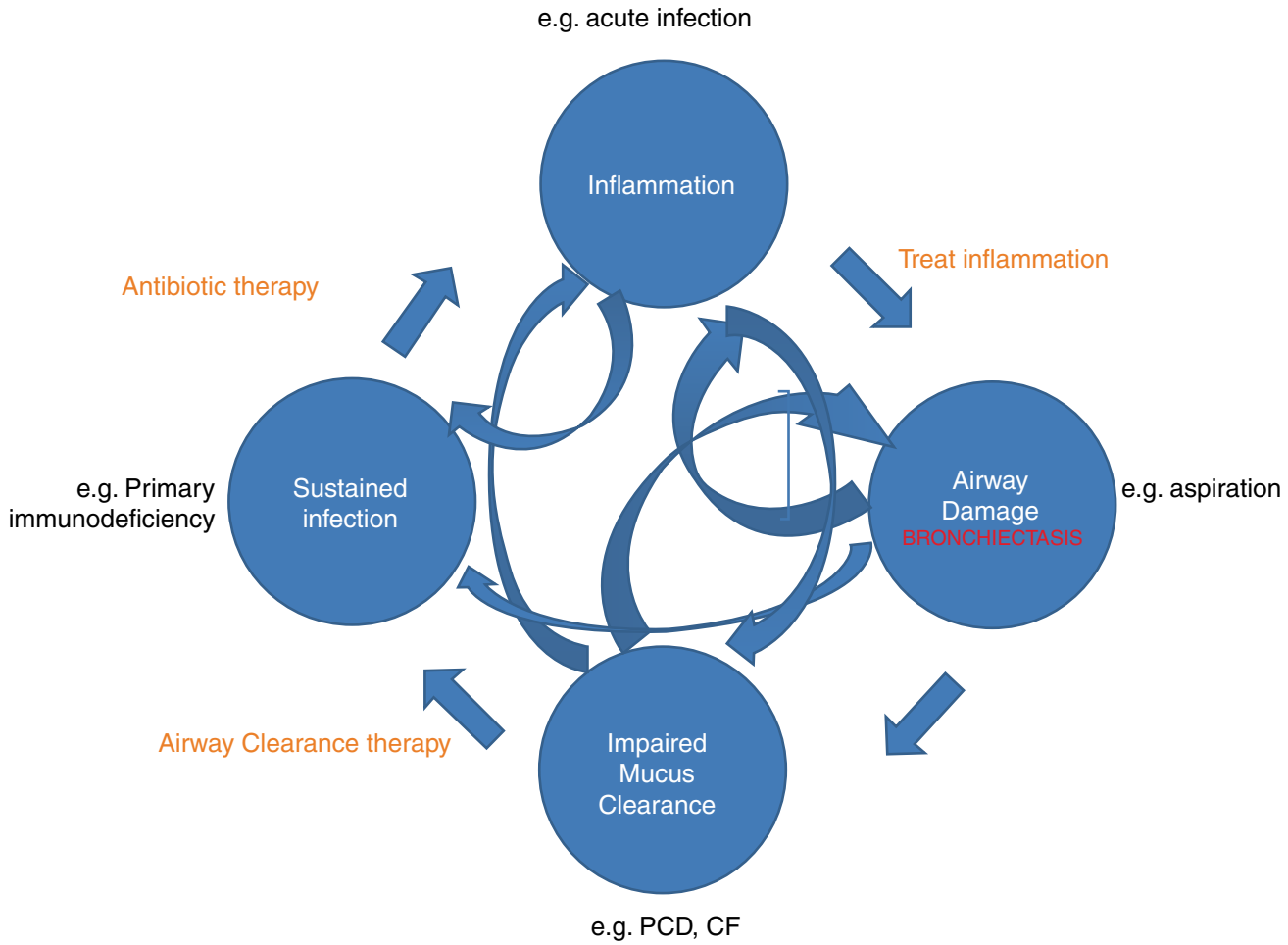


Fig. 25.1 A genetic condition (e.g. PCD or CF) or triggering event (e.g. severe infection) can result in a persistent and progressive cycle or 'vortex' of processes that eventually lead to bronchiectasis. Impaired mucociliary clearance and retention of airway secretions render the airways susceptible to recurrent and persistent infection. This process, in turn, incites an inflammatory response causing airways damage, which further impairs the clearance of mucus

posed the 'vicious cycle' mechanism of ongoing and self-perpetuating damage in bronchiectasis [9]. An environmental insult, often on a background of genetic susceptibility, impairs muco-ciliary clearance resulting in persistence of microbes. The microbial infection causes chronic inflammation resulting in tissue damage and impaired cilia function. This leads to further infection with a cycle of progressive inflammation causing lung damage. Inflammation tends to be neutrophilic, with increased levels of neutrophil proteases such as neutrophil elastase leading to airway damage. Recent data shows this protease release may be related to formation of neutrophil extracellular traps. Eosinophilic inflammation can also be present in up to 30% patients [10, 11]. More recently, it has been appreciated that these interactions are far more complex with each pathophysiological step contributing to all others, "a vortex" rather than a simple circle (Fig. 25.1) [12].

Clinical Presentation

Depending on the underlying cause, bronchiectasis can develop at any stage of life. Early investigation of persistent cough is essential if interventions are to be implemented before irreversible bronchiectasis ensues. Persistent wet or productive cough failing to respond to 4 weeks of antibiotic treatment is the key feature that suggests bronchiectasis, or a pre-bronchiectasis syndrome [13]. Most patients with established bronchiectasis expectorate sputum daily, with highly variable volumes. Reduced exercise tolerance and breathlessness may be present, and are generally associated with advanced disease [14]. Haemoptysis is relatively rare in children from affluent settings [15] but is more common in children from low-income settings [16], and in adults. Thoracic pain is relatively common. Individuals with bronchiectasis may wheeze but in contrast to people with asthma this is

almost invariably associated with *wet* cough; asthma can also co-exist with bronchiectasis.

The examination may be normal or may include crackles, wheeze, or chest deformity. Clubbing is reported to occur in some patients with bronchiectasis. Whilst it is an important sign it is not a sensitive one. In general, patients in less affluent settings have more severe diseases, presumably associated with later diagnosis and less aggressive/targeted management [16].

Epidemiology

The introduction of immunisations against pertussis in the 1950s and measles in the 1960s contributed greatly to the decline of post-infective bronchiectasis, as has the decline of pulmonary tuberculosis and the general improvement in social circumstances. However, the genetic and idiopathic disease has proportionally increased in recent times and disease prevalence has risen by more than 40% over the past 15 years. In the UK recent studies suggest a prevalence of 566 per 100,000 in women and 485 per 100,000 in men making bronchiectasis the third most common lung condition behind asthma and COPD [4]. One of the highest prevalence worldwide has recently been reported in the USA with an average of 701 patients per 100,000 people [2].

Bronchiectasis can occur at any age from early childhood, however, the average age in Western cohorts is 60–70 years [14]. It is more prevalent at a younger age in countries where there is a high incidence of pulmonary tuberculosis [17] or in certain indigenous subpopulations, including Pacific Islanders, Indigenous Australians and the Inuit community in North America [18–20]. Poor access to antibiotics and immunisations may partially explain these differences, although it is likely that genetic propensity may also play a role [21, 22]. Certainly, children of consanguineous parents are at a disproportionately high risk of genetic causes of bronchiectasis [23]. Moreover, although environmental, immune or anatomical factors may explain the observation that non-CF bronchiectasis is more common in females, this too may have a genetic basis [24]. Differences between nations may partly reflect genetic and environmental discrepancies; however, it is likely that the diagnosis of bronchiectasis in children is often delayed or never considered, making true prevalence difficult to establish.

The most common genetic cause of diffuse bronchiectasis is cystic fibrosis (CF), the incidence of which is estimated to be 1 in 2500 births in white Caucasians. Reports of primary ciliary dyskinesia (PCD) prevalence in European populations have varied greatly from older estimates of 1:40,000 to more recent estimates based on genetic data of 1:7500 [25, 26]. As with most orphan diseases this variation is likely to reflect a lack of awareness of the disease amongst clinicians, absence of a gold standard test, and lack of facilities for investigation, all leading to considerable under-diagnosis. A survey by a European PCD Taskforce suggested that PCD in children is under-diagnosed and diagnosed late, particularly in countries with low health expenditures [27]. The prevalence of other genetic causes of bronchiectasis is low and is considered individually later in this chapter.

Table 25.1 Examples of genetic causes of bronchiectasis

Disorders of mucociliary clearance	Cystic fibrosis Primary ciliary dyskinesia
Primary immunodeficiency	
Hypogammaglobulinaemia Neutrophil deficiency Innate immunity	Common variable immunodeficiency X-linked agammaglobulinemia Chronic granulomatous disease Shwachman-Bodian-Diamond syndrome Complement deficiency
Collagen disorders	Marfan syndrome
Other associations	Autoimmune disease e.g. rheumatoid arthritis, inflammatory bowel disease

Genetic Causes of Bronchiectasis

Bronchiectasis associated with genetic mutations is usually a consequence of recurrent or persistent pulmonary infection caused by disorders of mucociliary clearance or primary immunodeficiency (Table 25.1).

Disorders of Mucociliary Clearance

Ciliated respiratory epithelium lines the airways. The cilia, bathed in periciliary fluid, beat in a coordinated fashion, to propel the overlying mucus along with particles and bacteria to the oropharynx where it can be swallowed or expectorated (Fig. 25.2). Diseases affecting ciliary function, or that change the composition of the periciliary fluid and mucus can impair mucociliary clearance, leading to recurrent infections and inflammation which predispose to bronchiectasis.

Cystic Fibrosis

Cystic fibrosis (CF) is an autosomal recessive disorder and is the commonest inherited disease in white populations, with an estimated incidence of 1 per 2500 live births [28]. It is caused by mutations in the *cystic fibrosis trans-membrane conductance regulator* (*CFTR*) gene which is located on chromosome 7 and encodes for the CFTR chloride channel which sits in the cell membrane on the apical surface of the cell.

Mutations lead to abnormal ion transport regulation across the cell membrane which, in the lungs, results in abnormal airway fluid. Dehydrated mucus is characteristically highly viscoelastic, and adheres to the cilia and airway

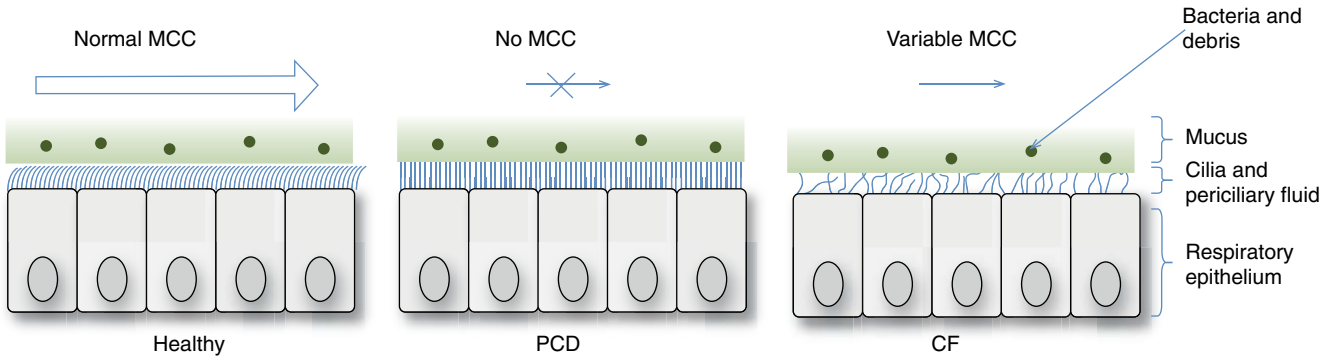


Fig. 25.2 In healthy persons, respiratory cilia beat in a coordinated sweeping pattern, which moves mucus and debris, including pathogens towards the oropharynx for swallowing or expectorating. In PCD, immotile or dyskinetic cilia do not beat effectively, and mucus and debris persist in the airways. In CF the inefficient mucociliary clearance (MCC) is due to an abnormal periciliary fluid layer compromising ciliary beating and viscous mucus which is resistant to clearance. (Image provided by Robert Scott)

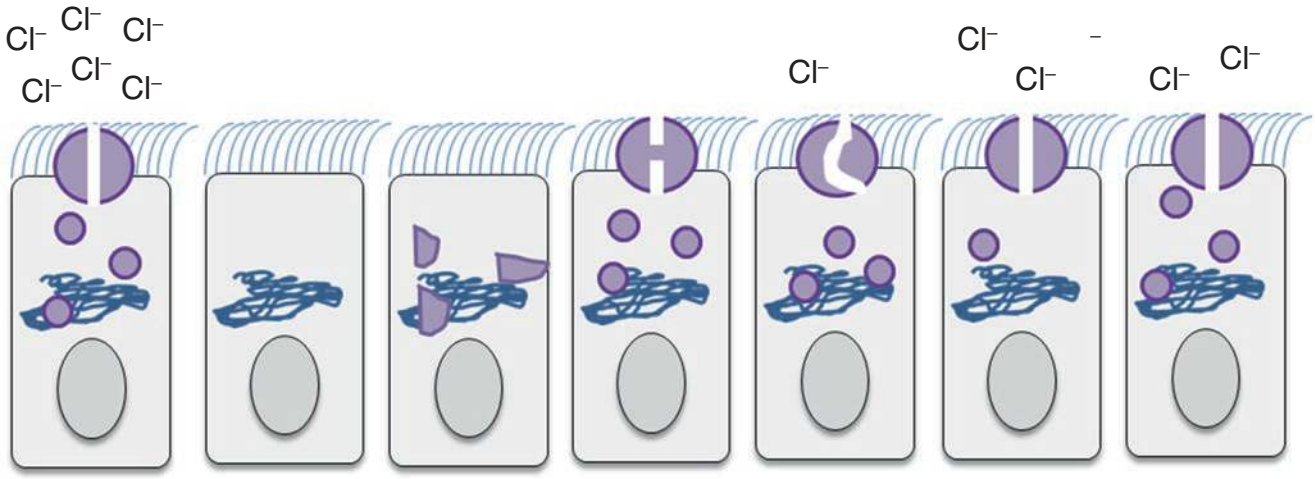
cells, causing airway plugging. The reduced-volume periciliary fluid layer does not adequately support and lubricate the cilia, and results in defects of ciliary function (Fig. 25.2). Adherent mucus and impaired ciliary function both contribute to reduced airway clearance, chronic infection and biofilm formation. Eventually, the chronic infection and inflammation lead to bronchiectasis, which can develop very early in life [29]. Bronchiectasis in CF predominantly affects the upper lobes initially, spreading to all lobes over time; the disparity with PCD, which tends to have worse disease in the middle lobe, is difficult to explain [30].

Since the *CFTR* gene was first sequenced in 1989, [31] our understanding of the underlying pathophysiology of CF has developed rapidly. At the time of writing, over 2000 mutations in CFTR have been described, of which about 350 are thought to be pathogenic (https://www.cftr2.org/welcome). These mutations have been grouped into classes, dependent on their effect on the CFTR protein (Fig. 25.3). For example, class 2 mutations, which include the most common p.Phe508del mutation, lead to a failure of the correct folding of the protein which is then rapidly broken down and hence not expressed on the apical surface of the cell; whereas with class 3 mutations the protein is correctly folded and is present on the apical surface but the channel is blocked closed, termed 'gating' mutations. Our understanding of the effects of mutations in *CFTR* has been fundamental in recent ground-breaking advances in the treatment of CF. It is now possible to correct CFTR dysfunction in patients with specific classes of mutations, and therapies for other mutations are in late-phase trials (see *Novel therapies for managing* CF).

Although respiratory disease accounts for the majority of morbidity and mortality, [32] CF is a multisystem disorder with manifestations including meconium ileus, pancreatic insufficiency leading to steatorrhea and failure to thrive, liver disease, diabetes, nasal polyposis, sinusitis and infertility in men due to congenital bilateral absence of the vas deferens . Since the widespread use of newborn screening (NBS) for CF, measuring immuno-reactive trypsin (IRT) levels in the blood at about 7 days of life, most cases of CF are diagnosed in infancy. However later presentation, even in adulthood, is not unheard of, particularly where individuals were born prior to initiation of NBS programmes and who carry mutations other than p.Phe508del, hence are more likely to be pancreatic sufficient [33]. The diagnosis is confirmed by assessing the function of the CFTR channel by measuring sweat chloride levels, with a level > 60 mmol/L being diagnostic. Whilst not essential for diagnosis, given the advent of novel therapies based on *CFTR* mutation class, it is recommended that CF patients go on to be genotyped. Importantly, due to the fact that not all mutations in *CFTR* are pathogenic, any individual first identified by genotyping (i.e. having two bi-allelic *CFTR* mutations) should go on to have a confirmatory functional CFTR assessment by sweat test. In difficult diagnostic cases measurements of nasal potential difference can be helpful.

Primary Ciliary Dyskinesia

Primary ciliary dyskinesia (PCD) is a rare, genetically heterogeneous disorder, usually transmitted in an autosomal recessive pattern [34, 35]. Mutations of PCD-causing genes effect the genesis, structure and/or function of motile cilia leading to impaired mucociliary clearance (Fig. 25.2). Cilia dysmotility in the airways classically leads to unexplained neonatal respiratory distress in term infants, daily wet cough from early infancy, bronchiectasis, chronic rhinosinusitis, and conductive hearing impairment [36]. PCD is estimated to affect approximately 1 in 7750 people [26, 37], but many people are undiagnosed or diagnosed late in life, and the true prevalence is unknown [38]. Whilst data from international consortia and large clinics are improving our understanding of disease progression, information concerning morbidity and mortality remain sparse. The International PCD Cohort (iPCD) has reported that lung function impairment during childhood is similar to that found in CF, but by adulthood forced expiratory volume in 1 s (FEV_1) is worse in CF [39]. Recent observations



Class of mutation

Normal	I	II	III	IV	V	VI
	No CFTR synthesis	Abnormal CFTR protein folding	CFTR channel blocked 'gating mutation'	Channel altered	Reduced synthesis	Reduced half life
Example mutations	Gly542X	Phe508del	Gly551Asp	Arg117His	3849+10kb C→T	4326delTC

Fig. 25.3 Mutations causing cystic fibrosis can be grouped into classes, dependent on their effect on the CFTR protein

from large adult clinics concur that pulmonary disease is heterogeneous in severity [40, 41]. Several studies have reported impaired growth in children with PCD, [42, 43] which may be associated with worse lung function [39, 42, 43].

Neonates typically present with respiratory distress of unknown cause and some have rhinitis [44]. Infants continue to have a persistent wet cough, and usually develop recurrent respiratory tract infections, rhinitis, and serous otitis media associated with conductive hearing difficulty. Respiratory symptoms continue into later childhood and adulthood. Bronchiectasis has been described in pre-school children and is almost universal by early adulthood (Fig. 25.4); in contrast to CF, disease typically affects the middle and lower lobes, with relative sparing of the upper lobes [45–48]. Bacterial pathogens isolated from the airways are similar to those described in CF, namely *Haemophilus influenza*, *Pseudomonas aeruginosa, Staphylococcus aureus*, *Streptococcus pneumoniae* and *Moraxella catarrhalis* [49–53].

Motile cilia are important in organs besides the respiratory tract, such as the Eustachian tubes, embryonic node, sperm flagella, the female reproductive tract, and ependyma of the brain and spinal cord. Extra-pulmonary symptoms caused by dysmotile cilia are therefore common, for example, serous otitis media, infertility and rarely hydrocephalus. Embryonic node motile cilia are responsible for left-right asymmetry, and 50% of people with PCD have *situs inversus* (Kartagener syndrome) or *situs ambiguous* (Fig. 25.4); associated congenital heart disease is relatively common [34, 54, 55].

Whilst the individual symptoms found in PCD are non-specific, a combination of symptoms indicates a need for prompt referral for PCD diagnostic testing (Table 25.2). Patients are symptomatic from birth or early infancy, yet the mean age of diagnosis is approximately 5 years. Large numbers of patients, particularly adults, have not been investigated and are therefore inappropriately labelled 'idiopathic bronchiectasis'. The variability in diagnostic rates between countries is considerable probably reflecting clinical knowledge amongst physicians as well as geographical access to diagnostic facilities [27, 58].

Recent European and North American Guidelines concur that diagnosis of PCD requires specialist investigation using

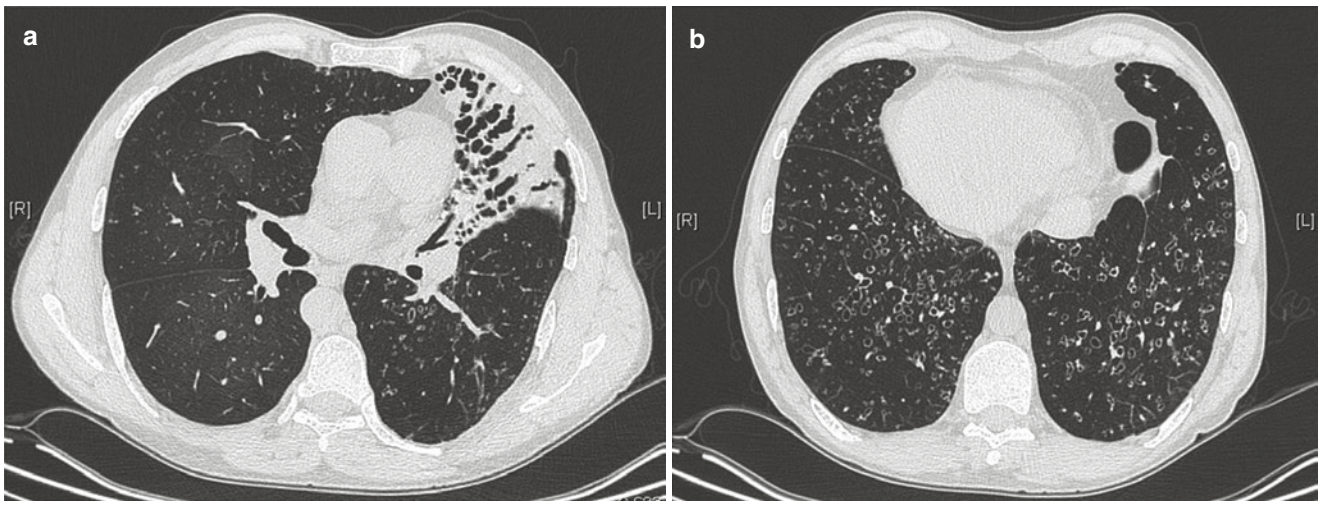


Fig. 25.4 (**a**) HRCT of the chest in a 49-years old man with primary ciliary dyskinesia and Kartagener syndrome at the time of evaluation for lung transplantation, demonstrating severe bronchiectasis and consolidation in the anterior lateral segment of the left lower lobe, and (**b**) bilateral bronchiectasis in the lung bases (associated with centrilobular nodules and tree-in-bud pattern suggestive of bronchiolitis). Note the presence of situs inversus

Table 25.2 Recommendations for who should be referred for PCD diagnostic testing, based on the European Respiratory Society guidelines [52]

Which patients should be referred for diagnostic testing?
• Patients should be tested for PCD if they have several of the following features: – Persistent wet cough; – Situs anomalies; – Congenital cardiac defects; – Persistent rhinitis; – Chronic middle ear disease with or without hearing loss; – Term infants with neonatal upper and lower respiratory symptoms or neonatal intensive care admittance, • Patients with normal situs presenting with other symptoms suggestive of PCD should be referred for diagnostic testing • Siblings of patients should be tested for PCD, particularly if they have symptoms suggestive of PCD • The use of combinations of distinct PCD symptoms and predictive tools (e.g. PICADAR [189]) is recommended

a combination of tests [56, 59]. Extremely low levels of nasal nitric oxide support the diagnosis of PCD [60]. However, some patients with PCD have normal nitric oxide levels, and levels can be low in other conditions including CF. Nasal nitric oxide measurement is therefore used as part of the diagnostic algorithm, but can neither confirm nor refute the diagnosis with certainty [25]. High-speed video microscopy can identify ciliary dysfunction (e.g. static, hyperfrequent, or circling cilia). Both nasal nitric oxide and cilia pattern observed by a high-speed video are highly predictive of PCD, and since analyses are available on the day of testing, counselling and treatment can be based on these provisional results [61]. However, confirmation of diagnosis by transmission electron microscopy or genetic testing is required for a definitive diagnosis [56, 59, 62]. Most, patients with PCD have diagnostic abnormalities of ciliary ultrastructure on transmission electron microscopy, and "hallmark abnormalities" confirm the diagnosis [63]. Electron microscopy used to be considered the 'gold standard' investigation but it is now recognised that approximately 15–20% of patients with PCD have normal ciliary ultrastructure. Similarly, immunofluorescence labelling to detect and localise intraciliary proteins (e.g. DNAH5) has excellent specificity but limited sensitivity to diagnose PCD [64].

Mutations in over 40 genes have been associated with PCD to date (reviewed in [34, 56], and summarised in Fig. 25.5). Bi-allelic pathogenic mutation or hemizygous X-linked mutation in a known PCD gene can confirm a diagnosis, [34, 56, 59] and approximately 70% of PCD cases diagnosed by other methods can be genetically confirmed. The diagnostic sensitivity should continue to improve as new genes are identified. The number and size of the genes results in a large number of variants, many of which are not pathogenic. To avoid false positive diagnoses, it is therefore important to ensure that the reported genotype correlates with phenotypic ciliary ultrastructure and function (Fig. 25.5b) [56]. For example, disease causing genetic variants in *DNAH5* are associated with absence of the outer dynein arms and static cilia. Mutations in *DNAH11* are associated with normal ciliary ultrastructure by transmission electron microscopy, and the cilia have a hyperfrequent vibratory pattern [34].

Whatever the genetic defect, people with PCD generally have severely impaired mucociliary clearance leading to the previously described features. However, only some genes are associated with laterality defects or infertility, and some

genes are associated with more severe pulmonary disease [55, 65, 66].

There is no cure for PCD and pulmonary management, therefore, aims to optimise health, social and psychological well-being whilst preventing the progression of lung damage. There have been few clinical trials in PCD and management is usually empirically based on evidence from CF. Given the differing underlying pathomechanisms and prognoses, evidence for PCD-specific treatments is urgently needed. Lack of evidence for treatment leads to the disparity of care between countries, and likely detrimental effects on exacerbation frequency, future lung function and health care costs [67]. Recent consensus statements provide guidance for the care of patients with PCD [30, 68]. Since patients with PCD also have extra-pulmonary disease, multidisciplinary care is required by a team including pulmonologists, physiotherapists, audiologists, ENT, cardiologists and fertility experts [68, 69]. General care for bronchiectasis is considered later in this chapter.

Other Ciliopathies

Non-motile or 'primary' cilia are found on the surface of many cells in the body. An increasing number of diseases are attributed to abnormal motile or primary ciliary function, collectively known as ciliopathies (http://www.ciliopathyalliance.org). For example, dysfunction of primary cilia in the eye can cause retinitis pigmentosa, and in the kidney can cause autosomal dominant polycystic kidney disease (ADPKD) or nephronophthisis.

OFD1 is an X-linked gene associated with several overlapping ciliopathies including oral-facial-digit syndrome and Joubert syndrome. Respiratory defects appear to be highly variable in males carrying *OFD1* mutations. Where there is a motile cilia defect the condition is termed Simpson–Golabi–Behmel syndrome. These individuals suffer from bronchiectasis, PCD symptoms, overgrowth and can also have abnormally large kidneys, liver and spleen [70]. There are also several case reports of patients with PCD-like disease in association with retinitis pigmentosa caused by X-linked mutations in retinitis pigmentosa GTPase regulator (RPGR).

Autosomal dominant polycystic kidney disease (ADPKD) is an example of renal ciliopathy associated with bronchiectasis. It affects between 1 in 400 and 1 in 1000 people [71]. The disease most commonly manifests in adulthood and is caused by defective ciliary function in renal epithelial cells. Two genes, PKD1 and PKD2 coding for proteins known as polycystins have been implicated in the pathogenesis of ADPKD. In ADPKD, impaired primary cilial sensing results in abnormal intracellular signalling, cell hyperproliferation, and cyst formation [72]. A predisposition to bronchiectasis is recognised, although the mechanism for this is not fully understood [73].

Dysfunction of motile cilia and bronchiectasis are also described in some but not all cases of Bardet Biedl syndrome (BBS). A mutagenic syndrome characterised by retinal degeneration, obesity, polydactyly, cognitive impairment, kidney anomalies and hypogonadism [74, 75]. Bronchiectasis in BBS has been associated with the gene *NPHP10*.

Whereas one non-motile, primary cilium is found per cell there are multiple motile cilia in the respiratory tract. Defects in genes coding for proteins in the pathway responsible for the generation of multiple motile cilia can lead to a condition

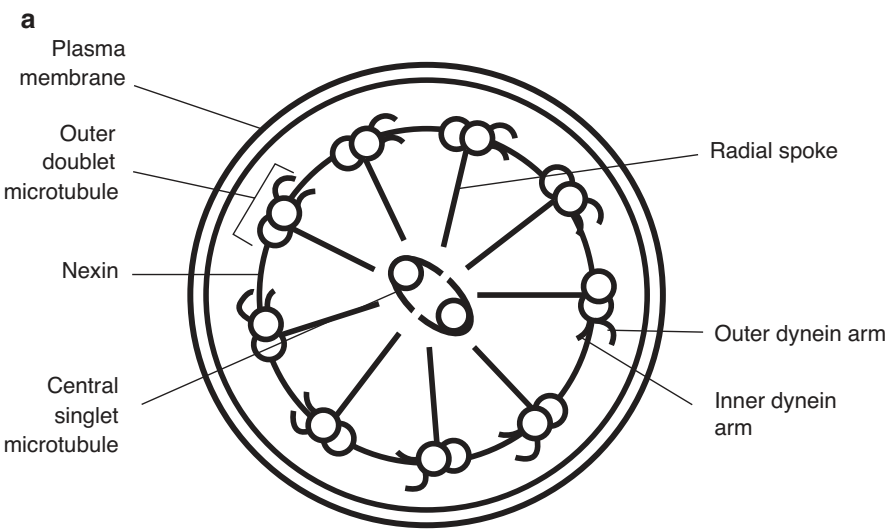


Fig. 25.5 (**a**) Diagram of the transverse section of a respiratory cilium as seen by transmission electron microscopy. Motile cilia have a "9 + 2" arrangement with nine peripheral microtubule doublets surrounding a central pair of single microtubules running the length of the ciliary axoneme. Nexin links and radial spokes maintain the organised structure. Attached to the peripheral microtubules are inner and outer dynein arms. Dynein is a mechanochemical ATPase responsible for generating the force for ciliary beating, hence abnormalities of the dynein arms affect ciliary beating. (**b**) Examples of transmission electron microscopy from patients with PCD. Their genetic cause predicts the ultrastructural findings

b

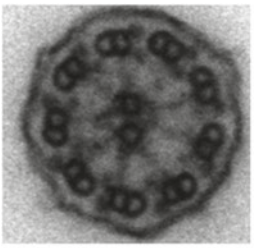
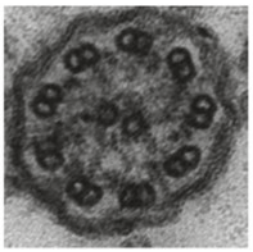
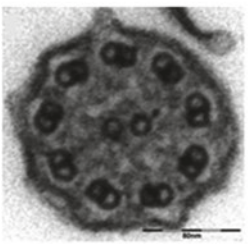
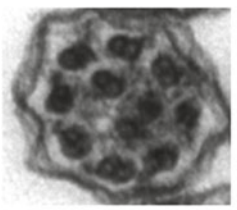
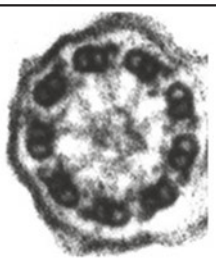
TEM Findings:	Associated genes	
Normal TEM	*C (DRC2)* *DNAH11, GAS2L2, HYDIN, LRRC56, STK36, NEK10, CFAP74*	
ODA defect	*ARMC4 (ODAD2), CCDC103, CCDC114 (ODAD1), CCDC151 (ODAD3), DNAH5, DNAH9, DNAI1, DNAI2, LRCC56, MNS1, NNE8, TTC25 (ODAD4)*	
ODA & IDA defects	C21orf59 (CFAP298), CFAP300 (c11orf70), DNAAF1 (LRRC50), DNAAF2, DNAAF3, DNAAF4 (DYX1C1), DNAAF5 (HEATR2), DNAAF6 (PIH1D3), DNAAF11 (LRRC6) RPGR, SPAG1, DNAAF7 (ZMYND10)	
Microtubule disorganisation & IDA defect OR Isolated microtubular disorganisation defect	*CCDC39, CCDC40 DRC1 (CCDC164), DRC2 (CCDC65), GAS8, TTC12*	
Central complex defect	*DNAJB13, RSPH1, RSPH3, RSPH4A, RSPH9, STK36, SPEF2*	
Reduced number of cilia and absence or mislocalisation of basal bodies within the cytoplasm	CCNO, MCIDAS, FOXJ1, TP73	

Fig. 25.5 (continued)

termed 'reduced generation of multiple motile cilia' (RGMMC). Assessment of airway cells reveals only a few motile cilia per cell, resulting in significant impairment of the mucociliary escalator. Individuals present with PCD like symptoms of rhinitis, neonatal respiratory distress, otitis media, and recurrent chest infections. In CCNO and MCIDAS bronchiectasis usually occurs in childhood and can be severe. Due to the multiple motile cilia of the brain being affected, hydrocephalus is also common [76–78]. In contrast to PCD, RGMMC is not associated with situs inversus since the cilia in the embryonic node are not affected. Recently defects in one of the master regulators of ciliogenesis FOXJ1 have also been described to cause bronchiectasis in an autosomal dominant inheritance pattern.

Primary Immunodeficiency Disorders

Primary immunodeficiency disorders (PID) account for a significant proportion of cases of bronchiectasis in developed countries. Series suggest as many as 7% of adults [79] and 20% of paediatric cases in higher-income countries may be attributable to PID [80]. PID includes a heterogeneous group of disorders of immune development or function affecting innate or adaptive immunity. Common variable immunodeficiency (CVID), X-linked agammaglobulinemia (XLA) and chronic granulomatous disease (CGD) are the most common immunodeficiencies found in association with bronchiectasis [81].

Common Variable Immunodeficiency

Common variable immunodeficiency (CVID) has an estimated prevalence of 1 per 25–50,000 population and is the commonest PID. Presentation is usually in young adulthood but diagnosis may be delayed [82]. Patients affected by CVID display a defective antibody response to protein and polysaccharide antigens and low levels of immunoglobulin (Ig) G, IgA and/or IgM. Affected individuals are at risk of recurrent bacterial infection, autoimmune disease and malignancy [83]. Clinical features vary, perhaps reflecting heterogeneity of underlying molecular defects or disease-modifying factors. To date, a monogenic cause has been identified in only 2–10% of cases [84]. Many disease genes have been identified in CVID, including those encoding receptors, ligands and intracellular signalling molecules.

Possibly as a consequence of delayed diagnosis, the risk of bronchiectasis is greater in patients with CVID than in those with X-linked agammaglobulinemia (XLA) and may approach 70% [85]. The additional immune dysregulation associated with CVID might also contribute to this high rate of bronchiectasis. One prospective study of CVID and XLA patients on immunoglobulin replacement therapy found older age and lower IgA levels to be risk factors for bronchiectasis in CVID, in contrast to XLA where the incidence of pneumonia was the major risk factor [86].

X-Linked Agammaglobulinemia

X-linked agammaglobulinemia (XLA) accounts for 85% of congenital agammaglobulinemia and is estimated to affect 1–2 per million people in the UK [87, 88]. It is characterised by an almost complete absence of circulating B lymphocytes and of all immunoglobulin [89]. Mutations of the Bruton tyrosine kinase (BTK) gene cause an incomplete block of B cell development at the pre-B cell stage [87]. Affected individuals are susceptible to infection by encapsulated bacteria and *Mycoplasma*. Autosomal recessive forms of agammaglobulinemia have been identified that are caused by mutations in genes that encode for other components of the pre-B cell receptor and its signalling pathway [90]. Pulmonary infections can occur shortly after birth but generally become noticeable beyond 6 months of age following the disappearance of maternal IgG. The most common age for diagnosis is under a year but presentations as late as 5 years have been known [91, 92]. Whilst the risk of developing significant lung disease increases over time, there is some evidence that severity can be reduced by early detection and treatment [93].

Chronic Granulomatous Disease and Other Disorders of Neutrophil Function

Chronic granulomatous disease (CGD) results from impaired function of NADPH oxidase. This enzyme is required for the effective functioning of the phagocytic respiratory burst and for superoxide production. Impaired NADPH oxidase is generally transmitted by X-linked inheritance but autosomal recessive variants are also recognised [94]. Mean age at presentation in autosomal recessive disease is 10 years, slightly later than X-linked disease where the mean is 5 years, suggestive of a more severe phenotype [95]. Patients are vulnerable to recurrent and severe bacterial and fungal infections, including *Staphylococcus aureus, Burkholderia cepacia, Serratia marcescens, Nocardia* and *Aspergillus* spp.

A similar pattern of recurrent pneumonia and lung aspergillosis may also be observed in patients with severe congenital neutropenia [96]. Most commonly this disorder occurs as a consequence of mutations in the gene encoding for neutrophil elastase [97] but it can also be attributable to mutations affecting a mitochondrial protein thought to be involved in protecting myeloid cells from apoptosis [98] or an endosomal protein involved in intracellular signalling [99]. The characteristic feature of this disease is low levels of circulating neutrophils and hence vulnerability to bacterial and fungal pathogens.

Other Immunodeficiency Diseases Associated with Bronchiectasis

It is currently difficult to identify many causes of innate immunodeficiency, and it is likely that as new defects are discovered, many individuals currently described as suffering from 'idiopathic bronchiectasis' will be found to have an

underlying disorder, some involving defects of innate immunity. Rare instances of bronchiectasis in association with deficiency of C2, mannose-binding lectin or L-ficolin have been reported [100]. Deficiencies affecting the complement cascade are also known to affect the severity of bronchiectatic disease in CVID [101] and in CF [102].

Ataxia telangiectasia is an autosomal recessive multisystem disorder resulting from mutation of the Ataxia telangiectasia mutated (ATM) gene, characterised by the development of telangiectasia and cerebellar ataxia. It affects 1 in 150,000 people in Europe [103]. It is the most common of the DNA repair disorders and is associated with chromosomal instability and cellular radiosensitivity, rendering sufferers susceptible to cancer and to infection. The ATM gene is involved in antibody class switch recombination and defects in this process may underlie the increased susceptibility of ataxia telangiectasia patients to bacterial infections [104]. The most common humoral immunological defects are diminished or absent serum IgA and IgG2, and impaired antibody responses to vaccines [105]. Protection against immune deficiency can be conferred by small amounts of preserved ATM function; mutations resulting in complete loss of ATM kinase activity have been shown to be more likely to be associated with recurrent respiratory infections than those associated with residual kinase activity [106]. Ataxia telangiectasia leads to thymic hypoplasia and variable T cell deficiency. It is likely that recurrent aspiration due to swallowing impairment also contributes to respiratory disease [107]. Bronchiectasis is reported in 10–50% of patients, becoming established by late childhood. The overwhelming bronchopulmonary disease can be fatal and the median survival is 19 years [108].

Bronchiectasis, alongside severe types of pneumonia, empyemas and pneumatoceles, is common in children with hyper-IgE or Job syndrome, which is associated with a wide variety of lymphocyte and humoral function defects as well as very high levels of serum IgE [109]. Job syndrome is inherited in an autosomal dominant pattern; most often due to a loss of function mutation of the signal transducer and activator of transcription 3 or STAT3 gene, [110] although in some cases the responsible mutation is unknown. STAT3 is a transcription factor that influences the expression of a variety of genes and plays a key role in many cellular processes such as growth and apoptosis. An autosomal recessive form of hyper IgE syndrome is recognised, this is less common than the autosomal dominant form and less likely to have respiratory complications. Bronchiectasis is also seen in association with Shwachman-Bodian-Diamond syndrome, caused by deficiency in DOCK8 which is involved in actin polymerisation and cytoskeletal rearrangement. This rare autosomal recessive disorder is characterised by exocrine pancreatic insufficiency, bone marrow dysfunction, leukemia predisposition, and skeletal abnormalities. In most cases, bone marrow dysfunction results in neutropenia in the majority of patients and may be accompanied by defects in neutrophil mobility, migration, and chemotaxis. Where neutropenia is less prominent a clinical phenotype similar to that of CVID can arise [111].

Other Genetic Disorders Predisposing to Bronchiectasis

Although the majority of genetic causes of bronchiectasis are related to defects of mucociliary clearance or PID, congenital abnormalities affecting the structure of the bronchial wall can predispose to bronchiectasis. For example, Marfan syndrome is a rare hereditary disorder characterised by skeletal, cardiovascular and ocular abnormalities. It follows an autosomal dominant inheritance with a variable expression which results in a defect in Type 1 collagen. Pulmonary abnormalities occur in approximately 10% of patients, the commonest being spontaneous pneumothorax and emphysema. Rarely cases of bronchiectasis have been described in adults and children with Marfan syndrome.

Epithelial sodium channels (ENaC) are important in the airways for regulating the osmolarity of periciliary fluid, and maintaining the periciliary fluid volume necessary for mucociliary clearance. The role of mutations encoding ENaC proteins (*SCNN1A, SCNN1B, SCNN1G*) in bronchiectasis is currently unclear. It is proposed that polymorphisms in ENaC genes, as well as ENaC mutations *in trans* with CFTR mutations might be risk factors for bronchiectasis, but it is not invariably associated with disease [112, 113].

Alpha-1 antitrypsin (AAT) deficiency is an autosomal co-dominant disorder that is caused by SERPINA1 mutations and leads to emphysema. Bronchiectasis has been reported, most frequently, in association with severe PiZZ genotypes, this is largely seen in adulthood. A study of 74 patients with severe AAT deficiency found high-resolution CT scan evidence of bronchiectasis in 70 subjects, this was judged clinically significant in 20 [114]. AAT deficiency alleles are over-represented in patients with bronchiectasis and asthma combined, suggesting that bronchiectasis may occur as a consequence of airway obstruction, in turn reducing airway clearance [115]. In individuals with humoral immunodeficiency lower AAT levels have been found in those with bronchiectasis, suggesting that where infection causes persistently elevated neutrophil elastase activity higher levels of AAT might be necessary to protect the lower airways [116].

Several autoimmune diseases with predominant symptoms outside the airways are associated with bronchiectasis, most notably rheumatoid arthritis and inflammatory bowel disease (IBD). Whilst causative genes have not been identified for these conditions, associated genetic risk loci have been reported in IBD and variations in human leukocyte antigen (HLA) genes, especially the HLA-DRB1 gene, are a risk factor for rheumatoid arthritis.

Young syndrome, is a poorly defined clinical diagnosis characterised by bronchiectasis, chronic sinusitis and impaired fertility. The cause of Young syndrome is not known, but it has been suggested to have an unresolved genetic cause, whilst others speculate that it could be due to mercury exposure. Young's syndrome has overlapping symptomatology, with PCD and CF, and since there is little to support the existence of Young syndrome as an entity in its own right, perhaps most patients in fact have one of these conditions.

The cause of bronchiectasis in some syndromes is likely to be multifactorial. For example, Down syndrome may be associated with immunodeficiency, uncoordinated swallowing, gastro-oesophageal reflux and tracheomalacia; all of these may contribute to a predisposition to bronchiectasis.

Idiopathic Bronchiectasis

ERS guidelines for the management of bronchiectasis suggest a minimal set of aetiological investigations upon diagnosis [1]. These include differential blood count, serum immunoglobulins (total IgG, IgA, IgM) and testing for allergic bronchopulmonary aspergillosis (ABPA). Additional tests are recommended where specific clinical features are present or in patients with severe or rapidly progressive disease. Despite thorough investigation, an underlying cause cannot be found in at least 30% of patients with bronchiectasis; these cases are referred to as idiopathic [18, 79–81, 117]. A typical patient with the idiopathic disease is a non-smoking, post-menopausal female, although any age and both genders can be affected. Increasingly in the USA individuals with the idiopathic disease have chronic infection with non-tuberculous mycobacteria (NTM).

Some cases of idiopathic bronchiectasis are familial and it is likely that a number of patients have unrecognised impairment of the innate immune system, or have one of the increasingly recognised *CFTR* mutations associated with milder CF phenotypes associated with isolated lung disease. *CFTR* mutations have been found to be overrepresented in individuals identified as suffering from idiopathic bronchiectasis who do not have a full CF phenotype. The 5 T *CFTR* mutation in particular has been found at high frequency in this patient group. Recent data suggest that the 5 T polythymidine tract sequence of intron 8 on specific haplotype backgrounds (TG12 and M470V) may underlie low levels of full-length functional CFTR protein and cause CF-like lung disease [118]. Furthermore a significantly higher number of patients with pulmonary NTM have been found to have low-frequency, protein-affecting variants in immune, CFTR, cilia, and connective tissue genes [119].

The idiopathic disease is often not as severe as CF or PCD. A comparison of data in the European bronchiectasis registry (EMBARC) between individuals with the idiopathic disease compared to PCD and immune deficiency showed that individuals with bronchiectasis due to PCD had increased disease severity, measured by a bronchiectasis severity index 7.5 (±4.9), when compared to age- and gender-matched cohorts with idiopathic disease 5.7 (±5.2) or immune deficiency 5.9 (±4.7). Analysis of components contributing to the bronchiectasis severity index score revealed an average 10% reduction in FEV_1% in PCD and an increased incidence of *Pseudomonas* isolation from sputum in PCD patients (46%) [120].

Diagnosis of Bronchiectasis

Whilst recent evidence-based guidelines recommend approaches to identify and investigate adults for bronchiectasis, paediatric practice is based on expert opinion and personal practice [16, 121, 122]. The criteria for diagnosing bronchiectasis, based on the guidelines and opinion documents are summarised in Box 25.1. Ideally, patients at risk of bronchiectasis should be identified before irreversible damage develops. For example, it is widely accepted that newborn screening for CF reduces long-term pulmonary morbidity because of the early introduction of airway clearance physiotherapy, treatment of infections and pancreatic enzyme therapy. Similarly, in PCD, observational data suggest that lung function decline is stabilised and can even be reversed following diagnosis and instigation of appropriate pulmonary management. We expect that onset of bronchiectasis might also be delayed. Moreover, patients and their families believe that an early diagnosis is beneficial [58].

Guidelines suggest that bronchiectasis should be considered in patients with persistent production of mucopurulent sputum, particularly if they have risk factors [1, 121]. The investigation should be considered in patients with rheumatoid arthritis or inflammatory bowel disease if they have a chronic productive cough; and in patients with COPD who are having frequent exacerbations and a previous sputum culture for *Pseudomonas aeruginosa* [121]. It should be considered in otherwise healthy adults with a cough that persists for more than 8 weeks, particularly if the cough is productive of sputum [121]. Children with a chronic wet cough failing to respond to 4 weeks of oral antibiotics, or recurrent episodes of protracted bacterial bronchitis are at high risk for bronchiectasis [13, 16]. The diagnosis should also be considered in patients with positive sputum culture for organisms such as *Pseudomonas aeruginosa,* people with persistent chest signs, haemoptysis or finger clubbing [16, 121].

A baseline chest x-ray should be performed, and an HRCT should then be used to confirm the diagnosis [121]. Dilated airways with thickened walls are sometimes visible on chest X-ray as parallel 'tram tracks' or 'ring shadows', and fluid-filled bronchi may be visible as 'gloved-finger'

shadows. Situs inversus might direct investigations for PCD. However, a chest X-ray is not sensitive to detect the structural changes associated with bronchiectasis. HRCT has very good sensitivity and specificity to detect bronchiectasis not identified by chest X-ray (Fig. 25.4). Characteristically bronchiectasis is defined by bronchial dilation seen on HRCT as one or more of the following: broncho-arterial ratio >1, lack of tapering, airway visibility within 1 cm of the costal pleural surface or touching mediastinal pleura [121]. The following are also associated with bronchiectasis: bronchial wall thickening, mucus impaction and air trapping on an expiratory scan [123]. HRCT should not be performed during acute respiratory exacerbations as bronchial dilation is difficult to assess in the presence of consolidated lung, whilst pulmonary collapse can cause misleading 'traction bronchiectasis' by pulling on neighbouring bronchi [124]. In conditions without biological markers to identify which patients will go on to develop significant lung disease repeat CT assessments might be required. Caution is advised particularly in patients with PID who have genetic defects affecting DNA recombination and DNA repair. Lung MRI may become a possible alternative to CT scanning [125].

In addition to imaging, further tests are important to confirm the disease severity, and to identify co-morbidities or underlying aetiology. Lower airway samples should be sent from all patients with bronchiectasis for routine and mycobacterial culture [16, 121]. Measures of lung function are non-specific and non-sensitive in bronchiectasis, but contribute to the assessment of disease severity. FEV_1 is often normal in early disease although a reduced FEV_1 in the presence of normal functional vital capacity is common. The lung clearance index is a measure that has been suggested to be a good monitor of disease in CF [126] and is being evaluated as an early marker of lung disease in other bronchiectatic diseases such as PCD [127–130].

Fibreoptic bronchoscopy can be considered to assess airway structure and calibre and exclude pathology such as severe tracheomalacia, bronchomalacia or tracheal bronchi which may contribute to bronchiectatic change. The bronchoscopic examination can also provide lavage fluid for evidence of chronic aspiration measured by pepsin, amylase or fat-laden macrophages, and for culture and microscopy.

Once a diagnosis of bronchiectasis has been made, an investigation of the underlying cause should be sought. The clinical history should direct investigations which will usually include investigation for CF, PCD and PID [1, 121].

Management of Patients with Bronchiectasis

Several guidelines have recently been published for the management of bronchiectasis. For CF, guidelines include evidence-based documents from NICE [131], the CF Trust and CF Foundation. There is the paucity of evidence for treating other causes of bronchiectasis. At best, recommendations for non-CF-bronchiectasis and PCD are conditional and based on the low or very low quality of evidence, but are mostly based on the consensus of experts [1, 6, 30, 68, 69, 121]. No treatments have been licenced worldwide for the treatment of non-CF bronchiectasis. The underlying aetiology may impact the treatment plan; in children, it is estimated that identification of a specific cause of bronchiectasis prompts a management change in over 50% of cases [132].

The overall aim is to delay progression of bronchiectasis, and maximise lung function, exercise tolerance, quality of life and nutrition. A multifaceted approach is needed to treat infections and inflammation, whilst promoting mucus clearance (Fig. 25.1).

Pulmonary exacerbations are a cause of significant morbidity and need to be prevented, recognised and treated in an attempt to prevent further lung damage caused by the infection and inflammation (Fig. 25.1) [123, 133]. Epidemiological, clinical and laboratory evidence suggest that bacterial and viral infections are major causes of pulmonary exacerbations; environmental pollution might also contribute. Some patients do not recover the accompanying reduction in lung function despite aggressive treatment of the episode with antibiotics and physiotherapy, and in CF patients with higher exacerbation rates have an increased rate of decline in lung function [134–136]. Pulmonary exacerbations are related to neutrophilic inflammation, and neutrophil serine proteases, including neutrophil elastase, are increased in the sputum of patients at baseline and increase further during exacerbations. Brensocatib, an inhibitor of neutrophil serine proteases, reduced exacerbations in a 24 week phase 2 trial [137].

Management includes promoting clearance of secretions and the use of antibiotic therapies both to prevent and to treat the recurrent infection. In addition to routine vaccination schedules, patients should receive pneumococcal and influenza vaccinations and avoid exposure to tobacco smoke. Some CVID patients have been shown to raise antibodies in response to the influenza antigens but XLA patients do not. Family members of people with PID should also be vaccinated [138].

As with many Orphan Diseases, evidence for efficacy of treatments (e.g. PCD) is often extrapolated from studies of more common disorders such as CF, and may not be appropriate for other forms of bronchiectasis [30, 67]. Indeed, a number of trials have confirmed that efficacious drugs for CF do not necessarily benefit those with non-CF bronchiectasis [6, 139–141]. Randomised controlled trials (RCTs) are urgently needed for individual diseases, which by the necessity for rare diseases will be multicentre and likely require international collaboration. The results of the only multinational RCT for PCD recently confirmed that azithromycin prophylaxis is efficacious and safe to reduce pulmonary exac-

erbations [142, 143]. An important step in designing the RCTs includes careful consideration of disease-appropriate endpoints which might also differ for bronchiectasis of different causes. Exacerbation frequency or time to exacerbation is a clinically important endpoint, and consensus definitions are now in place for CF, PCD and non-CF bronchiectasis [123, 133, 144]. Quality of life instruments are also in place, but responsiveness to treatment still needs to be established for QOL-B and QOL-PCD [145–148]. There is an urgent need for disease-specific endpoints for trials in bronchiectasis.

Airway Clearance Therapy (ACT)

A variety of physiotherapy techniques are available to assist airway clearance, including chest percussion, postural drainage, breathing exercises and mechanical interventions such as cough-assist and positive expiratory pressure (PEP) adjuncts and oscillatory-PEP [149, 150]. The aims of ACT include mobilising and aiding clearance of secretions to optimise sputum expectoration, relieve symptoms, and improve well-being. Although of proven benefit in CF, there are few studies demonstrating the efficacy of physiotherapy in non-CF bronchiectasis that can guide frequency or choice of therapy. Generally, it is agreed that all patients should be taught and encouraged to conduct regular ACT [1, 30, 68, 69, 121, 149–151].

The choice of technique will depend in part on the age of the patient, their clinical state, and patient acceptability. Often a combination of techniques is employed. A commonly used ACT, particularly in adults, is the active cycle of breathing technique; this is based upon deep breaths followed by 'huffs' and 'coughs' to aid sputum clearance interspersed with periods of relaxed controlled breathing. The active cycle of breathing can be combined with postural drainage and manual techniques. Positive end expiratory pressure (PEP) techniques using oscillating PEP devices, such as a Flutter valve or Acapella, can be combined with postural drainage or forced expiration techniques. A further option is the technique of autogenic drainage in which a sequence of controlled breaths at low then progressively higher lung volumes is used to collect and expectorate sputum.

Nebulised treatments have been shown to assist mucus clearance in patients with CF, but efficacy differs in patients with bronchiectasis or other causes. For example, recombinant human DNase (rhDNase) lyses neutrophil DNA which originates mainly from decaying neutrophils at sites of airway inflammation. There is good evidence for its use in CF [152]. However, a large study of patients with non-CF bronchiectasis showed a faster decline in FEV_1 and more frequent exacerbations in patients who received rhDNase in comparison to those treated with placebo [153]. rhDNase is therefore not generally recommended outside CF [1, 30, 121].

Agents such as hypertonic saline and mannitol are often used to assist with mucus clearance as an adjunct to airway clearance therapy. Nebulised hypertonic saline and mannitol often benefit patients with CF, particularly older children and adults when used as regular therapy, or during exacerbations [154, 155]. However, the benefits for bronchiectasis of other causes are less clear, perhaps due to the heterogeneity of the studies and populations [1, 139, 156–159].

Associations between physical exercise and lung function in CF are inconsistent. However, the benefits of exercise are multifactorial and exercise is generally considered an important component of management with the aim to improve exercise tolerance and quality of life. Exercise programmes have been beneficial in CF inpatient, outpatient and community settings. Moreover, exercise programmes impact exercise capacity in adults with non-CF bronchiectasis, with benefits achieved in 6–8 weeks [1]. Exercise is therefore advocated for all patients with bronchiectasis [1, 30, 68, 69].

Management of Infections

Antibiotic therapy can be prescribed either as long-term prophylaxis or in response to infections.

Guidelines recommend offering long-term antibiotics to adults with bronchiectasis who have three or more exacerbations per year [1, 121]. Long-term macrolide treatment, for example with azithromycin, is beneficial to reduce the number of pulmonary exacerbations [143, 160–162]. Macrolides have anti-inflammatory effects beyond their anti-bacterial actions which may be useful in the context of bronchiectasis [163]. In patients with chronic *P. aeruginosa* infection, long-term inhaled antibiotics e.g. nebulised colistin, is recommended [1, 121]. There is a concern that long-term use of antibiotics may accelerate the development of antibiotic resistance; regular surveillance of sputum by culture and sensitivity is essential.

Pulmonary exacerbations require prompt treatment with antibiotics. Antibiotic choice should reflect results of sputum culture and sensitivities when available, and empirical antibiotics can be started whilst awaiting microbiology results [1, 68, 69, 121]. Sputum culture is possible only in adults and older children who are able to expectorate. In younger children, cough swabs or nasopharyngeal aspirates can be taken for bacterial culture, although upper airway specimens are inferior and broncho-alveolar lavage specimens may be required. In general, antibiotic courses for 14 days are prescribed, but the duration should be individualised depending on the patient's condition. Intravenous antibiotics are sometimes required when patients are unwell or do not respond to oral therapy, particularly following a second course..

Based on the poor clinical outcomes of patients with *P. aeruginosa* infection, eradication therapy is recom-

mended for patients with CF and new growth of the pathogen [164]. Eradication is similarly recommended for new isolates in non-CF cases, although the evidence base is low [1, 69, 123].

Anti-Inflammatory Management

As already discussed, the anti-inflammatory effects of macrolide therapy may be beneficial in patients with bronchiectasis, but the risks of antibiotic resistance and other side-effects need consideration. There is no evidence for the use of inhaled corticosteroids in patients with bronchiectasis, except where patients have co-existing asthma or COPD [1, 69, 121]. Similarly, there is insufficient evidence to recommend statins as an anti-inflammatory agent for bronchiectasis [1, 121]. A number of approaches to target neutrophil-driven inflammation are under investigation (e.g. neutrophil elastase or cathepsin C inhibition).

Immune Therapy

Efforts to reconstitute the immune system can be effective in PID. Recombinant IFNγ therapy, for example, is effective in reducing the number of severe infections in CGD [165] and recombinant granulocyte stimulating factor can be used in severe congenital neutropenia [96]. Systemically administered AAT augmentation therapy can be used to treat the imbalance between elastases and inhibitors within the lung and, in the future, inhaled AAT might be possible. This would reduce costs since less protein would be necessary to target the lungs directly [166].

Patients with CVID benefit from immunoglobulin substitution therapy [167]. Subcutaneous infusions are better tolerated by patients than intravenous infusions and may achieve more stable trough levels with a lower risk of adverse reactions [168]. Doses may need to be increased in the presence of active lung disease as this increases immunoglobulin turnover [169]. Subcutaneous immunoglobulin infusion has been demonstrated to reduce the frequency of exacerbations and to slow bronchiectasis progression [170]. However, lung involvement can progress despite immunoglobulin replacement. Risks of viral contamination are low, although a finite risk exists, particularly of prion-related disease. Previous guidelines recommended a trough IgG level of at least 5 g/L, however in more recent studies higher and individualised levels have been recommended.

Newborn screening for primary immune deficiencies might be possible to allow treatment before bronchiectasis develops. One approach would be based on the detection of kappa-deleting recombination excision circles (KRECs). KRECs are produced during immunoglobulin gene rearrangement throughout B-lymphocyte maturation, patients with B-lymphocyte defects will have low levels of or absent KRECs regardless of the exact aetiology of the defect [171].

The only curative treatment at present for many immune deficiencies is matched stem cell transplantation; patients must receive antimicrobial cover, particularly for the organisms they are known to be colonised with for the duration of immunosuppression related to this procedure [172, 173]. Since the majority of affected individuals will not have a healthy HLA-matched sibling donor, techniques including T-cell depletion were developed to facilitate donations from unrelated donors or HLA-mismatched parental donations. Low-toxicity pre-conditioning regimens using targeted busulfan doses or treosulfan in combination with fludarabine have demonstrated excellent engraftment and survival [174].

Gene therapy provides an alternative strategy with which to cure or alleviate select inherited diseases. A corrected copy of a gene is transferred to the somatic cells of affected individuals. Correction of genetic defects is limited to either terminally differentiated, long-lived post-mitotic cells or easily accessible stem cells. To treat haematopoietic system stem cells, implicated in primary immunodeficiency, a viral vector capable of integrating within the host genome is necessary for gene delivery. Barriers to the success of this treatment strategy are: (1) low protein expression due to poor gene transfer [175], (2) risk of insertional mutagenesis, [176] and (3) immunogenicity of the vector or transgene product [177]. Nevertheless gene-modified autologous bone marrow transplantation represents a promising treatment, free from the immunological complications associated with transplantation from an HLA-mismatched donor.

In order to replenish the peripheral pool of immune cells with cells containing the transduced gene, the transduced cells must have a selective advantage. For example in adenosine deaminase (ADA) deficiency (a severe combined immunodeficiency associated with pneumocystis and other bacterial, viral and fungal respiratory infection although not commonly bronchiectasis) genetically modified T lymphocyte precursors are able to metabolise toxic purine products and have a selective advantage over unmodified lymphocytes [178]. Similarly, rare spontaneous partial phenotypic correction of severe T cell immunodeficiencies has been observed in which clonal expansion of one or several T cell precursors carrying a wild-type sequence of the disease-causing gene can differentiate into mature, functional T cells capable of supporting normal immunity [179]. For haematopoietic disorders in which wild-type gene expression is essential to the function of terminally differentiated cells, chances of success can be improved by mild myelosuppressive treatment prior to gene-therapy which leads to a higher proportion of transduced progenitor cells due to better engraftment.

Following the success of gene therapy treatments for severe combined immune deficiency these techniques have been applied to a number of monogenic immune deficiencies, including X-linked CGD [180]. Initially trials using

gamma-retroviruses were complicated by clonal expansion of myeloid cells, thought to be due to insertions near cellular proto-oncogenes. More recently gene delivery vectors have been developed, derived from the lentivirus class of retroviruses. These can be produced with enhancer elements that "self-inactivate" reducing the chances of turning on cellular genes near their integration sites. Conditions such as CVID which are caused by one of several genes, present a challenge for gene therapy. Correcting each gene defect will require a separate development process. Moreover, gene therapy will need to be very effective and safe before it is considered preferable to current best medical therapy.

For genes involved in processes such as cell activation and intracellular signalling it is important to preserve normal expression patterns in addition to restoring function. An alternative solution for genes such as BTK, involved in XLA, is to repair the disease-causing gene in its native chromosomal site. Gene editing relies on systems such as homing endonucleases, zinc finger nucleases, Transcription activator-like effector nucleases (TALENs), Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) and CRISPR associated protein 9 (CRISPR/Cas9). A repair in the target DNA is then directed by providing single or double-stranded DNA copies of the target sequence. Recent pre-clinical work using CRISPR/Cas9 has demonstrated successful repair of defects in stem cells from patients with CGD [181]. New conditioning regimens using monoclonal antibodies to haemopoietic stem cells proteins might increase safety and permit use of gene editing in milder immune deficiencies such as XLA.

Surgery

Surgical intervention is generally not recommended, although it can be considered in patients with localised non-functioning lung segments, where it is anticipated that lobectomy may prevent infection of adjacent healthy areas [1]. Close collaboration between the surgeon and pulmonologist is essential throughout the work-up and peri-operative period, with particular attention to pre-operative nutrition and pulmonary rehabilitation.

Transplantation should be considered in patients with untreatable end-stage respiratory failure. Particular planning is needed for PCD patients with situs anomalies.

Novel Therapies for Managing Cystic Fibrosis

Over recent years ground-breaking small molecule therapies that improve and can normalise CFTR function have been developed and come into widespread clinical use in CF patients. The first of these, a 'potentiator' called ivacaftor causes the CFTR channel to be 'wedged open' and was demonstrated to cause significant improvements in FEV_1 (10.6%) and body mass index, alongside normalising of sweat chloride levels in patients over 12 years with p.Gly551Asp mutations (a class 3 'gating' mutation; Fig. 25.3) [182]. Further studies demonstrated similar improvements in younger children, and it is licensed in Europe for people with susceptible mutations from 6 months of age [183–185]. However ivacaftor had mixed results with class 4 mutations, ion transport defects (Fig. 25.3), with improvements in FEV_1 seen in adults but not in children and did not work in class 2 mutations, protein folding defects that include far the most common mutation p.Phe508del [186].

Therefore, in order to impact on CFTR function in the majority of CF patients with class 2 mutations, the same manufacturer developed 'corrector' molecules that act to correct the abnormal folding of the CFTR protein, hence allowing it to be transported successfully to the apical surface of the cell. The first 'corrector' developed was lumacaftor, which was combined with ivacaftor a marketed drug. However, whilst a large RCT showed reasonable improvements in exacerbation rates and severity, the improvement of FEV_1 was small, (2.6–4.0%) in homozygous p.Phe508del patients over 12 years of age [187]. Subsequent trials in younger patients have demonstrated similar modest benefits [188]. The manufacturer has since released a further combination therapy, swapping lumacaftor for an alternative 'corrector' tezacaftor. Whilst this drug seems to have a similar effect on lung function to lumacaftor/ivacaftor it has an advantageous side effect profile [189, 190].

However, most recently, data on a triple combination therapy has been published. This combines the two medicines tezacaftor/ivacaftor) with a second 'corrector', elexacaftor. This triple therapy led to good improvements in FEV_1 in p.Phe508del. homozygotes and heterozygotes (10–11% and 13.8% respectively, over and above the beneficial effect tezacaftor/ivacaftor), [191, 192] and may be a game-changer for the management of the majority of patients with CF.

However, whilst these medicines have a dramatic effect on CFTR function they come at a very high cost. All the medicines described here have been marketed at well over £100,000 per patient per year, with the list price for triple therapy at over $300,000, making them unaffordable to many who would benefit most from them. The price tag for the new triple therapy is, as yet, unknown.

It is also important to mention the efforts made to pursue an alternative treatment strategy to correct CFTR dysfunction. This was led by the CF Gene Therapy Consortium in the UK, which developed a nebulised gene therapy. This had the potential advantage of correcting all classes of CF mutations and was assessed in a phase 2b RCT. However, whilst establishing the proof of principle of this complex science, the actual clinical improvements seen in CF patients were small, with only a 3.7% difference in FEV_1 between the treatment and placebo arms [193].

Vignette

A patient was referred for PCD diagnostic testing at 4 years of age (see PCD details above). She had been born at term and was noted to have nasal congestion and tachypnoea from shortly after birth, but did not require medical intervention. Throughout infancy, she had recurrent chest infections and a daily wet productive cough. She also had glue ear treated with grommets which resulted in otorrhea and no improvement in hearing. She had normal cardiac *situs* and her parents are white Caucasian and non-consanguineous. Her sister has a glue ear but there is otherwise no family history of note.

Using high-speed video analysis it was impossible to obtain an accurate beat frequency on two separate occasions. The cilia demonstrated stiff vibrating movements rather than the usual coordinated sweeping motion. Electron microscopy demonstrated normal ultrastructure (Fig. 25.5) with the normal arrangement of microtubules radial spokes and outer dynein arms. In view of the normal transmission electron microscopy, genetic analysis was undertaken, confirming mutations in *DNAH11* gene; this gene had previously been reported as a cause of PCD with normal ciliary ultrastructure [194].

Since diagnosis, she has commenced twice daily airways clearance (physiotherapy) and is aware of the need for prompt treatment of any intercurrent infection. In addition to the usual childhood vaccinations, she has influenza cover annually. She is reviewed by a multidisciplinary team that includes a respiratory pediatrician, ENT consultant, physiotherapist and respiratory nurse 4 monthly. She also has audiology reviews annually to monitor the need for hearing aids.

Learning Points from the Case

- PCD often presents in the neonatal period but diagnosis is often delayed until later childhood [27].
- Diagnostic evaluation is often complicated and requires specialist expertise [56, 195].
- Although 50% of patients have *situs inversus*, the diagnosis should be suspected in patients with *situs solitus* if other symptoms are present.
- Management of non-pulmonary disease necessitates the involvement of a multidisciplinary team, which may include ENT, audiology, cardiology, and fertility specialists.
- Consensus statements are available to provide guidelines for management of PCD [30, 68, 69]. However evidence is extrapolated from more prevalent diseases, mostly CF; this is almost certainly inappropriate.

Summary

It is likely that the true incidence of bronchiectasis with a genetic basis is underestimated. As our understanding of innate immunity, cilia biology and ion-transport disorders are better characterised, the aetiology of many cases currently labeled as ‘idiopathic’ will become better understood. As with other Orphan Diseases, the diagnosis and management of patients with bronchiectasis are largely determined by local interests and provision, and many patients find it difficult to access appropriate care. Most doctors have little experience with rarer causes of bronchiectasis and will base management on evidence from CF. Indeed, the evidence base for managing non-CF bronchiectasis is poor. The CF community has made substantial advances in recent decades, resulting in improved morbidity and mortality. Whilst these advances have been beneficial to the care of patients with non-CF bronchiectasis, disease-specific treatments are urgently needed.

Box 25.1

Diagnostic criteria for bronchiectasis in adults and children (adapted from British Thoracic Society guidelines for adults 2019 [121] and an expert statement for children [16])

Bronchiectasis is defined as thin-section CT scan showing one or more of the following:
- Broncho-arterial ratio > 1
- Lack of bronchial tapering
- Airways visible within the lung periphery

Other CT features commonly associated with bronchiectasis include:
- Bronchial wall thickening
- Mucus impaction
- Mosaic perfusion/air trapping on expiratory CT

Following a diagnosis of bronchiectasis, investigate the underlying cause. Consider:
- Cystic fibrosis
- Primary ciliary dyskinesia
- Immune deficiency
- Rheumatoid arthritis
- Chronic obstructive pulmonary disease (COPD)
- Inflammatory bowel disease

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Pulmonary Vascular Manifestations of Hereditary Hemorrhagic Telangiectasia

26

Els M. de Gussem and Marie E. Faughnan

Abbreviations

ACVRL1	Activin-A type II like kinase I
AVM	Arteriovenous malformation
BMP-9	Bone morphogenetic protein
BMPR2	BMP type II receptor
HHT	Hereditary hemorrhagic telangiectasia
PAH	Pulmonary arterial hypertension
PH	Pulmonary hypertension
TGFBR2	TGF-ß type II receptor
TGF-ß	Transforming growth factor ß
TTCE	Transthoracic contrast echocardiography
VEGF	Vascular endothelial growth factor
VM	Vascular malformation

Clinical Vignette 26.1

A 25-year-old woman presents to the emergency room with sudden onset of shortness of breath. She is 37 weeks pregnant, G1P0. Past medical history is unremarkable. Her pregnancy had been uncomplicated to date. On physical examination, she has a respiratory rate of 25/min, heart rate of 100/min, blood pressure of 100/50 mmHg, temperature of 37.1 °C, and oxygen saturation on pulse oximetry is 92%. Mucocutaneous telangiectasia is visible on the lip and right index finger. Percussion of the left hemithorax is dull with corresponding decreased breath sounds. Chest X-ray (Fig. 26.1a) reveals left-sided pleural effusion with an obscured left hemi-diaphragm. CT chest (Fig. 26.1b–d) reveals a moderate left-sided effusion (suspected hemothorax) with pulmonary arteriovenous malformations (AVMs) in the left lower lobe, left upper lobe, and the right lower lobe. Transcatheter embolization of the pulmonary AVMs was performed by an experienced interventional radiologist. The patient went into labor at 38 weeks of pregnancy and gave birth to a healthy child. Chest X-ray performed in follow-up shows the embolization coils bilaterally (Fig. 26.2). On further history, the patient reports recurrent spontaneous epistaxis in the father, as well as stroke. The patient, and eventually her family, was thus diagnosed with hereditary hemorrhagic telangiectasia (HHT).

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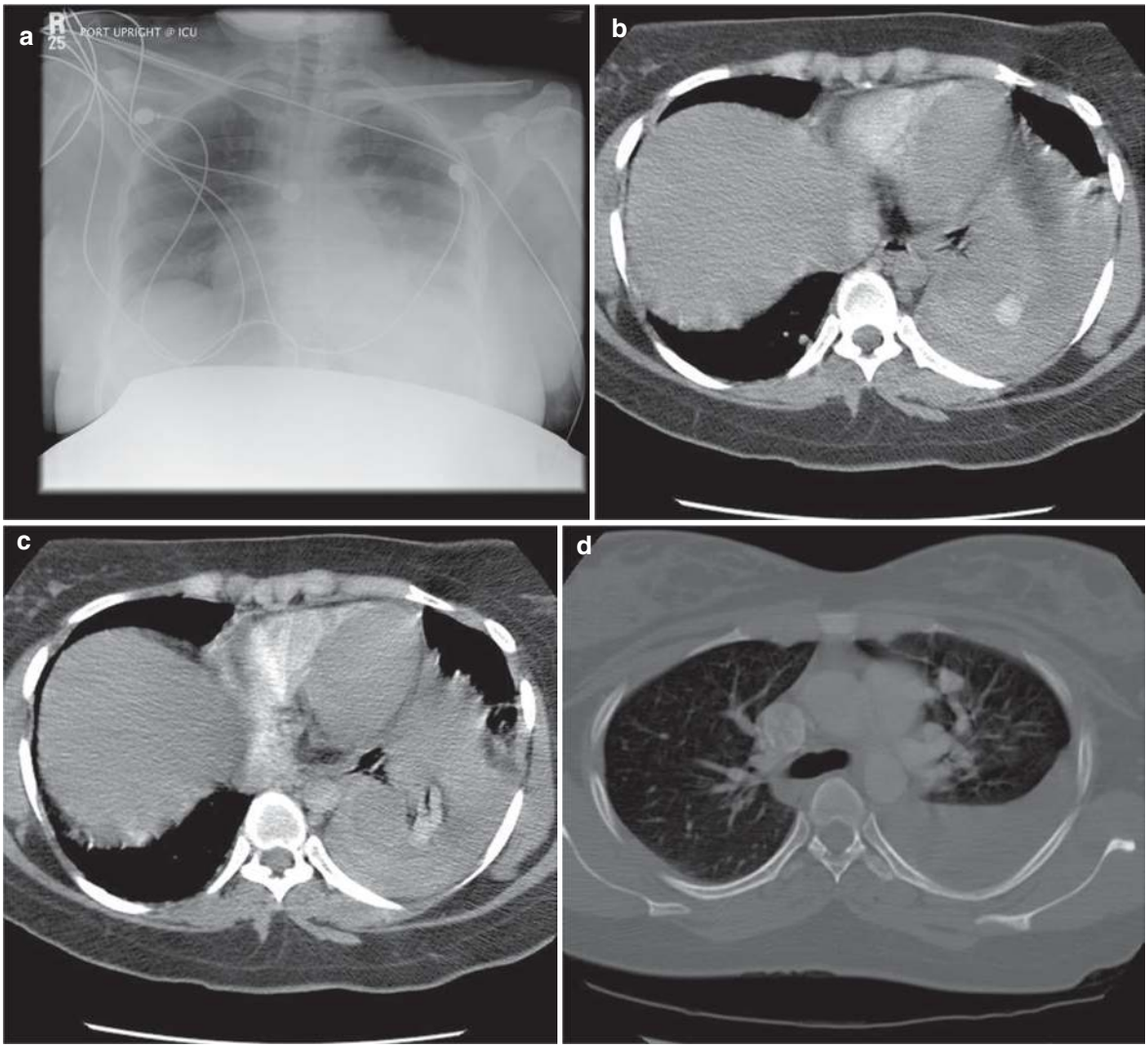

Fig. 26.1 (**a**) Case 1: chest X-ray shows that the left diaphragm is obscured by a pleural effusion. The abdomen is protected by a lead shield. (**b**–**d**) Case 1: CT chest (selected images) showing the left hemothorax and the left lower lobe AVM (**b**, **c**) and left upper lobe AVM (**d**)

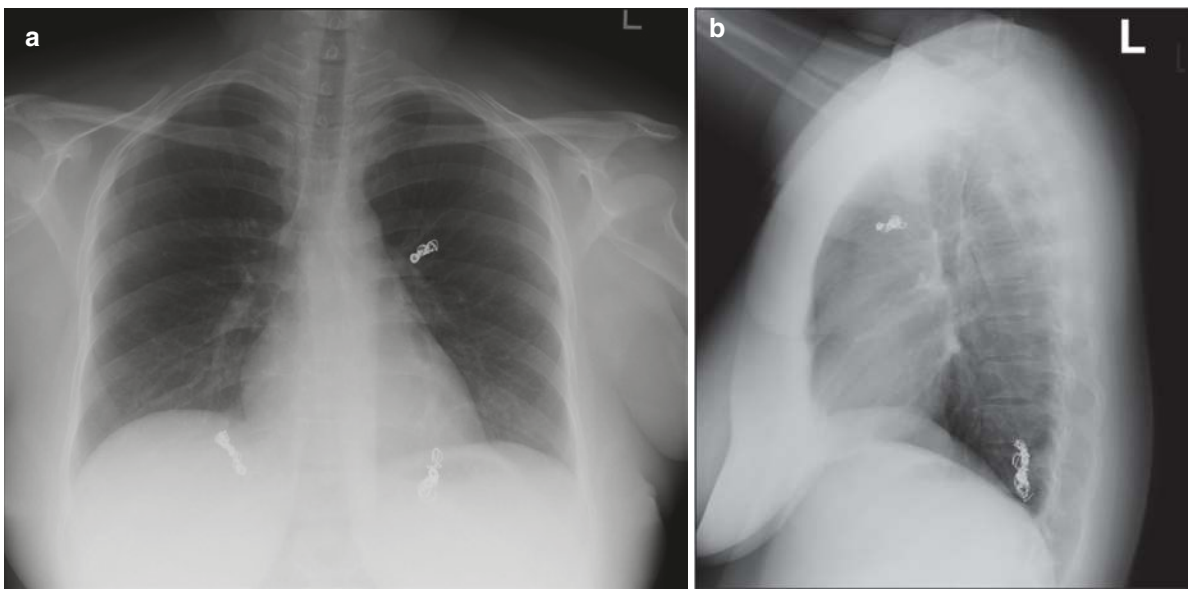

Fig. 26.2 (**a**, **b**) Case 1: chest X-ray (PA and lateral) after embolization, shows coils in the left upper lobe, left lower lobe, and right lower lobe

Pulmonary Arteriovenous Malformations

Background Pulmonary AVMs

Pulmonary AVMs are associated with HHT in more than 80% of patients [1]. If not associated with HHT, pulmonary AVMs are considered idiopathic [2]. Rarely, pulmonary AVMs have been reported in association with hepatopulmonary syndrome, mitral stenosis, trauma, schistosomiasis or actinomycosis, Fanconi's syndrome, and metastatic thyroid carcinoma [3]. The detection of pulmonary AVMs, or their complications, may predate the HHT diagnosis, particularly as HHT is an under-recognized disorder.

HHT is an autosomal dominant disorder, characterized by the presence of vascular malformations (telangiectases and AVMs) and caused by a mutation in either the *Endoglin* gene or the *Activin-A type II like kinase 1* (*ACVRL1)* gene in 85% of families [4]. Approximately 2% of persons with HHT are affected by a mutation in the *SMAD4* gene and these patients typically have an overlap syndrome with Juvenile Polyposis [5]. Pulmonary AVMs have a higher prevalence in patients with an *Endoglin* mutation (49–75%) than in patients with an *ACVRL1* mutation (5–44%) [6–8].

Anatomy Pulmonary AVMs

Most (80%) pulmonary AVMs are simple fistulas consisting of a single feeding artery directly connected to a draining vein, with only an intervening aneurysmal sac but no capillaries (Fig. 26.3). About 20% of pulmonary AVMs are complex with multiple feeding arteries, or multiple draining veins, or a septated aneurysmal sac [9]. A diffuse form of pulmonary AVMs is present in approximately 5% of pulmonary AVM cases (Fig. 26.4). Diffuse pulmonary AVMs have been defined as AVMs involving every subsegmental artery of at least one pulmonary lobe [10, 11].

Clinical Presentation of Pulmonary AVMs

Patients with pulmonary AVMs do report exertional dyspnea, though only in approximately 50% of patients. Less than 10% of patients present with classical features such as cyanosis, clubbing, and pulmonary bruit. More typically, patients present with complications from pulmonary AVMs, such as a massive hemorrhage or stroke. Hemorrhagic complications develop due to spontaneous rupture of a pulmonary AVM, leading to massive hemoptysis or hemothorax. This complication has typically occurred in 3–13% of patients by the time of diagnosis of pulmonary AVMs. Even more frequently patients develop neurologic complications due to paradoxical emboli, such as stroke, transient ischemic attack, or cerebral abscess, with frequencies of 10–60%, by the time of diagnosis of pulmonary AVMs [1, 12–14]. The presumed mechanism for stroke is via paradoxical embolization of thrombus from the leg deep venous system or alternatively from in situ thrombus in the AVM. Cerebral abscess in these patients can be caused by a variety of pathogens but is most commonly due to pathogens typical of periodontal

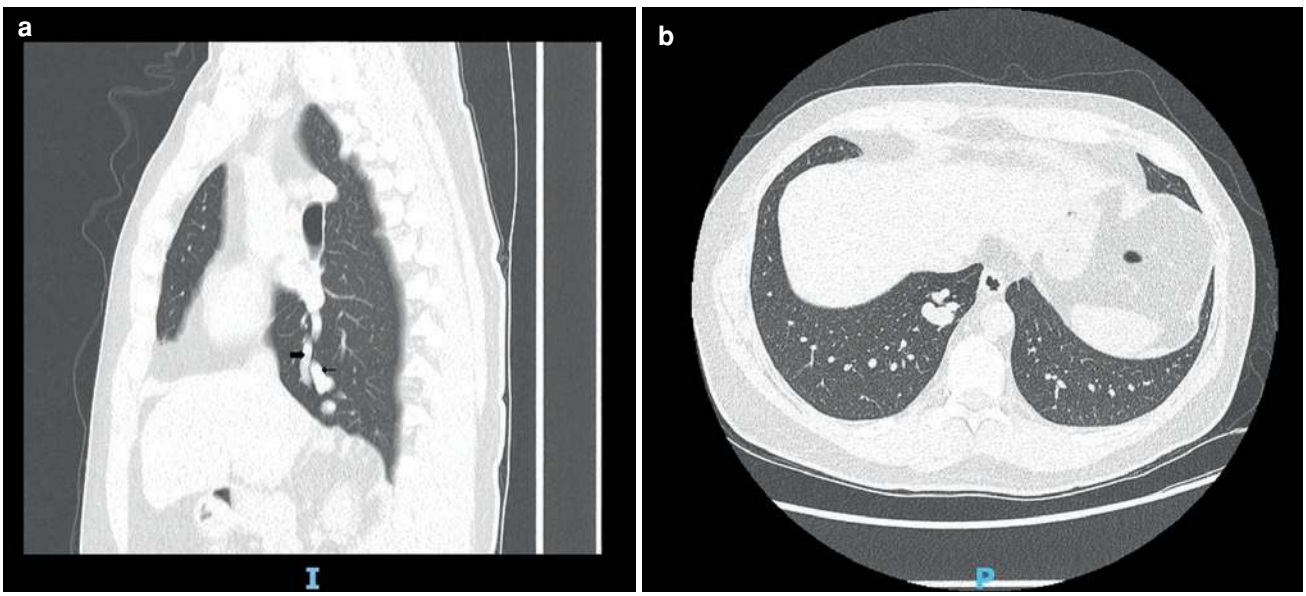

Fig. 26.3 (**a**, **b**) Pulmonary AVM in the right lower lobe. Screening for the presence of pulmonary AVMs is done by an unenhanced low-dose CT chest. (**a**) shows the feeding artery (narrow arrow) and the draining vein (bold arrow) of the pulmonary AVM, (**b**) shows the nidus of the pulmonary AVM

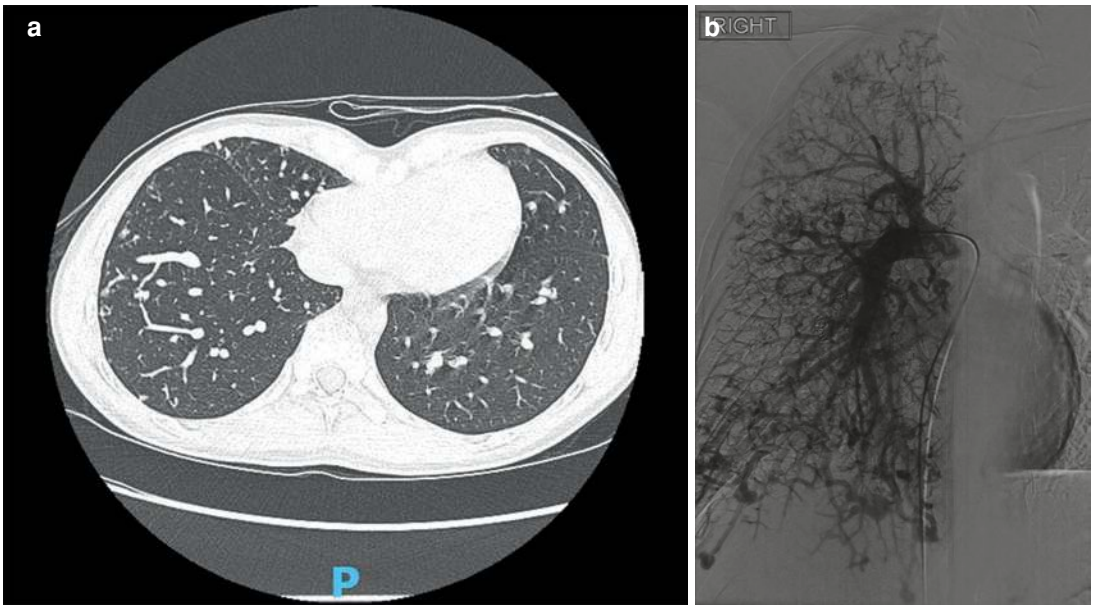

Fig. 26.4 (**a**) Axial plane CT chest and (**b**) pulmonary angiography of the right lung of a person with diffuse pulmonary AVMs

source [15–17]. Interestingly, migraine is also frequently reported in HHT patients with a pulmonary AVM, particularly migraine with aura [18, 19]. There are multiple mechanistic theories for the connection between migraine and pulmonary AVM, from impaired pulmonary capillary clearance (due to shunting) of vasoactive molecules to recurrent paradoxical emboli through pulmonary AVMs.

Screening Pulmonary AVMs

Pulmonary AVM complications can be largely prevented, with appropriate screening and preventative therapy. The International HHT Guidelines [20, 21] recommend screening all patients with HHT (or suspected HHT) for pulmonary AVMs and treating them preventatively. The recommended first-line screening test is transthoracic contrast echocardiography (TTCE) with agitated saline, for the detection of a right-to-left shunt. This is a low-risk and minimally invasive screening test with high sensitivity (93%) and an excellent negative predictive value (99%) for the presence of a pulmonary AVM [22–24]. When there is evidence of right-to-left shunt on TTCE, CT chest is the recommended diagnostic test to confirm or rule out the presence of pulmonary AVMs [20] and this can be done without enhancement in most cases.

The degree of shunt on TTCE can be graded (1–3) according to the number of microbubbles appearing in the left ventricle after four or more cardiac cycles [24]. The number of cardiac cycles after which contrast appears in the left ventricle is not predictive of an intracardiac or intrapulmonary shunt [25]. Increasing shunt grade is associated with increased positive predictive value of the presence of pulmonary AVMs requiring embolization [23, 25, 26].

For patients with HHT with negative TTCE at baseline, rescreening is recommended every 5 years. Patients who are found to have small pulmonary AVMs on CT chest, with feeding artery <2 mm diameter and not causing complications, can be observed and followed with repeat CT chest every 1–3 years to detect growth and subsequent indication for embolization.

Pulmonary AVM precautions are recommended in all HHT patients with pulmonary AVMs, regardless of treatment, and all HHT patients with a right-to-left shunt on TTCE, even if there are no CT-detectable pulmonary AVMs [20]. First, patients should receive prophylactic antibiotics for all bacteremic procedures, to prevent cerebral abscess and other septic emboli. In addition, dental hygiene should be optimized. The specific choice of antibiotics for prophylaxis depends on the procedure, following the antibiotic choices detailed in the Subacute Bacterial Endocarditis (SBE) guidelines of the American Heart Association [20, 27]. Second, to reduce the risk of air embolus, caution should be used to avoid air bubble introduction with intravenous access, preferably by the use of an air-elimination filter, if available. Finally, it is recommended that patients avoid SCUBA diving to prevent complications from decompression.

Treatment Pulmonary AVMs

Preventative transcatheter embolotherapy is recommended, by an experienced interventional radiologist with the goal to occlude pulmonary AVMs with a feeding artery of 2–3 mm or greater [20]. Currently, there are several devices being used for embolization, including various types of coils and Amplatzer plugs. The reperfusion rates (mostly secondary to recanalization) after embolization with coils and Amplatzer plugs are similar, 7–10% [28]. Embolization is generally performed as a day procedure, or with overnight admission, under local anesthesia and conscious sedation.

The most common complication of embolization is pleuritic chest pain post-procedure, occurring in up to 30% of patients. The pain is usually self-limiting, lasting on average 7–10 days, and treated with non-steroidal anti-inflammatory drugs, as needed. Other complications, although rare, include lung infarction, transient hemoptysis (vessel perforation), migration of the device into the systemic circulation, and very rare complications are angina pectoris, transient ischemic attack, cerebral infarction [28, 29]. A migrating device typically occurs at the time of device placement and in most cases, the device can be retrieved by the interventional radiologist via the catheter, during the same procedure.

Follow-up after embolization is routinely performed 1 month after the procedure with an arterial blood gas (including oxygen shunt testing where available) to document improvement in PaO_2 and a chest X-ray to assess for early involution of the aneurysmal sac and draining vein. Subsequent follow-up is recommended 6–12 months after embolization, with a repeat unenhanced CT chest to confirm involution of the aneurysm and of the draining vein of the embolized AVMs [20, 30]. If there is not sufficient involution, reperfusion is suspected, and retreatment should be considered. The second goal of CT is to detect the growth of residual small AVMs and the rare development of new AVMs. In the case of a negative CT chest after embolization, repeat follow-up by CT chest is recommended after 3 years [20].

Pregnancy and Pulmonary Arteriovenous Malformations

Pregnancy is associated with an increased risk of hemorrhage from pulmonary AVM [17, 31], presumably secondary to the increased cardiac output and increased stroke volume [32]. To reduce this risk, screening for the presence of pulmonary AVMs in women with HHT is recommended prior to pregnancy, with preventative embolotherapy if indicated. If not screened prior to pregnancy, women with HHT should be screened with TTCE in the early second trimester [19]. When pulmonary AVMs are newly diagnosed during pregnancy, embolization is recommended during the early second trimester to prevent complications [19]. If pulmonary AVMs are present and not treated during pregnancy, the pregnancy should be considered high-risk [19]. If embolization is performed during pregnancy, it should be performed by an experienced radiologist, with every effort to minimize radiation exposure for the fetus. Exposure reduction can be achieved by covering the abdomen and pelvic area with a lead apron, collimation of the radiation field, and limiting the fluoroscopy time. Taking these precautions will expose the fetus to a radiation dose of 0.01–0.66 mGy, which is below the estimated threshold dose of 250 mGy that could potentially have an effect on the fetus in the second trimester [33].

Children with Hereditary Hemorrhagic Telangiectasia

Children with HHT should be screened for pulmonary AVMs as well [21, 34]. Twenty-three percent of asymptomatic children with HHT diagnosis have pulmonary AVMs, of these 70% with a significant feeding artery diameter of ≥3 mm [35, 36]. Initial screening for pulmonary AVMs in the pediatric population can be done by the combination of history, physical examination, saturation on pulse oximetry ≥96% and chest radiography and/or TTCE [21, 35, 36]. When screening is positive, CT chest is recommended, as it is in adults, to confirm the presence of pulmonary AVMs and measure the feeding artery diameter. Embolization is recommended in children who are symptomatic of the pulmonary AVMs, who are hypoxemic, or who are found to have a large pulmonary AVM on imaging. Treatment of asymptomatic children should be considered on a case-by-case basis [21]. Treatment by transcatheter embolotherapy in children is low risk in experienced hands, with complication rates comparable to those in adults [37]. Screening for the presence of pulmonary AVMs in asymptomatic children with HHT or at risk of HHT should be repeated every 5 years [21].

Reports of pulmonary AVMs in neonates are rarer. There are 18 case reports of neonates with pulmonary AVMs, 39% died within the first week. We suspect there is a reporting bias here, with primarily severe cases being identified and reported at birth. Embolization can be performed in neonates, as in children.

Diffuse Pulmonary Arteriovenous Malformations

Diffuse pulmonary AVMs are pulmonary AVMs occurring in every subsegmental artery of one or more pulmonary lobes. They occur in 4.4% of patients with pulmonary AVMs and these patients more frequently present with cyanosis,

hemoptysis, and/or neurologic complications. Most (81%) patients with diffuse pulmonary AVMs have HHT. Patients can have unilateral or bilateral diffuse pulmonary AVMs, the latter occurring in the majority of patients (72%), mostly affecting women. Usually, patients present at a young age, mean 24 years old, with cyanosis. The majority of patients (70%) have had neurologic complications by the time of diagnosis [11].

The mean PaO2 at presentation is 47 mmHg and 75% of patients have polycythemia due to chronic hypoxemia. Diffuse pulmonary AVMs are associated with increased mortality of 25% during a mean follow-up of 8.3 years, only reported in patients with bilateral involvement [10]. Death was due to pulmonary hemorrhage, cerebral abscess, or complications from other organ involvement from HHT. Treatment for diffuse pulmonary AVMs is similar to patients with focal pulmonary AVMs, with preventative embolization of AVMs with a feeding artery diameter of ≥3 mm. Post-embolization, the PaO_2 improves in patients with unilateral involvement, but not significantly in most patients with diffuse involvement.

Patients with HHT can be affected by other vascular malformations (VMs) besides pulmonary AVMs. The most common locations for other VMs are the brain and liver. Though there is no international consensus on asymptomatic screening for brain VMs in adults, it is the current standard of care in HHT Centres of Excellence across North America, using MRI [38]. Routine screening for brain AVMs is recommended in children with HHT [19]. Diagnostic testing for liver VMs can be offered to patients with HHT who are asymptomatic from liver involvement. Imaging for liver VM is typically recommended in symptomatic patients since preventative treatment for liver VM is not available, or in cases where the documentation of liver VMs might help complete the diagnosis of HHT based on the clinical criteria [21].

Clinical Vignette 26.2

A 70-year-old woman presents with progressive exertional dyspnea and ankle edema. On physical examination her jugular venous pressure is elevated, she has mucocutaneous telangiectasia and she has ascites. An electrocardiogram reveals atrial fibrillation. Transthoracic echocardiography reveals an elevated estimated right ventricular systolic pressure of 43 mmHg, suggestive of pulmonary hypertension. Doppler ultrasound of the liver reveals a dilated hepatic artery at 7.5 mm with an increased hepatic artery peak flow velocity (120 cm/s) and decreased resistive index (0.55). Multi-detector triphasic helical CT reveals diffuse liver vascular malformations with an arterioportal shunt.

Pulmonary Hypertension

Pulmonary hypertension (PH) refers to an increased pulmonary arterial pressure, which can subsequently lead to right heart failure. Patients with HHT can present with PH, most commonly secondary to the presence of liver VMs (class 2 pulmonary hypertension), or patients can develop pulmonary arterial hypertension (PAH) (class 1 pulmonary hypertension) [39]. Patients PH secondary to liver VMs mostly present with increased cardiac output and are found to have an increased pulmonary artery wedge pressure with an increased cardiac index on right heart catheterization, while patients with class 1 PAH have an increased pulmonary vascular resistance [37, 40].

Pulmonary Hypertension Secondary to Liver Vascular Malformations

Liver VMs are highly prevalent in HHT, associated with all genotypes, though more frequent in patients with *ACVRL1* mutation (84%) versus patients with an *Endoglin* mutation (60%) [8]. Only 5–8% of patients with liver VMs are symptomatic, based on cross-sectional studies [41, 42]. Liver VMs are more prevalent in HHT patients over 40 years of age and women appear to be more frequently affected than men [43, 44]. Liver VMs with severe shunting can eventually lead to high-output cardiac failure, typically in the sixth or seventh decades of life. Rarely women can also present with high-output heart failure from liver VMs during pregnancy [45, 46].

High-output heart failure develops secondary to arteriovenous (hepatic artery to hepatic vein) shunt and /or portosystemic (portal vein to hepatic vein) shunt. Arterioportal (hepatic artery to portal vein) shunts more typically lead to portal hypertension, ascites, and esophageal varices. There is often evidence of mixed shunt in symptomatic patients. Arteriovenous shunting leads to a hyperdynamic circulatory state. Subsequently, increased left atrial pressures and impaired pulmonary vasodilatation cause PH. PH and volume overload will lead to right ventricle strain and eventually dilatation, which subsequently lead to right ventricle enlargement and contractile dysfunction, leading to tricuspid regurgitation and eventually right heart failure [47].

Patients with PH secondary to live VMs typically present with symptoms of high-output heart failure: fatigue, palpitations, exertional dyspnea, orthopnea, and peripheral edema. On physical examination, a triad can be found of wide arterial pulse pressure, systolic ejection murmur at the left sternal border due to tricuspid regurgitation and a hepatic bruit.

Liver VMs can be detected by Doppler ultrasound of the liver. Major findings on Doppler ultrasound in these patients are hepatic artery dilatation (>0.7 cm) and intrahepatic arterial hypervascularization. Minor criteria are the presence of

increased hepatic peak velocity >110 cm/s, decreased hepatic artery resistance index <0.6, an increased portal vein peak velocity >25 cm/s, and the tortuous course of the extrahepatic artery [48]. Multiphasic hepatic CT, MRI, or mesenteric angiography are the options for diagnostic confirmation of liver VMs and also provide more detailed information regarding the type(s) of the shunting present as well as other complications (biliary cystic dilatation, focal nodular hyperplasia, etc.) [21].

The suspicion of PH and high-output heart failure is generally confirmed on TTE, but right heart catheterization is helpful in cases where the association with liver VMs, or the cause of PH, is uncertain. Patients with PH secondary to liver VMs will have elevated mean pulmonary artery pressure, increased cardiac output, normal pulmonary vascular resistance, normal transpulmonary gradient, and elevated pulmonary capillary wedge pressure [49].

Routine management of high-output heart failure due to liver VMs includes salt restriction, diuretics, beta-blockade, and treatment of anemia and atrial fibrillation [19, 50]. In refractory cases, treatment with bevacizumab can be considered and/or liver transplantation [21]. Bevacizumab is an antibody against vascular endothelial growth factor (VEGF). Treatment with bevacizumab has been shown to improve NYHA class [51] and to improve the cardiac output in a patient with liver VM and high-cardiac output, with a complete response in 22% of patients and a partial response in 65% of patients at a 6-month follow-up. A complete response is considered a normalization of the cardiac index, which should be 2.5–3.9 L/min/m^2 in men and 2.5–3.6 L/min/m^2 in women. Bevacizumab treatment also reduced the mean duration of epistaxis and improved quality of life. Treatment had no effect on hepatic artery diameter or peak flow velocity [52].

Liver transplantation is considered in refractory liver VM patients, for high-output heart failure, portal hypertension, or biliary necrosis [21]. Perioperative mortality of liver transplantation in patients with HHT is reported at 10–17%, due to hemorrhage (intraoperative, cerebral, pulmonary, gastric), heart failure, or rejection of the liver or primary nonfunctional liver. After liver transplantation, the cardiac function improved in 75% of patients and stabilized in 21% of patients. The 10-year survival rate after liver transplantation in patients with HHT is 83% [53]. Patients with increased cardiac output and normal peripheral vascular resistance and normal right ventricle function are eligible for liver transplantation. Patients with severe pulmonary hypertension (mean pulmonary artery pressure ≥35 mmHg), elevated pulmonary vascular resistance (≥250 dyn s cm^{-5}), and right ventricle dysfunction unfortunately are considered at higher risk as liver transplantation in these patients is associated with increased mortality [54].

Surgical hepatic ligation and percutaneous hepatic artery embolization have been performed to treat the intrahepatic shunt. These procedures carry a significant risk of developing biliary ischemia and/or hepatic necrosis. In view of these serious complications, these procedures are generally not recommended, though are occasionally considered for patients with the refractory disease who are not considered candidates for liver transplantation [21, 53, 55].

Pulmonary Arterial Hypertension

Familial PAH is a rare disorder, with an estimated prevalence of 15 per million and is rarely caused by HHT [56]. PAH also occurs in HHT patients, though rarely (approximately 1% of HHT patients). Most affected patients to date have an *ACVRL1* mutation [57–59]. PAH can be suspected based on symptoms: dyspnea, syncope, fatigue, and edema. HHT patients with PAH present with similar symptoms as patients with idiopathic PAH. Pathologic characteristics of arteriopathy in patients with HHT PAH consist of intimal proliferation, medial hypertrophy, plexiform lesions, and in situ thrombosis. The diagnosis is suspected based on symptoms or if an elevated peak tricuspid regurgitation velocity ≥ 2.9 m/s is found on transthoracic echocardiography or the presence of other echocardiographic signs characteristic of PH. PAH should be confirmed by right heart catheterization, as in patients with idiopathic PAH. Hemodynamic criteria for the diagnosis of PAH are the presence of an elevated mean pulmonary arterial pressure of ≥25 mmHg in rest, with a normal left atrial or wedge pressure (≤15 mmHg) and increased pulmonary vascular resistance >3 Wood units [39].

Complications from PAH in patients with HHT can be precipitated by anemia, leading to right heart failure. Patients with HHT are at increased risk for anemia due to hemorrhage, most commonly from epistaxis or from telangiectases in the gastrointestinal tract. Severe hemorrhage can lead to hypovolemia or anemia. Hypovolemia leads to reduced cardiac output and anemia will lead to decreased oxygen delivery which both can contribute to worsening right ventricular failure. Right heart failure can also be precipitated by embolization of pulmonary AVMs in patients with pulmonary arterial hypertension. Closing the shunt in the pulmonary AVM can lead to increased mean pulmonary artery pressures, with a subsequent increase in the right ventricle afterload. However, the risk of massive hemorrhage from untreated AVMs is likely greater in patients with PAH, and therefore decisions about embolization of pulmonary AVMs in the patients must be made on a case-by-case basis.

Management of PAH in patients with HHT is similar to management of patients with idiopathic PAH: besides lifestyle recommendations, medical management according to the guidelines for pulmonary hypertension is recommended [39]. Pulmonary vasodilators, i.e. bosentan, an endothelin receptor antagonist, have been reported to have a beneficial

effect in patients with HHT and PAH [60–62], though there is limited evidence. Caution is warranted with the use of pulmonary vasodilators since systemic vasodilatation could increase any systemic shunt and worsen heart failure. Sildenafil, a phosphodiesterase-5 inhibitor has also been reported to be beneficial in one case of PAH in HHT [63]. Anticoagulation is not absolutely contraindicated in HHT patients, but its use, rather, should be decided on a case-by-case basis.

Background HHT

HHT is an autosomal dominant inherited disorder affecting 1 in 5000–10,000 persons, characterized by the presence of vascular malformations. HHT has also been previously referred to as Osler-Weber-Rendu disease. HHT is characterized by the presence of mucocutaneous telangiectases (Fig. 26.5), recurrent epistaxis, visceral AVMs, and positive family history. These characteristics are the four diagnostic criteria for HHT (Table 26.1). The diagnosis of HHT is definite if patients meet ≥3 criteria. The diagnosis is possible if they meet two criteria and the diagnosis of HHT is unlikely if patients meet ≤1 criterion [64].

Patients have recurrent spontaneous epistaxis, with an average age of onset of 12 years. Ninety-five percent of patients have recurrent epistaxis by the age of 40. The average diagnostic delay, between ENT consultation for epistaxis and HHT diagnosis, is approximately 15 years [65]. Mucocutaneous telangiectasia is typically present on the lips, oral cavity, nasal mucosa, and skin of the face and hands. Mucocutaneous telangiectasia increases in number with aging. By the age of 20 years, 55–60% of patients have visible mucocutaneous telangiectasia [66, 67]. Visceral AVMs can be present in the lungs, liver, brain, spine, or rarely other organs. Clinical heterogeneity is the rule, with HHT clinical manifestations being often highly variable amongst families and within families. Genotype-phenotype correlations are described above and detailed in Table 26.2. Since epistaxis and mucocutaneous telangiectasia are not always present during childhood or adolescence, HHT cannot always be diagnosed or ruled out based on clinical criteria in younger patients, and therefore genetic testing is often required.

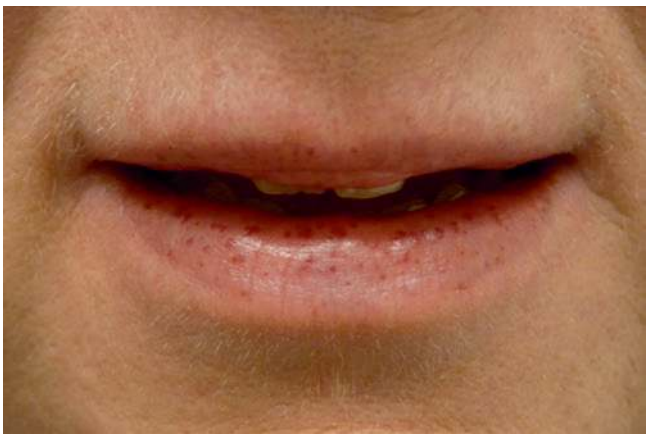

Fig. 26.5 Mucocutaneous telangiectasia on the lips

Table 26.1 Clinical diagnostic criteria for hereditary hemorrhagic telangiectasia

Mucocutaneous telangiectasia
Frequent recurrent spontaneous epistaxis
Visceral arteriovenous malformations
Affected first-degree relative

Table 26.2 Genotype-phenotype correlation of organ involvement in patients with hereditary hemorrhagic telangiectasia [6–8]

	Endoglin mutation (%)	*ACVRL1* mutation (%)
Pulmonary AVM	49–76	5–44
Cerebral VM	9–22	0–4
Liver VM	8–60	41–83
Gastrointestinal telangiectasia	60–72	51–66

AVM arteriovenous malformation, *VM* vascular malformation

Eighty-five percent of patients have a mutation in the *Endoglin* (*ENG*) gene on chromosome 9 (HHT-1) [68], or a mutation in the *ACVRL-1* gene on chromosome 12 (HHT-2) [69, 70]. Less common mutations for HHT are mutations in the *SMAD4* gene on chromosome 18 occurring in 2% of patients and generally associated with an overlapping juvenile polyposis syndrome [5, 71]. Approximately 90% of patients with HHT have a mutation in one of these three genes [4].

Pathogenesis

Endoglin and ACVRL1 are surface proteins on endothelial cells. Endoglin is a coreceptor, enhancing bone morphogenetic protein (BMP) 9 and BMP10 ligand binding to the ACVRL1/BMPR2 receptor on epithelial cells. This binding activates the SMAD 1/5/8 signaling pathway, which normally inhibits VEGF signaling. VEGF signaling is important in angiogenesis. In HHT, because of haploinsufficiency of the endoglin or ACVRL1 gene, there is a loss of function of the endoglin and ACVRL1 receptor expression on cell surfaces. It is hypothesized that a second hit is required for AVM development: for example, inflammation and subsequent cytokine release lead to biallelic loss of endoglin or ACVRL1 gene expression. Current understanding is that this leads to a loss of BMP9/10 signaling, driving a corresponding local increase

in PI3K–AKT–mTOR signaling and an untempered response of VEGF with increased endothelial cell proliferation, which contributes to AVM formation, as recently reviewed [72].

Treatment of persons with HHT with the VEGF inhibitor bevacizumab has shown to decrease the severity of epistaxis and to improve high-output heart failure due to shunting from liver vascular malformations [52], and is recommended for severe and refractory disease [21]. Smaller studies have shown that pazopanib, a tyrosine kinase inhibitor that inhibits the VEGF receptor, reduced the frequency of epistaxis in persons with HHT [73] and reduced blood transfusion requirements in severe bleeders. Several anti-VEGF therapies and other pathway-based therapies are currently being investigated in pre-clinical and clinical trials and offer hope for effective systemic treatment of HHT [74].

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Pulmonary Alveolar Microlithiasis

27

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Introduction

Pulmonary alveolar microlithiasis (PAM) is a rare inherited lung disease caused by inactivating mutations in the sodium phosphate co-transporter, SLC34A2, resulting in the widespread deposition of calcium phosphate crystals in the distal airways and alveoli of the lung. Malpighi, a prominent Italian scientist, first described the gross pathologic appearance of lungs affected by the disease in 1686 [1]. It was not until 1918 that its histopathologic and radiologic features were carefully detailed by Norwegian physician Harbitz [2]. The Hungarian pathologist Puhr named the disease "microlithiasis alveolaris pulmonum" in 1933 [3] Since that time, over 1000 cases have been reported worldwide, and important insights into the pathogenesis of the disease have emerged [4]. Here, we review epidemiology, pathophysiology, notable clinical features, and management considerations.

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Epidemiology

The overall prevalence of PAM is unknown. Cases have been reported worldwide, but the large majority of subjects have been identified in Asia (56.3%) and Europe (27.8%). Patients from Turkey, China, Japan, India, and Italy account for over half of the cases in the literature.

While PAM has been described in all age groups, it has been most commonly discovered in the second or third decade of life, often on chest radiographs obtained for incidental chest complaints or for military or job screening. Mariota noted that 35.8% of PAM patients were diagnosed before the age of 20. Newborns and toddlers have been reported, rarely, including twins who died within 12 h of birth [5]. Although most patients are diagnosed prior to age 50 (88.2%), multiple octogenarians with PAM have been appeared in case reports [6, 7]. PAM has no clear gender or ethnic predilection.

PAM is an autosomal recessive disorder with high penetrance, since it transmits vertically and is associated with consanguinity [8]. In a recent review of 1022 cases, 37.2% of patients had a family history of the disease [4]. The Japanese, Turkish, and Italian cohorts have even greater rates of familial occurrence (43–50%), typically in association with consanguineous marriages [5, 9, 10]. Of interest, the frequency of *SLC34A2* mutations in the Japanese general population was estimated to be less than 0.008 [11].

Pathogenesis

Accumulation of microliths in the alveoli is the hallmark of PAM. These calculi are round or ovoid in shape, range from 50 to 5000 μm in diameter and are composed primarily of calcium phosphate with small amounts of calcium carbonate, magnesium, and iron [12–16]. Under the microscope, they can be easily highlighted with von Kossa staining and have a lamellar, "onion-skin" appearance. (Fig. 27.1) At autopsy or transplant, resected lungs are enlarged, heavy,

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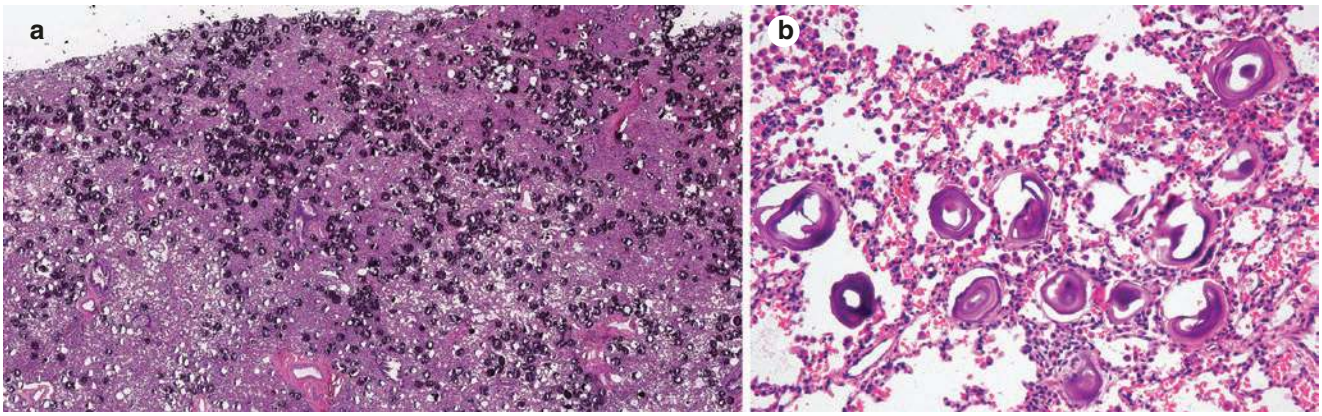


Fig. 27.1 Pathologic appearance of pulmonary alveolar microlithiasis (**a**) Low power view of lung biopsy from an infant with PAM, *H&E stain*, (**b**) High power view of intra-alveolar microliths with PAS positive lamellar structure

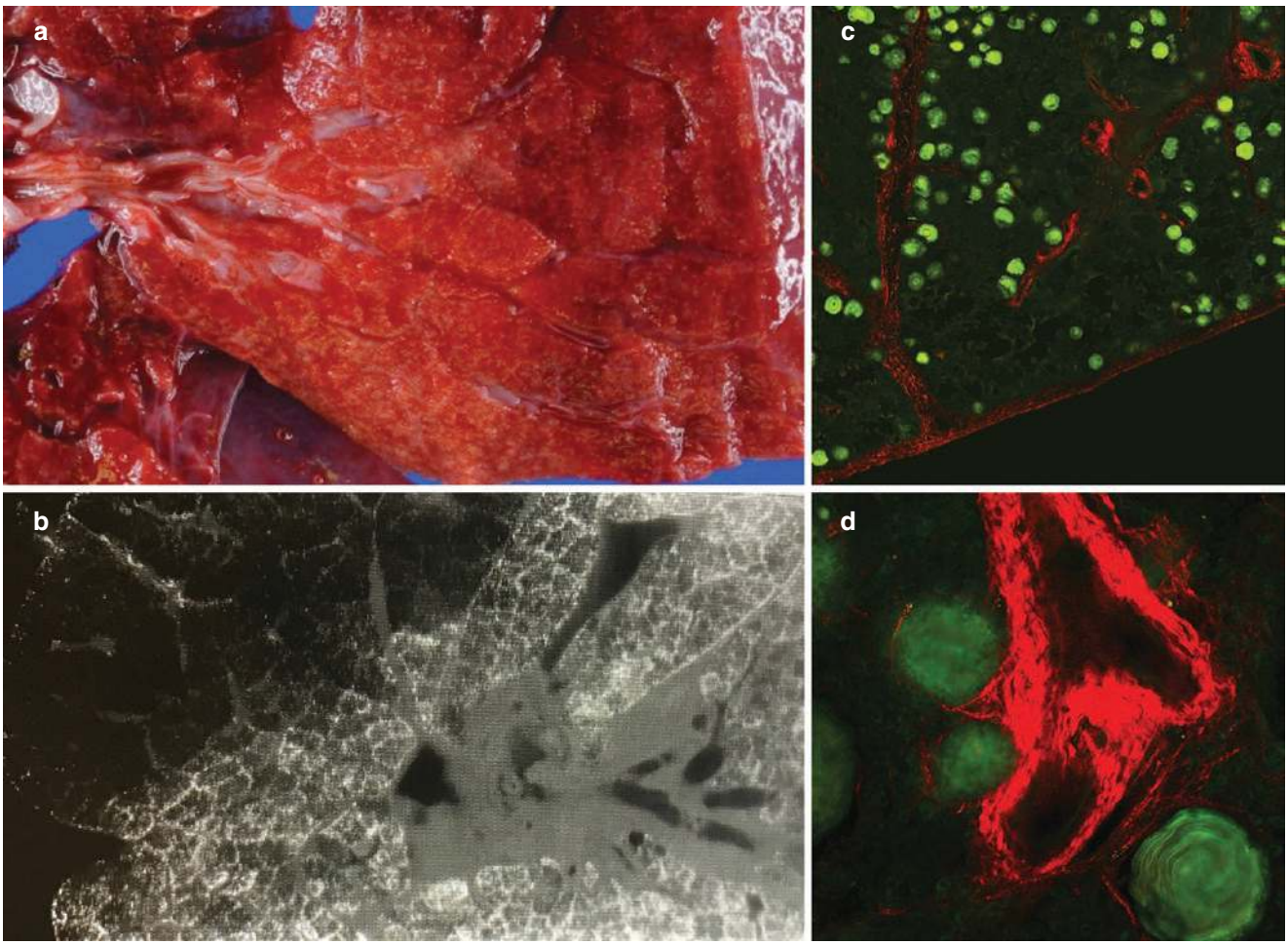


Fig. 27.2 Pathological evaluation of infant PAM lung, showing orientation of stones along interlobular septa. (**a**) Gross appearance of lung explant from infant with PAM showing sandy appearance of cut surface, (**b**) Micro-CT of region of lung shown in **a**, showing pattern of interlobular and intralobular septal hyperdensity, (**c**) Second harmonic generation of fibrillar collagen (red) and autofluorescence (green) showing microliths lining up along alveolar septa consistent with the pattern in **b**, (**d**) Higher power view of microliths revealing lamellar structure

non-collapsible, and non-buoyant [17, 18]. Gross sections have a gritty cut surface. (Fig. 27.2) On a micro-CT image of the lung explant from a 2-year-old PAM infant who was transplanted at our institution, the hyperdense calculi are seen lining up along interlobular septa: a pattern that is confirmed with second harmonic imaging (Fig. 27.2). Although heterotopic ossification in patients with PAM is typically confined to the lungs, extrapulmonary calcifications have been reported in the pleura [19], diaphragm [20], lumbar sympathetic chain, and testicles. It is not clear whether these calcified lesions outside lung are truly part of the pathogenesis of PAM or chance occurrences.

Initially, alveolar gas exchange remains intact, but as microliths grow in number and size and fill the alveoli, pulmonary architecture is distorted [21]. As disease progresses, patchy inflammation develops, and variable degrees of interstitial fibrosis can be seen [12]. Intimal and medial thickening of pulmonary vasculature can also be found in more advanced cases, likely due to pulmonary hypertensive changes related to hypoxia [22, 23].

The genetic basis of PAM was discovered in the mid-2000s. Huqun used high-density homozygosity mapping of three Japanese families to identify a chromosomal segment, 4p15.2, that cosegregated with disease and confirmed that the sodium phosphate transporter within that locus contained protein-truncating mutations in SLC34A2. They also demonstrated that SLC34A2 is highly expressed in alveolar type II cells and postulated a role for the transporter in the export of alveolar phosphate [11]. Corut and colleagues also identified SLC34A2 as a PAM gene in seven patients in Turkey [24]. Since those reports, at least 27 unique mutations have been identified in 41 patients [4, 25, 26]. (Table 27.1) Mutations appear to cluster in exon 8 in Chinese cases and exons 7 and 8 in Japanese cases [37]. The heterogeneity in

Table 27.1 Known *SLC34A2* mutations

Location	Mutation	Effect on translation	Protein	First author, year
Promoter exon 1	c.[-6773_-6588del]	p.?	Not synthesized	Corut, 2006 [24]
Exon 2	insT [not specified]	p.?	Truncation	Dogan, 2010 [27]
Exons 2–6	5.5 Kb deletion	p.?	Truncation	Ishihara, 2009 [28]
Exon 3	c.114delA	p.?	Truncation	Corut, 2006 [24] Ozcelik, 2010 [29]
Exon 3	c.226C>T	p. Gln76X	Truncation	Corut, 2006 [24]
Exon 4	c.316G>C	p. Gly106Arg	Substitution	Corut, 2006 [24] Ozcelik, 2010 [29] Ozbudak, 2012 [30]
Exon 4	c.316G>A	p. Gly106Arg	Substitution	Jönsson, 2020 [Unpublished]
Exon 5	c.[IVS4+1452]_IVS5+660del	p.?	–	Dandan, 2018 [31]
Exon 6	c. 560G>A	p. Gly187Glu	Substitution	Jönsson, 2020 [Unpublished]
Exon 6	c.575C>A	p. Thr192Lys	Substitution	Ma, 2014 [32]
Exon 7	c.646G>T	p. Gly216Ter	Substitution	Jönsson, 2020 [Unpublished]
Exon 7	insdel857_871	p.?	Truncation	Huqun, 2007 [11]
Exon 8	c.906G>A	p. Trp302Ter	Substitution	Jönsson, 2020 [Unpublished]
Exon 8	c.910A>T	p.?	Truncation	Zhong, 2009 [33] Yin, 2013 [34] Wang, 2014 [35]
Exon 8	IVS8+1G>A	p.?	Truncation by splicing failure	Huqun, 2007 [11]
Exon 10	c.1136G>A	p. Cys379Tyr	Substitution	Jönsson, 2020 [Unpublished]
Exon 11	c.1238G>A	p. Trp413Ter	Substitution	Jönsson, 2020 [Unpublished]
Exon 11	c.1327delC	p. Leu443Ter	Substitution	Jönsson, 2020 [Unpublished]
Exon 11	c.1328delT	p.?	Truncation	Corut, 2006 [24]
Exon 12	c.1342delG	p. Val448X	Truncation	Corut, 2006 [24]
Exon 12	c.1363T>C	p. Tyr455His	Substitution	Wang, 2014 [35]
Exon 12	c.1390G>C	p. Gly464Arg	Substitution	Izumi, 2017 [26]
Exon 12	c.1393_1404delACC	p. Thr468del	Aberrant (threonine deletion)	Jönsson, 2012
Exon 12	c.1402_1404delACC	p. Thr468del	Aberrant (threonine deletion)	Jönsson, 2012
Exon 12	c.1456C>T	p.?	Truncation	Proesmans, 2012 [36]
Intron 9	c.1048+1G>A	p.?	–	Huqun, 2007 [11] Izumi, 2017 [26]
Intron 11	c.1333+1G>A	p.?	–	Jönsson, 2020 [Unpublished]

mutations found thus far is inconsistent with a founder effect, and almost all mutations have been homozygous, suggesting identity by descent. Nonsense mutations resulting in premature protein truncation are most common [24, 32, 37]. The few family studies that have been completed demonstrate 100% penetrance with no apparent correlation between genotype and age at disease onset [24]. That more than one gene is involved in the disease process appears unlikely because mutations in *SLC34A2* have been identified in almost all cases analyzed [4].

Comprised of 13 exons, *SLC34A2* encodes a 2280-nucleotide mRNA. Its product is Npt2b, a sodium phosphate co-transporter expressed on the alveolar surface of the surfactant-producing type II pneumocytes [38, 39]. Npt2b is also expressed in the gut—where it likely functions as the major transporter for uptake of phosphate under conditions where dietary phosphate intake is limited—as well as the breast, liver, testes, prostate, kidney, pancreas, and ovaries [40, 41]. Other sodium phosphate co-transporters include SLC34 family members Npt2a and Npt2c, which are predominantly expressed in the kidneys, and ubiquitously expressed SLC20 family members Pit1 and Pit2. Mouse lungs have been shown to express Pit1 and Pit2 but not Npt2a or Npt2c [42]. The spectrum of transmembrane phosphate transporters expressed in the human lung has not been well characterized.

In the lung, Npt2b expressed on the alveolar epithelium is thought to resorb the phosphate liberated by the catabolism of surfactant phospholipids by alveolar macrophages [38, 39]. In the absence of functional Npt2b, phosphate likely accumulates in the alveolar lining fluid, binds to free calcium, and eventually forms the lamellated microliths that are characteristic of PAM [42]. Microlith formation probably depends on a favorable milieu created by multiple factors, including but not limited to optimal alveolar lining fluid calcium and phosphate concentrations, pH, and presence of nucleating proteins, lipids, and other small molecules. Surfaces that provide a platform for crystal growth may include phosphate within the polar headgroups of phospholipids that form the surfactant monolayer at the air-liquid interface. Better understanding of these factors may help to predict conditions that promote progression of disease and perhaps to develop strategies to inhibit stone formation and growth.

A recently developed mouse model supports the role of Npt2b in the molecular pathogenesis of PAM. Knockout mice with an epithelial deletion of Npt2b develop a progressive process with diffuse alveolar microlith accumulation, radiographic opacification, restrictive physiology, and pulmonary inflammation and fibrosis, closely mimicking the human disease process [42]. While the serum concentrations of calcium and phosphorus were unchanged when comparing the knockout and wild-type mice, calcium and phosphorus concentrations in alveolar lavage fluids increased roughly tenfold in the Npt2b knockout mice, confirming the central role of Npt2b in alveolar calcium and phosphorus homeostasis. Interestingly, alveolar phosphate levels fluctuate with dietary phosphate levels in PAM mice but are low and unaffected by diet in wild-type animals. The microliths isolated from the mice are composed calcium phosphate salts in proportions that are consistent with hydroxyapatite. Monocyte chemotactic protein-1 (MCP-1) and surfactant protein-D (SP-D) were found to be elevated in both the alveolar lavage and serum of knockout mice as well as in the serum of PAM patients (Fig. 27.3).

Interestingly, the Npt2b knockout animals also developed an unexpected increase in alveolar phospholipids. Although this finding has not been reported in humans, to our knowledge, elevated serum surfactant levels [43], oil red O-positive alveolar macrophages [44], and the abundant eosinophilic material reported to fill the alveoli of infant identical twins in PAM [45] may all be consistent with variable degrees of phospholipidosis. Like the mice, these findings may prove to be related to altered surfactant catabolism by dysfunctional alveolar macrophages.

Microliths transferred into the lungs of wild-type mice produced marked macrophage-predominant inflammation and elevation of serum MCP-1 that peaked after 1 week and resolved at 1 month, suggesting that the normal lung has the capacity to dissolve the stones and return to a normal state. EDTA lavage of the lung, ex vivo, was effective at reducing the burden of stones. Administration of a very low phosphate diet to young knockout animals prevented microlith formation and reduced serum SP-D (Fig. 27.3). In older animals with established PAM lesions, low phosphate diet reduced the profusion of hyperdense infiltrates on radiographs and micro-CTs. Mechanisms involved with the beneficial effects of low phosphate diet on microlith burden remain unclear, but given preliminary findings that dietary phosphate intake has a direct effect on alveolar phosphate levels and osteoprotegerin levels in the alveolar lining fluid, possibilities being considered include upregulation of alternative phosphate transporters and activation of pulmonary osteoclast-like cells (unpublished data, personal observations).

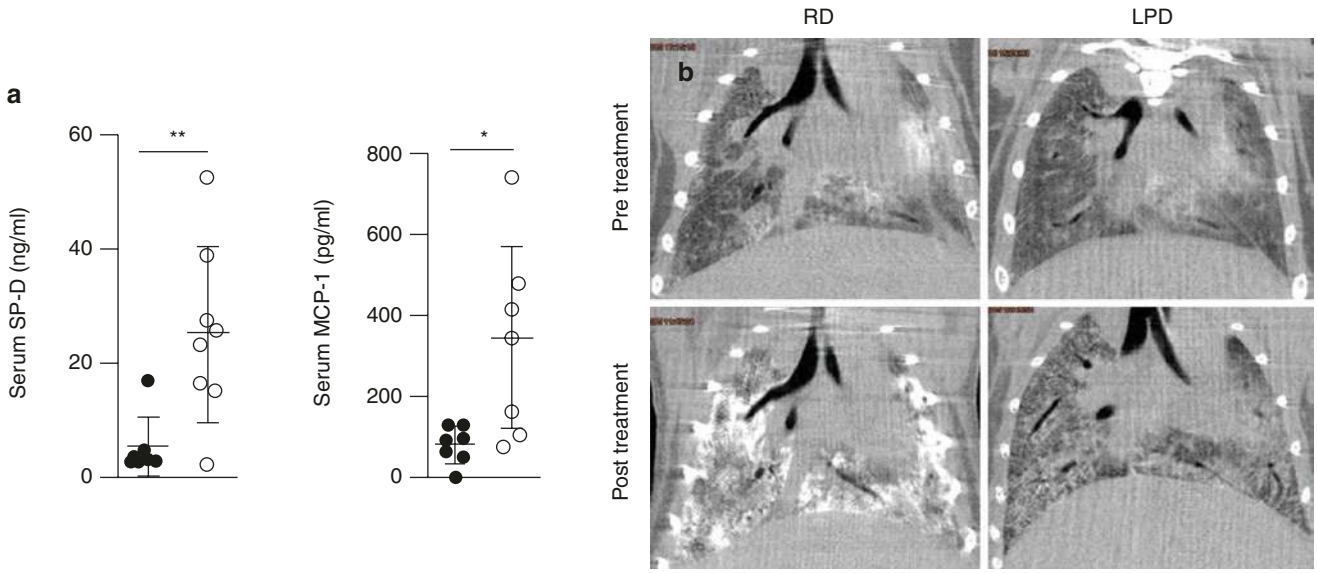


Fig. 27.3 Biomarkers and dietary intervention in PAM. (**a**) Serum levels of SP-D and MCP-1 are elevated in PAM patients (open circle) compared to healthy volunteers (closed circle). (**b**) Low phosphate diet (LPD) prevents microlith accumulation in mice, when compared to mice on regular diet (RD). (From Saito, A., Nikolaidis, N.M., Amlal, H., et al. Modeling pulmonary alveolar microlithiasis by epithelial deletion of the Npt2b sodium phosphate cotransporter reveals putative biomarkers and strategies for treatment. Sci Transl Med 2015;7(313):313ra181; with permission)

Clinical Features

Approximately 50% of PAM patients are asymptomatic at time of diagnosis [46]. Dyspnea with exertion is the most frequent presenting symptom, occurring in about a quarter of patients at diagnosis. Nonproductive cough, chest pain, weakness, cyanosis, and hemoptysis have also been reported as presenting manifestations. Subjective complaints are commonly less severe than chest imaging suggests, a characteristic long associated with PAM and described as "clinical-radiological dissociation." [47] Pneumothorax can occur, likely as a result of subpleural cyst rupture, but is uncommon. Smoking and pulmonary infection may accelerate disease progression, thought the available evidence is circumstantial and anecdotal [24].

While Npt2b is expressed in the mammary glands, intestines, kidneys, skin, prostate, and testes, extrapulmonary disease is not typically seen. Deposition of microliths in the male genitalia has been described in patients with PAM and can result in hematuria, testicular atrophy, obstructive azoospermia, and infertility [48–53]. This has led some to conclude that testicular microlithiasis is associated with PAM. It is important to note that testicular microlithiasis is quite common, affecting 0.6–9% of males in the general population, and that chance associations of a common disease with a rare disease are often difficult to exclude. Corut et al. were not able to identify a clear link between testicular microlithiasis and mutations in *SLC34A2* [24]. Until this issue is better understood, due consideration of testicular microlithiasis is probably reasonable in males with PAM, since it is thought to predispose to testicular malignancies and male infertility [54–56].

Discoid lupus, rheumatoid arthritis, psoriasis, antiphospholipid syndrome, Sjogren's syndrome, lymphocytic interstitial pneumonitis, non-Hodgkin lymphoma, pericardial cysts, osteopetrosis, hypertrophic osteoarthropathy, and pectus excavatum have all also been reported in patients with PAM. These were mostly limited to single patient reports, so it is unclear if there is any true association between these disorders and PAM. Some comorbid conditions, such as hypertrophic osteoarthropathy, were likely underreported in prior literature. Others, such as the autoimmune diseases listed above, seem more likely to be chance occurrences. Other heritable diseases have also reported in PAM, including diaphyseal aclasis (associated with multiple osteochondromas) and autosomal recessive Waardenburg-anophthalmia syndrome (associated with malformation of the eyes and the skeleton); but it is difficult to distinguish between disease co-transmission in consanguineous marriages and a direct relationship between PAM and genetic disorders in these cases.

Pulmonary function tests can initially be normal. A restrictive ventilatory defect and reduced diffusing capacity (D_{LCO}) typically develop over time. Echocardiography may reveal pulmonary hypertension and evidence of right heart failure [57], findings which may prompt expedited evaluation for lung transplantation.

Serum phosphate and calcium are typically normal in patients with PAM, most likely because SLC34A2 is not abundantly expressed in the kidney and is not required for phosphate uptake in cases when dietary phosphate is abundant [58]. Takahashi et al. found elevated serum levels of surfactant protein-D (SP-D) in two consecutive patients, which may reflect higher alveolar SP-D levels, compromised alveolar basement membrane integrity, altered polarity of alveolar type II cells, or a combination of the three [24]. Patients with PAM have also been shown to have elevated serum MCP-1 [42]. These reports suggest SP-D and MCP-1 as potential diagnostic biomarkers or indicators of disease activity or progression, though further investigation is needed.

The calcified microliths of pulmonary alveolar microlithiasis produce highly characteristic radiographic findings, defined by a fine diffuse basilar-predominant micronodular pattern that produces the classic "sandstorm" appearance described in the literature. (Fig. 27.4) These infiltrates can obscure the heart borders, diaphragm, and great vessels (the "vanishing heart" phenomenon) [59]. Air bronchograms can often be seen coursing through areas of consolidation as well.

High-resolution computed tomography of the chest shows widespread microcalcifications throughout both lungs. (Fig. 27.3) Although these densities are typically diffusely distributed, they can also predominate in the posterior segments of the lower lobes. An increase in microliths in the upper lobes has been described in smokers. Ground-glass opacities and airspace consolidations can occupy large proportions of the lung fields, particularly in patients with progressive disease [53, 60]. Linear radiolucencies at the pleural boundaries abutting the heart, diaphragm and chest wall can produce the "black pleura" sign, another characteristic radiological feature of PAM that is likely secondary to the subpleural cystic changes that are often seen on cross sectional imaging and pathological evaluations [61, 62]. These cystic changes appear to be the result of alveolar duct dilation [53]. In a small series of cases in Brazil, ground-glass opacities and small parenchymal nodules were the primary CT findings. In addition, small subpleural nodules and subpleural cysts were seen frequently (in 92% and 85% of cases, respec-

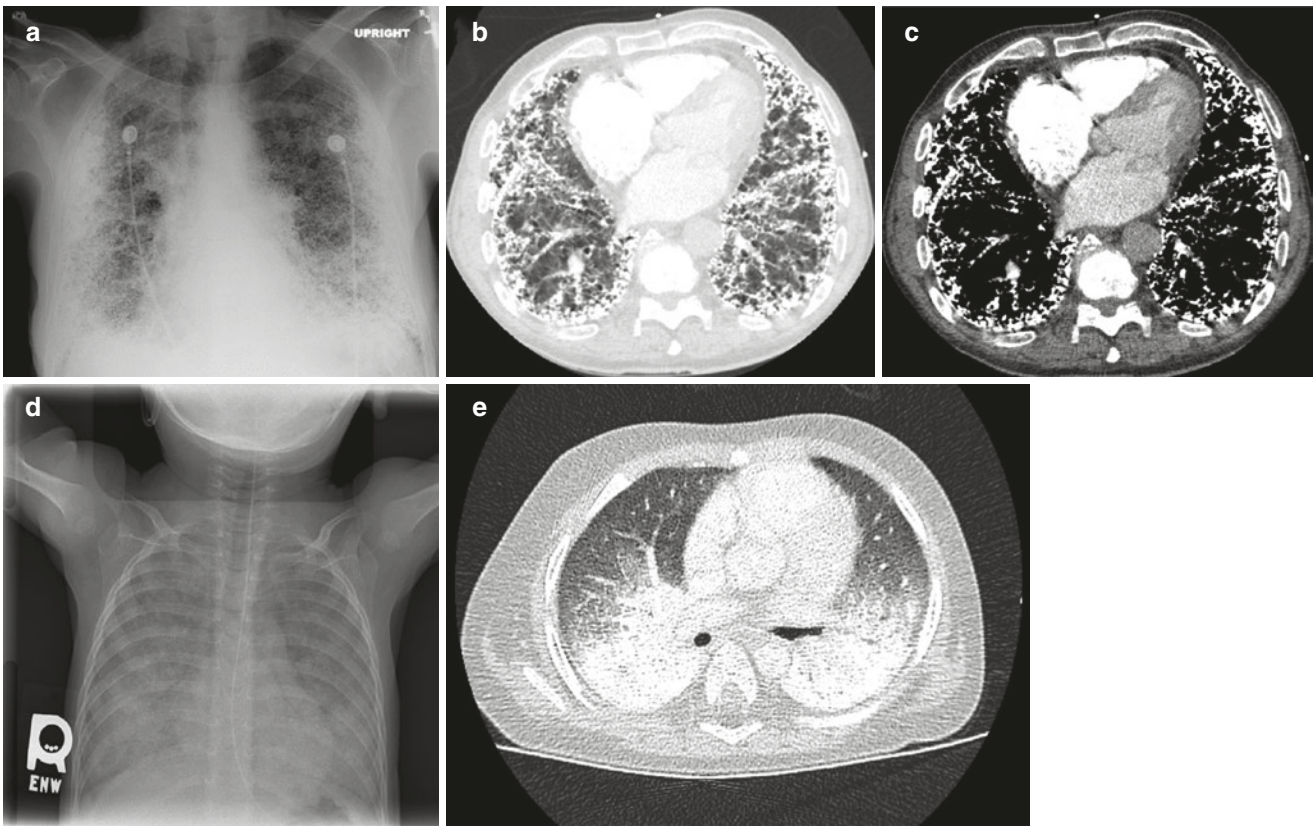


Fig. 27.4 Radiographic appearance of pulmonary alveolar microlithiasis. (**a**) Chest radiograph and high-resolution computed tomography of the chest, (**b**) lung windows, and (**c**) mediastinal windows of an elderly male with PAM. Note the diffuse basilar-predominant micronodular "sandstorm" appearance on chest radiograph and small subpleural, fissural, and septal microcalcifications along with diffuse ground-glass opacities seen on HRCT. (**d**) Chest radiograph and (**e**) HRCT lung windows showing ground-glass infiltrates from a 2-year-old infant with PAM who underwent transplant (see Figs. 27.1 and 27.2). (https://doi.org/10.1016/j.ehpc.2018.04.004)

tively). Other common findings in decreasing order of prevalence included subpleural linear calcifications, crazy paving, nodular fissures, interlobular septal calcifications, and dense consolidations [63]. In general, these radiographic findings tend to correlate well with pathologic findings [58].

PAM is most often confused with miliary tuberculosis, in part because the regions where consanguineous marriage is common frequently overlap with areas with high tuberculosis prevalence. Sometimes this overlap manifests in the same patient; there have been at least five cases of superimposed tuberculosis infection in patients with PAM [4]. Once felt to be pathognomonic for pulmonary alveolar proteinosis, crazy paving on high resolution CT has also been described in PAM and can lead to misdiagnosis; however, the bone-level density of pulmonary parenchymal opacities noted on the mediastinal windows distinguish PAM from PAP [4, 64]. Another consideration in the differential is metastatic pulmonary opacification which can occur in the setting of end-stage renal disease or in hyperparathyroidism, milk-alkali syndrome, talcosis, amiodarone toxicity, iodinated oil embolism, and aspirated or extravasated contrast media [65]. Additional mimics include healed varicella or variola pneumonia; pneumoconioses like silicosis; pulmonary hemosiderosis; and granulomatous diseases like sarcoidosis, histoplasmosis, and amyloidosis. (Fig. 27.5)

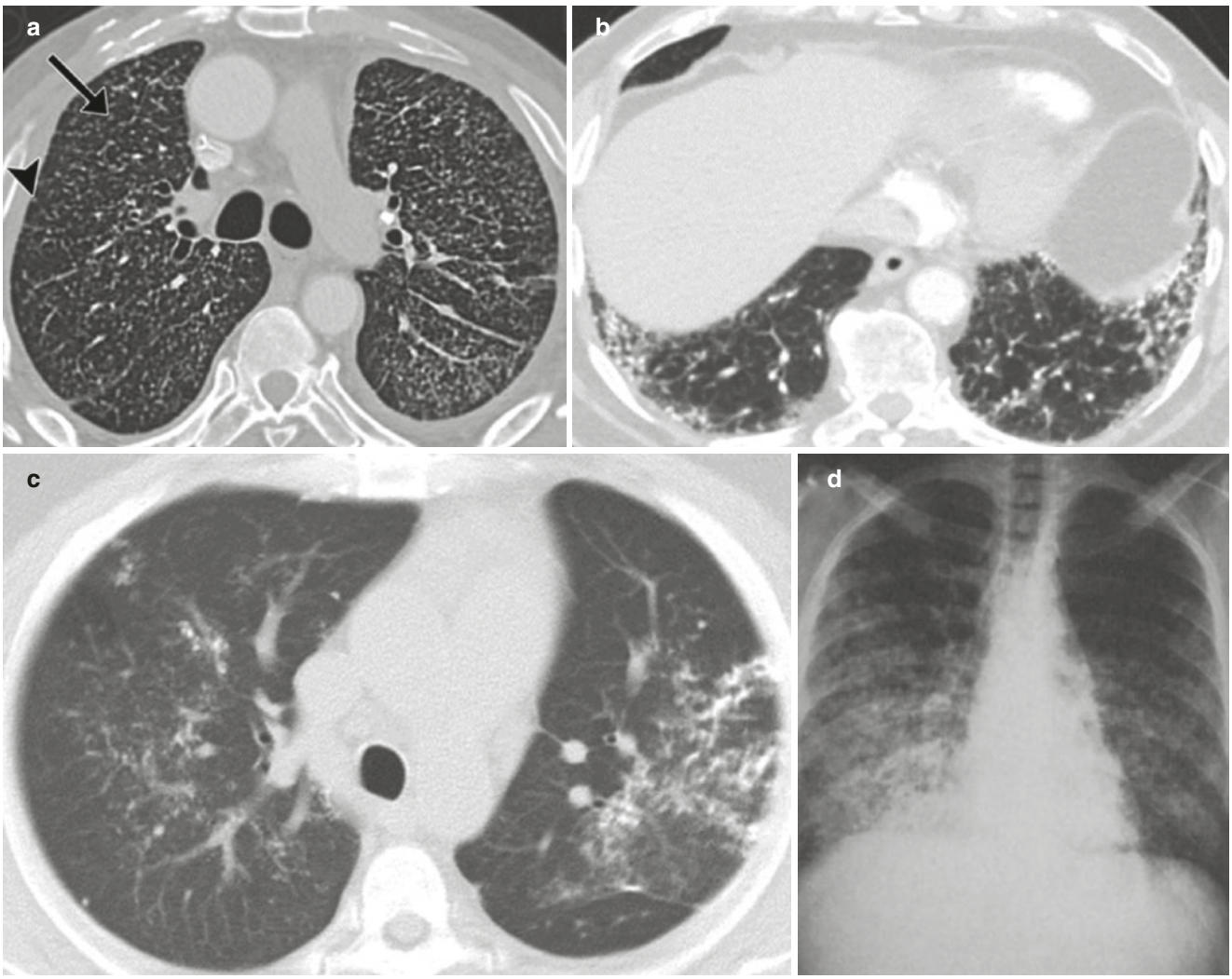


Fig. 27.5 Differential diagnosis of pulmonary alveolar microlithiasis. (**a**) Miliary tuberculosis. [Note centrilobular (arrow) and subpleural (arrowhead) nodules] (**b**) Dendriform ossification. (**c**) Metastatic pulmonary calcifications. (**d**) Healed Varicella pneumonia. [(**a**) Reprinted with permission of Radiological Society of North America. Copyright © 2020. Nachiappan A C, Rahbar K, Shi X, et al. Pulmonary tuberculosis: Role of radiology in diagnosis and management. RadioGraphics 2017;37:52–72. (**d**) Reprinted with permission of the American Thoracic Society. Copyright © 2020 American Thoracic Society. George, R., Weill, H., et al. 1967. "Roentgenographic Appearance of Viral and Mycoplasmal Pneumonias." Am Rev. Resp Dis*. Vol 96; pp. 1144–1150. *Journal now titled: the American Journal of Respiratory and Critical Care Medicine]

Diagnosis

The diagnosis of PAM is often readily established with characteristic imaging, especially in the setting of positive family history. In those cases where doubt still exists, further diagnostic studies may be helpful. Expectorated sputum has produced microliths in some cases [66, 67]. Bronchoalveolar lavage can aid in diagnosis: Although the sensitivity and specificity for such findings is unknown, BAL can produce microliths with the typical morphological appearance or lamellar structure and periodic-acid Schiff-positive staining on histological sections. Scanning electron microscopy can reveal the porous surface reminiscent of bone that is typical for microliths. In addition, a lavage is useful for exclusion of other possible differential diagnoses, such as infectious diseases. Transbronchial lung biopsy appears to have reasonable yield and safety profile but is not required when the presentation and imaging are characteristic [68]. Despite the multiple avenues available for making a non-invasive diagnosis, use of lung biopsy is still quite common. In their review of 1022 worldwide cases, Castellana et al. found that since 1980, 56.6% of patients underwent invasive procedures for diagnosis (BAL and/or transbronchial biopsy, open lung biopsy, or autopsy) as compared to 36.7% in the previous era [69]. The rate of open lung biopsies remained steady (23.1% vs. 25.4%), however. These findings suggest that the disease remains unfamiliar to many physicians, which is not surprising given its rarity. In general, lung biopsy should be reserved for cases where uncertainty persists despite more conservative diagnostic methods.

Screening family members of the index case for disease should be considered in those who wish to proceed after appropriate genetic counseling. Genotyping for *SLC34A2* mutations is now commercially available. Documenting the mutation is not currently helpful for disease management given the absence of any reports of clinically relevant genotype-phenotype associations.

Management

The long-term prognosis of PAM is incompletely understood. The wide range of ages of patients reported in the world literature suggest a variable course that may be modified by environmental factors including smoking. Few case series have reported longitudinal outcomes of patients with PAM. The largest of these was a 2009 study of 53 Japanese subjects which included 28 patients who were first diagnosed in childhood. Of those who had 20- to 49-year follow-up periods, 42.9% had died of respiratory failure related to PAM, with a mean age of death of 46.2 years. These results suggest a poor overall long-term prognosis, even in asymptomatic patients diagnosed in childhood [58]. MCP-1 and SP-D, as noted above, are potential biomarkers for diagnosis and disease activity, but they require further testing to validate their role in management.

Of the empiric therapies that have been reported, the bisphosphonate, etidronate, is perhaps the most frequently employed but is controversial. Etidronate is FDA-approved for treatment of Paget's disease and heterotopic ossification, though a subsequent Cochrane review on the efficacy of the approach for the latter was withdrawn. Etidronate not only inhibits bone resorption by osteoclasts, which would not necessarily be desirable if these or other myeloid derived cells play a role in controlling stone accumulation, but also prevents hydroxyapatite crystal formation and bone mineralization [70, 71]. This property is unique to etidronate, and gives it a theoretical advantage over other bisphosphonates. Since 1992, several case series have highlighted use of etidronate for PAM, especially in pediatric patients [29, 72–77]. The data are limited, and results are mixed. Several showed improvements in lung function and reduction of radiographic opacification of the lungs. In another three cases, etidronate did not provide any benefits in these clinical parameters [76]. To our knowledge, use of etidronate has not been reported in adults with PAM and further studies are needed before the drug can be routinely recommended in any patient population.

Other treatments that have been attempted have not been effective. Corticosteroids and chelating agents like systemic sodium thiosulfate have not been shown to modify disease course [78]. Serial whole-lung lavage was considered a possible treatment modality in the past since microliths are confined to the alveolar lumen but unfortunately there is no evidence for the merit of this approach [79–81].

At this point, treatment is primarily supportive. All patients who are hypoxemic at rest, during sleep, or with exertion should be started on supplemental oxygen. As with all patients with chronic lung diseases, PAM patients should receive pneumococcal and influenza immunizations. Referral to pulmonary rehabilitation is likely helpful as well. Screening for the development of secondary pulmonary hypertension and right heart failure with serial transthoracic echocardiography is reasonable, as many patients eventually develop cor pulmonale.

Patients who develop spontaneous pneumothorax may not respond to conservative treatment with chest tube placement [82] and may require early surgical pleurodesis.

Patients with end-stage disease—especially those with right heart failure or chronic hypoxemic respiratory failure—should be referred to regional lung transplant centers. Optimal timing is not clear given the insidious nature of PAM and the lack of prognostic biomarkers or models [4]. As of late 2019, UNOS had records of lung transplantation being performed in 20 PAM patients [83–89]. The most common approach was bilateral lung transplantation (15/20 patients), although single lung transplantation has also been performed. Pleural adhesions and calcifications may make resection of the native lung during transplantation more technically difficult, but strategies exist to mitigate risk [87, 90]. Transplant outcomes for PAM patients have not been compared to outcomes of patients with other lung diseases, but available reports in the world literature are reassuring. Importantly, since the first transplant for PAM almost 30 years ago, no recurrence of alveolar microlithiasis has been reported in the allografts, as would be expected based on our new understanding of disease pathogenesis [21].

Summary

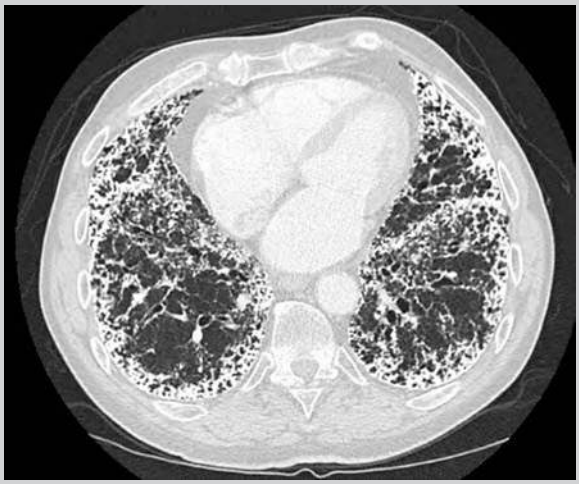
PAM is a hereditary disease characterized by the deposition of calcium phosphate crystals in the alveoli of the lungs caused by mutations in the type IIb sodium phosphate co-transporter. Patients typically present in their second or third decade of life and are often asymptomatic or only mildly dyspneic at the time of diagnosis, even when the imaging suggests extensive lung involvement. Characteristic chest tomography with widespread microcalcifications, diffuse ground-glass opacities, and dense airspace consolidations is frequently diagnostic, especially in the setting of a positive family history. Progressive disease ultimately results in worsening exertional dyspnea and respiratory failure. Treatment is primarily supportive. In patients with end-stage disease, lung transplantation may be an option; and timely referral for evaluation is essential. Recent development of an animal model has led to promising avenues of inquiry for further trials.

Box 27.1 Clinical Vignette

A 24-year-old male graduate student presents to clinic for evaluation of abnormal chest imaging. He had recently injured his shoulder in a minor car accident, and X-ray incidentally noted a diffuse micronodular pattern that prompted computed tomography of the chest.

He is asymptomatic. He has no environmental or occupational exposures. He is unsure whether there is any family history of respiratory diseases. Physical examination and laboratory data are unremarkable. Patient grew up in a region with endemic tuberculosis, so consecutive acid-fast bacilli smears and cultures are obtained and return negative. Given characteristic imaging, he is diagnosed with pulmonary alveolar microlithiasis. Whole genome sequencing for SLC34A2 reveals a mutation consistent with the diagnosis.

The patient's clinical status remains stable for decades until he develops insidious onset progressive dyspnea on exertion and requires supplemental oxygen. He is ultimately referred for bilateral lung transplant, which he undergoes successfully.



Box 27.2 Diagnostic Criteria

Definite PAM

Characteristic HRCT findings
PLUS
Histopathologic evidence of PAM on expectorated sputum, bronchoalveolar lavage, transbronchial biopsies, or surgical lung biopsy
OR
SLC34A2 mutation
OR
Affected first degree relative

Likely PAM

Characteristic HRCT findings
AND
No alternate diagnosis

Based on algorithm recently proposed by our group (Kosciuk P, Meyer C, Wikenheiser-Brokamp KA, McCormack FX Eur Respir Rev 2020). No validated criteria exist at present.

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Rare Diffuse Lung Diseases of Genetic Origin

28

Paolo Spagnolo and Nicol Bernardinello

Abbreviations

DC	Dyskeratosis congenita
HPS	Hermansky-Pudlak syndrome
HRCT	High-resolution computed tomography
ILD	Interstitial lung disease
NF1	Neurofibromatosis 1
NPC	Niemann-Pick C
NPD	Niemann-Pick disease
NSIP	Nonspecific interstitial pneumonia
SFTP	Surfactant protein
UIP	Usual interstitial pneumonia

Introduction

A 48-year-old Italian woman was seen in our outpatient clinic in April 2010. She reported a 2-year history of progressive dyspnea and reduced exercise tolerance. She had sought medical attention when her cough, which her doctor attributed to an upper respiratory tract infection, did not go away with broad-spectrum antibiotics. She had smoked 20 cigarettes daily for 25 years and was on no regular medication. She also reported a history of menorrhagia, decreased visual acuity with horizontal nystagmus, and easy bruising. She had no joint involvement or other signs or symptoms to suggest an underlying connective tissue disease. She denied significant environmental or occupational exposures and no precipitins to alveolitic antigens were detected. Family history revealed that one of the patient's siblings had albinism. On examination, she had fair skin and digital clubbing; widespread velcro-type end-inspiratory crackles could be heard on lung auscultation. Oxygen saturation at rest on room air was 94% but rapidly dropped to 85% during a 6-min walk test. Chest radiograph showed bilateral reticular opacities. A CT thorax confirmed the presence of diffuse interstitial fibrosis with extensive subpleural honeycombing particularly in the upper zones (Fig. 28.1). Lung function tests showed a restrictive ventilatory defect (forced vital capacity 60% of predicted) with a severe reduction in gas transfer (27% of predicted). Cardiac ultrasonography showed an estimated right ventricular systolic pressure of 60 mmHg. The right ventricle was dilated and mildly hypokinetic, with no hypertrophy. She was treated with supportive care only. The patient rapidly deteriorated and died 11 months later while listed for lung transplantation.

Pulmonary fibrosis may occur in the context of several genetic disorders, the most common being dyskeratosis congenita and Hermansky-Pudlak syndrome. Disorders caused by the inheritance of a single defective gene are referred to as *monogenic* or single gene disorders. They may be either "recessive" (i.e., they produce the diseased phenotype only if a copy of the abnormal gene is transmitted by both parents) or "dominant" (i.e., the transmission of a single copy of the abnormal gene is sufficient for the disease to occur), and are generally due to rare genetic variants (i.e., *mutations*) often leading to a single amino acid change in the encoded protein. Conversely, *complex* diseases result from genetic variations relatively common in the general population (termed "polymorphisms") and, importantly, involving multiple genes, each contributing an effect of varying magnitude. In addition, gene-gene and gene-environment interactions are believed to contribute significantly to disease pathogenesis and clinical manifestations.

The genetics of diffuse parenchymal lung disease is complex. For example, idiopathic interstitial types of pneumonia display considerable genetic heterogeneity and carriage of both rare (i.e., within surfactant protein C, surfactant protein A2, telomerase reverse transcriptase and telomerase RNA component genes, among others [1–7]) and common variants (i.e., within *MUC5B* gene) [8] increases the risk of developing the disease. In familial forms of pulmonary

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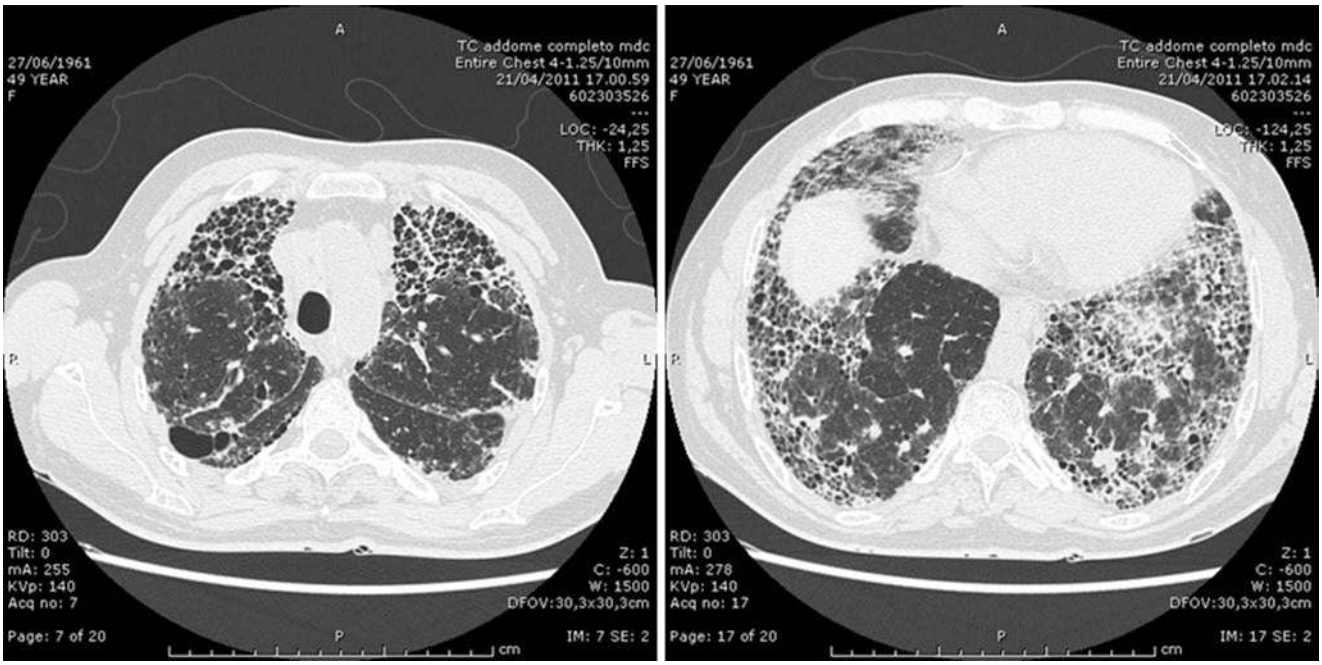


Fig. 28.1 Hermansky-Pudlak syndrome. CT images through upper and lower lung zones showing extensive subpleural honeycombing bilaterally, more prominent in the lower lung zones where ground glass opacity is also present

fibrosis, many of the pedigrees show vertical transmission consistent with an autosomal dominant pattern of inheritance, though with variable penetrance. Indeed, as many as 45% of the pedigrees display phenotypic heterogeneity, suggesting that the underlying genetic factors may lead to an increased "generic" predisposition to pulmonary fibrosis with additional (largely unidentified) factors acting as disease modifiers [9].

Hermansky-Pudlak Syndrome

Hermansky-Pudlak syndrome (HPS) is a rare autosomal recessive disorder characterized by oculo-cutaneous albinism, bleeding diathesis, and accumulation of ceroid lipofuscin, an amorphous lipid-protein material, in the reticuloendothelial system of various tissues [10, 11]. Seemingly disparate, these abnormalities are believed to be related to defective formation, intracellular trafficking, or function of lysosomes (ceroid lipofuscin deposition), or lysosome-related organelles such as melanosomes (oculocutaneous albinism) and platelet dense bodies (bleeding dysfunction) [12]. Specifically, hypopigmentation is secondary to impaired melanosome formation, trafficking, or transfer to keratinocytes, while the bleeding diathesis is caused by the absence of platelet dense bodies, which are involved in secondary platelet aggregation.

Ten types of HPS associated with mutations in 10 different genes have been described. HPS types 1 and 4 are the most severe forms of the disease and are associated with pulmonary fibrosis, hemorrhage, and granulomatous colitis while types 3, 5, and 6 diseases are associated with a milder phenotype. Prevalence is estimated at 1–2 per million population worldwide but is as high as 1 in 1800 in northwestern Puerto Rico, making it the most common single-gene disorder in this population and accounting for approximately 50% of all cases globally [13]. Notably, most Puerto Rican individuals affected by HPS type 1 carry the same 16-base-pair duplication in exon 15 of *HPS1* gene (10q23.1), suggesting a founder effect [14]. Additional mutations associated with HPS are located within *AP3B1* (5q14.1; HPS-2), *HPS3* (3q24), *HPS4* (22q11.2-q12.2), *HPS5* (11p15-p13), *HPS6* (10q24.32), *DTNBP1* (6p22.3; HPS-7), *BLOC1S3* (19q13; HPS-8), *PLDN* (15q21.1; HPS9), and *AP3D1* (19p13.3; HPS10), which encode components in one of four protein complexes (i.e., adapter protein 3 [AP-3] and biogenesis of lysosome-related organelles complex 1, 2, and 3 [BLOC-1, BLOC-2, BLOC-3]) that support intracellular biogenesis and trafficking of lysosome and lysosome-related organelles [11].

The diagnosis of HPS can be suspected in patients with skin and hair color lighter than the other family members and with a history of excessive bleeding and bruising, early-onset pulmonary fibrosis, or granulomatous colitis, but is generally established by "whole mount" electron microscopy of plate-

lets showing the absence of dense bodies [15, 16]. Conversely, bleeding time assessment is not reliable and is not recommended in the diagnostic work-up of HPS [17]. Genetic testing confirms the diagnosis of HPS and determines the disease subtype. All HPS subtypes are associated with oculocutaneous albinism, although with variable degrees of hypopigmentation. Bleeding diathesis is similarly present in all HPS patients with severity ranging from easy bruising and epistaxis to postpartum hemorrhage and serious bleeding during surgery [18].

Progressive pulmonary fibrosis, the most serious complication, usually presents in the third or fourth decade—although has been reported as early as in adolescence—and occurs only in patients with HPS types 1 (100% of cases), 2, and 4 [19, 20]. While the pathogenic mechanisms of HPS-related pulmonary fibrosis remain largely unknown, dysfunction of lamellar bodies in type II pneumocytes, which synthesize, store, and release surfactant, is probably a contributing factor in causing deposition of ceroid and degeneration and death of type II cells [21]. However, the early development of pulmonary fibrosis in HPS suggests that environmental or external insults, acting either alone or coupled with abnormal repair mechanisms, may represent contribute to disease pathogenesis. Chest radiograph and high-resolution computed tomography (HRCT) show nonspecific patterns of diffuse, peripheral reticulation, traction bronchiectasis and bronchiolectasis, subpleural cysts, and ground glass opacities [22]. Honeycombing, when presents, prevail in the lower lobes but is not predominantly subpleural as in the usual interstitial pneumonia (UIP) pattern of pulmonary fibrosis seen in idiopathic pulmonary fibrosis (IPF). Similarly, the active *fibroblastic foci* characteristic of UIP are rarely present in HPS [23]. HRCT findings tend to differ somehow as the disease progresses. In milder cases, the most common abnormalities include thickened interlobular septa, reticular changes, and ground glass opacities [22]. Histologic examination of the lung, in addition to the extensive fibrosis of the alveolar walls, reveals the presence of macrophages filled with ceroid throughout the interstitium and alveolar spaces. Lung disease is the leading cause of death in HPS, followed by gastrointestinal and hemorrhagic complications. There are currently no effective treatments for HPS-related pulmonary fibrosis and the average life expectancy of individuals affected is 40–50 years. Therefore, lung transplantation remains the only potentially life-extending therapy for progressive lung disease, though only in a selected minority of patients [24]. An initial trial of 21 Puerto Rican patients with HPS type 1 suggested that pirfenidone, a drug approved for the treatment of IPF, might delay disease progression in individuals with forced vital capacity (FVC) >50% predicted [25]. However, a subsequent study in patients with HPS-related pulmonary fibrosis and preserved lung function showed no benefit from pirfenidone and was prematurely discontinued [26].

Telomerase-Associated Pulmonary Fibrosis

Telomeres are regions of repetitive nucleotide sequences (TTAGGG) that protect the ends of the chromosomes from degradation. Indeed, with repeated cell division, telomeres tend to shorten and the chromosomes may become unstable, fused, or lost, leading to cell apoptosis or senescence. In addition to age, environmental factors, such as smoking, affect telomere function by reducing their length [27]. A complex of proteins and RNA called *telomerase* is essential in extending telomeres, by adding TTAGGG repeats to the chromosome end, thus preventing its shortening. The reverse transcriptase component *TERT* and the RNA template component *TERC* are key components of the *telomerase complex*, whereas several small nucleolar ribonucleoproteins are responsible for the assembly and stability of the telomerase [28]. Mutations in the genes encoding any of the factors implicated in telomere function lead to abnormally short telomeres.

Dyskeratosis congenita Dyskeratosis congenita (DC) is a rare systemic disorder with an overall incidence of 1 in 1,000,000 persons that generally manifests in the first or second decade with bone marrow failure, the leading cause of death, and the classic triad of abnormal skin pigmentation dystrophic nails, and oral leukoplakia [29]. DC is considered a syndrome of premature aging as suggested by features, such as premature graying of the hair, pulmonary fibrosis, dental abnormalities, arteriovenous malformations, testicular atrophy, cryptogenic cirrhosis, osteoporosis, and increased risk of several malignancies (i.e., myelodysplastic syndrome, leukemia, and solid tumors). Further corroborating this hypothesis, DC has been the first disease recognized to result from impaired telomere maintenance [30]. The majority of DC patients carry a pathogenic mutation in one of the following genes encoding components or regulators of the telomerase complex: *ACD* (adrenocortico dysplasia homolog), *CTC1* (conserved telomere maintenance component 1), *DKC1* (dyskerin 1), *NAF1* (NEF-associated factor 1), *NHP2* (non-histone protein 2), *NOP10* (nucleolar protein 10), *PARN* (polyadenylate-specific ribonuclease), *RTEL1* (regulator of telomere elongation helicase 1), *STN1* (subunit of CST complex), *TERC* (telomerase RNA component); *TERT* (telomerase reverse transcriptase), *TINF2* (TRF1-interating nuclear factor 2), *WRAP53* (WD repeat-containing protein antisense to TP53). The mode of inheritance may be autosomal dominant, autosomal recessive, or X-linked, depending on the affected gene. Specifically, the autosomal dominant disease has been observed with mutations in, among others, *TERC*, *TERT*, *PARN*, *TINF2,* and *RTEL1*; autosomal recessive disease has been observed with mutations in, among others, *TERT*, *PARN,* and *RTEL1*; whereas X-linked DC results

from mutations in *DKC1*. Accordingly, there is a wide variation in severity and spectrum of manifestations, although the more clinically severe forms of DC are associated with the greatest reduction in telomere length. For instance, patients carrying mutations in *TINF2* have extremely short telomeres and tend to present with bone marrow failure before 5 years of age [31]. Affected cases may also demonstrate genetic *anticipation*, the occurrence of more severe and earlier onset disease in later generations secondary to the progressive shortening of telomeres [32]. While telomere length is uniformly reduced in DC, thus indicating a shared mechanism, as many as 30% of patients do not have an identifiable pathogenic mutation.

The range of pulmonary phenotypes associated with mutations in telomere-related genes is wide, ranging from pulmonary fibrosis to emphysema and pulmonary vascular disease [33]. Pulmonary fibrosis develops in approximately 20% of cases and tends to present in adulthood (fourth or fifth decade). The histology most often demonstrates UIP, although other patterns such as bronchiolocentric inflammation and nonspecific interstitial pneumonia (NSIP) have also been described. The prognosis of DC patients after the development of pulmonary fibrosis is poor, with death occurring 12–40 months after the onset of dyspnea [34]. Pulmonary complications may also arise after stem cell transplantation is used to treat bone marrow failure [30].

Carriage of mutations in genes involved in the telomere biology and short telomere length is also well described in familial and sporadic pulmonary fibrosis cases without features of DC. Approximately one-quarter of familial cases and 10% of sporadic cases of idiopathic pulmonary fibrosis are associated with mutations within telomere-related genes [33], and individuals carrying such mutations invariably have telomeres shorter than age-matched controls [35]. However, short telomeres are also found in 25% of sporadic and 37% of familial cases of pulmonary fibrosis that do not carry pathogenic mutations within telomere-related genes [4].

In a large series of patients with mutations in *TERT* ($n = 75$), *TERC* ($n = 7$), *RTEL1* ($n = 14$) and *PARN* ($n = 19$), 46% had IPF, 20% unclassifiable lung fibrosis, 12% chronic hypersensitivity pneumonitis, 10% pleuroparenchymal fibroelastosis (10%), 7% interstitial pneumonia with autoimmune features, 4% idiopathic interstitial pneumonia (other than IPF) and 4% connective tissue disease-related interstitial fibrosis [36]. Notably, mutations in these genes were associated with progressive disease irrespective of the underlying specific diagnosis. Moreover, there is evidence that short telomere length may be a risk factor for the development of diseases outside the lung, such as liver cirrhosis, cancer, diabetes, sepsis, and stroke [37–40].

Lysosomal Storage Diseases

Lysosomes are cytoplasmic membrane-bound organelles involved in the breakdown and recycling of macromolecules such as lipids, proteins, and carbohydrates. Lysosomal storage diseases (LSDs) are a highly heterogeneous group of inherited disorders of lysosomal catabolism, with an estimated incidence ranging from 1 in 50,000 to 1 in 250,000 live births [41]. LSDs are characterized by specific enzyme deficiencies resulting in endolysosomal accumulation of non-degraded or partially degraded substrates and impaired lysosomal function. LSDs typically manifest in infancy and childhood with a broad spectrum of clinical phenotypes depending on the substrate involved, residual enzyme activity, and site of accumulation. Because LSDs are systemic disorders, virtually all organs may be involved, including the respiratory system, either at presentation or as a late-onset complication.

Gaucher's Disease Gaucher's disease (GD)—the most common LSD—is an autosomal recessive disorder caused by mutations in glucocerebrosidase 1 (*GBA1*) gene, leading to defective glucocerebrosidase activity and endolysosomal accumulation of insoluble glucocerebroside (glucosylceramide) in monocytes and macrophages [42]. GD has been identified throughout the world and has an estimated prevalence of 0.7–1.75 per 100,000 [43]; however, the disease is more common among Jewish [44]. The pathologic hallmark of GD is the accumulation of lipid-laden and distended macrophages (*Gaucher cells*) in the macrophage-monocyte system, particularly in the liver, spleen, and bone marrow. Gaucher cells, which are 20–100 μm in diameter, have a characteristic wrinkled-paper appearance and stain positively with PAS, can also infiltrate the lung interstitium, alveolar spaces, or pulmonary vasculature, although the precise mechanism by which organ damage develops remains unclear [45].

Patients with GD may display a number of clinical phenotypes ranging from subclinical adults to children with devastating neurological diseases. Indeed, GD is classified into three broad phenotypes based on the presence or absence of neurological involvement: type 1 (*non-neuronopathic*), the most common, type 2 (*acute neuronopathic*), and type 3 (*subacute neuronopathic*) [42].

GBA1 gene is located at 1q21 and comprises 11 exons. Nearly 300 mutations within *GBA1* have been identified in GD, including frame-shift mutations, point mutations, deletions, insertions, splice site mutations, and recombinant alleles [46]. Based on the level of glucosylceramidase production, these mutations are commonly classified as *null*, *severe,* or *mild*. In the presence of *null* mutations, such as

c.84dupG (84 GG), there is no enzyme production, while severe mutations, such as c.1448 T > C (L444P), though leading to enzyme production, are usually associated with Type 2 or 3 diseases when inherited with a null or another severe mutation. Conversely, mild mutations, such as c.1226A > G (N370S), are only associated with type 1 disease [47]. Type 1 GD is often referred to as adult-type GD, but the majority of symptomatic patients are diagnosed with the disease before reaching adulthood [45]. Hepatosplenomegaly, and hematological and bone abnormalities are the predominant manifestations of the disease [48], whereas pulmonary involvement is a rare finding (<5% of cases) [49]. However, pulmonary function or radiological abnormalities have been observed in as many as 68% and 17%, respectively, of (mostly asymptomatic) patients [50]. Type 2 disease manifests before the first year of life with a rapidly progressive course leading to death in the early years of life whereas type 3 GD patients tend to experience a slowly progressive disease course [51]. The distinction between type 2 and type 3 diseases is often difficult, and some authors believe they may represent a spectrum of disease manifestations. The diagnosis of GD requires the detection of deficient glucocerebrosidase activity in peripheral blood leucocytes; genetic testing can detect pathogenic variants within *GBA1* thus confirming the diagnosis.

Four patterns of pulmonary involvement may be observed, namely intracapillary, patchy interstitial infiltrates in a lymphatic distribution, massive interstitial thickening of alveolar septa and intra-alveolar infiltrates, which result from infiltration of alveolar, interstitial, perivascular, and peribronchial spaces by Gaucher cells. Accordingly, chest X-ray and HRCT show bilateral interstitial infiltration, in the form of either a predominant ground glass pattern with superimposed thickening of interlobular septa ("crazy paving") or a diffuse reticular infiltration [52]. L444P homozygotes appear at major risk for developing the pulmonary disease, even at an early age [52]. On the other hand, pulmonary hypertension, strongly associated with splenectomy and female gender, may occur in subjects with non-N370S mutation, positive family history, and angiotensin-converting enzyme I gene polymorphism [53]. Despite significant advances in our knowledge of the spectrum of *GBA1* mutations, the possibility to make prognostic predictions from genotype data remains limited. Indeed, while it is possible to enumerate individual mutant alleles encountered in patients with type 1, 2, and 3 GD, the clinical phenotype results from the combination of mutations on both alleles. In addition, similar phenotypes may result from different genotypes, but, at the same time, individuals sharing the same genotype can exhibit different disease manifestations, clinical courses, and responses to therapy [46].

Gaucher disease is the first lysosomal lipid storage diseases to be successfully treated by enzyme replacement therapy (ERT) [54]. However, ERT, which consists of intravenous infusions of recombinantly produced glucocerebrosidase, is a costly and lifelong treatment. In addition, in contrast to the remarkable effect of ERT on hepatosplenomegaly and hematological abnormalities, the response to pulmonary disease is variable [55]. Similarly, ERT does not prevent or halt neurologic involvement, as it does not cross the blood–brain barrier. Plasma chitotriosidase, a biomarker of macrophage activation may be useful for monitoring disease severity and the effectiveness of therapy. Indeed, a chitotriosidase level usually decreases and remains stable with adequate ERT or substrate reduction therapy [56]. Successful bilateral lung transplantation has been described in a patient with pulmonary hypertension [57] but this remains a viable therapeutic option for only a selected minority of patients.

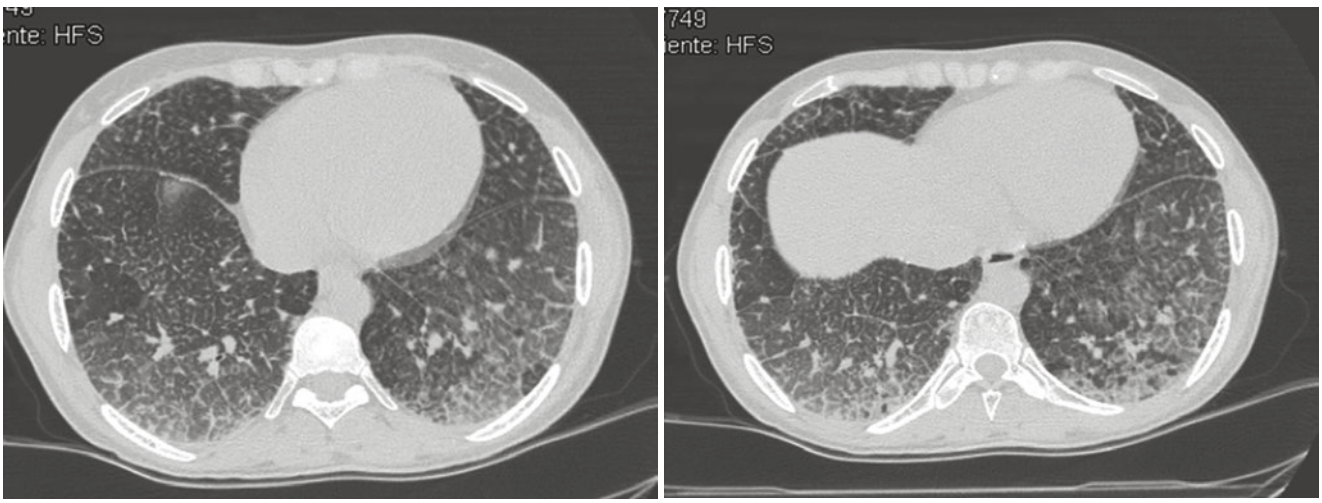
Niemann-Pick Type Disease The eponym "Niemann-Pick disease" (NPD) refers to a heterogeneous group of autosomal recessive disorders of lysosomal lipid storage characterized by sphingomyelin and cholesterol accumulation in reticuloendothelial and parenchymal tissues, with or without neurological involvement [58]. NPD is commonly classified into three major subgroups, which, despite a common name, differ in disease mechanisms, pathogenesis, and clinical manifestations. NPD type A is characterized by severe and early central nervous system deterioration and massive visceral and cerebral sphingomyelin storage leading to death in the first years of life; type B has a chronic course with marked visceral involvement but a sparing of the nervous system; type C is characterized by a subacute nervous system involvement with a slower course and milder visceral storage. NPD types A and B are caused by deficient lysosomal acid sphingomyelinase activity secondary to mutations in the sphingomyelin phosphodiesterase 1 gene (*SMPD1*). Most of the *SMPD1* mutations that cause types A and B NPD are "private," having been described only in one or a few families. Frameshift mutations, small and large insertions, and deletions, and splicing defects typically result in little or no residual acid sphingomyelinase activity and are called *type A* alleles. Conversely, mutations that retain significant residual activity (>5% of in vitro-expressed wild-type activity) are neuroprotective and are called *type B* alleles [59]. Inheritance of two type A alleles predicts a type A phenotype with neurodegenerative disease. In contrast, the inheritance of only one type B allele is neuroprotective and predictive for a type B phenotype, even if the other allele has a type A abnormality. The overall prevalence of type A/B NPD is estimated at around 1:250,000 [60] and the diagnosis requires the observation of elevated plasma levels of oxysterols, particularly lyso-sphingomyelin, along with the identification of pathogenic *SMPD1* variants. Type C NPD is caused by nonfunctional *NPC1* (95% of patients) or *NPC2* genes that alter lipid processing and transport result-

ing in multiorgan (mainly brain, liver, and spleen) accumulation of low-density lipoprotein cholesterol [61]. The disease, which has an estimated prevalence of about 1 in 150,000 [61], is transmitted in an autosomal recessive manner with nonsense or frameshift mutations within *NPC1* being associated with the most severe neurological involvement. Abnormal NPC1 and NPC2 proteins are believed to function in a coordinate fashion in the post-lysosomal/late endosomal transport of cholesterol and other molecules, although their precise function is unknown [62, 63].

Clinical presentation of NPC disease is extremely heterogeneous with the age of onset ranging from the perinatal period to adulthood. Similarly, the lifespan of the affected individuals varies widely, although the majority of patients experience progressive deterioration and die within the second decade of life. Apart from a subset of patients who die at birth or within the first 6 months of life from hepatic or respiratory failure, all patients will ultimately develop progressive neuropathy, which manifests with cerebellar ataxia, dysarthria, dysphagia, and progressive dementia. The majority of cases show also a characteristic vertical supranuclear gaze palsy [64].

The prevalence of lung involvement in NPD is unknown. In a retrospective study of 13 patients, with type A ($n = 1$), type B ($n = 10$), and type C ($n = 2$) disease aged 2 months to 9 years at diagnosis, respiratory symptoms were present at diagnosis in 10 patients and developed during follow-up in the remaining 3 patients. In addition, all patients showed signs of interstitial lung disease either on chest X-ray or CT scan. Bronchoalveolar lavage fluid analysis was performed in seven patients and revealed a marked accumulation of foamy macrophages (Niemann-Pick cells) in all patients. At follow up, one patient died of respiratory failure, five required long-term oxygen therapy, six patients manifested chronic obstructive pulmonary disease and one complained of chronic cough [65]. In a study of 53 patients with type B disease, interstitial abnormalities on HRCT were present in 51 of them (98%) with upper lobe predominant ground glass opacity and basilar predominant interlobular septal thickening representing the most common features (Figs. 28.2 and 28.3) [66]. When abnormal, pulmonary function tests generally reveal a restrictive ventilatory defect with or without the reduced diffusing capacity of the lung for carbon monoxide (DL_{CO}) [66]. ILD may be the presenting feature of type C disease; indeed, a subset of infants carrying loss-of-function *NPC2* mutations may develop pulmonary alveolar proteinosis (PAP) and respiratory failure secondary to the endoalveolar accumulation of cholesterol-rich surfactant [67]. Pulmonary disease may also manifest as endogenous lipoid pneumonia, which is characterized by the accumulation of sphingomyelin-laden and foamy-appearing macrophages that stain deep blue with May-Grunwald-Giemsa ("sea-blue histiocytes" or Niemann-Pick cells; Figs. 28.4 and 28.5) within bronchial walls, alveolar spaces and alveolar septa [66, 68]. Improvement of endogenous lipid pneumonia has been reported with whole lung lavage [68]; however, progressive respiratory failure leading to death following whole-lung lavage has also been reported [69]. Lung transplantation has also been successfully performed in type B disease, although this represents a realistic therapeutic option for only a selected minority of patients [70]. No specific therapies for NPD are available, but the search for novel treatments is very active.

Fabry Disease Fabry disease (FD), also known as Anderson-Fabry disease, is a rare X-linked disorder, resulting from



Figs. 28.2 and 28.3 Type B Niemann-Pick disease. A transverse CT scan of middle lung zones in a 33-year-old woman shows severe interstitial changes. Note the presence of ground-glass opacities and the intermixed thickened interlobular septa and intralobular lines in some areas; these findings are suggestive of the "crazy paving" sign

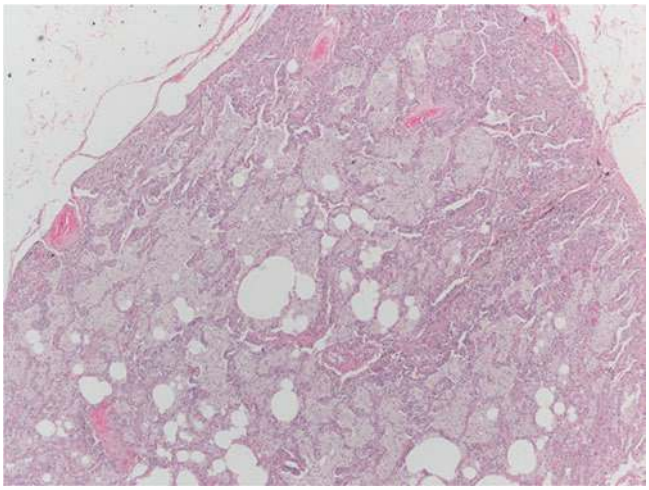


Fig. 28.4 Surgical lung biopsy in a 33-year-old woman with type-B Niemann-Pick disease. At low magnification, alveoli are filled with pale-staining macrophages (hematoxylin-eosin, 20×). (Slide courtesy Alberto Cavazza, MD)

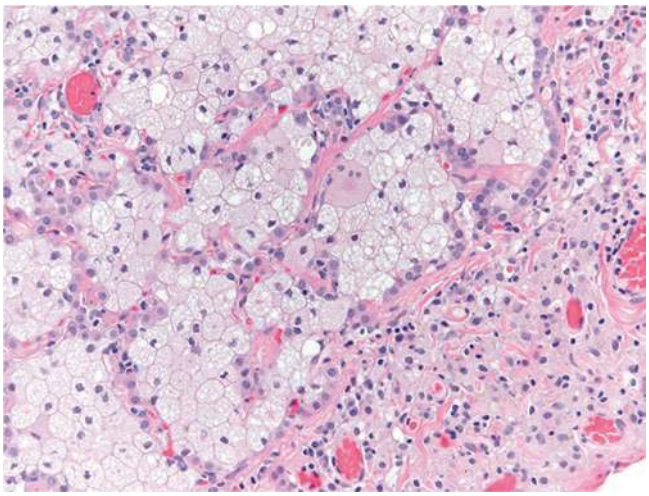


Fig. 28.5 Higher magnification showing the finely vacuolated cytoplasm of the intra-alveolar macrophages (hematoxylin-eosin, 200×). (Slide courtesy Alberto Cavazza, MD)

deficient lysosomal α-galactosidase A activity secondary to mutations in the gene encoding α-galactosidase A (*GLA*). FD is characterized by lysosomal accumulation of glycosphingolipids—mainly globotriaosylceramide and, to a lesser extent, galactosylceramide, within virtually all cell types, although vascular endothelial cells and smooth muscle cells are the main targets of the disease [71]. The disease generally manifests in childhood with a median age of survival of 55 years, although patients with the milder disease can survive to older ages and be diagnosed incidentally because of cardiac involvement causing left ventricular hypertrophy, arrhythmias, or myocardial fibrosis [72]. The classic and most severe form of FD occurs in males and manifests with neuropathic pain in the distal extremities, corneal and lenticular opacities, and cutaneous vessel ectasia, while death usually results from cardiac or cerebrovascular disease or renal failure. The diagnosis requires the demonstration of deficient GLA activity or increased levels of urinary globotriaosylceramide. Pulmonary involvement generally manifests as progressive bronchial narrowing—leading to bronchial obstruction—secondary to the accumulation of glycosphingolipids within the bronchial cells [73–75]. Pulmonary disease may also manifest as pulmonary fibrosis [76] or diffuse alveolar hemorrhage associated with renal failure (pulmonary-renal syndrome) [73].

Enzyme replacement therapy (ERT) with recombinant α-galactosidase A may provide clinical benefits to several outcomes and organ systems [77]. Recently, Germain and colleagues conducted a systematic review of original articles on ERT for the treatment of FD in adult patients [78]. ERT was associated with improved glomerular filtration rate, cardiac wall thickness, left ventricular mass, and quality of life in males (166 publications including 36 clinical trials) and with improvement in cardiac parameters, quality of life, and plasma and urinary globotriaosylceramide levels in females (67 publications, including 6 clinical trials) [78]. Conversely, the efficacy of ERT on pulmonary involvement remains to be proven [79]. New therapies for FD are being developed, including chaperones for patients with amenable *GLA* mutations.

Lysinuric Protein Intolerance

Lysinuric protein intolerance (LPI) is an autosomal recessive disorder characterized by defective transport and excessive urinary loss of proteins such as lysine, arginine, and ornithine [80]. LPI is caused by mutations in the solute carrier family 7A member 7 (SLC7A7) gene, which encodes y^+ LAT-1 protein, the catalytic light chain subunit of a complex belonging to the heterodimeric amino acid transporter family [81]. LPI is found worldwide but its prevalence is higher in Finland and Japan (approximately 1/60,000 newborns) [82]. Affected individuals manifest failure to thrive, growth retardation, hepatosplenomegaly, hypertonicity, and osteoporosis. The diagnosis, which requires plasma and urinary amino acid assays demonstrating low plasma concentration and increased urinary excretion of lysine, arginine, and ornithine, is confirmed by the identification of pathogenic variants within *SLC7A7*. Pulmonary involvement ranges from asymptomatic interstitial abnormalities to acute and life-threatening acute respiratory failure secondary to PAP [83]. In a recent study, lung disease was reported in 10/16 LPI patients during follow-up [84]. Notably, all ten patients had PAP and six of

them died from respiratory failure. In PAP cases, typically, chest radiograph reveals diffuse alveolar infiltrates more prominent in the perihilar regions ("butterfly" or "bat wing" appearance), whereas HRCT shows a characteristic pattern of ground glass opacity superimposed over thickened interlobular and intralobular septa forming irregular polygonal shapes ("crazy paving"). Similar to other forms of PAP, the treatment of choice is whole-lung lavage [85], although the inhaled human recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF) sargramostim might be beneficial in a subset of LPI patients with complicated PAP not responding to maximal conventional therapy [86].

Familial Hypocalciuric Hypercalcemia

Familial hypocalciuric hypercalcemia (FHH) is a rare autosomal dominant disorder with variable penetrance, characterized by familial hypercalcemia with hypocalciuria, granulocyte dysfunction, and interstitial lung disease (ILD) [87]. FHH is caused by inactivating mutations in the calcium-sensing receptor (CaSR) gene leading to calcium-hyposensitivity, compensatory hypercalcemia—in order to obtain intracellular response despite inactive receptors—and hypocalciuria. The low urine calcium levels distinguish FHH from primary hyperparathyroidism, in which urine calcium excretion is increased. Three forms of FHH have been described: FHH1, the most frequent subtype, is caused by mutations within CaSR (3q21–24), FHH2 is caused by mutations within GNA11, which encodes the G-protein subunit α_{11}, whereas FHH3 is caused by mutations within AP2S1, which codes for the adaptor related protein complex 2, σ1 (AP2 σ) [88]. Lung involvement consists of a granulomatous disease, characterized by foreign body giant cells and mononuclear cells infiltration of the alveolar interstitium. However, contrary to sarcoidosis, there are no well-formed granulomas and urine calcium is normal or low while the level of 1,25-dihydroxyvitamin D3 is within normal limits. In general, FHH is a benign condition that does not require treatment. As such, the main argument for establishing the diagnosis is to avoid unnecessary parathyroidectomy. However, in chronic severe cases complicated by lung fibrosis, life expectancy is reduced. Chondrocalcinosis and acute pancreatitis have also been reported [89, 90]. The third feature of FHH is granulocyte dysfunction due to a myeloperoxidase deficiency and reduced anti-staphylococcal killing [91].

Neurofibromatosis Type 1

Neurofibromatosis 1 (NF1), previously known as von Recklinghausen's disease, is a frequent systemic disorder with a prevalence of approximately 1 in 3500 caused by loss-of-function mutations within the *NF1* gene (17q11.2) that encodes neurofibromin, a tumor suppressor protein [92]. Despite its autosomal dominant pattern of inheritance, approximately half of the cases are spontaneous (i.e., caused by de novo mutations within *NF1*). NF1 is characterized by the typical presence of multiple (>6) *café-au-lait* spots along with axillary and inguinal freckling, optic gliomas, bone lesions, and cutaneous neurofibroma [93]. In addition, pigmented hamartomas highly specific for NF1 (Lisch nodules) can be observed in the iris of over 90% of adult patients but only in <10% of affected children younger than 6 years of age. These lesions do not affect vision. The diagnosis of NF1 is based upon the presence of characteristic clinical features and genetic testing is generally not required. The spectrum of clinical phenotypes ranges from mild and paucisymptomatic disease to malignant tumors arising from peripheral nerves in 10–13% of cases [94]. On average, the life expectancy of NF1 patients is reduced by 10 years compared to the general population [95].

ILD, which generally manifests between 35 and 60 years of age, complicates 10–20% of cases [96]. Chest X-ray and HRCT typically demonstrate bibasilar reticular infiltrate, ground glass opacities, and upper lobe and peripheral predominant cystic bullous changes [97–99]. Thin-walled bullae are present in almost all patients with ILD, although they may be seen in isolation. Mediastinal masses may also be seen [99]. Histologically, alveolar septal fibrosis represents the major abnormality, whereas an alveolitic process consisting of mononuclear cell infiltration may be observed in earlier phases of the disease [100]. Functionally, NF1-associated ILD is characterized by a mixed obstructive and restrictive ventilatory defect. NF1-associated ILD is often progressive and may lead to pulmonary hypertension (PH) and right heart failure [101, 102]. NF1-associated PH is classified as Group 5 PH (i.e., "PH with unclear and/or multifactorial mechanisms") and is characterized by female predominance, advanced age at diagnosis, association with ILD in the majority of cases, and poor long-term prognosis [102]. Additional pulmonary complications of NF1 include large-airway obstruction, bronchial or intraparenchymal neurofibromas (leading to diaphragmatic paralysis), scar carcinoma complicating fibrotic lung disease, and primary lung cancer developing in the walls of emphysematous cysts, and pneumothorax [103–105]. No specific medical treatment for NF1 exists.

Surfactant Dysfunction Disorders

Genetic surfactant dysfunction disorders (SDDs) are caused by mutations within genes encoding proteins needed for the production and normal function of surfactant, a mixture of phospholipids and proteins synthesized, packaged, and secreted by alveolar type II cells that lower

surface tension at the air-liquid interface and prevent atelectasis at end-expiration. SDDs may manifest as familial or sporadic lung disease and are associated with a wide spectrum of clinical presentations ranging from neonatal respiratory failure to adult-onset ILD. Surfactant proteins (SPs) A, B, C, and D are highly expressed in the lung. Additional proteins important for the production of the surfactant include ABCA3 and TTF-1.

Surfactant Protein B (SFTPB) Deficiency Surfactant protein B (SFTPB) deficiency is a rare autosomal recessive disease with an estimated incidence of <1 in 1,000,000 live births [106] that manifests in infants and is characterized by rapidly progressive respiratory failure [107]. Over 40 loss-of-function mutations within *SFTPB* gene have been identified so far; they result in partial to complete absence of SP-B protein. The most common mutation—a GAA substitution for C at genomic position 1549 in codon 121 (formerly referred to as "121ins2" mutation)—accounts for approximately 70% of cases and results in the absence of pro- and mature SFTPB protein [108]. The absence of SFTPB, in turn, leads to abnormal surfactant composition, decreased surfactant function, and structural disruption of lamellar bodies (the organelles in which surfactant is stored). Accordingly, SFTPB deficiency is characterized histologically by the accumulation of granular, eosinophilic, periodic acid-Schiff (PAS)-positive, lipoproteinaceous material in the alveolar spaces, which often contains desquamated alveolar type II cells and foamy alveolar macrophages.

Most infants with SFTPB deficiency present within hours of birth with respiratory failure requiring mechanical ventilation. Chest radiograph and HRCT appearance mimic that of hyaline membrane disease in premature infants with diffuse haziness and air bronchograms. However, infants with SFTPB deficiency are only transiently or minimally responsive to surfactant replacement therapy and, with rare exceptions, patients succumb within days of birth to 3–6 months without lung transplantation [109]. Children with mutations that allow for the partial expression of the SFTPB protein appear to survive longer and go on to develop a chronic ILD [110].

Surfactant Protein C (SFTPC) Deficiency Surfactant protein C (SFTPC) deficiency is a rare disorder originally described in an infant with NSIP whose mother had desquamative interstitial pneumonia (DIP). Both the infant and her mother carried heterozygous guanine to adenine substitution, leading to the skipping of exon 4 and deletion of 37 amino acids, in keeping with the autosomal dominant pattern of inheritance [2]. Subsequently, Thomas and colleagues described a five-generation kindred with 14 affected members, including four adults with biopsy-proven UIP and three children with NSIP, all carrying a rare heterozygous missense mutation substituting a polar residue (glutamine) for a neutral one (leucine) and predicted to hinder the processing of SP-C precursor protein [1]. Over 35 dominantly expressed mutations within *SFTPC* have been identified so far, half of which arise de novo, thus causing sporadic disease, whereas the remaining are inherited. The most common mutation, a T to C transition at genomic position 1295, results in a threonine substitution for isoleucine in codon 73 (I73T), and accounts for approximately one-third to one-half of all reported cases [111, 112].

The pathophysiology of lung disease due to *SFTPC* mutations is only partially understood. One hypothesis is that misfolded proSP-C may induce the unfolded protein response, resulting in inflammation and apoptosis of alveolar type II cells [113]. The severity of disease and age of onset is highly variable, ranging from fatal respiratory distress in infants to subclinical pulmonary fibrosis in older adults [114]. A recent study from the Netherlands found that *SFTPC* mutations account for as many as 25% of familial pulmonary fibrosis cases [115]. Conversely, *SFTPC* mutations are rarely associated with sporadic pulmonary fibrosis [116]. Respiratory involvement is highly variable and may change over time; in a study of five children from a single family with long-term follow-up, HRCT showed initially ground glass opacities and subsequently the development of cysts, which was associated with a reduced extension of ground glass and clinical improvement [117].

Whether the nature and location of *SFTPC* mutations affect the severity of lung disease is unknown. However, affected family members harboring the same *SFTPC* mutation display considerable variability in the onset and severity of lung disease [1]. Such variability precludes accurate assessment of prognosis and complicates interpretation of treatment response in individual patients.

Adenosine Triphosphate Binding Cassette Family Member 3 (ABCA3) Deficiency Mutations in the Adenosine Triphosphate Binding Cassette family member 3 (*ABCA3*) gene are the most common cause of genetic SDDs in humans [118, 119], with an estimated disease incidence ranging between 1 in 4400 and 1 in 20,000 [120]. *ABCA3* mutations result in loss or reduced functional activity of the ABCA3 protein, which facilitates the translocation of phospholipids into lysosomally-derived organelles called *lamellar bodies* for the production of surfactant. Over 200 mutations have been reported to date. Glu292Val, the most common, accounts for <10% of all identified mutations and is associated with relatively mild disease [121, 122]. However, disease severity and presentation vary widely, mainly based on the genotype. The most severe phenotype is characterized by neonatal respiratory failure and death by 1 year of age and is associated with mutations predicted to impede *ABCA3* expression on both alleles (null/null) [123, 124], consistent with an autosomal recessive manner of inheritance. However,

Table 28.1 Surfactant dysfunction disorders

Disease	SFTPB deficiency	SFTPC deficiency	ABCA3 deficiency	Brain-thyroid-lung syndrome
Locus	*SFTPB*	*SFTPC*	*ABCA3*	*NKX2.1*
Chromosome	2p11.2s	8p23	16p13.3	14q13.3
Inheritance	Autosomal recessive	Autosomal dominant or sporadic	Autosomal recessive	Sporadic or autosomal dominant
Age of onset	Birth	Birth-adulthood	Birth-childhood	Childhood
Mechanism	Loss-of-function	Gain-of-toxic-action or dominant negative	Loss-of-function	Loss-of-function (haploinsufficiency)
Phenotypes	Neonatal RDS	Neonatal RDS, ILD	Neonatal RDS, ILD	Neonatal RDS, ILD, childhood chorea, congenital hypothyroidism
Natural history	Lethal	Variable	Generally lethal, may be chronic	Variable
Treatment	Lung transplantation or compassionate care	Supportive care, lung transplantation (if progressive)	Lung transplantation (if progressive)	Supportive care

SFTPB surfactant protein B, *SFTPC* surfactant protein C, *ABCA3* adenosine triphosphate binding cassette, *RDS* respiratory distress syndrome, *ILD* interstitial lung disease

patients may also present later in infancy or childhood. Notably, discordant outcomes have been reported in siblings carrying the same *ABCA3* mutations, suggesting that factors other than genotype contribute to disease severity [125]. The predominant histopathological patterns of ILD include PAP, DIP, and NSIP. However, a UIP pattern of pulmonary fibrosis has also been described in a 15-year-old boy carrying mutations in *ABCA3* [126].

NK2 homeobox 1/Thyroid Transcription Factor 1 (NKX2–1/TTF-1) Mutations *NK2 homeobox 1* (*NKX2-1*) encodes thyroid transcription factor 1 (TTF-1), which is a critical regulator of SP-B, SP-C and ABCA3 expression. Deletions or loss-of-function mutations on one *NKX2.1* allele (haploinsufficiency) can cause severe respiratory distress syndrome and ILD [127]. Lung disease is thought to result from decreased amounts of several gene products in combination or reduced amounts of a key protein, particularly SP-B or ABCA3, below a critical level. The incidence and prevalence of lung disease due to *NKX2.1* haploinsufficiency are unknown. The majority of reported variants have occurred de novo [128], but an autosomal dominant pattern of inheritance has also been observed [129]. Haploinsufficiency for *NKX2.1* may cause neurological symptoms (i.e., muscular hypotonia, ataxia and choreoathetosis), hypothyroidism, and lung disease, a triad of manifestations commonly referred to as "Brain-Thyroid-Lung syndrome" [130]. Affected individuals may present during the neonatal period with rapidly progressive respiratory failure, while other patients may develop a more chronic phenotype characterized by recurrent pulmonary infections [131]. In a study of 21 patients, 76% presented with neonatal lung disease and 19% with ILD [132].

Irrespective of the gene involved, lung histology findings in SDDs are similar and include prominent hyperplasia of alveolar type II epithelial cells, thickening of the interstitium with mesenchymal cells and foamy macrophages, and accumulation of granular, eosinophilic proteinaceous material within the air spaces [133]. To date, no specific therapies for SDDs have been demonstrated to be effective. The mainstay of treatment remains therefore supportive care. Neonates presenting with clinical and radiographic features of respiratory distress syndrome are often treated with exogenous surfactant, which may improve transiently lung function but does not correct the underlying intracellular defects. The main features of surfactant dysfunction disorders are summarized in Table 28.1.

Concluding Remarks

The umbrella term "rare diffuse lung diseases of genetic origin" refers to a large spectrum of disorders with complex pathogenesis, diverse clinical manifestations (Table 28.2), specific histopathologic and radiographic features (Table 28.3), and variable natural history and prognosis. In the past decade, there have been major advances in our knowledge and understanding of these entities but much work remains to be done. For instance, how multiple susceptibility alleles interact with each other and with environmental factors to determine disease risk and phenotypes is poorly understood. Ongoing basic research will also provide insights into the molecular basis of ILD pathogenesis (including genetic factors causing familial disease) and is expected to identify markers of disease, pathways of disease regulation, and novel potential targets for therapeutic intervention. To this end, the importance of international collaboration cannot be overemphasized. Hopefully, this will help reduce the considerable morbidity and mortality associated with these disorders.

Table 28.2 Clinical and diagnostic aspects of diffuse parenchymal lung diseases of genetic origin

Disease	Age of onset of pulmonary manifestations	Mode of presentation	Extrapulmonary manifestations	Diagnosis	
				Suggestive features	Confirmatory tests
Hermansky-Pudlak syndrome	Third or fourth decade	Pulmonary fibrosis	Granulomatous colitis	Oculo-cutaneous albinism	Genetic testing
			Renal failure	Bleeding diathesis	Absence of platelet-dense bodies
				Puerto Rican origin	
Dyskeratosis congenita	First or second decade	Pulmonary fibrosis	Bone marrow failure	Skin hyperpigmentation	Genetic testing
			Osteoporosis	Oral leukoplakia	
			Increased risk of malignancy	Nail dystrophy	
				Premature greying of the hair	
Gaucher's disease	Highly variable	Interstitial lung disease	Neurological involvement (in type 2 and 3 diseases)	Variable (depending on the disease type)	Measurement of glucocerebrosidase activity in peripheral blood leukocytes
		Recurrent lung infections	Hepatosplenomegaly		Genetic testing
			Anemia, thrombocytopenia		
			Skeletal abnormalities		
			Pulmonary hypertension		
Niemann-Pick disease	Highly variable	Lipoid pneumonia	Neurological involvement (in type A and C disease)	Variable (depending on the disease type)	Measurement of sphingomyelinase activity in peripheral blood leukocytes
		Pulmonary fibrosis	Visceral involvement		Genetic testing
		Lung nodules			
Fabry's disease	Third decade (in subjects with airway obstruction); fifth decade (in subjects without airway obstruction)	Airway obstruction	Renal failure	Acroparesthesias	Measurement of α-galactosidase A activity in peripheral blood leukocytes
		Alveolar hemorrhage	Cardiac dysfunction	Angiokeratoma	
		Pneumothorax	Strokes	Corneal and lenticular opacities	
		Recurrent lung infections		Hypohidrosis	
Lysinuric protein intolerance	Infancy-to-childhood	Interstitial lung disease	Growth retardation	Vomiting and diarrhea on a protein-rich diet	Increased urinary excretion and low plasma levels of lysine, arginine, and ornithine
		Alveolar proteinosis	Hepatosplenomegaly	Hyperammonemia	
		Alveolar hemorrhage	Hypertonicity	Alopecia	
			Osteoporosis		

(continued)

Table 28.2 (continued)

Disease	Age of onset of pulmonary manifestations	Mode of presentation	Extrapulmonary manifestations	Diagnosis	
				Suggestive features	Confirmatory tests
Familial hypocalciuric hypercalcemia	Variable	Granulomatous lung disease	Chondrocalcinosis	Hypocalciuria	24-h urine calcium/ creatinine clearance ratio
		Pulmonary fibrosis	Acute pancreatitis	Hypercalcemia	Genetic testing
				No signs or symptoms of primary hyperparathyroidism	
Neurofibromatosis Type 1	Fourth to sixth decade	Pulmonary fibrosis (lower zones)	Neurological involvement	*Café-au-lait* spots, axillary and inguinal freckling	Genetic testing
		Bullous changes (upper zones)	Optic gliomas	Lisch nodules	
		Pulmonary neurofibromas	Osseous lesions		
		Pulmonary hypertension	Cutaneous neurofibromas		
Surfactant dysfunction disorders[a]	Birth-childhood	Respiratory distress syndrome	Variable (depending on the specific disease)	Variable (depending on the specific disease)	Genetic testing
		Interstitial lung disease			

[a] See also Table 28.1

Table 28.3 Radiographic patterns of lung involvement on high-resolution computed tomography

Disease	Radiographic pattern
Hermansky-Pudlak syndrome	Diffuse, peripheral reticulation; subpleural cysts; ground glass opacity, peribronchovascular thickening; bronchiectasis
Dyskeratosis congenita	Subpleural bibasal honeycombing, traction bronchiectasis, reticular opacities
Gaucher's disease	Reticular changes, ground glass opacities
Nieman-Pick Type disease	Ground glass opacities with an upper lobe predominance, and basilar predominant interlobular septal thickening
Fabry's disease	Diffuse ground glass and mosaic attenuation
Lysinuric protein intolerance	Ground glass opacities superimposed over a pattern of fine overlapping lines forming irregular polygonal shapes ("crazy paving")
Familial hypocalciuric hypercalcemia	Reticulo-nodular infiltrates, honeycombing
Neurofibromatosis Type 1	Bibasilar (usually symmetrical) reticular changes, ground glass opacities, upper lobe predominant (usually asymmetrical) small cysts, and thin-walled bullae
Surfactant dysfunction disorders	Diffuse ground glass opacities, septal thickening, parenchymal cysts

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Part VI

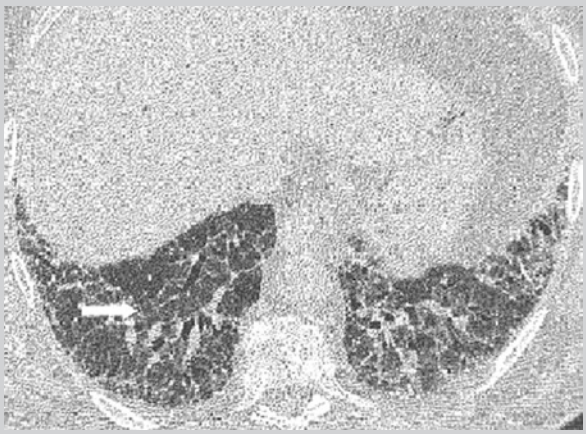
Interstitial Lung Diseases, Non Systemic

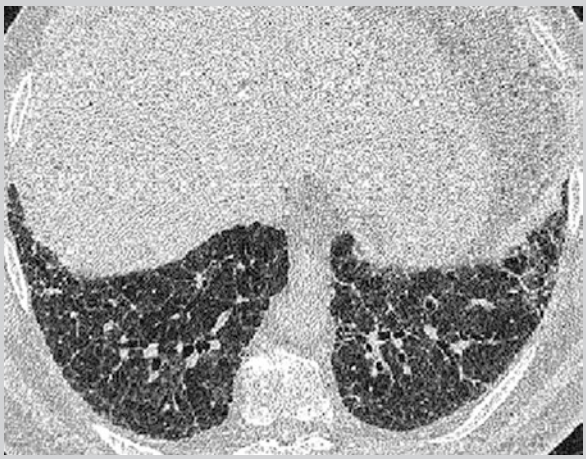
Imaging Approach to Interstitial Lung Disease

29

Teresa M. Jacob, Tahreema N. Matin, and Joseph Jacob

Clinical Vignette





A 71-year-old male 100-pack-year ex-smoker presented with a cough to his local hospital. On the initial axial computed tomography (CT) image (left), there was evidence of lower zone predominant fibrosis in a basal, peripheral and subpleural distribution. Traction bronchiectasis and reticulation were evident in the right lower lobe, but no honeycombing was present. According to the 2011 ATS/ERS/JRS/ALAT consensus guidelines for idiopathic pulmonary fibrosis, the patient demonstrated a possible usual interstitial pneumonia pattern on CT imaging. The major change to CT categorisation that has resulted following the publication of the 2018 ATS/ERS/JRS/ALAT consensus guidelines for idiopathic pulmonary fibrosis is that this pattern of lower zone predominant traction bronchiectasis without honeycombing is now classified as a probable usual interstitial pneumonia pattern.

The clinical history suggested an idiopathic cause for the fibrosis and following discussion by a multidisciplinary team the patient was diagnosed with idiopathic pulmonary fibrosis. The patient did not attend

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routine follow-up but returned 15 months later with worsening symptoms. A CT scan was repeated (right). The fibrosis consisting of reticulation and traction bronchiectasis has coarsened and increased in extent suggesting both maturation of fibrosis and disease progression. No honeycombing was present. The maturation of fibrosis is evidenced in the left lower lobe by structures in the lung such as airways and vessels being pulled closer together. An increase in fibrosis extent (disease progression) is demonstrated by previously normal-appearing lungs now containing ground glass density and reticulation (arrow).

The identification of disease progression on serial CT imaging of fibrosing lung diseases is going to become increasingly important in the years to come. As the use of antifibrotic medication becomes more widespread, increasing numbers of patients will undergo declines in pulmonary function tests that lie within the range of measurement variation. Changes in CT variables, both measured visually and quantitively using computer tools may prove a more sensitive measure of disease worsening. Identifying changes in CT measures may allow arbitration of marginal lung function declines.

Introduction

Interstitial lung disease (ILD) encompasses a group of disorders which affect the connective tissue framework of the lung, termed the pulmonary interstitium [1]. There are many causes of ILD, and although not an exhaustive list, some of the most common aetiologies include connective tissue diseases (CTD), drug and antigen exposures, and idiopathic causes. ILD appearances can be challenging to interpret on CT imaging and individual ILDs may demonstrate different rates of disease progression over time. The formulation of a diagnosis requires the interpretation of radiological features alongside the patient's clinical and exposure history, laboratory results and histopathological findings. Consideration of these varied components is best achieved in the setting of a multidisciplinary team discussion where imaging interpretation plays a central part [2].

Diseases of the interstitium can be fibrosing and associated with permanent and progressive destruction of the connective tissue framework. Detailed descriptions of the role of imaging for the numerous fibrosing lung diseases (FLDs) and non-fibrosing ILDs are beyond the scope of this chapter. Instead, we will focus on characterising the radiological features of the main FLDs, with an emphasis on those conditions with formalised imaging classifications and diagnostic guidelines.

The chapter will also outline the challenges associated with determining disease progression on CT imaging and why this has particular relevance for both clinical management and drug trials in the era of antifibrotic therapies. We will also outline the role that computer analysis of CT imaging may play in the years to come as an alternative to visual CT interrogation.

Background

Chest Radiographs and High-Resolution Computed Tomography

Imaging techniques are a core component of the diagnostic pathway for interstitial lung diseases which comprise over 200 distinct entities [3]. Whilst some are rare, most ILDs manifest a well-described combination of shortness of breath and changes on the chest radiograph [4]. In addition to identifying the presence of an ILD, a comparison of serial chest radiographs acquired at different time points can confirm the presence of disease progression. In clinical practice, chest radiographs are most commonly employed as the first-line diagnostic test in a patient with shortness of breath with the aim of broadly excluding other pathology, for example, left heart failure, infection or lung cancer. However, radiographs may appear normal in patients with ILD [5]. Chest radiographs are also commonly utilised when a patient with a known ILD diagnosis presents with worsening breathlessness, as complications requiring urgent management such as a pneumothorax or infection can be rapidly diagnosed.

High-resolution computed tomography (HRCT) has been emphasised as being essential in the diagnosis of ILDs in the most recent American Thoracic Society/European Respiratory Society clinical practical guidelines [6]. HRCT is a more sensitive modality for ILD detection than chest radiography and conventional thoracic computed tomography. HRCT can also allow the identification of appropriate sites for bronchoalveolar lavage and lung biopsy and can guide treatment strategies [7]. As a large array of diseases can affect the pulmonary interstitium, separation of CT appearances into those exhibiting fibrosis and those without obvious fibrosis allows the identification of patients that are more likely to develop a progressive disease course. The following sections will first describe the optimal HRCT acquisitions that should be used to image fibrosing lung diseases. Subsequently, we will outline the specific HRCT features that are used to describe the appearances of the various fibrosing lung diseases.

Image Acquisition

The 2018 Fleischner Society diagnostic criteria for idiopathic pulmonary fibrosis (IPF) emphasised in clear and precise terms how important good quality CT acquisitions are to allow definitive interpretation of disease patterns [8]. These recommendations were echoed in the 2018 update to the IPF diagnostic guidelines [6]. In line with the 2011 IPF diagnostic guidelines [7], CTs evaluating suspected FLDs were recommended to be performed supine, without the administration of intravenous contrast (Table 29.1). However, reflecting the general improvement in scanner technology in the intervening decade, the 2018 IPF guidelines stipulated that CTs be acquired volumetrically (without gaps between slices) and were required to have a maximum slice thickness of 1.5 mm. The 2011 guidelines accepted the acquisition of HRCTs with gaps of between 1 and 2 cm between image sections. The necessity for gaps between images was predominantly related to limitations in scanner acquisition abilities, but also allowed dose reductions in CT studies. Interspaced imaging essentially sampled the lung parenchyma to provide an overall impression of disease patterns. Yet subtle features could be missed when acquiring non-contiguous images, for example small nodules (<1 cm in size) representing early lung cancer might have developed in the gaps between CT slices. Similarly, the architectural distortion and deformation of lung parenchyma in patients with fibrosis could make the identification of disease progression on serial interspaced imaging much harder than when examining their volumetric equivalents.

The 2018 IPF diagnostic guidelines recommended the routine use of expiratory CT imaging in the work-up of fibrosing lung disease patients [6], whereas in 2011 it remained an optional acquisition [7]. Expiratory imaging which can be performed volumetrically or interspaced can accentuate the presence of air-trapping and thereby help identify the presence of small airways disease in conditions such as connective tissue disease-related ILD (CTD-ILD) and hypersensitivity pneumonitis (HP) [9]. Guidelines related to the use of prone CT imaging to confirm the presence of subtle dependent lung changes that could be confused with atelectasis have not changed since 2011. However, the emergence of iterative reconstruction techniques that can reduce CT doses has been recommended for use in the evaluation of FLD. Specifically, low-dose CT acquisitions at a dose range of 1–3 mSv are suggested. Ultra-low dose imaging (<1 mSv) which can be associated with an excess of imaging noise is not recommended for routine clinical evaluation.

Finally, the utility of performing a non-contrast CT prior to a CT pulmonary angiogram (CTPA) was highlighted in the 2018 iteration of the IPF guidelines [6]. CTPAs are often requested in patients with acute shortness of breath or more commonly in the case of patients with FLD when acute shortness of breath supervenes on chronic breathlessness. Lung fibrosis can result in heterogenous vascular perfusion of the lung which following contrast administration can manifest with subtle foci of increased parenchymal attenuation related to altered vascular distributions. Hyper-attenuation secondary to contrast material can be confused with increased parenchymal density from infection, pulmonary oedema, aspiration or an acute exacerbation of FLD, all of which constitute the differential diagnoses of acute worsening of breathlessness. To distinguish artefactual increased parenchymal density consequent to contrast administration from appearances resulting from genuine lung damage, a non-contrast CT should be acquired immediately prior to a CTPA. The parenchymal appearances on an interspaced non-contrast CT can then be used as a reference to determine whether hyperdense parenchymal changes are genuine or artefactual.

Table 29.1 Optimal acquisition techniques for computed tomography (CT) imaging in the evaluation of fibrosing lung diseases. *mm* millimetre, *mSV* millisievert, *CTPA* CT pulmonary angiogram

Optimal CT series	Optimal acquisition
Non contrast supine inspiratory CT	Volumetric, collimation <1 mm
Expiratory supine CT recommended	Interspaced or volumetric
Prone inspiratory CT to confirm solely dependent abnormalities	
CTPA with or without initial non-contrast CT	Non contrast CT: Interspaced or volumetric
Dose reduction techniques advised to achieve 1–3 mSv dose	No CTs to be acquired at <1 mSv dose

Key Features of Fibrosis

Two key radiological features of lung fibrosis are traction bronchiectasis and volume loss. The Fleischner Society glossary of terms defines traction bronchiectasis as "irregular bronchial and bronchiolar dilatation caused by surrounding retractile pulmonary fibrosis" [10]. Traction bronchiectasis is typically seen in the lung periphery and exists amidst other features of fibrosis such as ground glass opacification and/or reticulation [11]. It is important to differentiate traction bronchiectasis from other causes of abnormal airway dilatation unrelated to fibrosis. In the latter case, the surrounding lung will appear normal or hyperlucent as opposed to dense and fibrotic. Distinguishing between traction bronchiectasis and honeycombing on HRCT can prove challenging, particularly where conglomerate peripheral traction bronchiectasis at the lung bases may mimic honeycombing. A review of

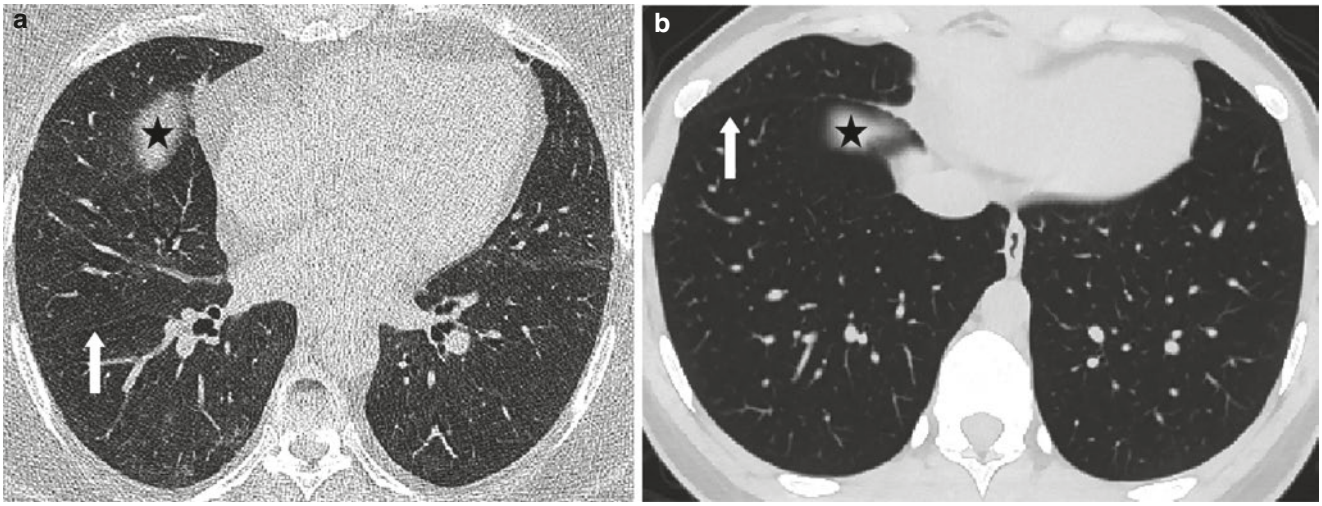

Fig. 29.1 Lobar volume loss can be identified by the position of the lung fissures at the level of the hemidiaphragms. In a patient with connective tissue disease-related lung fibrosis (**a**) the right oblique fissure (arrow) has only reached the mid-point of the chest when the right hemidiaphragm first comes into view (star). In a normal healthy patient, however (**b**), the right oblique fissure (arrow) is visible at the anterior aspect of the chest at the level of the right hemidiaphragm (star)

imaging on multiplanar reformats (MPR) and employment of post-processing reconstruction algorithms, for example, minimum intensity projection can help to distinguish traction bronchiectasis from honeycombing [12].

Parenchymal volume loss is useful in determining the distribution of fibrotic disease, particularly if honeycombing and traction are not obvious. Volume loss can be assessed by comparing the position of the oblique fissures relative to each other and whether they reach the anterior chest wall at the level of the hemidiaphragms as observed in normal lungs [11]. In idiopathic pulmonary fibrosis (IPF) for example, which is a lower zone predominant disease, preferential contraction of the lower lobes will retract the oblique fissures posteriorly, with the result that they only reach the midpoint of the chest wall at the level of the hemidiaphragms (Fig. 29.1).

When fibrosis is severe, honeycomb cysts can occur representing end-stage lung. The Fleischner Society defines honeycombing as "destroyed and fibrotic lung tissue containing numerous cystic airspaces with thick fibrous walls" [10]. Honeycomb cysts are typically well-defined cystic spaces 3–5 mm in diameter which can extend to 25 mm in size. In the setting of IPF, they often cluster in a peripheral, subpleural and basal distribution [13]. However, honeycomb cysts can occur in FLDs other than IPF, where their distribution can vary. Several stacked layers of cysts or even a single subpleural layer of two or three adjoining cysts are a key characteristic of the UIP pattern of fibrosis which is associated with a poor outcome in several FLDs.

Ancillary Features of Fibrosis

Reticulation and ground glass opacification are commonly seen in FLD, although both may also occur in non-fibrosing conditions. On chest radiographs, reticulation reflects innumerable small linear opacities which relate to interlobular or intralobular septal thickening on CT [10]. Ground glass opacification represents areas of increased density, which on CT preserves the margins of the bronchovascular structures.

The 2011 IPF guidelines [7] stipulated that a CT that contained ground glass opacities which were more extensive than the extent of reticulation would be inconsistent with a diagnosis of IPF. The 2018 guidelines [6] suggest that CTs with predominant ground glass opacities should necessitate consideration of an alternative diagnosis to IPF. The underlying rationale has been that IPF is generally not associated with inflammation and therefore a CT demonstrating extensive inflammation reflected in ground glass opacities is more likely to reflect an alternative diagnosis.

Yet a fundamental challenge exists with what CT patterns radiologists choose to define as a ground glass opacity. Figure 29.2 demonstrates two CTs that show distinct imaging patterns but which have been described using the same "ground glass opacity" terminology. In Fig. 29.2a, the increased lung density in the right lower lobe is associated with underlying reticular lines and traction bronchiectasis, whilst in Fig. 29.2b, the increased lung density in the medial left lower lobe is overlaid on normal background lung parenchyma. In Fig. 29.2a the co-existence of fibrotic features

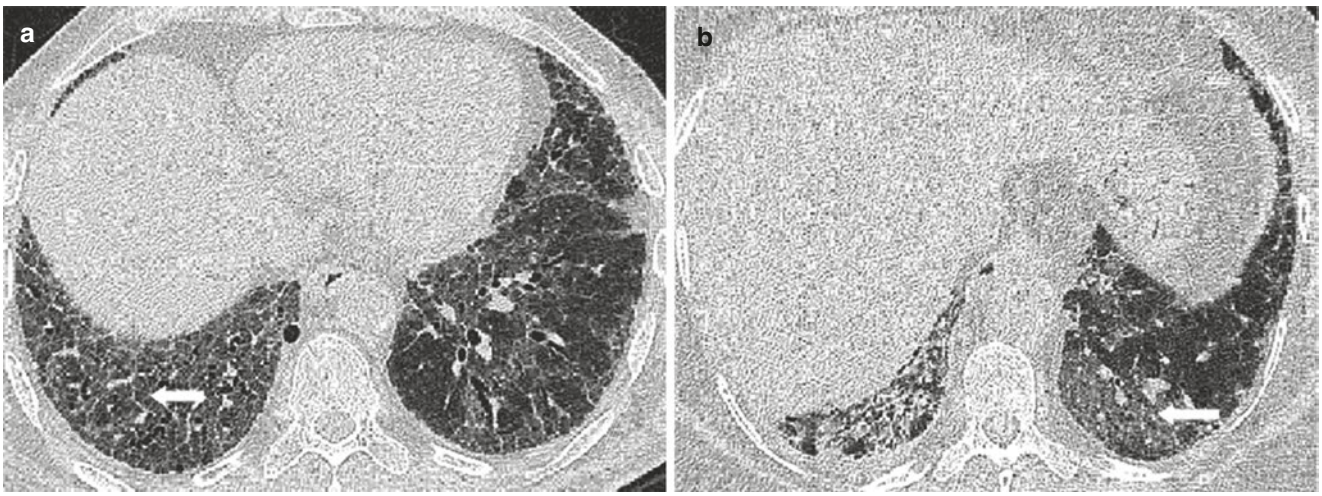

Fig. 29.2 The two types of ground glass opacity are visible on computed tomography (CT) imaging in patients with fibrosing lung disease. Increased density parenchyma is visible in the right lower lobe (**a**) and occurs in the background of reticulation and traction bronchiectasis (arrow). The increased density is likely to reflect fine fibrosis and thickening of the inter- and intralobular septae beyond the resolution of CT imaging. Increased density (arrow) in the posterior left lower lobe (**b**) occurs on background normal lung which has no evidence of architectural distortion. The appearances are more in keeping with inflammation supervening within the airspaces rather than fine fibrosis

(reticulation and traction bronchiectasis) amongst the increased density lung suggests that this pattern reflects fine fibrosis and should be compatible with an IPF diagnosis. Increased density occurring on background normal lungs as in Fig. 29.2b has a greater likelihood of being a transitory abnormality and is more likely to represent inflammation. Ground glass opacities are now understood to reflect either the replacement of air within airspaces by fluid, blood, pus or cells [14, 15] or the summed increase in density that results from lung regions where the interstitium is thickened, the individual components of which are beyond the resolution of CT [16, 17]. The conflation of two distinct patterns of abnormality as "ground glass opacities" on CTs of patients with FLD has long been a cause of confusion. Better appreciation of these two distinct CT appearances which happen to share a common descriptor should help resolve some of the earlier challenges in CT interpretation of the term ground glass opacity.

Other Imaging Findings in FLD

Small foci of calcification (<3 mm in size) which may be linear or nodular are more common in CTs of patients with usual interstitial pneumonia (UIP) pattern of fibrosis than in patients with non-specific interstitial pneumonia (NSIP) pattern of fibrosis (Fig. 29.3). The lesions, which are due to ossification [18], are predominantly located within areas of fibrosis and are more commonly seen in cases of IPF than HP [19]. Though not specified as diagnostic criteria in current guidelines, the identification of nodular ossifications may help refine the characterisation of a UIP pattern of fibrosis.

A variation in the attenuation characteristics of lung parenchyma represents a mosaic attenuation pattern. In the context of FLD, the extensive presence of low attenuation pulmonary lobules (the low attenuation component of a mosaic attenuation pattern) reflecting small airways disease has been strongly linked with a diagnosis of HP [20]. However, CTs of IPF patients not uncommonly contain low attenuation pulmonary lobules [20, 21] (Fig. 29.4), which are thought to occur secondary to smoking-related damage to the airways [22]. A more nuanced measure to distinguish HP from IPF outlined in the Fleischner IPF guidelines [8] involves identifying low attenuation lobules in spared/non-fibrotic regions of the lung, which are more commonly seen in HP as a consequence of the airway-centred fibrotic process [23]. In cases where fibrosis is extensive and spared regions of the lung may be sparse, the examination of historic CTs, acquired when the disease was limited in extent may increase the likelihood of identifying low attenuation lobules within the normal lung parenchyma. More recent work has also highlighted the value of the "headcheese sign" (Fig. 29.5), also termed the three density pattern [24], where ground-glass attenuation, normal attenuation and low attenuation lobules co-exist in the same lobe and may represent a good differentiator between chronic HP (CHP) and IPF [25].

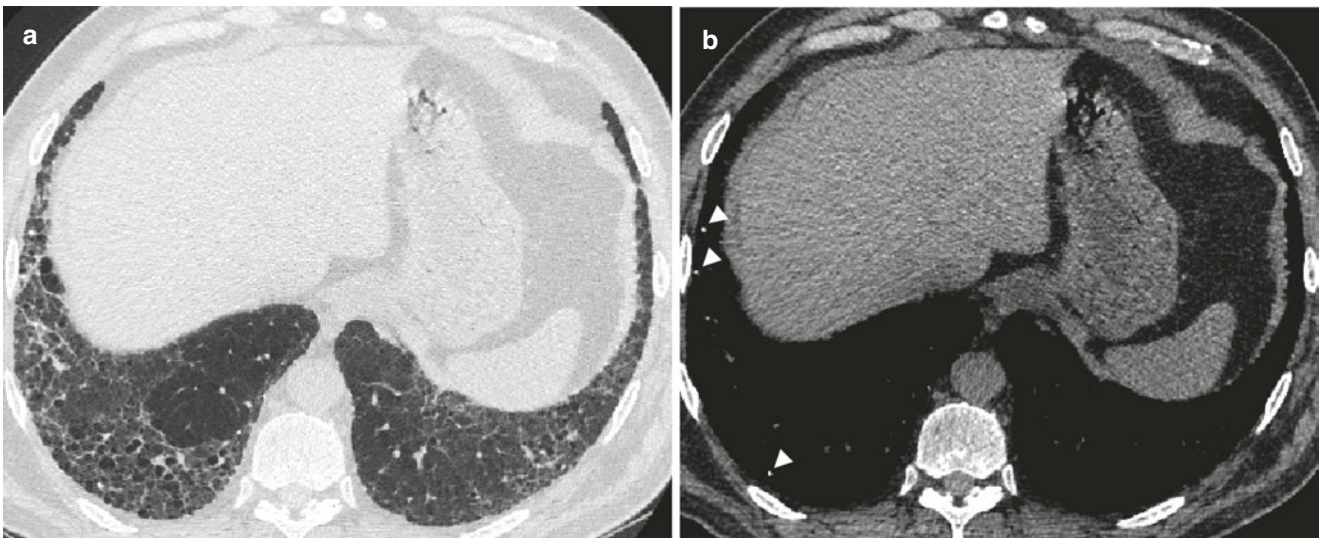

Fig. 29.3 Nodular ossification in a patient with idiopathic pulmonary fibrosis. The lung window imaging (**a**) demonstrates peripheral traction bronchiectasis and honeycombing most marked within the right lower lobe. There are subtle nodules (<3 mm in size) of calcified density within the fibrotic lung, which are more readily visible (arrowheads) on the mediastinal window image (**b**)

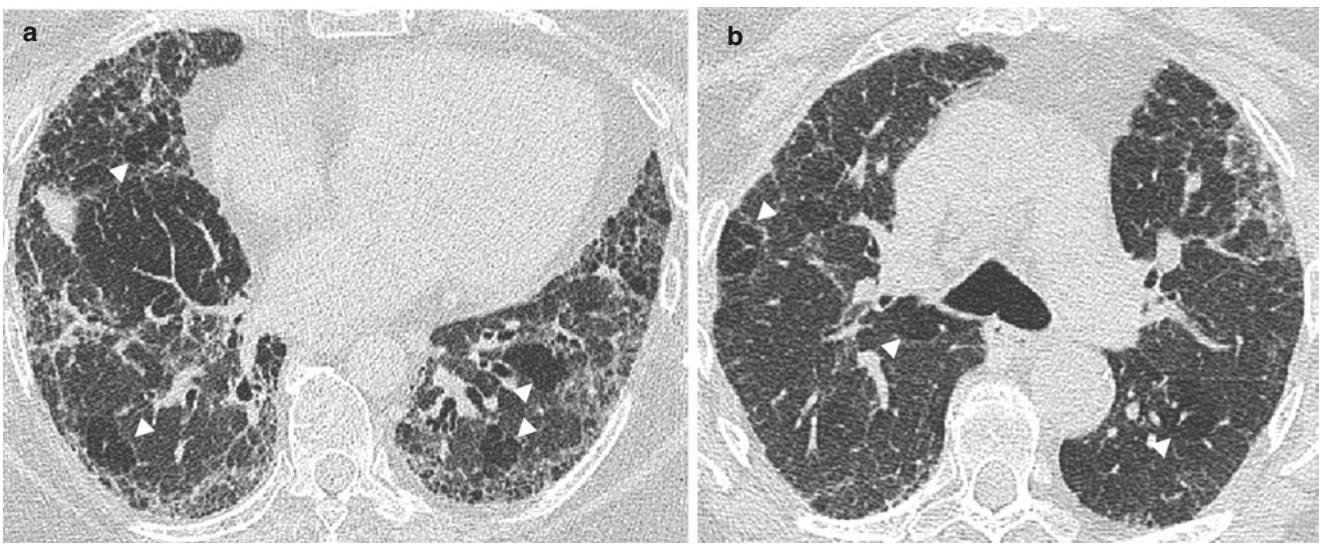

Fig. 29.4 Variable distributions of low attenuation lung (arrowheads) in two fibrosing lung diseases. In a patient with idiopathic pulmonary fibrosis (**a**), expanded low attenuation secondary pulmonary lobules are visible within or adjacent to areas of the fibrotic lung, but no low attenuation lobules were visible within the normal lung. In a patient with hypersensitivity pneumonitis, however (**b**), low attenuation secondary pulmonary lobules are visible within the normal parenchyma (arrowhead), a feature that may increase the likelihood of a diagnosis of hypersensitivity pneumonitis

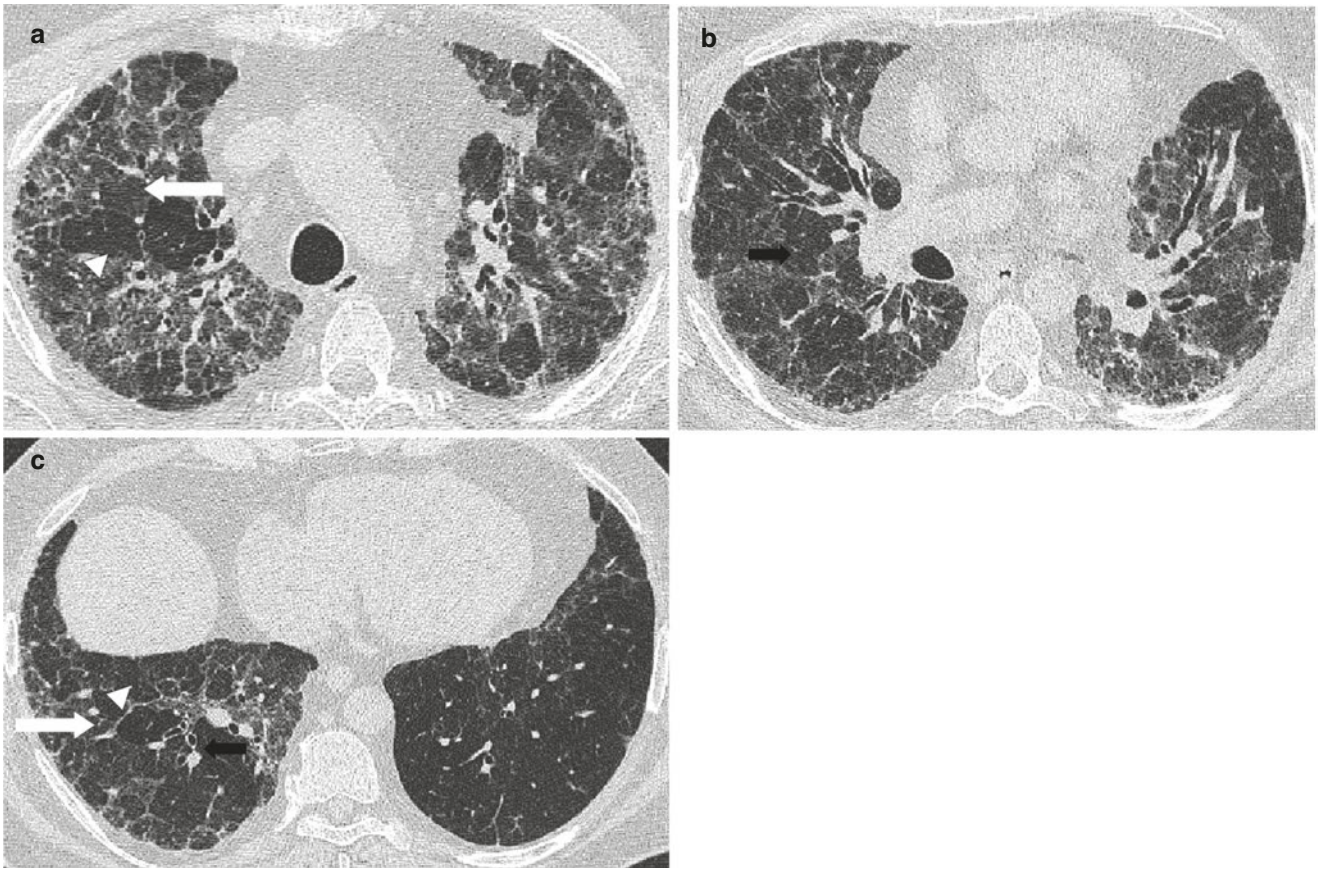

Fig. 29.5 Axial computed tomography images in the upper (**a**), middle (**b**), and lower (**c**) regions of the lungs in a patient with hypersensitivity pneumonitis. The combination of normal (black arrows) and low (arrowheads) attenuation secondary pulmonary lobules and increased (white arrows) density lobules represents the "headcheese" sign which improves the specificity for reaching a diagnosis of hypersensitivity pneumonitis

UIP in IPF

IPF is a chronic, progressive, fibrosing interstitial pneumonia of unknown cause, occurring predominantly in older adults, associated with the histopathological and/or radiological pattern of usual interstitial pneumonia (UIP) [6]. The 2018 ATS/ERS/ALAT/JRS diagnostic guidelines [6] and Fleischner Society guidelines [8] require that to make a diagnosis of IPF, there must be (a) exclusion of other known causes of ILD, (b) the presence of a definite/probable UIP-IPF pattern on HRCT and (c) where CT features are indeterminate, histopathological confirmation of UIP (Table 29.2). In cases where imaging is indeterminate for a UIP-IPF pattern and surgical biopsy is not possible, case discussion in a multidisciplinary meeting may allow assignation of a working diagnosis of IPF. The working diagnosis may be revisited/confirmed as the particular evolutionary trajectory of a patient's disease becomes clearer over time. The following sections will describe the imaging criteria required to assign a UIP pattern appropriate for an IPF diagnosis (UIP-IPF).

Definite UIP-IPF

In the appropriate clinical context, honeycombing with or without traction bronchiectasis, located in a subpleural and basal predominant distribution (Fig. 29.6a–c), without features of an alternative diagnosis, strongly correlates with histopathological UIP [26]. If honeycombing is present but in an atypical distribution (not lower zone predominant), an alternative diagnosis should be considered.

Probable UIP-IPF

A probable UIP-IPF pattern (Table 29.3) is analogous to a definite UIP-IPF pattern but where peripheral traction bronchiectasis or bronchiolectasis is distributed subpleurally and basally and no honeycombing is present (Fig. 29.6d–f). The derivation of the term "probable UIP pattern" emerged following histopathological studies that identified UIP features in patients labelled possible UIP using the 2011 guidelines [27, 28]. Similar rates of disease progression were also shown between patients with definite and possible UIP patterns in drug trial cohorts emphasising the prognostic importance of traction bronchiectasis in idiopathic pulmonary fibrosis [29].

Indeterminate

An Indeterminate UIP-IPF pattern may reflect two scenarios. Subpleural and basal predominant reticulation may be identified without honeycombing or traction bronchiectasis being present (Fig. 29.7a–c). Whilst this may reflect the very earliest signs of UIP-IPF, a UIP pattern cannot be assigned on CT analysis until progression to traction bronchiectasis occurs. The second scenario associated with an indeterminate UIP-IPF pattern occurs when CT features and disease distribution are not typical for UIP-IPF (Fig. 29.7d–f) and no features suggestive of an alternative diagnosis are identified on the CT.

Table 29.2 Computed tomography (CT) features are required to be present in a basal peripheral lower zone distribution when classifying a usual interstitial pneumonia pattern in the context of idiopathic pulmonary fibrosis. CT features suggestive of an alternative diagnosis including predominant ground glass opacities and low attenuation lobules within the normal background lung parenchyma, cysts, nodules and consolidation should not be present. An indeterminate usual interstitial pneumonia pattern may also reflect fibrosis where the distribution of disease does not specify a particular aetiology and where CT features do not suggest an alternative diagnosis

CT feature	Definite	Probable	Indeterminate
Honeycombing	+	–	–
Traction bronchiectasis	+/–	+	–
Reticulation	+/–	+/–	+

Table 29.3 The importance of traction bronchiectasis presence in defining the likelihood of a usual interstitial pneumonia pattern on computer tomography (CT) imaging has been the primary change in the 2018 imaging classification of idiopathic pulmonary fibrosis

CT feature	Consensus Guideline Definition: 2011	Consensus Guideline Definition: 2018
Honeycombing	Definite	Definite
Traction bronchiectasis	Possible	Probable
Reticulation	Possible	Indeterminate

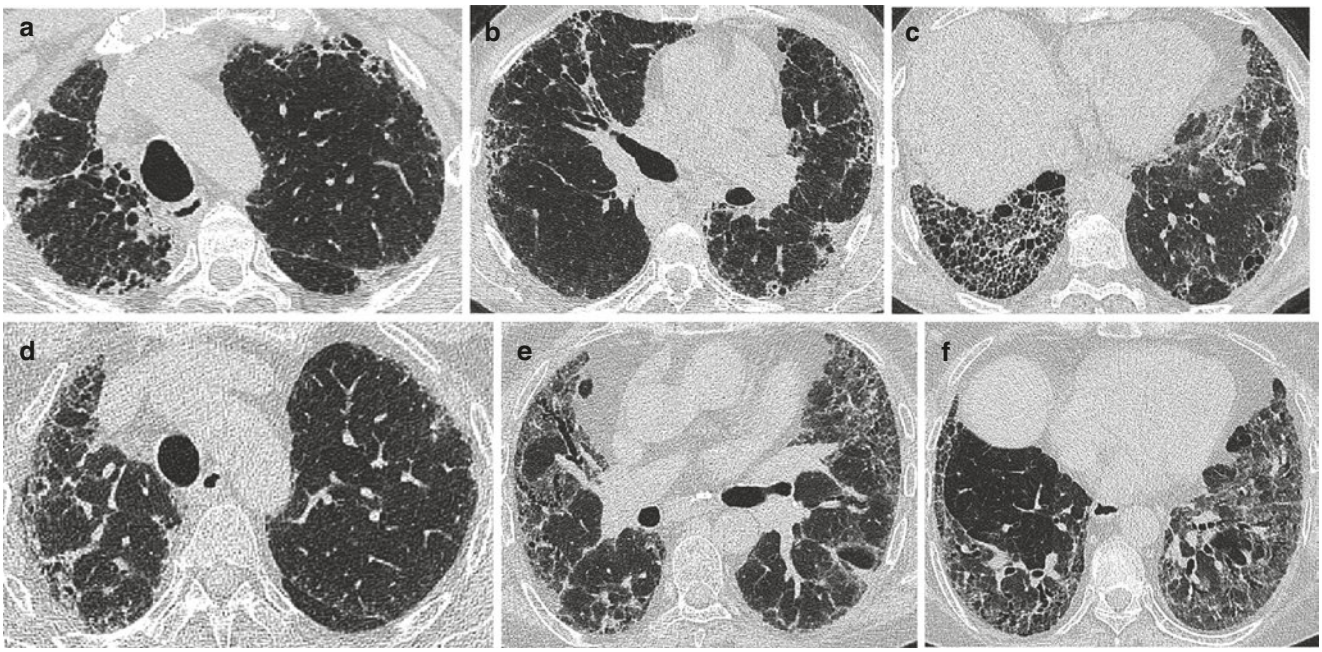

Fig. 29.6 Axial computed tomography images in the upper (**a** + **d**), middle (**b** + **e**), and lower (**c** + **f**) regions of the lungs in two idiopathic pulmonary fibrosis patients with a definite and probable usual interstitial pneumonia pattern. A definite usual interstitial pneumonia pattern (**a**–**c**) demonstrates honeycombing in a predominantly basal, peripheral and subpleural distribution. The fibrosis is relatively asymmetrical being worse in the right lung. A probable usual interstitial pneumonia pattern (**d**–**f**) demonstrates traction bronchiectasis in a predominantly basal, peripheral and subpleural distribution with no evidence of honeycombing on the scan

Alternative Diagnosis

An alternative diagnosis is reached when fibrosis is observed on a CT but features suggesting a non-idiopathic cause are also present. These primarily include an atypical distribution of disease, predominant ground glass opacities and low attenuation lobules (both occurring on background normal lung), the presence of cysts, nodules, and consolidation. However, care should also be taken to search out signs suggestive of an underlying connective tissue disease such as a dilated oesophagus (systemic sclerosis; Fig. 29.8a–c) or distal clavicular erosions (rheumatoid arthritis) as well as pleural plaques, effusions and pleural thickening (Fig. 29.8d–f).

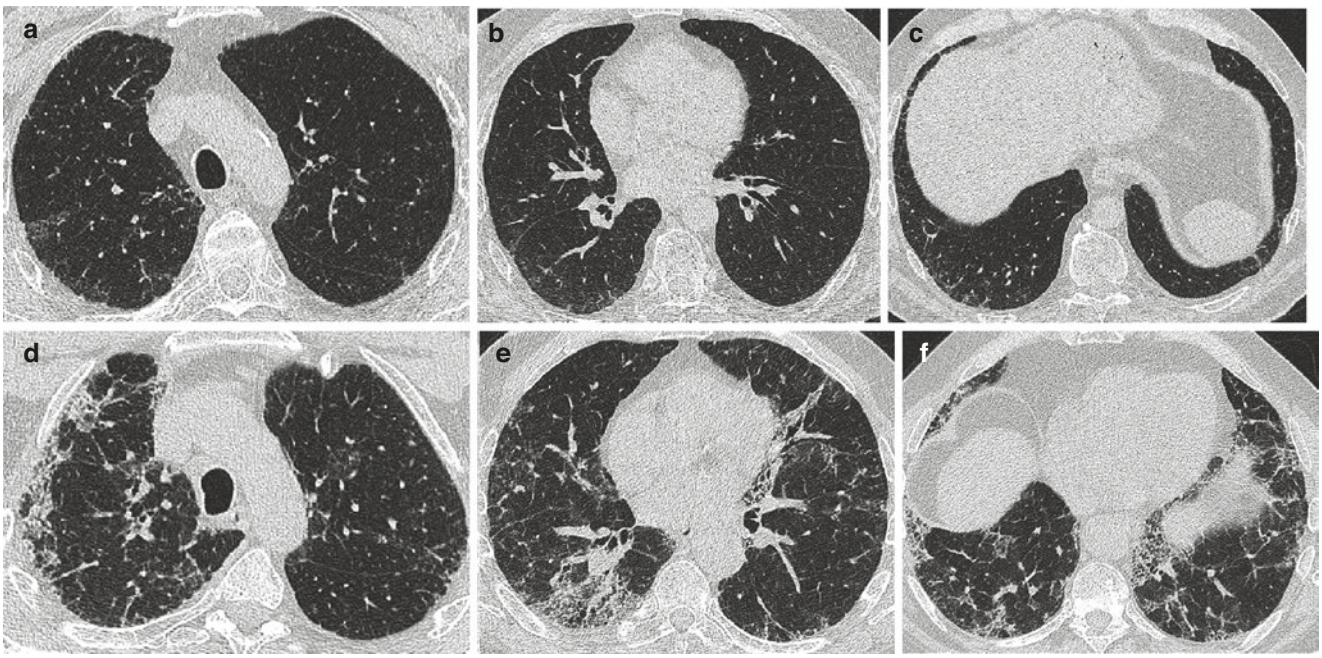

Fig. 29.7 Axial computed tomography images in the upper (**a** + **d**), middle (**b** + **e**), and lower (**c** + **f**) regions of the lungs demonstrate the two scenarios that can give rise to an indeterminate usual interstitial pneumonia (UIP) pattern. The presence of reticulation in a predominantly basal, peripheral and subpleural distribution (**a**–**c**) with no evidence of honeycombing or traction bronchiectasis on the scan can result in a pattern indeterminate for UIP. Alternatively, despite the presence of honeycombing or traction bronchiectasis the distribution of disease throughout the lung may not be typical for idiopathic pulmonary fibrosis-related usual interstitial pneumonia (basal predominant). In this case (**d**–**f**) fibrosis with traction bronchiectasis and reticulation appears evenly distributed throughout all zones of the lungs

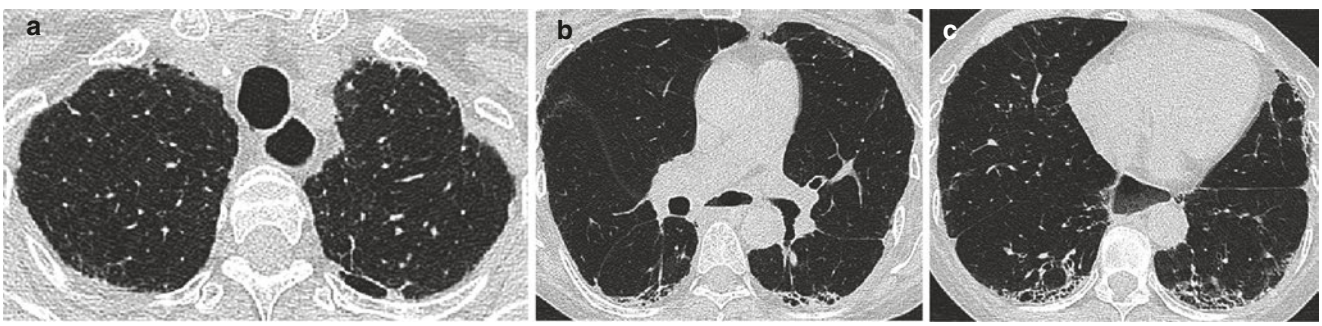

Fig. 29.8 Axial computed tomography images in two patients with connective tissue disease-related lung fibrosis. A patient with lower zone predominant fibrosis characterised by traction bronchiectasis has a dilated oesophagus throughout the length of the mediastinum (**a**–**c**) suggesting a diagnosis of systemic sclerosis. In a second patient with rheumatoid arthritis-related fibrosis (**d**–**f**) parenchymal bands are visible originating from the lung periphery in the midzones in keeping with an old exudative pleural effusion. In the lower zones, there is evidence of pleural effusion on the right (arrow)

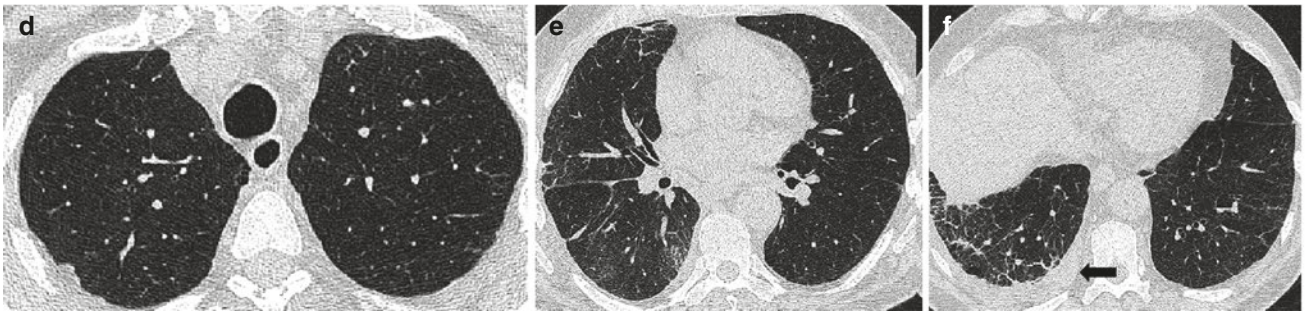

Fig. 29.8 (continued)

UIP in Other Fibrosing Lung Diseases

As mentioned previously, a UIP pattern of fibrosis in IPF suggests a progressive form of lung disease. Whilst the consensus diagnostic guidelines on which CT evaluation is predicated revolve around the diagnosis of IPF, it must be remembered that honeycombing is not infrequently seen in other fibrosing lung diseases including CHP [20, 30] (Fig. 29.9a–c), rheumatoid arthritis-related interstitial lung disease (RAILD) (Fig. 29.9d–f) and sarcoidosis. Though the distribution of fibrosis and honeycombing may be different from UIP-IPF, studies have shown that patients with CHP [31] and RAILD [32, 33] with a UIP pattern have comparable mortality to IPF patients, independent of their disease severity.

Pleuroparenchymal Fibroelastosis (PPFE)

PPFE was originally described as an upper lobe predominant condition that was idiopathic [34], familial [35] or occurring in patients undergoing organ transplantation [36]. However, it has been increasingly recognised in several fibrosing lung diseases including IPF (Fig. 29.10a–c), CHP (Fig. 29.10d–f) and systemic sclerosis (Fig. 29.10g–i). In IPF [37] and CHP [38] PPFE has been shown to predict mortality independent of patient age, gender and baseline disease severity. PPFE has also been linked to worsening forced vital capacity (FVC) decline in patients with IPF [37].

The CT characteristics of PPFE include peripherally distributed triangular foci of dense consolidation (pleural fibroelastosis) with well-defined centrally placed foci of dense aggregated tissue (parenchymal fibroelastosis). Patients often have a narrowing of the antero-posterior diameter of the chest wall which is associated with a depression in the contour of the suprasternal chest wall (Fig. 29.10). PPFE invariably involves the upper lobes but can extend to involve the middle and lower lobes and is associated with an increased risk of pneumothoraces. The 2018 IPF diagnostic guidelines [6] specified that whilst the presence of PPFE should be noted, the patient's radiological description should focus on the underlying fibrosing lung disease. Therefore, in the case of Fig. 29.10a–c, the patient would be described as having a UIP pattern with PPFE.

Combined Pulmonary Fibrosis and Emphysema

The co-occurrence of lung fibrosis and emphysema is a relatively frequent finding in several fibrosing lung diseases such as IPF [39] and RAILD [40] given the high proportion of heavy smokers often seen in both patient groups. The importance of CPFE relates to the observation that extensive emphysema can elevate lung volumes thereby potentially masking the severity of a patient's lung fibrosis when severity is evaluated using forced vital capacity measurements. In CPFE disproportionate reductions in the transfer factor for carbon monoxide (DLco) are often present. Furthermore, extensive co-existing emphysema has been shown to affect the rate of FVC decline in IPF [41]. Though CPFE is not a formal diagnosis, patients have been noted to have an increased risk of developing pulmonary hypertension [42] and lung cancer [43], necessitating careful scrutiny of CT imaging for evidence of a dilated main pulmonary artery and new pulmonary nodules. A characteristic appearance noted in areas where emphysema and fibrosis co-exist in that of conglomerate cystic airspaces which can increase in size over time (Fig. 29.11). Intriguingly there is also increasing evidence that emphysema may develop in patients with FLD who have never smoked [40] suggesting potential autoimmune mechanisms responsible for lung damage [44].

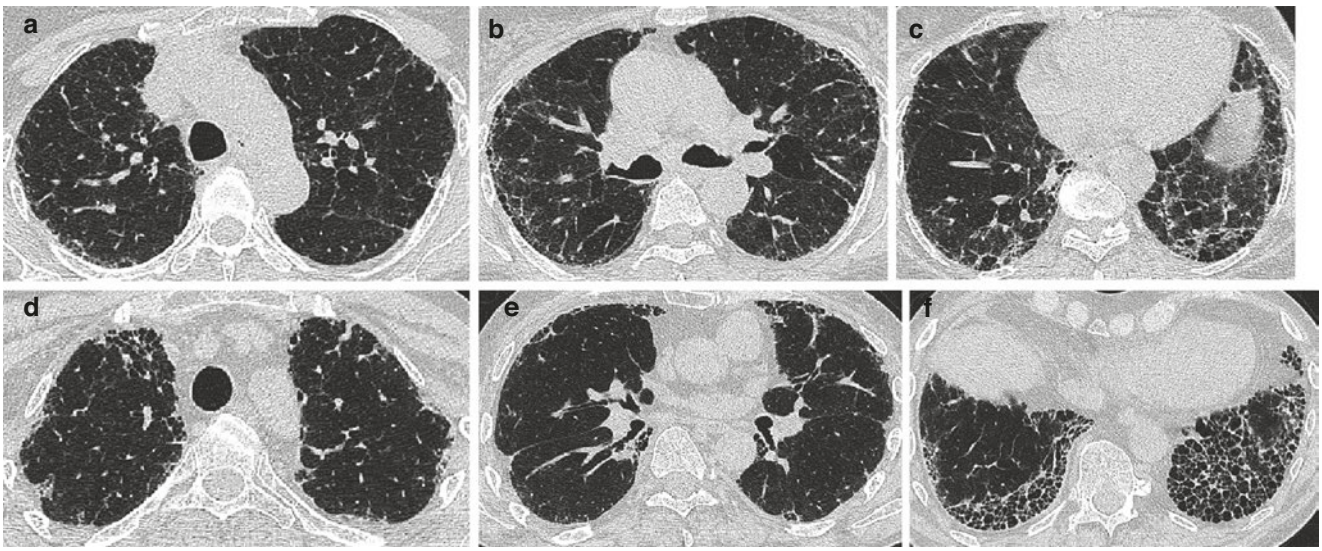

Fig. 29.9 Axial computed tomography images in two patients with diagnoses other than idiopathic pulmonary fibrosis where a usual interstitial pneumonia (UIP) pattern can be observed. A patient with hypersensitivity pneumonitis (**a**–**c**) demonstrates a lower zone predominant distribution of fibrosis and low attenuation lobules within normal regions of the lung. In the left lower lobe honeycomb cysts are visible signifying a UIP pattern. In a patient with rheumatoid arthritis-related interstitial lung disease (**d**–**f**), there is a lower zone predominance to the fibrosis where honeycomb cysts are visible bilaterally signifying a UIP pattern

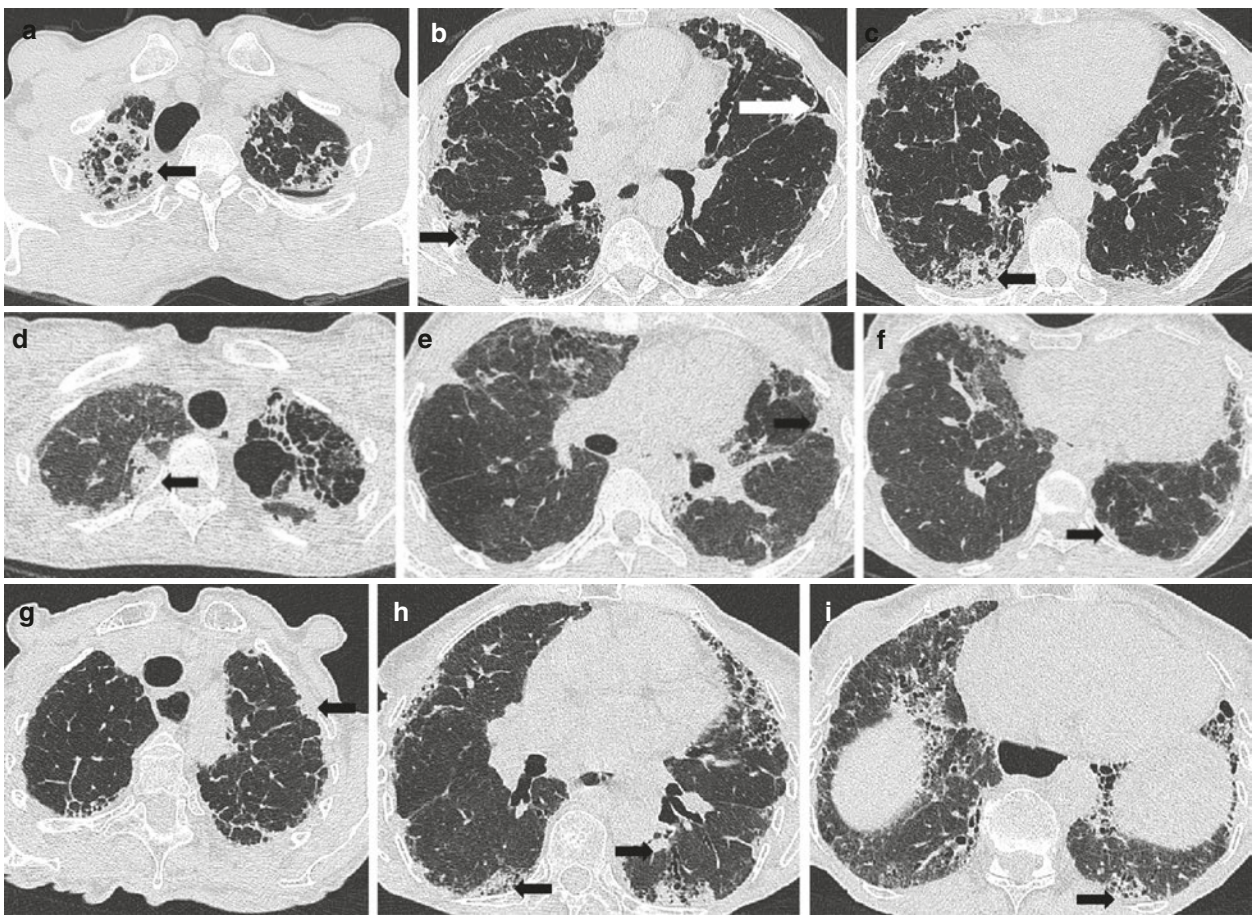

Fig. 29.10 Three patients with a computed tomography pattern of pleuroparenchymal fibroelastosis (PPFE) and lung fibrosis. In patients with idiopathic pulmonary fibrosis (**a**–**c**), hypersensitivity pneumonitis (**d**–**f**) and systemic sclerosis (**g**–**i**) there is evidence of a suprasternal depression in the anterior chest wall contour. Triangular foci of dense consolidation are visible originating from the pleural surfaces (black arrows), extending down to the lower lobes. A pneumothorax (white arrow), which not uncommonly complicates PPFE is visible in the mid-zone of the patient diagnosed with idiopathic pulmonary fibrosis (**b**)

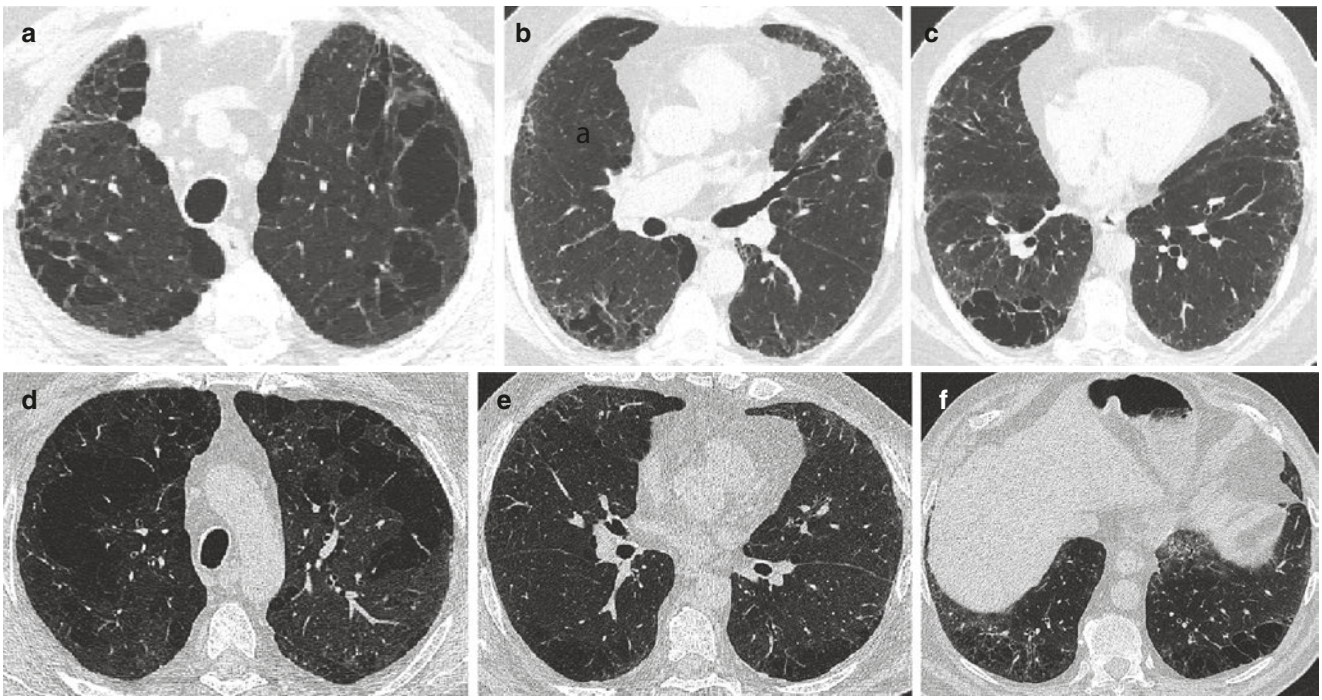

Fig. 29.11 Combined pulmonary fibrosis and emphysema in a patient diagnosed with idiopathic pulmonary fibrosis (**a**–**c**) and hypersensitivity pneumonitis (**d**–**f**). Traction bronchiectasis in a lower zone predominant distribution was seen in both cases. Emphysema co-located amongst areas of fibrosis is evident in the right lower lobe (**c**) and left lower lobe (**f**) as conglomerative thick-walled cystic lesions

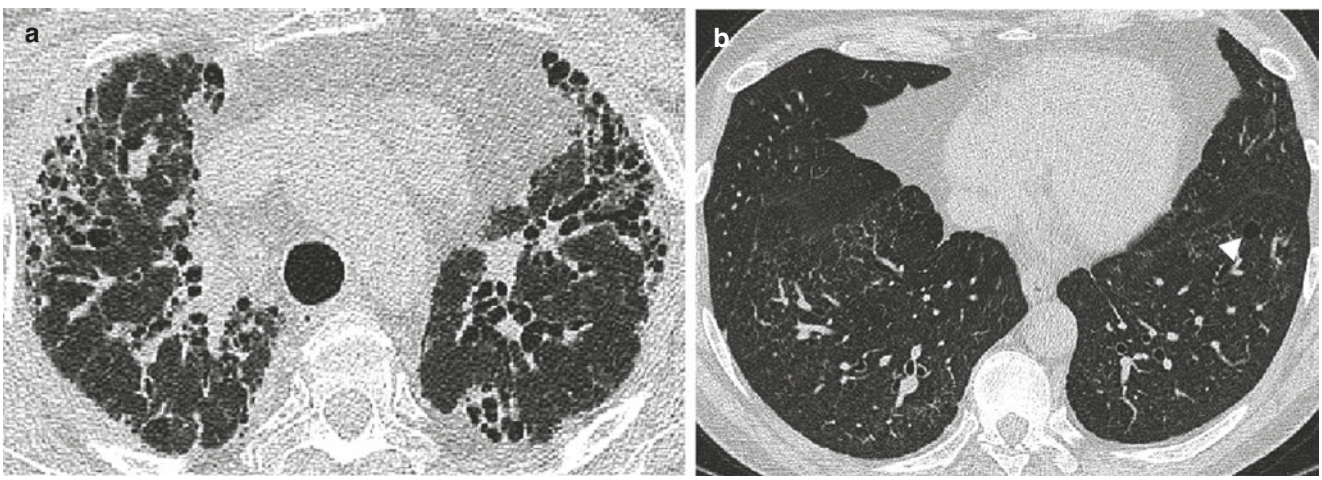

Fig. 29.12 Accessory signs of hypersensitivity pneumonitis were identified on computed tomography. Bronchocentric fibrosis (**a**) is preferentially located around the airways as seen in the left upper lobe. Cysts (arrowhead) are also associated with hypersensitivity pneumonitis (**b**)

Chronic Hypersensitivity Pneumonitis

Differentiating CHP from IPF is one of the most common challenges faced by a multidisciplinary team. Although typically considered an upper and mid-zone predominant disease [45, 46], CHP can be lower lobe predominant in a third of cases [20]. Ancillary features in addition to the presence of low attenuation lobules that may suggest CHP include a bronchocentric distribution to lung fibrosis, poorly defined centrilobular nodules (indicating subacute disease) and cysts [20, 24] (Fig. 29.12).

Unclassifiable Fibrosing Lung Disease

Patients with unclassifiable FLD may constitute up to 15% of fibrosing lung disease cohorts [47]. These patients either do not have an obvious diagnosis that can be made with over 50% certainty based on all available information or reflect patients in whom a clear diagnosis cannot be determined even following surgical lung biopsy [48]. Patients with an indeterminate UIP pattern where disease distribution is not lower zone predominant could be labelled as unclassifiable FLD or managed with a working diagnosis whilst disease behaviour is monitored, and the patient re-evaluated at a future date.

Other Fibrosing Lung Diseases

Non-specific Interstitial Pneumonia Pattern

HRCT features traditionally associated with a non-specific interstitial pneumonia pattern include a more central distribution of traction bronchiectasis than is typically seen in UIP-IPF [49], and the presence of subpleural sparing [50] (Fig. 29.13). Following the publication of the 2011 guidelines for UIP [7], there has been a reduction in the number of idiopathic NSIP cases diagnosed by multidisciplinary teams. As the focus of diagnosis has moved towards identifying UIP-IPF, many cases that would have previously been assigned NSIP on HRCT were labelled as possible UIP from 2011 and probable UIP from 2018 onwards. An NSIP pattern is common in connective tissue disease-related interstitial lung disease (CTD-ILD), and if idiopathic pneumonia with autoimmune features (IPAF) [51] gains consensus as a disease entity, idiopathic NSIP might indeed become a rare diagnosis.

Fibrosing Sarcoidosis

The upper lobe predominance of sarcoidosis typically distinguishes it from UIP-IPF, but distinguishing fibrosing sarcoidosis from CHP can be challenging. In fibrosing sarcoidosis architectural distortion and fibrosis originate at the lung hilum and extend to the posterior segments of the upper lobes [52]. In addition to volume loss and traction bronchiectasis, fibrobullous apical destruction can also be seen [53]. Perilymphatic and perifissural nodularity with calcified or non-calcified mediastinal and hilar lymph nodes can aid CT diagnosis. Of note, sarcoidosis may very rarely present with typical UIP-IPF features on HRCT [54].

CTD-ILD and Drug-Induced FLD

As the diagnosis of CTD-ILD requires serological confirmation, diagnosis in an MDT setting is less problematic than for other fibrosing lung diseases. However, this is not to underplay the wide variety of radiological appearances that CTD-ILD may manifest, including airways disease [55], lung fibrosis, organising pneumonia, pleural disease and pulmonary hypertension disproportionate to the severity of lung fibrosis [56, 57]. Recognising drug-induced FLD requires an appropriate clinical history, but typical HRCT patterns are those of organising pneumonia and/or NSIP [58].

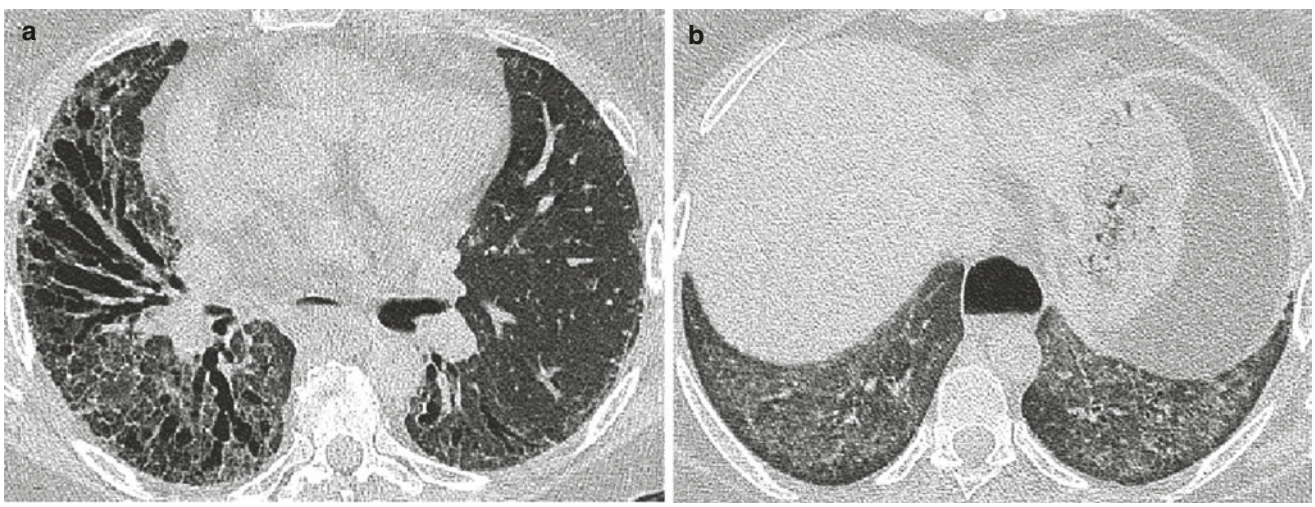

Fig. 29.13 Imaging features associated with non-specific interstitial pneumonia include central bronchiectasis (**a**) which contrasts with the predominantly peripheral bronchiectasis seen in idiopathic pulmonary fibrosis. Subpleural sparing (**b**) can also be seen and is often most marked in the lower lobes

Complications

In patients with interstitial lung disease, there are several important complications to consider during the assessment of cross-sectional imaging. These include the presence of pulmonary hypertension, lung cancer or evidence of an acute exacerbation of ILD.

Pulmonary hypertension can be suggested on CT by observing a pulmonary artery with a diameter greater than 29 mm [59], straightening or leftward bowing of the interventricular septum of the heart and right ventricular dilatation. The association between main pulmonary artery diameter and the likelihood of pulmonary hypertension has been shown to be maintained in patients with and without lung fibrosis [60]. Pulmonary hypertension is not an uncommon finding during fibrosing lung disease assessment, with a higher prevalence associated with IPF [61] and CTD-ILD [62].

There is an increased risk of lung cancer in patients with ILD, linked to the presence of fibrosis itself, but also related to the existence of common risk factors, such as smoking and occupational exposures [63]. When lung cancer develops, it is often a solid lesion found peripherally within an area of fibrosis and commonly within the lower lobes [64]. Therefore, the presence of a new nodule on a CT scan requires careful scrutiny and work up (Fig. 29.14).

Although ILDs are typically chronic conditions they can also undergo acute phases of deterioration. Whilst accelerated decline may be secondary to an infection, cardiac failure or pulmonary embolism [65], an acute exacerbation should always be considered. An acute exacerbation typically presents with new bilateral ground glass opacities with or without consolidation which may be peripheral, multifocal or diffuse and has no identifiable cause [66]. Acute exacerbations have an incidence of 4–20% [67] per year and have a dismal prognosis with a median survival of 3 months [68]. The presence of an acute clinical deterioration should also raise the possibility of a complicating pneumothorax or pneumomediastinum.

Prognosis

As well as its utility in formulating a diagnosis, baseline HRCT interpretation can also aid in predicting a patient's likely prognosis. This is exemplified in the importance given to the identification of a UIP pattern of disease on CT which essentially signifies disease that has a poor outcome. Yet even within a UIP pattern of disease, visual CT scoring can refine prognostic likelihoods. The combined extents of honeycombing and reticulation have been shown to independently predict mortality in patients with IPF [13]. Honeycombing extent and severity of traction bronchiectasis have also been reported as independent predictors of mortality in both CHP [69] and CTD-ILD [70]. When patients with a variety of fibrosing lung diseases were examined together, it was found that across the range of aetiologies, the total extent of fibrosis indicated a poor prognosis [71].

More challenging for visual evaluation is the identification of disease worsening on serial CT imaging. Change in ILD extent is the metric most commonly used to determine disease worsening. Yet when fibrosis occurs in the lungs, damaged parenchyma contracts and reduces in volume, and non-fibrotic regions of the lung can hyperexpand to compensate for damage elsewhere. Therefore, when fibrotic disease increases in extent, as more lung contracts and spared regions hyperexpand, the degree of disease worsening can be underestimated on serial imaging. A consequence is that below a certain threshold of change, it may not be easy to visually quantify an increase in ILD extent on serial CTs (Fig. 29.15).

A further challenge in detecting disease worsening on serial CT imaging involves distinguishing the progression of

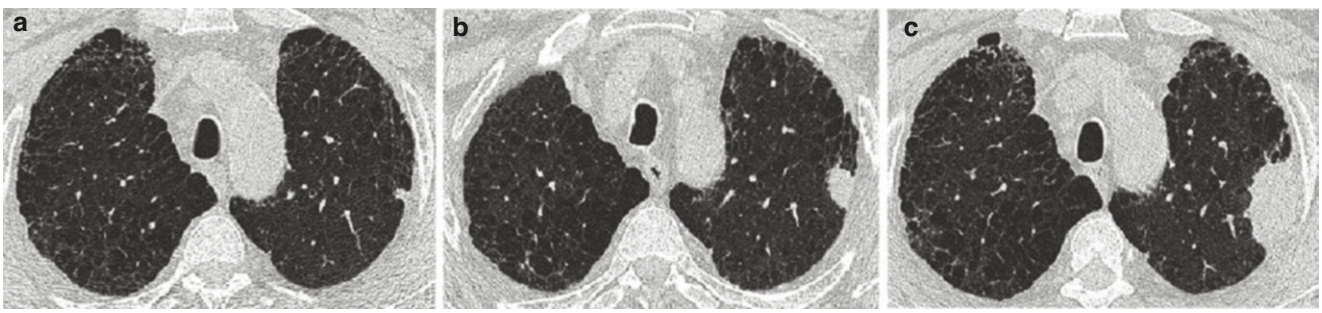

Fig. 29.14 Patients with fibrosing lung diseases, and in particular the subgroup that has a history of smoking have an increased incidence of lung cancer. Careful scrutiny of imaging is necessary to identify new lung nodules that may represent lung cancer. The three axial images show serial computed tomography scans in a patient diagnosed with idiopathic pulmonary fibrosis. The nodule in the left upper lobe on the first scan (**a**) was identified but the patient was not medically fit for surgery. On follow-up imaging 16 months later (**b**), the nodule has grown in size significantly. When imaged a further 8 months later (**c**) the nodule has become a large mass

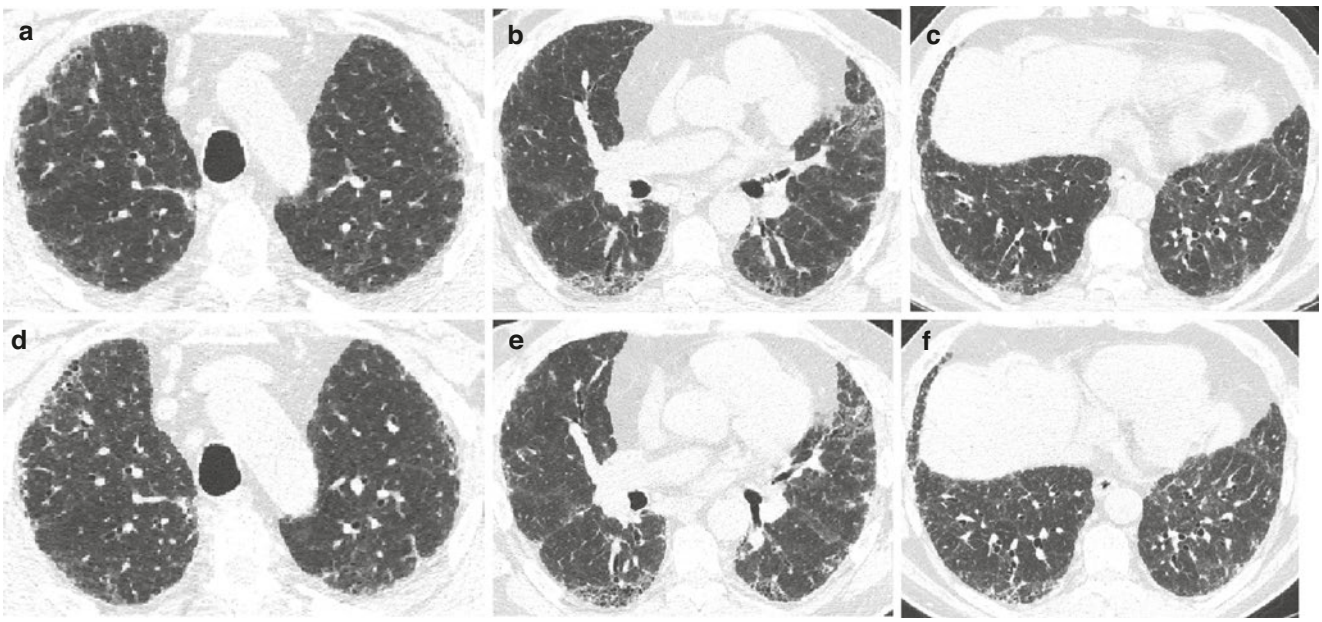

Fig. 29.15 Serial computed tomography scans were performed 12 months apart in a patient diagnosed with idiopathic pulmonary fibrosis. On the initial scan (**a**–**c**) there is fibrosis with reticulation and traction bronchiectasis visible in the middle and lower zones. At the second time point scan (**d**–**f**) it is challenging to distinguish disease maturation from disease progression using visual computed tomography analysis

disease from the maturation of disease. Maturation describes changes in the appearance of a region of fibrosis as it evolves over time following the reparative processes of the body. Disease maturation may not result in worsening lung damage even though the CT appearances change over time. Disease progression however implies fibrotic or inflammatory involvement of new areas of the lung which may be incorporated into pre-existing regions of damage. Should previously normal lung on the edges of the fibrotic lung become damaged, maturation and contraction of areas of long-standing damage may result in the entire volume of the involved lung in a region appearing grossly unchanged. In such situations, identifying the encroachment of damage towards adjacent structures (such as vessels) may be an alternative indicator of disease progression (Fig. 29.15).

Computer Analysis of CT Imaging

Quantitative CT (QCT) describes the many computer-based CT image analysis methods developed to measure changes in lung structure in patients with ILD. Most QCT methods employ density or texture-based analysis of varying complexity and offer improved objectivity, speed, reproducibility and scalability compared to visual CT scoring. QCT-derived metrics show potential as prognostic imaging biomarkers with reported utility in the assessment of disease severity at baseline and disease progression on serial CTs.

By simulating human visual perceptual and learning processes, texture-based QCT algorithms can describe CT patterns, previously exclusively within the domain of radiologists [72]. An example of QCT is the Computer Aided Lung Informatics for Pathology Evaluation and Rating (CALIPER) tool developed by the Biomedical Imaging Resource at the Mayo Clinic Rochester, Minnesota, USA. CALIPER characterises HRCT data using morphological and 3D histogram features, enabling voxel volumes to be labelled according to a conventional radiological lexicon: normal lung, ground glass opacity (GGO), reticulation, subtypes of low-attenuation and honeycombing [73]. CALIPER variables were proven more accurate in predicting survival than equivalent visual CT scores, with CALIPER honeycombing extent capable of independently predicting mortality (hazard ratio 1.18; $p = 0.002$) [74].

A unique attribute of CALIPER is the ability to quantify vessel-related structures. The vessel-related structure corresponds to pulmonary vessels (arteries and veins) and associated structures, for example, perivascular fibrosis which has no visually scored equivalent. CALIPER vessel-related structure was an independent predictor of mortality in IPF (hazard ratio 1.53; $p < 0.0001$) and superior to traditional visual CT scores [74]. In the future, vessel-related structures and other emerging, novel QCT imaging biomarkers that are not easily appreciated by the human eye and which identify features with no morphological correlate or radiological descriptor may play a significant role in the prognostication of ILD. Longitudinal QCT evaluation on serial HRCT also has the advantage of improved precision and potential for identification of patient phenotypes, for example, the progressive fibrotic phenotype [75].

The Progressive Fibrotic Phenotype

As our understanding of FLD has increased it has become increasingly apparent that diagnosis and prognosis do not always go hand in hand. For example, some patients with IPF survive for up to 10 years with no major incremental disability each year. As described earlier, however, some patients with CHP or RA-ILD can have disease trajectories that are indistinguishable from IPF. Assigning a diagnosis to a patient not only allows one to develop a plan of management for a condition, but it also envisions a likely prognosis, gleaned from knowledge about disease trajectories for patients with the same diagnosis. But when related but distinct diseases manifest similar rates of disease progression, it would be logical to ask whether management strategies shown to be successful in one disease might have utility in the related disease.

To answer this question in the FLDs, studies have investigated whether antifibrotic medication could curtail further disease progression in patients that have been identified as having a progressive form of fibrosis. The INBULD trial [76] examined the role of antifibrotics in patients with a variety of non-IPF FLDs where fibrosis was found to be progressive using lung function, symptomatic or imaging measures of deterioration. The study demonstrated that nintedanib slowed the rate of disease progression characterised by a reduction in forced vital capacity decline [77]. A consequence of the study is that the treatment of fibrosing lung disease may become diagnosis-agnostic, with progression becoming the most important disease characteristic that needs identification to guide management.

It is also possible that alternative longitudinal measures of disease worsening in the FLDs will be sought in the near-term. The current gold standard measure used to identify disease progression is an annual FVC relative decline of >10% per year. But as awareness of IPF grows, patients are being identified at earlier stages of the disease. The institution of lung cancer screening in various countries around the world is also likely to increase the earlier detection of patients with FLD. Antifibrotic use in IPF patients, coupled with earlier recognition of patients in their disease course is likely to result in a larger proportion of patients undergoing FVC declines <10% per year. FVC declines of <10% per year are in the range of measurement variation for the test. The coming years are likely to identify larger proportions of IPF patients in whom FVC measurements are unable to distinguish genuine physiological deterioration from measurement variation. Challenges in discerning real from artefactual change are also likely to be encountered in the non-IPF FLDs which often have a smaller rate of annualised FVC decline. Should antifibrotic prescription become licensed for use in non-IPF FLDs, even more patients will routinely have marginal declines in FVC.

Alternatives to FVC decline are being sought, both in terms of patient reported outcome measures, peripheral blood biomarkers and with visual and quantitative CT analysis. Avenues of CT research include identifying variables that might confirm that a marginal FVC decline (5–9.9%) represents real physiological deterioration. This may take the form of a CT measure proven to predict the outcome, that is used to adjudicate marginal FVC declines [78]. More than visual CT analysis, QCT tools hold the potential for identifying disease progression at much shorter intervals than that is possible with FVC decline.

Should change in a QCT metric definitively identify disease progression over a period of 3–6 months, future drug trials could be shortened and consequently become cheaper. This would in turn improve the feasibility of drug development in FLD. In a future where there are several potential drugs available to treat progressive FLDs, identifying disease progression in a patient taking one drug could provide the evidence to implement a change in therapy. Then, if a patient progresses despite therapy, combination drug therapy could be advocated, or in situations where the disease progresses despite several therapies being trialled, the patient could be referred early for lung transplantation.

Nevertheless, whilst CT analysis, and in particular QCT evaluation hold great promise, the limitations and measurement noise associated with CT acquisitions need further study. Specifically, measurement inaccuracies that are associated with serial CT imaging can include variability when different CT scanners or reconstruction algorithms are used at consecutive imaging time points in the same patient. FLD patients are often short of breath when scanned, and breathlessness can also contribute to measurement variation as the effort with which patients inspire can differ at different imaging time points. Optimising and limiting these sources of measurement inaccuracy will be crucial to improve the sensitivity and accuracy of QCT disease progression measurement.

Other Imaging Techniques

In addition to HRCT imaging, there are novel applications of existing imaging techniques e.g. magnetic resonance imaging (MRI) and positron emission tomography (PET) that have the potential to allow functional and structural assessment of ILDs [79]. Acquisition of thoracic MRI is inherently challenging due to the low signal-to-noise ratio of air and artefacts that result from cardiac/respiratory motion. These limitations can however be addressed by newer proton MRI methods. For example, ultrashort echo times (UTE) offer an

enhanced resolution that can identify structural changes in the lung [80]. Hyperpolarised noble gas MRI techniques also offer the potential to assess lung ventilation, microstructure and gas transfer in patients with ILD [81].

PET is rarely employed in clinical practice for the investigation of ILD. However, PET has demonstrated high standard uptake values (SUVs) of ^{18}F-fluorodeoxyglucose (FDG) in regions of lung fibrosis, questioning the longstanding assumption that these regions are 'burned out' and metabolically inactive [82]. There is also evidence of increased FDG uptake in apparently normal lung tissue as determined by visual CT inspection in patients with ILD, suggesting a possible role of PET in the identification of subclinical disease. PET also has a key role in characterising/confirming the malignant risk of nodules within areas of fibrosis, identified on routine clinical CT imaging.

Conclusion

Imaging techniques are an essential part of the diagnostic pathway in ILD. Chest radiography is frequently the initial indicator of ILD, with HRCT playing a key role in diagnosis and differentiation between specific ILDs. Typical imaging features, including those for UIP-IPF as described in this chapter, are well described in international consensus guidelines. In addition to aiding diagnosis, HRCT may be employed to exclude important complications and determine progression. Prediction of ILD prognosis is possible using traditional visual HRCT scoring methods and newer QCT analyses. Quantification of lung density changes and parenchymal textural features by advanced QCT algorithms has the potential to standardise and enhance the role of HRCT in ILD. Whilst the role of MRI and PET in ILD remains exploratory, there is significant potential for these techniques to complement the structural information derived from HRCT with measures of functional damage to the lung. Comprehensive assessment of lung structure-function changes in ILD, for example, using HRCT alongside hyperpolarised xenon MRI, as well as application of emerging QCT-derived imaging biomarkers may enable more accurate diagnosis, monitoring of treatment response and prognostication of ILD in the future.

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Bronchoscopic Approach to Interstitial Lung Disease

30

Claudia Ravaglia, Silvia Puglisi, Christian Gurioli, Fabio Sultani, Antonella Arcadu, and Venerino Poletti

Introduction

An interstitial lung disease is a heterogeneous group of disorders with different clinical-radiological presentations and evolution. Diagnosis of these diseases is usually based on medical history, laboratory tests, pulmonary function tests, and CT scans. Bronchoscopic techniques are required when these data alone are inconclusive and tissue or alveolar fluid is necessary for a definitive diagnosis or for therapeutic decisions [1]. Bronchoscopic procedures involved in the diagnostic process of diffuse parenchymal lung diseases include bronchoalveolar lavage (BAL), conventional transbronchial lung biopsy (TBB), and transbronchial lung cryobiopsy (TLCB).

Bronchoalveolar Lavage (BAL)

Technique

BAL is a minimally invasive procedure, well tolerated, and easily performed with a flexible bronchoscope introduced through the mouth or nose in a wedge position (in a segmental or sub-segmental bronchus). Sterile normal saline, usually 100–300 mL divided into 3–6 multiple aliquots, is instilled into a subsegment of the lung; after the instillation of each aliquot, instilled saline has to be retrieved using negative pressure (<100 mmHg) and volume retrieved should be in total >5% (optimal >30%) [2]. The recovered fluid should be collected into a container to which cells are poorly adherent and quickly send to the laboratory to enable processing within 1 h (BAL cells deteriorate rapidly in saline). The BAL sample will be divided into measured aliquots, for example, more than 20 mL for BAL cytology/flow cytometry, 10 mL for microbiology, and, if needed, 20 mL for electron microscopy (Table 30.1). Normal values of cytological profile are reported in (Table 30.2). A variety of stains may be used in the diagnostic interpretation of BAL. It is possible to differentiate blood cell types by employing the Wright Giemsa stain or the more commonly used Diff Quick stain which requires shorten staining time but does not stain mast cells. For infectious conditions, the Wright Giemsa stain can be used to detect clusters of the pneumocystis in *Pneumocystis jirovecii* Pneumonia, and confirmed by using the silver stain. The Giemsa stain is also useful to identify intracellular organisms, such as in bacterial pneumonia (Table 30.3).

Table 30.1 Technical recommendations to perform BAL

1. Perform BAL under local anesthesia with lidocaine and use pre-medication with a sedative compound
2. Decide the appropriate site to perform BAL and gently wedge the tip of the bronchoscope into the selected subsegmental bronchus
3. Sequentially introduce and aspirate standard aliquots of saline (total volume should be no less than 100 mL and should not exceed 300 mL).
4. For an optimal sampling of distal airspaces, the volume retrieved should be in total >5% (optimal >30%), so that a minimal volume of 5 mL is required for BAL cellular analyses
5. Send the BAL sample to the laboratory within 1 h because BAL cells deteriorate rapidly in saline

Table 30.2 Cellular profile of bronchoalveolar lavage fluid: normal values

Cell type	Non-smokers	Smokers
Macrophages	>80	>90
Lymphocytes	<20	<10
Neutrophils	<3	<4
Eosinophils	<0.5	<3
Mast cells	<0.5	<0.5
Plasma cells	0	0
Squamous epithelial cells	<5	<5

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Table 30.3 Useful stainings of BAL

Stain	Use	Clinical correlation
Wright-Giemsa	Inflammatory cell differential counts	Non-infectious granulomatous lung disease pulmonary fibrosis
Ziehl-Neelsen	Acid or alcohol-fast organisms	*Mycobacterium tuberculosis*
		Atypical mycobacterial infectious organisms
Papanicolaou	Virus (herpes simplex, cytomegalovirus)	Viruses and bacterial pneumonia
	Bacteria (filamentous bacteria-actinomycotic and Nocardia)	
Red oil O	Lipid-laden macrophages	Chronic microaspiration or lipoid pneumonia
PAS	Structures that contain high concentrations of carbohydrate macromolecules (e.g., glycogen, glycoprotein, proteoglycan)	Alveolar proteinosis
Perl stain	Haemosiderin-laden macrophages	Diffuse alveolar hemorrage
Prussian blue	Macrophages that have taken up red cells during chronic bleeding	Diffuse alveolar hemorrhage
CD 1a immunostaining	Langerhans cells	>5% Langerhans cell histiocytosis

BAL is a relatively low-risk technique and the most frequently observed side effects are self-limited fever and hypoxia, bronchospasm. Rarely hypotension, pneumothorax, bleeding, can be observed in critically ill patients. Finally acute exacerbations of idiopathic pulmonary fibrosis (IPF) within 30 days after the procedure has been reported [3].

Interpretation

The diagnostic value of BAL in discriminating between different forms of ILD is still a challenging issue. Analysis of BAL cell counts, cytology, and culture provides insights into immunologic, inflammatory, neoplastic, and infectious processes occurring at the alveolar level. BAL results should be interpreted in the context of the clinical and radiological presentation on the basis of several features such as the appearance and the cell pattern analysis of BAL fluid (BALF).

The appearance of BALF can provide diagnostic information. The presence of blood, with a progressive increase in the intensity of bloody discoloration in the retrieved BALF with sequential aliquots during the BAL procedure suggests a pulmonary alveolar hemorrhage syndrome [4]. If the BALF is grossly cloudy ("milky") or light brown to whitish, cloudy appearance the diagnosis of pulmonary alveolar proteinosis is suggested [5]. Cytological features may be considered diagnostic in alveolar proteinosis, exogenous lipoidic pneumonia, diffuse alveolar damage or may confirm a professional exposure to asbestos (Fig. 30.1).

In the American Thoracic Society clinical practice guideline, concerning the role of BAL cellular analysis in the diagnosis of ILDs, it was stated that BAL cellular analysis may add more information in the diagnostic evaluation of patients with suspected ILD. A differential cell count of lymphocytes, neutrophils, eosinophils, and mast cells is recommended to identify an inflammatory cellular pattern (increased lymphocytes, eosinophils, and/or neutrophils) orienting the diagnosis through a specific type of ILD. BAL samples obtained from healthy, never-smoking individuals should contain, on average, a majority of alveolar macrophages (80–90%), some lymphocytes (5–15%) and very few neutrophils (≤3%) or eosinophils (<1%); smoking increases the absolute number of BAL macrophages and neutrophils. When neutrophil counts are very high it is important to check for intracellular bacteria, which can indicate active bacterial pneumonia.

In ILD patients a variety of changes in the relative and absolute numbers of individual cell constituents have been described. Usually, these changes are nonspecific, but occasionally, the pattern is sufficiently characteristic to guide the differential diagnosis [6].

Increased lymphocytes (>25%) can be associated with granuloma formation (such as sarcoidosis and hypersensitivity pneumonitis) or drug toxicity. BAL lymphocytosis can also be observed in other diseases, such as cryptogenic-organizing pneumonia (COP) secondary organizing pneumonia, lymphocytic interstitial pneumonia (LIP), cellular NSIP (non-specific interstitial pneumonia), or lymphoproliferative disorders [1]. The T-lymphocyte component can be sub-categorized by flow cytometry with reference to T helper (CD4+) versus T suppressor (CD8+) phenotypes, using antibodies directed against those two lymphoid antigens. Assessment of the CD4/CD8 ratio should not be performed routinely but only in the presence of ≥15% lymphocytes [6]. Usually, a CD4+/CD8+ ratio in BAL from clinically healthy, younger adults usually is 1.0–3.5 (average values 1.5–2.0). CD4+/CD8+ ratio >3.5 combined with BAL lymphocytosis and normal neutrophil count is relatively specific for sarcoidosis, but sensitivity is low so that it is possible to have sarcoid patients with the normal ratio in almost 50% of cases

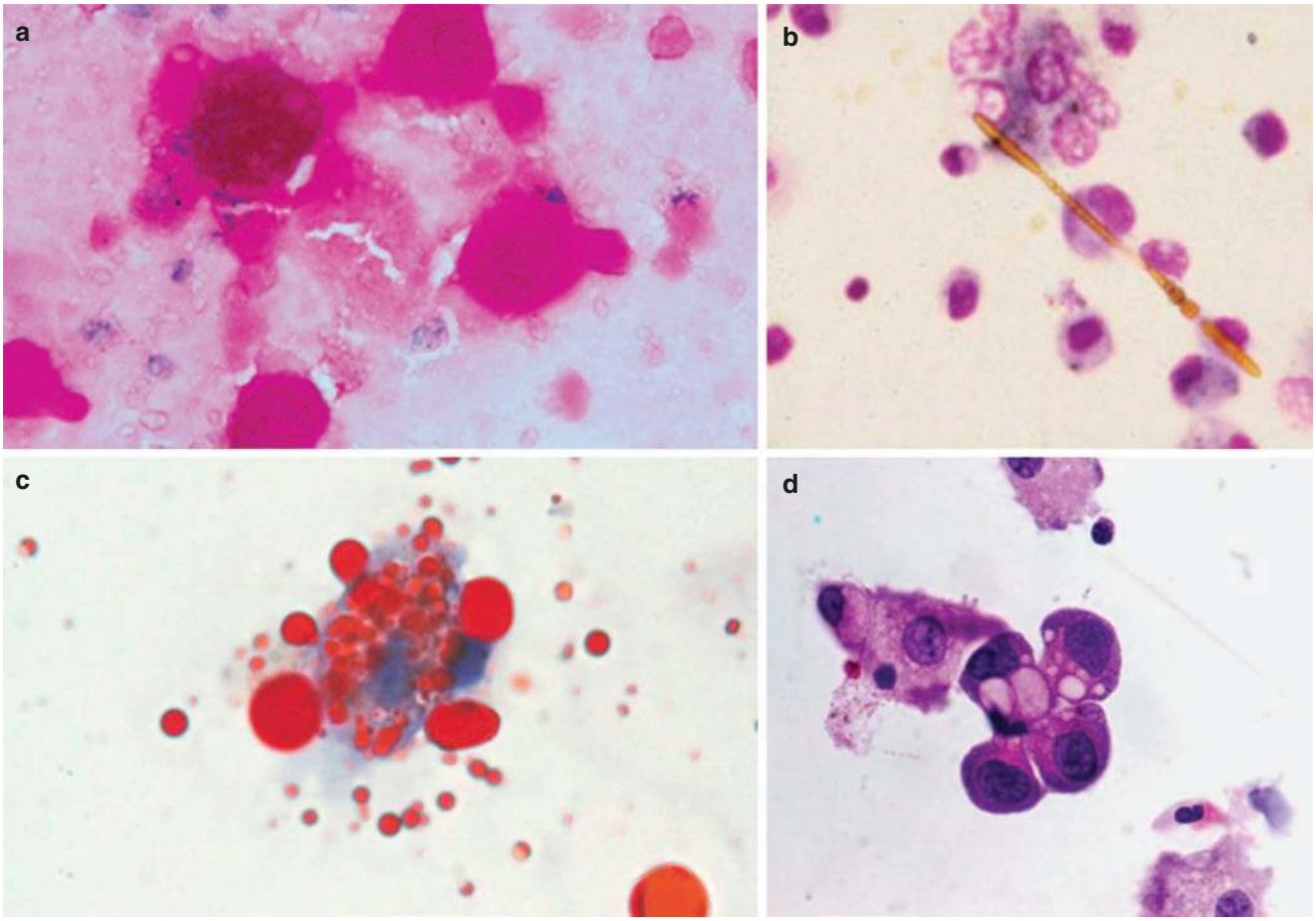

Fig. 30.1 (**a**) Periodic Acid Schiff staining in BAL confirming pulmonary alveolar proteinosis (PAP); (**b**) asbestos fiber in bronchoalveolar lavage; (**c**) lipid-laden alveolar macrophages marker of aspiration; (**d**) diffuse alveolar damage (DAD): the epithelial component displays various degrees of nuclear atypia. (Source: Pathology Department, G.B. Morgagni – L. Pierantoni Hospital, Forlì, Italy)

[7]. The CD4/CD8 ratio is usually decreased in subacute HP (ratio <1) [1, 8], it can be increased in normal elderly subjects [9]. The BAL lymphocytosis in HP is often dominated by CD8+ T cells, resulting in an inverted CD4/CD8 ratio with mean values of 0.5–1.5, together with an increase in relative numbers of mast cells and neutrophils [10]. Several studies have evaluated the utility of integrin CD103, expressed on CD4+ T lymphocytes in BAL, as a putative marker for sarcoidosis, with controversial conclusions [11, 12].

Increased number of mast cells (1–2%) have been associated with HP, drug reactions, sarcoidosis, ILD associated with collagen vascular disease, IPF, COP and malignancy. A more prominent "lymphocytic inflammation" on BAL is frequently present in NSIP patients with clinical/radiological characteristics suggestive of organizing pneumonia (OP), which usually have a better outcome and treatment response. NSIP with more prominent "fibrotic changes," that is characterized by no lymphocytosis on BAL, is associated with a worse outcome [13].

Eosinophil differential cell counts >25% are likely to be caused by eosinophilic lung disease, especially eosinophilic pneumonia [14], although eosinophilia may be present in desquamative interstitial pneumonia (DIP) [1]. In acute eosinophilic pneumonia type II dysplastic/reactive pneumocytes may be also detected [1].

A predominance of macrophages containing smoking-related inclusions, within significant increases in other cell types such as eosinophils, is consistent with smoking-related ILD such as desquamative interstitial pneumonia (DIP) or pulmonary Langerhans cell histiocytosis (PLCH) [1, 15]. In respiratory bronchiolitis eosinophils are not increased.

A finding of raised neutrophils (>5%) and eosinophils (>2%) is characteristic but not diagnostic of IPF [16]; in a minority of patients, it is possible to find a mild BAL lymphocytosis, which seldom exceeds 25% of the differential cell count [17]. BAL in IPF should be considered in all patients with suspected infection, malignancy. In such cases, it might be diagnostic.

Various types of acute and subacute lung injury can cause severe reactive pneumocyte atypia: diffuse alveolar damage (of known or unknown cause), "explosive" organizing pneumonia, acute fibrinous and organizing pneumonia (AFOP). In BAL these cells may be detected and they present with marked cytomegaly, vacuolated cytoplasm, prominent nucleoli, frequent binucleation. Recently a peculiar aspect labeled as "Napoleon hat" sign has been described [18, 19]. BAL is also useful in the detection of disseminated epithelial neoplasms and lymphoproliferative disorders [19, 20].

In addition to changes in the number and proportion of cells, other findings in the BALF analysis are useful in ILD diagnoses such as the presence of lipid-laden macrophages (in chronic microaspiration or lipoid pneumonia) [Fig. 30.1c] and mineral dust (in some pneumoconiosis) [Fig. 30.1b] (Table 30.3).

The 2022 guidelines from the American Thoracic Society/European Respiratory Society on IPF suggest that BAL could be indicated for patients with a first ILD diagnosis of apparently unknown cause with a CT pattern of probable usual interstitial pneumonia (UIP), indeterminate UIP, or an alternative diagnosis [21].

BAL may also have a prognostic value: some studies have reported that BAL findings at the time of diagnosis reflect the severity of ILD and may predict the prognosis. Increased neutrophils with a low lymphocyte count suggest a poor prognosis in chronic/fibrosing HP and increased neutrophils have been reported to predict mortality in IPF [22]. Similarly, an increased neutrophil count in BAL may be associated with an unfavorable outcome in newly diagnosed patients with sarcoidosis and it may indicate the need for active treatment [23].

Despite the presence of some controversies, BAL should be regarded as a useful tool in the clinical management of ILD. However it should not be used as an isolated tool for making a diagnosis, but always be interpreted in the context of disease history, clinical, laboratory, and radiological findings and it can become particularly important if the biopsy is not feasible.

New research frontiers could be related to BAL cell gene expression patterns (nucleic acid microarray analysis), correlation of gene analysis profiles and proteomic analysis with specific diagnoses, detection of specific infection via microbial oligonucleotide analysis, construction of diagnostic algorithms, and disease activity and management guidance.

Recent studies have found that cells secrete vesicles containing proteins, lipids and nucleic acids (including RNA, miRNA) involved in the signal transduction to neighboring and distant cells. Exosomes represent one type of such vesicles, and the exosome-associated microRNA has drawn a lot of attention because of its accessibility in body fluids (plasma, serum, BAL fluid) and of its potential role as a biomarker.

It has been demonstrated a decreased expression of miR-30A-5p in the BAL fluid exosome of IPF patients compared to healthy subjects. The miR30a5p has been reported to suppress migration and invasion and have also antifibrotic role in liver fibrosis so that miR30a5p could be proposed as a potential biomarker for IPF [24].

The exosomes present in the BAL fluid of sarcoidosis patients is characterized by the presence of miRNA (miR-146a and miR-150), the expression of which correlates negatively with pulmonary function indices [25].

Transbronchial Biopsy (TBB)

Transbronchial lung biopsy (TBB) using flexible forceps yields small biopsy samples, on the order of 1–3 mm in the greatest dimension, often with significant crush artifact [26]. The procedure itself is associated with a low complication rate: pneumothorax (2–10%), severe bleeding (less than 2% of cases). Other complications (including acute exacerbation of interstitial lung diseases or air embolism) are even rarer. TBB is a common diagnostic technique used to define lesions that have a centrilobular, alveolar, and/or perilymphatic distribution [1]. The lung specimens obtained with these small forceps come from the centrilobular regions and the zone centered upon small airways, so that lung disorders centered around terminal bronchioles or along the lymphatic routes may be reached by these forceps.

Therefore it is diagnostic mainly in organizing pneumonia, sarcoidosis, chronic eosinophilic pneumonia, diffuse alveolar damage, organizing pneumonia (OP) [Fig. 30.2], subacute hypersensitivity pneumonitis, low-grade B cell lymphomas and carcinomatous lymphangitis.

On the other hand, TBB is rarely sufficient to establish the diagnosis with confidence in diseases characterized by heterogeneous histological patterns or in those with the main histological abnormalities located in the periphery of the secondary lobule (such as UIP). Barbescu et al. reported that

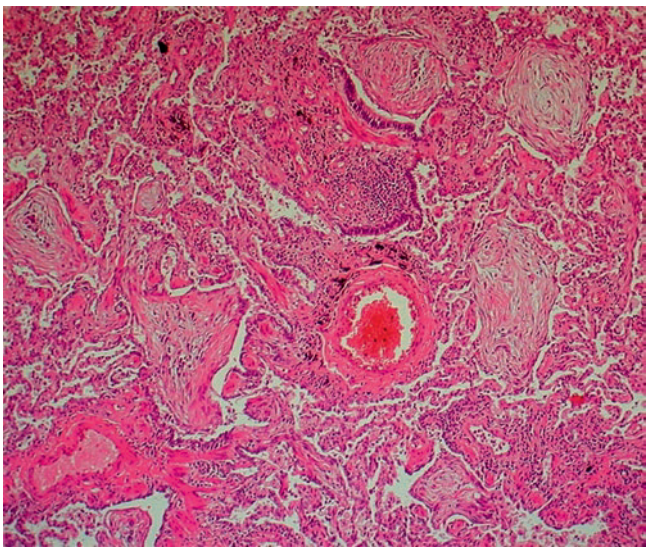

Fig. 30.2 Trans-bronchial biopsy of the lung showing myxoid fibroblastic plugs typical of organizing pneumonia (OP). (Source: Pathology Department, G.B. Morgagni - L. Pierantoni Hospital, Forlì, Italy)

TBB can allow the recognition of the hall marks of the UIP pattern [27]: when patchy fibrosis, honeycombing, and fibroblastic foci are recognized, its specificity for the UIP pattern appears to be high.

However, TBB has a very low sensitivity and specificity when other patterns, such as nonspecific interstitial pneumonia (NSIP) and desquamative interstitial pneumonia (DIP) are identified [28]. It should also be considered that the sensitivity of the procedure is very low because of frequent crash artifacts resulting in the difficult interpretation of areas of patchy fibrosis.

Recently it has been suggested that with the use of a genomic-based machine trained to identify a specific molecular signature identified from RNA sequencing on tiny transbronchial lung biopsy samples, the sensitivity of the procedure increases significantly. In this prospective study, the classifier recognized UIP pattern in transbronchial lung biopsy samples with 90% specificity and 62% sensitivity [29].

The 2018 guidelines from the American Thoracic Society/European Respiratory Society on IPF make no recommendation for or against the use of conventional TBB in patients with newly detected ILD of apparently unknown cause, clinically suspected of having IPF and with an HRCT pattern of probable UIP, indeterminate, or suggesting an alternative diagnosis. For patients with newly detected ILD of apparently unknown cause, clinically suspected of having IPF and with an HRCT pattern of UIP, TBB is strongly not recommended [26].

Transbronchial Lung Cryobiopsy (TLCB)

Before the recognition of the multidisciplinary (MDT) diagnosis as the gold standard for ILD diagnosis, surgical lung biopsy (SLB) was considered the reference diagnostic procedure to obtain sufficient histological information to distinguish UIP patterns from other interstitial lung diseases [30]. SLB is associated to risky complications, and costs. Adverse events include chronic chest pain, observed in more than 50% of the cases and lasting for months, prolonged air leakage, and infections. The mortality rate, when performed in a elective setting is around 2%, increasing significantly in elderly, in patients witha clincial diagnosis of IPF or Collagen Vascular Disease, or in those with rapid progressive pulmonary function deterioration. Pneumothorax is usually not considered a complication because it occurs in 100% of cases but the patient's discomfort related to the chest tube should be considered [31]. Balancing the risk/benefit ratio, surgical lung biopsy is obtained in <15% of ILD cases, and the indication of biopsy has to be carefully considered by the multidisciplinary team that plays the leading role in the diagnostic process of ILDs.

Transbronchial lung cryobiopsy (TLCB) is a promising and less invasive alternative to surgical lung biopsy (SLB) to diagnose interstitial lung diseases (Table 30.4) [32–35].

TLCB allows to obtain larger and higher quality lung tissue samples without the crushed artifacts seen with conventional transbronchial lung biopsy using flexible forceps, but the specimens are usually smaller than those obtained by surgical lung biopsy (SLB) [36].

Samples obtained through cryoprobe are usually 40–50 mm^2 in size and contain peripheral structures of the secondary pulmonary lobule (visceral pleura, interlobular septa) allowing to recognize morphologic patterns of ILDs with high confidence, especially UIP pattern [37]. The optimal lung biopsy specimen size in the diagnosis of ILDs has not been established; anecdotally pathologists suggest that adequate specimens should measure at least 5 mm in diameter [35]. Different studies document that a diagnostic morphologic pattern may be identified in more than 80% of subjects with ILD through TBLC [38]. Casoni et al. demonstrated that pathologists can detect UIP patterns with high confidence in about half of the cases with a very good overall interobserver agreement and that the diagnostic

Table 30.4 Comparison of SLB and TBLC

SLB	TBLC
Not in elderly patients	No age limitations
Pneumothorax in 100% of patients	Pneumothorax 19.2% patients
	Not always requiring a chest tube
Hospitalization required	Outpatients

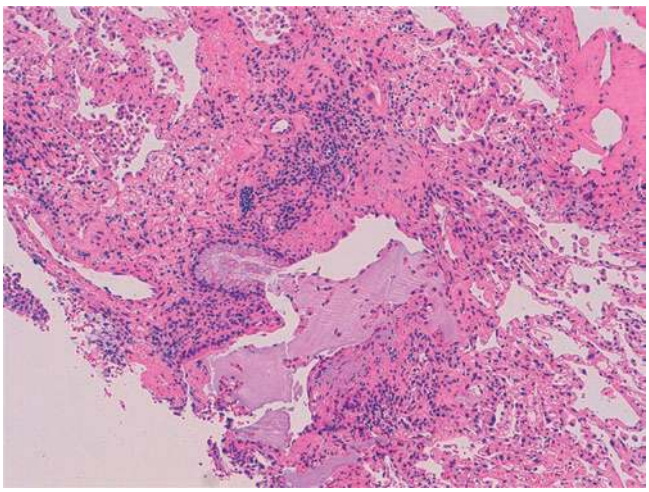

Fig. 30.3 Trans-bronchial lung cryobiopsy (TLCB) showing diffuse alveolar wall thickening by uniform fibrosis with interstitial lymphocyte inflammatory cells infiltration and Masson bodies filling bronchiolar lumina and alveolar ducts and spaces (organizing pneumonia with overlapping non-specific interstitial pneumonia). (Source: Pathology Department, G.B. Morgagni - L. Pierantoni Hospital, Forlì, Italy)

yield is related to the size of specimens [38]. Histological diagnosis of the UIP pattern is feasible on TLCB: elements of the UIP pattern (patchy fibrosis, fibroblastic foci, honeycomb changes) can be identified with high confidence in cryosamples and the inter-observer variability between expert pathologists for diagnosis of the UIP pattern on TLCB seems to be similar to that described in SLB [39, 40] [Fig. 30.3].

Studies comparing the diagnostic accuracy of TBLC and SLB in the same patients who underwent consecutively both procedures are limited. The COLDICE study (Cryobiopsy versus Open Lung biopsy in the Diagnosis of Interstitial lung disease allianCE) showed high levels of agreement between TBLC and surgical lung biopsy for both histopathological interpretation and MDT. The TBLC MDT diagnoses made with high confidence were particularly reliable, showing excellent concordance with SLB MDT diagnoses [41].

The TLCB technique has been standardized [37, 38, 42]. Intubation with dedicated oro-tracheal tubes or rigid tubes are the preferred approach. C arch fluoroscopy is strongly suggested and Fogarty baloon or bronchial blocjkers are considered mandatory in preventing or controlling major bleeding. Four to six biopsies are usually taken [43].

Ravaglia et al. showed that the strategy of performing two biopsies obtained from two different segments within the same lobe may be associated with an increased diagnostic yield [44]. In a larger series of 699 patients, Ravaglia and colleagues, showed that the diagnostic yield was significantly influenced by the number of samples taken and the sampling strategy, improving dramatically when ≥2 samples were performed (instead of only one) and when biopsy was obtained in two different sites (yields did not differ whether sites were represented by different segments of the same lobe or segments coming from different lobes) [44].

TBLC is a safe procedure, the main complications described in the literature are represented by pneumothorax, prolonged air leak, and transient respiratory failure. Acute exacerbation of the underlying ILD has been reported in less than 0.3 per cent of cases In a recent meta-analysis it was reported that the risk of pneumothorax can be influenced by procedure-related factors, like the type of sedation/airway control: a higher proportion of pneumothorax occurred among intubated patients undergoing the procedure under deep sedation with invasive jet ventilation compared to patients under sedation and spontaneous breathing. The risk of pneumothorax seems to be influenced also by patient-related factors (such as radiological fibrotic score and UIP pattern), or procedure-related factors (such as distance from the pleura, size of the probe used, the skill level of the operator) [32].

Bleeding is the most life threatening complication of cryobiopsy.

In the Ravaglia and colleagues study moderate bleeding was reported in 7.6% of patients and severe bleeding (resolved with prolonged Fogarty balloon bronchial occlusion but requiring admission to intensive care unit and prolonged intubation for <6 h) in 0.7% of patients [45–47].

The risk of acute exacerbation needs to be evaluated before the procedure: the presence of new patchy ground glass areas on CT scan [45], increased dyspnea on exertion in the last month, and/or high levels of inflammatory or more specific markers (KL-6) could be predictors of high acute exacerbation risk [48].

Currently, the absolute contraindications for TBLC are the presence of a bleeding diathesis, anticoagulant therapy, treatment with thienopyridines and new antiplatelet drugs, and thrombocytopenia with a platelet count of less than 50×10^9/L. Patients with clinical or radiological signs of pulmonary hypertension should have a preprocedural evaluation and if the estimated systolic pulmonary artery pressure on echocardiography is >50 mmHg, this represents a relative contraindication. Acute deterioration in respiratory status should be considered a relative contraindication, such as severely impairment of pulmonary function (diffusing capacity <35% or forced vital capacity <50%) even if some reports are present in literature, indicating that TBLC is safe in this group of patients. Anecdotal data suggest that complications are more frequent when the pulmonary function is severely impaired. In a large cohort of 699 patients who underwent TLCB to investigate ILD, pneumothorax incidence was significative higher when FVC was <50% but it was not influenced by DLCO value. So that FVC <50% should be considered as a relative contraindication to transbronchial cryobiopsy. Significant hypoxemia, defined as PaO_2 <55–

60 mmHg on room air or while receiving 2 L/min of nasal oxygen, has also been considered a contraindication [49]. Also a high body mass index (BMI) can result in failure of the procedure may be related to desaturation during the procedure [50]. Recently the European respiratory Society presented clinical guidelines on transbronchial cryobiopsy that will help clinicans to insert thia technique in the diagnostic work-up of patients with ILD [51] and transbronchial lung cryobiopsy is suggested as a valid alternative to SLB in the recent IPF/progressive pulmonary fibrosis guidelines [52].

Endobronchial Ultrasonographic Transbronchial Needle Aspiration (EBUS-TBNA) and Endo-esophageal Ultrasonographic Fine Needle Aspiration (EUS-FNA)

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is often required to evaluate enlarged mediastinal and hilar lymph nodes, frequently associated with ILDs [53–55].

In sarcoidosis, EBUS and EUS-guided TBNA have a great diagnostic value, especially when combined with endobronchial and transbronchial biopsies [56, 57]. The diagnosis of lymphoproliferative disorders may be done with this approach but the use of smaller cryoprobes (1.1 mm) is advised [58].

EUS may have the advantage of allowing the sampling of sub-diaphragmatic organs, contributing to the diagnosis of lymphomatoid granulomatosis or other kinds of lymphoproliferative disorders involving the liver, spleen, or even adrenal glands.

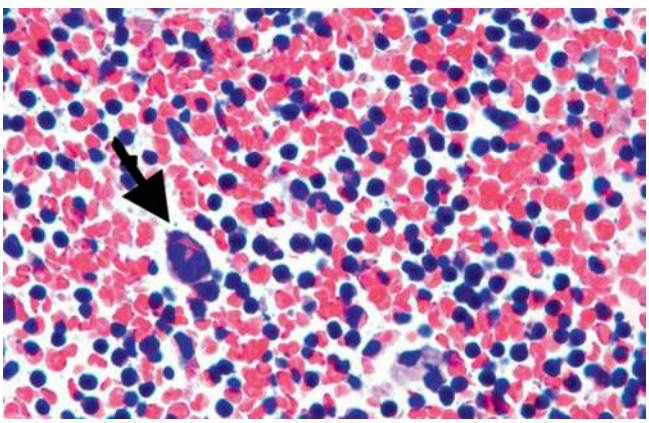

Fig. 30.4 EBUS-TBNA performed on a mediastinal lymph node in a patient with nodular sclerosis (cellular phase) Hodgkin's lymphoma (black arrow shows Reed Sternberg cell). (Source: Pathology Department, G.B. Morgagni - L. Pierantoni Hospital, Forlì, Italy)

Clinical Vignette

We report the case of a 45-year-old female evaluated in our clinic complaining of progressive dyspnea, dry cough, and weight loss in the last 3 weeks. The patient reported substantial clinical wellness up to 3 weeks ago with no signs or symptoms suggestive of collagen vascular disease.

She was a never smoker and her past medical history was notable for gastroesophageal reflux, and allergic asthma (diagnosed 5 years before).

Asthma was well controlled with medical treatment but in the last 2 years, the patient reported three respiratory exacerbations requiring oral steroids and antibiotics treatment. She also reported the presence of increased eosinophils levels in blood tests performed 1 year before (eosinophils 2900/mmc).

At the point of our presentation, she was on treatment with fluticasone and salmeterol, omeprazole, and antiacids. On physical examination, sporadic wheezing was detected.

The patient's laboratory investigations revealed increased WBC level (tot 20,100/mmc, Eosinophils 6750/mmc- 42.9%), increased PCR 31 mg/L, negative proteinuria, and Bence Jones test, IgE normal level, negative IgG to *Aspergillus*. Autoimmunity work-up (including ANA, ENA, ANCA, anti-CCP) was negative.

Pulmonary function tests, performed at the presentation, showed a mild obstructive pattern (FVC 119% FEV1 93% Tiffenau 0.67), normal walking test with no significative desaturation, a mild decreased DLCO (69%), and normal blood gas values.

CT scan showed ground glass areas in the dorsal segment of the right upper lobe and in the apical segment of the left and right inferior lobes (Figs. 30.5 and 30.6).

Bronchoscopy with BAL and cryobiopsies (in two segments of the right upper lobe) was carried out. The differential cell count on BAL fluid showed eosinophilia [Fig. 30.6] (total cells 735,000, neutrophils 16%, eosinophils 73%, lymphocytes 8%, macrophages 3%) while microbiology tests were negative (included SARS COV2). Cryobiopsies samples showed diagnosis was compatible with chronic pulmonary eosinophilia [Fig. 30.7]. Tests for mutation of JAK2 and FLIP1 were negative.

The diagnosis after multidisciplinary discussion was CEP.

The patient started treatment with methylprednisolone 40 mg intravenously for 3 days then oral prednisone 25 mg/die (0.5 mg/kg/die) for 4 weeks and

gradual tapering. The chest X-ray performed after 10 weeks of treatment showed complete resolution.

The clinical and radiological pattern was very specific and in this case bronchoscopy allowed, with just one exam, to reach the correct diagnosis without wasting time to start the correct treatment.

BAL fluid showed eosinophilia and exclude infections, so that the differential diagnosis included chronic esoninophilic pneumonia (CEP), and EGPA. Transbronchial biopsy using cryoprobe offered the histological confirmation of CEP with no added risks for the patient.

Chronic eosinophilic pneumonia (CEP) is an idiopathic disorder characterized by an abnormal accumulation of eosinophils in the lung. CEP occurs predominantly in women and nonsmokers; it often presents as a subacute illness with cough, fever, progressive breathlessness, weight loss, and wheezing; asthma accompanies or precedes the illness.

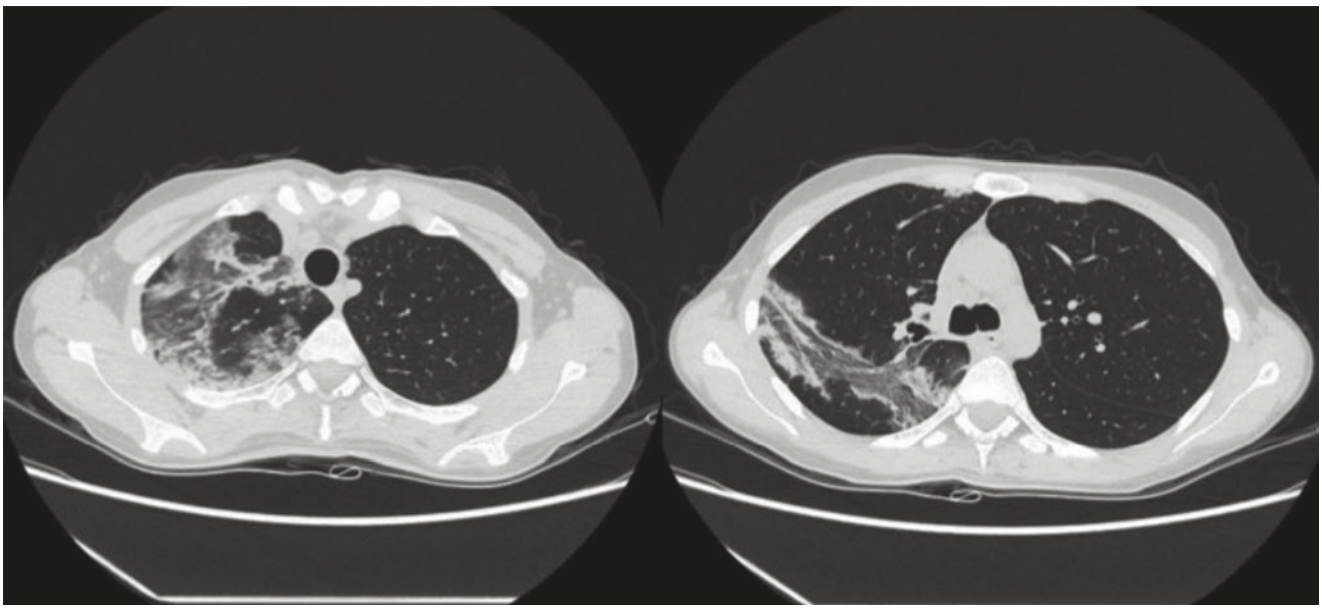

Fig. 30.5 CT scan showing patchy and mainly subpleural ground glass opacities in the upper lobes

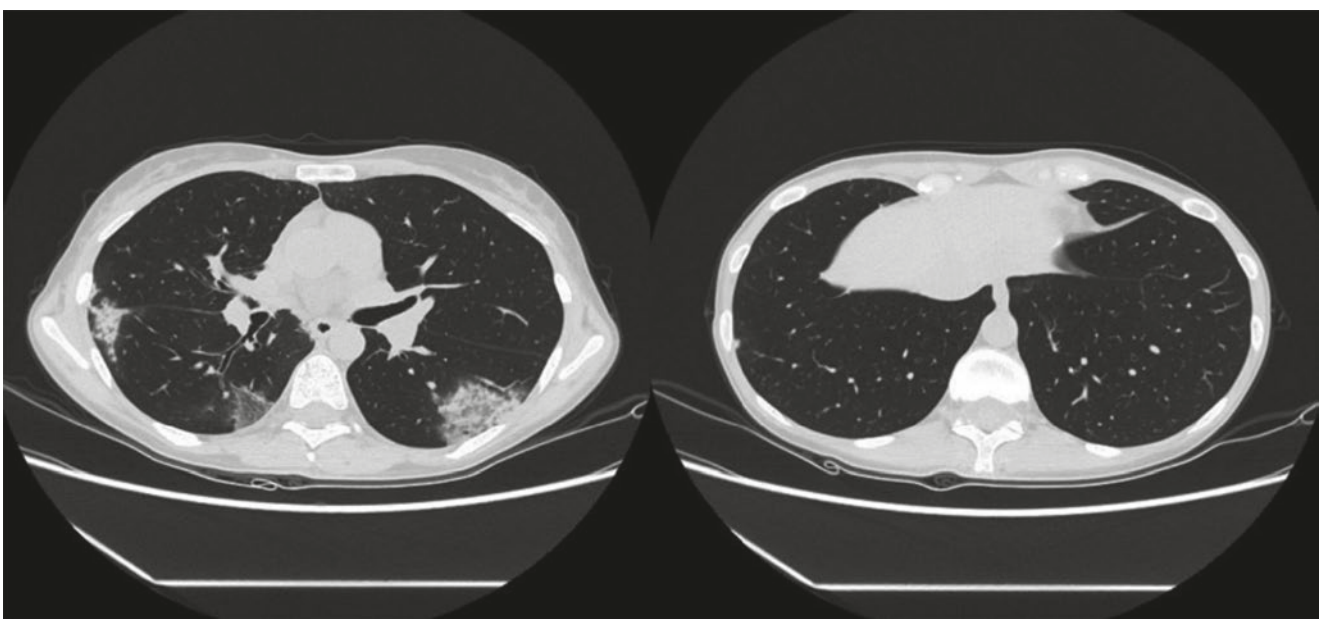

Fig. 30.6 CT scan showing ground glass opacities and alveolar consolidations predominantly in the upper lobes

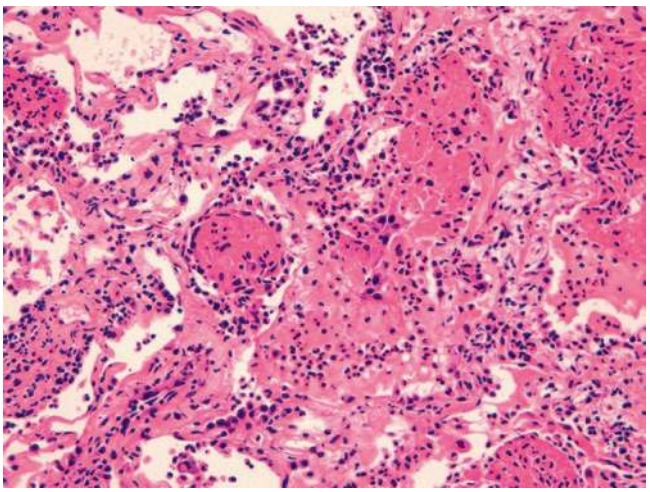

Fig. 30.7 Lung parenchyma showing an interstitial and alveolar infiltrate rich in eosinophils (H&E, mid-power)

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An Integrated Approach to Diagnosing Interstitial Lung Disease

31

Christopher J. Ryerson

Clinical Vignette

A previously healthy 67-year-old male former smoker of 25 pack-years reports worsening exertional dyspnea and an occasionally productive cough. An initial evaluation for potential cardiac etiologies does not reveal any obvious cause and the patient subsequently undergoes a pulmonary function test (PFT) and chest computed tomography (CT). The PFT reveals slightly reduced flow rates and lung volumes in a restricted pattern, with a diffusion capacity of the lung for carbon monoxide of 62% predicted. The CT shows peripheral and lower lung predominant reticulation and traction bronchiectasis without honeycombing, nodularity, ground glass, or mosaicism. The community radiologist reports this as a possible usual interstitial pneumonia pattern based on previous clinical practice guidelines, and the patient is considered to have unclassifiable ILD by his initial respirologist given the absence of a clear cause and an inconclusive imaging pattern.

The patient is referred to an ILD center and has an extensive assessment that more confidently excludes the possibilities of fibrotic hypersensitivity pneumonitis, connective tissue disease-associated interstitial lung disease (ILD), or drug-induced ILD. A multidisciplinary discussion is performed in collaboration with an experienced chest radiologist who concludes that the CT pattern is that of probable UIP using the updated contemporary clinical practice guidelines. On that basis, the patient is provided a working diagnosis of idiopathic pulmonary fibrosis (IPF) and a surgical lung biopsy is felt to be unwarranted in that context. The patient is offered and agrees to start taking an antifibrotic medication.

Introduction

Interstitial lung disease (ILD) is a collection of approximately 200 diverse conditions that result in inflammation and/or fibrosis of the lung parenchyma. Common fibrotic ILD subtypes include idiopathic pulmonary fibrosis (IPF), connective tissue disease-associated ILD (CTD-ILD), and fibrotic hypersensitivity pneumonitis (HP), with a substantial percentage, also considered to have an unclassifiable ILD. Fibrotic ILDs are chronic and progressive diseases that are frequently characterized by disabling dyspnea and cough, reduced quality of life, and early mortality. The prognosis of IPF, which is the most common idiopathic interstitial pneumonia (IIP), appears to be improving with slightly longer median survival in recent cohorts (3–5 years from the time of diagnosis) compared to the historical median survival of 2–3 years [1]. The incidence and prevalence of common fibrotic ILDs are also increasing [2], although it is not clear whether this reported increase is simply a consequence of greater recognition.

Distinguishing ILD subtypes is challenging, often requiring a multidisciplinary effort by an experienced team of ILD clinicians, chest radiologists, and lung pathologists [3, 4]. This multidisciplinary discussion (MDD) of relevant clinical, radiological, laboratory and histopathological features is best accomplished with a face-to-face dynamic interaction of these subspecialists. Previous studies have suggested higher diagnostic accuracy, represented by greater diagnostic agreement, in academic centers compared to healthcare providers working in community settings [5]. Diagnoses assigned by experienced physicians working in academic centers similarly carry greater prognostic significance compared to diag-

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noses by less experienced clinicians, also suggesting higher diagnostic accuracy among experts [6]. The clinical impact of the MDD approach is illustrated by the change in diagnosis and change in treatment for approximately 50% of patients subjected to this process [7, 8].

In this chapter, key components of the clinical, radiological, laboratory, and bronchoscopic and histopathological assessment are discussed, followed by a review of the typical approach to the integration of these features. This chapter focuses on fibrotic ILD subtypes given the more frequent diagnostic challenges that are encountered with these diseases. The specific features of each major ILD subtype are provided in the chapters that address each of these diagnoses.

Overview of ILD Diagnosis

Patients with fibrotic ILD typically present with chronic onset of dyspnea that becomes noticeable over several months or even years. Unless ILD is detected incidentally, dyspnea is almost universally present at the time of diagnosis. Approximately 85% of patients also report chronic cough at the time of diagnosis, which can be even more disabling than dyspnea in some patients [9]. These symptoms and associated functional limitations are nonspecific, with more frequent etiologies such as chronic obstructive pulmonary disease (COPD) and heart disease typically being considered by general practitioners prior to identification of ILD on chest imaging. As a consequence, patients with ILD are frequently provided one of these incorrect diagnoses based on an incomplete evaluation, and frequently spend months and sometimes years being ineffectively treated for these conditions before the correct diagnosis is made. Aside from the emotional toll that accompanies a missed diagnosis [10], these delays can have a significant prognostic impact with worse survival in patients who have a delayed referral to an experienced ILD center [11]. It is therefore important that general practitioners consider ILD in their differential diagnosis of new unexplained dyspnea, cough, or functional limitation, potentially using some of the clinical features described below to help identify these patients at an earlier stage of their disease.

Once ILD is considered, patients will typically undergo a pulmonary function test and chest imaging. Based on their relative availability and lack of radiation exposure, pulmonary function tests are often used as a screening tool for patients at risk for ILD or as the first test in patients with a new suspected ILD; however, many patients with early ILD have normal pulmonary function tests or only a mild isolated reduction in gas transfer (i.e., a reduced diffusion capacity of the lung for carbon monoxide [DLCO]). Pulmonary function tests are therefore not sensitive nor specific enough to rule in or rule out ILD in many of the more common clinical scenarios.

The definitive tool used to identify the presence of an ILD is computed tomography (CT), with most conventional CT scanners now providing the appropriate high-resolution images that are needed to adequately characterize ILD morphology. ILD can be subclassified radiologically into fibrotic and non-fibrotic forms, with non-fibrotic subtypes of ILD including a variety of inflammatory, cystic, and nodular processes. Within each of these main ILD patterns, there are additional sub-patterns that further narrow the differential diagnosis, with many of these sub-patterns being diagnostic when considered in the corresponding clinical context. For example, patients with usual interstitial pneumonia (UIP) pattern without an underlying identified etiology after a thorough clinical and laboratory evaluation can be provided a confident diagnosis of IPF without the need for tissue confirmation [12].

The specific diagnostic criteria for each ILD subtype are provided in the corresponding chapters, with the remainder of this chapter focusing on the general approach that applies across the full spectrum of clinical settings and how various features should be integrated in order to arrive at a final diagnosis.

Clinical Assessment

There are no clinical features that are pathognomonic for ILD. Dyspnea, cough, and functional limitation are frequent manifestations of ILD, but are also observed in other more common diseases such as COPD and heart disease. The presence of a family history of ILD, hypoxemia, auscultatory crackles, or clubbing are nonspecific features, but should prompt consideration of fibrotic ILD in patients with chronic dyspnea, cough, or functional limitation. Importantly, auscultatory crackles are not typical findings of asthma, COPD, or CHF other than during acute exacerbations or episodes of volume overload. Hypoxemia and clubbing are not common findings in these conditions and also indicate the need to consider alternative or additional diagnoses. The initial evaluation in patients with any of these high-risk features should typically include complete pulmonary function tests (pre- and post-bronchodilator spirometry, lung volumes, and DLCO) and CT imaging of the chest. Patients with features suggesting a predisposing condition (e.g., connective tissue

disease, recent exposure history) should be approached in a similar manner in the context of new or worsening dyspnea, cough, or functional limitation.

A more comprehensive clinical assessment is required in patients with ILD that has been documented by chest CT with the primary goal of identifying an underlying etiology, in addition to assessing disease severity. This assessment should include a thorough history that identifies both risk factors and associated symptoms of different ILD subtypes. This can broadly be categorized as features suggesting an underlying chronic systemic disease (i.e., CTD-ILD), a history of exposure to agents known to cause ILD (e.g., antigens associated with HP, drugs associated with drug-induced ILD, inorganic exposures associated with pneumoconioses), and other ILD risk factors (e.g., age, smoking, dysphagia, comorbidities). Some of these risk factors can be very subtle; however, this is a critical component of the evaluation of ILD since identifying one of these risk factors for ILD can eliminate the need for more invasive testing in the appropriate clinical and radiological context.

The physical exam for a patient with newly identified ILD follows a similar approach. Auscultatory crackles suggest the presence of fibrosis and have prognostic significance in some ILD subtypes [13], but do not help distinguish among fibrotic ILD subtypes. The presence of inspiratory squeaks or expiratory wheeze suggests an airway-centered process such as hypersensitivity pneumonitis [14], but is not sensitive or specific enough to alter the decision of whether to pursue additional more invasive testing. Clubbing was historically thought to suggest IPF, but is now recognized as a nonspecific manifestation of a variety of fibrotic ILDs. The extrapulmonary examination has greater utility in distinguishing the cause of ILD, including a musculoskeletal and dermatologic evaluation that is used to identify what can be subtle manifestations of a CTD or systemic vasculitis. Signs of right heart dysfunction in the context of mild ILD can suggest systemic sclerosis or another CTD as a cause of the ILD, but this is less specific in more advanced ILD that can be associated with pulmonary hypertension regardless of the underlying etiology of the ILD.

Although there are many clinical features that help distinguish ILD subtypes, there is no standardized method for integrating these individual features in the diagnosis of ILD. This is therefore a subjective process that depends on the thoroughness of the evaluation, the experience of the clinician, and the information conveyed by the remainder of the multidisciplinary team. As a result, the clinical assessment is typically conceptualized as a gestalt impression of the relative likelihood of different ILD diagnoses, which is then refined after a review of imaging findings with a chest radiologist or in the context of a full MDD.

Radiological Assessment

The initial imaging study that suggests an ILD is often a plain chest radiograph; however, this is an insensitive test that is often normal in patients with mild ILD. A chest CT with high-resolution images (spatial resolution of <1.5 mm) is required for adequate morphological assessment that can frequently be combined with clinical and laboratory data to arrive at a confident diagnosis. CT protocols typically used in evaluating patients with ILD include continuous image acquisition and performance of both inspiratory and expiratory scans. Images acquired in the prone position are sometimes helpful in patients with mild abnormalities in order to help distinguish early ILD from dependent atelectasis. Chest CT can also be used to document disease severity and progression, with this most often being a qualitative assessment. This can include the demonstration of overt worsening of fibrosis, or often subtle changes in morphology in a given lung region from a more inflammatory (e.g., ground glass) to a more fibrotic appearance. Assessing the severity of disease on chest imaging can be difficult as the lung will typically contract with worsening fibrosis, with the progressively fibrotic lung taking up less intrathoracic space compared to the remaining normal or potentially hyperexpanded lung. It is frequently helpful to also inspect earlier abdominal and cardiac imaging studies that can provide a general sense of previous ILD severity, which is particularly useful for the assessment of long-term disease progression.

For patients with ILD, it is important for chest radiologists to comment on individual features, disease distribution, and overall pattern. Individual features relevant to the characterization of ILD include reticulation, traction bronchiectasis, honeycombing, ground glass, consolidation, and gas trapping (Fig. 31.1). The location of abnormality should be considered according to its craniocaudal distribution, including upper, lower, and diffuse locations (Fig. 31.2). Some ILDs are also characterized by subpleural, peripheral (sometimes with subpleural sparing), or peribronchovascular involvement (Fig. 31.3). These features and their distribution are integrated to identify specific imaging patterns. For example, a UIP pattern is characterized by peripheral and lower-lung predominant reticulation, traction bronchiectasis, and honeycombing, with minimal ground glass, consolidation, or gas trapping (Fig. 31.4) [12, 15]. An NSIP pattern often has similar features with peripheral and lower-lung predominant reticulation and traction bronchiectasis, but with subpleural sparing in 25% of patients, and variable amounts of ground glass that can represent either microfibrous or concurrent inflammation (Fig. 31.5) [16, 17]. A CT suggesting fibrotic HP will frequently have gas trapping in addition to other findings of inflammation and fibrosis [18],

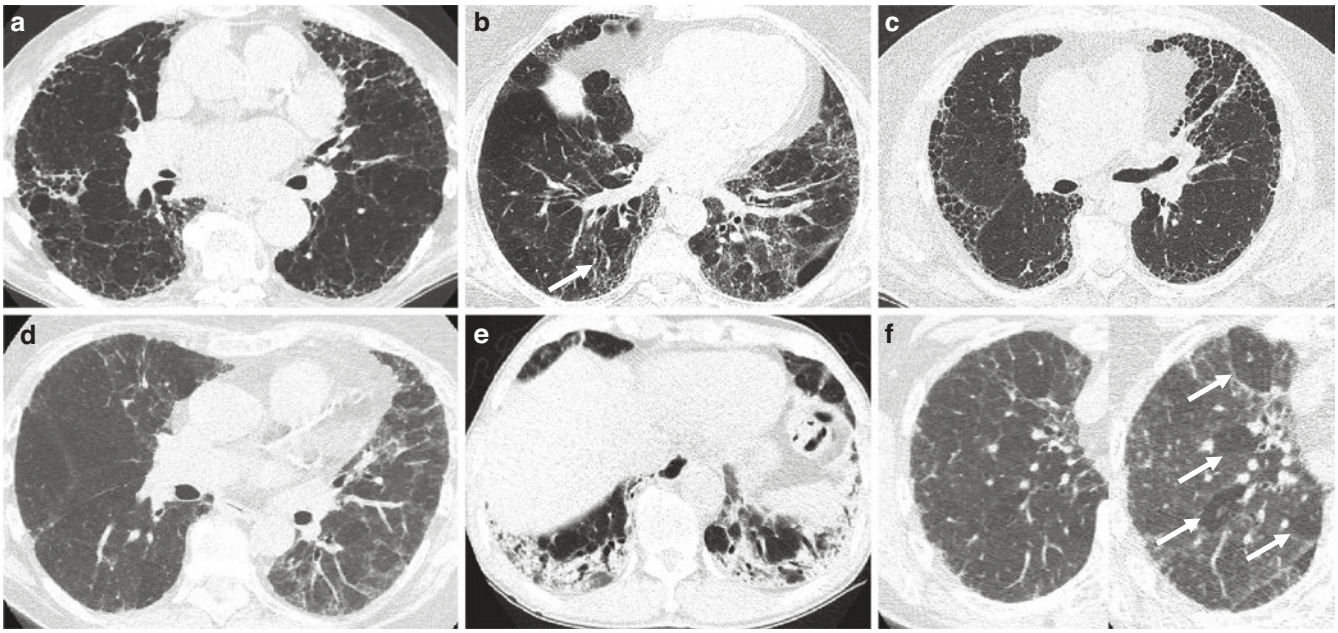

Fig. 31.1 Radiological features of interstitial lung disease, including (**a**) reticulation (lines of scar tissue), (**b**) traction bronchiectasis (arrow), (**c**) honeycombing, (**d**) ground glass, (**e**) consolidation, and (**f**) lobular areas of gas trapping (arrows) comparing inspiratory (left) to expiratory (right) images

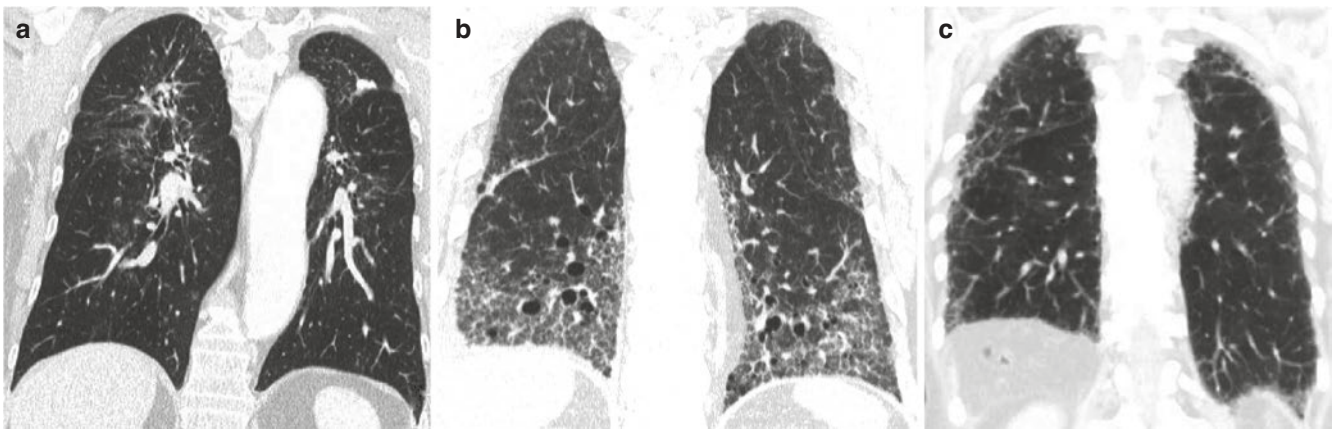

Fig. 31.2 Common craniocaudal distributions of ILD, including upper lung predominance in a patient with sarcoidosis (**a**), lower lung predominance in a patient with idiopathic pulmonary fibrosis (**b**), and diffuse involvement in a patient with hypersensitivity pneumonitis (**c**)

and will more often have an upper lung or diffuse distribution that can also have some peribronchovascular extension (Fig. 31.6) [19].

The overall pattern suggested by a chest radiologist requires contextualization with the clinical scenario. Some diagnoses (e.g., CTD-ILD, drug-induced ILD) can be associated with multiple imaging patterns, while some imaging patterns (e.g., UIP, NSIP) can be seen in a variety of ILD subtypes. The decision of whether to move on to more invasive bronchoscopic or histopathological sampling is therefore dependent upon the combined clinical-radiological impression. This clinical-radiological integration is provided in relatively clear terms for making a diagnosis of IPF with recent guidelines providing a similar approach for the diagnosis of HP [12, 20]; however, this is currently less standardized for idiopathic

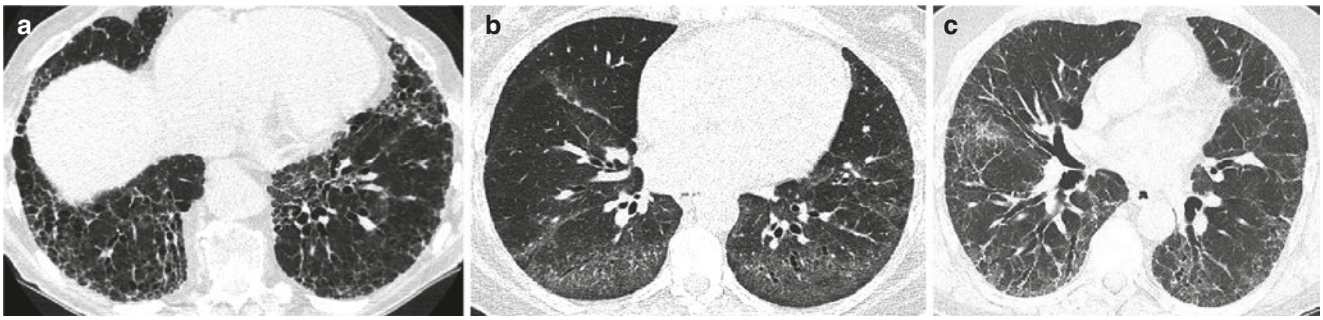

Fig. 31.3 Fibrotic ILD demonstrating a peripheral pattern with subpleural involvement in a patient with biopsy-proven usual interstitial pneumonia (**a**), peripheral pattern with subpleural sparing consistent with nonspecific interstitial pneumonia in a patient with systemic sclerosis (**b**), peripheral pattern with peribronchovascular extension in a patient with biopsy-proven hypersensitivity pneumonitis (**c**)

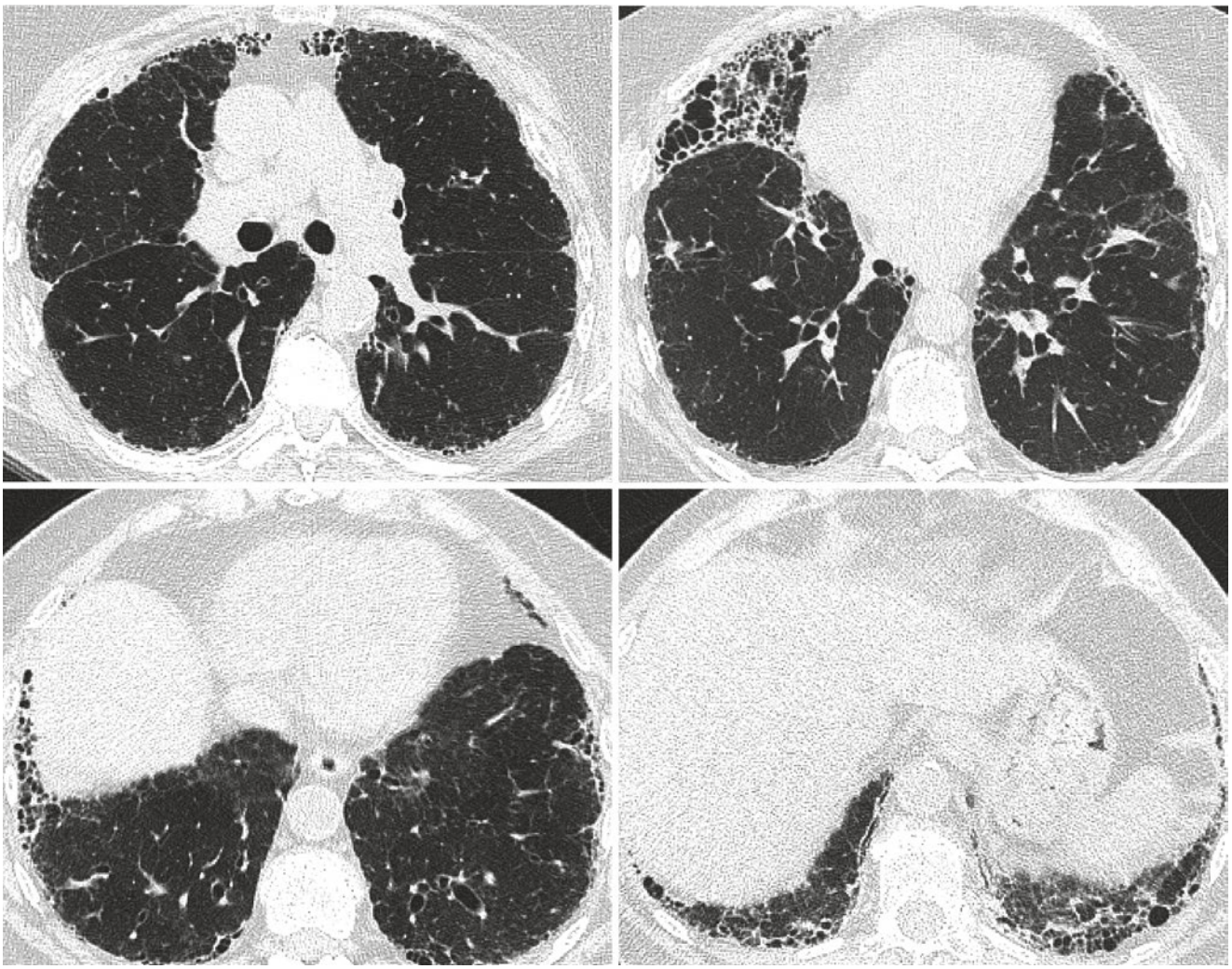

Fig. 31.4 Transaxial chest CT in a patient with idiopathic pulmonary fibrosis showing a pattern of usual interstitial pneumonia, characterized by lower lung predominance of peripheral reticulation, traction bronchiectasis, and honeycombing

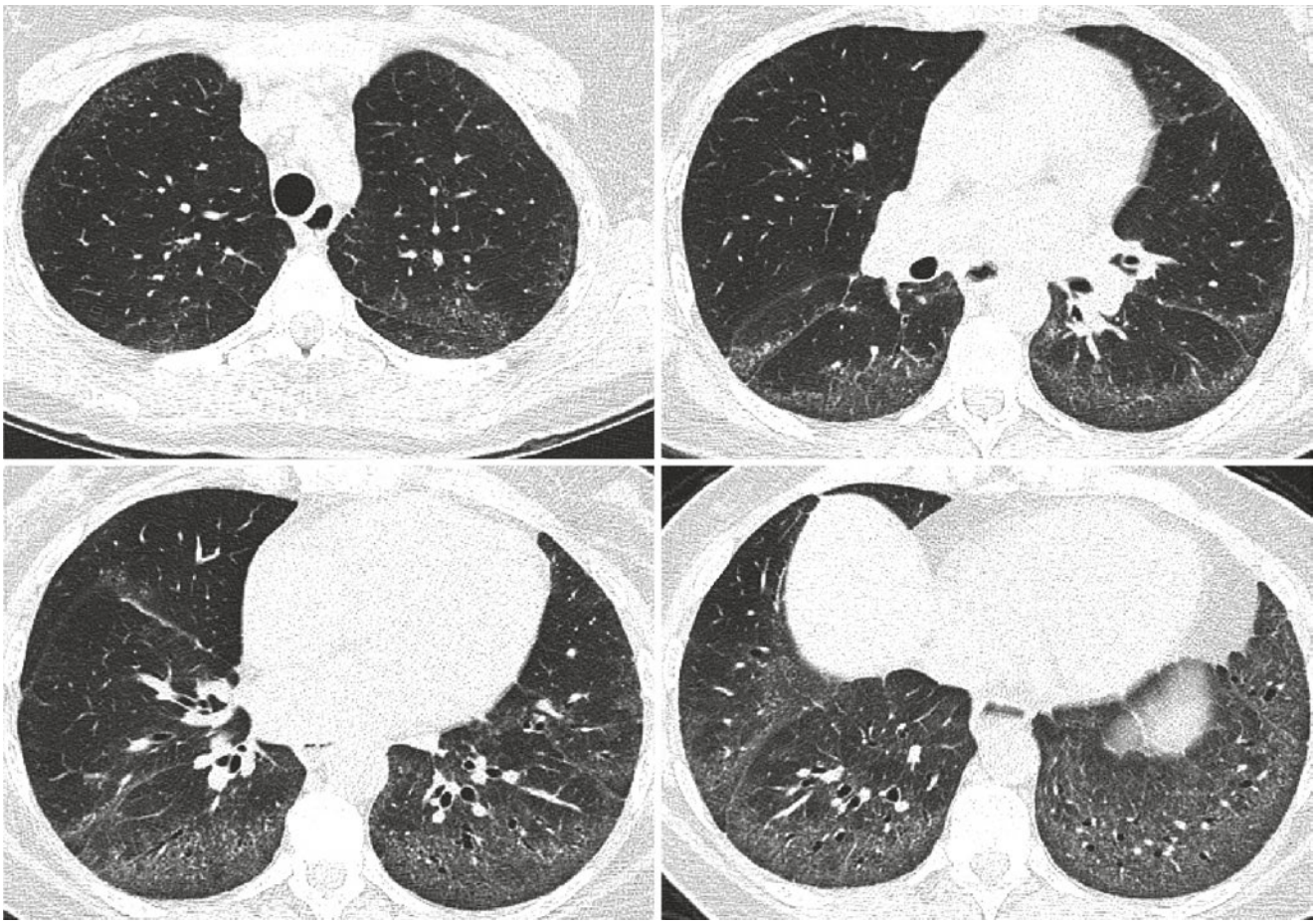

Fig. 31.5 Transaxial chest CT in a patient with systemic sclerosis showing a pattern of nonspecific interstitial pneumonia, characterized by lower lung predominance of ground glass, reticulation, and traction bronchiectasis in a peripheral distribution, but with immediate subpleural sparing

NSIP, which lacks established diagnostic criteria. Previously suggested criteria for idiopathic NSIP required a surgical lung biopsy to confidently make this diagnosis given the frequent alternative diagnoses that are identified on biopsy in patients with an imaging pattern suggestive of NSIP (e.g., IPF, fibrotic HP, CTD-ILD) [17]. For this reason, identifying an imaging pattern of NSIP was not considered sufficient to make a diagnosis of idiopathic NSIP. Conversely, identifying an imaging pattern of UIP is specific enough for a histopathological pattern of UIP that further confirmation of this with biopsy is not necessary for most patients [12]. Common to all of these imaging patterns is the need to integrate a thorough clinical assessment with a careful radiological evaluation.

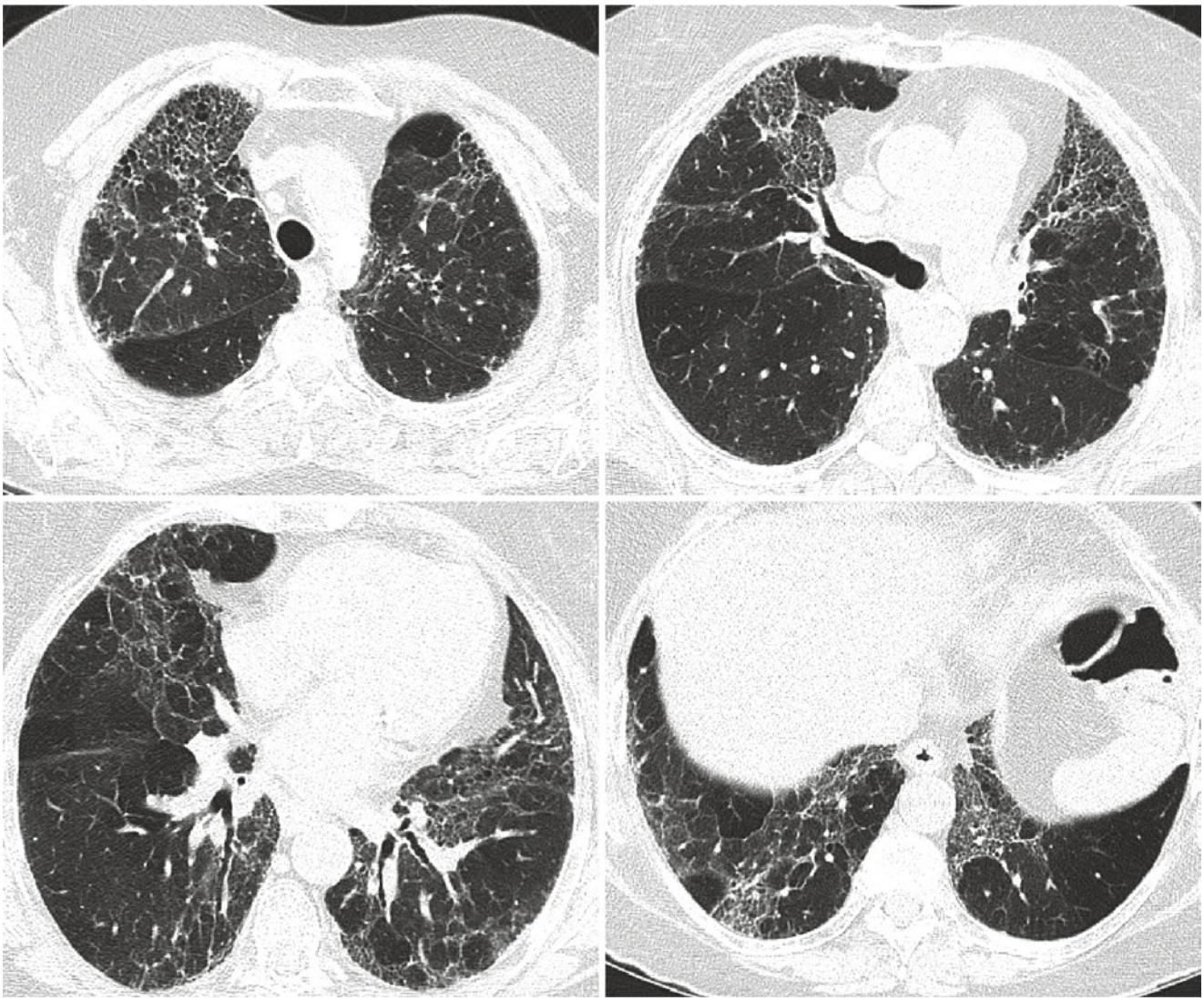

Fig. 31.6 Transaxial chest CT in a patient with exposure to bird antigen showing features of hypersensitivity pneumonitis, including diffuse craniocaudal involvement of ground glass, reticulation, mosaicism, and areas of lobular sparing

Laboratory Assessment

The laboratory assessment for ILD typically follows confirmation of ILD on CT imaging. This assessment is primarily composed of autoimmune serologies used to suggest the presence of a CTD or systemic vasculitis, with additional specific tests pursued in some patients. Clinical practice guidelines on the diagnosis of IPF recommend screening for autoimmune disease in patients with suspected IPF [12], with the majority of panelists routinely testing for C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), antinuclear antibodies (ANA), rheumatoid factor, anti-cyclic citrullinated peptide, and a myositis panel. Additional autoimmune serologies are generally reserved for patients with negative initial studies who still have a high suspicion of an underlying CTD, including anti-cytoplasmic antibodies (ANCAs) in patients with a possible vasculitis. Patients with ILD will frequently have abnormal autoimmune studies even in the absence of overt extrapulmonary manifestations. These results then have to be contextualized with the clinical and radiological findings in order to determine whether these autoimmune markers are false positives or whether a patient might have a subtle autoimmune disease that is predominantly affecting the lung. Although criteria for interstitial pneumonia with autoimmune features (IPAF) were proposed exclusively as a research tool to support further study of this population [21], this designation may be helpful to guide further evaluation and management decisions in these patients who have relatively specific autoimmune features despite not meeting criteria for a defined CTD. The appropriateness of this approach still requires validation in future studies and endorsement in updated clinical practice guidelines.

Additional laboratory studies are considered on a case-by-case basis. These include serum immunoglobulin levels and IgG subclasses that are helpful in suggesting IgG4 disease or immunodeficiency (e.g., as a cause of lymphocytic interstitial pneumonia [LIP]; Fig. 31.7). Testing for human immunodeficiency virus (HIV) is particularly relevant in patients with LIP, but HIV is also a risk factor for other ILD subtypes and is an important comorbidity to identify prior to initiation of immunosuppressive therapy. Vascular endothelial growth factor-D (VEGF-D) is frequently increased in lymphangioleiomyomatosis and is specific enough that a biopsy is not required in the appropriate clinical setting when high VEGF-D levels are present (Fig. 31.8) [22]. Genetic evaluation for patients with ILD (e.g., MUC5B) may be helpful for family counseling [23] but does not currently have sufficient prognostic or therapeutic impact to justify widespread use.

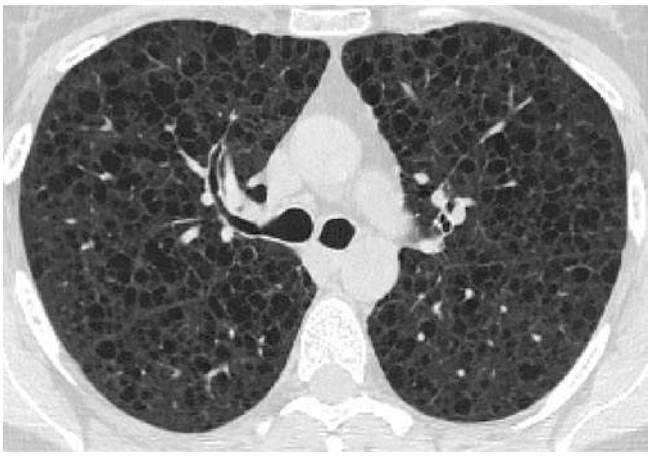

Fig. 31.8 Transaxial chest CT in a patient with lymphangioleiomyomatosis showing diffuse thin-walled cysts

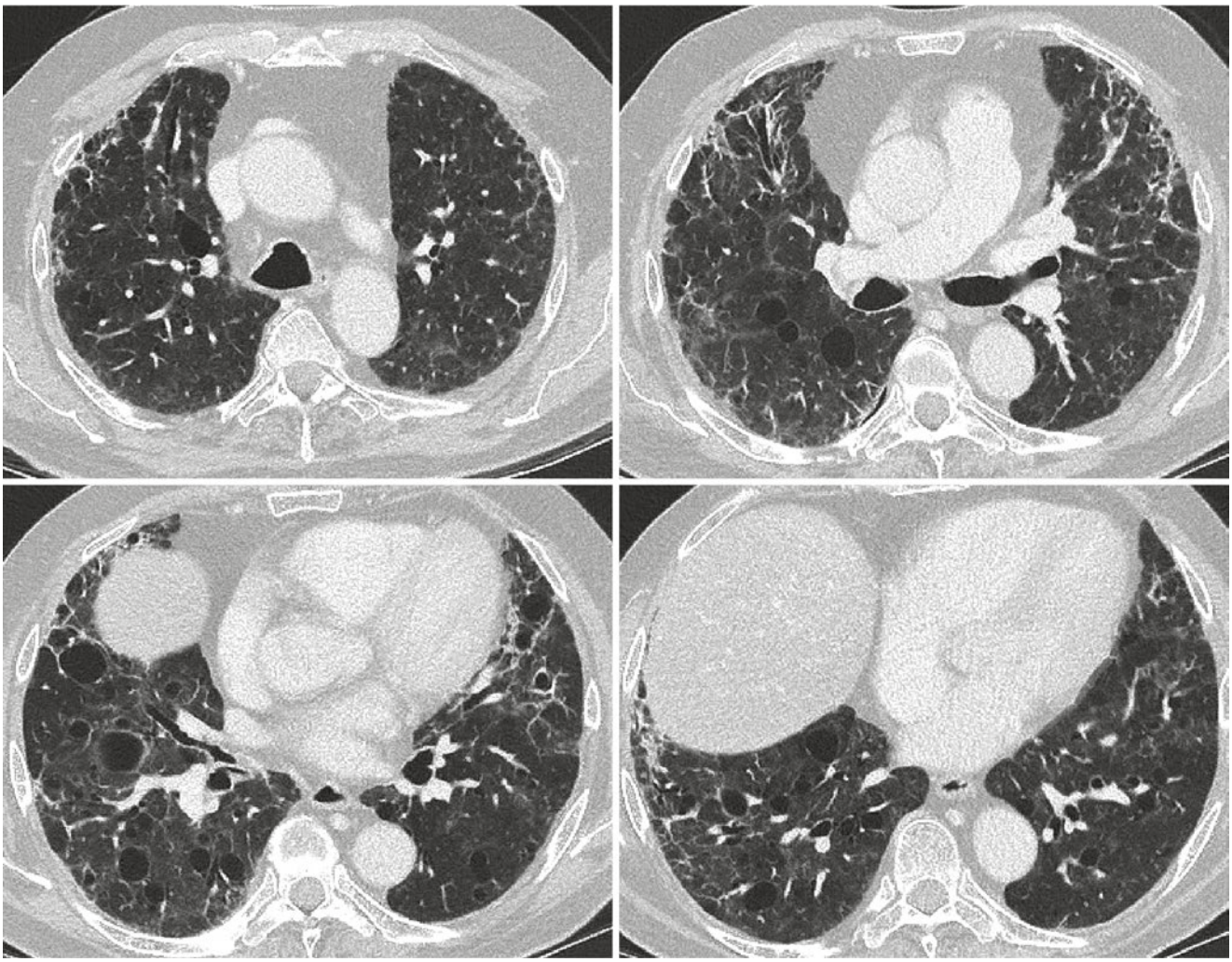

Fig. 31.7 Transaxial chest CT in a patient with human immunodeficiency virus infection showing features of lymphocytic interstitial pneumonia, including multiple thin-walled cysts as well as predominantly peripheral reticulation and traction bronchiectasis with some peribronchovascular extension

Many of these laboratory studies are highly specific in the appropriate context and can eliminate the need for more invasive studies. These tests should thus be considered in all patients prior to the pursuit of histopathological sampling. Conversely, false positives are also common with many of these tests, indicating the need to contextualize abnormal laboratory studies with clinical and radiological features, ideally supported by an MDD of experienced individuals.

Bronchoscopic and Histopathological Assessment

The decision of whether to perform a bronchoscopy or a surgical lung biopsy should be made on a case-by-case basis after considering all information available after less invasive tests. Bronchoalveolar lavage cellular analysis showing lymphocytes >30% can be useful to suggest HP in the appropriate setting [24]; however, the absence of a lymphocytosis is less helpful in excluding fibrotic HP. Transbronchial biopsies are typically unhelpful in fibrotic ILD although can be diagnostic in some patients [25], particularly in sarcoidosis, while more complex genetic or molecular analyses of bronchial biopsies may also provide diagnostic information in some situations [26, 27]. The utility of transbronchial lung cryobiopsy varies across studies; [28] however, this can be a helpful test when performed in an appropriate setting and with results interpreted within a multidisciplinary discussion [29]. Lymph node biopsies can also be diagnostic in sarcoidosis, but are not informative in other fibrotic ILD subtypes.

Whether to pursue a surgical lung biopsy is a major decision in the evaluation of fibrotic ILD given the potential for complications, including mortality [30, 31]. It is therefore critical that all patient data be considered prior to the performance of this more invasive test, including both the potential utility of a biopsy and the potential for procedure-related complications. Specifically, a surgical lung biopsy should only be pursued if there is a reasonable expectation of establishing a diagnosis and affecting management decisions. For example, it may be appropriate to delay surgical lung biopsy in patients with mild and non-progressive ILD that would not likely be treated regardless of the diagnosis, recognizing that having IPF on the differential diagnosis may still suggest a role for biopsy in mild ILD given the apparent benefit of antifibrotic therapy in patients with early IPF [32, 33]. There are several risk factors for complications from surgical lung biopsy, suggesting that biopsy should be avoided in patients older than 75 years of age, with a high or low body mass index, on supplemental oxygen, with pulmonary hypertension, or with severe ILD (e.g., DLCO <35–45%). In these situations, patients may need to be provided with a working diagnosis, with diagnostic confidence that might still be sufficient to support the initiation of therapy [34].

If a biopsy is pursued, it is important to ensure adequate sampling in terms of both the number and size of biopsies. For transbronchial biopsies and transbronchial lung cryobiopsies, typically 5–7 different biopsies are obtained from different regions of a single lung, while surgical lung biopsies should be obtained from upper, mid, and lower lungs. Recommendations have been provided for how to perform both transbronchial lung cryobiopsy and surgical lung biopsy, including the desired size of each sample [35, 36]. Isolated pathologist interpretation of lung tissue is suboptimal [3, 5, 37], and it is, therefore, critical that all biopsies are evaluated by an experienced lung pathologist as part of an MDD.

Integration of Individual Features

The integration of individual features to support a diagnosis of fibrotic ILD is fluid, with the approach varying for each case. A central concept of this process is to consider new data as they become available in order to reassess diagnostic confidence. Most importantly, there is a need to carefully consider the potential impact of invasive procedures such as a surgical lung biopsy before these are performed. This is best accomplished through an MDD, which should ideally be performed both before considering and after completing a lung biopsy. A common approach to the diagnostic process is shown in Fig. 31.9.

Multidisciplinary Discussion

MDD is a dynamic process in which clinical, radiological, laboratory and histopathological data are integrated to arrive at a final diagnosis. MDD is the current standard for diagnosing fibrotic ILD [16], emphasizing that no single domain is sufficient to make an ILD diagnosis in isolation. This approach increases diagnostic confidence [3], particularly among experienced subspecialists [5], and can also be used to improve prognostication and facilitate management decisions, through either establishment of a confident diagnosis or with a less confident working diagnosis [6, 34]. In particular, the distinction between IPF and non-IPF fibrotic ILD has important implications given the worse prognosis of IPF compared to other fibrotic ILDs [38], and the use of antifibrotic therapies in IPF and the use of predominantly immunosuppressive medications in non-IPF fibrotic ILDs. Several recent studies suggest MDD results in a change in diagnosis and in pharmacotherapy recommendation in approximately half of all patients [7, 8].

The participants of an MDD vary across centers [4], typically including at a minimum an ILD clinician, a chest radiologist, and a lung pathologist, as well as trainees from all

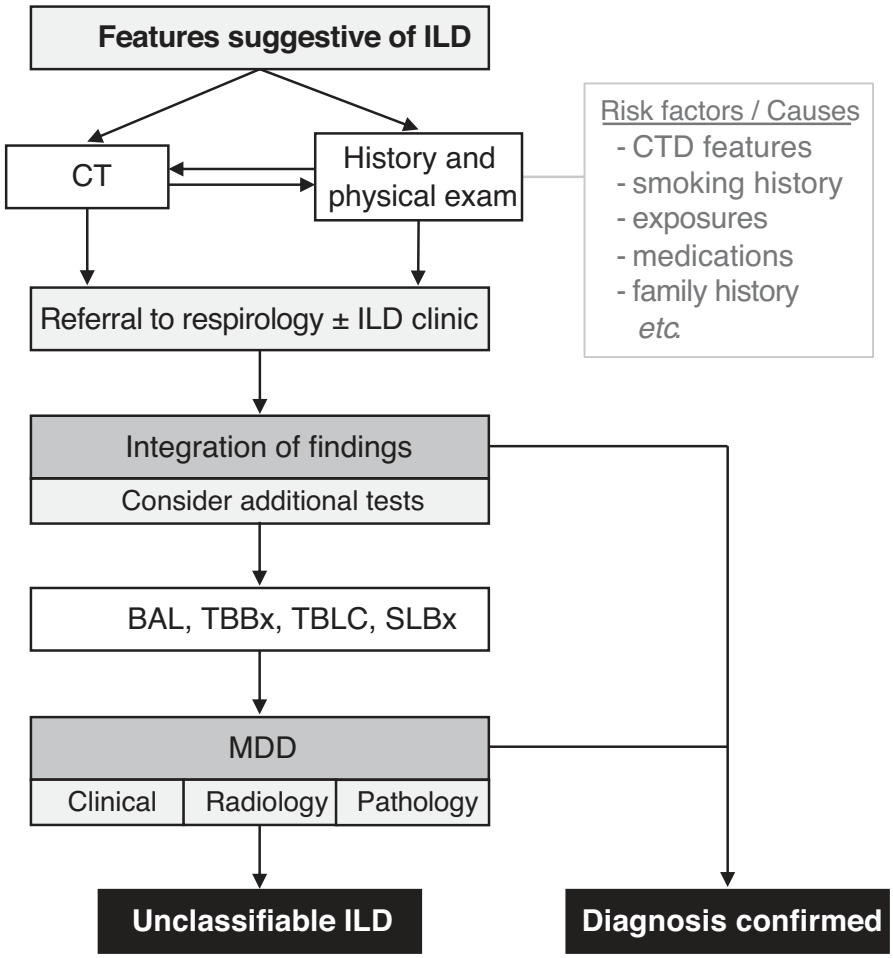

Fig. 31.9 Proposed algorithm for the diagnostic process for patients with fibrotic ILD. BAL, bronchoalveolar lavage, CTD, connective tissue disease; MDD, multidisciplinary discussion; SLBx, surgical lung biopsy; TBBx, transbronchial biopsy; TBLC, transbronchial lung cryobiopsy

disciplines. Some ILD MDDs also include a rheumatologist, thoracic surgeon, or nurse specialist. Most ILD MDDs are face-to-face with a structured approach to the presentation of relevant data that is followed by discussion. Typically, the clinician first presents the relevant clinical and laboratory features, followed by the radiologist presenting imaging findings, and the pathologist presenting pathological findings if performed. There is frequent discussion and requests for clarification of individual findings and overall clinical impression at each stage of this process, with a secondary goal to also educate the participants. Presentation of full CT scans and biopsy slides (or electronically captured images of the complete slides) is preferred to the presentation of only selected images. Ideally, patient volume is sufficient to support at least monthly meetings, with at least several patients reviewed at each MDD. Following a review and discussion of all relevant data, each patient should be provided a consensus diagnosis (or a list of differential diagnoses if a single diagnosis cannot be confirmed) as well as specific recommendations for additional testing and/or treatment.

Some centers are unable to support an MDD with all desired features and are forced to consider alternative approaches. For example, some geographic regions have limited access to a chest radiologist or lung pathologist and instead use a virtual MDD that allows review of relevant patient information without the physical presence of all individuals. An additional strategy is to have patient information sent to a central MDD that reviews all relevant data in a face-to-face meeting, potentially including actual imaging studies and biopsy slides. Recommendations are then provided by the MDD to a remote physician without the patient being seen by an ILD clinician [7]. Although both of these approaches are likely inferior to a comprehensive in-person assessment of a patient at an ILD clinic followed by a review at a face-to-face MDD, these are likely viable alternatives that improve access to necessary expertise for selected patients. These approaches also provide an excellent opportunity for ongoing education of referring physicians.

Diagnostic Ontology

The primary goal in evaluating a patient with ILD is to arrive at a confident diagnosis; however, this is inherently a subjective process and there is often substantial uncertainty even

after open and collaborative discussions among an experienced multidisciplinary team. Even in patients who are provided a specific diagnosis, there is frequently some diagnostic uncertainty that can have important management implications [39]. A key purpose of the MDD is to also document this uncertainty and provide recommendations for how this uncertainty might impact management decisions or prompt future investigations that could solidify a specific diagnosis. Importantly, all ILD diagnoses should be reconsidered at subsequent visits, and this is particularly true for patients without a confident diagnosis.

One way to document this uncertainty is to categorize ILD diagnoses as confident (≥90% confidence), provisional high confidence (70–89%), and provisional low confidence (51–69%) [39]. Using this framework, patients with a confident diagnosis typically do not require additional testing. Additional testing may be appropriate in those with a provisional high confidence diagnosis (e.g., 70–89%), but this level of confidence may be sufficient to support management decisions in some situations, with this unresolved uncertainty needing to be balanced against the potential benefits and risks of additional more invasive tests [34]. Accepting lower diagnostic confidence is particularly relevant to situations in which IPF has already been confidently excluded from the differential diagnosis, given the relatively similar prognosis and approach to pharmacotherapy for the remaining diagnostic possibilities; however, this needs to be carefully assessed on a case-by-case basis. Overall, this approach appears to have therapeutic and prognostic utility despite the lack of specific standardization [6, 34], although additional studies are needed to document its reproducibility and validate its clinical utility.

Unclassifiable ILD

Unclassifiable ILD is defined as the absence of a leading diagnosis that is considered more likely than not (i.e., there is no diagnosis that is considered at least 51% likely after MDD) [39]. This situation applies to approximately 12% of patients with an ILD even after a surgical lung biopsy and MDD [40]. Common reasons for ILD being considered unclassifiable include an incomplete evaluation, the presence of multiple findings that are suggestive of distinct ILD subtypes, and identification of only nonspecific findings that are not diagnostic of any single ILD [40]. The high prevalence of unclassifiable ILD in experienced centers should not be interpreted as justification for the avoidance of potentially diagnostic tests. It remains important for many reasons that physicians establish a confident diagnosis whenever feasible, striking a balance between the benefits of narrowing the differential diagnosis and the risks of invasive tests.

Whether to pursue invasive tests or to accept diagnostic uncertainty is often a challenging discussion to have with patients who must be the focal point of this shared decision. In some situations, patients may be comfortable with their ILD remaining unclassifiable and will refuse tests that the physician believes would be appropriate. In the other less common extreme, patients may wish to pursue all available testing to the point that physicians may need to refuse the performance of a specific test that is unlikely to be diagnostically helpful or that may be unsafe. Although patients are left with an unclassifiable ILD in both of these situations, MDD can often help limit the differential diagnosis and/or determine what management approach is most appropriate, including what pharmacotherapy could be attempted for low confidence working diagnosis. Beyond these initial discussions, it is important to regularly revisit the diagnosis in the event that new information allows for narrowing of the differential diagnosis. This could include disease behavior or response to treatment, results of new or repeated tests (e.g., repeat autoimmune serologies), or identification of a cause of ILD that was not initially apparent (e.g., a new CTD diagnosis or newly recognized exposure). It is not uncommon for unclassifiable ILD to be characterized as a specific ILD subtype upon reassessment after such new information becomes available.

Conclusions

In summary, the diagnosis of ILD is frequently challenging given the need to integrate information from multiple complex domains, but without a standard method of doing so. The ideal approach to diagnosing ILD includes a face-to-face MDD of at least an experienced ILD clinician, chest radiologist, and lung pathologist, which results in the establishment of a more confident and likely more accurate diagnosis. MDD leads to a change in management for approximately half of the patients, resulting in more appropriate use of medications that are likely to alter disease course, and avoidance of medications that have limited potential for benefit as well as a significant risk of harm. In regions without full access to a comprehensive MDD, alternative strategies may still provide benefits; however, there are many potential approaches and limited data on which of these provides the optimal outcomes for patients.

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Idiopathic Pulmonary Fibrosis and the Many Faces of UIP

32

Fabrizio Luppi and Luca Richeldi

Introduction

Interstitial lung diseases (ILDs) refer to a broad category of more than 200 lung diseases encompassing a variety of illnesses with diverse causes, treatments, and prognoses. These disorders can be separated in those with an underlying disorder, including connective tissue diseases (CTDs) and Hermansky-Pudlak syndrome (HPS), or known exposure, such as hypersensitivity pneumonitis, asbestosis, drug-induced ILD, and many others. In the absence of exposure or underlying cause, the disease belongs to the group of idiopathic interstitial cases of pneumonia (IIPs) [1]. In this group, idiopathic pulmonary fibrosis (IPF) is the most frequent and most aggressive form of IIP [2]. ILDs might have several similarities, including radiological and pathological presentation which makes it the main challenge to make a confident diagnosis and an appropriate treatment approach. Particularly, a number of these disorders show usual interstitial pneumonia (UIP) pattern, suggesting that UIP is not itself diagnostic of IPF. For these reasons, the diagnosis of ILDs—including those with a UIP pattern—needs a full work-up to exclude prior exposures or an underlying disease.

In this process, the input of different specialists is considered mandatory in different stages of the care of the patient. The first stage is the diagnostic work-up in which the input of various experts is necessary: various studies have shown that multidisciplinary discussion (MDD) is associated with higher levels of diagnostic confidence and better interobserver agreement when compared to any single component of the multidisciplinary team alone [3–5].

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The aims of this book chapter include the definition of the UIP pattern according to current guidelines, the differential diagnosis, and the clinical description of the various clinical entities presenting a UIP pattern, stressing similarities and discrepancies between these different clinical entities. Finally, we will discuss, the "non-IPF fibrotic lung disease" with a focus on patients with a progressive phenotype.

Radiological and Pathological Definition of a UIP Pattern According to Current Guidelines

Updated guidelines by the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association (ATS/ERS/JRS/ALAT) and a multidisciplinary document provided by the Fleischner Society have been both published in 2018 for the diagnosis of IPF, including criteria for four categories of confidence of a histologic UIP pattern [6, 7].

In both documents, also high resolution computed tomography (HRCT) features integrate four diagnostic categories: (1) usual interstitial pneumonia (UIP) pattern, (2) probable UIP pattern, (3) indeterminate for UIP pattern, and (4) alternative diagnosis.

HRCT features essential for a definition of UIP pattern include basilar and subpleural predominant reticulation and honeycombing; traction bronchiectasis and bronchiolectasis are often detectable. Subpleural basal predominant reticular abnormalities with peripheral traction bronchiectasis or bronchiolectasis, but without honeycombing is a category defined as "probable UIP" pattern. A few "high-quality" studies have shown that the absence of honeycombing should not exclude a UIP diagnosis, if all other features of UIP are observed, including subpleural and basal predominance and traction bronchiectasis. The presence of the other features essential to define a "definite" UIP pattern, but without "honeycombing" can be categorized as a "probable" UIP pattern, with about 90% of these patients having a

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probable or definite UIP histopathological pattern on surgical lung biopsy [8, 9]. In assessing the likelihood of UIP in these patients, it is also essential to incorporate an estimate of the clinical probability of IPF, which is increased in subjects who are older than 60 years, are current or former smokers, and have no history of other potential causes of fibrosis [10, 11].

An "indeterminate for UIP" pattern should include subtle evidence of subpleural and basilar predominant reticulation with or without mild ground-glass opacities or architectural distortion. This category includes those patients with very limited subpleural reticulation or ground-glass opacities without other obvious features of pulmonary fibrosis and for whom there is some suspicion for an early or probable UIP [12].

Atypical radiographic features suggestive of an alternative diagnosis include various patterns, including upper lobe bronchocentric fibrosis, air trapping, and extensive ground-glass opacities with subpleural sparing.

Consistent with the imaging categories, four categories of histopathologic findings on biopsies have been suggested. A UIP pattern is characterized by patchy dense fibrosis with honeycomb change involving the subpleural and paraseptal parenchyma. Dense collagen deposition and scattered fibroblast foci are commonly seen in this pattern. A probable UIP pattern will have some but not all of the above-mentioned features. The isolated presence of honeycombing is also considered a probable UIP pattern. Both UIP and probable UIP patterns can include mild, sparse lymphocytic-predominant interstitial infiltrates and/or type 2 pneumocytic hyperplasia. Biopsies showing histopathologic patterns of fibrosis with different findings compared to UIP or probable UIP are identified as indeterminate for UIP. Finally, in a biopsy may be observed characteristic features that indicate an alternative diagnosis.

Clinical diagnosis of IPF requires the exclusion of other known causes of ILD, including environmental exposures, CTD, and drug toxicity, together with either the presence of an HRCT pattern of UIP or specific combinations of HRCT patterns and histopathology after lung biopsy. The diagnostic algorithm for IPF diagnosis is shown in Fig. 32.1.

In conclusion, patients with suspected IPF need a stepwise approach to diagnosis. Initial evaluation should focus

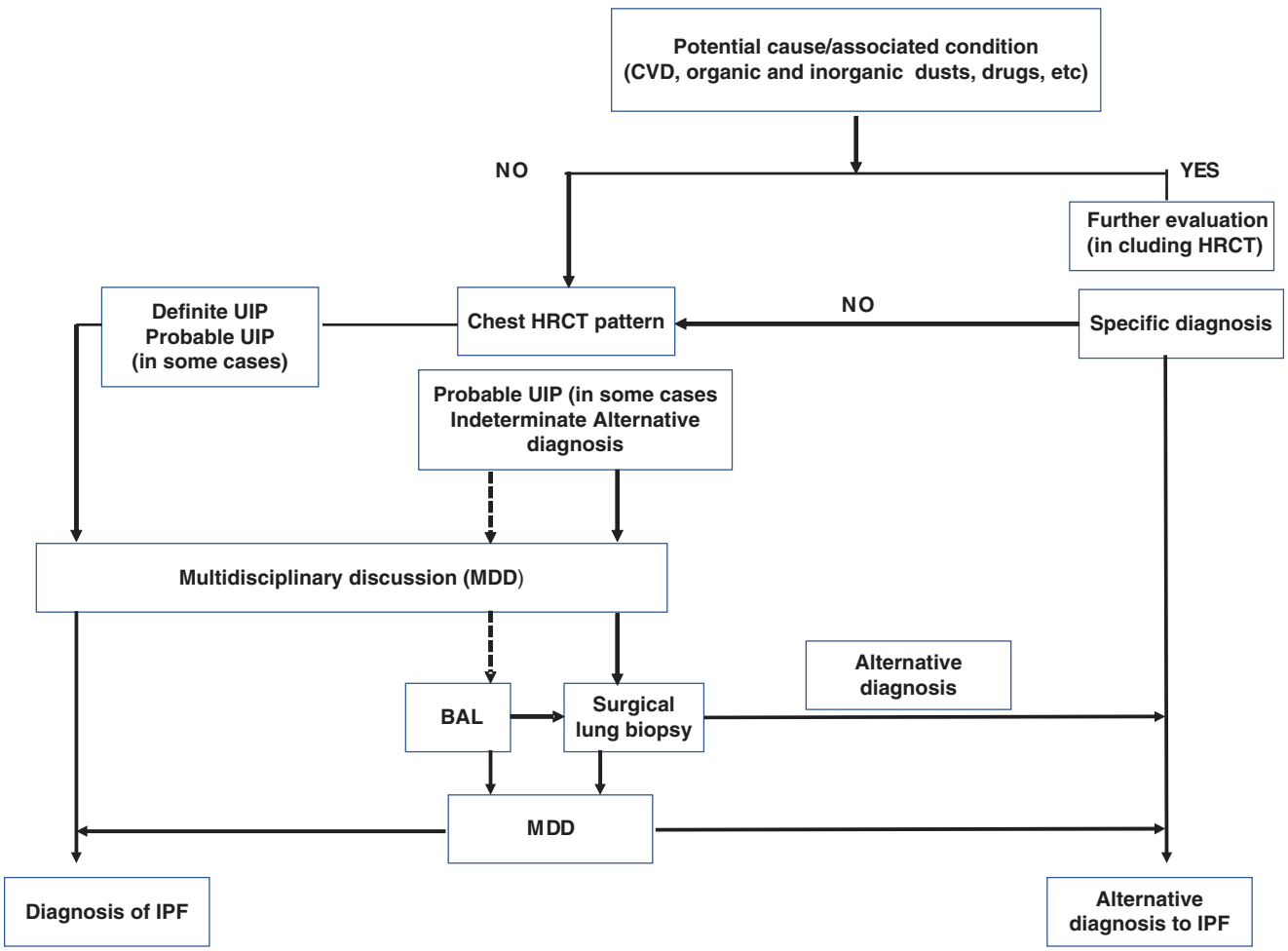

Fig. 32.1 Diagnostic algorithm for idiopathic pulmonary fibrosis. (Modified from [6])

on identifying the underlying known causes of ILD. If a specific diagnosis is not made, then an MDD focused on clinical findings, HRCT features, and, as appropriate, lung biopsy may help in determining or excluding IPF diagnosis.

Clinical Differential Diagnosis of the UIP Pattern

Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis is the most common type of idiopathic interstitial pneumonia. It is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs, and associated with the histopathologic and/or radiologic pattern of UIP [13]. However, as discussed previously, a UIP pattern is not synonymous with IPF and the differential diagnosis with other ILDs showing a UIP pattern may be hard, requiring the thorough exclusion of all known causes of pulmonary fibrosis [14].

The disease should be suspected particularly in male, current or ex-smokers, about 60 years of age, with unexplained dry cough and exertional dyspnea and should be discussed during an MDD. An integrated approach is particularly necessary in cases of discordant radiological and/or histopathological abnormalities (e.g., HRCT inconsistent with UIP, but SLB suggestive of UIP) [14]. Differentiating between IPF and "secondary" UIP has well-defined therapeutic and prognostic implications.

In the next paragraphs, we will describe the ILDs showing a UIP pattern and the potential findings useful for a differential diagnosis with IPF.

Chronic Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis (HP) is an interstitial lung disease that results from repeated inhalation and sensitization to various antigens [15], and appears to be driven by cell-mediated immunity. HP is classified clinically as acute, subacute and chronic.

Alternatively, Vasakova and colleagues proposed a new classification method, including two main categories based on clinical-radiologic-pathologic correlation: an acute/inflammatory HP and a chronic/fibrotic HP, avoiding the term "subacute" [16] (Fig. 32.2). The acute/inflammatory HP form shows symptom duration usually within 6-months,

	Clinical behaviour	Typical HRCT findings	Histopathology Patterns
Acute HP : symptom duration usually few weeks/months (<6 months)	- Mostly reversible - Complete resolution possible - Symptoms related to exposure/s to the - HP inducer, which can resolve completely after persistent avoidance	Upper- and middle-lobe predominant ground-glass opacities, poorly defined centrilobular nodules; mosaic attenuation, air trapping or, rarely, consolidation.	- Inflammatory (cellular) HP -Lymphoplasmocytic/mononuclear (macrophage) infiltrates - Airway-centric lymphocytic infiltrates/peribronchiolar - Poorly/loosely formed granulomas - Multinucleated giant cells - NSIP cellular -like
Chronic HP : symptom duration usually several months (>6 months)	- Potentially reversible, only to some extent - Risk of progression	Upper- and middle-lobe predominant fibrosis, peribronchovascular fibrosis, honeycombing, mosaic attenuation, air trapping, and centrilobular nodules, relative sparing of the bases	- Fibrotic HP UIP-like NSIP fibrotic –like Airway-centered fibrosis, NOS Unclassifiable - Histopathologic signs of inflammatory HP can be present on the background of fibrosis

Abbreviations: HP = hypersensitivity pneumonitis; HRCT = high-resolution computed tomography; NOS = not otherwise specified;; NSIP = nonspecific interstitial pneumonia; UIP = usual interstitial pneumonia.

Fig. 32.2 Novel classification of hypersensitivity pneumonitis. (Modified from [16]). *HP* hypersensitivity pneumonitis, *HRCT* high-resolution computed tomography, *NOS* not otherwise specified, *NSIP* nonspecific interstitial pneumonia, *UIP* usual interstitial pneumonia

is often reversible, and is characterized by inflammatory radiologic and histopathologic patterns. In contrast, the chronic/fibrotic HP, is usually non-reversible and can show radiologic and/or histopathologic patterns including organizing pneumonia (OP), nonspecific interstitial pneumonia (NSIP), and usual interstitial pneumonia (UIP).

At HRCT of the chest, honeycombing is frequent in CHP, although it has frequently a patchy, mid-upper predominance [16, 17]. Ground glass opacities and mosaic attenuation, indicating "air trapping", are clues useful to differentiate CHP from IPF.

Specific histological features of a UIP pattern in CHP include some "ancillary findings," such as centrilobular and bridging fibrosis, organizing pneumonia, bronchiolitis, granulomas, and giant cells [18]. Recent HP diagnostic criteria have been described in recent guidelines [19].

The prognosis of CHP is related to its histopathological patterns: cases of CHP with a UIP-like pattern tend to have the worst prognosis, and a course similar to that observed in IPF patients [20]. Similarities between IPF and CHP can result in clinically indistinguishable diseases and the latter can be misdiagnosed, particularly when the causative agent appears as unidentifiable. This could be a frequent opportunity as can be observed in up to 50% of patients with fibrotic HP [16, 17].

Therefore, in the differential diagnosis between CHP and IPF, a very detailed clinical history is of paramount importance. Specific questionnaires to identify potentially relevant exposures for HP have been proposed, but have not yet been validated [21].

Laboratory tests include the detection of precipitins or specific IgG. However, positivity to these tests indicates exposure, but not necessarily disease. In contrast, negativity is not discriminatory, as they disappear with time [21].

Bronchoalveolar lavage (BAL) lymphocytosis has been proposed as a diagnostic criterion for HP diagnosis [22]. However, the ability of BAL fluid lymphocyte analysis to discriminate between HP from other ILDs, including sarcoidosis and IPF, is unknown, as is the optimal threshold BAL lymphocyte count to diagnose HP [10–12]. A recent systematic review showed that—although the percentage of BAL fluid lymphocytes is higher in CHP than in IPF or sarcoidosis—a threshold that distinguishes HP from IPF or sarcoidosis with both high sensitivity and high specificity was not identified [23].

Connective Tissue Disease

Connective tissue diseases (CTDs), also referred to as collagen vascular diseases, are a group of diseases characterized by circulating autoantibodies and systemic manifestations considered to be related to autoimmune-mediated organ damage [24]. The spectrum of CTDs encompasses rheumatoid arthritis (RA), systemic sclerosis (SSc), systemic lupus erythematosus (SLE), primary Sjögren's syndrome (pSS), inflammatory idiopathic myopathy (dermatomyositis, polymyositis, myositis associated with anti-synthetase antibodies), and mixed CTD, each of them with international consensus diagnostic criteria [25].

Interstitial lung disease (ILD) can occur in any CTD with different frequencies and severity [26, 27]. The only current classification of CTD-ILD is the histological classification of idiopathic interstitial types of pneumonia (IIP) [24]. All histological patterns are seen in IIP [28], including the UIP pattern, are also reported to occur in CTD-ILD [29] (Table 32.1). However, in various CTD-ILDs, NSIP is the most prevalent histological pattern, including in ILD associated with SSc [30], polymyositis–dermatomyositis [31], and pSS [32]. In contrast, a UIP pattern may be prevalent in patients with RA [33] and less frequently in SSc [25]. Furthermore, in these disorders, whether the histological distinction between UIP and NSIP has prognostic importance is unclear [24]. In SSc-ILD, a histological pattern of UIP was not associated with a worse outcome in the largest histological series of 78 patients [30], although this conclusion has been questioned in one small series, in which UIP was associated with a very poor outcome [34].

Table 32.1 Prevalence of histological patterns in various CTDs

Lung pattern	Rheumatoid arthritis	Systemic sclerosis	SLE	Polymyositis–dermatomyositis	Primary Sjogren's syndrome
Usual interstitial pneumonia	+++	+	+	+	+
Nonspecific interstitial pneumonia	++	+++	++	++	++
Desquamative interstitial pneumonia) and/or RB-ILD	+	±	±	±	±
Organizing pneumonia	+	+	±	++	±
Lymphocytic interstitial pneumonia	±	±	±	±	++
Pleuroparenchymal fibroelastosis	±	+	?	?	?
Diffuse alveolar damage	+	+	+	±	+

Modified from [24]
RB-ILD respiratory bronchiolitis-interstitial lung disease

In contrast, various data suggest that UIP is more prevalent than NSIP in RA; moreover, UIP appears to have a worse prognosis than NSIP in some series [35, 36].

Patients with RA-ILD with a histologic UIP pattern are usually older, male, and smokers or former smokers compared with patients with RA-related ILD with a non-UIP pattern [37] and showed a poorer prognosis compared with patients with an RA-ILD showing a non-UIP pattern [24].

ILD may be detected at any point in the natural history of a CTD [25]. This complexity explains the potentially difficult differential diagnosis with IPF. In fact, ILD may develop in the context of an already diagnosed CTD with characteristic manifestations. However, ILD may be the first presenting manifestation of a CTD, the features of which may not yet have been identified, the ILD may be initially diagnosed as an IIP, including IPF if a UIP pattern is detected, and CTD diagnosis may be challenging, mainly because systemic symptoms may be absent or subtle. There is no standardized approach to the assessment for underlying CTD in patients initially diagnosed as affected by IIPs. However, in clinical practice, detailed history and physical examination are required, together with testing for circulating autoantibodies. In this context, when clinical exams and laboratory testing arise suspicion of an underlying CTD, a multidisciplinary approach represents the diagnostic "gold standard." Therefore ILD might be the first sign of a yet uncovered CTD: in this case a follow-up is crucial.

Moreover, patients with interstitial pneumonia can present with some aspects of CTD, but not enough to diagnose a specific CTD diagnosis. These patients, in whom it seems that the lung is the only or most clinically important manifestation of an occult CTD, are suspected of having a systemic autoimmune disease. The latter might be identified by the presence of circulating autoantibodies, specific histopathological features on surgical lung biopsy samples, or subtle extra-thoracic manifestations these patients are classified as having an "interstitial pneumonia with autoimmune features" (IPAF), rather than an idiopathic disease. IPAF however is a research tool, rather than an established diagnosis at the present moment [38]. In this specific setting, a multidisciplinary discussion may confirm the absence of criteria to define a specific CTD and decide on the specific treatment and follow-up [39].

Drug-Induced Lung Diseases

Many drugs have been related to the possible onset of ILD, showing that ILDs represent between 1.8% and 2.1% of the total number of ILDs in Italy, 2.6% in Germany and between 1.9%, and 3.5% of total ILDs in the USA [40]. However, there are no definitive data and the real incidence of drug-induced ILDs is probably still underestimated.

A paradigmatic drug in inducing pulmonary toxicity is amiodarone, which is an antiarrhythmic agent commonly used to treat supraventricular and ventricular arrhythmias. Although the broad heterogeneity of the clinical and radiological picture of amiodarone-induced pulmonary toxicity, irreversible pulmonary fibrosis and ARDS are the most serious manifestations of amiodarone-induced lung toxicity [41].

In various publications describing patients affected by amiodarone pneumonitis, septal thickening, non-specific inflammation and interstitial fibrosis in combination with the presence of lipids within interstitial, endothelial and alveolar cells have been described [41, 42].

Amiodarone pneumonitis is more frequent in male patients and is unusual in patients who are younger than 40. The risk of developing pulmonary toxicity in patients taking amiodarone increases with age, and, on average, with daily dosage of the drug [43].

The prevalent histological and radiological pattern of amiodarone-induced pulmonary fibrosis is classified as a NSIP type [42, 44]. However, interstitial reticular opacities, and traction bronchiectasis with subpleural and basal predominance have been observed on HRCT in cases of pulmonary fibrosis [41, 43]. Honeycombing is unusual at the time of diagnosis [43]. Amiodarone-induced pulmonary fibrosis is irreversible, response to corticosteroids is very limited or of short duration, and the disease adversely impacts life expectancy [43]. Amiodarone-induced pulmonary fibrosis appears milder and slowly progressive compared to IPF [41]. The histopathologic features of amiodarone-induced pulmonary fibrosis showed thickened alveolar septa, type II cell hyperplasia/dysplasia, and the accumulation of foamy alveolar macrophages [43]. Alveolar foam cells are seen, depending on the time from biopsy to discontinuation of the drug.

In conclusion, although amiodarone is characterized by various clinical entities, pulmonary fibrosis may occur; the most frequent pathological and radiological pattern is considered NSIP, but also—in a few cases—a UIP pattern may be identified with a need for a differential diagnosis also with IPF.

Radiation Pneumonitis

The lung is susceptible to radiation damage more than any other organ and then it tends to be easily damaged by radiation beams. The functional unit that is highly sensitive to ionizing radiation is the alveolar-capillary barrier [45]. In lung cancer, it is estimated that about 5% to nearly 40% of lung cancer patients will develop radiation-induced lung injury.

Radiation-induced lung disease following radiotherapy is separated into two phases: an acute phase, characterized by lung infections and pneumonitis, that usually occurs during the first 6-months, and a permanent phase, in which the prominent radiological feature is characterized by pulmonary fibrosis and occurs at least 6-months after radiotherapy [46] and it is characterized by a tissue repair response triggered by chronic inflammation. It can continuously progress for several years.

Although the opacities of radiation pneumonitis can gradually resolve without radiologic sequelae when the injury to the lung is limited, in cases of more severe injury there is usually a progression to fibrosis [46]. Radiation fibrosis manifests at HRCT as a well-defined area of volume loss, linear scarring, consolidation, and traction bronchiectasis. Consolidation usually coalesces and typically has a relatively sharp border that conforms to the treatment portals rather than to anatomic boundaries [47]. Occasionally, these findings are associated with ipsilateral displacement of the mediastinum and adjacent pleural thickening or effusion [47]. With the evolution of radiation fibrosis, the demarcation between normal and irradiated lung parenchyma often becomes more sharply defined [47].

Currently, there are no approved treatment options for patients with radiation-induced pulmonary fibrosis partly due to the absence of effective targets [48].

Asbestosis

Asbestos is related to a group of naturally occurring fibers composed of hydrated magnesium silicates that are commercially valuable due to its strength, flexibility, and resistance to electrical, thermal, and chemical degradation. Two categories of asbestos exist serpentine, long, curly fibers; and amphibole—long straight rod-like structures. Chrysotile is the only significant commercially used serpentine fiber. Amphibole fibers include crocidolite, amosite, anthophylite, actinolite, and tremolite. Chrysotile fiber use is more common, whereas amphibole fibers are considered more toxic [49]. In addition to its association with lung cancer, mesothelioma, small airways disease, and pleural disease, asbestos exposure can lead to asbestosis, a form of interstitial lung disease often indistinguishable from IPF [50].

As discussed above, the diagnostic work-up of any patient with ILD includes a comprehensive history, high-resolution chest CT scan, and pulmonary function testing. Biopsies are not routinely required [51].

Given the long latency between exposure and disease, clinicians should consider present and past jobs and employers, as well as the presence of disease among co-workers.

Whereas asbestosis CT scans may appear indistinguishable from IPF patients, the presence of certain radiographic clues may be particularly helpful in patients who have indeterminate or unknown asbestos exposure. Such clues include the presence of pleural diseases such as pleural plaques and pleural thickening. Bilateral pleural plaques are very specific for asbestos exposure [51].

For the asbestosis patient, a strong exposure history in the presence of fibrotic lung disease on HRCT is sufficient for diagnosis and does not require further investigation. Therefore, histopathologic confirmation is not usually required.

In the absence of a definitive UIP CT scan, surgical lung biopsy should be considered. Whereas histopathologic findings in advanced asbestosis usually show a UIP pattern, early asbestosis features may show only a bronchiolocentric disease. In contrast to UIP, fibroblastic foci are less prominent, whereas mild fibrosis of the visceral pleura is more commonly seen [51].

Hermansky-Pudlak Syndrome

The Hermansky-Pudlak syndrome (HPS) is a group of autosomal-recessive disorders characterized by tyrosinase-positive oculocutaneous albinism, bleeding diatheses, and, in selected individuals, neutropenia, granulomatous colitis, and early onset accelerated pulmonary fibrosis, the latter occurring only in HPS-1, HPS-2, and HPS-4 [52]. So far, 10 genetically distinct subtypes (HPS-1 to HPS-10) exist [52].

Patients affected by HPS generally develop ILD in the third decade of life [53] but some reports indicate the presence of symptomatic lung disease in late adolescence [53]. The diagnosis of ILD is established with a chest HRCT scan because lung biopsy is not recommended for ILD diagnosis in HPS patients, because the risk of bleeding is considerable and the pretest likelihood that fibrotic changes are very high in HPS patients [53]: for all these reasons surgical lung biopsy is usually not recommended. Chest HRCT in general shows reticular opacities, thickened interlobular septa, and ground-glass infiltrates in addition to traction bronchiectasis and honeycombing [54]. These imaging findings progress over time. The severity of changes in HRCT has been shown to correlate with a decline in lung function and mortality [54].

When available, lung tissue from HPS patients with pulmonary fibrosis has shown changes that are similar to the UIP pattern characteristic of IPF. Additional characteristic changes are foamy swelling of alveolar macrophages and epithelial cells.

Similar to IPF, pulmonary fibrosis in the framework of HPS is characterized by progressive diseases, ultimately leading to death from respiratory failure [55]. similarly to IPF, including increased dyspnea initially manifesting only on exertion and subsequently progressing to dyspnea at rest and the need for supplemental oxygen over time.

One important difference between IPF and HPS-PF is the age of diagnosis, as the disease occurs much earlier in HPS patients [55].

Another major difference is that the survival after diagnosis differs from IPF: the survival rate is much better in HPS patients, who usually live approximately 10 years after diagnosis [55]. Treatment options for individuals with HPS include pirfenidone and lung transplantation [56].

Non-IPF Progressive Fibrotic Interstitial Lung Diseases

Pulmonary fibrosis can occur in many ILDs, including those in the context of underlying systemic diseases, such as CTDs or sarcoidosis, and conditions that are limited to the lung, such as CHP, drug-induced pulmonary fibrosis, idiopathic non-specific interstitial pneumonia, and IPF [57].

The natural course of IPF without antifibrotic treatment is characterized by progression to respiratory failure in potentially every patient with a definite diagnosis [14].

In contrast, about half of all patients with a diagnosis of pulmonary fibrosis other than IPF have stable, chronic disease or improvement with immunomodulatory agents [58].

However, despite appropriate treatment, a subgroup of patients with various non-IPF ILDs will show progressive pulmonary fibrosis associated with worsening respiratory symptoms, a decline in lung function, a decreased quality of life, and a risk of early death, independent of the specific type of the ILD [59] (Fig. 32.3). Outcomes may be similar to those of IPF, especially in patients with a UIP pattern, such as those with RA–ILD and a subgroup of patients with CHP [60].

At this stage, there is no universal definition of disease progression in patients with pulmonary fibrosis and various definitions of the term "progressive" have been proposed in the context of fibrotic lung disease [60].

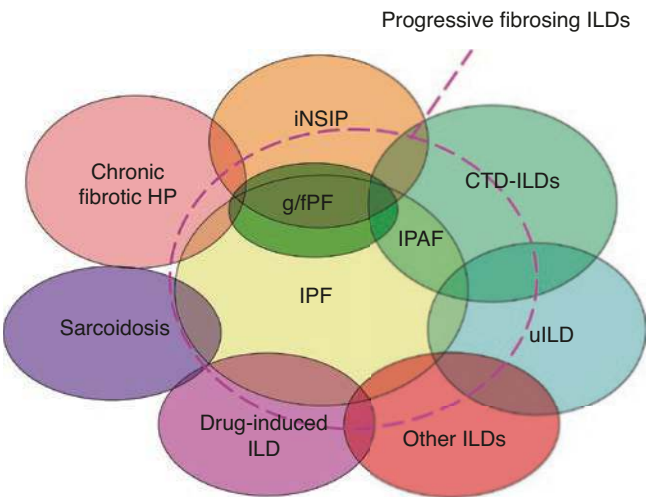

Fig. 32.3 Interstitial lung diseases that may be associated with a progressive fibrosing phenotype. (Modified from Cottin V. Eur Respir. Rev. 2019 Oct 1;28(153):190109)

In the INBUILD study, among patients with fibrosing lung disease affecting >10% lung volume on HRCT, progression was defined as satisfying at least one of the following within 24 months: (1) relative decline of FVC of 10% predicted, (2) relative decline in FVC of 5% to <10% and worsening respiratory symptoms or increased fibrosis on HRCT, (3) worsening respiratory symptoms and increased fibrosis on HRCT [61].

Cottin and colleagues defined "progressive" patients with a fibrotic lung disease as meeting one of the following criteria within 24 months: (1) relative decline of ≥10% FVC, (2) relative decline of ≥15% DLCO, or (3) worsening symptoms or worsening radiographic appearance *with* ≥5–10% relative decline in FVC [57].

A recent position paper from the "Erice ILD working group" defined progressive fibrosis in clinical practice as a demonstration of one or more of the following over 24 months in spite of treatment: (1) relative decline of ≥10% FVC, (2) relative decline of ≥5% FVC with a decline in DLCO of ≥15%, (3) relative decline of FVC of ≥5% with increased fibrosis on HRCT, (4) relative decline of FVC ≥5% with progressive symptoms, (5) progressive symptoms with increased fibrosis on HRCT [59].

The main challenge of such criteria includes how to measure worsening of respiratory symptoms as well as other factors that may be considered as surrogate of progression, such as a reduction in exercise capacity and a worsening quality of life.

Risk Factors for Progression

Various risk factors predispose some patients to progressive fibrosis. In fact, patients with a UIP pattern showed the greatest rate of decline and the poorest survival compared to other patients with a progressive ILD [59]. For example, patients with RA-ILD and a UIP pattern might have a similar survival to patients with IPF [33]. Similarly, patients with CHP and a UIP pattern have survival rates similar to IPF patients [62]. In CHP, also older age is considered an independent prognostic factor for poor survival [62].

Patients with extensive fibrotic lung disease showed also the greatest risk of disease progression. In patients with SSc-ILD - those with extensive disease - defined by an ILD extent on HRCT of more than 20% or, if indeterminate on HRCT, an FVC of less than 70% of the predicted value, have more than a three-times increased risk of death than those with less extension disease [63]. Similarly, in patients with RA-ILD the HRCT disease extension is associated with poorer survival [64]. In patients with ILD, it is also hypothesized that

gastro-esophageal reflux disease is associated with progressive fibrosis through repeated microaspiration events [65].

In patients with fibrotic HP, the absence of an identified antigen is, therefore, a risk factor for poor prognosis, with a higher risk of progressive fibrosis. This is an example that highlights the central importance of establishing a precise diagnosis when assessing patients with fibrosing ILD.

Little is known regarding which patients with nonfibrotic ILD may progress to a fibrotic ILD [58, 59]. A recent study of 245 patients with fibrosing ILD followed at two Italian ILD referral centers found that 31% had progressive disease with iNSIP, CTD-ILD, chronic HP, and sarcoidosis most likely progressive [66]. Progression was defined based on the INBUILD trial criteria; most of the patients met criteria for progression based on an FVC decline of ≥10%. In a similar vein, a study of pulmonologists experts in the ILD field - reported physician estimates that 18–32% of patients with non-IPF ILD will have progressive fibrosis [67]. In this study, unclassifiable ILD, RA-ILD, idiopathic NSIP and SSc-ILD were identified as the ILDs most often evolving to a progressive fibrotic phenotype [67].

Diagnosis

A detailed history, including environmental exposures, medication use, and extrapulmonary signs, should be carefully identified [6]. Serologic testing is recommended, at least for antinuclear antibodies and anti-citrullinated peptide antibodies [6]. If there is a clinical suspicion of an autoimmune condition, consultation with a rheumatologist—possibly in a multidisciplinary discussion - and more extensive serologic testing are recommended, including ANCA, rheumatoid factor, anti-ENA screen, that determines the levels of seven different autoantibodies including anti-Sm, anti-RNP, anti-SSA, anti-SSB, anti-Jo-1, anti-Scl 70, and anti-CENP-B. Each antibody (or combination of antibodies) is specific to a different collagen disease.

Moreover, HRCT of the chest establishes the diagnosis of pulmonary fibrosis by revealing a UIP pattern (see radiological classification described by guidelines). In contrast, the most common pattern in CTD-ILDs, hypersensitivity pneumonitis, and drug-induced ILDs, together with an idiopathic clinical entity is that of NSIP, which consists of mixed reticulation and ground-glass attenuation to a varying extent, often with traction bronchiectasis, central axial distribution, and sparing of the subpleural area. Expiratory imaging may be useful, especially in CHP [28].

Lung function tests (LFTs) are useful to assess disease severity and - using serial LFTs - represents the most accurate tool for estimating ILD progression. Since FVC is highly reproducible, in the absence of major extrapulmonary restriction due to pleural disease or muscle weakness, changes in FVC are specific to ILD [68], together with a decreased diffusing capacity of the lung for carbon monoxide. However, normal lung function does not rule out the presence of pulmonary fibrosis. Bronchoalveolar lavage mainly contributes to the diagnosis of hypersensitivity pneumonitis and sarcoidosis.

A multidisciplinary approach is recommended in the diagnostic work-up of these patients. In fact, a multidisciplinary evaluation became the current diagnostic reference standard for ILD and is reported to improve diagnostic confidence and agreement compared to individual participants of the MDD. This multidisciplinary team should require expert pulmonologists in ILD, expert ILD radiologists, rheumatologists, and histopathologists. Although a confident diagnosis can be performed in the great majority of cases, a subgroup of ILD cases remains unclassifiable even after thorough assessment [69].

Next to the MDD for diagnosis, there is a need for another multidisciplinary team that should be available for treatment and follow-up of these often complex clinical syndromes. This team should include specialists of different levels: pulmonologists rheumatologists, thoracic surgeons, cardiologists, specialist ILD nurses, physiotherapists, psychologists, and social workers [70].

Pharmacological Management

The natural history of IPF is variable and unpredictable, however, the great majority of patients experience a progressive, inexorable decline, finally leading to respiratory failure [71].

For decades, the recommended IPF treatment was the combination of steroids and immunosuppressive agents [2]. However, the PANTHER trial, designed to assess the efficacy of high dose prednisolone and azathioprine together with N-acetylcysteine, showed that immunosuppression was associated with a higher incidence of adverse events, including hospitalization, and death, proving definitively that this combined regimen is deleterious [72].

In the last years, IPF therapy has considerably changed with the world-wide registration of two new antifibrotic drugs, pirfenidone and nintedanib. Both drugs have been observed to reduce the annual rate of decline in forced vital capacity (FVC) in patients affected by IPF [73, 74]. In fact, FVC is considered the best surrogate for mortality in this disease. The use of both treatment options is recommended in the most recent IPF guidelines [75].

In contrast—despite the absence of "good quality" evidence coming from well-designed placebo-controlled trials—other forms of fibrotic interstitial lung disease, including iNSIP, CHP, sarcoidosis, and CTD-ILD, were still being treated with unapproved drugs - mainly systemic corticosteroids and/or immunosuppressants [76].

So far, the more robust evidence in this field has been exhibited by the Scleroderma lung trials I [77] and II [78], which showed the efficacy of cyclophosphamide and mycophenolate mofetil in slowing the progression of lung function decline in SSc-ILD. No good quality studies support the treatment options in the other CTD-ILDs, such as RA-ILD and pSS-ILD [76].

Recently, the results of the SENSCIS trial showed the efficacy of nintedanib in SSc-ILD [79], in which a reduction in the rate of decline of FVC was shown in patients treated with nintedanib compared to patients enrolled in the placebo arm. The effect of nintedanib was lower in patients with SSc-ILD than in patients with IPF (INPULSIS trials), but the relative reduction in the rate of FVC decline was observed with nintedanib versus placebo was similar (44% and 49%, respectively) [79]. In this study, approximately half of the trial population received MMF. The decline in FVC in the placebo group and the magnitude of the effect of nintedanib differed depending on MMF use, suggesting a potential benefit of MMF on lung function.

The results of the INBUILD trial [61], investigating the efficacy of nintedanib in different forms of progressive pulmonary fibrosis, including iNSIP, CHP, CTD-ILD, and unclassifiable interstitial lung disease. The study by Flaherty and colleagues substantially replicated the results of the INPULSIS trials conducted in IPF, as nintedanib slowed down the decline of FVC by approximately 60% as compared to placebo in these patients [13]. To date, this is the first published randomized placebo-controlled trial that has provided compelling results in such different diseases.

Data on the efficacy of pirfenidone in unclassifiable fibrotic lung disease has also been provided by a recent randomized, placebo-controlled, phase II trial. This trial demonstrated potential benefit of pirfenidone in such diseases, even if the results were affected by the study design [80].

Conclusions

In the differential diagnosis of various ILDs, it is very important to distinguish the radiological and/or pathological UIP pattern and to differentiate between the idiopathic UIP (i.e. idiopathic pulmonary fibrosis) from secondary UIP. In fact, UIP is not synonymous with IPF, because the UIP pattern can be observed also in several secondary conditions, such as CTD, CHP, drug-induced lung diseases, asbestosis, late radiation pneumonitis, and Hermansky-Pudlak syndrome. The UIP pattern observed in IPF can often be distinguished from other common forms of diffuse lung fibrosis by close examination of the clinical context, radiological features, and histopathology in the individual patient.

Because these entities have different pathogenesis, clinical features, response to therapy, and prognosis, to perform a correct diagnosis is crucial.

Within this complexity, multidisciplinary discussion has become the leading methodology to ensure quality and consistency in the diagnostic process and is recommended as the "gold standard" by current international guidelines.

Finally, despite appropriate treatment, a subgroup of patients with various non-IPF ILDs will show progressive pulmonary fibrosis associated with worsening respiratory symptoms, a decline in lung function, a decreased quality of life, and a risk of early death, independent of the specific type of the ILD, this subgroup of ILD patients shows overlapping characteristics that are similar to the prototype of the fibrosing ILD with a progressive phenotype, i.e., IPF.

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The Syndrome of Combined Pulmonary Fibrosis and Emphysema

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Vincent Cottin

Pulmonary emphysema and the idiopathic interstitial pneumonias, of which idiopathic pulmonary fibrosis (IPF) is the most frequent, are separate entities characterized by distinct clinical, functional, radiological, and pathological characteristics. However, recent studies have revealed that emphysema, among other comorbid conditions, is more frequently associated with IPF than previously appreciated, leading to consideration of CPFE as a distinct syndrome. Moreover, it has recently been better recognized that the combination of pulmonary fibrosis and emphysema alters the clinical presentation and outcome, with implications for clinical practice and trial design. A specific research definition and set of criteria for CPFE clinical syndrome has been proposed.

Historical Perspective

In 1948, Laurence L. Robbins reported on a form of IPF and emphysema [1]; areas of fibrosis were interspersed with areas of emphysema at chest radiograph, with emphysema described as thin-walled bullae or blebs. The same year, T. B. Mallory et al. described a young woman with pathologically confirmed IPF and emphysema [2].

In 1990, Wiggins and colleagues from the group headed by Dr Margaret Turner-Warwick at the Brompton hospital (London, UK) reported on eight patients with IPF (that was called "cryptogenic fibrosing alveolitis" at the time), in whom combined emphysema was observed on chest computed tomography (CT) [3]. The combination of ILD and emphysema was associated with dramatically decreased carbon monoxide transfer factor (DLco) in the setting of well-preserved total lung capacity (TLC) and a normal or nearly normal forced expiratory volume in 1 s (FEV_1): forced vital capacity (FVC) ratio. This report mostly emphasized that high resolution (HR) CT of the chest was helpful to provide with a working diagnosis in patients with severe dyspnea and subnormal spirometry.

In 1997, Wells et al. [4] described the functional impact of emphysema in patients with "cryptogenic fibrosing alveolitis," citing higher lung volumes, lower DLco, and decreased gas exchange in patients with emphysema as compared to those with pulmonary fibrosis alone. In 2003, Wells et al. [5] introduced a sophisticated approach to characterizing how emphysema impacts pulmonary function in IPF, and derived a score (the "composite physiologic index," CPI) from disease extent on HRCT to correct the mortality risk calculation in IPF patients (which uses FVC and DLco) for the confounding effects of emphysema. Although this study contributed to a more accurate prognostic determination in IPF, and provided a useful tool for clinical research, it did not draw attention of the clinicians to the profound consequences of emphysema in IPF patients.

Despite isolated reports [6, 7] of observations similar to that of Wiggins et al. [3], it was not until 2005 that combined pulmonary fibrosis and emphysema (CPFE) was individualized as a distinct syndrome by the *Groupe d'Etude et de Recherche sur les Maladies "Orphelines" Pulmonaires* (GERM"O"P) [8] (a French group of clinical research, now named OrphaLung), occurring in smokers or ex-smokers and representing more than a mere comorbid condition. CPFE was defined at chest HRCT by the presence of upper lobe emphysema and pulmonary fibrosis of the lower lobes, with the interstitial lung disease (ILD) corresponding to IPF in most of the patients. This comprehensive description in a large group of patients (n = 61) lead to a greater appreciation for the high prevalence of CPFE and prognostic significance of pulmonary hypertension (PH) in patients with the disorder [8].

Since then, nearly 100 original articles on CPFE have contributed to a more complete description of the syndrome, as reviewed in this chapter. The presence of emphysema in smokers with IPF is now systematically evaluated routinely. Causes other than tobacco smoking have been identified.

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More importantly, the role of tobacco smoking is better identified as a risk factor for the wide spectrum that comprises IPF, CPFE, and chronic obstructive pulmonary disease with emphysema [9], altogether belonging to smoking-induced lung diseases [10]. Lung cancer [11] and PH may also be part of the spectrum. Importantly, it has become clear that CPFE encompasses a number of radiological and pathological patterns; such heterogeneity and lack of consensus definition and terminology until recently have hampered comparisons between clinical series from different groups and clinical research.

It is still unclear whether CPFE corresponds to the coincidental association of IPF and emphysema by chance or to a genuinely unique entity with causal links between the two pathologies. Much remains to be learned about the pathophysiology of this syndrome, diagnostic boundaries with IPF, and management. However, CPFE clearly presents with a characteristic clinical and functional profile, and an increased risk of precapillary PH, lung cancer, and mortality, not to mention significant relevance for clinical care, approach to monitoring, and trial design. Therefore, CPFE is considered a clinical syndrome [12].

Epidemiology and Etiologies

Tobacco Smoking and Male Sex

Emphysema has been reported in 21–33% of patients with IPF (up to 67% in some series) [13–23], most of whom are current or past tobacco smokers. A lower prevalence (8%) was found in a series from the USA [13], likely accounting for the lesser use of tobacco in this population. In addition to variations in smoking, differences in the prevalence of emphysema between studies and countries are likely due to definitions used for CPFE and to underlying genetic susceptibility. Tobacco smoking is by far the predominant etiology of the CPFE syndrome, with a smoking history present in 98% of patients [24], and a mean tobacco history of about 40 pack-years [8, 11, 25, 26]. Interestingly, exposure to tobacco smoke may cause both fibrosis and emphysema in an animal model [27]. A comprehensive review of common and distinct mechanisms of disease pathogenesis in IPF and chronic obstructive pulmonary disease can be found elsewhere [28, 29].

CPFE associated with tobacco smoking in the absence of any other potential etiologic factor has a 9:1 male:female ratio [24]. Both IPF and emphysema also separately predominate in males [30–33], but the male predominance of CPFE is particularly important. It is not unknown whether the male predominance of the CPFE syndrome is related solely to the higher prevalence of tobacco smoking in men, and to the link between tobacco smoking and both emphysema and IPF. Smoking rates in men versus women generally tend to become similar over time as the prevalence of smoking falls in western countries, and likely do not explain the totality of the gender difference in CPFE. Emphysema generally precedes fibrotic ILD. A large epidemiologic study would be required to study the respective role of gender and tobacco smoking in predisposing to CPFE.

Patients with a smoking history as the only etiologic or risk factor for developing CPFE will hereafter be referred to as "CPFE" to distinguish them from those with more clear-cut etiologic factors for ILD. CPFE in the absence of tobacco smoking should suggest the presence of connective tissue disease (which is probably by itself a risk factor for CPFE) [17, 34–36] or hypersensitivity pneumonitis [37–40].

Genetic Predisposition

It has been postulated [12] that a particular genetic background may predispose a subset of smokers to develop the typical syndrome of CPFE, in much the same was as the risk of emphysema or IPF in smokers is through to depend on largely unknown genetic factors that likely impact lung aging and cell senescence [28, 41–43]. The potential genetic basis of CPFE is only beginning to be explored, with a few cases of mutations conferring a Mendelian risk of CPFE or IPF appearing in the literature (Table 33.1). However, it is likely that CPFE may result from both a genetic predisposition and a second hit with tobacco smoking or exposure to other aerocontaminants or risk factors. Identifying genetic mutations that render individuals vulnerable to CPFE would provide great pathophysiological insights into the disorder, with the caveat that epigenetic alterations almost certainly also play a major role [62].

The CPFE syndrome was reported in a patient with familial ILD carrying a mutation in the surfactant protein C gene [49]. Typical CPFE was found in a 41-year-old non-smoker

Table 33.1 Genetic variants and polymorphisms that are associated with CPFE

Genetic variants and polymorphisms associated with CPFE		References
Rare genetic variants	Telomerase-related genes (*TERT*, *RTEL1*)	[44–48]
	Surfactant-related genes (*SFTPC*, *ABCA3*)	[49–54]
	Other genes (*Naf1*, *PEPD*)	[55, 56]
Genetic polymorphisms	*Matrix metalloprotease (MMP)-9* and *Transforming growth factor-beta-1* (*TGF-beta-1*) genes	[57–59]
	AGER gene	[60]
	rs2736100 (*TERT*), rs2076295 GG (*DSP*)	[61]

patient with a pathological mutation in the *ABCA3* gene [50]. Some "emphysema-like" lesions were further observed in patients with familial (genetic) IPF with mutations in the surfactant protein C gene [51, 52] or in the telomerase complex [44, 45]. As telomere length is reduced both in COPD and IPF patients, telomeres would be expected to be shorter than normal in patients with CPFE [12, 24], a concept that requires further study [63]. Germline mutations were identified in telomerase as a Mendelian risk factor for COPD susceptibility that clusters in families with autosomal dominant telomere-mediated disease including pulmonary fibrosis [46]. For example, a CPFE syndrome was present in a family with *TERT* mutation, with one individual presenting nonspecific interstitial pneumonia (NSIP) and emphysema with scattered ill-defined granulomas, another with usual interstitial pneumonia (UIP) and emphysema, and one (exposed to wood dust) who had emphysema with mild pulmonary fibrosis of the lower lobes [47]. As observed in familial pulmonary fibrosis (without emphysema), mutations in genes associated with surfactant or telomerase, when present in a family, can be associated with a diversity of patterns, especially UIP and NSIP. Incidentally, scattered cystic lesions and ILD with mostly ground-glass attenuation can be observed in patients with neurofibromatosis, albeit with an imaging pattern that is not typical of that of (tobacco-related) CPFE syndrome [64]. Gene mutations and genetic modifiers that confer a specific predisposition to CPFE have not been explored.

Systemic Diseases

The CPFE syndrome may occur in virtually any of the connective tissue diseases, with no clear differences in presentation according to the individual systemic diseases or autoantibody type [65]. The prevalence of coexistent emphysema has been formally studied in only a few cohorts of patients with connective tissue diseases and associated ILD. In one study, the prevalence of emphysema at HRCT was 23% in patients with ILD associated to connective tissue diseases and 44% in patients with IPF ($p = 0.05$) [66]. The emphysema score at HRCT was significantly lower in patients with connective tissue diseases and a pathological UIP pattern than in those with IPF in a retrospective study, however, a difference in smoking history could have accounted for this difference [67].

In a study of 34 patients with typical CPFE occurring in connective tissue diseases [26], the predominant underlying diseases were rheumatoid arthritis (Fig. 33.1) and systemic sclerosis (Fig. 33.2) (limited or diffuse cutaneous variant), possibly owing to the relative frequency of these diseases in the general population. The diagnosis of CPFE followed that of connective tissue disease by a median of 4 months in two thirds of the patients, whereas both diagnoses were simultaneous in the other cases [26]. The onset of a CPFE syndrome before the occurrence of the connective tissue disease is very rare [26].

In 150 consecutive patients with rheumatoid arthritis [68], 19% had ILD, 15% had the so-called emphysematous bullae, and 8% (12 out of 150) had both ILD and emphysema. In 116 never smokers with rheumatoid arthritis-associated ILD, emphysema was present on HRCT in 27% [34]. Emphysema was observed in 24% of 63 patients with rheumatoid arthritis and ILD [69], and was significantly more frequent among patients with an HRCT pattern of UIP (38%) than in other ILD patterns; patients with UIP also had a higher prevalence of smoking and a greater smoking history than those with other patterns. Antoniou et al. reported the presence of emphysema on chest HRCT in 48% of ever-smoker patients with rheumatoid arthritis and ILD, and in 35% of ever-smoker patients with IPF, despite median smoking histories of less than 25 pack-years in both cohorts [17]. These data suggest that subjects with rheumatoid arthritis who smoke may be particularly vulnerable to emphysema. In addition, patients with rheumatoid arthritis and a history of smoking had a "coarser" fibrosis at imaging than never smokers. In rheumatoid arthritis, interaction of genetic background (e.g., the human leukocyte antigen DRB1 shared epitope) with environmental exposures (especially tobacco smoking) and autoimmunity (e.g., anti-cyclic citrullinated peptide antibodies) is well established [70]. Briefly, tobacco smoking is responsible for inflammation and citrullination of proteins within the lung, a post-translational modification that converts L-arginine residues into L-citrulline residues through the activity of peptidyl arginine deiminase. This modification is thought to alter protein folding and charge, and enhance degradation by proteases and exposure of cryptic epitopes, which in turn increases the risk of developing anti-cyclic citrullinated peptide autoantibodies produced in the lung. In this model, the end result is an autoimmune response that leads rheumatoid arthritis [71], in which antibodies developed against modified self-proteins in the lungs leads to emphysema in the lungs and inflammation of the joints [72]. Tobacco smoking increases the incidence and severity of rheumatoid arthritis [73], including an enhanced risk of developing extra-articular complications [74], possibly including ILD [75, 76]. Acute exacerbation of ILD is known to occur in patients with CPFE and rheumatoid arthritis, occasionally upon institution of drug therapy [77]. Whether emphysema in rheumatoid arthritis is also a consequence of autoimmune processes promoted by cigarette smoking is unknown. Of note, anti-elastin antibodies are not found in patients with CPFE [78].

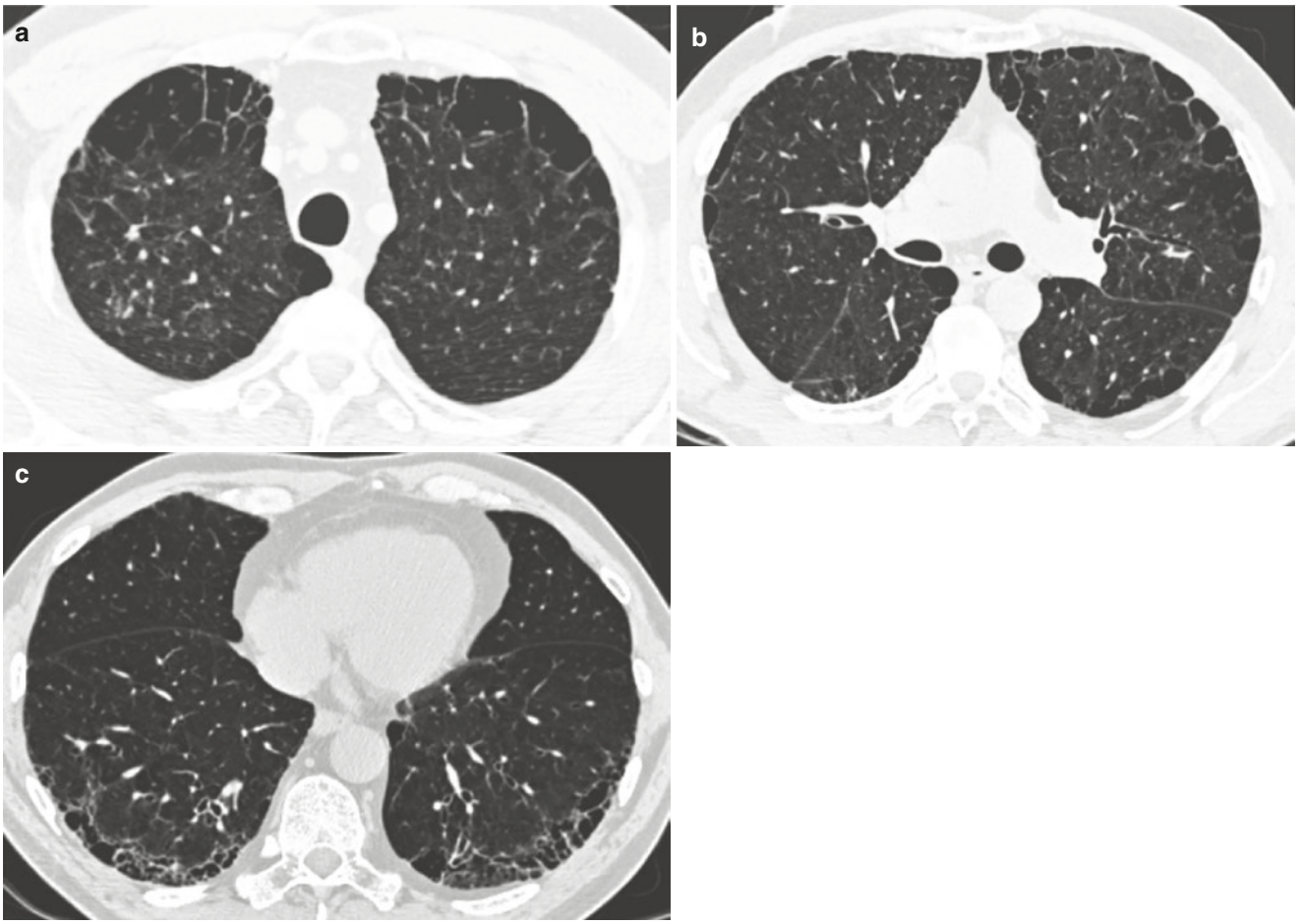

Fig. 33.1 CPFE syndrome at chest HRCT in a patient with rheumatoid arthritis (male, smoker). (**a**) upper lobes showing centrilobular and paraseptal emphysema; (**b**) mid regions of the lungs, showing predominantly paraseptal emphysema, with thickening of the interlobular septa; (**c**) lower zones showing usual interstitial pneumonia pattern with reticulation, honeycombing, and traction bronchiectasis

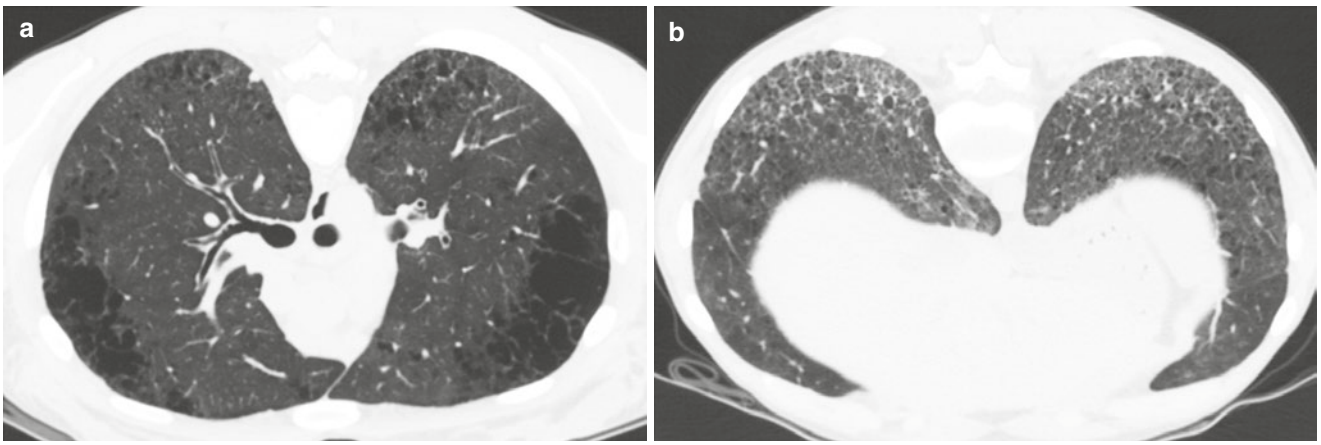

Fig. 33.2 CPFE syndrome at chest HRCT in a 28-year-old female patient with severe systemic sclerosis and high-titer anti-U1-RNP autoantibodies, with a smoking history of less than 5 pack-years. (**a**) upper lobes demonstrating centrilobular and paraseptal emphysema; (**b**) lower zones showing nonspecific interstitial pneumonia pattern with reticulation, ground-glass opacities, and mild traction bronchiectasis

CT evidence of emphysema was found in 8.4% of 225 patients with systemic sclerosis [79], with extent of emphysema greater than 10% in about a quarter of these, as compared to 12% of patients with IPF and 22% of patients with idiopathic NSIP. Tobacco smoking negatively influences FEV_1:FVC and DLco in patients with systemic sclero-

sis [80, 81]. Emphysema is more prevalent in systemic sclerosis patients with pulmonary fibrosis than in control smokers without connective tissue disease or IPF, after adjustment for the smoking history [35]. In 470 patients with systemic sclerosis, 43 had CPFE on chest HRCT, including 24 (58%) who had never smoked [36]. Approximately 5–10% of patients with systemic sclerosis-associated ILD have radiological findings of CPFE [35, 81–83]. The CPFE syndrome may occur in patients with only mild or no smoking history [17, 34, 35, 84, 85], suggesting that systemic sclerosis itself might contribute to the development of emphysema, a hypothesis that remains to be confirmed.

Of note, spontaneous emphysema and right heart hypertrophy develop spontaneously in tight-skin mice that harbor a duplication in the *fibrillin-1* gene and exhibit a phenotype that resembles human systemic sclerosis [86, 87]. Modulation of inflammatory markers in animal models [88–93] supports the hypothesis that the connective tissue disease per se may play a role in the pathogenesis of the CPFE syndrome, possibly through mechanisms that lead to chronic inflammation or epigenetic dysregulation (post-translational modifications of histone proteins and hypermethylation) [22, 94].

CPFE has been reported in patients with polymyositis, Sjögren syndrome, mixed connective tissue disease, overlapping connective tissue disease, with consistent antibody profiles [26]. Emphysematous changes were found in 3 of 65 autopsy cases of polymyositis/dermatomyositis [95]. Tobacco smoking also increases the risk of developing systemic lupus erythematosus [96], however, CPFE seems rare in lupus.

The CPFE syndrome may occur in patients with the so-called interstitial pneumonitis with autoimmune features (also referred to as ILD in undifferentiated connective tissue disease [97], autoimmune featured connective tissue disease [98] or lung-dominant connective tissue disease [99]) (e.g. the individualized research condition with manifestations suggestive of connective tissue disease but not satisfying the criteria of any defined disease entity [100]). For example, a syndrome of CPFE was found in 7% of subjects with lung disease and anti-cyclic citrullinated peptide antibodies but not rheumatoid arthritis [101].

The CPFE syndrome may also develop in patients with systemic vasculitis, especially microscopic polyangiitis [102, 103]. In one study, autoimmune markers including perinuclear anti-neutrophil cytoplasmic antibodies were more frequently found in patients with CPFE than in subjects with IPF and no emphysema, correlating with infiltration of the fibrotic lungs by clusters of CD20+ B lymphocytes within lymphoid follicles [14]. It is speculated that anti-myeloperoxidase antibodies in microscopic polyangiitis may promote the degranulation of neutrophils, with release of reactive oxygen species that may participate in disease pathogenesis.

Table 33.2 Exposures and etiologies that are associated with CPFE

Variables associated with CPFE		References
Risk factors and demographics	Cigarette Smoking	[13, 21, 23, 26, 104–111]
	Male sex	[8, 21, 24, 105–110, 112, 113]
Diseases	Idiopathic pulmonary fibrosis	[13–22]
	Connective tissue disease	[26, 34–36, 81, 83, 95]
	ANCA-associated vasculitis	[102, 103, 114, 115]
	Hypersensitivity pneumonitis	[37–40]
Inhalational exposure	Coal dusts	[24, 116, 117]
	Asbestos	[118–121]
	Silica and mineral dust	[122]
	Agro-chemical compounds	[123]
	Talc	[124]
	Other inhalational exposures	[125–127]

ANCA anti-neutrophil cytoplasmic antibodies

Other Etiological Contexts

CPFE has been occasionally reported in subjects with exposure to various compounds or a variety of conditions (Table 33.2).

Clinical Manifestations

Patients with the CPFE syndrome have a mean age of 65–70 years [8, 24], with younger individuals overrepresented in those with connective tissue disease or genetic predisposition to ILD (Clinical Vignette). The male:female ratio is greater than 9:1 in CPFE, with 60 men and only one woman in the seminal series [8], and 73–100% male predominance depending on the series [8, 13–22, 105–110, 112, 113]. In patients with connective tissue disease, the CPFE syndrome is less strongly associated with male gender (68% of males), however, male predominance in patients with CPFE does sharply contrast with the female predominance found in series of patients with connective disease and ILD (without emphysema) [128].

Patients with CPFE usually report severe dyspnea at exercise [3, 7, 8, 13, 25, 26, 123, 129–133]. Chronic bronchitis may be present. Clinical examination generally demonstrates basal "velcro" crackles similar to that found in IPF. Finger clubbing is present in one third of the patients [26].

The most frequent comorbidities in patients with CPFE are lung cancer and PH [11, 25]. Coronary artery disease, perivascular artery disease, and diabetes are also frequent [134].

Pulmonary Function and Physiology

Patients with CPFE syndrome present with limitation to exercise capacity, and severely impaired DLco and transfer coefficient (Kco), contrasting with subnormal spirometry [24, 26, 135–137]. Spirometric values and lung volumes are preserved, and FVC, TLC, and/or FEV_1:FVC are often normal or near normal. The FVC/DLco ratio is increased in most patients [35]. In the seminal series, the mean FVC was 90 ± 18% of predicted value, TLC was 88 ± 17%, FEV_1 was 80 ± 21%, FEV_1:FVC was 89 ± 13%, whereas DLco was 37 ± 16% of predicted and Kco was 46 ± 19%. In patients with CPFE and associated PH [25], lung volumes were comparable with FVC of 88 ± 18% of predicted, however DLco was only 24 ± 14% of predicted and Kco was 28 ± 16% of predicted.

Data from three merged study populations [8, 25, 26] indicated that only 36% of 132 patients had TLC lower than 80% of predicted values. Only 41% of 132 patients had FEV_1:FVC lower than 0.70 (out of whom 11% had FEV_1 greater than 80% of predicted, corresponding to GOLD [Global initiative for Obstructive Lung Disease] stage 1); 37% were classified as GOLD stage 0 (FEV_1:FVC ≥ 0.70 and FEV_1 ≥ 80% of predicted) and further 22% were unclassified according to GOLD (with FEV_1:FVC ≥ 0.70 and FEV_1 < 80% of predicted). In another study, smokers with emphysema were less likely to meet GOLD criteria for chronic obstructive pulmonary disease if ILD changes were present at imaging [138]. Compared to isolated IPF, patients with CPFE have higher vital capacity and lung volumes (FVC and TLC), generally comparable FEV_1, higher residual volume (RV), lower DLco, lower Kco, and lower PaO2 [4, 13, 15, 20–22, 112, 129, 131, 137, 139–144], even with adjustment for the extent of fibrosis [4, 131]. Thus, the relative preservation of spirometric values may lead to underdiagnosis of the CPFE syndrome.

These observations are attributed to the counterbalancing effects of the restrictive physiology due to the increased elastic forces imparted by pulmonary fibrosis (with presumably increased elastic recoil, as well as prevention by traction forces of expiratory airway collapse), and the effects of the alveolar destruction that decreases elastic recoil and the obstructive physiology with propensity to hyperinflation due to emphysema. This is illustrated correction of FEV_1:FVC toward normal values as dyspnea and DLco worsen with disease progression [145]. The annual change in FEV_1:FVC has been shown to moderately increase in patients with CPFE, as compared to the annual decrease in the ratio that is typical for those with chronic obstructive pulmonary disease alone [146]. TLC correlates positively with the emphysema score at HRCT, and inversely correlates with the fibrosis score; conversely, FEV_1:FVC negatively correlates with the emphysema score at HRCT, and positively correlates with FEV_1:FVC [147]. Analysis of respiratory impedance by multi-frequency forced oscillation technique found lower whole-breath, inspiratory or expiratory resistance in CPFE patients than in chronic obstructive pulmonary disease, and lower whole-breath and expiratory resistance in CPFE than in ILD without emphysema, further supporting the hypothesis of pseudo-normalization of lung mechanics in CPFE [148]. Conversely, both disease components lead to reduced alveolar capillary gas exchange through either decreased capillary blood volume or alveolar membrane thickening.

Severe decrease in arterial oxygen saturation and hypoxemia at exercise even of minor intensity is very common, especially when CPFE is complicated by severe PH. In one series [8], the room air partial pressure of oxygen in arterial blood (PaO_2) decreased at exercise (20–50 W) by a mean of 1.5 ± 1.6 kPa (11.2 ± 12 mmHg). During a 6-min walk distance test, the arterial oxygen saturation measured by pulse oximetry decreased by 9 ± 6%. In another group of patients with CPFE and PH, the arterial oxygen saturation measured by pulse oximetry decreased by 15 ± 8% [25]. Hence, exercise limitation with decrease in oxygen saturation, and isolated [149] and/or severe [150] reduction in DLco or Kco contrasting with normal or near normal spirometry should raise the suspicion for CPFE syndrome. Hypercarbia occurs only very late in the disease course and patients may die from the physiological consequences of hypoxia before significant hypercarbia takes place.

As compared to patients with IPF and no emphysema, those with CPFE have higher lung volumes (FVC and TLC), generally comparable FEV_1 and residual volume (RV), lower DLco, and lower PaO_2 [4, 13, 15, 139]. The mean FEV_1:FVC is within the normal range or close to the lower limit of normal in CPFE, however it is lower than in IPF where it is usually increased (e.g., greater than 0.80) [15, 139]. Comparison of physiology between groups may be hampered by differences between studies in the severity of emphysema, fibrosis, and emphysema versus fibrosis, despite attempts to adjust for severity of fibrosis [13]. Demographics of CPFE and IPF are similar in those studies, however patients with CPFE tend to have greater tobacco smoking history [13, 15]. As expected, FEV_1 and FEV_1:FVC are preserved in patients with CPFE as compared to those with chronic obstructive pulmonary disease, who also tend to have more hyperinflation and less altered DLco [146].

Importantly, the presence of significant emphysema impacts longitudinal lung volume measurement, attenuating the effect of fibrosis on lung function parameters. Patients with CPFE experience a slower decline in FVC and DLco than IPF patients without emphysema [15, 18, 142]. Therefore, changes in FVC and DLco are not reliable indica-

tors of disease progression in patients with CPFE. It is preferable that patients with a clinical syndrome of CPFE be excluded from IPF trials [12, 134] and trials of ILD in connective tissue disease [65] that use FVC as a primary endpoint. In clinical practice, serial changes in FVC and DLco are used to monitor disease progression in IPF [33], but they are not appropriate in CPFE patients, with unfortunately no clear-cut alternate functional parameter proposed so far. In one study, a decline in FEV_1 by 10% or more at 6 or 12 months was useful to assess disease progression, and predicted a poor outcome [132]; FEV_1:FVC might also be useful [151]. Whether these observations are useful in the clinic awaits further evaluation. Overall, disease progression in CPFE is usually monitored using a combination of clinical, imaging, and multiple functional parameters, with less emphasis on FVC trends than in the monitoring of ILD without concurrent emphysema.

Imaging

Chest radiograph may show hyperlucency of the upper zones of the lungs, and diffuse parenchymal infiltrates in the lower lobes (Fig. 33.3). HRCT of the chest has dramatically enhanced the recognition of CPFE and is key to the diagnosis. Patients with CPFE present with CT radiographic features suggestive of both emphysema and pulmonary fibrosis (mostly in the lower lobes). Emphysema generally predominates in the upper lobes, but may be present in the lower zones or be admixed with fibrosis. CPFE is characterized by a wide variety of appearances on chest HRCT.

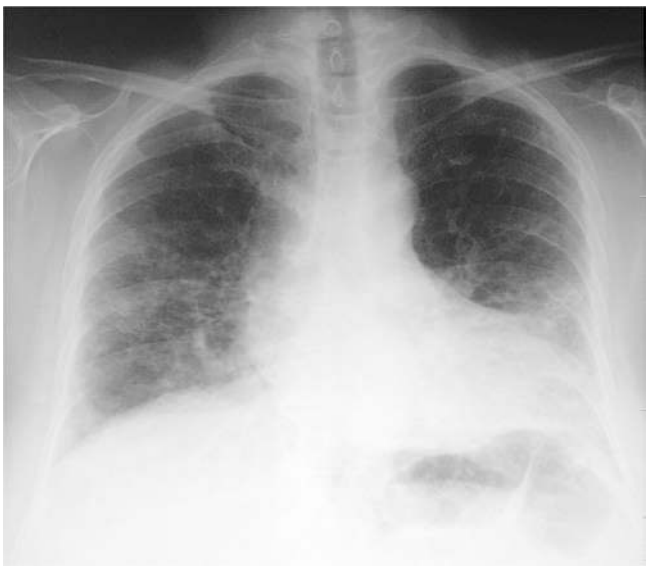

Fig. 33.3 Chest radiograph of CPFE syndrome showing hyperlucency of the upper zones of the lungs, and diffuse parenchymal infiltrates in the lower lobes (male, smoker)

Computed Tomography Characteristics and Patterns

CPFE is characterized by the presence of emphysema and interstitial fibrosis. Emphysematous foci, identified on HRCT as a region of low attenuation not bounded by visible walls [152], can be categorized as centrilobular, paraseptal, or panacinar [153]. Fibrosis on chest HRCT is identified as regions of increased parenchymal attenuation, with reticulation and/or ground-glass opacities, variably associated with honeycombing, traction bronchiectasis and/or volume loss. A majority of patients have an HRCT pattern of UIP [8], however, other patterns have been reported on imaging and/or histopathology [8, 154–157] (Table 33.3). Mild to moderate ground-glass attenuation is more prevalent in CPFE than in typical IPF patients [8], likely corresponding to NSIP [156] or to various smoking-related ILDs such as desquamative interstitial pneumonia [154] or respiratory bronchiolitis-associated ILD. Therefore, not all patients with (tobacco-related) CPFE have IPF [12], and not all patients with CPFE in the setting of connective tissue disease have a pattern of UIP [26].

In the seminal series [8], interstitial changes were characterized by honeycombing (95%), reticulation (87%), traction bronchiectasis (69%), and architectural or bronchial distortion (39%), predominating in the lower lung zones and in subpleural areas. Non-prominent ground-glass attenuation

Table 33.3 Main radiological and histopathological patterns in patients with CPFE. Several patterns or features may be combined in one individual

Radiological patterns of emphysema	Paraseptal
	Centrilobular
	Panacinar
Radiological patterns of interstitial lung disease	Usual interstitial pneumonia (UIP)
	Fibrotic nonspecific interstitial pneumonia (NSIP)
	Desquamative interstitial pneumonia (DIP)
	Respiratory bronchiolitis-interstitial lung disease (RB-ILD)
	Indeterminate fibrotic pattern
	Admixed fibrosis and emphysema
Histopathological patterns	Usual interstitial pneumonia (UIP)
	Nonspecific interstitial pneumonia (NSIP)
	Desquamative interstitial pneumonia (DIP)
	Respiratory bronchiolitis-interstitial lung disease (RB-ILD)
	Smoking-related interstitial fibrosis (SRIF), airspace enlargement with fibrosis (AEF), RB-ILD with fibrosis[a]
	Indeterminate fibrotic pattern

[a] These terms are used to describe overlapping patterns of fibrosis linked to cigarette smoking

was present in two thirds of the patients. Some degree of centrilobular emphysema was present in 97% of the patients [8, 123]. In addition, paraseptal emphysema present in 93% of patients with CPFE represented the predominant type of emphysema in more than half of patients [8]. Importantly, paraseptal emphysema seems to be more frequent in CPFE than in COPD [130], and may actually be considered a hallmark of the syndrome [12, 123]. Panacinar emphysema is seldom observed. Dilatation of pulmonary artery suggestive of PH may be present at HRCT.

Thick-Walled Large Cysts

One peculiar pattern observed in CPFE is that of thick-walled large cysts (or "air spaces with fibrotic walls") of the lower zones of the lungs [26, 65, 158]. Thick-walled large cysts are frequently observed in areas where reticulation is present. They are larger than 2.5 cm in diameter and delimitated by a wall at least 1 mm thick. They may be associated or not with typical honeycombing, from which they differ by the larger size of the cysts and lack of clustering, whereas honeycombing corresponds to clustered, cystic air spaces, 3–10 mm and up to 2.5 cm in diameter [152]. They may be associated with more extensive emphysema at imaging [158]. Thick-walled large cysts likely result from the development of pulmonary fibrosis in the setting of emphysematous lung, with enlargement of the cysts due to retraction forces in fibrotic lung [147, 159]. Enlargement over time of thick-walled large cysts has been described [158]. They are considered as one feature of the CPFE syndrome [26], and may often correspond to histopathological lesions of smoking-related interstitial fibrosis (SRIF) [65, 113, 158]. The evolution of these thick-walled large cysts is yet to be described.

Imaging Phenotypes

Due to the high heterogeneity of imaging in patients with CPFE, attempts were made to identify distinct imaging phenotypes [147] including:

1. emphysema in the upper zones and fibrosis in the lung bases, with no or little overlap of emphysema and fibrosis in between (separate processes) (Fig. 33.4);
2. progressive transition from emphysema lesions to fibrosis, with significant overlap or admixture in mid areas (Fig. 33.5);
3. conspicuous paraseptal emphysema with predominant subpleural bullae/cysts with thickened walls (Fig. 33.6).
4. the pattern of thick-walled large cysts (Fig. 33.7) [26], which may overlap with that of predominant paraseptal emphysema.

In addition, a number of observations do not fit into one of the above categories [147]. When adjusting for severity of fibrosis, patients with a pattern of predominant paraseptal emphysema had higher (e.g., normal) FEV_1:FVC and lower FVC and TLC values, with similar DLco, as compared to those with separate processes and progressive transition between emphysema and fibrosis [147]. In one study, emphysema admixed with fibrosis was associated with preserved lung volumes, while cases of CPFE with emphysema distant from fibrosis on HRCT were associated with more pronounced alteration of DLco [111]. However, whether these subgroups have physiological relevance, and whether the pattern of predominant paraseptal emphysema really is associated with preserved spirometry, as shown in patients with chronic obstructive pulmonary disease [160], warrant confirmation.

A pattern of UIP on HRCT is associated with greater mortality as compared to non-UIP patterns of ILD in CPFE [16]. In contrast, a pattern of admixed fibrosis and emphysema, suggestive of SRIF, may be associated with a better prognosis [113]. Further study is needed to decipher the potential clinical and physiologic relevance of imaging phenotypes in CPFE, especially with regard to outcome.

Pitfalls

Interpretation of HRCT imaging is particularly difficult in patients with ILD and concurrent emphysema, owing to difficulties to ascertain honeycomb changes in patients with associated emphysema. In other words, association of a pattern of NSIP and emphysema [156], with small thick-walled cystic changes, may falsely resemble honeycombing at HRCT [157], a situation sometimes coined "possible honeycombing" [161]. Presence of emphysema is one of the main reasons for disagreement between radiologists in the HRCT assessment of honeycombing [162]. Because the international criteria for the diagnosis of IPF [163] are largely based on HRCT imaging and especially the presence of honeycombing to define the UIP pattern, particular attention must be exerted to distinguish honeycombing from non-UIP interstitial changes with admixed emphysema, especially when emphysema is visible in the upper zones. Paraseptal emphysema is constituted by a single row of subpleural cystic spaces preferentially in the upper zones, contrasting to the clustered subpleural cysts (more specific if two rows or more) in honeycombing that predominates in the lung bases [164].

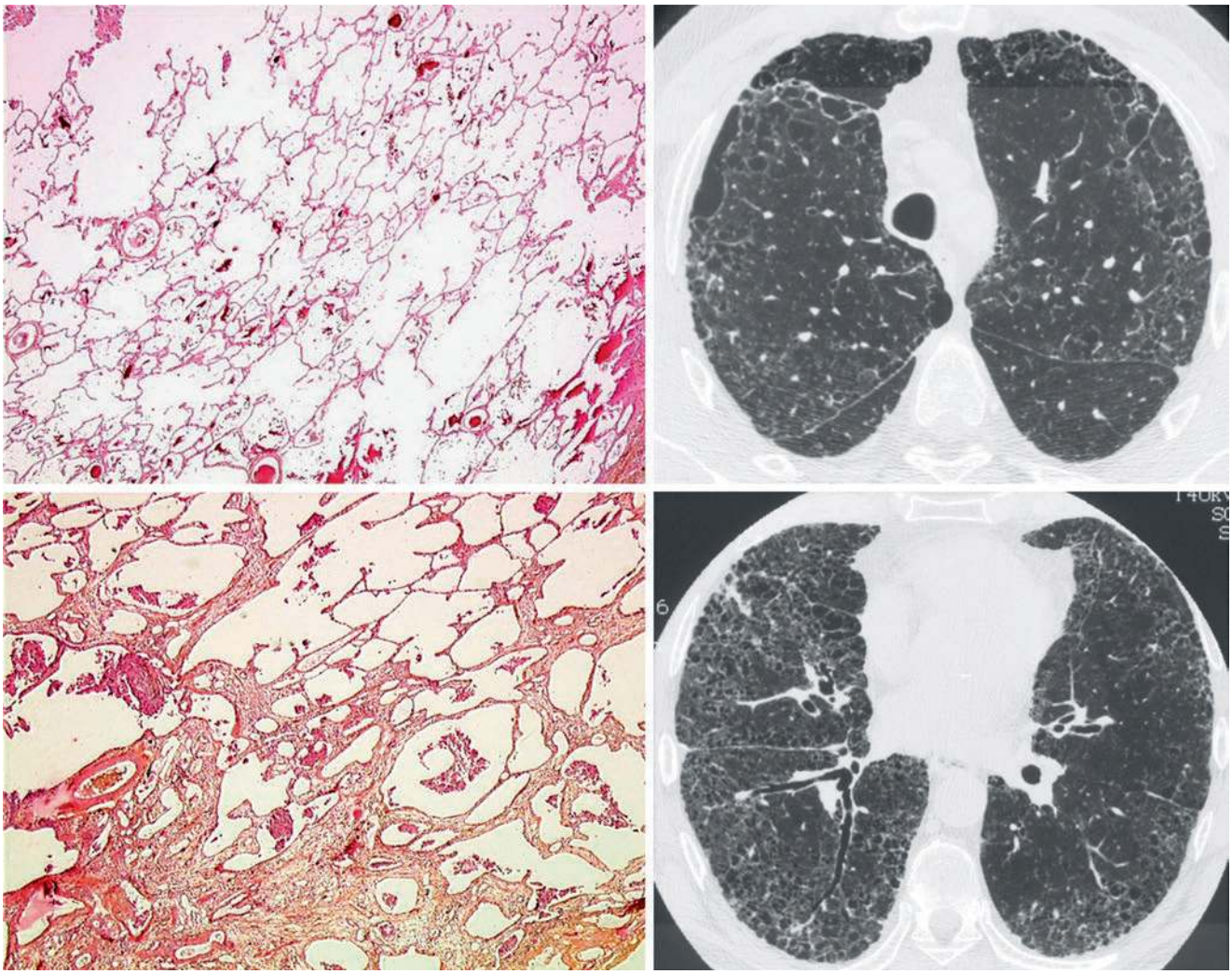

Fig. 33.4 CPFE syndrome with centrilobular emphysema and usual interstitial pneumonia (male, smoker). Upper left panel: lung biopsy in right upper lobe showing centrilobular emphysema; upper right panel: chest HRCT at the level of the trachea showing moderate centrilobular emphysema, along with reticular changes; lower left panel: lung biopsy in right lower lobe showing usual interstitial pneumonia pattern, with interstitial fibrosis and architectural distortion; lower right panel: chest HRCT in lower lung zones showing usual interstitial pneumonia pattern, with reticulation, traction bronchiectasis, honeycombing, and some ground-glass attenuation. Pathology slides courtesy of Dr Lara Chalabreysse, Lyon (France)

Quantification of Emphysema Extent

Radiographic quantification of emphysema features is necessary for research and to assess whether classification criteria for CPFE clinical syndrome (see below) may be met. Quantification of emphysema extent (over whole lung volume) in patients with CPFE mostly relies on semi-quantitative visual HRCT assessment. It may be challenging, however, with interobserver variation. Computer-based measurement of lung density is poorly suited in CPFE due to difficulties in differentiating honeycomb cysts from emphysema. Emphysema thresholds used to characterize CPFE on imaging vary in published studies. An ongoing international task-force proposes to use a threshold of 5% emphysema extent for a research definition of CPFE, and a threshold of 15% emphysema extent to define CPFE clinical syndrome. A minimal threshold extent of lung fibrosis on HRCT imaging is rarely used in CPFE, however interstitial lung abnormalities [165] (in the absence of formal ILD) associated with emphysema should not be described as CPFE.

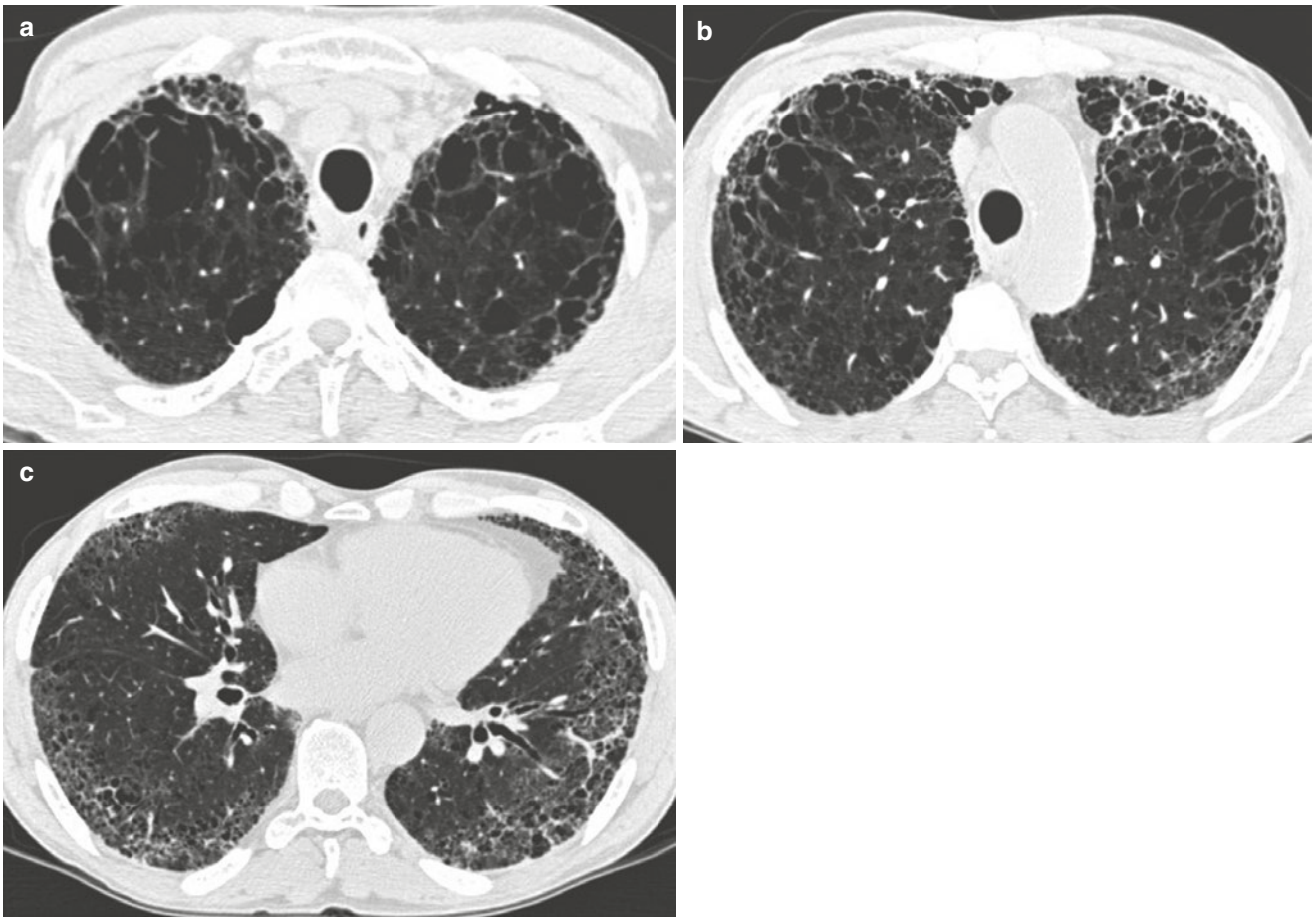

Fig. 33.5 CPFE syndrome at chest HRCT with centrilobular emphysema and usual interstitial pneumonia pattern, progressive transition phenotype (male, smoker). (**a**) upper lobes showing centrilobular emphysema predominantly in anterior areas, with thickening of the interlobular septa; (**b**) mid regions of the lungs, showing admixture of centrilobular emphysema and fibrosis; (**c**) lower zones showing usual interstitial pneumonia pattern with reticulation, traction bronchiectasis, some honeycombing, and superimposed ground-glass attenuation, predominating in the posterior areas

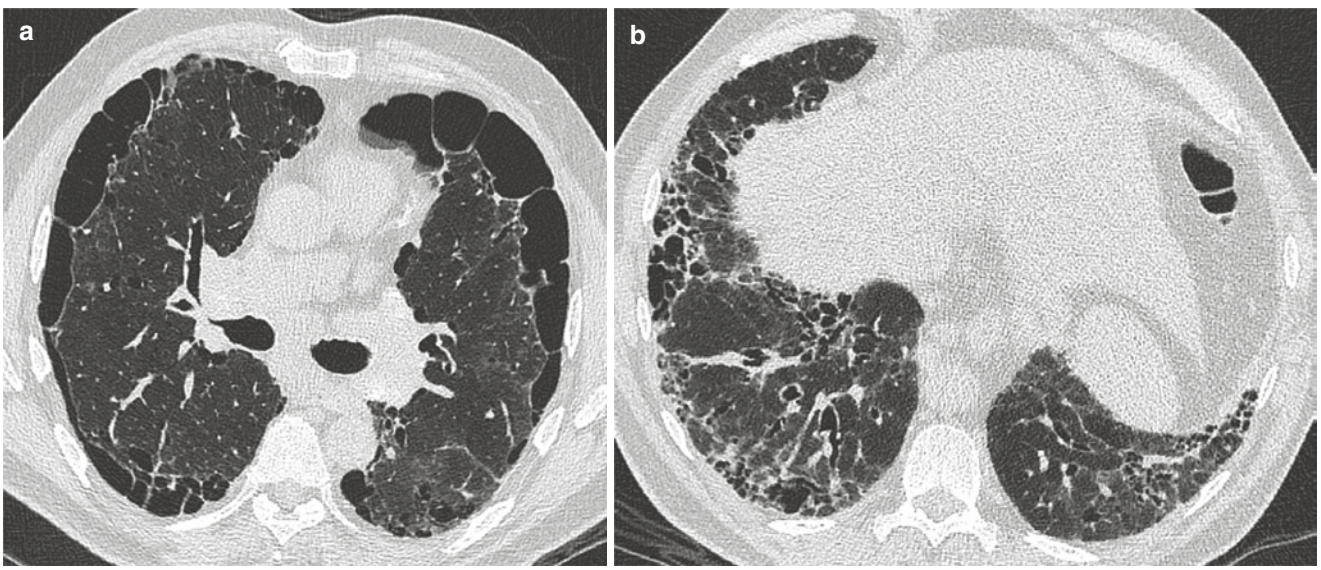

Fig. 33.6 CPFE syndrome at chest HRCT with predominantly paraseptal emphysema (male, smoker). (**a**) upper lobes showing predominantly paraseptal emphysema, with mild thickening of the interlobular septa; (**b**) lower zones showing fibrotic changes with honeycombing, traction bronchiectasis, and reticulation, predominating in the right lower lobe

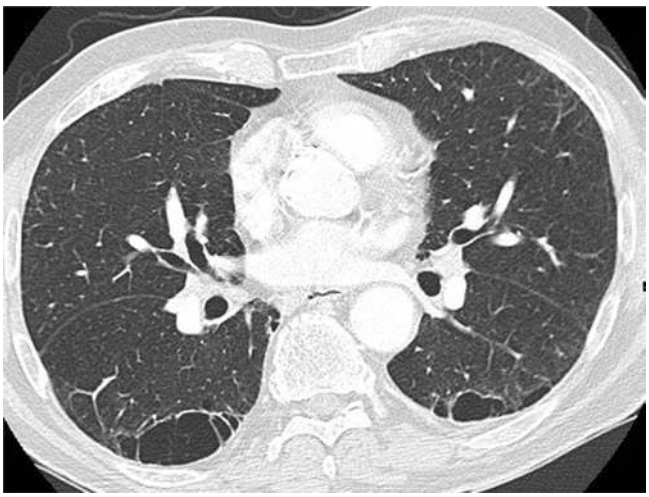

Fig. 33.7 Chest HRCT showing thick-walled large cysts (male, ex-smoker). In this example, large subpleural cysts are relatively isolated, with little reticulation in the area surrounding the cysts. Septa are visible inside the right lower lobe cyst

Pathology

Due to emphysematous changes, frequent comorbidities, and severity of gas exchange impairment, very few patients with CPFE at imaging are subjected to lung biopsy by video-assisted thoracoscopic surgery. Therefore, only limited and likely skewed data are available regarding lung pathology in patients with CPFE, consisting of small series of autopsy cases or explants [158, 166, 167]. Patterns of fibrosis observed in patients with CPFE are histologically heterogeneous [168, 169].

Histopathologic findings are dominated by the UIP pattern (Fig. 33.8), and commonly by overlapping patterns of smoking-related ILD and pulmonary fibrosis, including respiratory bronchiolitis-associated ILD, desquamative interstitial pneumonitis, and Langerhans cell histiocytosis (Table 33.3) [8, 24, 154–156, 170]. Due to the presence of emphysema, and to the frequent overlap of smoking-related

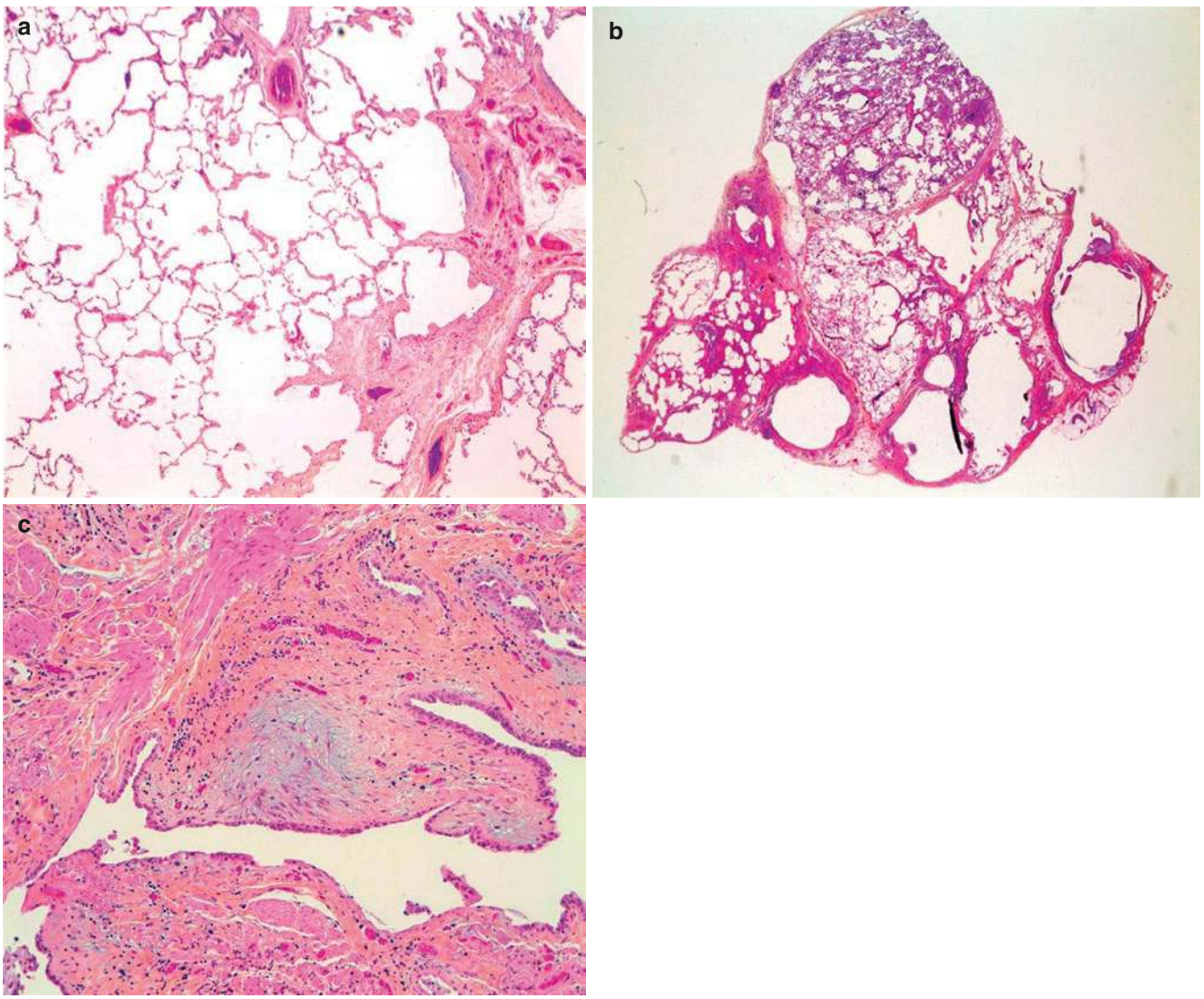

Fig. 33.8 Lung pathology in a patient with the CPFE syndrome. (**a**) emphysema adjacent to interstitial fibrosis (upper right lobe); (**b**) dense fibrosis with subpleural pathological honeycombing (lower right lobe, low magnification); (**c**) fibroblastic focus in an area of dense fibrosis, at the center of the slide (lower right lobe, high magnification). (Courtesy of Pr Françoise Thivolet-Béjui, Lyon (France))

abnormalities, classifying subtypes of pulmonary fibrosis may be challenging in the setting of CPFE [8, 167].

In an autopsy series of 22 cases including 15 (68%) with a UIP pattern at HRCT—and 19 with lung cancer—a pathological pattern of UIP was observed in all cases [158]. Honeycombing coexisting with emphysema was present in half of the patients. Interestingly, thick-walled large cysts at imaging corresponded pathologically to thick-walled cystic lesions lined by bronchiolar epithelium, located in the centriacinar/centrilobular region, involving one or more acini, with emphysematous changes and enlargement of membranous and respiratory bronchioles, dense collagen fibrosis of the walls, and occasional fibroblastic foci, surrounded by honeycombing and normal alveoli. Thick-walled large cysts were not observed in IPF without emphysema [158]. Non-prominent bronchiolocentric fibrosis was occasionally present.

Histopathology of lung specimens in patients with emphysema has demonstrated thickened interstitium in addition to enlargement of alveolar spaces [171]. Excess of collagen and elastin deposition was present in the interstitium at electron microscopy, especially in septal walls of diseased areas [171]. Clinically occult interstitial fibrosis is surprisingly common in lobectomy specimens in smokers [172]. These abnormalities have been described with various terminologies with likely overlapping features [173]: "smoking-related interstitial fibrosis" (Figs. 33.9 and 33.10) [174], "clinically occult interstitial fibrosis" [172], "airspace enlargement with fibrosis" [175], "fibrosis superimposed on emphysema" [173], "respiratory bronchiolitis-associated ILD" [176], "respiratory bronchiolitis-associated ILD with fibrosis" [170], and unclassifiable smoking-related interstitial fibrosis [172]. Such histopathological changes may only rarely be associated with physiological or radiological features of an ILD [173]. For the pathologist, the further presence of tobacco-laden alveolar macrophages is helpful as an indicator that the fibrosis is likely related to smoking and "superimposed on emphysema" [173]. Collectively, these

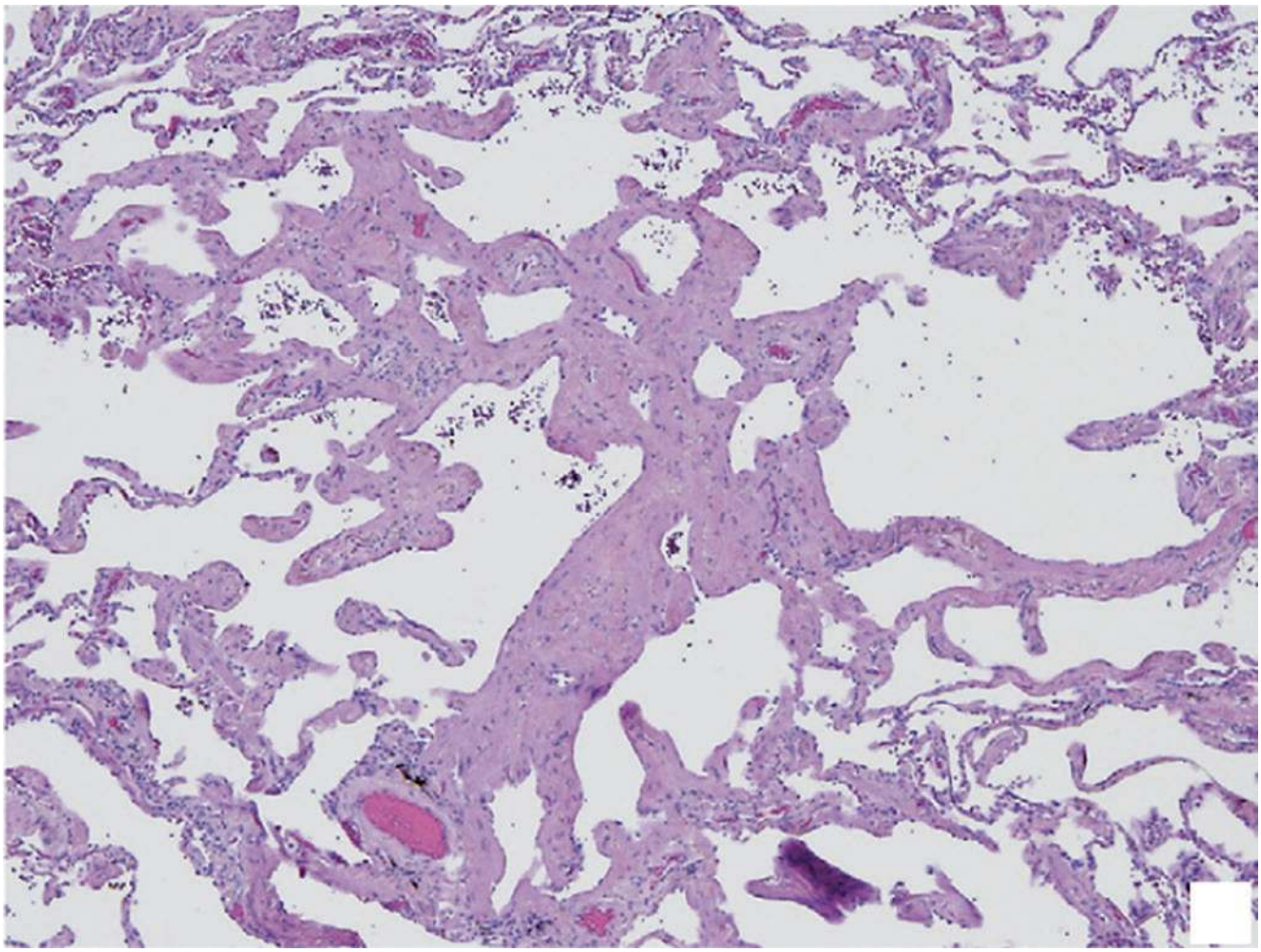

Fig. 33.9 Smoking-related interstitial fibrosis. Severe interstitial fibrosis involving deep parenchyma in a centrilobular distribution associated with emphysema. Very little inflammation is present. (From Katzenstein AL et al., figure 2, panel B, [172] with permission)

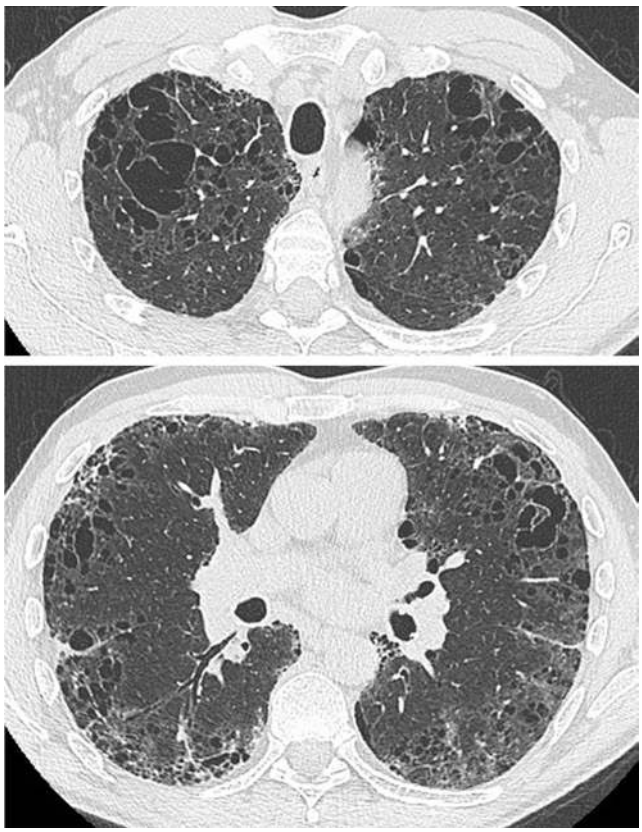

Fig. 33.10 Chest HRCT in a patient with smoking-related interstitial fibrosis at histopathology. Upper panel: upper lobes demonstrating centrilobular emphysema. Lower panel: combination of fibrotic interstitial lung disease with ground-glass attenuation, suggestive of desquamative interstitial pneumonia, admixed with cystic changes distant to the pleura and with thickened walls, suggestive of smoking-related interstitial fibrosis

observations suggest that remodeling of the alveolar interstitium takes place in patients with predominant emphysema, even in the absence of ILD changes at imaging, further suggesting that emphysema with mild fibrosis of alveolar walls only at the histopathologic level on the one hand, and overt CPFE syndrome on the other hand, may be part of a continuum of smoking-related lung disease.

Indeed, SRIF is a distinctive pattern of fibrosis observed in CPFE and linked to cigarette smoking. Described by A. L. Katzenstein [113, 167, 172, 174], SRIF is characterized by densely eosinophilic collagen deposited in expanded alveolar septa with preservation of lung architecture and little or no inflammation. It overlaps with previous descriptions of airspace enlargement with fibrosis [175, 177, 178], respiratory bronchiolitis-associated ILD with fibrosis [170], respiratory bronchiolitis with fibrosis [179], and desquamative interstitial pneumonitis [174]. SRIF may be frequently combined with paraseptal emphysema, likely accounting for the "thick-walled cystic lesions" observed on HRCT that are unique to CPFE and distinct from the honeycomb cysts of UIP [65, 113, 158].

Extensive vascular changes (intimal thickening, medial hypertrophy, and occasionally plexiform lesions) are more frequent in CPFE than in IPF or emphysema alone [166], and may involve emphysematous, fibrotic, and relatively preserved parenchyma. Malignancy, especially squamous cell carcinomas, is also not uncommon in CPFE [105].

Diagnosis

CPFE syndrome is defined by the combined presence of emphysema (generally predominating in the upper lobes) and pulmonary fibrosis (mostly in the lower lobes). Lack of consensus on criteria for CPFE has limited our ability to compare cohorts and draw consistent conclusions about the features, outcomes, and optimal management of these patients [180]. The role of multidisciplinary discussion has not been formally studied in CPFE but is likely as important as in IPF [163].

The following diagnostic criteria used in the seminal description of the CPFE syndrome and later series [8, 25, 26] comprised: (1) "conspicuous" emphysema (centrilobular and/or paraseptal) defined as well-demarcated areas of low attenuation delimitated by a very thin wall (≤1 mm) or no wall; and (2) bibasilar reticular abnormalities with basal and subpleural predominance, traction bronchiectasis and/or honeycombing, and with minimal ground-glass opacities on HRCT scan. Although not based on semi-quantification of emphysema, this rather simple approach for diagnosing emphysema (e.g. noticeable without quantification of imaging features) has revealed to select patient populations with very reproducible physiology [8, 25, 26].

However, such criteria do not specify what extent of emphysema and fibrosis at imaging is needed to classify an individual has having CPFE rather than isolated IPF (or emphysema with no significant ILD), which hampers reproducibility and research. Several studies have therefore defined CPFE as IPF (according to international criteria for the diagnosis of IPF at the time) with associated emphysema at imaging, using various thresholds or definitions for emphysema, including emphysema being notable or at least equivalent in extent to the fibrosis ("moderate emphysema") [132]; or IPF with emphysema score ≥4/24 and fibrosis score ≥4/24, with scores based on estimates of the percentage of low attenuation areas (or of areas with reticulation/honeycombing) at three anatomic levels in both lungs (with emphysema and fibrosis considered significant when present in over half of the total lung fields) [148]; or IPF with >10% of the lung affected with emphysematous changes [21]; or IPF with total emphysema score ≥10% [13], a thresholds that corresponds to GOLD stage II or worse in patients with isolated chronic obstructive pulmonary disease; or fibrotic ILD combined with emphysema using a specific threshold of emphysema

extent of >5% [131, 142], >10% [13, 21, 181–183], >15% [130], >20% [184], or >25% [167] of total lung volume. >5%, 10%, 15%, 20% or 25% of total lung volume.

An ongoing international taskforce proposes a common terminology, and provisional definition and classification criteria (Table 33.4). CPFE is defined as the combination of emphysema and any subtype of fibrosing ILD. Emphysema predominates in the upper lobes but may be present in the lower zones or be admixed with fibrosis. When reporting CPFE in the individual patient, it is useful to describe the radiologic and, if available, the histopathologic pattern, as well as the etiological context. As an example, a case with UIP on HRCT and emphysema in a smoker may be described as smoking-related "CPFE—radiologic UIP." A case with fibrotic NSIP on biopsy and emphysema may be described as idiopathic "CPFE—histologic NSIP." A case of UIP pattern and emphysema on HRCT in a non-smoker with rheumatoid arthritis may be described as "rheumatoid arthritis-associated CPFE—radiologic UIP." Thresholds of emphysema extent are proposed. The *research definition* for CPFE was developed to enable future research and uses a threshold of 5% emphysema extent; and the provisional classification criteria of the CPFE *clinical syndrome* was developed to delineate a scenario which may serve clinicians managing patients with CPFE, and use a threshold of 15% emphysema extent on HRCT.

Table 33.4 Proposed *research definition* of CPFE (to serve research purposes) and classification criteria of CPFE *clinical syndrome* (intended to have clinical relevance)

***Research definition* of CPFE**	Coexistence of both pulmonary fibrosis and emphysema
	Patients must have both criteria on HRCT:
	• Emphysema of any subtype at HRCT defined as well-demarcated areas of low attenuation delimitated by a very thin wall (≤1 mm) or no wall[a, b, c] and involving at least 5% of total lung volume[d]
	• Lung fibrosis of any subtype[e]
Classification criteria of CPFE *clinical syndrome*	Patients must have CPFE (see above) and one or more of the following:
These additional criteria serve research purposes, and may be considered depending on the objective of the study	• Emphysema extent ≥15% of total lung volume[d, f]
	• Relatively preserved lung volumes and airflow with very or disproportionately decreased DLco, especially in patients with limited extent of HRCT abnormalities, and in the absence of pulmonary hypertension
	• Precapillary pulmonary hypertension considered not related to the sole presence of emphysema (FEV_1 > 60%), fibrosis (FVC > 70%), or the etiological context (e.g. absence of connective tissue disease).

CPFE combined pulmonary fibrosis and emphysema, *DLco* diffusion capacity for carbon monoxide, *FEV_1* forced expiratory volume in 1 s, *FVC* forced vital capacity, *HRCT* high resolution computed tomography, *ILD* interstitial lung disease

[a] Emphysema generally predominates in the upper lobes but may be present in other areas of the lung or may be admixed with fibrosis

[b] Emphysema may be replaced by thick-walled large cysts greater than 2.5 cm in diameter ("CPFE, thick-walled large cysts variant")

[c] Surgical lung biopsy is *not required* if the HRCT pattern is diagnostic, however, CPFE is suggested if lung biopsies show emphysema and any pattern of pulmonary fibrosis; emphysema can then be quantified on HRCT

[d] Emphysema extent is assessed visually by an experienced radiologist. Emphysema extent <5% is unlikely to impact physiology or outcome, and is more open to interobserver disagreement

[e] Signs of fibrosis on HRCT in a patient with ILD include architectural distortion, traction bronchiectasis, honeycombing and volume loss. Caution must be exerted for the identification of honeycombing in patients with associated emphysema. Ground-glass attenuation may be present. Interstitial lung abnormalities [165] are not sufficient to support the diagnosis of CPFE

[f] Emphysema extent greater than 15% is associated with relatively stable FVC over time. Several studies have used a 10% threshold, however association with outcome and FVC has not been demonstrated

One limitation of these criteria is that they require the assessment of emphysema extent on HRCT. In the future, diagnostic criteria for CPFE may be refined, and the assessment of whether emphysema is clinically significant in a patient with fibrotic ILD, e.g. whether criteria are met to consider CPFE clinical syndrome, may be supported by physiologic criteria. Indeed, pulmonary function tests may actually contribute to the diagnosis of CPFE when demonstrating a typical functional profile, with preserved physiology and decreased DLco, especially in patients with mild imaging abnormalities. When present, thick-walled large cysts may contribute to the recognition of the syndrome. Similarly, precapillary PH in a patient with suspected CPFE may be considered as an additional clue to the diagnosis, as it is its most frequent complication present in about half of the patients. Conversely, CPFE may be diagnosed at an early stage as a result of screening for lung cancer [138, 185, 186], as described for IPF.

CPFE Is a Syndrome

CPFE is considered a syndrome based on distinct clinical features (clinical utility), and pathogenetic considerations and to facilitate further potentially crucial pathogenetic research (pathogenic utility). The main clinical arguments in favor of CPFE being a syndrome include differences in outcome between patients with CPFE and those with isolated IPF (e.g. greater mortality and greater risk of PH for a given extent of fibrotic ILD), increased risk of lung cancer as compared to isolated IPF, implications for monitoring of disease progression which cannot be reliably based on FVC, and implications for clinical research (FVC is not a reliable endpoint in patients with IPF combined with emphysema). Pathogenic arguments in favor of CPFE being a syndrome

include the clustering of pulmonary fibrosis and emphysema (e.g. more frequent presence of emphysema on HRCT than expected in several fibrotic ILDs) [17, 35, 81, 156], and the existence of multiple pathways common to both pulmonary fibrosis and emphysema. However, whether CPFE might correspond to a single biologically unique entity in a proportion of cases warrants further study.

Biology

As in IPF and as observed in the general population, a minority of patients may have antinuclear antibodies, which in the absence of systemic clinical features have limited clinical relevance. As discussed above, anti-neutrophil cytoplasmic antibodies may also be found [14]. The serum levels of KL-6 (Klebs von der Lungen-6) and SP-D (surfactant protein-D) are elevated [187].

The differential cell count of bronchoalveolar lavage fluid is similar in CPFE to that of IPF and does not contribute significantly to the diagnosis [8, 22]; bronchoalveolar lavage is useful in the setting of acute worsening or suspicion of lung infection. Chemokines implicated in the recruitment of neutrophils (ENA-78/CXCL5 and IL-8/CXCL8) are elevated in the bronchoalveolar lavage fluid as compared to IPF [22] and may contribute to the development of emphysema.

Complications and Outcome

Making the diagnosis of the CPFE syndrome is highly relevant, because the outcome and risk of complications is distinct from that of either IPF or emphysema alone. The disease course of the CPFE syndrome is often characteristic, with emphysema preceding the onset of the pulmonary fibrosis in the majority of cases [8], and a dismal prognosis. PH may occur in about half of the cases after a median of 18 months following the diagnosis of CPFE [25] (Fig. 33.11). Survival is severely reduced, with a median of 12–18 months from the onset of confirmed precapillary PH. Lung cancer may occur after a median of 2 years after the diagnosis of CPFE (from 0.6 to 11.2 years in our series [11]).

Mortality

The overall median survival in CPFE is between 2.1 and 8.5 years [8, 13, 15, 20, 21, 129, 188–190]. In CPFE and connective tissue disease, the overall survival was 100% at 1 year, 94% at 2 years, and 73% at 5 years [26]. The main causes of deaths in patients with CPFE are represented by severe PH, intractable hypoxemia, pulmonary infection, and lung cancer. The relatively preserved lung volumes in CPFE may underestimate the severity of the pulmonary fibrosis.

The main variables associated with an increased risk of death in CPFE include a lower DLco [16, 25, 183, 191–193], FVC < 50% of predicted value [21], composite physiologic index ≥45 [137, 193, 194], oxygen saturation on room air <90% [144], home oxygen use [183], pulmonary hypertension [8, 16, 21, 25, 81, 137, 183, 195], presence of UIP pattern [16, 194] or honeycombing [16, 183, 191], and increased extent of fibrosis on HRCT [144, 192]. Over the course of disease, decline of ≥10% over 12 months [132], presence of lung cancer [108, 144, 158, 183, 191, 196, 197], or acute exacerbation of fibrosis [197] are also associated with a poor prognosis.

Comparison of survival between patients with CPFE and IPF has been controversial [189], as results may vary accord-

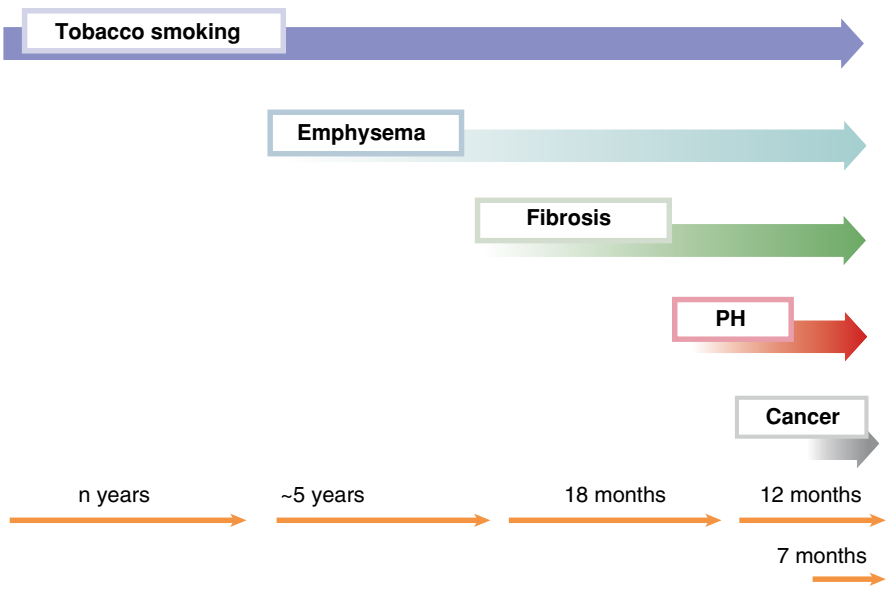

Fig. 33.11 Diagram of the main complications in tobacco-related CPFE syndrome. The median delay between emphysema and fibrosis is 5 years, and pulmonary hypertension may occur after a median of 18 months after the diagnosis of CPFE. Patients may die after a median of about 1 year from the diagnosis of pulmonary hypertension and a median of 7 months from the onset of lung cancer, with great inter-individual variability. *PH* pulmonary hypertension

ing to: (1) diagnostic criteria for CPFE, with survival in CPFE possibly confounded pathologies other than UIP especially NSIP (i.e. non-UIP CPFE); for example, the proportion of patients with NSIP was higher in the CPFE group than in the control group in one study that found better survival in CPFE than in pulmonary fibrosis without emphysema [188]; (2) difficulties in controlling for the severity of fibrosis; (3) survival time bias, with presumably earlier diagnosis due to more severe symptoms in patients with CPFE as compared to IPF after adjustment for the severity of fibrosis; patients with CPFE more frequently have chronic bronchitis than those with IPF and may seek medical attention earlier [189], which may explain why fibrosis and emphysema are inversely correlated at the diagnosis of CPFE [198]; (4) the method used to handle transplantation [189]. A composite physiologic index predicts mortality in isolated IPF and may account for disease severity [5], however, there are uncertainties regarding its use in CPFE [132]. In one series that defined CPFE as IPF (with a HRCT and/or pathological pattern of UIP) associated with emphysema, mortality was similar in patients with CPFE as compared to IPF after adjustment for the severity of fibrosis at imaging [13]. It should be emphasized that there is great variability of progression between patients with the CPFE syndrome, with individuals with slow or rapid progression of disease especially regarding the fibrosis (Fig. 33.12).

Comparison between CPFE and isolated IPF with quantification of both pulmonary fibrosis and emphysema was conducted in two retrospective cohorts of patients with IPF [111, 199], using both visual analysis to the nearest 5% [111, 199] and computer-based analysis with the CALIPER software [111]. The global disease extent on HRCT (i.e. the combined extent of fibrosis and of emphysema) and the baseline DLco both predicted mortality, reflecting the overall severity of parenchymal lung destruction [111, 199]. After correction for baseline severity using DLco, the presence or extent of emphysema did not impact survival [21, 111, 199, 200]. Overall, these data suggest that outcomes are worse for a given extent of fibrosis, when there is emphysema in addition to fibrosis, however, the risk of mortality and of developing PH does not differ in patients with both IPF and emphysema compared to those with fibrosis alone when adjusting for severity using baseline DLco or total disease extent on HRCT (e.g. total extent of fibrosis and emphysema) [19, 111, 201].

Pulmonary Hypertension

The main determinant of prognosis in CPFE is represented by PH [8, 21], which develops in up to half of patients with CPFE [8]. In various series, PH has been reported in 15–55% of patients with CPFE [8, 21, 26, 81, 151]. When present, PH may cause dilation of the pulmonary arteries at chest radiograph and HRCT. Magnetic resonance imaging may contribute to the evaluation of PH in CPFE [202], however, right heart catheterization remains the gold standard to diagnose PH.

The additional burden of emphysema, over and above a given extent of fibrosis, increases the risk of PH. However, the likelihood of PH does not differ for matched extents of disease (combined fibrosis and emphysema) on HRCT (or when adjusted for DLco) between patients with CPFE and those with fibrosis alone [19, 111].

PH in CPFE is likely due to the synergistic effect of emphysema and fibrosis on the pulmonary capillary bed, with further effects of hypoxia, possible sheer stress, and intrinsic pulmonary vascular abnormalities [203, 204]. In addition, there is accumulating evidence that tobacco smoking may directly contribute to PH [205–207], with obvious relevance in the CPFE syndrome.

Precapillary PH is defined by mean pulmonary artery pressure of 20 mmHg or greater, with pulmonary artery wedge pressure of 15 mmHg or lower, and pulmonary vascular resistance ≥3 Wood units. It is the main determinant of subsequent mortality in CPFE, with an overall probability of survival of only 60% at 1 year once confirmed by right heart catheterization [25]. Low cardiac index and high pulmonary vascular resistance are then the main determinants of shorter survival [25]. According to the World Symposium on Pulmonary Arterial Hypertension, PH is considered severe in patients with mean pulmonary artery pressure of 35 mmHg or greater, or in those with decreased cardiac index (lower than 2 L/min/m^2) [208]. In a series of 40 patients with CPFE and PH [25], 68% had a mean pulmonary artery pressure >35 mmHg [25]; 92% of patients needed long-term supplemental oxygen therapy; 15% had developed acute right heart failure after a mean follow-up of 8 ± 8 months; and death was due to hypoxemia and chronic respiratory failure in most cases. In patients with CPFE and connective tissue disease, PH mostly occurs in those with systemic sclerosis [26], a condition in which PH is frequent.

Lung Cancer

Lung cancer is increasingly recognized in patients with the CPFE syndrome (Fig. 33.13), which is hardly surprising given the increased risk of lung cancer in relation to tobacco smoking, chronic obstructive pulmonary disease, and IPF [9]. Lung cancer has been reported in 2–52% of patients with CPFE [108, 111, 112, 129, 130, 151, 181, 187, 190, 191, 209, 210]. A meta-analysis [211] found a higher risk of lung cancer in patients with CPFE (UIP and emphysema) than those with IPF alone, regardless of the extent of emphysema.

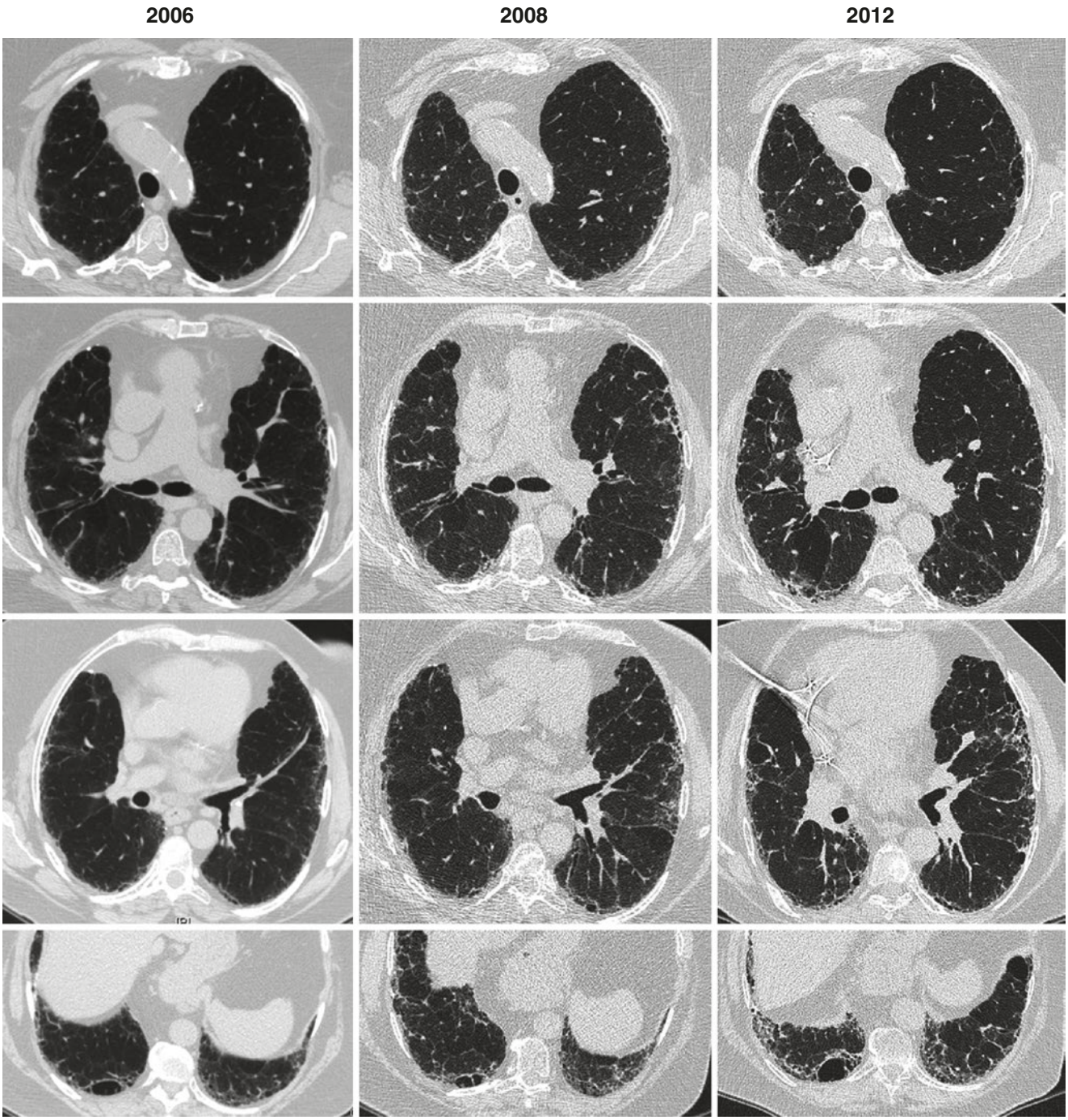

Fig. 33.12 Example of slow progression of disease in a woman with smoking-related CPFE syndrome (chest HRCT), who quit smoking at diagnosis. Only mild centrilobular emphysema is present in the upper lobes. Subpleural reticular changes predominate, which progress to a pattern of probable usual interstitial pneumonia. A thick-walled large cyst is present in the right lower lobe, which increases in size

In a series of 47 patients with lung cancer in the context of CPFE [11], all patients were men, all smokers, with a mean age of 68 years. Importantly, a pathological diagnosis was obtained in only 81% of patients, with the underlying CPFE limiting the diagnostic approach in the remaining cases due to severe functional impairment. Similarly, 43% of patients could not receive the standard of care treatment for lung cancer following international guidelines, despite a mean FVC of 87 ± 24% of predicted value, and FEV_1 of 74 ± 19% of predicted. The mean DLco was 44 ± 16% of predicted (range, 20–80), accounting for a large proportion of diagnostic and treatment limitations together with paren-

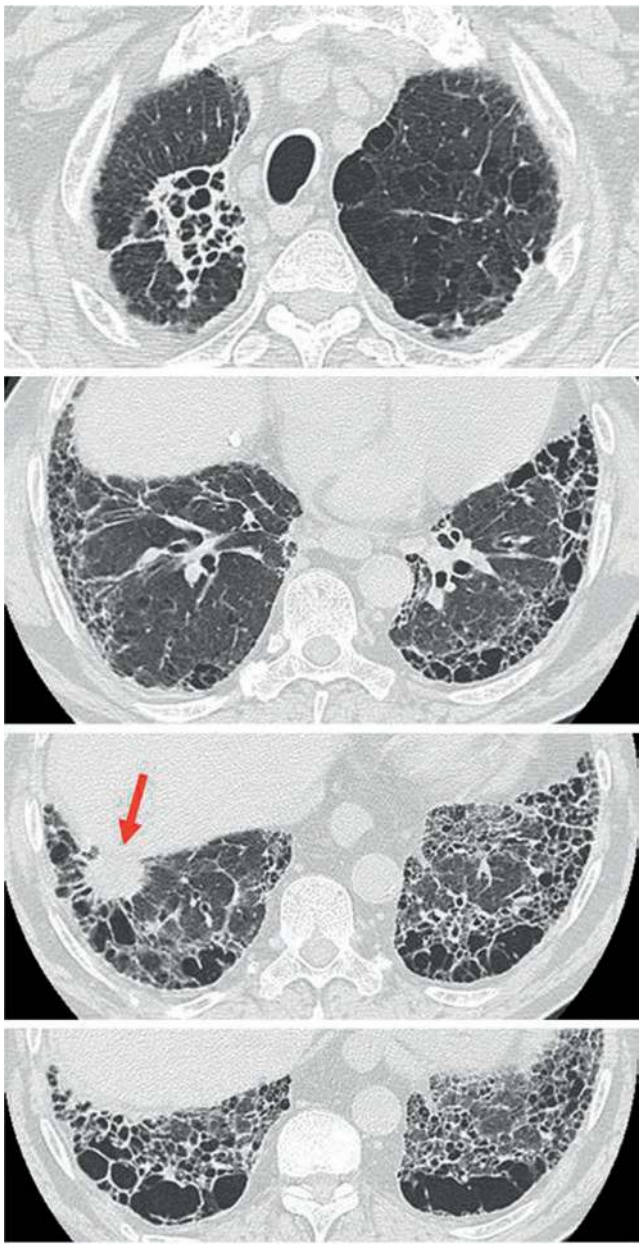

Fig. 33.13 Non-small cell lung cancer (squamous cell carcinoma) in a male patient with smoking-related CPFE syndrome (chest HRCT). Upper panel: centrilobular emphysema in the left upper lobe (and post-infectious bronchiectasis in the right upper lobe); upper middle panel: lower zones showing usual interstitial pneumonia pattern with honeycombing; lower middle panel: spiculated mass (arrow) in the right lower lobe, adjacent to honeycombing and reticulations; lower panel: thick-walled large cysts and honeycombing in the lung bases

chymal changes at imaging. The most frequent histologic type of lung cancer was squamous cell carcinoma (45% of cases) followed by adenocarcinoma (37%), whereas adenocarcinoma is the most common type of non-small cell carcinoma in Europe; the frequency of squamous cell carcinoma in CPFE may be related to heavy smoking history. Comparable histologic types were found in series from Japan [110, 130, 187, 212–219]. The majority of the lung cancers are located in the lower lobes [212, 218]. There is greater invasion and the diagnosis is made at a later stage compared to non-small cell lung cancer without CPFE [219, 220].

The molecular mechanisms underlying the carcinogenesis of lung epithelial cells in CPFE is largely unknown. A common susceptibility to emphysema, fibrosis, and lung cancer, possibly through the telomerase complex, has been hypothesized [11, 221, 222].

Among patients with lung cancer, those with CPFE seem to have a worse outcome as compared to patients with either emphysema or fibrosis [212, 219]. Acute exacerbation of fibrosis is a major complication in patients with CPFE, and may occur during treatment for lung cancer, especially following radiation therapy [11] or surgery [11, 151, 212, 223]. Acute respiratory distress syndrome may also follow chemotherapy for lung cancer [224]. These complications seem comparable to that occurring in patients with ILD especially IPF and undergoing cancer treatment, however with particularly high severity and risk of death in subjects with the CPFE syndrome and pronounced impairment of gas exchange. Stereotaxic radiotherapy has been suggested in this setting, however acute exacerbation in CPFE is largely unpredictable [11].

Acute Exacerbation of Pulmonary Fibrosis

The natural course of disease in CPFE may encompass episodes of acute exacerbation of pulmonary fibrosis [26, 151, 158, 182, 197, 212, 225]. In a series of 93 patients with CPFE, 24% developed acute exacerbation [151]. Risk factors have not been well identified in the setting of CPFE, however those identified in IPF without emphysema, especially low lung function and rapid decline 6 months after baseline, may presumably apply [226]. Interestingly, a study has demonstrated that PH at the time of evaluation for lung transplantation for IPF was associated with a high risk of subsequent acute exacerbation of IPF [227], with no other association with baseline variables being observed. In another study of IPF, presence of emphysema and low DLco were risk factors for acute exacerbation [228]. These observations suggest that patients with the CPFE syndrome may be at particularly high risk of acute exacerbation of pulmonary fibrosis.

Diffuse ground glass and/or consolidation on chest HRCT help to differentiate exacerbations of fibrosis from exacerbations of emphysema in CPFE [229]. The prognosis of acute exacerbation in CPFE might be better than that of isolated IPF [20, 225].

Other Comorbidities and Complications

Comorbidities especially related to tobacco smoking are frequent in CPFE [8]. As in IPF [230] and chronic obstructive pulmonary disease, patients with CPFE may present with cardiovascular disease (including ischemic heart disease, arterial hypertension, cerebral infarction, atrial fibrillation, etc.), diabetes mellitus, sleep apnea syndrome, gastroesophageal reflux disease, venous thromboembolism, depression, and osteoporosis. The respective frequency and contribution to morbidity and mortality has not been studied specifically in CPFE.

Management

There are no guidelines for a specific treatment of pulmonary fibrosis or emphysema in the setting of CPFE. It is unknown if treating these separate components of disease influences clinical outcomes.

General Measures and Treatment of Emphysema

Smoking cession should be strongly encouraged and is the cornerstone of treatment for emphysema. Inhaled bronchodilators may be beneficial on dypsnea and cough, and seem to be underutilized [13]. Long-term oxygen therapy is often required [231], especially when severe PH is present [8, 25]. Regular exercise and pulmonary rehabilitation may be useful for most patients with CPFE [232]. Influenza, pneumococcal, and COVID-19 vaccination are also recommended as per standard intervals, unless contraindicated [233, 234]. Patients with severe disease and especially with PH should be referred for lung transplantation [235], however, it is contraindicated in most patients by age and comorbidities [8, 13, 25].

Treatment of Pulmonary Fibrosis

Decisions about pharmacologic treatment are guided by the underlying diagnosis of fibrosing ILD [234]. Management of pulmonary fibrosis in the setting of CPFE is informed by the landmark clinical trials of nintedanib and pirfenidone [236–241]. Management of pulmonary fibrosis in CPFE generally may follow that of IPF or that of fibrosing ILD with a progressive phenotype. Antifibrotic medications may have benefit in IPF patients with CPFE, and in other forms of pulmonary fibrosis with CPFE, progressing despite management.

As most patients with significant emphysema on HRCT or significant airflow obstruction were excluded from these studies, no definite conclusion can be drawn regarding the potential efficacy of pirfenidone and nintedanib in the CPFE syndrome. It can be speculated, however, that similar efficacy may be obtained, at least in those patients with typical IPF associated with emphysema, with however less change in lung physiology over time. A post-hoc study of the INPULSIS trial that demonstrated the efficacy of nintedanib in patients with IPF, found that the presence of emphysema at baseline did not influence the study results [242]. Therapeutic trials should be designed specifically to include patients with CPFE, likely using endpoints that do not rely on physiologic surrogates such as FVC [12, 243]. Although data from the PANTHER trial have recommended against combination therapy with prednisone, azathioprine, and *N*-acetylcysteine in patients with definite diagnosis of IPF, oral corticosteroids and occasionally immunosuppressive therapy may be considered in patients with HRCT patterns more suggestive of NSIP, desquamative interstitial pneumonia, or hypersensitivity pneumonitis [234]. Gastroesophageal reflux disease when present might enhance progression of pulmonary fibrosis [244] and should be treated actively.

Management of Pulmonary Hypertension

Management of PH in chronic respiratory disease including the CPFE syndrome is mostly based on the optimal treatment of the underlying disease. A comprehensive review of PH in the setting of ILD including CPFE is beyond the scope of this chapter. Controlled data do not support the use of oral PH specific therapies in CPFE [208, 245], including endothelin receptor antagonists (bosentan, ambrisentan), phosphodiesterase-5 inhibitors (sildenafil, tadalafil), or stimulator of soluble guanylate cyclase (riociguat) [246], although uncontrolled observational studies show possible benefit from PH therapies [25, 247–251] with improvement of hemodynamic parameters, and there are encouraging secondary endpoint trends in trials using sildenafil in IPF [240, 252, 253]. Furthermore, treatment with ambrisentan and riociguat are deleterious in patients with fibrotic ILD [254, 255] and especially those with CPFE [256]. Treatment with PH drugs may occasionally worsen gas exchange in patients with chronic respiratory disease. Interestingly, nebulized treprostinil improved 6-min walk distance, decreased NT-pro-brain natriuretic peptide levels, improved FVC, and reduced the risk of clinical worsening compared to placebo in patients with ILD and group 3 precapillary PH confirmed by right heart catheterization including patients with CPFE [257, 258]; however, clinical implementation remains limited due to multiple challenges.

Further research is needed to evaluate the potential clinical benefit of PH therapy especially in patients with pre-

served spirometry, severe impairment of exercise capacity and gas exchange, exercise limitation mostly determined by the pulmonary vascular component of disease, right ventricular dysfunction, and/or severe PH.

Clinical Vignette

A 68-year-old male, ex-smoker, with a history of 48 pack-years of tobacco use, who had worked as a mason with no significant exposure to asbestos, was referred to the pulmonary clinic for severe dyspnea on exertion. He had a history of coronary heart disease, with myocardial infarction and coronary stenting 4 years prior to admission. Velcro-crackle rales of the lung bases were present at lung auscultation. The chest radiograph demonstrated mild hyperlucency of the upper zones, with hyperinflation, and reticular changes of the lower zones. Chest HRCT demonstrated both emphysema of the upper zones (centrilobular and paraseptal) and fibrosis of the lung bases, with subpleural reticulation, honeycombing, and traction bronchiectasis, with non-prominent superimposed ground-glass attenuation (Fig. 33.5). Areas of admixed pulmonary fibrosis and emphysema were observed in the mid sections of the lungs. Emphysema extent on HRCT was visually quantified by an experienced radiologist and estimated to represent 15–20% of total lung volume. Pulmonary function tests were: FVC 86% of predicted value, FEV_1 78% of predicted, FEV_1:FVC 0.68, TLC 89%, RV 117%, DLco 44%, Kco 57%, PaO_2 at rest 65 mmHg. Echocardiography showed slightly dilated right heart cavities with estimated systolic pulmonary artery pressure of 42 mmHg. No clinical signs of connective tissue disease were present, and antinuclear antibodies were negative. The patient was diagnosed with combined pulmonary fibrosis and emphysema syndrome at multidisciplinary discussion, with probable UIP pattern at HRCT, therefore corresponding to idiopathic pulmonary fibrosis combined with emphysema. Lung biopsy was not performed. Inhaled bronchodilators and an antifibrotic therapy were initiated. Fourteen months later, he was readmitted for acute right heart failure. Right heart catheterization demonstrated severe precapillary pulmonary hypertension, with mean pulmonary artery pressure of 42 mmHg, pulmonary artery wedge pressure of 12 mmHg, and cardiac index of 1.9 L/min/m^2. Sildenafil was initiated in the setting of a prospective registry, with moderate hemodynamic improvement at 3 months, and unclear clinical benefit. The patient died of acute respiratory failure 5 months after the diagnosis of pulmonary hypertension.

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34

Nonspecific, Unclassifiable, and Rare Idiopathic Interstitial Pneumonia: Acute Interstitial Pneumonia, Respiratory Bronchiolitis Interstitial Pneumonia, Desquamative Interstitial Pneumonia, Nonspecific Interstitial Pneumonia

Prince Ntiamoah, Russell Purpura, Susan Vehar, Curtis J. Coley II, Jennifer Hasvold, Lindsay A. Schmidt, Kevin R. Flaherty, and Leslie B. Tolle

Abbreviations

AIP	Acute interstitial pneumonia
ARDS	Acute respiratory distress syndrome
BAL	Broncho-alveolar lavage
DIP	Desquamative interstitial pneumonia
GGO	Ground glass opacification
HRCT	High-resolution computed tomography
ILD	Interstitial lung disease
NSIP	Nonspecific interstitial pneumonia
RB	Respiratory bronchiolitis
RB-ILD	Respiratory bronchiolitis interstitial lung disease
TPMT	Thiopurine methyltransferase
UCTD	Undifferentiated connective tissue disease
UIP	Usual interstitial pneumonia

Acute Interstitial Pneumonia (AIP)

Case

A 34-year-old woman with a history of hypothyroidism presents to her primary care doctor with a 1-week history of dry cough and myalgias. She reports a fever with a temperature of 38.4 °C 1 day prior to presentation. On exam she is mildly tachycardic, but she is not tachypneic. Her oxygen saturation is 97% on room air. Her lungs are clear to auscultation bilaterally, and she has no rashes or skin lesions. She is diagnosed with a viral upper respiratory tract infection and sent home with return precautions.

Over the next 3 days her cough persists, and she develops dyspnea with exertion causing her to present to the emergency department. She is more tachycardic and oxygen saturation is now 87% on room air. She has soft, diffuse crackles on exam. A chest radiograph demonstrates hazy opacifications bilaterally, without focal consolidation (Fig. 34.1). A

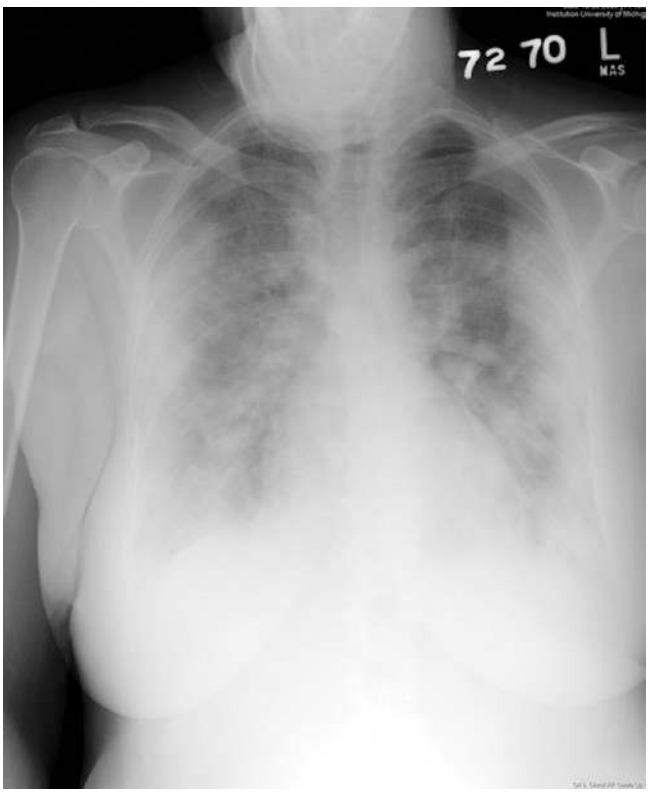

Fig. 34.1 Chest radiograph from a patient with acute interstitial pneumonia demonstrating diffuse bilateral infiltrates without focal consolidation

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pulmonary embolus protocol CT is negative for pulmonary embolus but shows diffuse patchy ground glass opacifications (GGO) without effusions (Fig. 34.2). She is admitted to the hospital and develops progressive respiratory failure requiring intubation for hypoxic respiratory failure on hospital day 2.

Her labs demonstrate a leukocytosis with a white blood cell count of 14,000 with a differential of 82% neutrophils. Urinalysis shows no evidence of infection, and blood cultures are negative. A transthoracic echocardiogram shows no evidence of increased pulmonary arterial or right ventricular pressure, and no left ventricular dysfunction. She is started on empiric broad spectrum antibiotics, but does not improve by hospital day 4 and subsequently 1 g of methylprednisolone daily is added to her regimen. A lung biopsy is performed on hospital day 6 and reveals diffuse alveolar damage. The final suspected diagnosis is acute interstitial pneumonia (AIP).

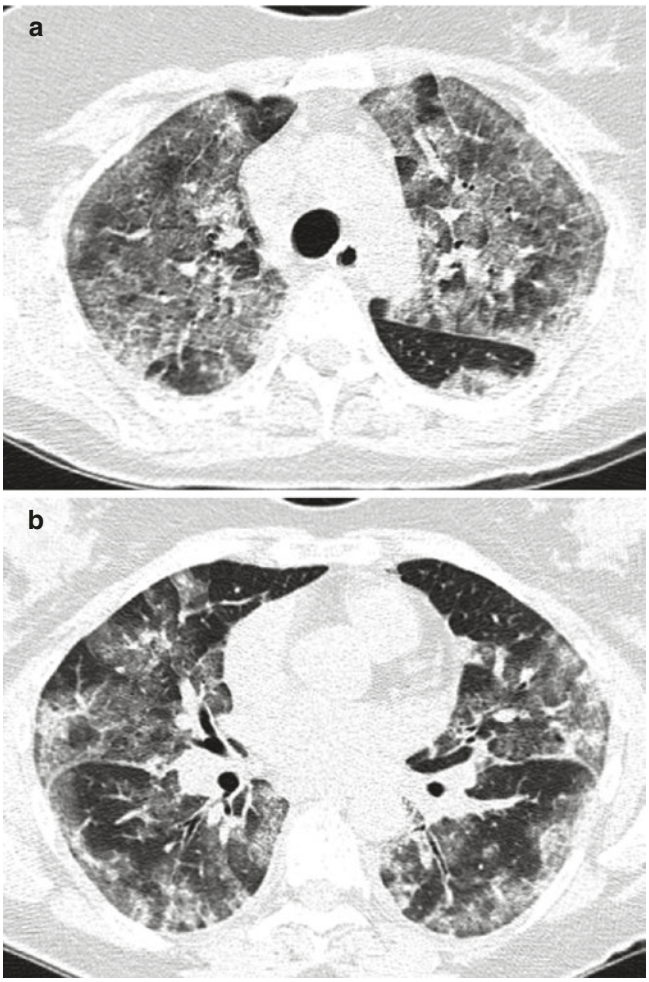

Fig. 34.2 High-resolution computed tomography images from the upper (panel **a**) and mid (panel **b**) lung fields demonstrating diffuse bilateral ground glass opacifications without consolidation or effusions

History and Definition

Acute interstitial pneumonia (AIP), also known as Hamman-Rich syndrome and first described in 1935, is an acute and fulminant form of diffuse parenchymal lung disease of unknown etiology [1, 2]. Characteristically it inevitably results in severe hypoxemic respiratory failure requiring mechanical ventilation with an estimated mortality rate greater than 50%. The presentation, both clinically and radiographically, is identical to acute respiratory distress syndrome (ARDS) and may represent a subset of idiopathic ARDS. AIP is one of six categories within the American Thoracic Society (ATS)/European Respiratory Society (ERS) of Idiopathic Interstitial Pneumonias (IIP) major classification with the latest update in 2013 [3].

By definition, AIP is an idiopathic respiratory disease with bilateral infiltrates and histological finding of diffuse alveolar damage (DAD). AIP is a diagnosis of exclusion and must have the proper work up, which is further discussed below [2].

Epidemiology

AIP is a rare lung disease that is likely underdiagnosed or misclassified as ARDS. The definition, which requires a lung biopsy, most likely precludes the diagnosis in most cases. Review of the literature suggests that an individual academic institution may diagnose only a few cases a year [4–6].

AIP generally affects previously healthy male and female patients equally. Most individuals are over the age of 40, but both pediatric and the elderly can be affected [6]. No clear risk factors have been convincingly identified in the literature, including tobacco exposure.

Presentation

Patients present within a week of developing a dry cough, dyspnea, and fever. Many mistake the symptoms for a viral upper respiratory tract infection. As the disease progresses, shortness of breath becomes the hallmark feature with room air hypoxemia [2, 5, 6]. Most patients will need non-invasive ventilation or mechanical ventilation (MV) with one case series from Vourlekis et al. noting mean duration of MV of 20 days [6]. Given the relatively nonspecific historical features, this condition is commonly misdiagnosed early on as pulmonary embolism, infection or congestive heart failure [2, 7].

Physical exam findings are relatively nonspecific, including tachypnea and diffuse crackles. Individuals with clubbing of fingers would suggest another chronic process and

unlikely to be AIP [8, 9]. All patients should be examined for joint, muscle or cutaneous abnormalities that might suggest the presence of connective tissue disease.

Virtually all patients with fulminant AIP are too ill to perform pulmonary function testing, which would likely reflect a restrictive pattern with reduced DL_{CO} [10]. Unlike ARDS, patients with AIP will not be in profound shock requiring vasopressors, or showing signs of multi-organ failure.

Diagnostic Evaluation

Infectious and cardiac etiologies of respiratory failure must be excluded. Thorough evaluation with microbiological and serological testing evaluating for respiratory viruses, blood cultures, and sputum cultures. Frequently bronchoalveolar lavage (BAL) or mini-BAL is required to exclude atypical infections such as pneumocystis pneumonia (PJP), legionella, mycoplasma, and fungal pneumonias. Typical thoracic imaging studies including chest X-ray and high-resolution computed tomography (HRCT) are appropriate. A transthoracic echocardiogram to evaluate for left ventricular dysfunction and valvular disease, along with troponin and brain natriuretic peptide are crucial. Basic labs like comprehensive metabolic panel and complete blood count with differential to evaluate for another organ damage can help trajectory of clinical course. Most patients will have a leukocytosis at time of presentation [6, 10].

Patients or surrogates require a thorough medical history focused on medications (e.g. chemotherapy, over-the-counter medications, supplements, and herbals), radiation exposure, social history (e.g. recreational drugs, toxic inhalants or occupational exposures), and any history of connective tissue diseases. A positive rheumatological antibody with the appropriate phenotype might be worrisome for an underlying connective tissue associated-ILD. A positive dsDNA or anti-smith antibody would be consistent with SLE. Positive anti-Scl-70 arises suspicion for systemic sclerosis, whereas a rheumatoid factor or cyclic citrullinated peptide suggests rheumatoid arthritis. Positive anti-Jo antibodies in conjunction with elevated CPK, aldolase and ALT would be consistent with an anti-synthetase syndrome [11].

BAL findings are indistinguishable from ARDS and typically include increased total cells, red blood cells, hemosiderin, and neutrophils [12]. These findings while supportive are not diagnostic, and the chief utility of a BAL is to exclude other etiologies of respiratory failure, like diffuse alveolar hemorrhage syndromes or acute eosinophilic pneumonia. A clinical decision to obtain diagnostic tissue via transbronchial, video-assisted thoracoscopic surgery (VATS), and/or open lung biopsy must be weighed carefully. Surgical lung biopsy specimen can aid in diagnosis like granulomatous diseases (sarcoidosis), certain infections or malignancy. However, these procedures can come with higher risk for mortality with varying degree of alterations in therapeutic plans [13–15].

Radiology

Common findings on HRCT are similar to ARDS, including diffuse GGO, air-space consolidation, interlobular septal thickening, and traction bronchiectasis. Patients with AIP are more likely to have a distribution of disease that is largely symmetric with a predilection for lower lung fields compared to ARDS [16]. Most patients have involvement that is quite diffuse, involving 45–95% of lung parenchyma [7]. There is some evidence that the presence of traction bronchiectasis may reflect fibrosis and portend a worse outcome [17]. However, this finding could also unveil an acute exacerbation of another interstitial pneumonias like IPF, nonspecific interstitial pneumonia or connective tissue disease [3, 9].

Histopathology

As mentioned earlier, the histopathologic hallmark of AIP is acute and organized diffuse alveolar damage (DAD). DAD has been described in three different phases: acute exudative, early organizing proliferative, and late proliferative (or fibrotic) stage. Organizing proliferative stage is the most common and characterized by thickening of alveolar septa secondary to edema, inflammatory cells, and collapse of alveolar septa. Other key features on biopsy include interstitial fibrosis and the presence of type II pneumocyte hyperplasia [5, 9, 10] (Fig. 34.3).

A key feature that distinguishes AIP from more chronic processes is the presence of extensive fibroblast proliferation and relative absence or paucity of collagen deposition. The relative uniformity of disease, as referred to "temporally uniform lesion," suggest a single insult in time compared to a chronic interstitial pneumonia that reflects multiple insults with varying degrees of inflammation and fibrosis [5, 9, 10].

Given the diffuse nature of the disease, however, AIP is one of the few interstitial pneumonias in which transbronchial biopsy can be helpful as even small transbronchial specimens may be sufficient to capture the pathologic characteristics [10]. Many diagnoses are made on autopsy [17].

Clinical Course

Onset of symptoms prior to rapid deterioration is somewhat variable, but patients typically have vague symptoms for 1–2 weeks before progressing to a critically ill state requir-

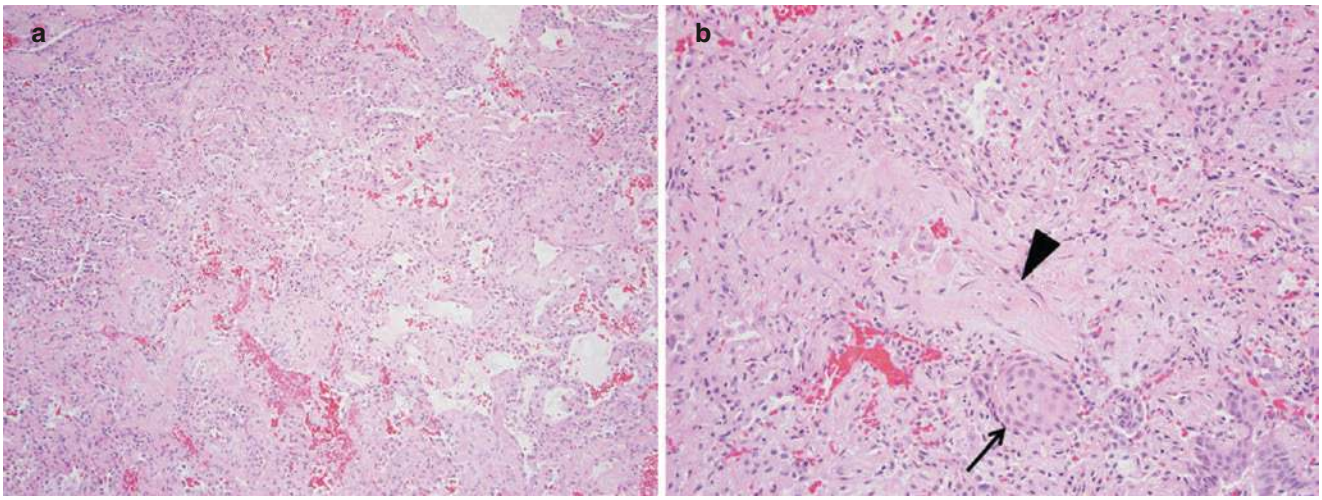

Fig. 34.3 At low power (panel **a**), acute interstitial pneumonia is characterized by diffuse interstitial thickening with associated alveolar septal collapse. At higher magnification (panel **b**), subepithelial proliferations of fibroblasts and myofibroblasts in a myxoid collagen background are common (arrowhead) and residual hyaline membranes are usually not prominent. Squamous metaplasia (arrow), although a nonspecific finding, is common in acute interstitial pneumonia

ing hospitalization in an intensive care unit. Many become ventilator dependent secondary to refractory hypoxemia. The mortality rate is greater than 50%, and average time to death is approximately 2 weeks [2, 4–8]. The minority of patients who survive AIP generally do well in the absence of other comorbidities. In addition, there have been some reports of recurrent AIP, but most patients go on to develop variable degrees of interstitial fibrosis or airway scarring [6, 7].

Treatment

Initial treatment is both empiric and supportive with supplemental oxygen and prevention of other complications like ventilator associated pneumonia or venous thromboembolism. All patients should receive lung-protective ventilation, as this is appropriate for most diagnoses on the differential. Broad spectrum antimicrobial coverage is appropriate until infection is satisfyingly excluded.

Once the diagnosis is established, however, there is unfortunately insufficient data for any evidence-based therapy. In addition to lung-protective ventilation strategies, many clinicians trial a course of corticosteroids. Some experts have suggested methylprednisolone 1 g/day IV for 3 days followed by 1 mg/kg/day IV or oral prednisolone for 4 weeks with subsequent tapering. Most observational trials had less than 30 patients total and with varying amounts of corticosteroids [2, 5–7]. There is limited evidence that patients who receive steroid therapy during the acute, exudative phase of their disease fare better than those whose lung biopsies already demonstrated proliferation and architectural distortion [7]. Alternative immunosuppressive treatments have been reported in case reports with limited success [18]. Lung transplantation has also been reported in only a few case reports to date [6, 19].

Smoking-Related Idiopathic Interstitial Pneumonias: Respiratory Bronchiolitis Interstitial Lung Disease (RB-ILD)/ Desquamative Interstitial Pneumonia (DIP)

Case

A 38-year-old man presents to his primary care clinic complaining of a persistent dry cough for approximately 1 year. He complains of mild dyspnea on exertion that does not limit any of his activities. In addition, he denies any fevers or chills and has not been exposed to any sick contacts. The patient is a current smoker of 1.5 packs per day and has been doing so for 21 years. On exam, his vital signs are normal, and he is not hypoxic. He has diffuse bilateral dry crackles but the rest of his physical exam is entirely normal. His primary care physician orders a chest X-ray that shows upper lung predominant reticulonodular opacities. At this point the patient is referred to a pulmonologist who performs pulmonary function testing. A mild obstructive defect is seen with normal lung volumes and a decreased DL_{CO}. A HRCT is performed and shows patchy GGO and centrilobular nodularity. Due to his persistent symptoms and abnormal imaging the patient undergoes a bronchoscopy with BAL and transbronchial biopsies. BAL cultures are unremarkable and cell count shows a normal differential. Biopsies reveal clusters of pigmented macrophages with associated fibrous scarring extending into the alveolar wall. A diagnosis of RB-ILD is made.

History and Definition

Respiratory bronchiolitis (RB) is a histopathologic lesion, seen in virtually all smokers, that was first recognized in 1974 on an autopsy series of young cigarette smokers who died of non-pulmonary causes [20]. The histopathologic features are characterized by clusters of brown pigmented macrophages in the first-order and second-order respiratory bronchioles commonly referred to as "smokers' macrophages" and "smokers' bronchiolitis." [13] Clinically, RB is associated with asymptomatic or a minimally symptomatic disease state characterized by mild cough and/or dyspnea [13–15]. In this scenario it is described as RB associated interstitial lung disease (RB-ILD) which is thought to be a more severe stage in which the alveolar accumulation and bronchiolar inflammation extends to the peribronchiolar interstitium [1, 21]. However, some pathologists believe RB cannot be distinguished from RB-ILD by pathological findings alone requiring the clinical and radiologic findings to be considered when making the diagnosis [22, 23].

It is important to note that the nomenclature and classification of all smoking-related interstitial pneumonias remains controversial. The 2013 American Thoracic Society and European Respiratory Society statement classified RB-ILD and DIP as smoking-related idiopathic interstitial pneumonias (SR-IIP) [3]. RB-ILD and DIP are considered separate, clinically distinguishable entities although some believe they are on a spectrum of disease in which RB-ILD is relatively mild compared to DIP.

Epidemiology

RB-ILD is typically seen in heavy smokers (>30 pack year) in the fourth and fifth decades of life with a 2:1 male predominance [1, 24, 25]. However, there are rare reports of RB-ILD seen even in patients with minimal tobacco use, heavy second-hand exposure, or use of electronic cigarettes (vaping.) [23, 26, 27] It is considered a rare disorder although likely underestimated as it may be noted incidentally in the background of other common complications related to heavy smoking. Given the difficulty with distinguishing RB-ILD from RB along with the changing nomenclature landscape of other smoking-related interstitial pneumonias, it remains difficult to determine additional epidemiologic features of this disease.

Presentation

The majority of patients present with nonspecific respiratory complaints including gradual onset of dyspnea and new or changing cough in the setting of tobacco use. Impairment in functional capacity is generally minimal and overlaps with early emphysema, making the diagnosis difficult. On exam, inspiratory crackles are the most prominent feature and are generally coarse in nature and occur throughout inspiration and occasionally into exhalation [28]. Rarely, do patients have any clubbing [1, 24, 25, 28].

Diagnostic Evaluation

The pulmonary function testing (PFT) pattern most often seen in RB-ILD is a mixed pattern of obstructive and restrictive physiology. The fibrosis and inflammation of the respiratory bronchioles seen in RB-ILD are similar changes to those in COPD and along with coexisting emphysema are responsible for the obstruction [22]. The interstitial disease causes the restrictive pattern along with impaired gas exchange affecting DLco. A significant response to inhaled bronchodilators is not typically seen due to the fact that the pathologic process is not bronchospastic. Overall, the most common PFT abnormality is a decreased DL_{CO} and often times will correlate with disease severity [1, 29]. Approximately 10% of patients have normal lung function at diagnosis [30].

There are no specific laboratory tests that aid in the diagnosis of RB-ILD. Disease severity can also correlate with imaging findings.

Radiology

Although there are no pathognomonic imaging findings associated with RB-ILD, common imaging patterns are seen. Chest radiography often appears normal but can have abnormalities such as thickening of the walls of the central or peripheral bronchi and fine reticulonodular opacities, typically diffuse or upper lung predominant [1, 24, 28]. HRCT is more clinically useful and frequently shows nonspecific changes such as centrilobular nodularity and patchy GGO with septal thickening (Fig. 34.4). The radiographic differential includes hypersensitivity pneumonitis and nonspecific interstitial pneumonia (NSIP) [31]. Since all of these patients are smokers or former smokers, concomitant emphysema is common as well.

Histopathology

As diagnostic uncertainty typically remains after detailed history and imaging review, the next step in the work-up of RB-ILD often includes a bronchoscopy, as is the case with many ILDs. In the case of suspected RB-ILD, bronchoscopy is not typically helpful but may assist in ruling out other

ILDs. The vast majority of BAL samples are indistinguishable from lavage fluid from otherwise healthy smokers (increased cells with normal differential). One difference seen in RB-ILD is that there are a relatively higher amount of pigmented macrophages compared to healthy nonsmoking individuals [1, 29]. This finding is nonspecific and may be seen other smoking-related lung diseases. A surgical lung biopsy is required to see definitive patterns of RB-ILD although there remains debate as to whether RB and RB-ILD can be fully elucidated by histopathological criteria even with surgical specimens. At present, clinical correlation remains important [21, 32].

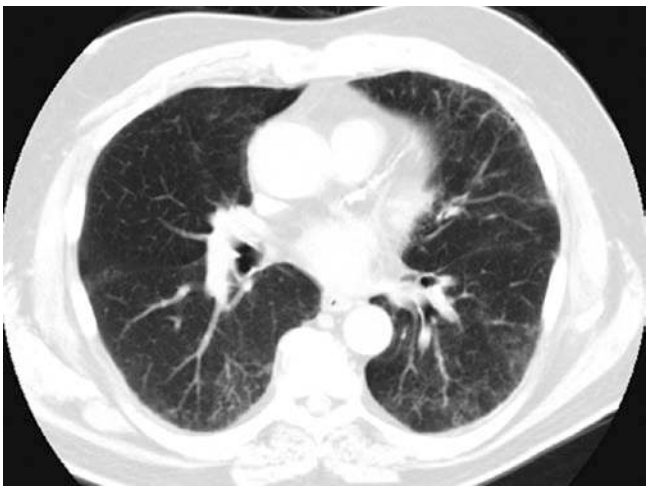

Fig. 34.4 High-resolution computed tomography images from a patient with respiratory bronchiolitis interstitial lung disease demonstrating areas of faint, patchy ground glass opacification, and reticular thickening

Histopathologically, RB-ILD generally differs from RB by demonstrating fibrous scarring that extends into the surrounding alveolar wall in addition to the aforementioned clusters of pigmented macrophages [22, 25]. These clusters are more frequently found near the bronchioles as compared to the rest of the lung parenchyma. In addition, these clusters are more prominent than those seen in healthy cigarette smokers [28]. Caution must be used in distinguishing RB from hemosiderin which may be found in diffuse alveolar hemorrhage or chronic passive congestion due to heart failure which are both highlighted in stains such as Prussian blue and depend on keen pattern recognition of the fineness and distribution by an experienced histopathologist [32]. RB-ILD lacks features of usual interstitial pneumonia (UIP) such as honeycombing and fibroblastic foci. Concomitant emphysema may be seen as well in RB and RB-ILD, owing to the strong association with smoking [22] (Fig. 34.5).

Clinical Course

The natural history of RB-ILD is difficult to ascertain as it is very rare. Previous studies are conflicted as to whether patients worsen, improve, or stabilize regardless of smoking status. Initial studies suggested that it was a benign disease process, however, more recent studies suggest that RB-ILD has a more sinister course [29, 33–35]. Additionally, there are reports of a disconnect between the patient's described sense of stable or improved dyspnea and objective measurements of validated dyspnea scores which clearly worsened over the same time [29]. There have been no deaths reported due to RB-ILD.

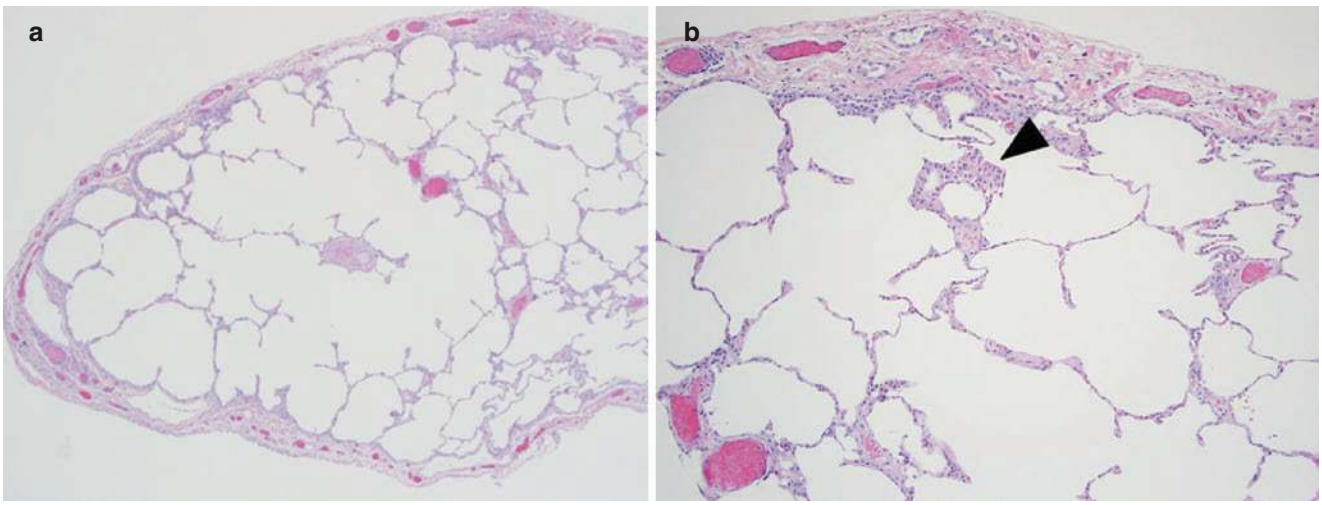

Fig. 34.5 The main histologic finding of respiratory bronchiolitis interstitial lung disease is similar to that of desquamative interstitial pneumonia, namely increased numbers of intra-alveolar macrophages (panel **a**). This process is limited to the small bronchioles and peribronchiolar airspaces (arrowhead panel **b**) in respiratory bronchiolitis interstitial lung disease and is more diffuse in desquamative interstitial pneumonia, although no quantitative histologic criteria have been established. Histologically, desquamative interstitial pneumonia and respiratory bronchiolitis interstitial lung disease likely represent the ends of a continuum of smoking-related disease

Treatment

Treatment options for RB-ILD are limited but must include smoking cessation at the forefront. Studies are mixed regarding the reversibility of the disease process with smoking cessation with some studies arguing that there are significant improvement in symptoms, pulmonary function, and imaging while others argue that there is merely stabilization [28, 29]. In some cases a trial of corticosteroids is used. Once again, results are mixed but studies suggest that there is no consistent improvement in symptoms or pulmonary function with corticosteroid treatment and therefore is not routinely recommended [29]. Empiric dosing of prednisone 0.5 mg/kg/day has been tried with most tapers lasting 3–9 months depending on response. Steroids are usually reserved for patient with a documented decline in lung function despite abstinence from smoking. The data on steroid-sparing second line immunosuppressive treatments such as azathioprine is very limited and has been used in patients with response to steroids who are unable to taper off the steroids [29]. It is unclear whether or not any intervention alters the natural history of the disease. Lung transplantation for RB-ILD has not been reported.

Desquamative Interstitial Pneumonia (DIP)

History and Definition

As mentioned above, DIP is another smoking-related idiopathic interstitial pneumonia that should be distinguished from RB-ILD. DIP was first described in 1965 as a case series of 18 patients noted to have similar pathology on open lung biopsy. This study defined a clinicopathologic syndrome characterized by a chest X-ray showing peripheral and basilar GGO and a clinical response to corticosteroid therapy with a combination of pathologic findings. While the initial description and name was descriptively termed by extensive desquamation of pneumocytes on histopathology, it was later recognized that the intra-alveolar cells are macrophages and not desquamated pneumocytes yielding the title as a misnomer [36]. DIP is currently characterized by the alveolar accumulation of pigmented macrophages followed by interstitial inflammation and fibrosis. Beyond the realization that DIP is a misnomer, there remains ongoing debate on the best nomenclature as some promote that smoking-related diseases should not be considered "idiopathic" [36]. RB-ILD and DIP remain related on a histologic spectrum but are considered separate as disease entities based on the clinical presentation, imaging findings, and response to treatment [3, 37].

Epidemiology

In contrast to RB-ILD which is invariably associated with smoking, approximately 90% of patients with DIP are smokers or former smokers. The remainder are seen with systemic disorders, infections, and environmental triggers [34, 35, 38, 39]. Due to its rarity and the inherent difficulties with disease recognition, it is difficult to make an accurate estimate of the incidence and prevalence of DIP. There are more than 290 reported cases in the literature [40]. The discovery of new cases of DIP has decreased recently. This is likely due to new classification systems from which cases that were previously described as DIP are now classified into other entities such as RB-ILD, NSIP, PLCH, or other diagnoses [30].

Presentation

Clinically, DIP behaves similarly to other ILDs, meaning, an insidious onset of dyspnea and cough over weeks to months. Presentation is usually in the fourth or fifth decades of life and has a male predominance, both similar to RB-ILD [1, 34]. On exam, most patients have inspiratory crackles and clubbing is common as well [1, 34, 35, 39]. The clinical distinctions between DIP and RB-ILD are subtle but notable as well with DIP causing generally more severe respiratory symptoms.

Diagnostic Evaluation

The work-up for DIP, as is common with the other ILDs, includes a detailed history and physical exam, pulmonary function testing (PFT), chest radiography/HRCT, and obtaining tissue specimens. On physical examination, clubbing is frequent in DIP but not seen in RB-ILD and pulmonary function testing can show obstruction in RB-ILD and this pattern is not seen in DIP [34, 35]. Pulmonary physiology may show normal lung volumes or varying amounts of restriction. This is consistent with the major pathology being a fibrotic process. The major and most consistent PFT abnormality is impairment in gas exchange signified by a low DL_{CO} [35, 39].

Radiology

Chest radiography can be normal or show patchy abnormality including GGO or linear or reticulonodular infiltrates with a lower lung and peripheral predominance [1, 29, 34, 38]. HRCT typically shows patchy GGO with a lower and peripheral lung zone predominance as well (Fig. 34.6).

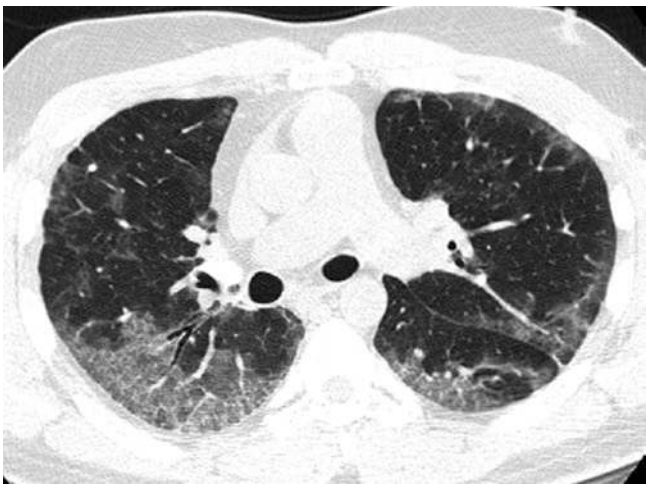

Fig. 34.6 High-resolution computed tomography images from a patient with desquamative interstitial pneumonia showing patchy ground glass opacification in a lower and peripheral lung zone distribution

Irregular linear opacities are another common finding on HRCT. Honeycombing is uncommon but thin-walled cystic changes can be seen within the areas of GGO [1, 24, 31, 34]. As these patients are usually current or former smokers, simultaneous emphysema may be present. In RB-ILD imaging studies show upper lung predominant disease whereas DIP is characteristically a lower lung and peripheral process. The HRCT differential includes RB-ILD, hypersensitivity pneumonitis, sarcoidosis, NSIP or atypical infection such as pneumocystis jirovecii pneumonia [1, 24]. HRCT abnormalities are less severe in DIP compared to UIP and are not thought to have a progression to UIP which is a distinct and separate entity.

Histopathology

Bronchoalveolar lavage (BAL) is not particularly helpful in the diagnosis of DIP but is done to evaluate for other ILDs and to rule out infection. Regardless, BAL typically shows increased number of macrophages containing "smoker's pigment." Fluid differential may have increased percentages of PMNs, eosinophils, or lymphocytes; however, all of these BAL findings are nonspecific [38, 40]. The yield of transbronchial biopsies remains limited and generally the diagnosis is best made by surgical lung biopsy [40].

Histologically, DIP is similar to RB-ILD with respect to the fact that pigmented macrophages are the dominant cell type. DIP is characterized by pigmented macrophages accumulating in the distal airspaces in a diffuse pattern throughout the lung parenchyma. Lymphocyte follicles and giant cells are also frequently seen in the distal airways indicating mild chronic inflammation. The interstitium is thickened by a sparse inflammatory infiltrate which is often composed of eosinophils and plasma cells and is lined by cuboidal pneumocytes [24, 34, 35, 41]. Additionally, there is fibrotic thickening of the alveolar septa. Underlying architecture is maintained and honeycombing is minimal or not present [1]. Pertinent characteristics that are not seen in DIP which differentiate it from other ILD, specifically UIP, are extensive fibrosis, smooth muscle proliferation, and organizing pneumonia [33, 35].

Pathologically, these distinctions, as discussed above, involve the amount of macrophage clusters and the presence of fibrous scarring that is seen in RB-ILD [22, 25]. DIP is characterized by higher levels of macrophages, diffuse rather than bronchocentric pattern of involvement and a greater amount of fibrosis compared to RB-ILD. DIP also demonstrates the presence of interstitial lymphoid follicles, eosinophils, Giant cells, and fibrous thickening of the alveolar septa which are not seen in RB-ILD [1, 24, 42] (Fig. 34.7).

Clinical Course

The natural history of untreated disease can range from mild to quite severe. Spontaneous remissions and acute exacerbations leading to fulminant respiratory failure have been reported [39, 42, 43]. There is an associated 5-year mortality of approximately 5% and 10-year mortality of approximately 30% [39]. If left untreated, an estimated two-thirds of patients will have clinical worsening [39, 40]. Lastly, DIP is generally considered a more severe disease with higher morbidity and mortality than RB-ILD and may progress despite smoking cessation and other treatments [44].

Treatment

Treatment consists primarily of smoking cessation although few studies have shown clear clinical benefit [34, 39]. Avoidance of any probable environmental or occupational exposures and treatment of underlying infection or systemic illness should also be considered as a general approach but research is lacking [38]. In a summary of studies dedicated to DIP a response rate of 71.2% was found when systemic corticosteroids were used [41]. The recommended dose of prednisone is around 0.5 mg/kg daily but varies widely among studies [40]. The duration of steroids also varies but is usually tapered over 3–9 months [30, 38]. Macrolides such as clarithromycin have shown to be helpful in patients with incomplete or refractory response to steroids in some studies

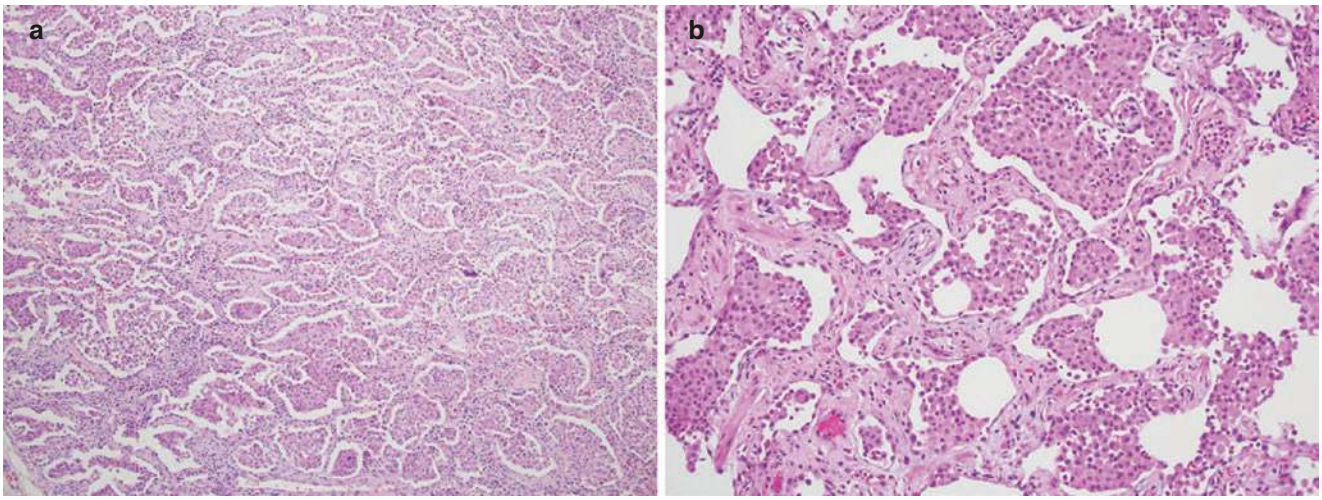

Fig. 34.7 At low power (panel **a**), the main histologic finding of desquamitive interstitial pneumonia is increased numbers of intra-alveolar macrophages. At higher magnification (panel **b**), the macrophages contain the coarsely granular, golden brown smoker's pigment. Mild alveolar septal fibrosis is also a common finding

[45]. Additional reports mention further immunosuppression with azathioprine and cyclophosphamide in refractory cases but the response rates to these therapies was not discussed [41]. With treatment, reversal of the GGO seen on CT may improve or disappear [1, 24]. In addition, patients who are treated may fully recover lung function [39]. Others may experience relapse even years after discontinuation of steroids and have shown some response to resumption of steroid treatment [41]. In extreme cases, those patients who continue to progress despite treatment may be referred for lung transplantation; however, there are reports of possible recurrence seen after lung transplantation as well [28, 46].

Nonspecific Interstitial Pneumonia (NSIP)

Case

A 55-year-old non-smoking female presents to her primary care physician due to several months of progressive shortness of breath and diffuse joint pain. She denies any fevers, recent travel or any other illness. She also admits to worsening reflux symptoms over the last several weeks. On further questioning, she describes predictable color changes to her hands when she puts foods in her freezer.

On physical exam, she is afebrile, normotensive, with normal respiratory and heart rates. Oximetry is noted be 92% on room air. Cardiac exam is normal. Posterior chest auscultation reveals faint crackles at the bilateral bases. She has mildly tender proximal interphalangeal joints, and knees bilaterally. There are no obvious changes to the skin. The remainder of the physical exam is normal.

Pulmonary function testing performed at the visit shows a mild restrictive ventilatory pattern with mildly impaired gas exchange. Chest X-ray is normal. Laboratory work drawn in the office shows normal cell counts, and a normal comprehensive metabolic panel. Antinuclear antibody (ANA) titer is positive to a dilution of 1:160, and rheumatoid factor is negative. Anti-Ro/SSA and anti-la/SSB antibodies are also noted to be positive. HRCT demonstrates diffuse intralobular septal thickening with a significant degree of GGO. The subpleural region is relatively spared throughout the chest. A surgical lung biopsy is planned for the patient given the findings, and her progressive functional decline. The final pathology report demonstrates diffuse fibrosis and inflammation that was temporally homogeneous suggestive of a pattern of NSIP.

History and Definition

Nonspecific interstitial pneumonia (NSIP) is a pathologic description of a chronic interstitial pneumonia that lacks the histopathologic features typical of other IIPs, despite many similarities in clinical and radiographic presentation. It originated as a histopathologic categorization reserved for surgical lung biopsies not demonstrating a clearly identifiable pattern [47]. This definition has been redefined over time, given concern that it was a "wastebasket" diagnosis [48]. It is well known that the histologic pattern of NSIP can be seen in association with other disease states including connective tissue diseases, drug-induced, autoimmune disease, hypersensitivity pneumonitis, and other rare entities such as IgG4-related disease, familial interstitial pneumonia, and graft versus host disease [49]. Commonly associated connective tissue diseases include systemic sclerosis, polymyositis/dermatomyositis, rheumatoid arthritis, and Sjogren's disease

[49]. Implicated drug-induced etiologies have been correlated with amiodarone, methotrexate, nitrofurantoin, statins, and chemotherapeutic agents [49].

Despite a correlation with NSIP and these various disease states, a causal relationship has not been demonstrated. Another category is idiopathic NSIP, which as the name implies, is disease without any known origin. Several studies, however, have reported that a substantial number of patients with idiopathic NSIP have positive autoantibodies [50]. This has led to the description of NSIP due to an undifferentiated connective tissue disease (UCTD), a clinical entity with symptoms and/or signs suggestive of connective tissue disease, but not fulfilling the classification criteria for any specific diagnostic entity [51]. NSIP with organizing pneumonia overlap is a controversial finding that has recently appeared in the criteria of interstitial pneumonia with autoimmune features (IPAF). However, details of this controversial entity are not well known [52].

Epidemiology

The incidence and prevalence of idiopathic NSIP are unknown. Since Katzenstein and Fiorelli's description of NSIP in 1994 [47], several cases that were previously classified as IPF were reclassified as NSIP in 11–43% of cases [52]. It constitutes 14–36% of cases of idiopathic interstitial pneumonia which is less common than usual interstitial pneumonia (UIP) (50–60%) but more common than desquamative interstitial pneumonia, respiratory bronchiolitis-associated interstitial lung disease (DIP/RB-ILD) (10–17%) and acute interstitial pneumonia (AIP) (0–2%) [49].

Idiopathic NSIP occurs mostly in middle-aged women who are non-smokers, while NSIP due to connective tissue disease is equal in men and women. Given the known prevalence of IPF, the extrapolated prevalence of idiopathic NSIP could range from 1 to 9/100,000 [52]. As radiographic and pathologic patterns of NSIP and UIP can be seen in the same patient (see below) the relationship between these entities is often questioned. At this time data are lacking to make concrete statements regarding the possibility that NSIP may evolve into UIP in some patients over time and the authors believe that they should be treated as separate entities.

Presentation

The typical patient with NSIP is a middle-aged adult presenting with cough and dyspnea developing over weeks to months prior to diagnosis [47, 48]. Two-thirds of the patients are women, and unlike patients with IPF, 70% are never smokers [48]. Patients may have nonspecific symptoms such as fever [48] and serologic abnormalities (antinuclear antibodies and rheumatoid factor) are common [53]. Many patients with NSIP meet the case definition of undifferentiated connective tissue disease, suggesting an autoimmune process [53]. Complaints of xerostomia, arthralgia, myalgia, rash, or Raynaud's phenomenon should raise clinical suspicion that a collagen vascular disease is the underlying cause of the disease. Additionally, a complete review of the patient's medications, HIV risk factors, and exposures to airborne antigens should be conducted, given their individual associations with NSIP [53].

Diagnostic Evaluation

The diagnostic evaluation of suspected NSIP, like most ILDs, includes a detailed history and physical exam, pulmonary function testing (PFT), chest radiography/HRCT, and obtaining tissue specimens. Due to the strong association of many systemic diseases and exposures with NSIP an ongoing search for potential causes is warranted as in some cases the lung disease may manifest prior to other signs of a systemic disorder. Similarly, prior or ongoing drug or hobby/occupational exposures may not be revealed at the time of the initial evaluation and only come to light through the course of patient follow-up. The majority of patients with NSIP have bibasilar crackles, but only 10–35% have clubbing [54]. Pulmonary function testing demonstrates a restrictive ventilatory defect, often times with impaired gas exchange, however, this is in no way specific to NSIP.

Radiology

Early in the course of NSIP, patients may present with normal chest imaging. Conversely, general imaging in late stage NSIP commonly demonstrates bilateral reticular or hazy opacities (Fig. 34.8). Though the lower lobes are involved, there is not as much of a clearly defined apical-basal gradient as seen in UIP [47, 48].

The most frequently seen HRCT findings are increased reticular markings with subpleural sparing, traction bronchiectasis, lobar volume loss, and GGO [48, 52] (Fig. 34.9). Other findings in late stage NSIP are subpleural cysts, or honeycombing, which are smaller and less extensive compared to those found in UIP [55]. If honeycombing is the predominant finding, UIP should be favored as the diagnosis [55–57]. Additionally, areas of GGO do not progress to honeycombing on serial HRCTs in NSIP, whereas this progression can be seen in UIP [51].

Despite typical HRCT findings, the ability to make a definitive diagnosis of NSIP via HRCT is limited [48]. Unlike UIP, the accuracy of HRCT for diagnosing NSIP can range from 66% to 68% [56, 58] Given the significant differ-

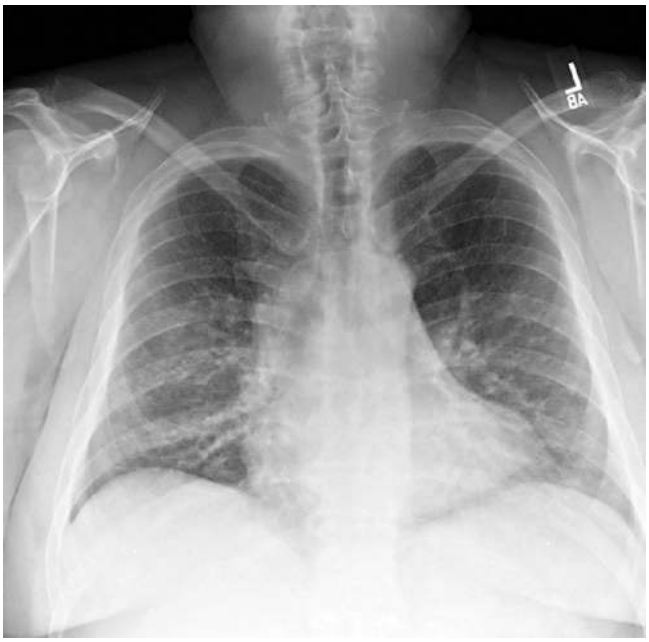

Fig. 34.8 Chest radiograph from a patient with nonspecific interstitial pneumonia showing bilateral interstitial infiltrates

ences in prognosis and treatment options between NSIP and UIP, a surgical lung biopsy should be performed to when HRCT suggests NSIP. In fact, this is the only way a definitive diagnosis of NSIP can be made [53].

Histopathology

Bronchoscopy, while useful to rule out infection or other interstitial lung diseases, cannot make a specific diagnosis of NSIP. When evaluated, broncho-alveolar lavage (BAL) findings in NSIP often demonstrate increased lymphocyte counts and a reduced CD4:CD8 ratio (cellular NSIP), although some patients present with increased neutrophils and eosinophils (fibrosing NSIP) [59, 60].

A surgical lung biopsy via VATS or thoracotomy is required to make a definitive diagnosis of NSIP. The role of transbronchial cryobiopsy is not well defined. Traditional transbronchial forceps lung biopsies have been reported to have a low diagnostic yield. Ideally, biopsy samples should be obtained from more than one lobe. The histopathology of NSIP is characterized by varied degrees of alveolar wall inflammation and fibrosis in a pattern that suggests temporal homogeneity, not fitting the patterns of other IIPs [1, 61] (Fig. 34.10).

Temporal homogeneity is the major feature which distinguishes NSIP from UIP, the histologic pattern for IPF. There are three subgroups into which patients with NSIP are further classified. Group I has interstitial inflammation as the primary finding (cellular NSIP). Group II has both inflammation and fibrosis. Group III has fibrosis as the primary

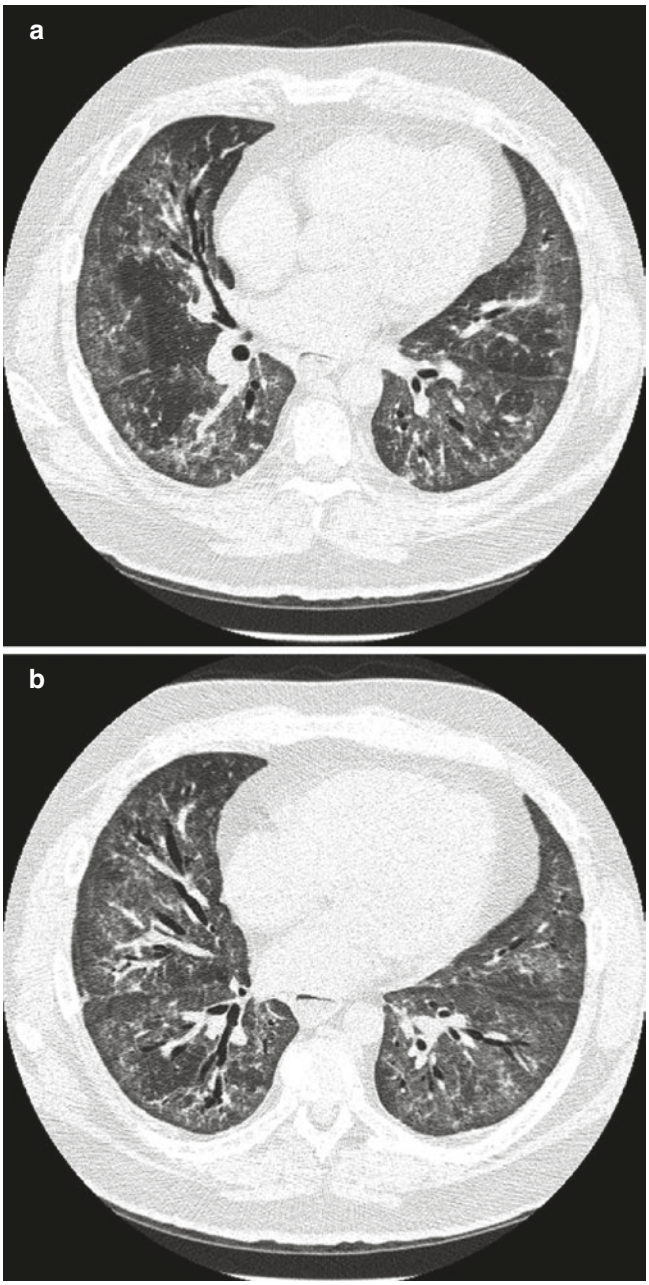

Fig. 34.9 High-resolution computed tomography from the mid (panel **a**) and lower (panel **b**) lung fields of patient with nonspecific interstitial pneumonia. The images demonstrate patchy areas of ground glass opacification, reticular thickening, and traction bronchiectasis. Some subpleural sparing of disease can be appreciated. Honeycombing is absent

finding (fibrotic NSIP). This third group is differentiated from UIP by the absence of fibroblast foci and the presence of temporal homogeneity [47]. In clinical practice most pathologists simplify the division into two groups (cellular or fibrotic NSIP). Even expert pathologists have difficulty distinguishing between NSIP and UIP on a particular biopsy specimen [62, 63]. Further complicating this process, both

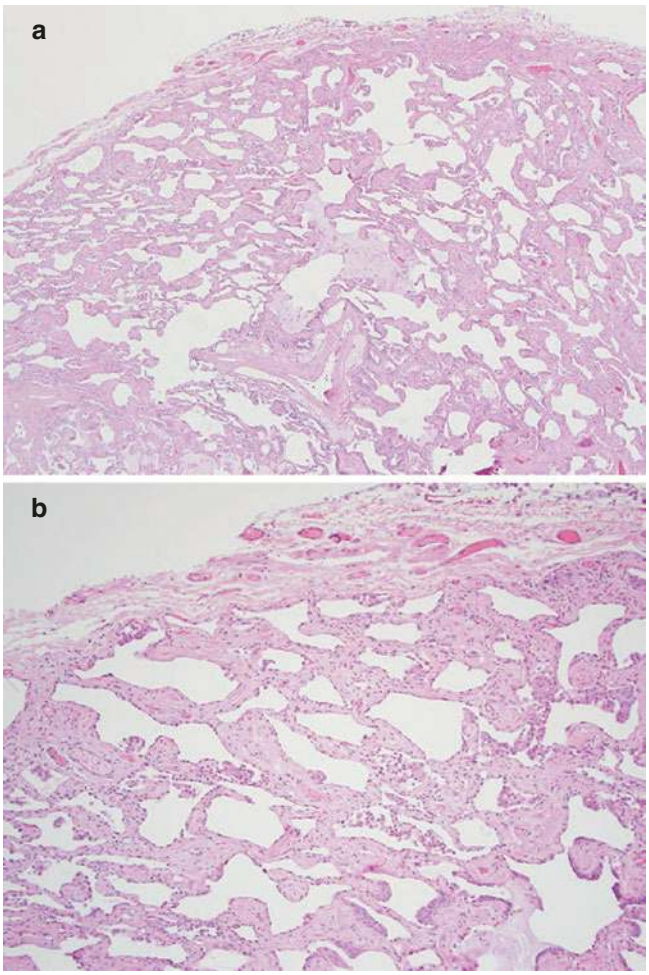

Fig. 34.10 At low power (panel **a**), fibrosing nonspecific interstitial pneumonia demonstrates prominent, uniform septal thickening by mature collagen. At higher power (panel **b**), the septal thickening is due mainly to thick collagen with minimal inflammation

NSIP and UIP patterns can be found in the same individual when biopsies are taken from multiple locations in 13%–26% of patients [64, 65]. Those with discordant biopsy results have a prognosis similar to UIP, and should be considered to have UIP in all lobes (Fig. 34.9).

Clinical Course

Patients with NSIP tend to have a better prognosis and response to treatment compared to those with UIP/IPF [59, 61, 66]. This difference persists after adjusting for age, gender, smoking history, and physiologic variables. 5- and 10-year survival has been estimated as 43% and 15%, respectively, among patients with UIP, compared to approximately 90% 5-year survival and 30% 10-year survival rates among patients with NSIP with the fibrotic component [49]. Survival is the better in patients with a purely cellular pattern, indicating that prognosis is determined by the degree of fibrosis [30, 31] That said, not all patients respond to therapy and progressive disease clearly occurs in some patients. The prognosis also depends on the presence of associated diseases and exposures and the ability to treat and mitigate these factors.

Treatment

Generally, the treatment and prognosis of NSIP vary significantly and rely on the identification and management of associated conditions or environment/occupational, and drug exposures [67–69].

For SSc-ILD, which is commonly associated with NSIP pattern, studies have favored the use of mycophenolate mofetil over the use of cyclophosphamide due to similar efficacy with a more tolerable side effect profile [70]. Other CTDs that may manifest ILD features include Sjogren's syndrome, rheumatoid arthritis, systemic lupus erythematosus, mixed connective tissue disease, and inflammatory myositis. There are no guidelines or consensus on the treatment of ILD associated with those CTDs due to lack of controlled trials. However, corticosteroid is often the first-line medication, while immunosuppressants such as azathioprine, cyclophosphamide, mycophenolate mofetil, or calcineurin inhibitors are considered as adjunctive, in steroid refractory cases, or in cases where corticosteroid is intolerable due to complications [71–73].

With regard to idiopathic NSIP, asymptomatic patients with mild disease may be followed without treatment [74]. However, for those with progressive disease or moderate to severe disease, corticosteroid treatment seems to be beneficial in stabilizing pulmonary function [75, 76]. The optimal dose and duration of glucocorticoid therapy is not known, however, a starting dose of 1 mg/kg ideal body weight per day (maximum 60 mg/day) for 1 month followed by 40 mg/day for an additional 2 months is recommended based on a compilation of studies [47, 54, 59, 61, 76].

Prednisone should be tapered to a goal of 5–10 mg daily to every other day in responders. After 12 months of treatment, practitioners can attempt to discontinue prednisone therapy. As prednisone is tapered or discontinued, some patients can experience clinical deterioration [66]; consideration of a longer prednisone course or steroid-sparing agents such as cyclophosphamide, azathioprine, or mycophenolate is appropriate in these cases. Combination therapy has also been shown by Kondoh et al. [65] to be effective in improving vital capacity percent predicted (VC % pred) in patients with idiopathic NSIP compared to IPF. Subjects in this study received methylprednisolone 1000 mg per day for 3 days weekly for 4 weeks, followed by combination therapy for 1 year with cyclophosphamide (1–2 mg/kg/day) plus low

dose prednisolone 20 mg every other day [65]. After pulse therapy, 33% of patients with NSIP had improved VC % pred versus 15% with IPF [65]. After 1 year of combination therapy, 66% of patients with NSIP had improved versus 15% of the IPF group [65].

Cyclophosphamide has also been used as a sole agent with either known or suspected NSIP. Despite having severe, progressive disease, patients receiving IV cyclophosphamide had stable lung function at 6 months. The generally accepted dose of cyclophosphamide is 1–2 mg/kg/day orally, with a maximum dose of 200 mg or 750 mg/m^2 body surface area.

When azathioprine is utilized, dosing is usually started at 50 mg daily, increased in 25–50 mg increments every 14 days to a dosage of 1–2 mg/kg/day (maximum dose of 150 mg daily) as long as blood counts and hepatic function are not impacted. Prior to initiation of this therapy, it is possible to evaluate patients for abnormal thiopurine methyltransferase (TPMT) enzymatic levels. If the TPMT level is low, a lower dose of azathioprine or an alternative immunosuppressive agent could be utilized.

For subset of patients with either idiopathic or secondary NSIP who suffer from progression regardless of aforementioned treatment, antifibrotic agents may be an option. Nintedanib and pirfenidone are the two antifibrotic agents available in the market which have successfully delayed the progression and suppressed acute exacerbation of idiopathic pulmonary fibrosis [77, 78]. Studies continue to explore the efficacy and safety of antifibrotic treatment in fibrotic NSIP due to multiple etiologies. Unfortunately, the trials have been limited or discontinued due to slow recruitment although some limited data suggested adding pirfenidone may slow the decline in FVC and thus disease progression [79].

In patients with severe, progressive NSIP or disease that is refractory to immunosuppressive therapy, lung transplantation can be considered [80]. Usually, patients should be referred for transplantation when the life-expectancy of the patient is between 24 and 36 months, however, poor quality of life can also be taken into consideration.

Unclassifiable Interstitial Pneumonia

Even with multidisciplinary discussions at top institutions there are cases that remain unclassifiable and now fall into its own category of IIP since the 2013 ATS/ERS update [3]. The ATS/ERS statement on the diagnosis and classification of idiopathic interstitial pneumonias lists the following areas that commonly lead to this situation including.

1. Inadequate clinical, radiographic, or pathologic data.
2. Major discordance between clinical, radiologic, and pathologic findings in the following situations.
   (a) Previous therapy resulting in substantial alteration of radiologic of histologic findings.
   (b) New entity, or unusual variant of recognized entity, not adequately characterized by the current classification.
   (c) Multiple HRCT and/or pathologic patterns that may be encountered in patients with IIP (2).

When these situations arise, the recommendation is to decide on treatment based on the most probable diagnosis. A 2012 retrospective series suggested that this situation may occur in approximately 10% of cases [69]. The main reasons for unclassifiable ILD diagnosis were too old or frail for lung biopsy (52%), conflicting data (18%), or mild/stable disease (9%). Patients with unclassifiable disease had a better prognosis compared to IPF (HR 0.62, $p = 0.04$), but a similar survival to other non-IPF controls (HR 1.54, $p = 0.12$) [69].

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Organizing Pneumonias and Acute Interstitial Pneumonia

35

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Abbreviations

AE-ILD	Acute exacerbation of interstitial lung disease
AFOP	Acute fibrinous organizing pneumonia
AIP	Acute interstitial pneumonia
ARDS	Acute respiratory distress syndrome
BAL	Bronchoalveolar lavage
BO	Bronchiolitis obliterans
BOOP	Bronchiolitis obliterans organizing pneumonia
COP	Cryptogenic organizing pneumonia
COPD	Chronic obstructive pulmonary disease
DAD	Diffuse alveolar damage
DNA	Desoxyribonucleic acid
ECMO	Extracorporeal membrane oxygenation
EGPA	eosinophilic granulomatosis with polyangiitis
GPA	Granulomatosis with polyangiitis
HRCT	High resolution computed tomography
IIP	Idiopathic interstitial pneumonias
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
NSIP	Nonspecific interstitial pneumonia
NYHA	New York Heart Association
OP	Organizing pneumonia
SOP	Secondary organizing pneumonia
TBB	Transbronchial biopsy

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Organizing Pneumonias

Definition and Terminology

Organizing pneumonia is a particular type of inflammatory and fibroproliferative process of the lung leading to a clinico-pathological syndrome. It is characterized clinically by symptoms and signs resulting from inflammation and consolidation of the lung parenchyma, and histologically by the presence of buds of granulation tissue filling the distal airspaces as a reparative process following damage to the alveolar epithelium. Although its histological features were known since the beginning of the twentieth century, the clinico-pathological syndrome of organizing pneumonia has only been described in the early 1980s [1, 2].

Although the term *bronchiolitis obliterans with organizing pneumonia* (*BOOP*) used in the original description [2] became rapidly popular, it led to a confusion with *bronchiolitis obliterans* (*BO*), a clinically and histologically distinct entity characterized by bronchiolar involvement and airflow obstruction, whereas BOOP mainly affects the alveolar spaces and bronchiolitis, if present, is only an ancillary a feature. To clarify this issue, the term BOOP has now been replaced by the more accurate term of *organizing pneumonia* (*OP*) [3]. If OP occurs in association with an identified cause or clinical condition, it is called *secondary* organizing pneumonia (SOP). If no cause is identified, OP is termed *cryptogenic* organizing pneumonia (COP). COP has been integrated in the international classification of idiopathic interstitial pneumonias (IIP) in 2002 [3], and further confirmed in the 2013 update of this classification [4]. The term "organizing pneumonia" has been used both by pathologists to designate a particular but otherwise unspecific histopathological lesion, and by clinicians to describe a specific clinico-pathological syndrome. To clearly identify these two distinct but overlapping concepts, the term *organizing pneumonia* is now used for the clinico-pathological syndrome, whereas the term *organizing pneumonia pattern* designates the histopathological lesion [3].

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Epidemiology

OP represents 2–10% of all interstitial lung diseases [5–7]. In the only dedicated epidemiological study available, performed in Iceland, the mean annual incidence of OP was 1.97/100,000, with 1.10/100,000 for COP and 0.87/100,000 for secondary OP [8], meaning that more than half of cases of OP were idiopathic. Men and women were equally affected, at a mean age of 60–70 years. Smoking has not been found a risk factor for OP occurrence.

Pathogenesis

OP is initiated by an injury to the alveolar epithelium leading to necrosis and shedding of epithelial cells. Denudation and formation of gaps in the basal membranes lead to increased alveolar permeability, and exudation of plasma proteins and coagulation factors into the alveoli [9, 10]. In contrast with diffuse alveolar damage (DAD), there are no hyaline membranes. The endothelium appears only mildly damaged.

The first step of intra-alveolar organization is characterized by activation of the coagulation cascade in the alveolar spaces leading to accumulation of fibrin clots containing lymphocytes, some polymorphonuclear neutrophils, and occasionally mast cells and plasma cells [9, 11, 12]. In the second step, fibroblasts from the alveolar interstitium migrate through gaps in the injured epithelial basal membranes and colonize the fibrin residues in the alveolar spaces. Fibroblasts proliferate and transform into myofibroblasts, which produce an extracellular myxoid matrix replacing the fibrin residues. Inflammatory cells infiltrate the alveolar interstitium, while type II pneumocytes proliferate to restore the epithelial lining of the basal membranes. During the third step, the intra-alveolar granulation tissue undergoes progressive organization into mature fibrotic collagen-rich bundles or "buds" filling the alveoli, alveolar ducts, and distal bronchioles without altering the overall parenchymal architecture (Fig. 35.1) [2, 11–14].

Clinical Features

The clinical features of OP are unspecific and mimic other pulmonary diseases especially infections and malignancies. Many patients initially receive one or more courses of empirical antibiotic therapy, and it is only when this treatment proves ineffective that further investigations are performed. The diagnosis of OP is thus frequently delayed by weeks or even months [2, 14–20].

Disease onset is usually subacute with flu-like symptoms, dry cough, mild dyspnea, fatigue, fever, and weight loss [2, 14, 17, 21]. Productive cough, chest pain, night sweats, arthralgias and myalgias are less frequent features. Hemoptysis is rare in most large series [20, 22–24], although it has been reported in up to 50% of cases in one study [25]. Finger clubbing is absent. At chest auscultation, sparse inspiratory crackles are usually heard over the affected areas [23, 24]. Wheezing is uncommon in OP. The frequency of clinical symptoms and signs in a large recent series of OP is summarized in Table 35.1 [24]. No significant difference was found between the clinical presentations of COP and SOP in this series, except for more common crackles in the latter [24]. On rare occasions, OP is incidentally discovered at chest X-ray in an asymptomatic patient [19, 20, 24].

At pulmonary function testing, OP is characterized by mild to moderate restrictive ventilatory defect. Airflow

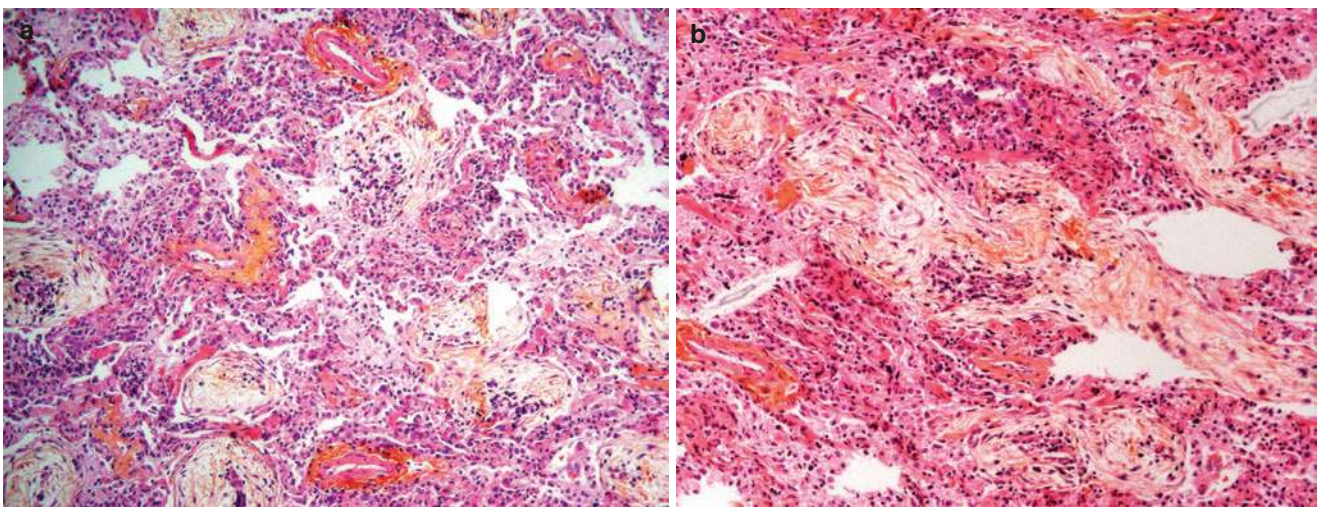

Fig. 35.1 (**a**, **b**) Histopathological pattern of organizing pneumonia at surgical lung biopsy: buds of granulation tissue containing myofibroblasts and inflammatory cells embedded in a loose connective matrix, and filling the alveolar spaces without disruption of the parenchymal architecture. Mild inflammatory infiltrate of the alveolar interstitium

Table 35.1 Frequency of symptoms and signs in organizing pneumonia[a]

No symptoms (incidental finding at chest X-ray)	6%
General	
Fever	43%
Malaise	53%
Night sweats	4%
Respiratory	
Cough	60%
Dyspnea	53%
Pleuritic pain	20%
Hemoptysis	2%
Inspiratory crackles	59%
Wheezing	8%

[a] Adapted from reference [24]

obstruction is found in only a minority of patients, usually smokers [2], and probably reflects pre-existing chronic obstructive pulmonary disease unrelated to the OP pathologic process. Carbon monoxide diffusion capacity is usually moderately reduced. Mild to moderate hypoxemia is common [2, 13–16]. Severe hypoxemia is rare and may result from right-to-left blood shunting through densely consolidated lung parenchyma [26].

Blood cell count usually discloses moderate leukocytosis and neutrophilia [19, 23, 24]. C-reactive protein level and erythrocyte sedimentation rate are usually increased [14, 23, 24, 27]. Bronchoalveolar lavage (BAL) typically shows a mixed pattern alveolitis [14, 17, 18, 20, 21, 28], with predominance of lymphocytes (20–40%), and a moderate increase of neutrophils (~10%) and eosinophils (~5%). Mast cells (~2%) may be found in one fourth of cases and plasma cells are occasionally present [20]. The lymphocyte CD4/CD8 ratio is usually decreased [14, 18, 20, 21, 28]. Predominance of eosinophils over lymphocytes is uncommon [28] and suggests the diagnosis of eosinophilic pneumonia rather than OP (cases with overlapping features of eosinophilic pneumonia and OP have occasionally been reported).

Imaging

The imaging characteristics of OP are variable, but can be broadly classified into four patterns: (1) multifocal alveolar opacities, (2) isolated nodule, (3) diffuse infiltrative opacities, and (4) others.

Multifocal Form

The multifocal form is the most typical presentation of OP and accounts for 40–70% of all cases [19, 20, 23, 29]. It is characterized by multiple bilateral alveolar opacities predominating in the subpleural regions and the lower lung zones, often containing an air bronchogram (Fig. 35.2) [14–16, 29–31]. Chest high resolution computed tomography (HRCT) is a useful non-invasive procedure if OP is suspected, as it often shows more opacities than the chest X-ray, and this multifocal pattern provides an important diagnostic clue for OP. Spontaneous disappearance of some opacities over time and appearance of new infiltrates in other sites occurs in 25–50% of cases of OP [20, 28], either before treatment or when a relapse occurs (Fig. 35.3). This phenomenon called "migratory opacities" provides another important diagnostic clue for OP, as the differential diagnosis is relatively narrow (Table 35.2). Positron emission tomography has shown a significant increase of fluorodeoxyglucose uptake in parenchymal lesions of OP [32], but this procedure is not part of the routine assessment of OP. Pleural effusion has usually been reported as uncommon in OP [16, 20], although a small effusion has been found in up to 35% of cases in one series [25]. A moderate enlargement of mediastinal lymph nodes may be found in about 14% of cases [33].

Isolated Nodular Form

This form has been termed "localized," "solitary," "nodular," or "focal" OP, and represents 5–20% of cases [14, 19, 23]. It appears as a solitary nodule or mass with smooth or irregular margins [14, 34–38] (Fig. 35.4a). In around half of patients, the lesion is found incidentally [36–39].

In pooled data from six series of nodular OP totalizing 150 cases [36–41], 71% were men (range across series 56–100%) and 73% were smokers or ex-smokers (range 57–93%). Only 57% were symptomatic (range 17–80%). A history of recent infection was found in 27% (range 12–57%). The upper lobes were affected in 35% of cases (range 24–58%). The mean size of the nodular opacity was 25 mm (range 6–68 mm). Irregular, lobulated or spiculated margins were present in 75% (range 54–94%). An air bronchogram was found in 34% of cases (range 5–56%). Satellite nodules were found in 40% (range 29–56%) and mediastinal lymphadenopathy in 13% (range 0–22%).

Isolated nodular OP presents with contrast enhancement on HRCT and positive tracer uptake on positron emission tomography [37, 38], and cannot be confidently distinguished from primary or metastatic malignancy at imaging. This tumor-like appearance frequently leads to surgical resection, and the diagnosis of OP is made retrospectively at pathological examination. In one report, lung resections for isolated nodular OP represented 0.8% of 1612 thoracic surgical procedures performed in a 3-year period at one institution [37]. In 150 patients with nodular OP from six series, preoperative transthoracic or transbronchial biopsy was performed in only 40% of patients (range 0–83%), whereas 70% underwent a wedge resection or a segmentectomy (range 17–100), and 7% had a lobectomy (range 0–24%). The surgical procedure was curative in most cases without the need for subsequent corticosteroid therapy [37, 38]. Of

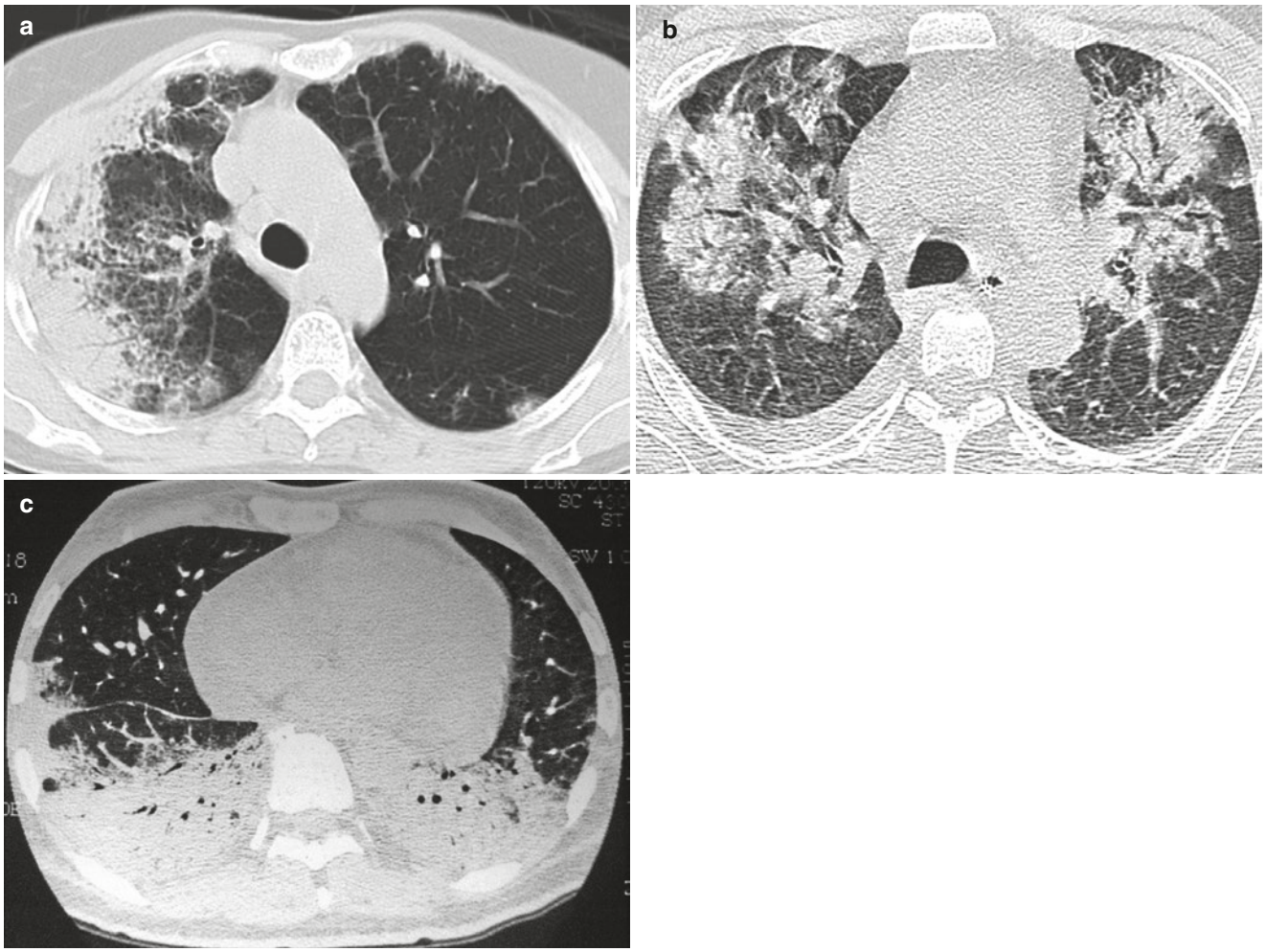

Fig. 35.2 (**a**–**c**) Chest CT scan in the classical multifocal form of organizing pneumonia in three patients: multiple bilateral alveolar opacities with an air bronchogram, mainly located in the subpleural areas and the lung bases

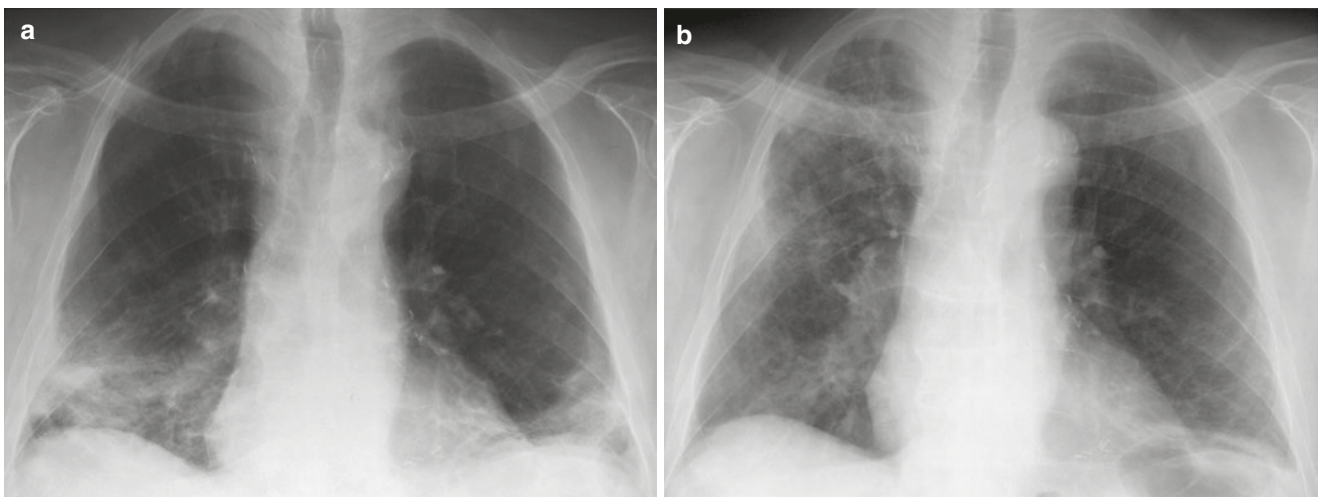

Fig. 35.3 Migratory opacities in organizing pneumonia. (**a**) Bilateral basal subpleural consolidations. (**b**) 3 weeks later, spontaneous healing of right basal consolidation and partial regression of left basal consolidation, but appearance of new ground glass opacities in the middle and upper fields of the right lung

note, in all non-operated cases, a spontaneous improvement of the opacity was observed [36, 40]. One practical difficulty in the management of nodular OP is thus to avoid unnecessary lobectomy in this benign disorder mimicking lung cancer. The causes of nodular OP are discussed later in this chapter.

Diffuse Infiltrative Form

A diffuse infiltrative imaging pattern has been reported to occur in 10–40% of cases in several series of OP [2, 10, 19, 23, 30, 42], some presenting with severe, rapidly progressive disease and respiratory failure [20, 43–49]. Some cases were associated with drugs, connective tissue diseases, or toxic exposure [48–50], whereas other appeared cryptogenic [20, 44, 45, 50].

Diffuse infiltrative OP probably represents a heterogeneous group. It has mainly been reported in early series of OP, suggesting misclassification or overlap with other entities, which were unknown at that time. Some early descriptions of diffuse infiltrative OP would probably be now better classified as nonspecific interstitial pneumonia (NSIP), an idiopathic interstitial pneumonia described in the 1990s and characterized histologically by homogeneous chronic interstitial inflammation and/or fibrosis with preserved lung architecture, in which intra-alveolar buds of granulation tissue are a common ancillary finding. Thus, OP pattern representing usually less than 10% (but sometimes up to 20%) of the total abnormalities is found in half of cases of NSIP at surgical lung biopsy [51, 52]. Sampling of such focal OP lesions by transbronchial biopsies might thus have led to misdiagnose NSIP as diffuse infiltrative OP. It has also been suggested that a continuum exists between OP and NSIP [52], and that OP/NSIP overlap might explain part of the diffuse infiltrative cases of OP [53]. Indeed, patients presenting at imaging with both interstitial changes (histologically corresponding to NSIP) and consolidations (histologically corresponding to OP) have been reported [54]. In a large series of NSIP, the distinction between OP and NSIP has been based upon whether OP pattern represents more or less than 10% or 20% of the total abnormalities at surgical lung biopsy, an arbitrary criterion [52]. In support of the concept of overlap between OP and NSIP, one study of 22 patients with OP proven by surgical lung biopsy and prolonged HRCT follow-up reported the evolution of OP consolidations into reticular changes resembling NSIP pattern in a subset of patients [55].

Other cases diagnosed as diffuse infiltrative OP may actually have had acute interstitial pneumonia, with OP being only a minor histopathological feature or overlapping with diffuse alveolar damage at the organizing stage. Other cases could correspond to "acute fibrinous and organizing pneumonia" (AFOP), a recently described entity combining clinical and pathological features of DAD and OP [56] (see below).

Table 35.2 Differential diagnosis of migratory pulmonary infiltrates

Organizing pneumonia (cryptogenic or secondary)
Chronic idiopathic eosinophilic pneumonia
Secondary eosinophilic pneumonias due to parasitic infections, drug toxicity, etc.
Eosinophilic granulomatosis with polyangiitis
Allergic bronchopulmonary aspergillosis
Granulomatosis with polyangiitis
Lupus pneumonitis
Hypersensitivity pneumonitis
Others

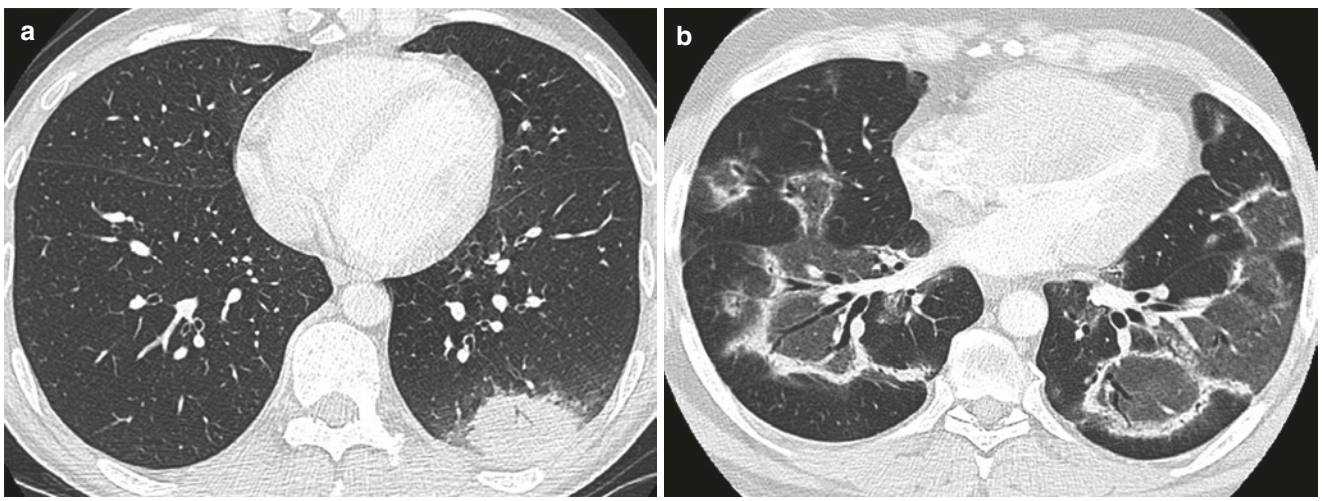

Fig. 35.4 (**a**) Isolated nodular form of organizing pneumonia: unique dense rounded mass with irregular margins located in the left lower lobe. (**b**) Reverse halo sign in organizing pneumonia: multifocal opacities characterized by dense margins and central ground glass opacities with air bronchogram. This feature is not specific and may be found in other inflammatory and infectious disorders

Finally, other cases initially reported as diffuse OP may have had acute exacerbation of interstitial lung disease (AE-ILD), an acute worsening of severe prognosis occurring in the natural history of idiopathic pulmonary fibrosis (IPF), NSIP and other fibrotic interstitial disorders [57]. AE-ILD has been associated with histological patterns of either OP or diffuse alveolar damage at lung biopsy, the former being correlated with a much better short term outcome [58]. Diffuse infiltrative OP still awaits better characterization. In the meanwhile, the above-mentioned disorders need to be considered in the differential diagnosis.

Other Imaging Patterns

Rarely, OP may present as multiple, sometimes cavitary nodules [59–62], a micronodular pattern, with multiple small well- or poorly-defined nodules, or nodules with an air bronchogram [63]. Other variants include a bronchocentric pattern, a perilobular pattern resembling thickened interlobular septa, circumferential subpleural linear opacities, and radial opacities [29, 59, 63–66]. A "ring-like," "reversed halo" or "atoll" pattern has rarely been reported in OP, consisting of a focal round area of ground glass surrounded by a crescent or ring of consolidation (Fig. 35.4b) [63]. Contrary to early beliefs, this sign is not specific to OP and may also be found in eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome), granulomatosis with polyangiitis (GPA, formerly Wegener granulomatosis), chronic eosinophilic pneumonia, lymphomatoid granulomatosis, tuberculosis, and various fungal infections [67].

Histopathological Diagnosis of OP Pattern

Buds of granulation tissue (Masson bodies) consisting of fibroblasts embedded in a myxoid matrix filling the distal airspaces (alveoli, alveolar ducts, and less commonly distal bronchioles) constitutes the histological hallmark of OP (Fig. 35.1). Associated features include mild interstitial inflammatory infiltrate, type II cell hyperplasia, and intra-alveolar foamy macrophages [2, 11, 13]. However, buds of granulation tissue are not specific and may be seen as an ancillary feature in many other disorders such as infections, the periphery of tumors, pneumonia distal to airway obstruction, hypersensitivity pneumonitis, NSIP, chronic idiopathic eosinophilic pneumonia, or GPA [11, 12, 68] (Table 35.3). For instance, OP pattern has been found in the vicinity of tumoral tissue in up to 40% of resected lung cancers [69]. Thus, a confident histopathological diagnosis of OP pattern requires: (1) the presence of buds of granulation tissue within distal airspaces as the dominant histopathological lesion and not only a minor feature, and (2) the absence of features suggesting another diagnosis such as prominent eosinophilic or neutrophilic inflammation, granulomas, hyaline membranes, acute bronchiolitis, or necrosis (see Box 35.1) [3, 11]. The main differential diagnosis of OP pattern at histopathology includes NSIP and the organizing stage of DAD [3].

Table 35.3 Disorders in which organizing pneumonia pattern may be found as an ancillary histopathological feature

Neoplasms
Pulmonary infections
Organization distal to airway obstruction
Aspiration pneumonia
Nonspecific interstitial pneumonia
Hypersensitivity pneumonitis
Desquamative interstitial pneumonia
Chronic idiopathic eosinophilic pneumonia
Secondary eosinophilic pneumonias
Eosinophilic granulomatosis with polyangiitis
Granulomatosis with polyangiitis
Primary pulmonary lymphoma
Diffuse alveolar damage
Drug reactions and toxic exposures
Others

Clinico-Pathological Diagnosis of OP Syndrome

The clinico-pathological diagnosis of OP requires the combination of clinical, imaging, and histopathological features. Thus, OP is essentially a multidisciplinary diagnosis. BAL is recommended in virtually all cases presenting with multiple or diffuse opacities at imaging in which a diagnosis of OP is suspected. It allows to exclude an infectious process and to differentiate OP from other inflammatory disorders having a similar picture such as eosinophilic pneumonias. A histological proof of OP should be obtained whenever possible [70]. Transbronchial lung biopsy (TBB) is the most commonly used method, whereas surgical lung biopsy is now performed in a minority of cases, although it can be considered as the gold standard for histological diagnosis of OP.

The diagnostic value of BAL and TBB to diagnose COP has been analyzed in one study [71]. In 37 consecutive patients presenting with clinical features suggestive of COP and bilateral patchy infiltrates at chest X-ray, BAL with >25% lymphocytes combined with 2 out of 3 other criteria (foamy macrophages >20%, neutrophils >5%, or eosinophils >2% and <25%) had a sensitivity of 63% and a specificity of 57% to diagnose COP [71]. A sensitivity of 20% and a specificity of 89% were found in another study using the same criteria [33]. Transbronchial biopsies showing buds of granulation tissue in distal airspaces, chronic inflammation of the alveolar walls, and preserved lung architecture were 64% sensitive and 86% specific for the diagnosis of COP [71]. Although generalization of these data is questionable, expert opinion-based current international guidelines consider that if the

clinical and imaging picture are typical with multifocal opacities, a TBB showing also typical intra-alveolar buds of granulation tissue is sufficient to confidently diagnose OP [3, 53].

If the initial clinical and imaging features are atypical (solitary nodular opacity, diffuse infiltrative pattern) and if an infection or tumor have not been found at bronchoscopy, a video-assisted thoracoscopic surgical lung biopsy may be necessary to make sure that OP is the dominant histopathological pattern and not just an ancillary finding in the frame of another pathological process (Fig. 35.5a) [70].

Transthoracic HRCT-guided needle biopsy has been reported as a useful minimally invasive diagnostic method for OP with a high diagnostic yield [72, 73]. Most patients studied had unilateral or bilateral consolidations or tumor-like lesions, and only a few had a diffuse infiltrative pattern [72, 73]. The most frequent complications were sub-clinical pneumothorax and minor hemoptysis, occurring in around 30% of cases. As transthoracic needle biopsy usually provides larger tissue samples than transbronchial biopsy, it may constitute an alternative to surgical lung biopsy in some cases (Fig. 35.5b). However, experience with this technique for the diagnosis of OP is currently insufficient to recommend it for routine clinical use.

Biopsy may be omitted in a minority of cases with typical clinico-radiological and BAL features, and a clearly identified causal agent of OP such as radiotherapy for breast cancer within the past year, recent documented infectious pneumonia, or obvious drug toxicity. In COP, a combination of typical BAL and multiple patchy parenchymal consolidations at imaging has been found diagnostic in half of cases in one series in the absence biopsy, and this strategy deserves further studies [33]. If the risk/benefit ratio of lung biopsy is considered unfavorable due to old age, frailty, or significant comorbidities, a presumptive diagnosis of OP and a therapeutic trial of prednisone may be an acceptable strategy. However, the disadvantages of prolonged empirical corticosteroid therapy in the absence of a clear diagnosis, and the risk of false diagnosis of OP, should also been kept in mind. Indeed, disorders mimicking the clinical and imaging features of OP may initially respond to corticosteroid treatment include GPA, primary pulmonary lymphoma, NSIP, or hypersensitivity pneumonitis. Therefore, if the disease follows an unusual course or the response to therapy is inadequate, the diagnosis of OP should be reconsidered, especially if the initial diagnosis was made without biopsy or with transbronchial biopsy only.

Differential Diagnosis

After having assessed the clinical, imaging, and histopathological features, which make OP a likely diagnostic hypothesis, one must consider other disorders presenting with similar features such as infections, tumors, and other inflammatory lung diseases. Imaging could be a starting point to address the differential diagnosis.

In cases presenting with single or multiple areas of parenchymal consolidation, the main differential diagnosis includes infections, minimally invasive or invasive adenocarcinoma, eosinophilic pneumonias (either idiopathic or secondary to a known cause), GPA, EGPA, and primary pulmonary lymphoma. The distinction between OP and GPA may be challenging in some cases, as GPA may present with clinical, imaging, and even histological features of OP pattern [11, 68]. Although the latter usually consist of small foci of OP at the vicinity of otherwise typical granulomatous

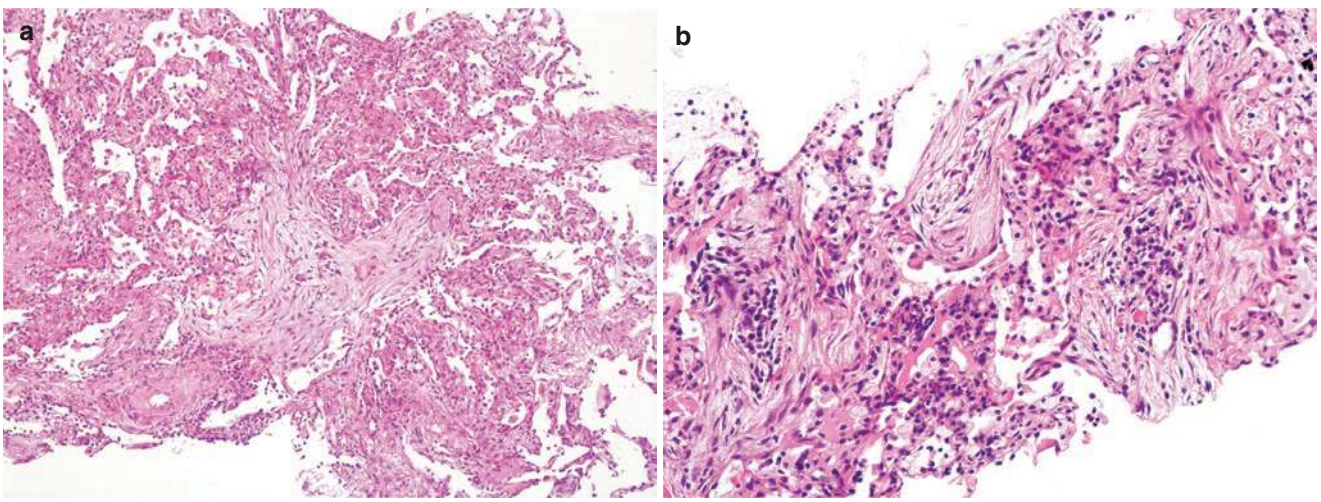

Fig. 35.5 (**a**) Transbronchial biopsy showing buds of granulation tissue filling alveolar spaces, with moderate lymphocytic inflammatory infiltrates of the alveolar walls, in a patient with unilateral ground glass opacities attributed to aspiration. (**b**) CT-guided transthoracic needle biopsy in organizing pneumonia. Numerous intra-alveolar buds of granulation tissue with fibroblasts and inflammatory cells embedded in a loose myxoid matrix are visible

lesions, OP pattern may occasionally be a prominent histological finding in GPA [11, 68].

In patients presenting with a solitary nodule or mass, lung cancer is the main working hypothesis until proven otherwise. When multiple nodules are present, the differential diagnosis includes metastatic tumors, lymphomas, and pulmonary infections including septic emboli.

If OP presents as a diffuse infiltrative disorder at imaging, the differential diagnosis mainly includes hypersensitivity pneumonitis, NSIP, acute interstitial pneumonia (AIP), other IIP, and AE-ILD.

Etiological Diagnosis of OP

The next step in the diagnostic process of OP is to distinguish between SOP and COP. The search for a cause or associated condition should not be overlooked, as removal of an offending agent, such as a drug, is an essential part of therapy. Since there is no clinical, radiological, or histological characteristic allowing to confidently distinguish COP from secondary OP [24], the diagnosis of COP is made by exclusion, when the search for a cause remains negative.

SOP has been associated with numerous causal agents and clinical contexts (Table 35.4) [24, 70]. It frequently occurs in association with various infections mostly caused by bacteria, but occasionally also by viral, fungal, and parasitic agents. Another frequent cause of OP is a drug reaction [70]. A comprehensive and updated list of incriminated drugs is available on www.pneumotox.com. OP can also arise in the context of connective tissue diseases such as idiopathic inflammatory myopathies or rheumatoid arthritis, and in various types of solid cancers and hematologic malignancies, where it should not be mistaken for neoplasm progression or recurrence [74]. One example is provided by bleomycin toxicity: besides diffuse interstitial lung disease, bleomycin can also occasionally induce OP manifesting as pulmonary nodules mimicking metastatic tumor [75–77]. OP can also occur during myelo- or lymphoproliferative syndromes, and after lung or bone marrow transplantation. In the latter, an association has been demonstrated between OP and both acute and chronic forms of graft-versus-host disease, suggesting that a causal relationship may exist between these two conditions [78]. Recently identified causes of OP or OP pattern at imaging or histopathology include treatment with immune checkpoint inhibitors [79–81], vaping-induced

Table 35.4 Causes of secondary organizing pneumonia, with relative frequencies of main categories (from reference [24])

Infections	**~45%**
Bacteria (*Actinomyces*, *Chlamydia pneumoniae*, *Coxiella burnetii*, *Legionella pneumophila*, *Mycoplasma pneumoniae*, *Nocardia asteroides*, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Staphylococcus aureus*, *Streptococcus group B*, *Streptococcus pneumonia*), **virus** (*adenovirus*, *cytomegalovirus*, *hepatitis C*, *herpes virus*, *human immunodeficiency virus*, *human T-cell lymphotropic virus*, *influenza A and B*, *parainfluenza*, *SARS-CoV-2 coronavirus*), **parasites** (*Plasmodium vivax*, *hydatic cyst)*, **fungi** (*Aspergillus fumgatus*, *Cryptococcus neoformans*, *Penicillium janthinellum*, *Pneumocystis jiroveci*)	
Drugs	**~20%**
Adalimumab, 5-Aminosalicylic acid, amiodarone, amphotericin, azacitidine, azathioprin, barbiturates, betablockers, bleomycin, busulphan, carbamazepine, cephalosporin, certinib, cetuximab, clomipramine, cocaine, durvalumab, erlotinib, etanercept, everolimus, gemcitabine, gold salts, interferon, lamotrigine, L-tryptophane, mesalazine, minocycline, nitrofurantoin, nilutamide, nivolumab, oxaliplatin, paclitaxel, pegylated interferon α, pembrolizumab, phenytoin, propylthiouracil, rituximab, sulfasalazine, tacrolimus, thalidomide, temozolomide, ticlopidine, transtuzumab. **See also** www.pneumotox.com	
Solid tumors and hematologic malignancies	**~15%**
Connective tissue diseases	**~11%**
Ankylosing spondylitis, Behçet disease, mixed connective-tissue disease, polymyalgia rheumatica, polymyositis and dermatomyositis including anti-synthetase syndrome, rheumatoid arthritis, Sjögren syndrome, adult-onset Still's disease, systemic lupus erythematosus, systemic sclerosis, undifferentiated connective tissue disease and interstitial pneumonia with autoimmune features	
Radiation therapy	**~9%**
breast carcinoma, lung carcinoma, rarely other tumors	
Allografts	
Lung, kidney, liver, bone marrow, hematopoietic stem cells	
Inflammatory bowel diseases	
Toxic exposures	
Acramin FWN (an aerosolized textile dye), crystalline silica, e-cigarette use, frying of jalapeño peppers, house fire, nitric acid fumes, paraffinic mineral oil, paraquat, sulfur dioxide, tetrachloroethylene, titanium dioxide nanoparticles in powder paint	
Post-obstructive pneumonia and aspiration pneumonia	
Others	
Anthracosis, chronic recurrent noninfectious osteomyelitis, common variable immunodeficiency, coronary artery bypass graft surgery, essential mixed cryoglobulinemia, gastroesophageal reflux disease, IgA nephropathy, IgG-4 disease, mesangiocapillary glomerulonephropathy, neuromyelitis optica, plasmocytoma, primary biliary cirrhosis, SAPHO syndrome, Sweet's syndrome, thyroiditis	

lung injury associated with e-cigarette use [82, 83], and SARS-CoV-2 infection [84–86].

OP has been reported after radiation therapy, especially in women irradiated for breast cancer [87–95], with a reported incidence of 1.4–1.8% in 2 large prospective series of 1176 and 2056 patients [91, 94]. Patients affected by this particular form of OP are women treated by tumorectomy or mastectomy followed by chemotherapy or hormonal therapy, and radiation therapy of approximately 50 Gy on the tumoral site and homolateral lymph nodes. The clinical picture is identical to COP and starts on average 14 weeks after the irradiation, although it can occur up to 1 year later [87]. In contrast to classical radiation pneumonitis, which is limited to the radiation field, radiation-induced OP also affects the lung outside the radiation field and frequently involves the contralateral lung. Opacities are frequently migratory [96]. BAL shows a typical mixed pattern alveolitis. The outcome is favorable under corticosteroid treatment [87]. Despite the frequent occurrence of relapses, a complete cured is usually observed. In milder cases, spontaneous disappearance without corticosteroids has been reported [93]. The particular tangential irradiation fields used for breast cancer might play a role in the occurrence of OP in this context. A bilateral lymphocytic alveolitis has been reported to occur in 85% of women receiving unilateral irradiation for breast cancer and, despite being asymptomatic in most cases, could be an early event in the occurrence of OP [97]. Hormonal factors could also be involved. Indeed, in one study, age >50 and antiestrogen therapy were significantly correlated with the occurrence of OP, with odd ratios of, respectively, 8.88 and 3.05 [92]. However, given the importance of hormonal therapy for tumor control in these patients, avoidance or interruption of hormonal therapy to prevent or cure OP is not recommended. In another large study, older age and smoking were identified as risk factors, whereas the type of previous surgery (mastectomy or breast-conserving surgery) and the irradiated volume were not associated with OP [94]. Although more frequently described in women irradiated for breast carcinoma, radiation-induced OP has also been reported in individuals of both genders irradiated for other types of tumors, especially after stereotactic ablative radiotherapy for localized non-small cell lung cancer [98, 99]. In the latter cases, OP affected 5% of irradiated patients, and previous symptomatic radiation pneumonitis around the tumor site was strongly associated with the occurrence of OP (hazard ratio 62) outside the radiation fields 2–7 months later [98]. Radiation-induced activation of inflammatory cells and pathways likely plays a role in this phenomenon.

The cause and mechanisms of focal OP are probably different from the other forms of OP. Although some authors found focal OP to be idiopathic in most cases [38], others have reported underlying COPD in up to 67% of cases, and recurrent respiratory infections in up to 57% [37], suggesting that focal OP may be triggered and preceded by an infectious process. In support of this hypothesis, one study reported the occurrence of small neutrophil aggregates in the vicinity of localized OP (with otherwise typical OP pattern at histopathology) in 73% of cases [39]. Aspiration of food particles may be another cause of focal OP [100]. In one retrospective study of 59 cases of aspiration pneumonia, OP pattern was the predominant histopathological pattern in 88%, usually associated with particulate foreign material, multinucleated giant cells, acute pneumonia, bronchiolitis, or suppurative granulomas [100]. Twenty-two percent of these cases presented as solitary nodules suspect of lung cancer, whereas food aspiration was clinically suspected in less than 10% [100]. Sub-clinical particulate matter aspiration pneumonia may thus be a relatively common cause of lung nodules presenting with OP pattern at histopathology.

In the majority of cases, OP has no recognizable cause [20] and is termed cryptogenic OP (COP). COP has been integrated in 2002 in the classification of idiopathic interstitial pneumonias [3], and maintained in the 2013 update of this classification in the category of acute/subacute disorders [4].

Treatment

Corticosteroids are the current standard treatment of OP [2, 14, 17, 19, 23, 28, 31], although spontaneous improvement has occasionally been reported [2, 93]. Clinical improvement usually occurs within 2–3 days after treatment onset. Pulmonary infiltrates at chest X-ray usually markedly improve within a few days. On average, a >50% improvement at imaging usually occurs within 3 weeks of treatment, and complete cure is observed after around 3 months [18, 19]. The spectacular and reproducible response to corticosteroids can even be considered as an additional diagnostic feature of the clinical syndrome of OP, and if this response is poor, the initial diagnosis should be reconsidered. Besides corticosteroids, removal of the causing agent should be done whenever possible in secondary OP.

Treatment intensity and duration have not been well defined. In patients with typical COP, an initial dose of prednisone of 0.75 mg/kg/day has been proposed for 2–4 weeks [19, 53]. Corticosteroids are then usually tapered over 6 months and stopped. However, this duration can extend up to 12 months or even longer due to relapses in a significant proportion of patients. Side effects of prolonged corticosteroid treatment occur in up to 25% [19]. In an attempt to better define the corticosteroid treatment in COP, a standardized therapeutic regimen has been proposed by one group (Table 35.5) [19]. A retrospective comparison of patients having received this standardized protocol with a group treated with other therapeutic regimens did not reveal any

Table 35.5 Proposed therapeutic regimen for typical COP[a]

Step	Duration	Doses of prednisone for the initial episode	Doses of prednisone for the first relapse
1	4 weeks	0.75 mg/kg/day	20 mg/day
2	4 weeks	0.5 mg/kg/day	20 mg/day
3	4 weeks	20 mg/day	20 mg/day
4	6 weeks	10 mg/day	10 mg/day
5	6 weeks	5 mg/day	5 mg/day

[a] Adapted from reference [19]

differences in terms of efficacy, delay to remission, occurrence of relapses, morbidity, or final outcome [19]. In contrast, cumulated doses of prednisone after 1 year were reduced twofold in the group who had received the standardized treatment [19]. This therapeutic regimen may thus provide a framework to guide management and limit the burden of corticosteroid therapy, while maintaining the same efficacy on disease control as higher doses of prednisone. However, given the wide clinical expression and severity of the disease, a unique treatment regimen cannot cover all clinical situations, and physicians need to adjust the prednisone dose to disease severity, response to therapy, and side effects. In severe OP, prednisolone IV boluses during 3 consecutive days [45–47] and immunosuppressive treatment with cyclophosphamide, azathioprine, mycophenolate mofetil, cyclosporine, rituximab, tocilizumab or intravenous immunoglobulins have been used [43, 44, 48, 49, 101–108].

Whether SOP should be treated differently from COP is currently unclear, but likely depends on the clinical context. Some reports suggest that SOP is associated with less frequent resolution of symptoms and higher mortality than COP [23, 109] although other studies do not confirm these findings [24, 110]. In a comparison of COP and OP secondary to connective tissue disease, treatment modalities, response rate and mortality rate were similar, although complete recovery was slightly more frequent in COP [111]. In clinically amyopathic dermatomyositis associated with anti-melanoma-differentiation-associated gene 5 (MDA5) autoantibodies, a rapidly progressive interstitial lung disease may occur with a pattern of OP at imaging and histopathology [112–114], whereas other cases present with NSIP or DAD [114–116]. This acute or subacute life-threatening condition may lead to death within weeks after disease onset [117, 118], and is usually refractory to corticosteroids alone, event at high doses. In a retrospective comparison of two treatment strategies in Japan, patients receiving simultaneous triple immunosuppression with high-dose glucocorticoids, tacrolimus, and IV cyclophosphamide had better survival than historical controls who received step-up treatment with high-dose glucocorticoids alone initially, and other immunosuppressants at a later stage (89% versus 33%, $p < 0.0001$) [119]. One national treatment guideline recommends a combination of high-dose corticosteroids and calcineurin inhibitors, with or without cyclophosphamide, as a first choice for this condition [120]. A similar picture of acute/subacute, life-threatening, and steroid-resistant interstitial lung disease can also be observed in other idiopathic inflammatory myopathies, especially those associated with anti-synthetase autoantibodies, with lung histological patterns of OP, NSIP or DAD [121, 122]. In these cases, a combined therapy of high-dose corticosteroids with another immunosuppressive agent appears associated with better outcomes than initial corticosteroid monotherapy with later addition of other agents [123, 124]. A management algorithm has been proposed to guide decisions in these difficult situations [125].

At the other end of the severity spectrum, not all cases of OP require treatment. In 6 large series totalizing 418 cases [2, 20, 24, 28, 50, 111], 12% of patients (range across series 3–23%) did not receive corticosteroids. Among 26 of these cases with reported outcome, spontaneous improvement was noted in 8/26 and complete cure in 16/26 [20, 50, 111]. In another study of 12 women with OP after radiation therapy for breast cancer detected by systematic chest X-ray, only six were symptomatic. Hormonal treatment was temporarily withheld in nine, and complete cure was observed in all without corticosteroids [93]. Thus, in asymptomatic patients with mild OP, corticosteroids may not be necessary, and careful clinical and chest-X-ray follow-up may be the best initial strategy.

Some macrolide antibiotics (erythromycin, clarithromycin, and azithromycin) possess anti-inflammatory properties, which have first proven beneficial in diffuse panbronchiolitis [126, 127], and later in cystic fibrosis, bronchiolitis obliterans syndrome after lung transplantation, bronchiectasis, and COPD. A therapeutic effect of erythromycin and clarithromycin has also been reported in series of COP and OP secondary to radiation therapy for breast cancer [128–133]. In three retrospective series of up to 40 cases published by one group, patients with mild to moderate COP received clarithromycin 1000 mg/day for 3–4 months. A complete cure was observed in more than 80% of cases, whereas a minority had only a partial response or no response, and required prednisone as rescue therapy [131–133]. As compared to a control group treated with prednisone for a mean of 9 ± 3 months, patients who received clarithromycin during 3 months had significantly less relapses (10% versus 55%, $p < 0.0001$) [132]. In responders to clarithromycin, a significant reduction of serum and BAL interleukin-6 was observed,

whereas non-responders had no such changes [133]. However, no benefit of clarithromycin was observed in another retrospective study, which compared 16 patients treated with a combination of clarithromycin and prednisone during 12 weeks, and 21 patients treated with prednisone alone during 24 weeks [134]. Complete radiological remission was achieved in only 63% of the combined therapy group and 81% of the prednisone alone group (p = 0.38). Symptomatic relapses occurred in 81% of the combined therapy group, and 52% of the prednisone alone group (p = 0.14) [134]. In these studies, the delay to clinical improvement appeared longer with macrolides than with corticosteroids (weeks instead of days) and therapeutic response was less frequent [128–133]. Taken together, these data suggest that macrolides might have an interest as corticosteroid-sparing agents in a subgroup of patients with mild OP, and might reduce the relapse rate. However, given the heterogeneity and purely retrospective nature of currently available data, macrolides cannot be recommended at the present time to treat OP in the usual clinical setting, and further studies are needed.

Clinical Course and Outcome

In typical multifocal COP, the outcome is usually excellent with disappearance of symptoms and normalization of imaging in more than 80% of cases [19]. In a minority of cases, some minor fibrous sequelae can persist at imaging. Overall mortality in COP is reported to be <5% [19, 20]. It has been suggested that the prognosis could be less favorable in SOP than in COP [2, 13, 23, 48], but a formal comparison did not find any significant difference between COP and SOP in clinical features, response to therapy, relapses, and outcome [24].

COP and SOP are characterized by the frequent occurrence of relapses when corticosteroid treatment is tapered or stopped [1, 2, 14, 19, 135–139]. Single or multiple relapses have been reported in up to 58% of cases of COP [19]. Most relapses occur within the first year, while patients are still taking low-dose prednisone (usually <10 mg/day) for the initial episode. A relapse occurring under higher doses (>20 mg/day) or >18 months after the initial episode is unusual and should prompt to carefully re-assess the diagnosis. The cause of relapses is unknown, but the initial episode of COP and the subsequent relapses may be viewed as a single pathological process, which progressively abates over time [19]. Relapses are not due to insufficient prednisone dose for the initial episode, but delayed treatment onset could be a risk factor [19]. Other factors associated with relapse occurrence were more severe hypoxemia at first examination [139], elevation of serum gamma-glutamyl-transferase and alkaline phosphatase [19], multifocal OP at imaging [137, 138], BAL neutrophilia [135], and fibrin deposits at lung biopsy [135, 136]. Importantly, relapses did not affect morbidity and mortality [19]. Therefore, preventing relapses by extending treatment duration appears unnecessary in most cases, and the strategy should rather aim at minimizing the adverse effects of corticosteroids. To avoid unnecessary concerns, the possible occurrence of relapses should be explained to the patient during tapering of prednisone for the initial episode. The occurrence of a relapse in OP should prompt to reconsider the hypothesis of a persisting causal agent, such as a drug, which has not been removed initially.

Aggressive treatment of relapses is unnecessary, as they usually constitute a relatively benign phenomenon, which can be controlled with a moderate increase of corticosteroid treatment. Accordingly, a low-dose regimen of 6-month duration to treat relapses of COP has been proposed (Table 35.5), starting with 20 mg/day of prednisone [19]. In localized OP, relapses are less common [37, 38], but also respond to corticosteroids. Mild asymptomatic relapses detected at chest X-ray may be observed without treatment.

Severe Forms of OP with Respiratory Failure

Patients with severe OP have been reported in several small series and isolated cases [20, 44, 45, 48, 49, 101, 103, 140, 141]. Some of these cases were secondary to connective tissue diseases, drugs, or toxic exposure to an aerosol textile dye [48, 49] and others were idiopathic [20, 44, 45, 103, 140, 141]. In the 38 cases from four series with available data [44, 45, 48, 49], all patients received high-dose corticosteroids, 32% received immunosuppressive drugs (mostly cyclophosphamide), and 34% required mechanical ventilation. Thirty-two percent recovered, 11% evolved to chronic respiratory insufficiency or required lung transplantation, and 58% died. Factors associated with a poorer outcome in OP include presence of connective tissue disease [48], diffuse infiltrative pattern at imaging [14, 142], absence of lymphocytosis and predominant neutrophilia at BAL [14, 48], and interstitial fibrosis with architecture remodeling and scarring of the lung parenchyma [44]. The term *fibrosing organizing pneumonia* has been used to describe these cases characterized by dense hyalinization and fibrosis of Masson bodies and alveolar septa, as well as obliterative fibrosis of alveolar ducts with loss of normal lung architecture [103, 143]. This fibrotic pattern at histopathology could explain the steroid-unresponsive character of these cases and the associated poorer outcome. Other severe cases may have in fact other disorders in which the OP pattern found at histopathology is only an ancillary histological finding, such acute interstitial pneumonia, ARDS, AE-ILD, or acute fibrinous and organizing pneumonia (see below). In other cases, OP may have been the initial pathologic process, but lung injury may have

occurred as a secondary event due to superimposed infection or drug toxicity. Severe and acute forms of OP occurring in idiopathic inflammatory myopathies are described above.

Acute Fibrinous and Organizing Pneumonia

Acute fibrinous and organizing pneumonia (AFOP) has been reported in 2002 as a histopathological entity with overlapping features of DAD and OP [56]. Two very different clinical courses have been observed with the same histological picture, and the imaging characteristics have not been fully characterized. Therefore, in contrast with OP, AFOP cannot be currently viewed as a clinico-pathological syndrome but rather as a particular and uncommon histopathological pattern, which clinical significance needs to be further clarified. AFOP has been integrated in the 2013 classification of idiopathic interstitial pneumonias in the category of rare histopathological patterns [4].

In the original report of 17 cases of AFOP identified retrospectively from surgical biopsy files [56], disease onset followed an acute or subacute course with a mean time from first symptoms to lung biopsy of less than 2 months (mean 19 days). The most frequent symptoms were dyspnea (71%), cough (24%), fever (35%), weakness (29%), and thoracoabdominal pain (29%). One or more associated conditions were identified in two thirds of cases including history of environmental exposure, drug exposure, connective tissue disease, and comorbidities resulting in altered immunity (Table 35.6). Other cases were idiopathic. Most frequent chest X-ray features included bilateral basal and diffuse opacities, but detailed chest imaging characteristics were not available. Two distinct disease patterns and outcomes were identified, each affecting about half of cases: (1) severe rapidly progressive disease resembling classical DAD and leading to death within less than 1 month, and (2) mild subacute disease course resembling classical OP (Fig. 35.6a), and leading to recovery. The overall mortality rate was 53%, which was similar to ARDS and much higher than classical OP. At lung histopathology, the dominant findings were prominent intra-alveolar fibrin balls filling around 50% (range 25–90%) of alveolar spaces, with a conspicuous patchy distribution and a relatively normal intervening lung parenchyma. OP with buds of fibroblasts within airspaces was present in all cases, but was usually less abundant than intra-alveolar fibrin (Fig. 35.6b). Associated features included mild to moderate interstitial infiltrate with edema, predominant lymphocytes, sparse neutrophils, and type 2 pneumocyte hyperplasia. There were no hyaline membranes, abscesses, or granulomas. No histological characteristics were found predictive of outcome. The histopathological features of AFOP are summarized in Table 35.7.

Table 35.6 Conditions associated with acute fibrinous organizing pneumonia[a]

Infections
Acinetobacter baumanii, *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Legionella pneumophila*, *Pneumocystis jiroveci*, human immunodeficiency virus, SARS coronavirus, SARS-CoV-2 coronavirus.
Drugs
Abacavir, amiodarone, bleomycin, busulfan, decitabine, nivolumab,
Autoimmune disease
Polymyositis, dermatomyositis, ankylosing spondylitis, systemic lupus erythematosus, primary biliary cirrhosis
Tumors
Lymphoma, acute lymphocytic leukemia, myelodysplastic syndrome
Environmental exposures
Construction worker, animal exposure (zoologist), excessive hair-spray use, coalminer
Allografts
Hematopoietic stem cell transplantation, lung transplantation
Other
Renal failure, avian exposure
Idiopathic

[a] Adapted from reference [56] and pneumotox.com

In its original description, AFOP was classified as a fibrinous variant of DAD, which, however, differs from classical DAD by several aspects: (1) organizing intra-alveolar fibrin was the dominant feature, whereas it is less prominent in classical DAD, (2) fibrin was organized into "balls" with a patchy distribution, as opposed to the widespread changes found in DAD, (3) intervening lung parenchyma appeared relatively normal in most cases, and (4) hyaline membranes were absent. AFOP differed from typical acute infectious pneumonia by the absence of significant neutrophilic inflammation. AFOP also markedly differed from classical OP by the predominance of intra-alveolar fibrin over intra-alveolar buds of granulation tissue. Besides histopathological differences, AFOP and classical OP were characterized by different disease course [56]. However, one cannot rule out that AFOP corresponds to a particular variant of severe OP, with lung biopsy performed at an early stage of the OP pathogenic process when fibrin fills the alveolar spaces before being colonized by proliferating fibroblasts to constitute the classical buds of granulation tissue. Further studies are needed to clarify this issue.

Similarly to the OP pattern, the histological AFOP pattern has been found as a minor nonspecific reaction in the vicinity of abscesses, necrotizing granulomas, GPA lesions, and lung carcinomas [56]. For this reason, and until more data become available, transbronchial biopsies should not be considered adequate to diagnose AFOP, and this pattern can currently be identified only by surgical lung biopsy.

Treatment of AFOP is not codified. In the original report, most patients received antibiotics and/or corticosteroids, but no correlation was found between treatment modalities

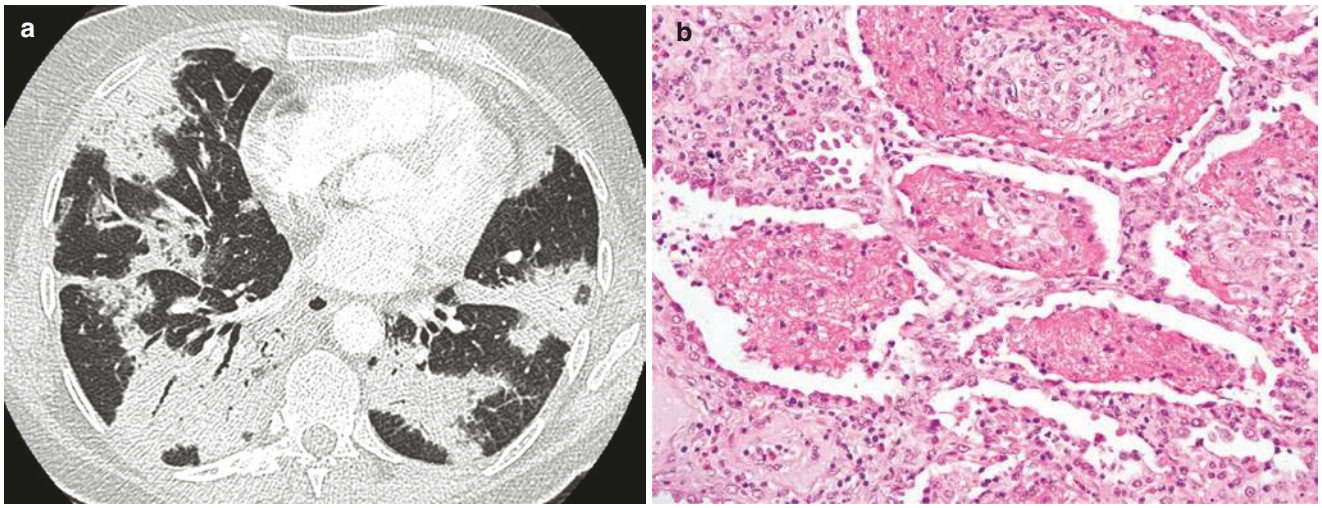

Fig. 35.6 Acute fibrinous and organizing pneumonia in a 68-old woman with symptoms of several months duration and lack of response to empirical antibiotic therapy. (**a**) Multifocal alveolar opacities with air bronchogram predominant at the lung bases. (**b**) Surgical lung biopsy showing prominent fibrin clusters filling alveolar spaces, with a lesser component of fibroblasts and inflammatory cells

Table 35.7 Histopathological features of acute fibrinous and organizing pneumonia[a]

Major features
Organizing intra-alveolar fibrin "balls" as dominant finding
Organizing pneumonia pattern, less prominent than fibrin balls
Patchy distribution of lesions
Minor features
Mild to moderate acute and/or chronic interstitial inflammation
Alveolar septal expansion by myxoid connective tissue
Type 2 pneumocyte hyperplasia
Interstitial changes co-localized with patchy intra-alveolar fibrin lesions, with only minimal changes in the intervening parenchyma
Absence of:
hyaline membranes
prominent eosinophilic inflammation
prominent neutrophilic inflammation or abscesses
granulomatous inflammation

[a] Adapted from reference [56]

and outcome [56]. However, more than half of the patients did not receive corticosteroids, or received them late in the disease course. It therefore cannot be concluded that steroids are not effective in AFOP. Furthermore, significant and even dramatic improvement with corticosteroids has been reported by some authors [144]. The usefulness of cyclophosphamide and mycophenolate mofetil in addition to corticosteroids has been occasionally reported [145, 146]. Similarly to classical COP, relapses have been reported in AFOP [144].

Until the clinical significance of the AFOP pattern is further clarified, this histopathological finding should lead the clinician to consider the disease course as potentially more severe and life-threatening than classical OP. Similarly to OP, a cause or associated condition should be looked for in AFOP, and removed whenever possible. Corticosteroids seem effective in a number of cases and a steroid trial should be attempted after having ruled out or treated an infectious process.

Granulomatous Organizing Pneumonia

A granulomatous variant of OP has been reported in a retrospective series of histopathological specimens obtained by surgical lung biopsy in patients investigated for thoracic malignancies, and termed "granulomatous OP" (GOP) [147]. It is characterized histologically by non-necrotizing poorly formed granulomas intimately associated with the plugs of granulation tissue of OP, in the absence of any microorganism, which could explain this finding. The clinical picture and chest imaging did not differ significantly from other patients presenting with either OP or AFOP at histopathology, except for being less likely to have had cancer and to have received prior chemotherapy, and more frequently presenting as a nodule or mass [147]. The clinical significance of GOP remains to be further characterized in other studies.

Acute Interstitial Pneumonia

Definition and Terminology

Acute interstitial pneumonia, formerly known as Hamman–Rich syndrome, defines an idiopathic form of acute lung injury characterized clinically by acute or subacute respiratory failure, bilateral lung infiltrates at imaging, and DAD at histopathology. By definition, no cause is identified despite comprehensive investigations. This combination of features was first described in 1935 by Hamman and Rich in four

cases [148] and named consequently Hamman–Rich syndrome. However, this term was later used incorrectly to describe more broadly other forms of subacute and chronic lung fibrosis, including IPF. Therefore, Katzenstein et al. introduced the term "acute interstitial pneumonia" (AIP) in 1986 to describe the very single acute idiopathic clinicopathological condition recognized by Hamman and Rich [149]. In 1990, Olson et al. confirmed that AIP is identical to Hamman–Rich syndrome [150]. In 2000 and 2002, American Thoracic Society/European Respiratory Society guidelines recognized AIP as a distinct form of idiopathic interstitial pneumonia (IIP) [3, 151]. In a revised version of the guidelines published in 2013, AIP was classified among the six major IIP in a subgroup of acute/subacute IIP, together with COP [4].

Epidemiology

Data on AIP are sparse and based on small case series. The disease is found at any age. Patients from 1 to 83 years old have been reported, with a median age between 50 and 60 years. AIP affects equally males and females. No risk factor was identified so far and in most cases AIP occurs in previously healthy individuals [149, 152–161].

Clinical Picture

AIP has an acute or subacute presentation, and usually begins as a flu-like syndrome with dry cough, sore throat, myalgia, fatigue, and headache in the first week of the disease. Fever may sometimes be present. In most cases, severe dyspnea occurs rapidly after the first symptoms, usually in the first day to 3 weeks [149, 153], and evolves towards respiratory failure. However, slowly progressive forms over 2 or 3 months have also been reported [153, 159–162]. On physical examination, patients appear ill, with tachycardia, tachypnea, diffuse pulmonary crackles and sometimes wheeze on chest auscultation. Associated signs of extra-pulmonary disease are uncommon and should raise the suspicion of another diagnosis [148, 161]. Digital clubbing, which is not a feature of AIP, is more suggestive of acute exacerbation of a pre-existing ILD (AE-ILD) [158]. Virtually all patients develop respiratory failure requiring mechanical ventilation. Only a few patients do not require hospitalization.

Imaging

Chest radiograph usually shows bilateral patchy or diffuse infiltrates. Pleural effusion is uncommon. At HRCT, ground glass attenuation and diffuse airspace consolidation are the main findings through the early stages of the disease. Traction bronchiectasis and distortion of bronchovascular bundles appear in the proliferative phase of the disease, and the number of affected lung segments may correlate with disease duration [163]. Honeycombing may also be found at a later stage. However, it is unclear whether its presence is the consequence of DAD or indicates pre-existing ILD undergoing acute exacerbation [152, 163].

Histopathology

Histopathology showing a DAD pattern of unknown cause constitutes a mandatory criterion for a definite AIP diagnosis. However, in clinical practice, the risks of performing a biopsy may outweigh the benefit in a patient with respiratory failure. After having carefully weighted the risk/benefit ratio, a (transbronchial or surgical) biopsy may be performed in a patient already on mechanical ventilation. In some cases, the histopathological diagnosis is obtained retrospectively at autopsy. If performed, surgical or transbronchial biopsy in AIP may show either one of two disease stages: an exudative stage in the first week of the disease, followed by an organizing stage. The tissue damage is usually diffuse and has a uniform temporal appearance. The exudative stage is characterized by interstitial and intra-alveolar edema, formation of hyaline membranes (amorphous eosinophilic structures plastered along alveolar septa and composed of necrotic pneumocytes and serum proteins), hyperplasia of type II pneumocytes, intra-alveolar hemorrhage, and a sparse interstitial infiltrate of mononuclear inflammatory cells. Alveolar collapse and thrombosis of small- to medium-sized pulmonary arterioles are common findings. The organizing stage begins one or more weeks following injury and is most prominent after 2 weeks. It shows hyaline membranes resorption by alveolar macrophages, or incorporation in the alveolar septa resulting from type II pneumocytes proliferation on the luminal side of the hyaline membranes. Loose fibroblastic proliferation occurs in the interstitium, and focally in the alveolar spaces. In the late phase, fibroblasts proliferation in the interstitium gives an image of interstitial thickening. Inflammatory cells, especially neutrophils, are usually scant. Recovery of lung architecture may be complete, or progression towards honeycomb fibrosis may be observed if the patient survives [3, 149]. Acute and organizing DAD frequently coexist on lung biopsies, as the process is a continuum. Temporally uniform lesions, presence of hyaline membranes, edematous stroma, an important number of fibroblasts and little collagen deposition are distinctive characteristics allowing to differentiate DAD from usual interstitial pneumonia, NSIP or OP pattern [3, 164]. Once DAD has been identified, a determined cause must be ruled out before accepting the diagnosis of AIP. To exclude an alternative

diagnosis, the histology must not show granulomas, necrosis, abscess or infectious agents. Biopsy may allow to identify the cause of DAD, such as pathogens that are not or slowly growing on culture, especially *Pneumocystis*, cytomegalovirus, mycobacteria, *Blastomyces*, and *Histoplasma* [165]. Biopsy culture is also recommended. Infections, drug toxicities, aspiration, and connective tissue diseases are typical causes of DAD [150]. The pneumotox.com website provides a comprehensive and updated list of drugs which can induce DAD. Other causes of DAD are listed in Table 35.8.

Diagnosis

AIP is a diagnosis of exclusion based on the following criteria [3, 149, 165, 168]:

1. rapid onset (<60 days) of respiratory symptoms leading to severe hypoxemia, and in most cases to acute respiratory failure
2. bilateral lung infiltrates on chest imaging
3. DAD on (ante- or postmortem) histopathology
4. absence of any etiology or predisposing factor after thorough investigations looking for infections, connective tissue disease, prior ILD, drugs, or toxic exposures.

Table 35.8 Causes of diffuse alveolar damage. From references [12, 165–167]

Aspiration
Acute exacerbation of usual interstitial pneumonia
Connective tissues diseases
Rheumatoid arthritis, Polymyositis/dermatomyositis, Systemic lupus erythematosus, Systemic sclerosis, Mixed connective tissue disease, Sjögren syndrome, Anti-synthetase syndrome
Drugs
Amiodarone, Azathioprine, Bleomycin, Busulfan, Carmustine (BCNU), Cocaine, Cyclophosphamide, Cytosine-arabinoside (Ara-C), Gemcitabine, Gold, Heroin and opiates, Melphalan, Methotrexate, Mitomycin, Nitrofurantoin, Penicillamin, others (see www.pneumotox.com)
Infection
Bacteria
Legionella, Mycoplasma, Rickettsia
Viruses
influenza, herpes simplex virus type 1, cytomegalovirus, adenovirus, respiratory syncytial virus, hantavirus, SARS, SARS-CoV-2
Fungi
Histoplasma, Cryptococcus, Pneumocystis
Nontuberculous mycobacteria
Oxygen toxicity
Radiation
Sepsis
Shock
Traumatic, hemorrhagic, neurogenic, cardiogenic
Miscellaneous
Acute pancreatitis, burns, cardiopulmonary bypass, high altitude, intravenous contrast material, leukemic cell lysis, molar pregnancy, near-drowning, peritoneovenous shunt, lymphangiography, toxic shock syndrome, transfusion, uremia, venous air embolism
Unknown cause
Acute interstitial pneumonia (Hamman–Rich syndrome)

Blood neutrophilia is present in many patients but laboratory findings are not specific.

A histological evidence of DAD is theoretically needed for the diagnosis of AIP, in contrast to the diagnosis of ARDS. If DAD is demonstrated without identified cause despite comprehensive work-up, the condition is diagnosed as AIP. In case of ARDS of undetermined origin without histologic examination, the condition will remain termed ARDS of unknown etiology [165]. Indeed, ARDS is defined solely on clinical grounds, whereas a diagnosis of AIP requires both clinical and histopathological data. Thus, some cases meeting the clinical definition of ARDS do not show DAD at histopathology but other features such as infection, OP, or alveolar hemorrhage. Additionally, the definition of AIP requires that DAD has no identified cause, whereas the definition of ARDS remains valid regardless of the existence of an underlying cause [165]. AIP and ARDS are therefore not two distinct entities but two different (and overlapping) ways of defining subsets of patients with acute lung injury. The relationships between AIP and ARDS definitions are illustrated in Fig. 35.7. However, one could question whether the historical definition of AIP strictly based on histopathology could be reconsidered, and incorporate a less rigid concept of "working diagnosis" based on a combination of criteria without histopathology, by analogy with other IIP.

Clinically, the differential diagnosis of AIP mainly includes congestive heart failure, infections such as viral or *P. jiroveci* pneumonia, diffuse alveolar hemorrhage, OP, acute eosinophilic pneumonia, acute hypersensitivity pneumonitis, drug-induced lung disease, toxic exposure, acute/subacute connective tissue disease-associated ILD occurring in some idiopathic inflammatory myopathies, and AE-ILD. A detailed clinical history and systems review is of high importance to identify systemic disease, predisposing drugs or toxic exposures [168]. A thorough clinical examination must also be performed to look for alternative diagnoses.

Lung function tests are rarely performed in AIP, as patients are too ill for such a procedure. If done, they show a restrictive ventilatory pattern with reduced carbon monoxide diffusion capacity.

BAL could be performed to exclude alternative diagnosis, if a spontaneously breathing patient could undergo the procedure without risk of subsequent intubation, or in an already intubated patient. BAL cytology findings in AIP are not specific, showing mainly increased neutrophils and sometimes red blood cells and/or hemosiderin. BAL allows the diagnosis of infection or alveolar hemorrhage, which should prompt

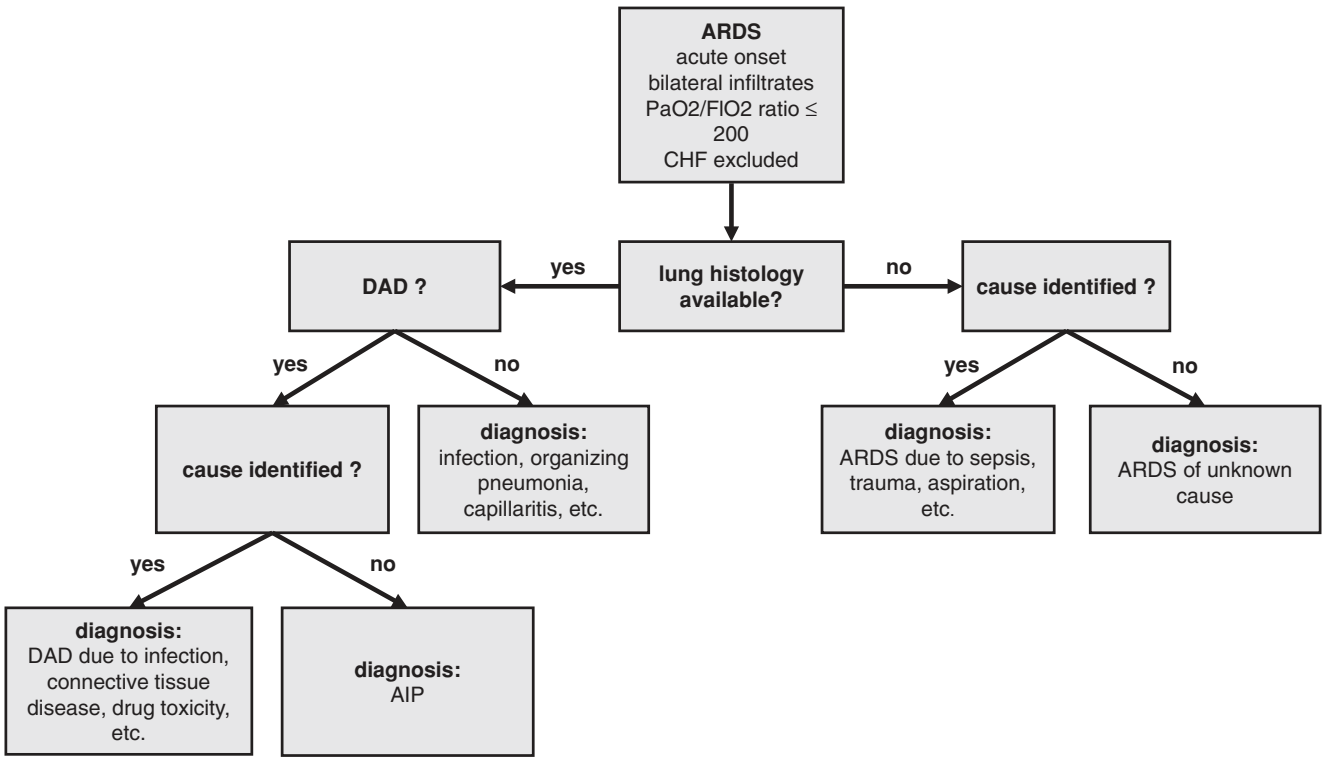

Fig. 35.7 Diagnostic relationships between acute respiratory distress syndrome (ARDS), diffuse alveolar damage (DAD), and acute interstitial pneumonia (AIP). Adapted from reference [165]

to look for systemic vasculitis or connective tissue disease. Blood, sputum and BAL fluid should be sent for culture, and serology performed for autoimmune diseases [3, 168].

In the absence of diagnosis after BAL, open lung biopsy is sometimes considered. However, in most cases, the patient's condition does not allow this invasive procedure. Transbronchial lung biopsy may be an acceptable alternative, as even small tissue specimens can allow confirmation of DAD pattern or give clue to alternative diagnosis [153]. In patients considered too ill for biopsy, empirical management is acceptable (see below).

Since AIP is an idiopathic condition, time between onset of symptoms and diagnosis is usually long because alternative diagnoses must be excluded.

Patients affected with ILD and especially IPF sometimes develop an acute form of their disease resembling AIP but which must be considered as a separate entity named "acute exacerbation of ILD" (AE-ILD), representing an acute-on-chronic process, whereas AIP is a purely acute event. In patients known for pre-existing ILD, the diagnosis of AE-ILD is easier than in those in whom the acute episode is the first manifestation of an underlying but previously unknown ILD, which is discovered only when the superimposed lung injury brings the patient to clinical attention. Clinically, it may be difficult to differentiate AIP from AE-ILD [165]. HRCT features are also similar, with ground glass opacities, consolidation, traction bronchiectasis and honeycombing in both cases [163]. Hence, the pathologic specimen is of foremost importance. In chronic interstitial fibrosis it demonstrates both acute and chronic lesions, in contrast to AIP which shows a homogeneous temporal injury [158]. As the concept of AE-ILD is more recent than AIP, it is likely that some older reports of AIP with traction bronchiectasis at imaging and UIP associated with DAD at histopathology are more consistent with AE-ILD than AIP [165].

Treatment

Given the rarity of the disorder, no controlled trial is available to guide the management of AIP. Therapeutic measures remain primarily supportive. Most patients require invasive mechanical ventilation with lung-protective settings. Extracorporeal membrane oxygenation (ECMO) may have a rescue role in patients with refractory respiratory failure. ECMO may also allow to minimize ventilator-induced lung injury, and carry out diagnostic procedures [155].

Many patients receive high-dose corticosteroids based on studies showing a lower mortality in ARDS patients receiving such a therapy, but conflicting data exist and the role of immunosuppressive treatment in AIP remains debated. The benefit of corticosteroids could depend on the disease stage.

Some authors advocate that the earlier pulse steroid therapy is administered, the lower the mortality rate [159, 160]. One group supports the efficacy of a standard therapeutic regimen of high-dose steroid pulse therapy consisting of 1 g/day IV methylprednisolone for three consecutive days followed by 1 mg/kg/day of IV methylprednisolone or oral prednisolone for 4 weeks with later progressive tapering [160]. Addition of vincristine or cyclophosphamide has been reported but efficacy is uncertain [161]. A recent randomized controlled trial of cyclophosphamide in acute exacerbation of IPF showed no benefit of this treatment, and even a trend for worse 3-month survival [169]. The benefit of lung transplantation could not be demonstrated either [170]. Whether this finding can be extrapolated to AIP is unknown.

Outcome

Despite aggressive therapy, the mortality rate of AIP is high, ranging between 12.5% and 100% [153], and averaging 70% in a review of ten series [168]. However, it seems to depend on the time between presentation and diagnosis, protective lung ventilation, and immunosuppressive therapy [153]. Outcome of patients who survive is variable. Whereas some suffer relapses or development of lung fibrosis, a minority may recover with almost no sequelae [159–161]. No correlation between histological or clinical features and long-term survival could be demonstrated [150, 161]. In one imaging study, the extent of ground glass attenuation or airspace consolidation combined with traction bronchiolectasis/bronchiectasis has been associated with worse survival, whereas the extent of pure ground glass/consolidation without traction bronchiolectasis/bronchiectasis was associated with better survival, suggesting that the fibroproliferative component of DAD is a determinant of outcome in AIP [171].

Box 35.1 Diagnostic Criteria of Organizing Pneumonia[a]

1. Compatible clinical picture, imaging and bronchoalveolar lavage (see text)
2. OP pattern at histopathology obtained by transbronchial, transthoracic, or surgical lung biopsy[b], showing:
(a) Presence of intraluminal organizing fibrosis in distal airspaces (bronchioles, alveolar ducts, and alveoli) as the predominant feature, patchy distribution of lesions, uniform temporal appearance, mild chronic interstitial inflammation, and overall preservation of lung architecture
(b) Absence of other significant abnormalities such as interstitial fibrosis, granulomas, neutrophilic infiltration or abscesses, necrosis, hyaline membranes, prominent airspace fibrin, prominent eosinophilic infiltration, and vasculitis.

[a] Adapted from reference [3]

[b] Modifying circumstances:

- A diagnosis of OP without biopsy is acceptable if a typical clinico-radiological picture and a well-identified cause is present, and if an infectious process has been ruled out.
- If the patient is too frail or too old for a biopsy, a therapeutic trial of corticosteroids may be acceptable, but the risk-benefit ratio of empirical therapy should be carefully weighted in individual cases. Mimics of OP should be ruled out by history and clinical examination, blood and/or urine analyses, and BAL, especially pulmonary infection, drug toxicity, environmental exposure, granulomatosis with polyangiitis (Wegener's), and lymphoproliferative disorder.
- If corticosteroids are administered empirically, a critical reassessment of the diagnosis should be performed after 2–4 weeks. A rapid and complete response to corticosteroids provides an additional argument in favor of OP, although disorders mimicking OP may also initially respond to corticosteroids (see text). Lack of response to corticosteroids after 2–4 weeks should lead to reconsider the initial diagnosis of OP.

Clinical Vignette

A 77-year old woman presented because of progressive dyspnea stage NYHA II, cough, fatigue, night sweats, anorexia, and loss of 10 kg over 1 year. A chest X-ray showed a left basal infiltrate. A course of antibiotic therapy had no effect, and the patient was referred to a respiratory physician. A chest CT-scan revealed multiple alveolar opacities with air bronchogram in the lingula, middle lobe, and left lower lobe. Bilateral crackles were present. The patient had never smoked, did not take any medication, had no symptoms of connective tissue disease, and no environmental exposure. C-reactive protein was 38 mg/dL. Hemoglobin was 114 g/L. Leucocytes differential count was normal. Antinuclear antibodies were positive at 1/320 but rheumatoid factor, anti-cyclic citrullinated peptide, anti-double strand DNA and anti-nucleoprotein antibodies were negative. BAL differential count showed 52% lymphocytes, 6% neutrophils, and 4% eosinophils. Cultures were negative. Transbronchial biopsies showed mild chronic interstitial inflammation and intra-alveolar fibroblastic buds. Cryptogenic organizing pneumonia was diagnosed. Because of old age, prednisone was started at only 0.5 mg/kg/day (25 mg/day). After 3 days, cough and general symptoms had completely resolved, and dyspnea was markedly reduced. After 2 weeks, chest X-ray was improved. Prednisone was well tolerated and maintained at the same dose for 2 more weeks then tapered over 6 months. The patient was informed about the risk of relapse.

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Pleuroparenchymal Fibroelastosis

36

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Introduction

Pleuroparenchymal fibroelastosis (PPFE) is a rare interstitial lung disease (ILD) characterized by predominantly upper lobe fibrosis involving the pleura and subpleural lung parenchyma [1–3]. In 1992, Amitani et al. had first described a peculiar series of Japanese patients with upper lobe-localized pulmonary fibrosis of unknown etiology [4], which was referred to as "idiopathic pulmonary upper lobe fibrosis." In 2004, Frankel et al. [1] subsequently introduced the term PPFE. Accordingly, they reported five cases with upper lobe-predominant pulmonary fibrosis of unknown origin similar to what described by Amintani, which they described as a "unique idiopathic pleuroparenchymal lung disease that is characterized by upper lobe radiologic predominance and pathologic findings that do not fit with any currently defined interstitial pneumonia." Fankel et al. proposed idiopathic PPFE to be a novel clinicopathologic entity of idiopathic interstitial pneumonias (IIPs). Since then, a growing body of literature has continued to report cases of PPFE, while the updated consensus statement for the multidisciplinary diagnosis of IIPs by the American Thoracic Society (ATS)/European Respiratory Society (ERS) has included idiopathic PPFE as a rare but distinct form of IIP [2].

Initially, the fibrotic lesions of PPFE had been thought to be restricted to the upper lobes. However, increasing evidence has demonstrated that quite a few patients with PPFE also had lower-lobe ILD [3, 5–9]. In addition, although PPFE was originally considered idiopathic, many studies have reported that PPFE also occurred in association with several conditions, including bone marrow and lung transplantation [10–12], chemotherapy [13, 14], and occupational exposure [15, 16]. To complicate matters, histologic PPFE patterns have also been found among patients with other ILDs, such as idiopathic pulmonary fibrosis (IPF) [17], ILD associated with connective tissue disease (CTD) [18], hypersensitivity pneumonitis [19], and familial interstitial pneumonia [19]. Moreover, recurrent/chronic pulmonary infection can cause PPFE [3, 20, 21]. Thus, although PPFE can be associated with a variety of underlying clinical conditions, the primary etiology and pathogenesis of PPFE have yet to be completely understood. This chapter will focus mainly on idiopathic PPFE (iPPFE) and describe current evidence related thereto, including its clinical, radiologic, and pathologic features. In addition, recently proposed diagnostic criteria, as well as current controversies concerning this disease entity, will be discussed.

Epidemiology

Two distinct forms of PPFE have been recognized: an idiopathic form, which occurs without any specific causes (iPPFE), and a secondary form, which is associated with underlying diseases or conditions (secondary PPFE) [22] (Table 36.1). While the precise incidence rates of each PPFE have yet to be clarified, Nakatani et al. recently reported 12 cases of PPFE (5.9%) out of 205 consecutive ILD cases undergoing surgical lung biopsy [23], among whom 8 (3.9%) were categorized as iPPFE and other 4 (2.0%) as secondary PPFE. In addition, among the patients with IIPs, 10.4% were

Table 36.1 Idiopathic and secondary pleuroparenchymal fibroelastosis (PPFE)

• Idiopathic PPFE
• Secondary PPFE: PPFE associated with underlying diseases or conditions
Bone marrow or stem cell transplantation
Lung transplantation
Autoimmune diseases
Rheumatoid arthritis, systemic sclerosis, ulcerative colitis, ankylosing spondylitis, psoriasis
Familial PPFE
Infection
Aspergillosis, Mycobacterium avium/intracellulare

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identified as iPPFE. Shioya et al. showed 29 cases of iPPFE (7.8%) out of 375 consecutive IIP cases [24]. More recently, Fujisawa et al. reported that the out of 444 biopsy-confirmed IIP cases, 4.1% were iPPFE cases diagnosed through multidisciplinary discussion (MDD) [25]. Thus, iPPFE may not be as rare as previously considered with respect to the clinical setting of IIPs. On the other hand, one study showed that secondary PPFE had a prevalence 0.28% and 7.54% in hematopoietic stem cell transplantation and lung transplantation, respectively [25].

Familial forms of PPFE have also been reported [26, 27]. Azoulay et al. had reported three sisters with bilateral isolated apical pleural fibrosis of unknown origin with poor prognosis [26]. Interestingly, mutations of telomere-related genes have been found in patients with PPFE [28]. Indeed, Newton et al. had been the first to demonstrate mutations in the telomere maintenance machinery genes, such as telomerase reverse transcriptase (*TERT*), telomerase RNA component (*TERC*), and regulator of telomere elongation helicase 1 (*RTEL1*), in eight patients with iPPFE. More recently, Nunes et al. identified *TERT* mutations in 5 out of 10 patients with PPFE, among whom three had iPPFE and two had PPFE associated with Sjogren syndrome [27].

Studies have shown that patients with iPPFE have a median age of 50–70 years with a wide range (13–87 years) [1, 3–5, 29, 30]. A systematic review by Thusen et al., which included a total of 78 patients with iPPFE and secondary PPFE, showed a bimodal distribution with an early peak at the third and a later peak at the sixth decade of life [31]. Generally, no gender predominance has been observed. However, PPFE patients with genetic mutations have female predominane [28]. Moreover, despite the absence of an association between smoking habit and iPPFE, 20%–40% of patients with iPPFE have smoking history [3, 5, 29, 30].

As described previously, PPFE can occur in association with underlying diseases or conditions (secondary PPFE) (Table 36.1). Most importantly, PPFE has been known as a serious late-onset non-infectious pulmonary complication of bone marrow or hematopoietic stem cell transplantation [10, 11, 32, 33] and lung transplantation [12, 34]. Moreover, chronic graft-versus-host disease has been considered a major possible cause of transplantation-associated PPFE. However, cytotoxic agents used for treating hematologic malignancies have also been associated with this disease. Recently, Higo et al. suggested chronic graft-versus-host disease as the main cause of PPFE following allogeneic hematopoietic stem cell transplantation given that majority of patients with PPFE had simultaneous bronchiolitis obliterans, a typical form of chronic graft-versus-host disease [35]. Drugs, especially alkylating agents, can cause PPFE [13, 14]. Beynat-Mouterde et al. described six patients with upper lobe fibrosis suggestive of PPFE who had a history of chemotherapy for malignancy [13]. Among the six patients, five received cyclophosphamide, while one received other alkylating agents. Moreover, several studies have revealed that occupational dust exposure, such as asbestos or aluminum, is associated with PPFE [15, 16, 36, 37]. Interestingly, the response to asbestos in the lung is thought to be more fibroelastic than fibrotic [38]. Chronic pulmonary infection is another condition possibly associated with PPFE [3, 20, 21]. In a series of 12 patients with PPFE, Reddy et al. showed that seven had recurrent pulmonary infections, such as aspergillosis, suggesting that recurrent infections may lead to PPFE [3]. Moreover, Watanabe et al. described patients with rapidly progressive idiopathic pulmonary upper lobe fibrosis who had pulmonary mycobacterium avium complex disease [6]. In addition, PPFE can also develop in patients with autoimmune diseases. Upper lobe fibrosis or apical pulmonary fibrosis, which is suggestive of PPFE, has been observed in patients with ankylosing spondylitis, ulcerative colitis, and psoriasis [39–42]. Patients with rheumatoid arthritis or Sjögren syndrome have also been found to develop PPFE [23, 27].

Clinical Manifestations

Dry cough and dyspnea on exertion are the most common symptoms among patients with idiopathic or secondary PPFE, while weight loss has been frequently observed among patients with advanced PPFE. Moreover, some patients complain of chest pain due to pneumothorax. A "flattened thoracic cage" or "platythorax," which is a reduction in the anteroposterior diameter of the chest wall, is often present especially in advanced stages [42]. Harada et al., who assessed the ratio between the anteroposterior and transverse diameter of the thoracic cage using chest computed tomography (CT) [42], found that it was much lower among patients with PPFE than among normal subjects and decreased as the disease progressed with a reduction in force vital capacity (FVC). Clubbing, which is frequently present among patients with IPF, is rare among those with PPFE. Indeed, Ishii et al. reported that only 2 (3.8%) of 52 patients with PPFE exhibited clubbing [7]. Another study showed that less than half of PPFE cases had audible crackles [22]. Particularly, patients with the lower-lobe ILD exhibit bibasilar crackles.

Laboratory Findings

Studies have shown that patients with PPFE had elevated serum levels of Krebs von den Lungen-6 (KL-6), a mucin-like glycoprotein, and surfactant protein D (SP-D), both of which are biomarkers of ILDs [5, 7, 29, 30, 43–45]. Generally, KL-6 levels remain around or slightly higher than the upper limit of the normal range, whereas SP-D levels

often increase more than twice the upper limit. These observations suggest that serum SP-D elevation is more conspicuous than that of serum KL-6. Indeed, Sato et al. showed that among four consecutive iPPFE cases who had markedly increased serum SP-D levels, three had KL-6 levels within the normal limit [46]. Patients with PPFE who had simultaneous lower-lobe ILD exhibited significantly higher serum KL-6 levels than those without the comorbidity [7]. Moreover, Oyama et al. demonstrated that patients with iPPFE had significantly lower serum KL-6 levels than those with IPF, whereas no difference in serum SP-D levels were observed between them [47]. Some patients with PPFE have serum autoantibodies, such as rheumatologic factor, antinuclear antibody, myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA) [3, 29].

Desmosines are unique amino acids that are derived from the breakdown of mature elastic fibers. Patients with PPFE have considerably increased amounts of elastic fiber in their lungs, which may lead to an elevation of its degradation products, such as desmosines. With this regard, Oyama et al. reported that patients with iPPFE had significantly higher urinary desmosines levels than those with IPF or COPD, suggesting that urinary desmosines may be a useful diagnostic marker for iPPFE [47].

Respiratory Function

Patients with PPFE usually show a restrictive impairment with marked decline in FVC on their pulmonary function test. In addition, total lung capacity (TLC) is also decreased, while the forced expiratory volume in 1 s (FEV1)/FVC ratio is increased. Importantly, the residual volume (RV)/TLC ratio is generally elevated, perhaps due to the compensatory hyperinflation of the lower lobes caused by fibrotic collapse of the upper lobes [30]. Although diffusing capacity for carbon monoxide (DL_{CO}) is usually decreased, the DL_{CO}/VA ratio is relatively preserved [22, 30]. A comparison among patients with iPPFE showed that those with coexisting lower-lobe ILD had significantly lower RV and TLC than those without [8].

During the early stages of PPFE, patients have almost normal partial pressure of oxygen in arterial blood (PaO_2), which usually decreases during advanced stages. Importantly, a mild elevation of a partial pressure of carbon monoxide ($PaCO_2$) is noted [30], resulting in a preserved alveolar–arterial gradient of oxygen ($AaDO_2$). Watanabe et al. speculated that the increased $PaCO_2$ in patients with PPFE results from mechanical restriction due to the subpleural parenchyma rather than concomitant obstructive lung disease [30]. This peculiar blood gas analysis profile is distinct from that observed in other ILDs showing a decrease in both PaO_2 and $PaCO_2$ together with an increased $AaDO_2$. Moreover, oxygen desaturation on a 6-min walk test (6MWT) is less frequent in PPFE than in other interstitial pneumonias, particularly IPF [48]. Among patients with ILDs registered for lung transplantation, those with PPFE had significantly smaller oxygen desaturation on the 6MWT than those with other ILDs [49].

Collectively, Watanabe et al. reported that the functional characteristics of PPFE include restrictive impairment with high RV/TLC which is often accompanied by a mild elevation of $PaCO_2$ and relatively preserved $AaDO_2$, resulting from subpleural parenchymal fibroelastosis, with a preserved parenchyma distant from the pleura [30].

Radiologic Features

Patients with PPFE have been shown to usually have marked thickening in the bilateral apical portions with an upward shift of hilar structures on chest X-ray (Fig. 36.1a) [1, 22, 50]. Moreover, typical high-resolution computed tomography (HRCT) features include bilateral irregular subpleural dense consolidations and reticulations in the upper lobes and less marked or no involvement of the lower lobes (Fig. 36.1b) (Table 36.2) [1, 3], with consolidations often having traction bronchiectasis with architecture distortion [51]. In advanced stages, consolidations and reticulations extend to the adjacent lobes, while subpleural cysts or bullae are often appreciated. Wedge-shaped pleural-based densities also protrude along parenchymal septa toward hila [3].

Remarkably, a considerable proportion of patients with PPFE have been shown to have lower-lobe ILD. Although Amitani et al. originally described idiopathic pulmonary upper lobe fibrosis as purely upper lobe-localized fibrosis [4]. recent studies have reported that 42–92% of patients with PPFE have coexisting lower-lobe ILD on HRCT (Table 36.3) [3, 5–9, 23]. The most common HRCT pattern in lower-lobe ILD is the usual interstitial pneumonia (UIP) pattern. Interestingly, Ishii et al. reported that five of eight patients with PPFE who initially had no fibrotic lesions in the lower lung fields developed lower-lobe ILD during the follow-up period, suggesting that the lower-lobe ILD may develop as the disease progresses [7].

Radiological PPFE-like lesions have been reported in a variety of ILDs other than PPFE [17–19, 52]. Oda et al. observed radiological PPFE-like lesions, defined as pleural thickening with associated subpleural fibrosis concentrated in the upper lobes, in 11 (10%) of 110 patients with IPF [17]. Moreover, radiologic PPFE-like lesions were found in 21 patients (19%) of 113 patients with CTD-associated ILD [18]. Interestingly, the presence of PPFE-like lesions was associated with poor prognosis. Furthermore, marked PPFE-like lesions on HRCT, which were associated with impaired lung function and increased mortality, were found in 23% of 233 patients with hypersensitivity pneumonitis [19].

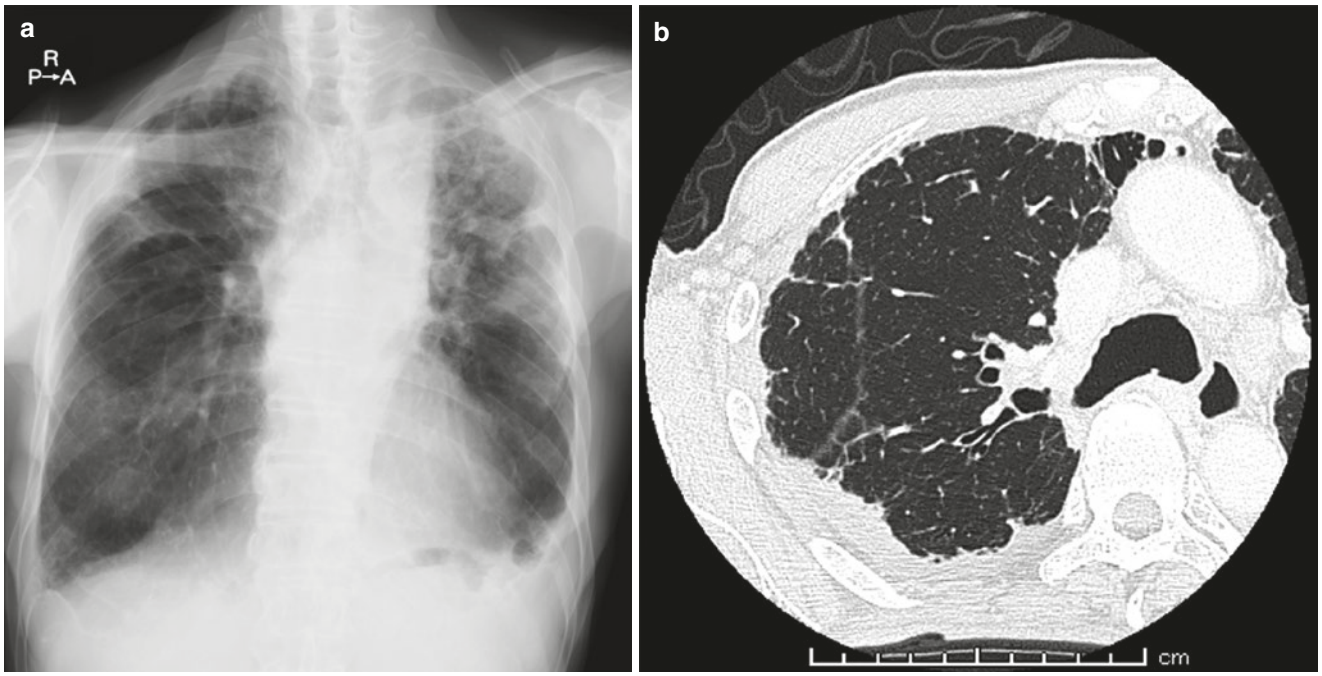

Fig. 36.1 (**a**) Chest radiograph of a patient with idiopathic pleuroparenchymal fibroelastosis (iPPFE) showing bilateral pleural thickening and parenchymal bands in apical portions accompanied by reticular and ground-glass opacities with left-lung predominance. Upper lobe volume loss and trachea deviation are also observed. (**b**) High-resolution computed tomography (HRCT) showing bilateral subpleural consolidation with pleural thickening

Table 36.2 High-resolution computed tomography findings of pleuroparenchymal fibroelastosis

• Subpleural dense consolidations and reticulations predominantly in the upper lobes
• Upper lobe volume loss
• Subpleural cysts in the advanced stages
• Occasional reticulations and/or honeycombing in the middle or lower lobes (UIP or NSIP features)
• UIP, usual interstitial pneumonia; NSIP: Nonspecific interstitial pneumonia

Table 36.3 Incidence and patterns of radiological coexisting lower-lobe interstitial lung disease in pleuroparenchymal fibroelastosis

Author	Year	Case number	Number of cases with coexisting lower-lobe ILD	Patterns of lower-lobe ILD
Redy, et al. [3]	2012	12	6 (50%)	
Watanabe, et al. [6]	2012	9	8 (89%)	
Nakatani, et al. [23]	2015	12	11 (92%)	UIP 5 Possible UIP 4 NSIP 1 Undefined 1
Enomoto, et al. [5]	2017	44	39 (89%)	
Ishii, et al. [7]	2018	52	43 (83%)	
Kato, et al. [9]	2019	36	27 (75%)	UIP 15 Possible UIP 7 NSIP 5
Kono, et al. [8]	2019	40	21 (53%)	UIP 13 Non-UIP 8

ILD interstitial lung disease, *UIP* usual interstitial pneumonia, *NSIP* nonspecific interstitial pneumonia, *HP* hypersensitivity pneumonitis

Pathologic Features

Originally, Frankel et al. demonstrated markedly dense fibrosis of the pleura and subpleural parenchyma in PPFE [1]. Fibrosis of the subpleural parenchyma is characterized by intra-alveolar fibrosis with prominent deposition of elastic fibers (fibroelastosis) (Fig. 36.2) (Table 36.4). An abrupt border between the fibrotic parenchymal areas and adjacent normal parenchyma is noted. A few fibroblastic foci at the interface of the fibrotic lesions and mild lymphocytic interstitial inflammation are also present [31]. In addition, bronchocentric intra-alveolar fibrosis is occasionally seen [3]. Fibrotic parenchymal lesions in PPFE are very similar to those of the pulmonary apical cap, and distinguishing between both has been histologically difficult. As described previously, although patients with PPFE often have the lower-lobe ILD, a few studies have focused on histologic findings of lower-lobe ILD in PPFE [27, 53, 54]. Accordingly, Nunes et al. reported that among four biopsy-confirmed patients with PPFE who had lower-lobe ILD, three exhibited a UIP pattern in the lower lobes, suggesting that a UIP pattern is a common histologic finding in lower-lobe ILD of PPFE [27].

One study showed that patients with PPFE have more lymphatic vessels in the lung of compared to those with an apical cap and IPF [55]. Notably, Enomoto et al. tested immunostaining markers that could distinguish PPFE from IPF or apical cap and found that podoplanin-positive myofibroblasts could be a pathologic hallmark of PPFE [56]. They hypothesized that "pleural" mesothelial-to-mesenchymal transition is associated with the fibrosis in PPFE given that podoplanin is usually expressed in mesothelial cells but not myofibroblasts.

Recent studies have shown that histologic PPFE patterns can also be found in other ILDs, such as IPF [17, 18, 52, 54, 57, 58]. Indeed, Oda et al. observed a histologic PPFE pattern in 9 (8.2%) of 110 consecutive patients with biopsy-

Table 36.4 Pathologic findings of pleuroparenchymal fibroelastosis

• Dense subpleural intra-alveolar fibrosis with elastic fiber deposition (sharp transition between fibrotic lesions and the normal lung)
• Fibrous visceral pleural thickening (apical portions or upper lobes)
• Mild lymphocytic inflammation
• Fibroblastic foci (rare, at the fibrotic lesion interface)

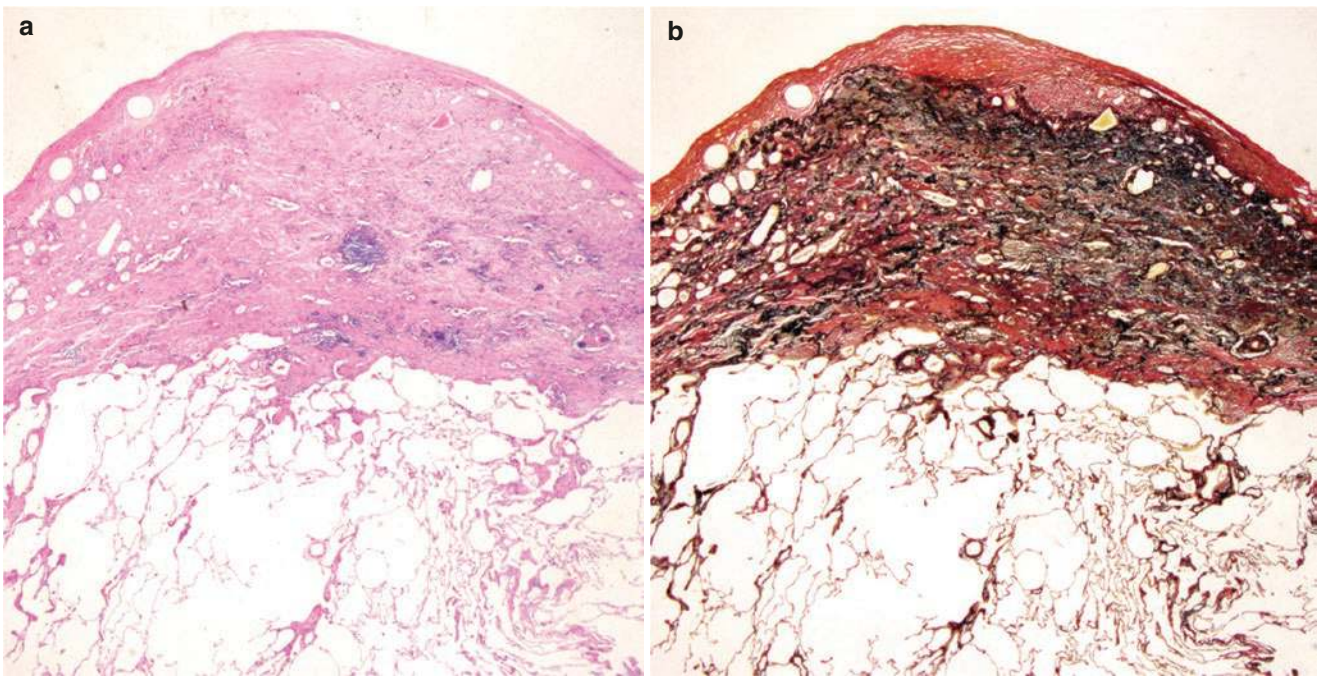

Fig. 36.2 (**a**) Surgical lung biopsy specimens from a patient with idiopathic pleuroparenchymal fibroelastosis (iPPFE). A lung section of the left upper lobe stained with hematoxylin and eosin showing subpleural fibrosis with an abrupt transition to normal lung parenchyma and fibroblastic foci. (**b**) A lung specimen with Elastica van Gieson (EVG) staining demonstrating depositions of dense elastic fibers (elastosis) and intra-alveolar collagen fibers in the subpleural fibrotic lung lesion (**b**). These features of PPFE on EVG staining are different from those of UIP, which show architectural destruction of normal alveoli. Pleural fibrosis is also observed

confirmed IPF [17]. In addition, Kinoshita et al. reported that 11 (22.9%) of 48 patients with biopsy-confirmed IPF exhibited a histologic PPFE pattern [58]. However, the extent of the subpleural parenchymal fibroelastosis in patients with IPF was much smaller than that in patients with PPFE. Moreover, histologic PPFE pattern was identified in 50% of 24 patients with CTD-associated ILD [52]. These observations suggest that the histologic PPFE patterns may indicate chronic lung injury, similar to UIP pattern, and are focally observed in association with a variety of conditions [54].

Diagnosis

Although several radiological and histological criteria for PPFE or PPFE pattern have been proposed [3, 31], no consensus regarding the diagnosis of iPPFE has yet been established. A definitive diagnosis of iPPFE ideally requires histologic confirmation of PPFE features following surgical lung biopsy. However, surgical lung biopsy is usually not feasible considering that patients with iPPFE, especially those with advanced diseases, have severe pulmonary function impairment and often develop persistent post-operative pneumothorax. Recent studies have demonstrated the diagnostic utility and safety of transbronchial lung biopsy (TBLB) and transbronchial lung cryobiopsy (TBLC) for iPPFE [59, 60]. However, given that these studies included only a small number of patients, a larger cohort of patients with iPPFE is needed to validate their findings. Therefore, clinical criteria without surgical lung biopsy have been desired for the diagnosis of iPPFE. Enomoto et al. recently proposed the following clinical criteria for iPPFE: (1) a radiologic PPFE pattern on chest CT (defined as bilateral subpleural dense consolidation with or without pleural thickening in the upper lobes and less marked or absent involvement of the lower lobes, (2) radiologic confirmation of disease progression, and (3) exclusion of other lung diseases with identifiable etiologies [5]. More recently, the Study Group on Diffuse Pulmonary Disorders in Japan has proposed a more comprehensive criteria for iPPFE, which consist of the following four categories: "definite iPPFE," "radiologically and physiologically probable iPPFE," "radiologically probable iPPFE," and "radiologically possible iPPFE" (Box 36.1 and Table 36.5) [61]. "Definite iPPFE" requires surgical lung biopsy, whereas "radiologically and physiologically probable iPPFE," "radiologically probable iPPFE," or "radiologically possible iPPFE" do not. Currently, validation studies of the aforementioned criteria are being undertaken.

Box 36.1 Diagnostic Criteria for Idiopathic Pleuroparenchymal Fibroelastosis (iPPFE) Proposed by the Study Group on Diffuse Pulmonary Disorders in Japan [62]

- **Definite iPPFE (with surgical lung biopsy)**
  1. Multiple subpleural foci of airspace consolidation with traction bronchiectasis located predominantly in the bilateral upper lobes on high-resolution computed tomography (HRCT) scans.
  2. Subpleural zonal or wedge-shaped dense fibrosis consisting of collapsed alveoli and collagen-filled alveoli with septal elastosis, with or without collagenous thickening of visceral pleura in surgical lung biopsy specimens.
  3. Exclusion of other diseases with known causes or conditions showing radiological and/or histological PPFE patterns, such as chronic hypersensitivity pneumonia, connective tissue diseases, occupational diseases, and hematopoietic stem cell or lung transplantation-related lung diseases.

Table 36.5 Summary of the diagnostic criteria for idiopathic pleuroparenchymal fibroelastosis [61]

Category of criteria[a]	Symptoms	Histology	Radiology		Physiology
			1	2	
Definite iPPFE		○	○		
Radiologically and physiologically probable iPPFE	○		○	○	○
Radiologically probable iPPFE	○		○	○	
Radiologically possible iPPFE			○		

Symptoms: dry cough or exertional dyspnea with insidious onset
Histology: subpleural zonal or wedge-shaped dense fibrosis consisting of collapsed alveoli and collagen-filled alveoli with septal elastosis
Radiology 1: subpleural airspace consolidation with traction bronchiectasis in the upper lobes
Radiology 2: bilateral upward shift of hilar structures and/or volume loss in the upper lobes. Physiology: "RV/TLC% pred. ≥115%" and/or "BMI ≤ 20 plus RV/TLC% pred. ≥80%"
[a] All categories need exclusion of other diseases with known causes or conditions showing radiological and/or histological PPFE patterns, such as chronic hypersensitivity pneumonitis, connective tissue diseases, occupational diseases, and hematopoietic stem cell or lung transplantation-related lung diseases

If all the above three criteria are met, definite iPPFE is diagnosed. If the lower lobes are involved by fibrosis, multidisciplinary discussion is necessary for the final diagnosis.

- **Radiologically and physiologically probable iPPFE (without surgical lung biopsy)**
  1. Dry cough or exertional dyspnea with insidious onset.
  2. Multiple subpleural foci of airspace consolidation with traction bronchiectasis located predominantly in the bilateral upper lobes on HRCT scans.
  3. Upward shift of the bilateral hilar structures on chest radiographs and/or volume loss of the upper lobes on HRCT scans.
  4. Exclusion of other diseases with known causes or conditions showing radiological and/or histological PPFE patterns, such as chronic hypersensitivity pneumonia, connective tissue diseases, occupational diseases, and hematopoietic stem cell or lung transplantation-related lung diseases.
  5. Percentage of predicted values of the ratio between residual volume and total lung capacity (RV/TLC %pred.) ≥ 115%.
  6. Body mass index ≤20 kg/m [2] and RV/TLC %pred. ≥ 80%.

  If criteria 1, 2, 3, 4, and 5 or 6 are satisfied, radiologically and physiologically probable iPPFE is diagnosed.

- **Radiologically probable iPPFE (without surgical lung biopsy)**
  1. Dry cough or exertional dyspnea with insidious onset.
  2. Multiple subpleural foci of airspace consolidation with traction bronchiectasis located predominantly in the bilateral upper lobes on HRCT scans.
  3. Upward shift of the bilateral hilar structures on chest radiographs and/or volume loss of the upper lobes on HRCT scans.
  4. Exclusion of other diseases with known causes or conditions showing radiological and/or histological PPFE patterns, such as chronic hypersensitivity pneumonia, connective diseases, occupational diseases, and hematopoietic stem cell or lung transplantation-related lung diseases.

  If all aforementioned criteria are satisfied, radiologically probable iPPFE is diagnosed.

- **Radiologically possible iPPFE (without surgical lung biopsy).**
  1. Multiple subpleural foci of airspace consolidation with traction bronchiectasis located predominantly in the bilateral upper lobes on HRCT scans.
  2. Exclusion of other diseases with known causes or conditions showing radiological and/or histological PPFE patterns, such as chronic hypersensitivity pneumonia, connective diseases, occupational diseases, and hematopoietic stem cell or lung transplantation-related lung diseases.

  If both criteria are satisfied, radiologically possible iPPFE is diagnosed. Radiologically possible IPPFE includes an apical cap with neither symptoms nor long-term progression in addition to the early and localized stages of iPPFE.

Differential diagnoses include a variety of diseases with upper lobe pleural thickening and/or fibrosis (Table 36.6), with pulmonary apical cap being one of the difficult conditions to differentiate. Both radiologic and histologic features of the apical cap are very similar to those of iPPFE. However, the apical cap usually occurs in older males with a history of smoking, whereas iPPFE affects relatively younger nonsmokers with no gender predisposition. Moreover, the apical cap commonly shows a localized upper lobe lesion, whereas iPPFE, despite having upper lobe predominance, often exhibits a more extended distribution beyond the upper lobes. Most importantly, patients with an apical cap usually do not show disease progression over time, unlike those with iPPFE. Other differential diagnoses include chronic hypersensitivity pneumonitis and radiation-induced pneumonitis. Furthermore, to diagnose iPPFE, secondary PPFE, such as drug-induced and post-transplant PPFE (Table 36.1), must be excluded.

Another difficulty encountered when diagnosing iPPFE is distinguishing between this disease and other types of ILDs

Table 36.6 Differential diagnoses of idiopathic pleuroparenchymal fibroelastosis

• Pulmonary apical cap
• Chronic hypersensitivity pneumonitis
• Advanced fibrosing sarcoidosis
• Radiation-induced pneumonitis
• Other ILDs (e.g., IIPs) with PPFE-like lesions in the upper lobes
• Secondary PPFE (see Table 36.1)

PPFE pleuroparenchymal fibroelastosis, *ILD* interstitial lung disease, *IIPs* idiopathic interstitial pneumonias

with radiologic PPFE-like lesions or a histologic PPFE pattern in the upper lobes given that certain patients with other ILDs, such as IPF and CTD-ILD, show radiologic PPFE-like lesions or a histologic PPFE pattern [17–19, 51, 52, 55, 58, 59]. In addition, a majority of patients with iPPFE often have lower-lobe ILD [3, 5–9, 24]. Thus, for patients with both upper- and lower-lobe fibrosis, determining upper lobe predominance, which is essential for the diagnosis of iPPFE, is occasionally challenging. Under such circumstances, MDD is necessary.

Treatment

To date, no effective treatments for iPPFE or secondary PPFE have been established.

Corticosteroids, immunosuppressants, or *N*-acetyl cysteine have been shown to achieve no improvement or, if any, transient response [48, 62, 63]. Nonetheless, very preliminary observations have suggested that anti-fibrotic agents, pirfenidone and nintedanib, might have some benefit [64, 65]. Sato et al. reported that pirfenidone treatment was followed by FVC stabilization in a patient with iPPFE [64]. Moreover, Nasser et al. showed that nintedanib treatment in five patients with PPFE, among whom three had iPPFE and two had PPFE secondary to chemotherapy, was followed by reduced FVC decline in all patients [65]. However, given that these studies included only a small number of patients, prospective studies including a larger cohort are needed to confirm their findings. Although several reports have recently demonstrated that lung transplantation may be an effective treatment option for iPPFE and secondary PPFE [62, 66–71], evidence has still been limited. Owing to reports of recurrent infections among patients with PPFE, such as aspergillosis and non-tuberculosis mycobacterial infection [3], infection control should be taken into consideration in such cases.

Prognosis

The prognosis of PPFE is heterogeneous. Yoshida et al. reported two patterns of disease progression: rapid FVC decline over a short time period and slow decline over a long period [72]. However, clinical differences at the baseline had not been described in detail between the two patterns. They speculated that, in patients with PPFE, FVC decline gradually to a certain point in time, after which FVC begins to drop rapidly. To date, several studies have performed survival analysis among patients with PPFE [5, 8, 9, 25, 72, 73], subsequently revealing 5-year survival rates and median survival durations ranging from 29% to 58% and 2.0–8.0 years, respectively, with wide variability (Table 36.7). Although a few studies have directly compared the prognosis between PPFE and other ILDs, such as IPF, Fujisawa et al. reported that patients with iPPFE had significantly shorter survival than those with IPF [25]. Collectively, these observations suggest that PPFE seems to have a poor prognosis.

Several prognostic factors have been identified. Indeed, Suzuki. et al. identified male gender and low erector spinae muscle attenuation (ESM_{MA}) determined through CT imaging as independent factors for poor prognosis among patients with iPPFE [73]. Similarly, Khiroya et al. found that male sex was a predictor of increased risk of mortality among patients with PPFE [53]. Histologically, the coexistence of granulomas was associated with a significant decrease in mortality. Moreover, multivariate analysis by Kono et al. and Kato et al. identified low %FVC and high fibrosis score assessed through HRCT as factors for poor prognosis in iPPFE, respectively [8, 9]. Recently, Ishii et al. reported that serum KL-6 levels were significantly associated with outcomes in 52 patients with PPFE (48 iPPFE, 4 secondary PPFE) such that patients with KL-6 levels >600 U/mL showed significantly shorter survival than those with KL-6 levels <600 U/mL [7]. Given that patients with PPFE usually have normal upper limits or slightly higher serum KL-6 levels, the increase in KL-6 levels might have been attributed to the coexistence of lower-lobe ILDs. This suggest that patients with PPFE who develop lower-lobe ILDs may have poor prognosis. Similarly, Kono et al. recently demonstrated that patients with iPPFE who had lower-lobe ILD exhibited significantly worse survival with higher serum KL-6 levels than those without the lower-lobe ILD [8]. More importantly, patients with a lower-lobe UIP pattern had significantly shorter survival than those with a lower-lobe non-UIP pattern, suggesting that a radiologic UIP pattern in the lower-lobe ILD is an important prognostic determinant. Accordingly, Kato et al. also described that a lower-lobe UIP pattern was an independent factor for poor prognosis among patients with iPPFE [9]. Moreover, patients with iPPFE who had a lower-lobe UIP pattern tended to exhibit poorer prognosis than those with IPF [17].

During the course of PPFE, two particular conditions should be considered: pneumothorax and acute exacerbation. Recurrent pneumothorax often occurs especially in advanced diseases with multiple bullae, with pneumothorax incidence rates ranging from 17% to 75% [3, 5, 6, 8, 9, 23, 72]. The pneumothorax is often intractable and occasionally accompanied by pneumomediastinum. Recently, it has become evident that patients with PPFE develop acute exacerbation, as seen in those with IPF [7, 17, 24, 73, 74]. Suzuki et al. reported that acute exacerbation occurred in 8 (18.6%) of 43 patients with iPPFE over a median observation period of 31.1 months [73], while Ishi et al. found acute exacerbation in 7 (13%) of 52 patients with PPFE [7]. Outcomes fol-

Table 36.7 Survival analysis of patients with pleuroparenchymal fibroelastosis

Author	Year	Case number (idiopathic/secondary)	Age, years	FVC, %	RV/TLC, %	DLCO, %	5-year survival rate, %	Median survival time, years
Nakatani, et al. [23]	2015	12 (8/4)	62* (27–70)	70.6 (53.8–108.6)				2.3
Yoshida, et al. [72]	2016	22 (20/2)	56.6 ± 11.0†	66.0 ± 20.1	46.4 ± 12.9	72.5 ± 23.5		7.3
Enomoto, et al. [5]	2017	44 (44/0)	70 (65–75)	54 (46–67)	55 (45–91)	68 (45–91)	28.9	2.9
Ishii, et al. [7]	2018	52 (48/4)	62.5 [14.5]‡	66.8 [21.3]	42.7 [9.3]	73.2 [40.2]	58	8.0
Suzuki, et al. [7]	2018	43 (43/0)	69.0 (64.0–74.0)	54.4 (45.8–65.7)		68.7 (47.9–91.9)	29.8§	2.9§
Kato, et al. [9]	2019	36 (36/0)	74 (35–84)	62.5 (38.3–98.3)		37.5 (7.7–67.0)		2.0
Kono, et al. [8]	2019	40 (40/0)	65.6 ± 22.1	65.6 ± 22.1	45.1 ± 8.9	99.1 ± 25.1	57.7§	6.7§
Fujisawa, et al. [25]	2019	18 (18/0)	68.5 (62.3–72.0)	67 (52.8–82.4)		76.0 (69.5–96.2)	35.0§	2.9§

*: median (range), †: mean ± standard deviation, ‡: interquartile range, §: unpublished data
FVC force vital capacity, *RV/TLC* residual volume/total lung capacity, DL_{CO} diffusing capacity for carbon monoxide

lowing acute exacerbation of PPFE have generally been poor and often fatal. Moreover, precise annual incidence rates or risk factors of acute exacerbation have yet to be fully determined.

Conclusions

PPFE has been recognized as a distinct pattern of pulmonary fibrosis with characteristic clinical, radiologic, and histologic features. PPFE has been classified as either idiopathic or secondary. iPPFE is currently characterized as a rare IIP, while secondary PPFE is associated with diverse conditions, such as transplantation, dust exposure, autoimmune diseases, and genetic mutations. Given that a variety of conditions cause PPFE, it may represent a pattern of chronic lung injury in response to various stimuli and/or in association with immune dysregulation and genetic predisposition. However, the precise pathogenesis has remained undetermined. While no effective therapy for PPFE has been established, its prognosis remains poor. Recently, awareness for PPFE has considerably increased, leading to studies showing that this disease is not rare as previously considered and that fibrosis is not confined to the upper lobes. Practically, validated clinical diagnostic criteria without surgical lung biopsy have been developed considering that performing lung biopsy in patients with PPFE is generally discouraged. Future large-scale studies will be required to further understand the precise clinical behavior and prognosis of PPFE, as well as develop effective treatments.

Clinical Vignette

A 73-year-old man, non-smoker, with no occupational exposure was referred to our hospital due to dry cough, progressive dyspnea on exertion, and weight loss. His physical examination revealed low body mass index (BMI), a flattened thorax, and bilateral fine crackles but no clubbed fingers or skin lesions. Serum KL-6 was slightly increased (563 IU/mL) (normal range: ≤500 IU/mL), while serum SP-D was remarkably elevated (372 ng/mL) (normal range: ≤110 ng/mL). Serological tests revealed no autoantibodies. Pulmonary function test showed low forced vital capacity (FVC) (39.9% predict.), low forced expiratory volume in 1 s (FEV_1) (49.8% predict.), normal FEV_1/FVC 100%, increased residual volume (RV) (160.5% predict.), and high RV/total lung capacity (TLC) (157.7%). Diffusing capacity for carbon monoxide (DL_{CO}) was decreased (70.4%). Blood gas analysis at room air showed decreased partial pressure of oxygen in arterial blood (PaO_2) (68 Torr) and slightly increased partial pressure of carbon monoxide ($PaCO_2$) (51 Torr). Chest radiography and computed tomography exhibited bilateral apical pleural thickening with parenchymal bands and reticulations in the upper lobes (Fig. 36.3a and b). Some reticular opacities were also found in the lower lobes. Based on these findings, idiopathic pleuroparenchymal fibroelastosis (iPPFE) was suspected, after which a video-associated thoracoscopic surgical lung

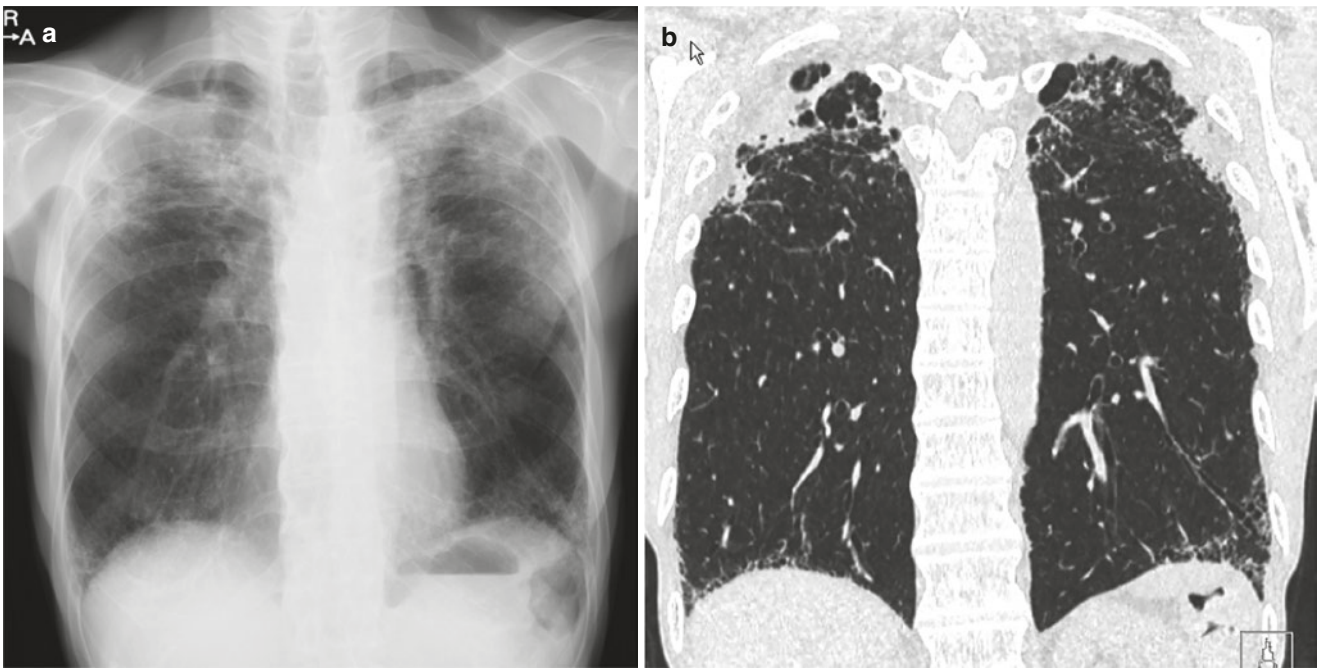

Fig. 36.3 Chest X-ray (**a**) and coronal section of a chest CT (**b**) of a patient with idiopathic pleuroparenchymal fibroelastosis. Upward shift of the bilateral hilar structures on chest x-ray and volume loss of the upper lobes on HRCT scan

biopsy was conducted to confirm the diagnosis. The biopsy revealed marked thickening of the visceral pleura and subpleural parenchymal intra-alveolar fibrosis with massive deposition of elastic fibers, which were consistent with the histologic pattern of PPFE. Thus, a diagnosis of iPPFE was established, and the patient had been followed up without treatment. During observation, he had developed intractable pneumothorax three times and eventually died of chronic respiratory failure 3 years after diagnosis.

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Interstitial Lung Diseases of Occupational Origin

37

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Case Vignette

Sarcoidosis was diagnosed in an asymptomatic dental technician aged 21 years. Two years later prednisolone treatment was initiated due to nonproductive cough and progressive defects in both vital and diffusion capacity. Relapses during tapering corticosteroids lead to prolonged therapy until 37 years of age. At this age, still typical clinical and radiological findings of sarcoidosis were present, and exposure to beryllium-containing dust in dental laboratories became known. In-vitro lymphocyte proliferation of peripheral mononuclear cells cultured in the presence of beryllium sulfate (beryllium LPT) yielded an elevated stimulation index demonstrating beryllium sensitization. Thus, a detailed occupational history with subsequent proof of beryllium exposure in combination with clinical and radiological findings typical of sarcoidosis and demonstration of beryllium sensitization lead to the diagnosis of chronic beryllium disease persistent after termination of exposure.

Introduction

Interstitial lung diseases (ILD) comprise a wide range of disease that manifest with radiological and /or histological alterations of the pulmonary interstitial tissue. These patterns and the clinical context allow their classification [1]. Occupational exposure plays an important role as contributing factor for interstitial lung diseases, even though the majority of interstitial lung diseases is not considered as being of occupational origin. However, detailed analysis of working environment together with a high grade of suspicion can result in linking workplace exposure to interstitial lung disease as described in the case vignette [2] and allow preventive strategies as it is, e.g., recommended for chronic beryllium disease or silicosis [3, 4].

Besides the prototypic occupation-related interstitial lung diseases discussed in detail, it should be noted that epidemiological studies reveal occupational risk factors for developing "idiopathic" interstitial lung diseases. For idiopathic pulmonary fibrosis epidemiological studies reveal a correlation between occupational exposure especially to metal and wood dusts, but also to vegetable or stone dusts [5–9]. In firefighters exposed to dust from World Trade Center collapse a higher incidence of sarcoidosis could be observed [10] emphasizing an exposure-related development of sarcoidosis. Additional studies demonstrated that employment in areas like metal working, health care or teaching represents a risk factor for mortality in sarcoidosis [11] and that environmental factors may mimic occupational exposure [12]. In this context a recent case report highlights the need for clinical suspicion to unravel occupational exposure in the setting of interstitial lung diseases. Two patients with granulomatous lung disease shared exposition to dust containing amorphous silica that was found within the granulomatous lesions. Stopping exposure lead to clinical and functional improvement [13].

Occupational exposure may cause different forms of interstitial lung diseases that can roughly be subdivided in subgroups, i.e., pneumoconiosis, hypersensitivity pneumoni-

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Table 37.1 Occupation-related interstitial lung diseases [294]

Pneumoconiosis		Hypersensitivity pneumonitis		Granulomatous lung disease		Other interstitial lung diseases	
Agent	*Occupation*	*Agent*	*Occupation*	*Agent*	*Occupation*	*Agent*	*Occupation*
Asbestos	Asbestos waste handler, carpenter, construction worker, electrician, mechanic, miner, railway worker, Shipyard worker	Bacteria	Compost worker, farmer, machinist, mushroom worker, swimming pool/spa worker	Beryllium	See Table 37.4	Indium–tin oxide	Manufactory and recycling liquid crystal displays
Coalmine dust	Coalminer	Fungi	Cheese worker, Mushroom worker, tobacco grower, woodworker	Cobalt	Diamond polisher, grinder operator, industrial tool sharpener	Acramin	Textile worker
Silica	Benchtop fabricator, ceramics worker, miner, quarry worker, stonemason, sandblaster, tunneller	Animal products	Bird breeder, laboratory worker, textile worker	Aluminum	Aircraft industries, chemis, metal recycler	Nylon	Textile worker
Talc	Talc miner and miller	chemicals	Dental technician, painter, plastic industry, polyurethane foam worker, yacht manufactory			Mineral oils	Mill operator
Kaolin	Ceramic manufactory						

tis, granulomatous lung diseases, and other interstitial lung diseases (Table 37.1). As depicted in Table 37.1 numerous toxic compounds and bioaerosols generated at workplaces are capable of inducing ILDs. In this chapter we will exemplary discuss a number of pulmonary disorders caused by the inhalation of metallic and organic chemical dusts at the workplace without claiming to be comprehensive. The diseases discussed in this chapter are either of immunologic origin or can be subsumed under pneumoconiosis. However, hypersensitivity pneumonitis, silicosis, and coal workers lung are discussed elsewhere in this monograph.

In the clinical context described for CBD above we will discuss CBD and the following disorders in this chapter: indium–tin oxide-lung disease, hard metal lung, flockworker's disease, asbestosis, siderofibrosis, popcorn worker's lung, and nanoparticle induced interstitial lung disease.

Acute Berylliosis

Even though safety measures in industrial countries reduced the risk of acute beryllium disease, acute berylliosis deserves a mention. It clinically manifests shortly after exposure to high dose of Beryllium exposure, as it can still accidentally happen [14, 15]. It shares clinical characteristics of acute sarcoidosis and toxic alveolitis with similarities to hypersensitivity pneumonitis [16]. Biopsy specimens of the lung show a lymphocytic interstitial pneumonitis indistinguishable from chemical pneumonitis due to other causes. Approximately one third of these acute cases progresses into chronic granulomatous lung disease [17].

Chronic Beryllium Disease

Definition

Chronic beryllium disease (CBD) is in general an occupational hypersensitivity disorder elicited by exposure to beryllium containing dusts and fumes. It phenocopies sarcoidosis with identical clinical, radiological, and histological findings (Table 37.2). Generally, chronic beryllium disease affects more likely organs with contact to beryllium-containing dusts (e.g., skin, lungs, and eyes). In the diagnostic work-up, chronic beryllium disease is characterized by (i) the exposition of the affected person to beryllium (which occurs in general at the working place) and (ii) tests demonstrating beryllium-sensitization. This sensitization is the only known difference between these two disorders. Beryllium sensitization is most frequently documented by the ex vivo beryllium-lymphocyte proliferation test (Be-LPT), which can be performed with lymphocytes from peripheral blood or from bronchoalveolar lavage. The latter one in our hands is more sensitive.

Table 37.2 Workplaces, components, and products with potential beryllium-exposure

Additives to glass, ceramic, plastics	Golf clubs	Pen clips
Aerospace industries (e.g., aircraft frames, engines, and brakes)	Gyroscopes	Personal computers
Automobile industries (engines, electronic parts)	Metallurgic industries/recycling	Precision instruments
Brass alloys	Microelectronics	Recycling workplaces
Camera shutters	Microwave devices	Satellites
Ceramic industries	Military vehicle armor	Springs
Chemical industries	Mirrors	Structural material in space technology
Dental workshops	Missile production and maintenance	Submarine cable housings
Electrical relays	Missile guidance systems	Transistor mountings
Electronic industries	Nonsparkling tools	Wheels
Fluorescent lamp production/disposal	Nuclear reactors and industries	X-ray tubes
Gems	Optical industries/ workshops	

Exposure

Beryllium-exposed individuals may be unaware of their exposure and physicians may be unaware of beryllium-related health effects leading to non-recognized beryllium sensitization and CBD. Therefore, an occupational case history covering the entire professional life is mandatory in the diagnostic workup of granulomatous disorders. Typical industries with use of beryllium and the hazard of occupational beryllium dust exposition are depicted in Table 37.3. Beryllium sensitization is usually recognized in occupational monitoring programs of exposed workers or in the diagnostic workup of granulomatous disorders. Asymptomatic individuals without any evidence for granulomatous disease and documented beryllium sensitization must not be diagnosed as CBD but are at risk to develop CBD and require counseling whether a change of workplace is appropriate to terminate exposure [18].

Beryllium is a metallic processed into beryllium oxide, beryllium metal, beryllium alloys, and composite materials. The addition of beryllium improves the electrical and thermal conductivity of alloys and increases the mechanical strength of alloys. The most important product is copper alloy containing 0.15 to 2.0% beryllium. More than 80% of the world's beryllium ore mining and processing is done in the United States. Beryllium is frequently used in electronic and microelectronic applications, in nuclear industries, as an additive to glass or plastics and found in gems. Workers potentially exposed to beryllium are miners, beryllium alloy fabricators, phosphor manufacturers, ceramic workers, missile technicians, nuclear reactor workers, electric, electronic, and optical equipment workers, and jewelers. Noteworthy, workers in down-stream industries and crafts using beryllium-containing parts may be exposed. Past exposure of workers involved in fluorescent powder manufacture and in the manufacture and salvage of fluorescent lamps may still cause disease. The recycling of electronic parts is a relatively new business with implied beryllium exposure.

Of note, several nonoccupational cases of CBD have already been diagnosed [12, 19, 20] and most cases masquerade as sarcoidosis [21, 22]. Those cases may be caused by indirect or paraoccupational beryllium exposure at the workplace such as secretaries or security guards [22], by exhaust air of beryllium utilizing industries endangering residents in their vicinity [23] or by contaminated clothing brought to the home affecting family members [24, 25]. The latter is of practical relevance since a genetic background defining susceptibility for [26, 27] and progression of CBD [28] is known

Table 37.3 Clinical, radiographic, and laboratory differences between CBD and sarcoidosis

Clinical Findings	CBD	Sarcoidosis
Onset	Insidious	Acute or insidious
Restrictive lung disease	Yes	Yes
Obstructive lung disease	Frequent	Yes
Reduced diffusion capacity	Yes	Yes
Erythema nodosum	No	Yes
Lupus pernio	No	Yes
Neurologic manifestations	No	Yes
Bone cysts	No	Yes
Extrapulmonary manifestations without pulmonary involvement	No	Yes
Ophthalmologic manifestation	Conjunctivitis only	Conjunctivitis, uveitis, retinal involvement
Hepatic manifestations	Occasional	Common
Cardiac manifestations	Rare	Occasional
Hypercalcemia	Rare	Rare
Chest Imaging		
Isolated hilar or mediastinal adenopathy	Very rare	Common
Parenchymal ground glass opacities	Common	Common
Parenchymal nodules	Yes	Yes
Bronchial stenosis	Yes	Very rare
Subpleural cysts	Yes	Rare
Conglomerate masses	Yes	Rare
Laboratory Findings		
Beryllium sensitization	Yes	No

and this background is shared by family members, so that an extended occupational history in the diagnostic workup is mandatory/highly required.

Epidemiology

Soon after industrial utilization of beryllium started in the 1930s, acute beryllium disease was recognized, leading to register acute and chronic beryllium diseases by the Atomic Energy Commission of the United States of America. The distribution of the chronic disease did not follow a linear exposure-response model which led to the hypothesis that CBD is a hypersensitivity disease with a genetic background defining susceptibility and in 1949 a workplace airborne exposure limit of 2 μg/m^3 averaged over an 8-h period was established that was later reduced to a Threshold Limit Value (TLV) of 0.05 μg/m^3 for an average 8-h period by the National Institute for Occupational Safety and Health of the United States into effect to prevent beryllium sensitization and subsequent CBD. However, reports on community acquired CBD indicate that low level exposure is sufficient to induce CBD in susceptible individuals [23] and preventive programs are able to reduce but not to eliminate sensitization [29].

Exact numbers of current or previous exposure of workers to beryllium are not known in any nation. Estimates for the United States name up to 135.000 current and up to 800.000 former beryllium exposed workers [30]. Downstream exposure (i.e., handling of beryllium-containing alloys) could not be included in this estimate and may increase the number of exposed, sensitized, and diseased individuals. Furthermore, CBD may be misdiagnosed as sarcoidosis. In a binational study in Germany and Israel obtaining a detailed occupational history in the diagnostic workup of suspected sarcoidosis in more than 500 patients, 84 disclosed a potential beryllium exposure and underwent beryllium lymphocyte proliferation testing, which demonstrated beryllium sensitization in 34 patients leading to the diagnosis of CBD [21], although all diagnostic criteria for sarcoidosis have been satisfied according to actual standards [31]. On the other hand, a Canadian study using a similar approach, even employing two different tests to check for beryllium sensitization, could not identity latent CBD in 34 sarcoidosis patients with exposure to metal dusts or fumes from whom 17 had documented beryllium exposure [32]. Non-recognized CBD will respond to corticosteroid therapy aimed to control sarcoidosis but due to persistent beryllium exposure relapses will occur resulting in a clinical phenotype of relapsing and therapy resistant sarcoidosis. Only the diagnosis of CBD entails termination of beryllium exposure, which is, although not formally proven, the first recommended step of therapy [3].

Immunopathogenesis and Pathology

When CBD was originally described it was demonstrated that patients developed a delayed-type cutaneous response to beryllium salts. Bronchoalveolar lavage and peripheral blood mononuclear cells of these patients proliferate ex vivo in response to a beryllium challenge which demonstrates the immunologic hypersensitivity nature of CBD. In contrast, no proliferation is detectable after beryllium-stimulation of cells from healthy controls or from patients with other granulomatous disorders. Thus, this reaction can be used to identify beryllium sensitization and is recommended as a diagnostic test for CBD in current guidelines [3]. A recent epidemiologic study showed that T cell sensitization depends on the peak concentration of exposure and progression to CBD on the cumulative exposure [33]. This demonstrates that CBD is a hypersensitivity disease in which beryllium is the specific antigen [34]. Beryllium induces conformational changes of the MHC-peptide complex inducing an oligoclonal T cell response [35]. These activated cells are then compartmentalized to the lung inducing an inflammatory response similar to sarcoidosis within the lung [36].

Although not pathognomonic or specific for CBD, the characteristic pathologic lesion in CBD is the non-necrotizing granuloma as it is seen in sarcoidosis, which consists of epithelioid histiocytes and multinucleated giant cells with a collar of predominantly CD4$^+$ T lymphocytes. As in sarcoidosis, their distribution follows lymphatics, bronchovascular bundles, and interlobular septae down to subpleural space. Histology of berylliosis is indistinguishable from that of sarcoidosis, but detection of beryllium within the granulomas may increase confidence to the diagnosis of berylliosis. Because of a missing generally accepted Beryllium threshold in histological specimen in surgical biopsies [37], this way of demonstrating exposure is not used in routine diagnostic workup. Furthermore, the absence of beryllium in tissue analysis and the fact that biorelevant tissue concentrations are below detection limits do not exclude the diagnosis [37, 38].

Genetics

The susceptibility to acquire beryllium sensitization progressing to CBD is linked to the individual genetic background. The presence of HLA-DPB1 alleles positive for glutamate at position 69 is the most powerful, known genetic risk factor [26] that has been confirmed in multiple studies. However, the question whether any or certain glutamate 69 positive alleles or allele combinations are required is not yet settled [39, 40]. Depending on ethnicity, a large minority of beryllium sensitized individuals and CBD patients do not

carry a glutamate 69 positive HLA-DPB1 allele. In Caucasian cohorts around a quarter of CBD patients are glutamate 69 negative [28], which demonstrates that genetic testing is futile in the diagnostic workup of CBD. In particular, gene–environment interactions may reduce or increase the risk of CBD. High exposure may devaluate a protective genetic background and genetic susceptibility may be irrelevant at low exposure workplaces [28]. Genetic testing is a politically sensitive matter in many countries and the high frequency of susceptibility gene variants would cause more cases of suspicion than identify real cases. For these reasons a genetic testing is discouraged.

Clinical Description and Natural History

Among metals capable to cause diseases mimicking sarcoidosis, beryllium is the most prominent [41]. It commonly produces granulomas in the lungs and in some cases also in liver, spleen, and heart muscle. In addition, it can cause skin nodules, contact dermatitis, poor wound healing, and symptomatic hypercalcemia. It develops insidiously with symptoms of dyspnea on exertion, cough, fatigue, chest pain, weight loss, night sweats, fever, and anorexia. In rare cases liver, spleen, myocardium, skeletal muscles, salivary gland, and bone involvement may imitate a systemic chronic inflammatory disease (Table 37.3). The link between this granulomatous disorder and beryllium exposure can be elusive because the latency from time of first beryllium exposure to the development of clinical disease ranges from a few months to several decades, and exposure dose and time may be minimal [42]. As in sarcoidosis, patients with early disease typically have a normal physical exam and patients with advanced disease report unspecific complaints, have unspecific findings in physical examination, and suffer from restrictive lung disease with distortion of gas exchange but obstructive lung disease is also frequently observed [42, 43]. In advanced cases clubbing and pulmonary hypertension with fatal courses may be seen [44]. Isolated extrathoracic manifestations of CBD other than dermatologic manifestations and fatigue are rarely observed. These and further differences between CBD and sarcoidosis are listed in Table 37.3.

Radiographic appearance of CBD on chest X-ray or CT-scan is identical to that of sarcoidosis, although mediastinal or hilar lymphadenopathy is less common. Chest radiographs range from small nodular opacities, with an upper level predominance, to the formation of conglomerate masses or can be normal. Moreover, even HRCT and pulmonary function tests can be normal in patients with granulomatous lung disease and therefore the diagnosis CBD must not be excluded on the basis of those negative results [45]. Mediastinal and hilar lymphadenopathy are present in approximately a third of individuals examined by chest radiograph or computed tomography. Further radiographic features are listed in Table 37.3. In aggregate, there are no radiographic findings differentiating CBD from sarcoidosis.

Beryllium sensitization is the first immunologic event leading to CBD but it does not result in any physical impairment. A clear dose dependency exposure could be established [33]. At present there is no medical therapy to prevent progression to CBD. However, theoretical considerations and epidemiological studies suggest that termination of exposure may remit sensitization [46]. Further exposure and its cumulative dose define progression to CBD [33], which can take place after a short time or after a latency of years or decades. Precipitating cofactors are not known [18, 46]. Overall, under continued exposure a progression rate of 6 to 8% per year of sensitized is reported [18]. After manifestation of CBD, many patients suffer from slow progression of symptoms and defects of pulmonary function, which can precede radiographic abnormalities [47]. However, next to those protracted courses, rapid ones are observed [44]. According to CBD registry data and epidemiological studies from the United States of America, mortality rates of CBD patients vary widely from 6 to 38%. In addition to CBD excess mortality rates for chronic obstructive pulmonary disease, lung cancer, urinary tract cancer, and nervous system cancer are reported [46, 48, 49]. Whether advances in diagnosing early disease and consecutive termination of exposure have lowered this number seems likely, however, is not known.

Diagnosis and Differential Diagnosis

The diagnosis is made in the setting of a granulomatous disease (typically with non-necrotizing granuloma) with a documented occupational (or in rare cases ambient) beryllium-exposure and proven beryllium hypersensitivity by a beryllium lymphocyte-proliferation assay. Granulomatous disease of other origin such as bacterial, fungal, viral, helminthic, or metallic need to be excluded in a diagnostic workup. Beryllium hypersensitivity differentiates between sarcoidosis and berylliosis, additional clinical clues are listed in Table 37.3. None of these clinical features, however, is adequately sensitive or specific to reliably distinguish between sarcoidosis and berylliosis in individual patients.

The pivotal step in the diagnosis of CBD is the demonstration of beryllium sensitivity by beryllium-lymphocyte proliferation test (Be-LPT) [3]. At present Be-LPT with blood or bronchoalveolar lavage mononuclear cells is the only routine laboratory test available to prove beryllium hypersensitivity [50]. Patch test (on skin) or intracutaneous injections of beryllium salts should be avoided because of

lacking clear diagnostic criteria and the risk of sensitization. There is a considerable risk of inducing sensitization by intracutaneous application of beryllium salts and clear diagnostic readout criteria are not defined. Originally, bronchoalveolar lavage cells have been employed in the Be-LPT [50] but for practicability reasons it has been adopted for the use of peripheral blood mononuclear cells [51], even though in our hands lavage Be-LPT seems to be more sensitive. In uncertain cases we recommend to use lavage cells for Be-LPT.

Blood Be-LPT measures the proliferation of viable cells under stimulation with beryllium-salts and use mitogens as positive controls [51, 52]. The mean plus two standard deviations is usually taken for the upper limit but other limits are also in use. To obtain a reliable value, multiple cell cultures should be performed. Generally, tests with at least two elevated proliferation values are considered abnormal. Since a specific positive control is not available, some authors demand two independent tests to accept the clinical consequence [53]. A test specification released by the Department of Energy of the United States of America in 2001 (Specification 1142-2001) to standardize Be-LPT for epidemiological purposes can be used as guideline to evaluate or to establish the test. In the United States of America laboratories offering Be-LPT are accredited according to the Clinical Laboratory Improvement Amendments. Similar procedures have to be established in most other countries.

It has to be noted that the sensitivity of Be-LPT from peripheral blood is under debate. Reported sensitivities comparing multiple testings to identify false negatives range between 38% [52] and 100% [51] with low interlaboratory reproducibility [54]. Consequently, there are cases of berylliosis which have not been diagnosed due to false negative test results. Thus, in those cases with negative Be-LPT results and doubtless exposure, the tentative diagnosis of CBD has to be either excluded or verified with multiple independent tests. The high specificity of Be-LPT, however, is generally accepted since positive test results have not been reported in non-exposed controls or patients suffering from other granulomatous disorders [51, 52, 55]. Its positive predictive value is comparable to other accepted medical tests with a sensitivity of 0.683, a specificity of 0.969, and a positive predictive value of one abnormal test of 0.253 [53]. In case of any doubt the test can be repeated with cells from bronchoalveolar lavage, which has been demonstrated to be more sensitive due to an higher proliferation capacity of these cells in response to beryllium [50] (see Fig. 37.1).

Importantly, Be-LPT should ideally be performed before starting therapy, because immunosuppressive drugs (including corticosteroids) can dampen the proliferation. In our experience, positive results for Be-LPT can be obtained in patients with a low-dose steroid therapy, but it is generally recommended to pause immunosuppressive therapy 3 weeks before performing Be-LPT.

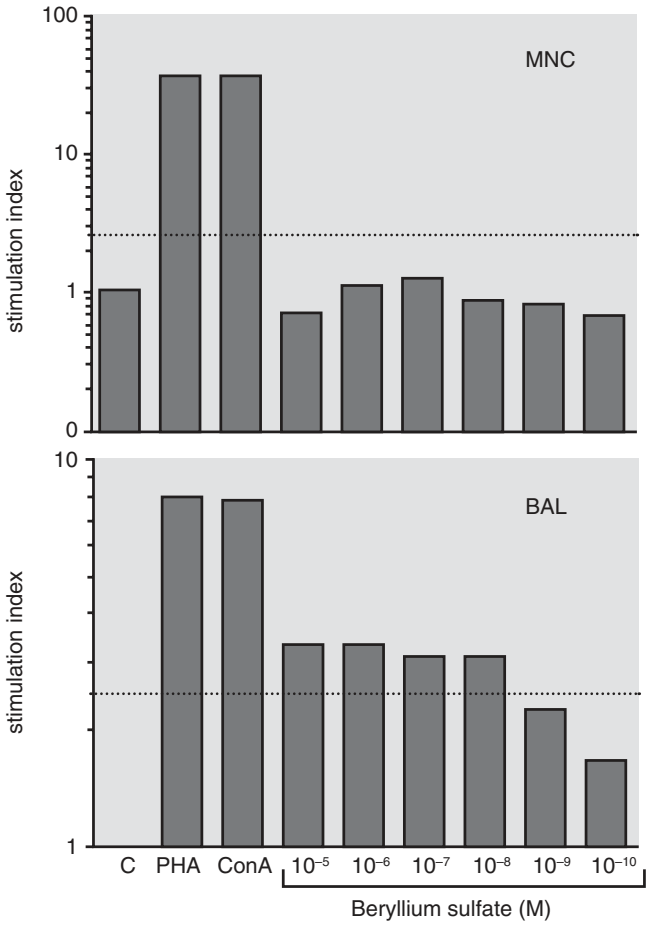

Fig. 37.1 Beryllium-lymphocyte proliferation tests with peripheral blood mononuclear cells (MNC, top) and bronchoalveolar lavage cells (BAL, bottom) of a patient with chronic beryllium disease are shown demonstrating the higher sensitivity of BeLPT using BAL-cells. The test with MNCs reveals a negative and the one with BAL cells a positive result. C: stimulation index (SI) of non-stimulated cells yields the background DNA replication and is set 1.0, PHA, ConA (phytohemagglutinin, concanavalin A): stimulation with lectins causes a high SI demonstrating the viability of the cells in in vitro culture. From the variation of the SI in C individual thresholds are calculated which are indicated by horizontal dotted lines. MNCs exhibit SIs below the threshold in all beryllium sulfate concentrations but cultures with BAL cells disclose SIs above the threshold in 4 out of 6 concentrations indicating the sensitization of this patient. The figure depicts the means of octuplet cultures for every concentration

Not every individual with a positive Be-LPT suffers from CBD [56]. Some beryllium exposed individuals have repeatedly positive results demonstrating sensitization without pul-

monary granulomas or other signs of disease. In a follow-up study 31% of those individuals progressed to symptomatic CBD within four years [18]. At present the test still remains the standard diagnostic test, since it is the only way to add an etiologic criterion. Whether patients with a positive Be-LPT in a surveillance program and the demonstration of granuloma suffer from early disease when they are asymptomatic and do not develop pulmonary function defects is a matter of debate.

The use of Be-LPT is cumbersome and alternatives using different readouts of cell activation are under investigation. Flow cytometry [57, 58], ELI-spot techniques [32, 59], and other cytokine based assays may be close to clinical practice. The use of metabolomic signatures to identify CBD and to differentiate CBD from beryllium sensitization is still in its infancy [60].

Measuring beryllium in urine and tissue samples may unequivocally identify exposure; however, concentrations of biological relevance are far below the sensitivity of routine tests, which limits the clinical value of negative results [37, 61–63].

Thus, for the unequivocal diagnosis of CBD the following criteria should be fulfilled [3]:

- A granulomatous disorder otherwise diagnosed as sarcoidosis needs to be established.
- Evidence of exposure.
- Proof of beryllium sensitization by positive Be-LPT findings or a positive equivalent.

In this context it has to be noted that granulomatous disease is not regarded mandatory for making diagnosis of CBD. Mononuclear alveolitis in the presence of beryllium exposure and hypersensitivity in combination with symptomatic disease may be sufficient to support the diagnosis. This is why some authors suggest for reasons of practicability to omit histopathologic criteria [43]. Many different criteria are used to define chronic beryllium disease. The differences in these criteria reflect the change in our understanding of the disease pathophysiology and the availability of diagnostic tests. Other differences may be related to the purpose of making the diagnosis such as clinical care, surveillance, research, or compensation.

Treatment and Monitoring

The first therapeutic measure is elimination of exposure as occupational studies reported reversibility of physiologic and radiographic defects when exposure is reduced or terminated [64, 65]. Although there are no studies demonstrating unequivocally a benefit of this step, it is recommended for CBD patients. Whether its social implications are justified in sensitized individuals has to be decided on an individual basis in combination with a genetic counseling [66]. Patients with early disease (i.e., sensitization in combination with granuloma but without symptoms or lung function defects) should be monitored using routine lung function tests, exercise physiology, and chest radiographs to detect progressive disease which is considered an indication for corticosteroid therapy. Serological markers of disease activity used in sarcoidosis, such as angiotensin converting enzyme, soluble interleukin-2 receptor or neopterin, can be used to gauge the inflammatory activity of CBD [67–69]. However, treatment decisions need to be made on the basis of symptoms and progressing organ dysfunction.

Systemic corticosteroids are the mainstay of CBD treatment and drug regimens established for sarcoidosis are used. Starting doses of 0.5–0.8 mg prednisolone per kg body weight per day are recommended, and stabilization or improvement will take place in most patients. However, under tapering the dose or after cessation of therapy some patients relapse, which may result in long-lasting maintenance therapy. The response to corticosteroids in CBD is quite variable. Long lasting remissions and recalcitrant disease have been observed [70]. Frequently recalcitrant disease can be suppressed with low dose corticosteroid maintenance therapy [70]. There have been no systematic studies of the use of other immunosuppressive, immunomodulatory or anti-inflammatory drugs in CBD. For patients who either do not respond to high doses of prednisolone, or require unacceptable high maintenance doses, second line therapy should be guided by experience in sarcoidosis, and corticosteroid-sparing regimens can be recommended as a second step [71, 72]. Relatively few patients progress to end-stage lung disease and lung transplantation should be offered to those who qualify for this type of therapy.

Supportive and rehabilitative therapy should be used as necessary. These include supplemental oxygen if rest or exercise-induced hypoxemia is present, bronchodilators if bronchial hyperresponsiveness or obstructive lung disease is present, pulmonary rehabilitation to maintain muscle strength and tone.

Prevention of Beryllium Sensitization and Chronic Beryllium Disease

At workplaces with contact with beryllium-containing substances, appropriate occupational safety measures should be

taken to protect workers from beryllium sensitization and CBD. In order to recognize diseases at an early stage, it is important to perform regular occupational health checks. After diagnosing CBD responsible authorities have to be informed to take action for the prevention of other workers at this particular workplace, their family members, and habitants in the neighborhood of the workplace. A Be-LPT screening program may be appropriate to identify beryllium sensitization and latent CBD in those cohorts although the high variability of Be-LPT makes its use difficult in cohorts with low prevalence [73]. However, with careful epidemiologic guidance this type of program can yield clinical and occupational important results but several positive tests might be required for a definite diagnosis [53, 74, 75].

Although genetic factors determining susceptibility for beryllium sensitization and the risk for progression to CBD are known [28], a genetic counseling cannot be suggested in primary or secondary prevention because the expected post-intervention CBD prevalence rates might not be low enough in the light of serious ethical, social, or legal concerns [66]. The hypersensitivity nature of the CBD implies that a complete eradication by industrial hygiene measures will not be possible as long as the use of beryllium is maintained. However, primary prevention by mandatory exclusion of individuals testing positive for certain genetic markers from workplaces with potential beryllium-exposure is no practical approach since the predictive value of the known markers is too low to enable an ethically correct verdict [66]. Voluntary genetic counseling of sensitized workers may be a cost-effective way of preventing CBD, however, sufficient data to do so is only available for the Caucasian ethnicity and therefore ethical and legal implications may prevent implementation [28, 66].

Indium–Tin Oxide-Lung Disease

Indium–tin oxide (ITO) is a sintered alloy containing a large portion (≈90%) of indium oxide and a small portion (≈10%) of tin oxide. It is used in the production of thin-film transistor liquid crystal displays (LCDs) for flat-panel displays used in television screens, touch screens, solar cells, and architectural glass. The use of ITO containing compounds in the electronics and semiconductor industry has risen by 500% over the last two decades. Little is known about the potential health hazard induced by occupational exposure to indium compounds. However, pulmonary toxicity has been demonstrated in experiments with hamsters.

In 2003 the first case of ITO interstitial pneumonia was identified by demonstrating indium and tin in intra-alveolar particles by energy dispersive X-ray analysis of a patient suffering from interstitial lung disease [76]. Chest CT-scan showed ground glass opacities all over the lung and subpleural honeycombing. Exposure time was three years but exposure dose could not be estimated. Therapy with prednisolone was initiated but no improvement was observed. The patient died from bilateral pneumothorax 7 years after first exposure [76].

Following this initial report, further indium–tin oxide-exposed worker were identified with interstitial lung disease, mainly with subpleural reticulation, honeycombing and bronchiectasis on the one hand, and centrilobular emphysema on the other hand. Lung function showed a mainly restrictive pattern [77]. The typical histopathological changes were foamy macrophages with cholesterol clefts, which can be pathophysiologically interpreted as an altered surfactant metabolism induced by indium–tin-oxide [77, 78]. In line with this hypothesis, case reports mention pulmonary alveolar proteinosis (PAP) in indium–tin-oxide-exposed workers [78, 79] and also PAS-positive material in lung biopsies emphasizing a role of disturbed surfactant handling a part of indium–tin-oxide lung disease [77]. Animal studies in rats and mice with inhaled indium support this hypothesis demonstrating alveolar proteinosis and inflammation preceding pulmonary fibrosis [80, 81].

Cross-sectional studies identified a substantial proportion of tin oxide-exposed persons exhibited pulmonary phenotypes, e.g., 21% of exposed persons with interstitial abnormalities and 13% with emphysema [82]. Workers exposed to higher indium–tin oxide concentrations exhibit higher plasma indium levels, and higher cumulative doses of inhaled indium–tin oxide correlate with higher pulmonary symptoms and serum biomarkers of lung disease [83, 84]. Notably several reports point towards a dose-dependency between indium–tin oxide exposition and pulmonary symptoms. However, also low indium–tin oxide exposition and plasma concentrations influence pulmonary symptoms, spirometric parameters, and lung disease biomarkers [83].

Indium–tin oxide-related lung disease has no uniform diagnostic criteria, however, should be suspected in patients with:

- Exposition to indium–tin oxide, which can be further verified by elevated plasma levels of indium.
- Restrictive or obstructive ventilatory defect in spirometry.
- Signs of interstitial lung disease (e.g., reticular and/or nodular alterations) on HRCT; alternatively also emphysematous changes may be present as sign of indium–tin oxide lung disease.

– Giant cells, foamy macrophages and/or cholesterol clefts in bronchoalveolar lavage or lung biopsy.

Cornerstone of the therapy is avoidance of ongoing exposition to indium–tin oxide, which might lead to amelioration of interstitial changes. However, long-term surveillance observations demonstrate progression of emphysema [85, 86]. The use of half-mask respirators that filter >99.95% of airborne particles reduced the serum levels of indium and Krebs von den Lungen-6 (KL-6) significantly in a cohort of indium-reclaiming plant workers despite ongoing exposition [87]. The role of steroid treatment of indium–tin oxide lung is a matter of debate [78]. Finally, lung transplantation remains a therapeutic option in patients with deteriorating lung function despite stopped exposition [88].

Animal models demonstrate an additional carcinogenic effect of indium [81, 89]. One case report of lung cancer in an indium-exposed worker demonstrated an accumulation of indium within the tissue by factor 1000 compared to serum, arguing for a causal relationship [90], however, another report demonstrated the nascent of cancer within the subpleural fibrosis zone [85], which is also the preferential localization of lung cancer in pulmonary fibrosis [91]. Even surveillance programs could not verify or deny the risk of indium-exposition for lung cancer nascent. Surveillance of indium-exposed workers identified four cases of lung cancer in 381 exposed persons. Standardized incidence ratio was elevated to 1.89, however, lacking statistical significance [90]. Therefore it remains unclear, whether indium–tin oxide exerts a direct carcinogenic or an indirect fibrosis-related effect in humans.

Hard Metal Lung

The term "hard metal" must not be confused with "heavy metals" such as lead, cadmium, and mercury. Hard metal consists to 90–94% of a tungsten carbide structure (also named Wolfram) which is blended with 6–10% cobalt as a binder and compressed into a polycrystalline material [92, 93]. It is heat and corrosion resistant and has an extraordinarily mechanical strength almost that of diamond. It is used in tools for drilling, cutting, or grinding [92–94]. Workers exposed to hard metals are toolmakers, blacksmiths, diamond polisher, and workers processing steel alloys containing hard metal [92, 95]. Abraham and colleagues were the first to publish that many cases described by Liebow as giant cell interstitial pneumonitis (GIP) were related to hard metal exposure [96]. Later, Ohori and colleagues confirmed the finding that GIP is almost pathognomonic for hard metal or cobalt exposure [97].

Animal experiments and case reports suggest that cobalt is the key agent inducing ILD by hard metal [98–101] with bound cobalt being even more toxic [102, 103]. Hard metal lung disease develops only in a small proportion of exposed individuals after a variable period and a dose-dependency cannot be observed [94, 104]. Therefore, an immunological mechanism with similarities to hypersensitivity pneumonitis is postulated [105, 106]. Genetic variants of the HLA-DP gene might confer to hard metal lung and being involved in the immunological process leading to interstitial lung disease [105, 107]. Another pathophysiological explanation of hard metal lung is increased oxidative stress that can be induced by cobalt an even more pronounced by tungsten carbide [102, 103, 108].

Clinically, cobalt related lung disease may manifest in acute /subacute or chronic form. The acute/subacute form presents during exposure to cobalt with constitutional and respiratory symptoms including cough, dyspnea, fever, and weight loss [94, 109]. The clinical presentation of the chronic form resembles more the presentation of interstitial lung disease, i.e., cough and dyspnea that arise without a temporal relation to exposure [104, 110].

Pulmonary function tests in hard metal lung generally reveal a restrictive pattern and reduction in diffusion capacity, however, in parallel with other occupational lung diseases (e.g., silicosis), obstructive pattern may occur [111–113]. There are no established laboratory tests to establish the diagnosis of hard metal lung, even though determination of cobalt in blood or urine samples may help to establish the diagnosis by proving exposition with urine concentration after working being relevant for occupational diagnostic steps in Germany [114]. Bronchoalveolar lavage may help to establish the diagnosis, if multinucleated giant cells ("cannibalistic cells," Fig. 37.3) are found in bronchoalveolar lavage, otherwise lavage has a lymphocytic pattern [115]. Histopathologically, interstitial giant cell pneumonitis (Fig. 37.3) is the prototypic finding for cobalt-related interstitial lung disease [116]. Nevertheless, a broad range of interstitial abnormalities can be found with patterns of organizing pneumonia, usual interstitial pneumonia or desquamative interstitial pneumonia [97, 117, 118]. In doubtful cases BAL or tissue can be used for detection of cobalt or tungsten to unequivocally establish the diagnosis [116].

Radiological findings in plain chest X-ray typically show nodular and/or reticular alterations that can be observed without gradients in distribution [113]. Fibrotic changes generally progress if exposition is ongoing [119]. In HRCT hard metal lung may present as NSIP pattern with ground-glass opacities and consolidations correlating to cellular infiltra-

tion in histology [115]. Besides NSIP pattern other radiological patterns are possible in hard metal lungs [120].

Unfortunately, criteria for the diagnosis of hard metal induced lung disease which are generally agreed on are missing. Thus, in view of the literature [121, 122] the following criteria are suggested:

- evidence of a diffuse parenchymal lung disease by HRCT,
- evidence of pulmonary function defects, and
- histological examination of lung specimens demonstrating giant cell interstitial pneumonitis.

In our outpatient clinic, we established the diagnosis of giant cell interstitial pneumonia (GIP) in an 82 year old, never-smoking, retired woman. HRCT revealed subpleural honeycombing combined with diffuse ground glass lesions (Fig. 37.2). She had been working for 20 years in a spinning mill and exposed to cobalt containing paints. This lead to the diagnosis of occupational hard metal lung. An example of giant cell pneumonitis is shown in Fig. 37.3.

Thus, even minimal exposure can cause hard metal lung disease. Course of the disease is variable: some patients might recover completely after avoiding further exposure, while others progress to irreversible pulmonary fibrosis. Older patients tend to have chronic and progressive disease. Several authors reported that patients benefit from prednisolone and other immunosuppressive treatment, but multicenter, placebo-controlled studies are lacking [95, 105, 123–125].

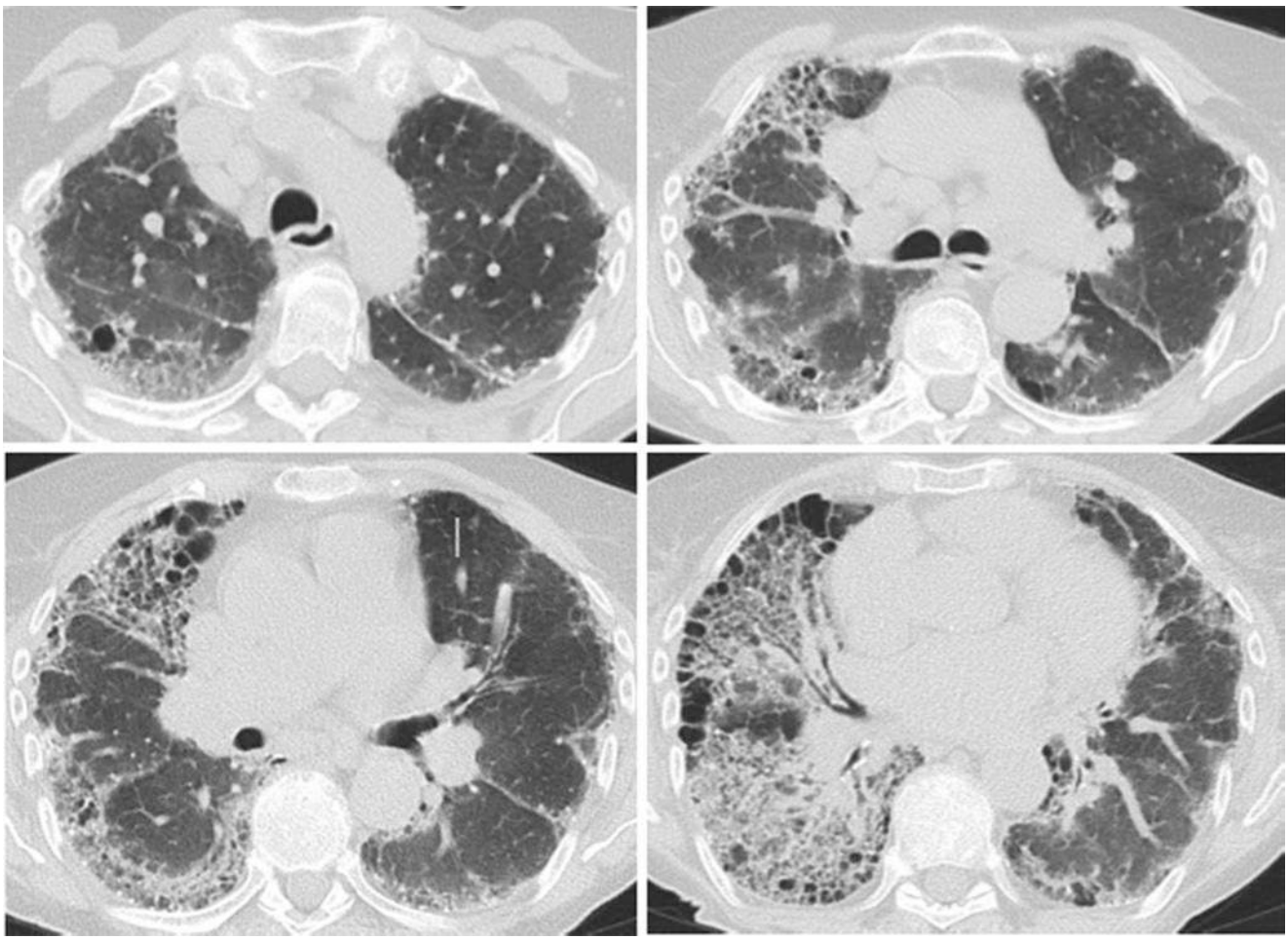

Fig. 37.2 HRCT scan of a 82-year-old patient with giant cell interstitial pneumonitis after Cobalt exposure at yarn factory. Histological diagnosis was obtained by transbronchial biopsy and confirmed by wedge biopsy. HRCT shows diffuse severe lesions, predominately in the right lung. There is severe subpleural honeycombing on both sides. Besides honeycombing, there are ground glass lesions at the left lung. Right lung shows coarse reticular lesions in the lower central areas and ground glass lesions in the upper regions

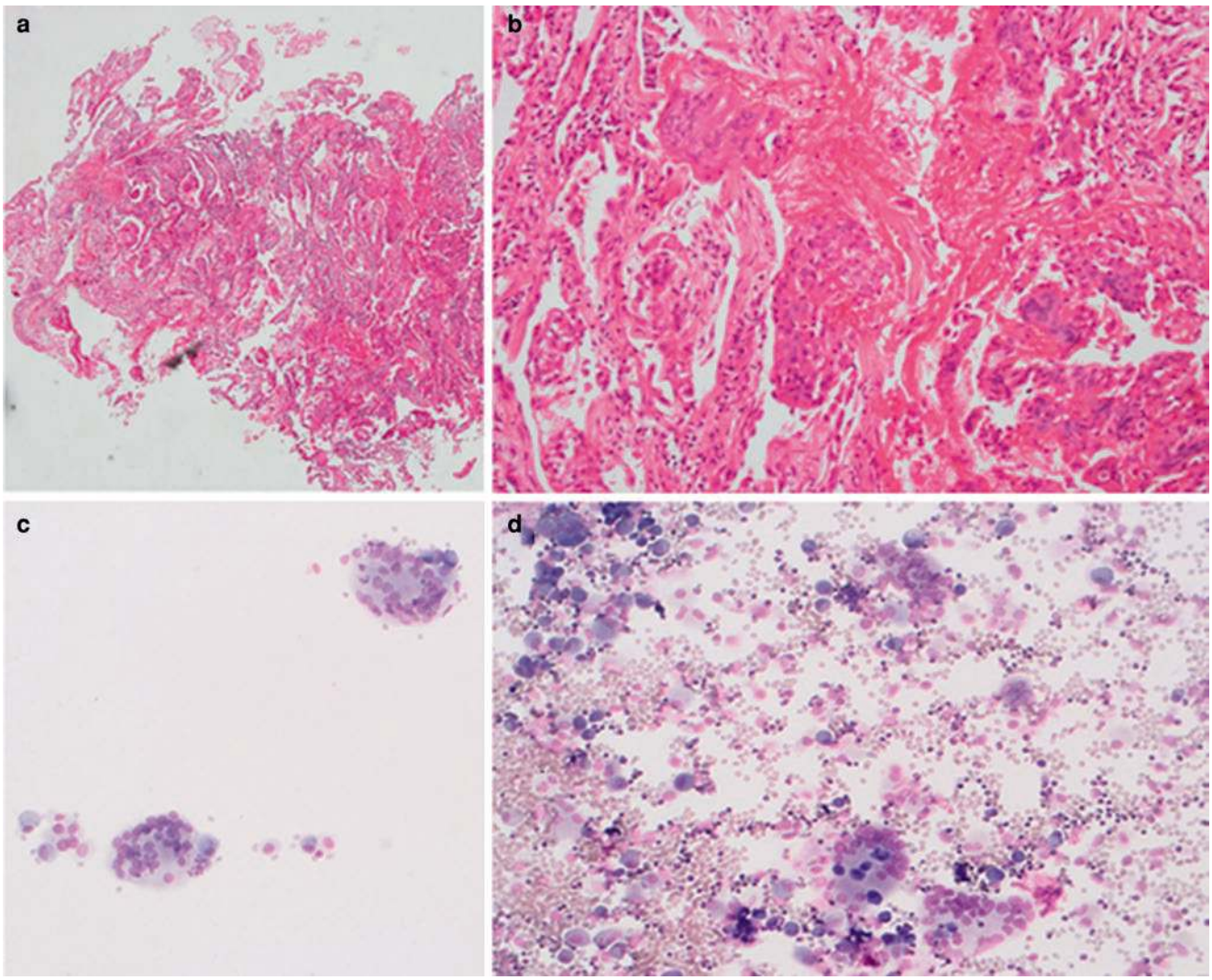

Fig. 37.3 Depicted are a transbronchial biopsy and a BAL cytology of a 82-year-old lady with giant cell interstitial pneumonitis. Panels (**a**) and (**b**): transbronchial biopsy and panels (**c**) and (**d**): BAL both with giant cells

Flock Worker's Disease

Short fibers (flock) cut from cables of synthetic microfilaments bound to adhesive fabric build a velvet-like surface used to produce upholstery, textiles, filters, coated fabrics such as fleeces and other materials. Flock can be derived from polyamide (nylon), cellulose acetate (rayon), polyester, polypropylene, polyethylene, and other olefins [126]. The diameter of the fibers ranges from 0.3 to 2.0 mm [127]. Depending of the cutting process, very small, breathable fibers might be generated [128]. First reports described ILDs in textile workers [129, 130]. The term flock worker`s disease was introduced 1998 by Kern and colleagues [128] who studied a case series in a flock plant in the U.S. In their initial article the authors described that all their patients had very similar lymphoproliferative lesions such as follicular bronchiolitis and lymphocytic interstitial pneumonitis. Further studies revealed that other pulmonary lesions such as desquamative interstitial pneumonitis (DIP) and non-specific interstitial pneumonitis (NSIP) as well as bronchiolitis obliterans organizing pneumonitis (BOOP) may be associated with exposure to flock [131–133]. Granuloma formation has not been described [132, 133]. An increase in lymphocytes can frequently be found in BAL, which might be accompanied by an increase in eosinophils and neutrophils. Most patients suffer from a subacute type of the disease presenting with dyspnea, dry cough, and chest pain [128, 134, 135]. The acute type of the disease can be associated with fever, fatigue, and weight loss. A substantial number of patients progress and require long-term oxygen treatment [131].

We observed one patient with a fatal course of flock worker`s disease, otherwise not reported. The 58-year-old patient, ex-smoker, worked in a plant producing nylon and rayon flock for cigarette filters and other products. One of his

daily jobs was to clean machines cutting flock and he did not use any respirator mask. He presented with dyspnea and dry cough. Pulmonary function test revealed severe restrictive lung disease. HRCT scan (Fig. 37.4) and histology of wedge biopsy were consistent with non-specific interstitial pneumonia (NSIP, Fig. 37.5). High dose prednisolone treatment did

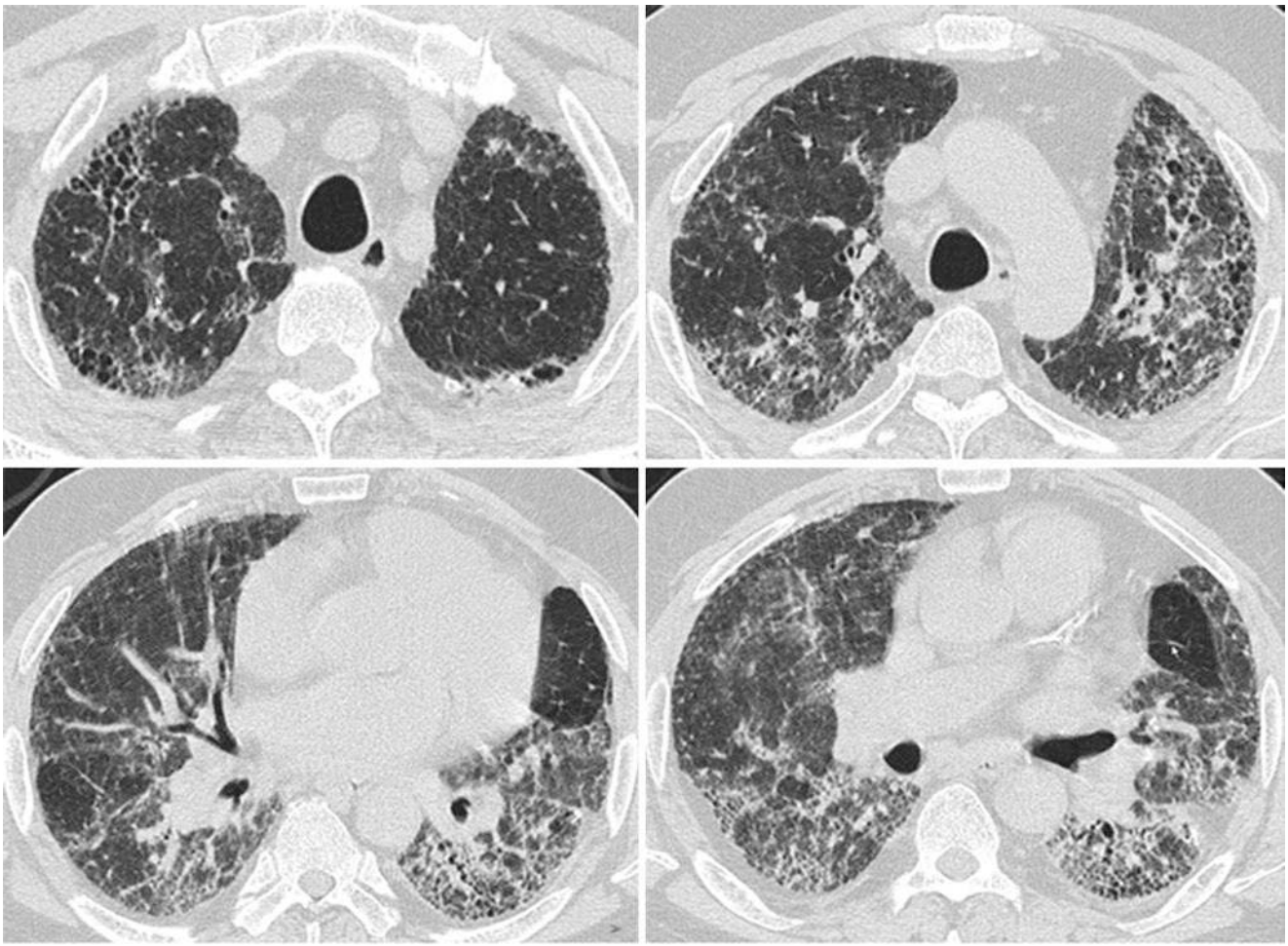

Fig. 37.4 HRCT scan of a 58-year-old patient with severe, subacute flock worker`s disease after exposure in a filter factory. Patient died because of acute exacerbation. HRCT shows severe diffuse ground glass lesions in both lungs and reticular bands. There is also some honeycombing in the lower subpleural regions and considerable pleural thickening

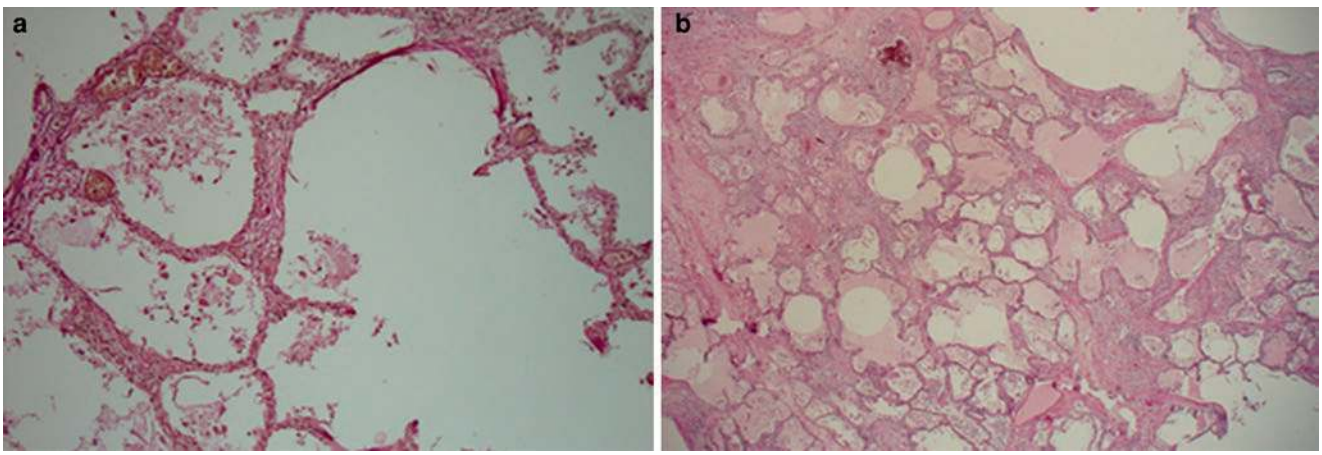

Fig. 37.5 Microphotographs from the lungs of the 58-year-old patient with flock worker`s disease who died because of acute exacerbation. Panel (**a**) and (**b**): Autopsy revealed morphology predominately consistent with NSIP and diffuse alveolar damage. Intra-alveolar edema and alveolar desquamation is due to respiratory failure and subsequent death

not show any effect and eight months after establishment of diagnosis he died due to acute exacerbation.

Symptoms and pulmonary lesions can completely resolve once patients avoid further exposure to flock. Ongoing exposure increases the risk of lung functional deterioration with a decline of 46 ml/year in FeV1 [136]. Re-exposure alters the risk of relapse and progressive disease [131]. Pulmonary function testing often shows a restrictive pattern but also obstructive lung disease was described in some cases. Diagnosis of flock worker's lung is based on:

- persistent respiratory symptoms;
- previous work in the flocking industry;
- histologic evidence of interstitial lung disease compatible with flock worker's disease [131, 137].

Patients with strong suspicion of flock worker's disease should strictly avoid any further exposure to flock.

Animal experiments showed similar findings as observed in humans and demonstrated dose-dependent reversible, inflammatory lung lesions induced by flock inhalation [126, 138].

There are no studies evaluating immunosuppressive treatment in flock worker's disease [131, 137]. Clinicians tend to treat the disease in analogy to other ILDs with similar pathology such as lung involvement in rheumatic diseases; however, benefit from immunosuppressive treatment is not unequivocally established.

Asbestosis

Asbestosis is an ILD caused by asbestos inhalation and is subsumed under the group of pneumoconioses [139, 140, 142]. Asbestos is a naturally occurring fiber composed of hydrated silicate and metals, such as magnesium. Asbestos fibers are classified in two different categories of mineral fibers: rod-like amphiboles and serpentine fibers. Due to its resistance to heat and degradation as well as its good insulation characteristics, it was ubiquitously used in the past. Asbestos was added to building materials and products used in textile industry, car production, shipbuilding, and electronics [143]. It is well established that there is a dose response relationship between pulmonary lesions and asbestos exposure [144–146]. The cumulative pulmonary burden is crucial for disease development [141]. Cigarette smoking by interfering with mucociliary clearance increases cumulative burden and aggravates asbestos induced pulmonary diseases [147]. Very common are pleural lesions caused by asbestos exposure and pleural plaques are considered as pathognomonic for asbestos exposure [139, 148].

There is a latency period of about 15–30 years between exposure to asbestos and development of asbestosis [140, 149]. Asbestos is of cellular toxicity and deposited in the respiratory bronchiole where it is phagocytosed by alveolar macrophages and alveolar epithelial cells [150] (Fig. 37.7). Alveolar macrophages transport fibers to the pleura via lymphatics. Multiple evidence derived from animal experiments documents dose-dependent asbestos induced pulmonary inflammation and fibrosis [151, 152]. Asbestos induces cellular production of radical oxygen species (ROS) and multiple inflammatory mediators. Recent evidence indicates that asbestos triggers inflammasome activation, a key event of inflammatory processes in innate immunity [153, 154]. Noteworthy, inflammasome activation results in pulmonary fibrosis [155]. Interestingly, signs of alveolar inflammation in asbestosis (high numbers of alveolar macrophages, elevated neutrophils and eosinophils) and higher numbers of asbestos bodies indicate a worse survival [156]. Asbestos inhalation induces dose-dependent inflammatory and consecutive fibrotic lesions starting from the respiratory bronchiole extending to the adjacent alveolar tissue. The College of American Pathologists [157] has developed histologic criteria for asbestosis and a grading system (I–VI). Alveolar collapse and honeycomb remodeling is the most severe grade (VI), however, histopathological grade I asbestosis does not seem to be a prerequisite for development of grade IV asbestosis [158]. Asbestos bodies can be identified in BAL and lung specimens using scanning/transmission electron microscopy. Noteworthy, this is also the case in specimen of healthy individuals and, therefore, a sole demonstration of asbestos bodies is not sufficient to make a diagnosis.

HRCT often shows bilateral, diffuse fibrotic changes with subpleural honeycombing, which is more prominent in lower lung fields and frequently resembles the pattern of usual interstitial pneumonia/idiopathic pulmonary fibrosis (IPF). In most cases subpleural fibrosis/reticulation is coarser in asbestosis than in IPF [159]. In some cases imaging will not reveal a sufficient evidence and histopathological examination showing lung fibrosis with peribronchiolar fibrosis will be required to support a diagnosis of asbestosis [160]. Typical changes are also pleural plaques, pleural thickening, rounded atelectasis, parenchymal bands and curvilinear lines [161–163] (Fig. 37.6).

Diagnosis of asbestosis requires:

- evidence of a diffuse parenchymal lung disease either by HRCT or histology,
- evidence of a causal relationship by demonstrating environmental history of asbestos exposure with plausible latency,

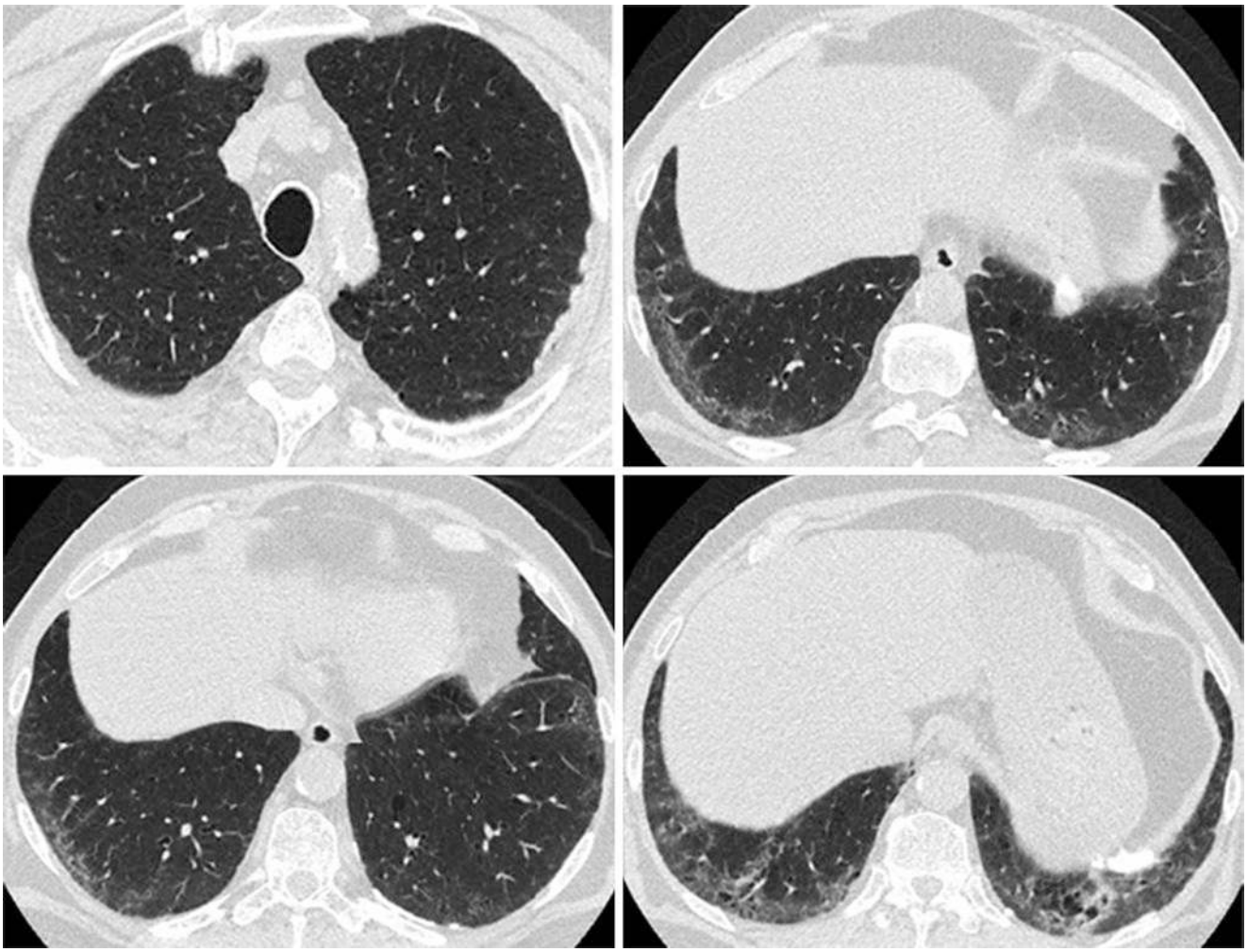

Fig. 37.6 HRCT scan of a 62-year-old plumber with asbestosis showing linear opacities and subpleural nodular opacities (upper left), ground-glass attenuation, subpleural honeycombing, and calcified plaques

- markers of exposure such as pleural plaques or recovery of asbestos bodies (BAL, lung specimen) [139, 164–167] (Fig. 37.7), and
- exclusion of competing diagnoses.

Patients often present with dyspnea, cough, and pleurodynia. Physical examination may reveal end-inspiratory crackles and finger clubbing. Pulmonary function test often shows restrictive ventilatory dysfunction, but also mixed or sole obstructive patterns have been reported [168].

In some patients asbestosis progresses rapidly, while in others the disease may be stable over years. Patients with a mainly interstitial fibrotic manifestation of asbestosis have a more rapid decline in lung function (annual decline of approximately 80 ml FVC/year) compared to patients with pleural manifestation [169]. Co-factors of progression have not been identified yet. Total asbestos exposition seems to be an important determinant of disease progression as the cumulative and continuous exposure predisposes to fibrotic disease rather than malignant disease [170].

There is no evidence based approach for treatment of asbestosis [171]. Smoking cessation and avoidance of further asbestos exposure are strongly recommended. Some patients might benefit from immunosuppressive treatment while others not, which might be dependent on the level of inflammatory processes involved. There is no recommendation for the use of immunosuppressive treatment [139]. Of note, one case series reports a beneficial effect of pirfenidone on asbestosis-related interstitial lung disease with UIP pattern [172].

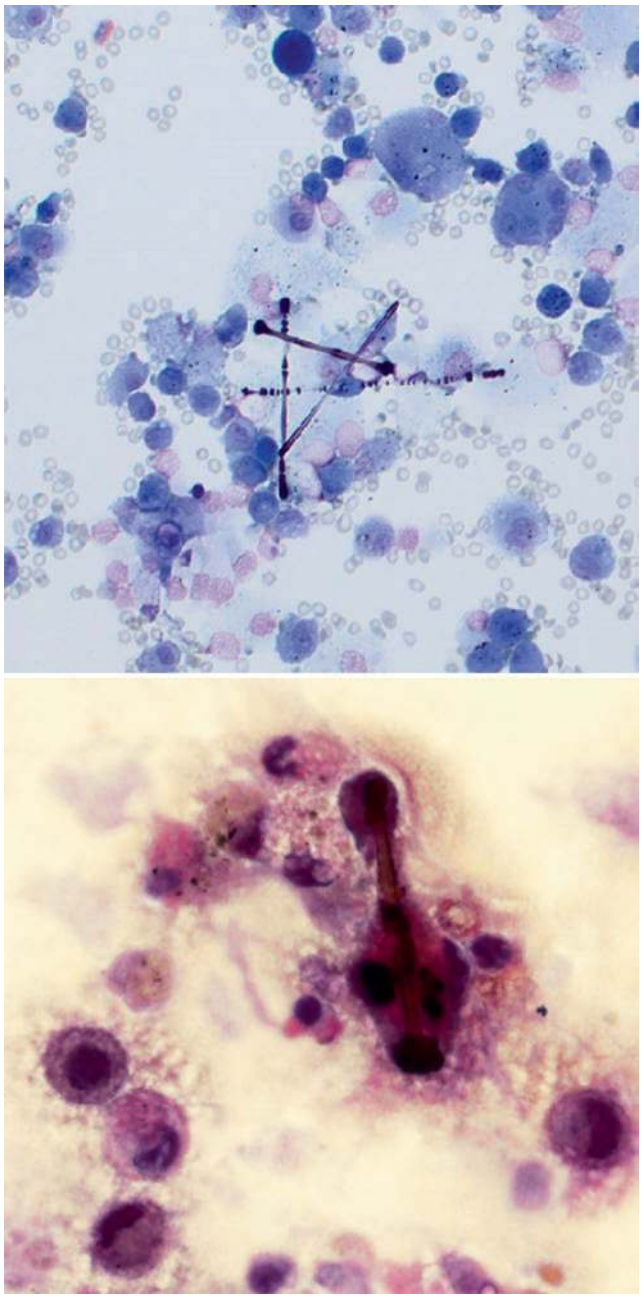

Fig. 37.7 BAL cytospin of a 62-year-old plumber with asbestosis showing four asbestos fibers

Nanoparticle Induced ILD

Nanoparticles are defined as particles sized between 100 and 1 nanometers [127] and can be composed of various organic and inorganic substances. They often contain metals which can lead to enhanced toxicity. They are generated by combustion processes such as diesel exhaust or by any process burning fuel. Worldwide man-made nanostructures are used in multiple and increasing application areas.

Several studies have shown that particle size has huge impact with less toxicity in the micrometer and high toxicity in the nanometer range. Extraordinary harmful are those with a high surface to volume ratio [173, 174]. Animal experiments clearly indicate that distinct nanoparticles induce ILDs. Several studies demonstrated induction of granuloma, inflammation, and pulmonary fibrosis in mice after intratracheal instillation of single wall carbon nanotubes [175, 176]. Single wall carbon nanotubes seem to be even more toxic than quartz [176]. Bonner and colleagues showed that vanadium pentoxide induces pulmonary fibrosis in rats [177]. The inhalation of titanium dioxide particles leads to pulmonary fibrosis in mice and rats and NiO and Co_3O_4 nanoparticles induce pulmonary delayed type hypersensitivity (DTH)-like responses [178, 179]. Although in animal models the toxicity of several nanoparticles has clearly been demonstrated and occupational exposure to nanoparticles is widespread, the number of reports documenting ILDs caused by nanoparticles is limited. Song and colleagues [180] described seven female workers exposed to spray paint under extreme working conditions without any extraction system. All exposed workers presented with pleural effusion, granuloma, and pulmonary fibrosis and two died due to progressive pulmonary fibrosis. The dust to which all workers were exposed to consisted of multiple substances including polyacrylate nanoparticles. The presence of these nanoparticles was confirmed in histologic specimens and pleural effusions. The authors failed to demonstrate data regarding the type and dose of nanoparticles and possible other substances [180, 181]. Therefore, this report does not proof that nanoparticles caused the described ILD, but it is likely that nanoparticle exposure contributed as one factor to the disease. Recently, Ferri et al. reported in a cohort of patients with systemic sclerosis an association with silica

nanoparticle exposure and more severe disease. Patients exposed to silica nanoparticles had higher serum levels and presented more likely with pulmonary fibrosis and myositis [182].

In the absence of international agreement on the diagnosis of nanoparticle induced lung disease the following criteria are suggested:

- exposure to nanoparticles at the workplace,
- evidence of a diffuse parenchymal lung disease by HRCT,
- evidence of pulmonary function defects, and.
- histological examination of lung specimens demonstrating interstitial lung disease and nanoparticles.

At present it is hard to estimate the hazards of nanoparticles. One major factor contributing to this uncertainty is the variety of nanoparticles. Some authors extrapolate from animal experiments a similar toxicity like asbestos and for some nanoparticle species thresholds have been delineated from animal studies although the differences between rodents and humans in the toxicological response to nanoparticles are not known [183, 184]. Nevertheless, current knowledge suggests that preventive occupational measures to reduce exposure to nanoparticles might be quite effective. There have been no cases reported so far from industrial countries with high safety standards [122, 159, 185].

Siderofibrosis

Siderofibrosis is a well established but rare interstitial lung disease of occupational origin and is different from the benign welder's siderosis. It is reported after long term and severe exposure to welding fumes in poorly ventilated workplaces [186]. A recent cross sectional study demonstrated a significant effect of welding fume exposure to pulmonary symptoms and lung functional impairment [187]. Interestingly this study found an association between different types of welding and the observed pulmonary impairment. Welding fumes mainly induce obstructive airway diseases especially when smoking is co-factor [188, 189]. However, several case series describe association between welding and pulmonary fibrosis, which might be a continuous process of inflammation, desquamation, and fibrosis [190]. In this context it is noteworthy that several studies demonstrate an inflammatory response leading to epigenetic changes in welding-exposed individuals [191, 192].

There are more than 80 types of welding technology and allied processes in commercial use. Sources of airborne particles are fumes from the base materials, fluxes, and filler metals used in powdered form. Relevant gases, which are combined with welding fumes, are ozone, nitrogen dioxide, fluoride, carbon dioxide, and carbon monoxide. Factors that influence the concentrations of fumes and gases at the workplace are [185]:

- Degree of confinement.
- Rate of progression of welding.
- Type of welding process.
- Adequacy of ventilation.

Extremely high concentrations of welding fumes occur, when employees work in partly-closed or confined spaces without using (local) extraction systems. Buerke et al. examined 15 welders with IPF [186]. The duration of work as welder was 28 years and the cumulative dose of welding fumes was 221 mg/m^3 (median). Pulmonary function testing showed a pattern of restriction or combined restriction-obstruction, lower diffusion capacity, and reduced blood oxygen tension at exercise. Examinations of lung tissue showed fibrotic reactions in close topographic relationship with deposits of welding fume particles.

Histologically, sidero-pneumoconioses are classified into three grades [193]:

- Grade I: Mostly alveolar but also interstitial accumulation of macrophages, which contain siderophilic particles, granular black (iron oxide) and minimal mixed dust deposits. Fewer macrophages or mixed dust in perivascular, interstitial, and paralymphatic tissue. Low-grade, fibrogenic reaction, only seen in microscopy.
- Grade II: Rising accumulation of activated alveolar macrophages and mixed dust particles in areas of perivascular, pleural, and septal lymphatic drainage. Fibrotic reactions in areas with mixes dust deposits.
- Grade III: Massive findings of mixed dust deposits. Perivascular pseudogranulomatous pattern with reactive fibrillary fibrosis. Focal deposits of welding fume particles with topographical relationship to interstitial fibrosis.

As siderofibrosis is a rare disease, epidemiological data are limited. The existing data leads to the conclusion that a causal relationship between IPF in welders with a long-term exposure to high concentration to welding fumes exists.

Flavoring-Induced Lung Disease

The flavoring-induced lung disease has been described in individuals working in popcorn factories and is therefore also named popcorn lung disease [194]. It is caused mainly by diacetyl (2,3-butanedione) and its substitute 2,3-pentanedione, that are used for flavor intensification and naturally occurs, e.g., in butter, caramel, coffee, and honey [195]. It is released as vapor at relatively low temperatures during the process of popcorn flavoring, coffee roasting or chocolate manufacturing.

The initial reports describe the disease as an obstructive pulmonary disease with signs of obliterative bronchiolitis. Animal studies mainly in rats emphasize these observations

showing that installation of these substances induces epithelial damage and airway-associated fibrotic reactions mimicking fibrotic obstructive bronchiolitis [196–198].

Frequently radiological signs of airway remodeling leading to mosaic attenuation can be seen. Centrilobular nodules are observed in the parenchyma [199].

Analyses of lung function derived from surveillance programs in food industries demonstrate a restrictive ventilation defect at least as prevalent as obstructive or mixed ventilation patterns [202, 203]. Importantly obstructive ventilatory limitation is higher in non-smokers exposed to diacetyl compared to smokers even though smokers inhale high concentrations of cigarette-released diacetyl [200, 201]. Longitudinal follow-up of spirometry revealed a more pronounced decrease in FeV1 in flavoring-exposed workers compared to healthy controls [203]. As a consequence, this results in an elevated rate of chronic obstructive lung disease-related mortality [204].

The lung function assessment of exposed workers demonstrate an association between exposure time and prevalence of lung functional impairment underscoring the need of preventive measures like technical improvement to minimize the occupational exposure to diacetyl and 2,3-pentanedione [202, 205].

Of note in this context is the observation that flavors used in electronic cigarette liquids contain high concentrations of diacetyl that exposes consumers to higher diacetyl concentrations than NIOSH limits [206, 207].

Silica-Induced Interstitial Lung Disease

Silicosis is one of the oldest occupational diseases and is caused by inhalation of crystalline silica that triggers a fibrotic response in the lung parenchyma. Silica (silicon dioxide, SiO_2) is one of the most abundant naturally occurring minerals and especially enriched in rocks. Because of the worldwide occurrence of silica, silica-related lung diseases are a concern in developed countries as well as in countries with low incomes [208]. Table 37.4 depicts some of the industries with occupational risk for silica exposure.

Approximately three million workers are exposed to silica-containing dusts in Europe, however, preventive measures have reduced morbidity and mortality in Europe and United States [209–212]. In contrast, China reported 500.000 cases between 1991 and 1995 with approximately 24.000 deaths per year [4].

With the shift of typical silica-associated industries like mining to countries with lower preventive measures and novel industrial procedures like sandblasting for demim jeans, silica-induced interstitial lung diseases remain an important medical problem [213–218]. Environmental exposure seems to be less important, even though recurrent exposure to sand storms may lead to silicosis [219].

Dose exposure clearly correlates with disease severity and mortality [212, 220–222]: Preventive strategies in reducing silico exposure (e.g. 0.05 mg/m^3 in US) have reduced, but not completely abolished the risk of silicosis [222].

Table 37.4 Occupations and industries related to silica dust exposure (modified according to [4, 295]

	Traditional industries	Novel industries
Stone breaking/ crushing	Tunneling/mining	Stonemason Stone crusher
Cutting	Mining Tunnelling	Stonecutter Agate mill worker Artificial stone benchtop
Sandblasting/ Sanding	Tomb stone production	Denim sandblasting Art and craft works
Polishing/Buffing	Art crafts	Jewellery

The underlying pathophysiology of silica-associated lung diseases requires the deposition of silica (especially in its crystalline form with a diameter < 10 μm) in the distal airway, where it causes an inflammatory and pro-fibrotic response. Engulfed silica particles (especially by macrophages) activate the NALP3 inflammasome, which is required for the development of silicosis [154, 155, 223]. Additionally, due to its piezoelectric properties, silica may induce the formation of reactive oxygen species, with further contribute to an inflammatory and fibrotic response [224, 225].

Therapeutic options are scare for silicosis. Therapeutic trials like whole lung lavage or corticosteroids have not proven any significant benefit [226–228]. Therefore preventive measurements like the avoidance of (ongoing) exposure, smoking cessation and addressing complications like tuberculosis and other infections remain the cornerstones of therapy. Additional bronchodilator therapy and long-term oxygen therapy may be of some help.

Silica-associated lung diseases have a long history in medicine. With the industrialization and machine utilization, e.g., in mining, the silica exposure and prevalence of associated chronic silicosis increased [4, 229, 230]. Novel industries and techniques on the one hand and lacking awareness to preventive measures on the other hand lead to outbreaks of chronic, but also of acute silicosis.

For example, sandblasting has been recognized a procedure with a high risk of silicosis. Outbreaks in Turkey in the recent years have demonstrated that silicosis may arise in young workers (between 20 and 40 years old) after a relatively short exposure period (2-4 years) [214, 231, 232]. Of 50 initial cases 7 had acute and 43 had accelerated silicosis. Similar observations of young age and short exposure period have been made for stonemasons in Iran [233, 234] and workers with artificial stones (e.g., in benchtops) in other countries [235–237].

Chronic Silicosis

Chronic silicosis typically arises several years after silica dust exposure [4, 238, 239]. The clinical expressions range from asymptomatic forms in the case of the simple chronic form to complicated progressive massive fibrosing form (PMF). The radiological hallmark of simple chronic silicosis is the presence

of discrete, well-defined nodules (with a diameter up to 1 cm) that exhibit upper lobe predominance [199, 240]. Additional signs are enlarged mediastinal lymph nodes that may exhibit calcifications [241]. Plain X-ray is mostly used for screening and radiological findings are classified according to the International Labor organization [242], however, computer tomography may be more sensitive and allows more information on lung architecture [243–245]. Lung function in these patients may be normal or demonstrate restrictive or obstructive ventilator defects [246–248].

Histology, when performed, may demonstrate nodules with dust-loaded macrophages, that in later stages has dense fibrosis in its surrounding [249]. Bronchoalveolar lavage may show a slight lymphocytosis and dust-loaded macrophages with birefringent material may be found.

Simple chronic silicosis may progress to complicated chronic silicosis (or conglomerate, progressive massive fibrosis) in 20–30% of workers within 5 years, especially ongoing exposure and smoking increase the risk of progression [250–252].

Complicated silicosis is radiologically characterized by conglomerate masses that tend to migrate to the hilar region [199, 253]. These conglomerates consist of hyalinized fibrotic foci. These fibrotic masses lead to distortion of airways, increase the risk of emphysema and pneumothoraces.

Typically, the diagnosis of chronic silicosis can be made based on the following criteria:

- Relevant occupational exposure that could have been occurred even decades prior to the diagnosis.
- Typical radiological findings:
  - well-defined small often symmetric nodules with upper lobe predominance in chronic simple silicosis.
  - Conglomerate masses with distortion of the lung architecture in complicated silicosis.
  - Calcifications may be present in the masses and/or the mediastinal lymph nodes.
- Exclusion of other diseases (e.g. sarcoidosis, (Non-Hodgkin) lymphoma, tuberculosis, metastasis, (fungal) infections).
- Histology and bronchoalveolar lavage may not be required for the diagnosis, but for the exclusion of differential diagnoses.

Acute and Accelerated Silicosis

In contrast to chronic silicosis, in which long-lasting exposure to silica at low concentrations is the causing culprit, acute and accelerated silicosis arise in cases of short term exposure to dusts with high silica concentrations (1–10 mg/m^3/year) [254].

These acute forms of silicosis develop within few years and may progress von initially ground-glass opacities and pleural thickening to nodules and progressives masses.

The underlying pathophysiology seems to be similar to the chronic silicosis, however, the elevated exposure may lead to a more pronounced inflammatory response, as bronchoalveolar lavage in these patients demonstrates high cell count, lymphocytosis, dust-loaded macrophages, and PAS-positive milky lavage fluid [255–258].

In line with these observations, radiological findings demonstrate initially centrilobular nodules and ground-glass opacities and sometimes a crazy-paving pattern [199, 214, 259].

The diagnosis of acute/accelerated silicosis can be made in patients

- With recent high exposure to dust with high silica concentrations.
- Radiological findings include typical findings in chronic silicosis, however ground-glass opacities, crazy-paving and rapidly progressive nodular opacities may be present.
- Bronchoalveolar lavage may demonstrate high cellularity, slight lymphocytosis and dust-loaded macrophages.
- Histology reveals silicotic nodules with birefringent particles and patchy fibrosis [236, 237].

Coal Workers Disease—Coal Mine Dust Lung Disease (CMDLD)

Coal mine dust lung disease describes a sum of different lung diseases that etiologically rise from inhalation of coal mining dusts [260, 261]. In resembles in some pathophysiological and radiological aspects silica-associated lung disease. In contrast to silicosis, CMDLD is caused by mixed dust exposure that normally occurs during coal mining. Importantly, CMDLD can be observed in underground and surface miners, however, prevalence seems to be higher in the former ones [262, 263].

Its prevalence differs between high- and low-to-middle income countries. Preventive measures as well as increased mechanization of working processes resulted in a significant reduction of CMDLD prevalence and mortality, with 2% of workers developing CMDLD in the 90s in US [260, 263, 264]. For China, prevalence of CMDLD ranges around 6% in the first decade of the twentieth century, compared to approximately 3% in US [265]. Nevertheless, in recent years an increase in the prevalence of CMDLD has been noted that goes also along with the more severe phenotype of progressive massive fibrosis. Notably, prevalence was especially increased in small mines with fewer miners [261, 262, 265].

Inhalation of coal dusts leads to its accumulation in the distal airways leading to airway anthracosis and accumulation in the bronchovascular tissues. Additionally, dust particles are engulfed by macrophages and may thereby trigger a proinflammatory and profibrotic response, engaging TNF and interleukins that are increased in the bron-

choalveolar lavage of coal workers [266–268]. Furthermore, mixed dusts in coal mines may alter (potentially via Fe^{2+}) the redox balance leading to more oxidative stress [269–271]. These cascades trigger the histologically and radiologically observed formation of nodules with dense collagen deposition [272]. Additionally, coal dust inhalation leads to histopathological signs of chronic bronchitis and emphysema that seem to correlate with dust exposure [273, 274].

CMDLD may present in different clinical pictures, the cornerstone of the diagnosis is a convincing work place history with appropriate dust exposure. Roughly, CMDLD may be separated in airway and interstitial lung disease [261], although clinical pictures may overlay.

Chronic Obstructive Disease in CMDLD

Coal dust exposure is able to cause an airway disease leading to a dust dose-dependent decline in FeV1 with signs of chronic bronchitis [275]. Initially, decline in FeV1 is more pronounced, with longer exposure the slope of lung functional decline decreases [276, 277]. The kinetic of FeV1 decline resembles the decline observed in smokers [278]. Additional to airway disease, centriacinar emphysema may develop especially in patients with airway deposition as demonstrated by coal dust macules. Importantly, the airway disease of coal-dust exposed workers contributes to an increased mortality [279].

Simple CMDLD

Simple CMDLD is mostly detected by chest X-ray (Fig. 37.8), as it causes no or only mild clinical symptoms like cough or exertional dyspnea. Classically defined as nodular, relatively small nodules (<1 cm diameter) with a symmetric distribution in the upper lobe, data from larger cohorts demonstrate, that nodules may be irregular in up to 40% of cases and observed in the lower lung zones as well [280]. These nodular opacities are radiological signs of coal mine dust exposure [281, 282].

Complicated CMDLD

Complicated CMDLD is characterized by a more rapid decline in lung function (FeV1: −60 ml/year), that predisposes to progressive massive fibrosis (PMF) [283–286]. Radiologically, opacities are of larger size and seem confluent with migration to the hiliar region (Fig. 37.9). Histologically, dense fibrosis with central coal dust can be found.

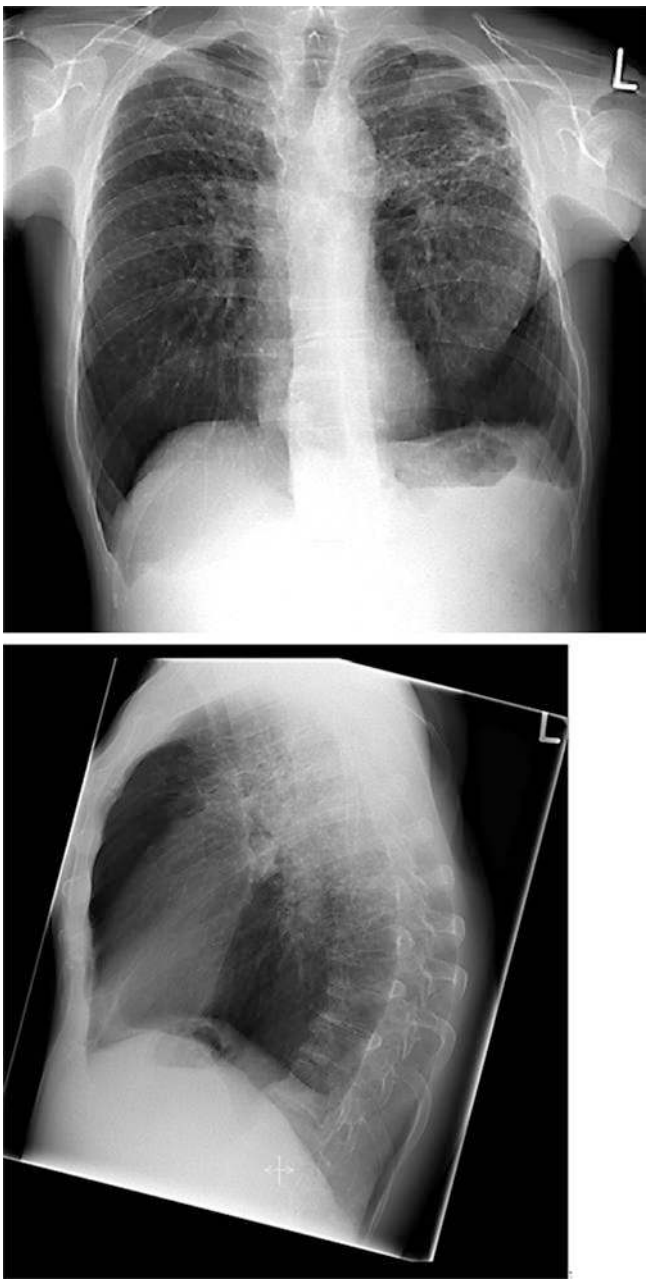

Fig. 37.8 Chest X-ray showing upper-lobe opacities, nodules, and reticulation compatible with silicosis in a patient with an appropriate occupational history

Dust Diffuse Fibrosis (DDF) in CMDLD

Dust diffuse fibrosis is a special entity in CMDLD. It describes a more peripheral fibrosis with lower lobe predominance. It resembles more the radiological and histological picture of idiopathic pulmonary fibrosis with honeycombing and traction bronchiectasis. The interseptal fibrosis is often coal dust loaded, which hints towards a causal relation [287–289].

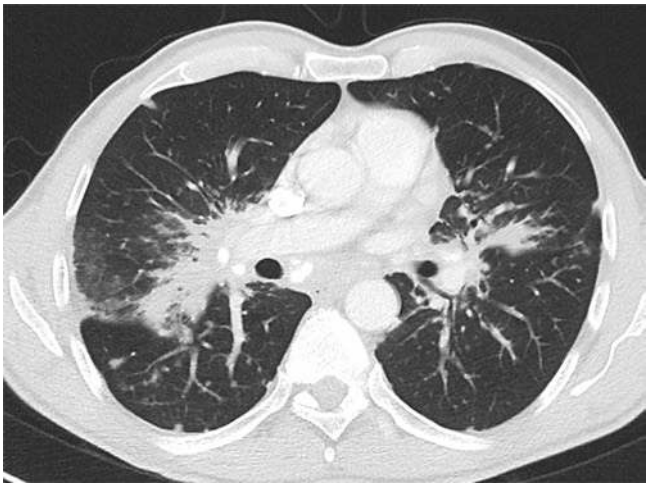

Fig. 37.9 CT scan of a patient with complicated silicosis hiliar masses and calcifications

Because of the aforementioned different phenotypes of CMDLD, the diagnosis of CMDLD relies especially on a detailed and complete work history. It is important to emphasize that CMDLD may develop years and decades after coal dust exposure underpinning the importance of a full working history [290–292]. The diagnosis can be made in patients with

- a work history compatible with coal dust exposure
- lung function may be normal or present an obstructive, restrictive or mixed ventilatory defect
- radiology may demonstrate signs of fibrosis or emphysema
- Bronchoscopy, bronchoalveolar lavage and histology may not be needed to prove the diagnosis, but to rule out differential diagnoses. They may show bronchial anthracosis (Fig. 37.10), coal dust-loaded macrophages or fibrosis with interstitial coal dust inclusion.

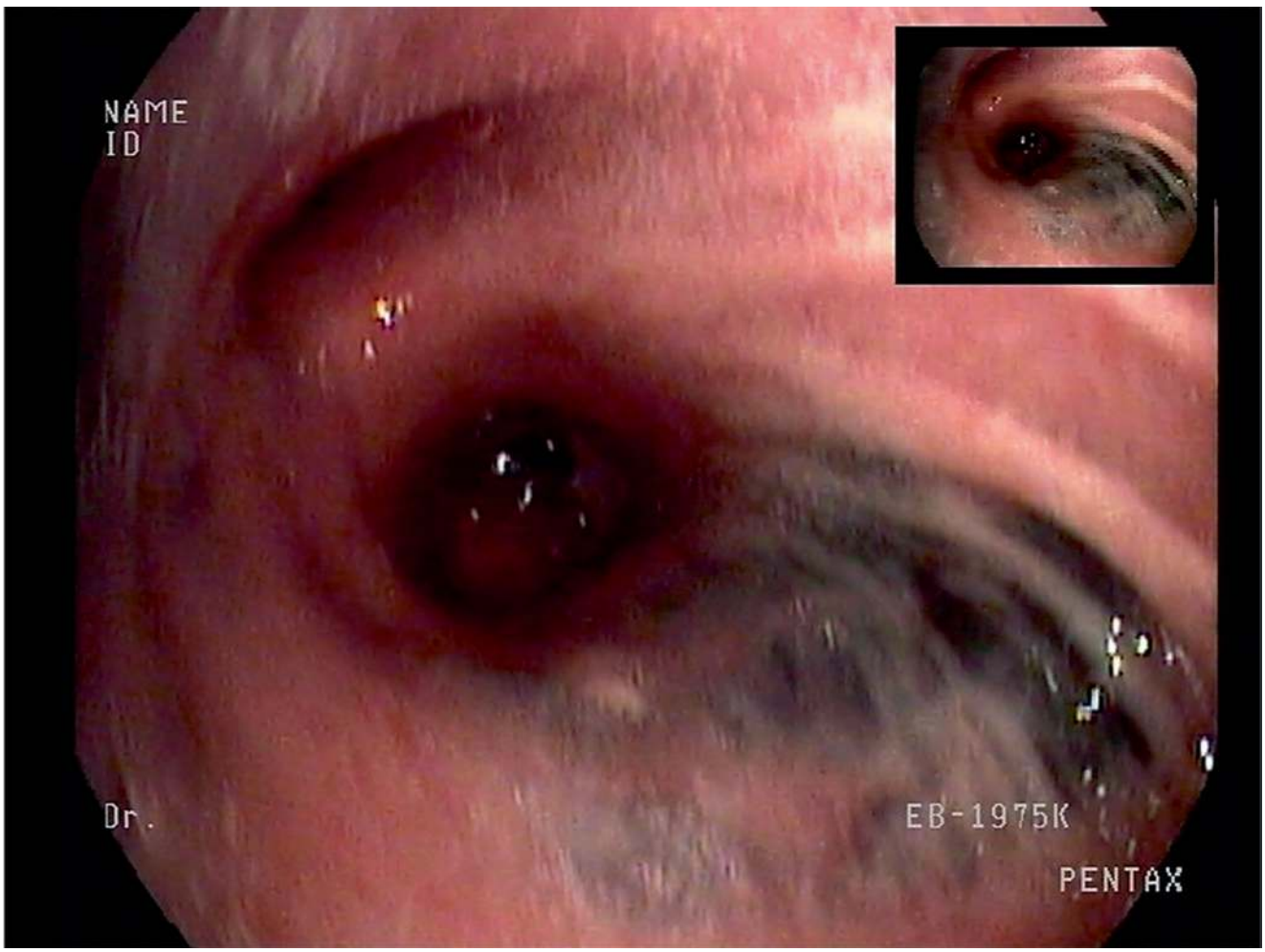

Fig. 37.10 Mucosal anthracosis

There is no therapeutic option for established CMDLD, so miners have to be identified earlier in the disease process. Therefore, recurring medical monitoring, including spirometry and chest radiography, is of highest importance to identify workers developing complications of CMDLD [293]. Prevention and termination of ongoing exposure is recommended. Bronchodilator therapy, oxygen supplementation, and early diagnosis and therapy of complications like tuberculosis or malignant disease are warranted.

Conclusion

With the enforcement of higher occupational safety standards in industrialized nations the incidence and prevalence of classical occupational interstitial lung diseases like siderofibrosis is going down but new entities emerge such as flock worker's disease or indium–tin oxide interstitial lung diseases, that both have been recognized only within the last decades. Awareness to potential occupational triggers needs to be high in the diagnostic workup of interstitial lung diseases, since hazards previously thought to affect just the directly exposed worker may be of relevance for bystanders and worker's family. Such bystander and paraoccupational diseases are frequently caused by the transport of hazardous material in the clothes of workers to other places and home. Outbreaks of paraoccupational diseases caused by beryllium and other compounds have been traced to contamination by industrial dust [25]. The most common hazardous scenario is the cleaning of contaminated work clothing at home. Consequently, the case record of patients undergoing clinical investigations to diagnose interstitial lung diseases need to be extended to occupational details of family members and possible bystander exposure by the dissemination of hazardous materials outside the workplace to recognize paraoccupational diseases. This can only be achieved by a high vigilance of medical professionals.

Diagnostic Box

General clinical and radiological features

- Respiratory symptoms e.g., shortness of breath, cough, dyspnea on exertion.
- Lung function impairment, especially restrictive ventilator defect.
- Radiological alterations in HRCT like reticulation, ground glass opacities and noduli.
- Detailed anamnesis of occupational environment for exposure to dust from different origins.

Disease-related diagnostic clues:

	Typical occupation	Typical radiology	Typical histology/BAL	Others
Chronic Beryllium Disease	– Electronic industries – Ceramic industries – Armaments industries – Atomic industries	– Lymphadenopathy – Perilymphatic noduli – Ground glass opacities	– Non-caseating granulomata	– Beryllium lymphocyte proliferation test (BeLPT)
Indium Tin Oxid Lung Disease	– Production of LCD displays or solar techniques	– Subpleural reticulation and honeycombing – Emphysema	– Giant cells – Foamy macrophages – Cholesterol clefts	– Manifestation as alveolar proteinosis
Hard Metal Lung-	– Tool maker – Diamond polisher – Steel industry	– NSIP pattern – Ground glass opacities – Reticulations	– Multinucleated cells in BAL – Giant cell pneumonitis	– Cobalt in urine or blood may help to prove exposure
Flock Worker's Disease	– Flocking industry – Textile industry	– Reticulation – Consolidation – Ground glass opacities	– Lymphocytes in BAL – Follicular bronchiolitis	
Asbestosis	– Building construction/ deconstruction – Shipbuilding – Textile industry	– Diffuse bilateral fibrosis with reticulation and honeycombing	– Peribronchiolar fibrosis – Asbestosis bodies	– Pleura plaques – Pleura thickening
Nano-particle induced ILD	– Different industries including paint spray industry, fuel industry	– Fibrosis – Pleural effusion	– Granulomata – Detection of nanoparticles in histological specimens	
Sidero-fibrosis	– Welding fumes, e.g. by thermal cutting and brazing	– Bronchiolitis – Desquamative interstitial pneumonia – Combined pulmonary fibrosis and emphysema	– Macrophages with siderophilic particles – Mixed dust deposits with fibrosis and pseudogranulomata	

	Typical occupation	Typical radiology	Typical histology/BAL	Others
Flavoring-induced lung disease	– Food industry especially in processes related to flavouring, e.g., coffee roasting	– Bronchiolitis – Mosaic attenuation – Centrilobular nodules	– Fibrotic obstructive bronchiolitis	
Coal mine dus lung disease	– Coal workers – Miners	– Small nodular opacities – Irregular opacities – Reticular fibrosis – Honeycombing	– Coal dust accumulation especially in the terminal bronchiole – Macrophage-rich nodules with dense fibrosis	
Chronic silicosis (simple or complicated)	– Miners – Quarry workers – Tunnel workers	– Round/irregular nodules with upperlobe predominance – Calcifications (i.e. of lymphonodes) – Conglomerate masses and fibrosis in complicated silicosis	– Fibrotic leasons with dust-loaded macrophages – Histiocytes and granuloma – Concentric fibrosis in later stages	– May be complicated by tuberculosis
Acute and accelerated silicosis	– Stonemasons – Artificial stone workers – Sandblasters – Stone crushers – Polishers	– Consolidations (i.e., perihilar) – Centrilobular nodules – Crazy paving	– Bronchoalveolar lavage with high protein concentrations (milky, PAS-positive) – Dust-loaded macrophages – Silicotic nodules with patchy fibrosis	– Often short exposure to high concentrations of silica

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Unclassifiable Interstitial Lung Disease

38

Sabina A. Guler and Christopher J. Ryerson

Clinical Vignette

A previously healthy 68-year-old man presented with a 1-year history of gradually worsening dyspnoea and fatigue. A chest X-ray had demonstrated bilateral basilar abnormalities, and he was treated with moxifloxacin by his family physician with no improvement. The patient had a history of gastroesophageal reflux for which he was on a proton pump inhibitor. He was on no other medication. He had quit smoking ten years earlier after a 30-pack-year smoking history. He reported no symptoms suggestive of connective tissue disease (CTD), no environmental or occupational exposures, and no remarkable family history.

His oxygen saturation was 93% while breathing room air, and decreased to 89% during a 6-min walk test. Physical examination revealed bilateral basal coarse crackles, no digital clubbing, and no signs of connective tissue disease or heart failure. Lung function tests included a forced vital capacity of 81%-predicted and diffusion capacity of the lung for carbon monoxide of 64%-predicted. Blood tests revealed a borderline increased creatinine kinase and C-reactive peptide. Autoimmune serologies included a mildly abnormal anti-cyclic citrullinated peptide and SSA antibody. Serum precipitins were negative. Chest CT demonstrated lower-lung predominant reticulation, traction bronchiectasis, and some superimposed ground glass with a pattern most suggestive of nonspecific interstitial pneumonia (Fig. 38.1. A surgical lung biopsy showed features of usual interstitial pneumonia, but with increased numbers of interstitial lymphocytes and both interstitial and airspace giant cells, beyond what would be expected in idiopathic pulmonary fibrosis.

A comprehensive assessment by a rheumatologist concluded there was no evidence of a connective tissue disease. Multidisciplinary discussion concluded an unclear aetiology of the ILD, with a differential diagnosis that included hypersensitivity pneumonitis, connective tissue disease-associated interstitial lung disease, and less likely idiopathic pulmonary fibrosis. The patient was treated with immunosuppressive medications based on the more likely differential diagnoses of hypersensitivity pneumonitis and connective tissue disease-associated interstitial lung disease. He had initial stabilization in his symptoms and lung function, but eventually had progression of his disease and passed away 6 years after initial presentation.

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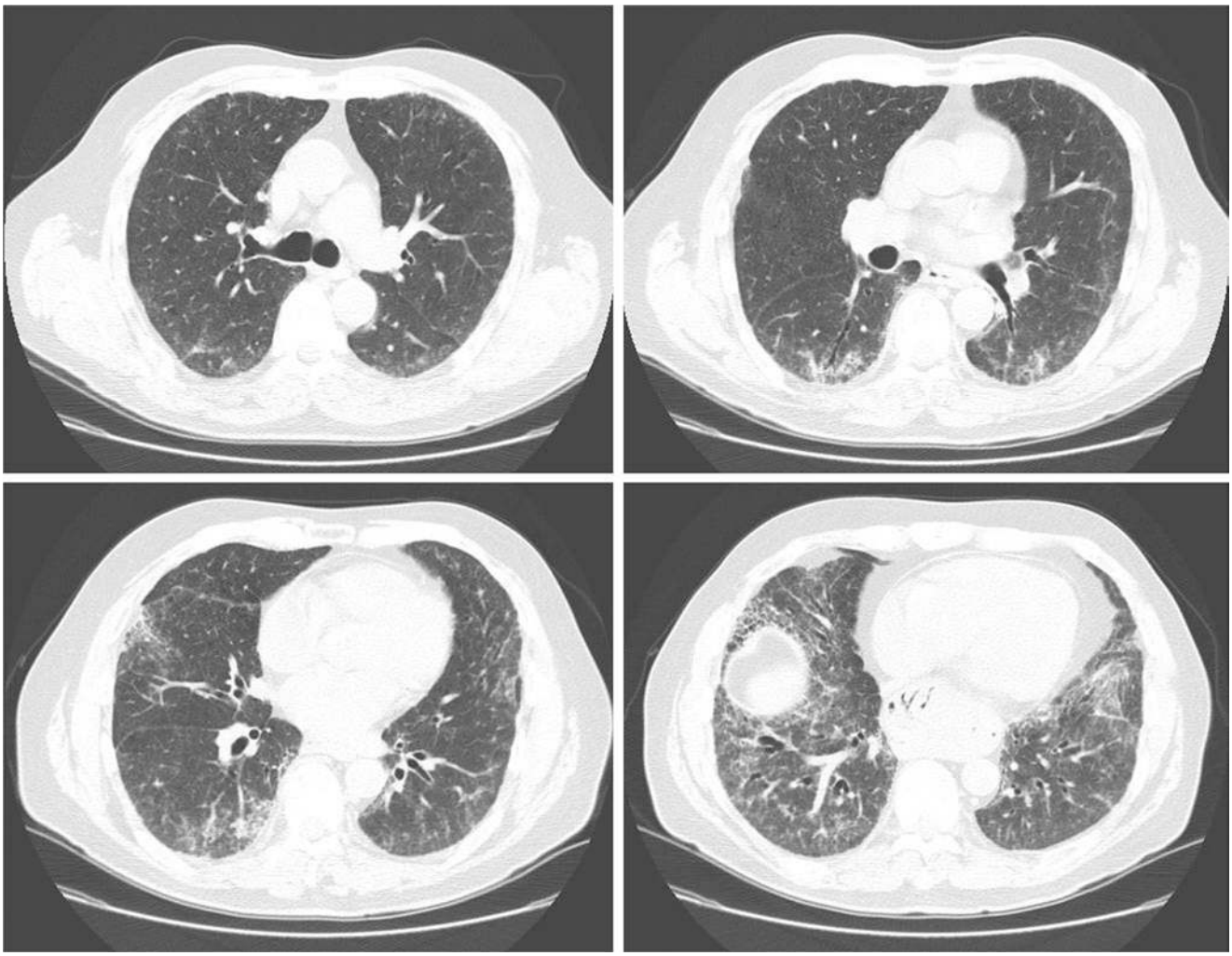

Fig. 38.1 Clinical vignette. Selected axial images from a high-resolution CT showing lower-lung predominant reticulation, traction bronchiectasis, and superimposed ground glass

Introduction

Interstitial lung disease (ILD) is a group of typically rare disorders that are distinct enough to be regarded as separate disease entities. ILDs damage the lung parenchyma in varying degrees of inflammation and fibrosis, with some having a known underlying cause and others where no cause can be identified [1]. The most common of the idiopathic interstitial pneumonias (IIP) is idiopathic pulmonary fibrosis (IPF). Other common ILDs include fibrotic hypersensitivity pneumonitis (HP), and connective tissue disease-associated ILD (CTD-ILD). Patients with ILD usually present with nonspecific respiratory symptoms such as progressive dyspnoea and cough. The classification into a specific ILD subtype can be challenging because the clinical, radiological, and pathological findings frequently overlap. Accurate ILD classification informs prevention, management, and prognosis: Associated exposures need to be eliminated, the indicated pharmacotherapy differs between ILD subtypes, and prognosis varies vastly. Most importantly, immunosuppressive therapy is frequently recommended for patients with CTD-ILD, [2, 3] whereas patients with IPF are potentially harmed by immunosuppression and are instead treated with antifibrotic medications [4–6]. Despite its importance, the classification of an ILD cannot always be achieved. Even with a thorough investigation for potential aetiologies or features that allow the categorization of the ILD, a subset of ILD patients cannot be provided with a specific ILD diagnosis and remain unclassifiable [7].

The classification of the IIPs has evolved substantially since the first classification by the pathologist Averill Abraham Liebow in 1968 [8]. In 2002, the American Thoracic Society (ATS) and the European Respiratory Society (ERS) provided the first standardized nomenclature and set of diagnostic criteria for the major IIPs [9]. The

authors of this consensus paper acknowledged the diagnostic dilemma of unclassifiable ILD with a subset of IIP patients that are not classifiable even after a thorough clinical, radiological, and pathological investigations. Mainly based on lack of clinical utility, it was decided against creating an unclassifiable ILD category at that time. The updated IIP classification consensus statement in 2013 introduced the category of unclassifiable ILD, with the caution that the use of the label unclassifiable ILD should not be used to justify avoidance of a thorough diagnostic process [1]. Over the last few years multiple cohort studies have described this heterogeneous population, tools to phenotype patients with unclassifiable ILD are emerging, and clinical trials investigating pharmacotherapies are ongoing.

In this chapter we address the clinical picture of unclassifiable ILD and discuss challenges and potential solutions for the management of these patients.

Definition

Unclassifiable, unclassified, undefined, and undetermined ILD are terms that have been used to label the group of ILD patients that cannot be provided with a specific, defined ILD [7]. There are no diagnostic criteria for unclassifiable ILD, and there is no universally accepted definition of the term. The most consistently used definition is the absence of a clear diagnosis following a multidisciplinary discussion that includes review of all available clinical, radiological, and pathological information [7, 10, 11]. Some clinicians and researchers have advocated to reserve the term *unclassifiable* ILD to patients where a multidisciplinary team has reviewed results from a complete diagnostic workup including SLB, before calling a case unclassifiable. In contrast, cases without a complete evaluation would be called *unclassified* ILD. *Unclassified* then indicates the possibility of classifying the ILD case later when new information becomes available (e.g., when a patient undergoes SLB) [10, 12]. Notably, patients with unclassifiable ILD despite a SLB could similarly still be provided a diagnosis eventually following discovery of new information (e.g., a new diagnosis of rheumatoid arthritis), indicating that the term "unclassifiable" is also a temporary designation in some patients.

A more standardized approach to the definition of unclassifiable ILD was proposed in an ontological framework for fibrotic ILD: A confident diagnosis is defined by having ≥90% diagnostic confidence, a provisional diagnosis by 51–89% confidence, and unclassifiable ILD by the absence of a single diagnosis that is more likely than not (i.e., <51% confidence; Fig. 38.2) [13]. Using this approach, it is also

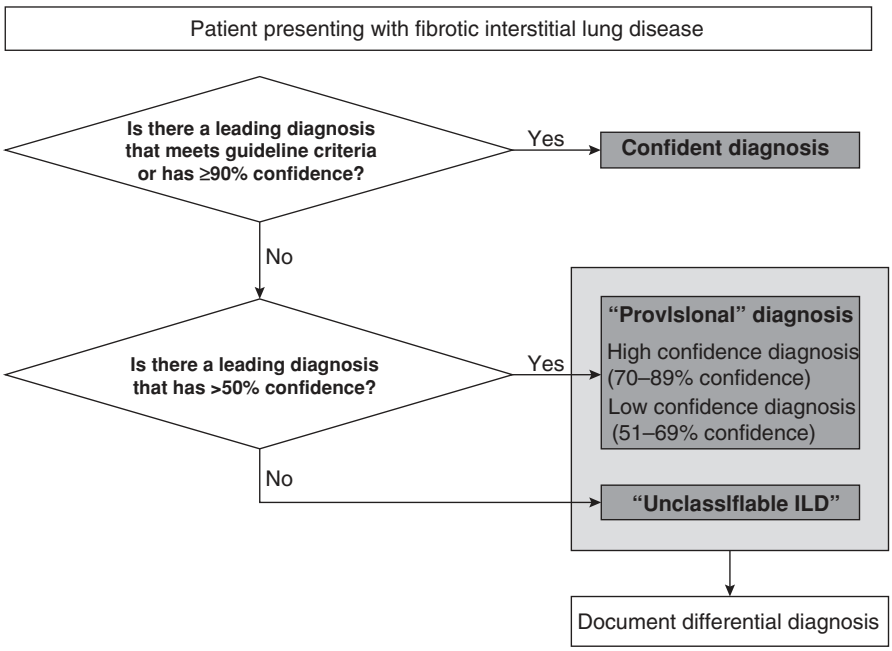

Fig. 38.2 Proposed approach to the classification of fibrotic interstitial lung disease (ILD). (Reprinted with permission of the American Thoracic Society. Copyright © 2019 American Thoracic Society. Ryerson CJ, Corte TJ, Lee JS, Richeldi L, Walsh SLF, Myers JL, Behr J, Cottin V, Danoff SK, Flaherty KR, Lederer DJ, Lynch DA, Martinez FJ, Raghu G, Travis WD, Udwadia Z, Wells AU, Collard HR. /2017/ A Standardized Diagnostic Ontology for Fibrotic Interstitial Lung Disease: An International Working Group Perspective/American journal of respiratory and critical care medicine/196/1249–1254. The *American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society)

recommended to note the availability of a SLB and the most likely differential diagnosis for patients with unclassifiable ILD given the potential investigation and management implications of these features.

Diagnostic Scenarios

There are multiple scenarios that can lead to fibrotic ILD remaining unclassifiable, most commonly including an incomplete evaluation or the presence of nonspecific, overlapping, or seemingly contradictory findings.

Common clinical scenarios leading to ILD remaining unclassifiable include a potential exposure history that is not obviously related to a fibrotic ILD, or the presence of both an exposure history and presence of a CTD with radiological and pathological features that often fail to distinguish between these two possibilities [10, 11]. Similarly, the chest CT scan might show very mild, extensive, or nonspecific abnormalities that fail to distinguish ILD subtypes, sometimes further confounded by heart failure, respiratory infections, or the effects of previous treatments that might alter typical morphology. In some situations, a high-quality HRCT might even not be available [14, 15].

One of the most frequent reasons for ILD remaining unclassifiable is the lack of an adequate SLB, which can occur for several reasons. First, physicians might decide against performing a SLB in patients with increased risk for complications. This is particularly common in elderly or frail patients with significant comorbidities or severely impaired pulmonary function, where the potential risk of SLB should be balanced carefully against the expected benefit resulting from the pathological information. Second, some patients decline to undergo this invasive diagnostic procedure given similar concerns about complications of the procedure. Third, if SLB is performed it might be from a non-diagnostic region of the lung [16]. Finally, even when performed, a SLB can be nonspecific or contradictory to other clinical-radiological data such that the ILD remains unclassifiable.

ILD diagnosis is ideally based on integration of clinical, radiological, and pathological information in the setting of a multidisciplinary discussion with experts from each domain discussing the importance of all relevant data in a face-to-face meeting [17]. Despite this being the ideal approach, multidisciplinary discussion is not available in every centre, and when available there are still situations when members do not agree on a diagnosis because they interpret and weigh findings differently or because the available information is contradictory [10, 11, 18].

Epidemiology

The prevalence and incidence of specific ILDs is challenging to estimate: Epidemiological studies frequently base their analyses on International Classification of Diseases codes instead of current ILD classification [19–21]. Furthermore, most studies originate from ILD referral centres or in-hospital populations, which introduces referral and selection bias with unrepresentative baseline populations. The most rigorous studies of IPF, the most common IIP subtype, suggest an incidence and prevalence of 9–18.7 and 20–41.8 per 100,000, respectively, depending on whether a narrow or broad definition is applied [22]. Based on general ILD cohorts from large referral centres, the incidence and prevalence of unclassifiable ILD is likely similar to or slightly less than that of IPF; [10, 11] however, there is substantial heterogeneity related to both the definition of unclassifiable ILD and other cohort characteristics. For example, some cohorts have almost no unclassifiable cases, [23] while others report a proportion of unclassifiable ILD cases up to 45% in a cohort of elderly patients with ILD [24]. On average, the prevalence of unclassifiable ILD within specialized ILD centres is estimated at 12%, with a systematic review and meta-analysis showing important heterogeneity between included studies, mainly in terms of study designs, definitions, and diagnostic approaches [7]. The conduct of a multidisciplinary discussion is associated with a lower prevalence of unclassifiable ILD within cohorts, [7] suggesting that this is partially effective in reducing the percentage of patients who cannot be provided with a confident ILD diagnosis.

Clinical Presentation

With unclassifiable ILD predominantly representing a mixture of patients with atypical presentations of fibrotic ILDs such as IPF, CTD-ILD, and fibrotic HP, it is unsurprising that the clinical manifestations are nonspecific and reflect an average general ILD population [10]. For example, patients with unclassifiable ILD are more frequently female than patients with IPF, and more frequently male compared to patients with CTD-ILD.

Previous cohort studies report a mean age at presentation between 58 and 75 years. Most studies report a balanced sex distribution, with 25% to 71% of patients being current or former smokers [7]. Patients with unclassifiable ILD frequently present with dyspnoea, first on exertion only and potentially at rest later in the course of disease. Dry or pro-

ductive cough, chest discomfort, reduced exercise capacity, and fatigue are other common symptoms.

Physical examination can reveal crackles on lung auscultation, occasionally digital clubbing, or features of CTD or other multisystem processes [11]. Pulmonary function tests at diagnosis typically show a mild reduction in forced vital capacity (FVC) with an average mean across cohort studies of 72% predicted. Diffusion capacity of the lung for carbon monoxide (DLCO) is moderately reduced with an estimated mean of 47% predicted at the time of diagnosis from a recent meta-analysis [7].

Diagnosis

Clinical Features

A thorough questioning of patients with a suspected ILD is critical, and a comprehensive assessment of symptoms, family history, and exposures becomes even more essential when confronted with an ILD that has been considered unclassifiable. The history should include screening for symptoms of CTD, including joint pain, swelling, and stiffness, particularly that lasts at least 1 h. Skin rashes, nodules or thickening, dryness of the eyes or mouth, muscle weakness or muscle pain, difficulties swallowing, and gastroesophageal reflux should similarly be assessed.

A multitude of inhaled antigens or environmental exposures can cause smoking-related ILDs, HP, or occupational ILD (i.e., pneumoconiosis). Patients should be questioned for the presence of these exposures with the establishment of an accurate timeline in order to estimate the likelihood of a causal relationship between the exposure and development of ILD. Recurring symptoms with re-exposure can provide particularly useful information; however, this is likely most informative in patients with more acute non-fibrotic forms of HP. [25] Some exposures such as asbestos can lead to ILD development only decades after the contact, which makes the establishment of a causal relationship very challenging, particularly given the coexistence of risk factors for other ILDs (e.g., an older age, male sex, and smoking history that also increase the likelihood of IPF). A detailed history of previous treatments associated with ILD development should include previous radiotherapy, oncologic medications (e.g., bleomycin, immune-checkpoint inhibitors), cardiovascular medications (e.g., amiodarone), and immunosuppressive medications (e.g., methotrexate).

There is a genetic background to several subtypes of ILD, and relatives of patients with ILD are at increased risk of developing ILD [26]. Familial forms of IPF are usually diagnosed at a younger age and often progress faster than sporadic forms of IPF [27]. Information on familial forms of other ILD subtypes or familial unclassifiable ILD is very limited.

Physical examination should similarly focus on identification of features suggesting CTD, sarcoidosis or some other systemic process. This should include assessment for joint inflammation, proximal muscle weakness, Raynaud's phenomenon, fingertip ulceration, digital fissuring, rash, and skin thickening [28].

Radiology

Conventional chest radiography may show signs of lung fibrosis but is not helpful in differentiating ILD subtypes.

For ILD classification, high-resolution contiguous HRCT imaging is needed. Some centres include both inspiratory and expiratory images, which can reveal air trapping that suggests concurrent small airways disease as can be seen in HP. Performing CT in the prone position can be useful to differentiate mild fibrosis and interstitial lung abnormalities from gravity-induced dependent atelectasis [15]. Recent guidelines on the diagnosis of IPF suggest classifying CT patterns for patients with possible IPF as usual interstitial pneumonia (UIP), probable UIP, indeterminate for UIP, and most consistent with a non-IPF diagnosis, [15, 29] while previous guidelines used the categories definite UIP, possible UIP, and inconsistent with UIP [30].

All of these patterns are observed in patients with unclassifiable ILD. Using the previous classification approach, two studies reported a definite UIP pattern in 6–17% of patients with unclassifiable ILD, and a possible UIP pattern in 26–50% of patients [10, 31]. Radiological patterns of nonspecific interstitial pneumonia (NSIP), desquamative interstitial pneumonia, and features typical of fibrotic HP have also been reported in unclassifiable ILD patients [11]. CT findings that are difficult to allocate to a specific pattern are common reasons for a case of ILD to remain unclassifiable. In these patients, there might be a coexistence of several patterns, or acute changes that obscure the underlying pattern [15].

Laboratory Investigations

With CTD-ILD almost always being a differential diagnosis of unclassifiable ILD, serological screening for CTD is recommended [28, 29]. Most experts suggest performing C-reactive protein, erythrocyte sedimentation rate, antinu-

clear antibodies, rheumatoid factor, anti-cyclic citrullinated peptide, and a myositis panel in all ILD patients as a baseline evaluation. Further serological tests are performed based on the clinical presentation [29].

Some experts advocate measurement of serum precipitins, performance of lymphocyte proliferation tests, and specific inhalation challenge testing for the diagnosis of HP. These tests may be helpful in the context of a subtle exposure of uncertain significance; however, the sensitivity and specificity of these tests is limited and they are otherwise of uncertain clinical utility [25].

Bronchoscopy with bronchoalveolar lavage is rarely diagnostic in the workup of a patient with ILD. However, in some cases bronchoalveolar lavage can identify underlying infection or malignancy. Cellular analysis might be helpful to phenotype patients with unclassifiable ILD, for example, with bronchoalveolar lavage lymphocytosis signifying features of autoimmunity, or prompting a more thorough search for an unidentified antigen causing HP. Overall, bronchoalveolar lavage is a low risk procedure that can be performed in some patients that would not qualify for SLB [32].

Pathology

Conventional transbronchial biopsy produces small biopsies of the lung parenchyma with the potential to diagnose sarcoidosis or organizing pneumonia, but rarely other lung parenchymal disorders. Transbronchial lung cryobiopsies (TBLC) provide larger tissue samples resulting in a higher diagnostic yield compared to conventional transbronchial biopsies [33]. The diagnostic utility of TBLC versus SLB has not been established yet: A recent study showed poor concordance between samples from TBLC and SLB in the same patient (kappa value 0.22) [34]. Nevertheless, TBLC might provide a possibility to get histopathological insight into the phenotype of unclassifiable ILD patients with an unfavourable risk-benefit ratio for SLB. Overall TBLC seems to be reasonably safe if performed by experts in well-selected patients [33]. Safety information on TBLC in patients not qualifying for SLB is still limited; however, there is evidence that the procedural risk of both transbronchial cryobiopsy and SLB is higher in patients with advanced ILD and for non-elective procedures [35–37].

Histopathological results from SLB integrated with clinical and radiological information on multidisciplinary discussion is the current reference standard for ILD diagnosis; [1] however, up to 10% of biopsied patients still remain unclassifiable [38, 39]. This most frequently happens in the context of overlapping histological patterns, and less frequently in biopsies that show only early and mild nonspecific fibrotic changes or end-stage "burnt-out" fibrosis [16]. Approximately one quarter of patients in previous cohorts of unclassifiable ILD had a SLB available for diagnosis, [10, 11, 31] indicating that physicians frequently considered the diagnostic benefit from SLB too low to justify the risk of the procedure. Although SLB is a relatively safe procedure with many studies reporting no deaths after SLB, [40] two large administrative database studies estimated the in-hospital mortality risk of elective SLB in patients with ILD at 1.7% [35, 36]. Remarkably, patients undergoing SLB during a non-elective admission had a mortality risk of 16%. These studies emphasize that patients should be carefully selected for SLB, which should be carefully planned and not performed in the context of acute exacerbation. Specifically, in elderly patients with significant comorbidities and severely impaired lung function the potential risk of SLB should be weighed carefully against its potential impact on management and prognosis. Patient preference and overall therapeutic goals usually play an additional important role in this decision.

Progression and Prognosis

Considering the heterogeneous mixture of unclassifiable ILD including patients with early/mild and advanced/severe ILD at time of diagnosis, it is unsurprising that outcomes are highly variable among patients and across ILD centres, with overall prognosis intermediate between IPF and non-IPF ILDs. One Danish cohort reported that 13% of patients with unclassifiable ILD had reversible disease, 34% had stable but residual disease, and the remainder had progressive lung functional decline. Hyldgaard et al. [11] reported risk factors for mortality include older age, crackles on lung auscultation, lower FVC, and lower DLCO. On CT a higher fibrosis scores, more severe traction bronchiectasis, and larger pulmonary artery diameter are also independent predictors of worse outcomes [10, 11, 31].

In the four cohort studies with available survival information for unclassifiable ILD, the estimated 1-year, 2-year, and 5-year survival rates are 84–89%, 70–76%, and 46–70%, respectively (Fig. 38.3) [10, 11, 31, 41].

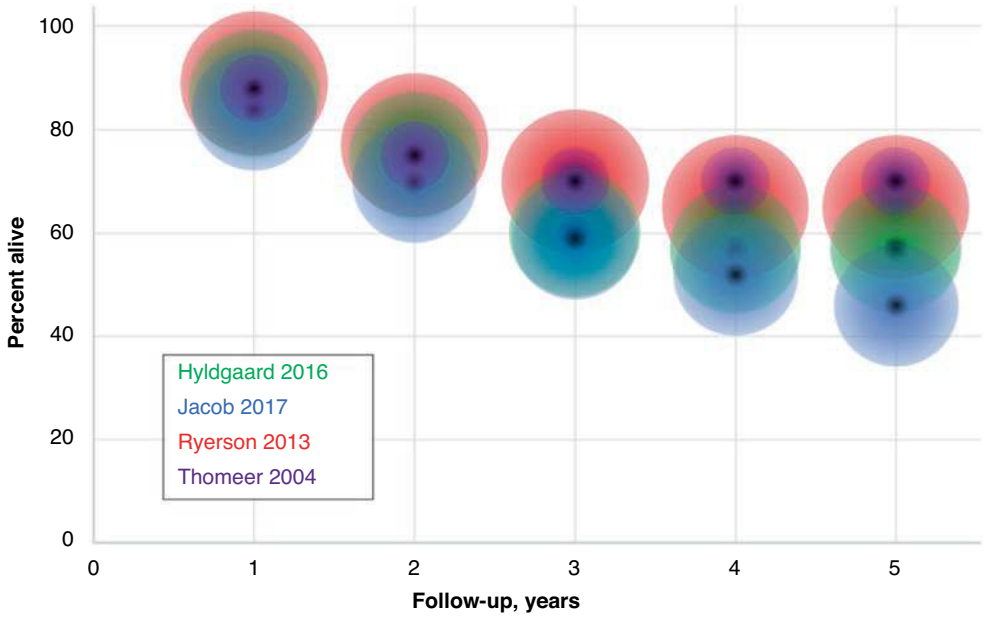

Fig. 38.3 Survival of patients with unclassifiable interstitial lung disease. The area of the circle is directly proportional to the baseline sample size for each study. The point estimate corresponds to the centre of the circle. (Reprinted with permission of the American Thoracic Society. Copyright © 2019 American Thoracic Society. Guler SA, Ellison K, Algamdi M, Collard HR, Ryerson CJ/2018/Heterogeneity in Unclassifiable Interstitial Lung Disease. A Systematic Review and Meta-Analysis./ Annals of the American Thoracic Society/15/854–63. Annals of the American Thoracic Society is an official journal of the American Thoracic Society)

Phenotyping Unclassifiable ILD

Patients with unclassifiable ILD have substantial heterogeneity in their clinical presentation, radiological findings, and pathological features at time of diagnosis [7]. The variable disease severity at diagnosis, and the heterogeneous underlying biology of patients with ILD are likely reasons for the variable disease progression and behaviour of patients with unclassifiable ILD [11]. This heterogeneity causes several issues for clinicians and researchers. For example, it is challenging to demonstrate efficacy of an intervention in clinical studies in this population because even if interventions are successful in some unclassifiable ILD patients, the "noise" arising from a heterogeneous response to therapy might prohibit detection of a meaningful benefit. In addition, estimating a patient's prognosis and response to treatment is difficult as the heterogeneity of the unclassifiable ILD population as a whole makes it challenging to extrapolate previous studies to any individual patient.

Phenotyping unclassifiable ILD patients for research and clinical practice by grouping patients with similar features reduces heterogeneity and might help to improve understanding of the underlying disease mechanisms, disease progression, and response to therapy. For unclassifiable ILD the traditional aetiology-based classification does not hold because per definition, the underlying ILD aetiology is unknown; further the identification of the aetiology might not be priority, once a thorough diagnostic workup has been performed. Previous guidelines suggested classifying patients with ILD according to their observed or expected disease behaviour, with this particularly applying to the heterogeneous population of patients with unclassifiable ILD [1, 11]. Multiple studies have shown that older age, male sex, lower FVC, and lower DLCO are associated with disease progression [10, 11, 42]., regardless of the etiological classification; however, it can be challenging to predict future disease progression from patients' baseline features or from past episodes of worsening. For example, in patients with systemic sclerosis associated ILD (SSc-ILD), future lung functional decline is difficult to predict from previous changes in lung function [43]. Honeycombing, traction bronchiectasis, and a radiological UIP pattern also predict a more progressive disease behaviour and unfavourable outcome [31, 44].

A *progressive fibrosing ILD* phenotype has been suggested as a potentially useful subgroup, including patients with a variety of diagnoses and certain high-risk features that culminate in a similar disease behaviour to IPF. This approach has already been validated in randomized controlled trials including patients with fibrotic ILDs other than IPF and previous progression, defined by a combination of decline in FVC, worsening of radiological changes, and increase in symptoms [45, 46]. The concept of *progressive fibrosing ILD* is also potentially useful for very rare ILD subtypes that have overlapping clinical and morphological features, and also applies to nonspecific strategies that likely apply to a wide range of ILD patients (e.g., oxygen, pulmonary rehabilitation). The potential downside of this "lumping" approach is the likely increase in heterogeneity of cohorts, which can be a concern for understanding specific biological mechanisms and study of new targeted therapies.

Table 38.1 Proposed features of interstitial pneumonias with autoimmune features

Domains	Features
Clinical domain	Distal digital tip ulcerations
	Mechanic hands (distal digital fissuring)
	Inflammatory arthritis or morning stiffness ≥60 min
	Palmar telangiectasia
	Raynaud phenomenon
	Digital oedema (*puffy fingers*)
	Gottron's sign (papules on digital extensor surfaces)
Serologic domain	ANA ≥1:320 or ANA nucleolar/centromere pattern any titre
	Rheumatoid factor ≥ 2× upper limit of normal
	Positive anti-CCP, -dsDNA, -SSA, -SSB, -RNP, -Sm, -Scl-70, -tRNA synthetase, -PM-Scl, -MDA-5
Morphologic domain	
Radiological patterns	Nonspecific interstitial pneumonia (NSIP)
	Organizing pneumonia (OP)
	Lymphoid Interstitial Pneumonia (LIP)
Pathological patterns	NSIP, OP, LIP
	Interstitial Lymphoid aggregates with germinal centres
	Diffuse lymphoplasmacytic infiltration
	Multicompartment involvement
	Pleural or pericardial effusion/ thickening
	Airway disease
	Pulmonary vasculopathy

Adapted from: *An official European Respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features* [47]

One way to phenotype patients with unclassifiable ILD is to identify patients with features of autoimmunity. A previous research statement from the ATS and ERS proposed the label of *interstitial pneumonia with autoimmune features (IPAF)* could be used to indicate patients with ILD who have relatively specific features of a CTD, but without meeting specific criteria for a defined CTD [47]. Suggested criteria for IPAF include at least one feature from at least two out of the three clinical, serologic, and morphologic domains (Table 38.1, Fig. 38.4) [47]. Some cohort studies report that approximately 20% of their unclassifiable ILD patients fall in the IPAF category [48, 49].

The diagnostic dichotomy with the most significant management implication is differentiation between IPF and non-IPF ILD given the different prognosis and pharmacotherapy used in these two populations. It is therefore frequently clinically helpful to integrate the available demographic, serological, radiological, and histopathological features to suggest whether the overall presentation is more consistent with an IPF-like biology or if a non-IPF ILD is more likely. Several individual factors have been associated with an IPF diagnosis (e.g., older age, male sex, a history of smoking cigarettes; Fig. 38.5) [50–54]. Although there is no standardized way to integrate these features in a diagnostic model, experienced clinicians are able to incorporate these into an overall gestalt

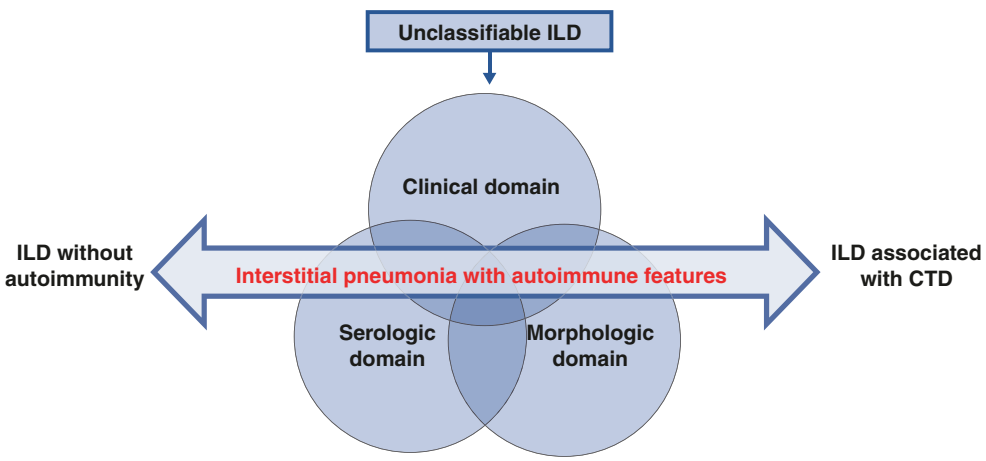

Fig. 38.4 Proposed concept for determining the likelihood of autoimmunity in patients with unclassifiable interstitial lung disease (ILD). *Interstitial pneumonias with autoimmune features* requires at least one feature from at least two domains (Table 38.1)

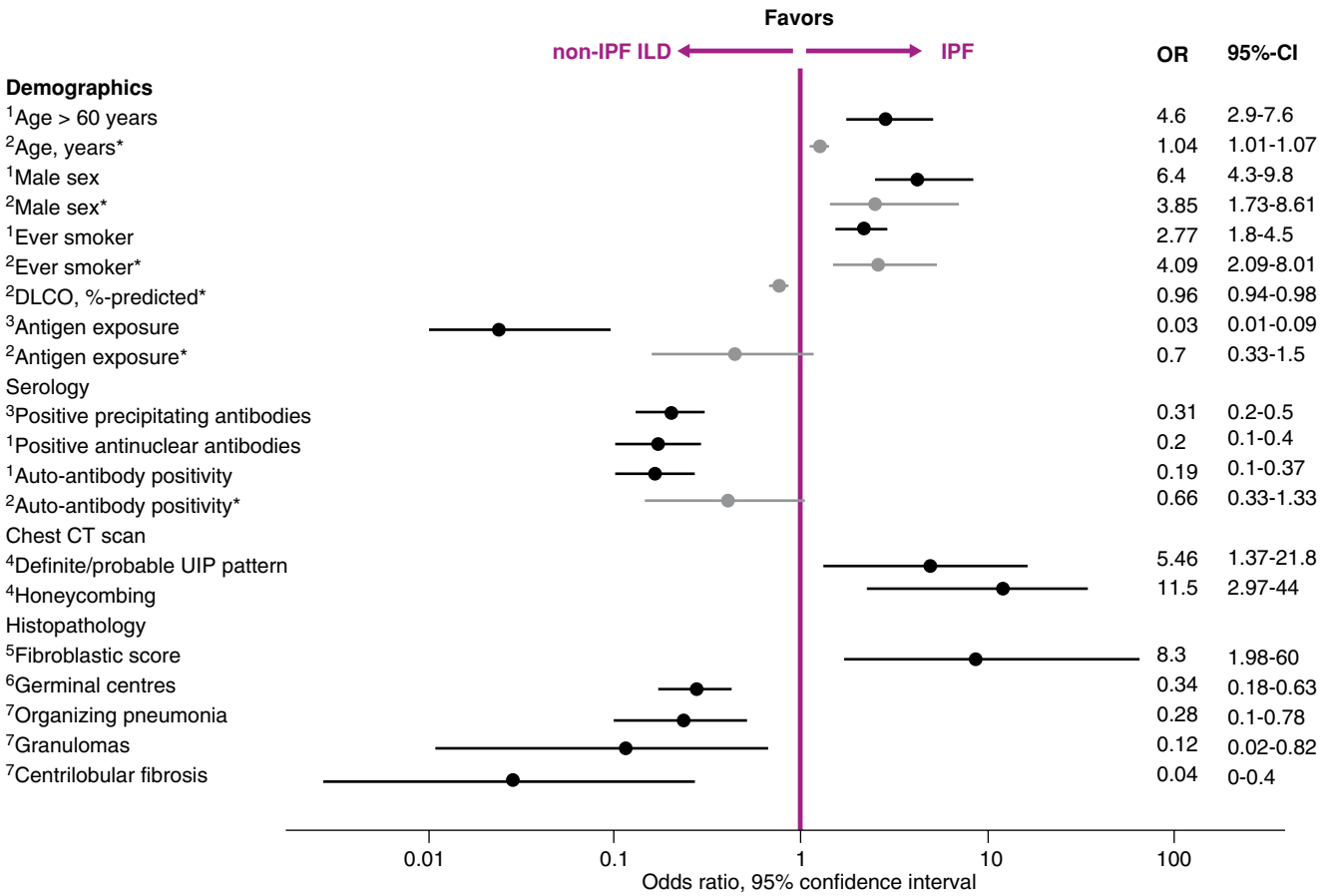

Fig. 38.5 Selected diagnostic characteristics favouring IPF and non-IPF ILDs. (1) Guler et al. 2018 [66]; (2) Walsh et al. 2019 [55]; (3) Lacasse et al. 2003 [50]; (4) Hunninghake et al. 2003 [51]; (5) Flaherty et al. 2003 [52]; (6) Song et al. 2009 [53]; (7) Takemura et al. 2012 (chronic HP versus IPF) [54] *Physician rated likelihood of IPF [55]. *95% CI* 95% confidence interval, *ANA* antinuclear antibody, *CTD* connective tissue disease, *ILD* interstitial lung disease, *IPF* idiopathic pulmonary fibrosis, *OR* odds ratio, *UIP* usual interstitial pneumonia

likelihood of IPF. Typically, respiratory physicians consider an IPF working diagnosis if the diagnostic confidence for IPF is 70–89%. Patients with a working diagnosis of IPF and a definite IPF diagnosis (≥90% diagnostic confidence) have a similar prognosis, and the approach of a working diagnosis can facilitate management decisions [13, 55].

Management and Treatment

Non-pharmacological management strategies typically apply to all ILD subtypes and should be similarly offered to patients with unclassifiable ILD. Smoking cessation and avoidance of potentially causative agents are crucial. Patients should be instructed to avoid potential exposures if HP cannot be confidently excluded. Work-place safety with protection from occupational exposures is also important. Medications that might cause ILD should be exchanged for alternatives wherever possible, although continuation of such medications that clearly lack a relationship with ILD onset or worsening may be appropriate. Annual influenza vaccinations and pneumococcal vaccination every 5 years are generally recommended, as well as management of comorbidities and symptom management strategies.

Oxygen supplementation and pulmonary rehabilitation can relieve symptoms and improve exercise capacity, among other benefits [56, 57]. Lung transplantation is an option for some patients, but is contraindicated in many patients with fibrotic ILD. Frail patients with advanced impairment might benefit from prioritizing symptom management over ILD-specific pharmacotherapy, and palliative care might offer great support for patients and caregivers [58].

Pharmacotherapy choices in fibrotic ILD are challenging, with an absence of direct data to support any specific approach. All recommendations for ILD-targeted medications are therefore off-label and should be considered on a case-by-case basis ideally after careful review by an experienced multidisciplinary team. When it is considered appropriate, pharmacotherapy in unclassifiable ILD generally consists of either antifibrotic and/or immunosuppressive therapy.

The antifibrotic medications pirfenidone and nintedanib are recommended in clinical practice guidelines for the treatment of IPF [59]. Both medications reduce the rate of FVC decline by approximately half and might reduce the risk for exacerbation and improve survival [5, 6]. Evidence is emerging that antifibrotic medications can be similarly effective in patients with non-IPF ILDs. Nintedanib slows progression of FVC decline in SSc-ILD, and the drug is now approved for this indication [60]. Recently a randomized controlled study demonstrated that nintedanib slows the rate of FVC decline by approximately half in patients with progressive non-IPF ILDs, similar to what was observed in the previous antifibrotic trials for IPF [46]. This effect was consistent in several subgroups including the 17% of patients with unclassifiable ILD [61]. Pirfenidone seems to similarly reduce the loss in pulmonary function in patients with unclassifiable ILD, as demonstrated in a phase 2 clinical trial [45].

Clinicians have been very cautious in prescribing immunosuppressive therapies to patients with an IPF-like phenotype following publication of the PANTHER trial that demonstrated increased risk of death and hospitalizations in IPF patients with the combination of prednisone, azathioprine and acetylcysteine [4]. In contrast, other fibrotic ILD subtypes benefit from immunosuppression. For example, large studies including patients with SSc-ILD have demonstrated a favourable response to cyclophosphamide and mycophenolate mofetil [2, 3], and weaker evidence of a beneficial effect of tocilizumab and rituximab [62, 63]. Patients with chronic hypersensitivity pneumonitis might benefit from treatment with mycophenolate mofetil or azathioprine with a retrospective study demonstrating an improvement of DLCO following initiation of therapy [64]. Another recent retrospective study of patients with unclassifiable ILD reported a favourable treatment response to cyclophosphamide, especially when patients lacked features more consistent with an IPF diagnosis [65]. Given that undiagnosed fibrotic HP and CTD-ILD likely represent a substantial percentage of unclassifiable ILD, immunosuppression is likely a valid treatment option for some of these patients, particularly when IPF has been confidently excluded.

Regardless of the specific medication being considered, the anticipated disease behaviour can aid in management decisions. Most often, this includes prioritization of more aggressive treatment approaches in patients who are suspected to have rapidly progressive fibrosis. Conversely, active pharmacotherapy is typically avoided in patients with mild and likely non-progressive disease.

Regardless of the underlying phenotype, patient preference and the patient's attitude towards diagnostic and therapeutic uncertainty should always be considered in the decision-making process.

Conclusion

Unclassifiable ILD represents an important and challenging subgroup of patients. A meticulous ILD workup is essential to minimize the proportion of patients who cannot be provided with a confident, specific ILD diagnosis. A multidisciplinary discussion including clinicians, radiologists, and pathologists is frequently valuable and might reduce the proportion of patients which remains unclassifiable. The term unclassifiable ILD is poorly defined, resulting in a heterogeneous population with clinical features intermediate between that of IPF and other ILD subtypes.

Attempting to understand the underlying biology of individual patients can potentially help in management decisions and prognostication; however, there is no validated approach to this determination. There is a clear need for new non-invasive diagnostic tools, particularly since the risk–benefit ratio for SLB disqualifies many ILD patients for this invasive procedure. Molecular and genetic phenotyping by various methods of transcriptomics, proteomics, metabolomics, and epigenetics are currently being developed to advance the current approach to ILD classification.

Suggested Definition for Unclassifiable ILD

- Fibrotic interstitial lung disease.
- No single specific ILD diagnosis >50% likely after:
  - Gathering of all available diagnostic information.
    - Clinical information including exposure history.
    - Physical examination and pulmonary function tests.
    - Autoimmune serology.
    - Chest computed tomography.
    - Bronchoalveolar lavage results.
    - Histopathology: Surgical lung biopsy (or lung cryobiopsy).
  - Multidisciplinary team discussion.
- Document availability of SLB for diagnosis and most likely differential diagnosis.
- Re-evaluate when new diagnostic information emerges.

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Part VII

Miscellaneous Orphan Lung Diseases

Lymphoproliferative Lung Disorders

39

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Introduction

In the lung, primary lymphoproliferative disease represents a wide and overlapping spectrum of conditions from reactive polymorphous and polyclonal processes through to various entities of malignant lymphoma (Table 39.1) [1, 2]. The natural history of many of the conditions is variable with further heterogeneity recognized within distinct disease entities. Primary pulmonary lymphoproliferative diseases are rare, whereas secondary pulmonary lymphoma occurs in up to 20.5% of autopsy cases. The lung is a potential organ for tumor deposition in disseminated haematolymphoid disease.

Reactive pulmonary lymphoproliferative diseases encompass a spectrum of inflammatory and reactive lesions that are often difficult to diagnose since they are difficult to differentiate from other reactive and neoplastic entities. They includes different clinicopathological patterns: intrapulmonary lymph nodes, nodular lymphoid hyperplasia, follicular bronchitis/bronchiolitis, lymphocytic interstitial pneumonia (LIP).

Malignant lymphoproliferative diseases are distinguished in *Hodgkin and non-Hodgkin* lymphomas (HL and NHL), affecting B or T/NK cells. Malignant lymphoproliferative disorders may arise either as *primary pulmonary lymphomas* (PPL) within the lung parenchyma (without evidence of extrapulmonary involvement at diagnosis or in the subsequent 3 months) or as *secondary pulmonary lymphomas* spreading from systemic lymph nodes through the circulation and/or from neighboring sites (e.g., from mediastinal lymph nodes or thymus).

Malignant proliferative diseases more frequently occur in immunocompromised hosts, having in *post-transplant* and in *HIV infected patients* slightly different clinical and pathological profiles from patients with autoimmune disorders or immune competent hosts.

Reactive Pulmonary Lymphoproliferative Diseases

Hyperplasia of lymphoid elements, such as intrapulmonary lymph nodes, mucosa-associated lymphoid tissue (MALT) and lymphoreticular aggregates in the terminal bronchioles, may be seen in a variety of lung disease.

Intrapulmonary lymph nodes are distributed at the hilum and occasionally found in the vicinity of the pleura. Hyperplasia of intrapulmonary lymph nodes may be due to a wide spectrum of causes ranging from common hyperplastic and reactive processes to malignant changes. To evaluate the nature of intra-parenchymal lymph nodes, high-resolution computed tomography (HRCT) and positron emission computed tomography (PET-CT) are useful tools, but surgery is necessary to obtain a definitive diagnosis.

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Table 39.1 Main lymphoproliferative lung disorders

Clinical entity	Clinico-pathologic key points	Main CT scan features	Main diagnostic step(s)	Therapeutic options
Follicular bronchitis/ bronchiolitis	Background of autoimmunity (Rheumatoid Arthritis, Sjogren…)	Small nodules (centrilobular/ bronchocentric) bronchial wall thickening	Surgical biopsy (BAL is an ancillary test)	Macrolides
	Immunodeficiency (familial, common variable immunodeficiency, HIV…) Dyspnea on effort, bronchorrhea			Steroids
	Obstructive impairment			
	Lymphoid follicles (B cells) around bronchioles			
LIP	Background of autoimmunity (Sjogren….)	Centrilobular nodules, septal thickening, ground glass attenuation, cysts	Surgical lung biopsy	Steroids, Azathioprine
	Dyspnea on effort, cough restrictive impairment		CryoTBB	Cyclophosphamide
	Diffuse interalveolar infiltration of lymphocytes (CD3 + cells), lymphoid hyperplasia (follicles consisting of B cells around bronchioles) scattered granulomas			
MALT Lymphoma	Mean age 60 years	Rounded or segmental shaped consolidations	Surgical biopsy	Chemotherapy
	Asymptomatic (minority of cases)	Air bronchogram	CT scan guided or TBB biopsy (cryoTBB)	Rituximab
	B symptoms (fever, asthenia,…) in a minority of cases)	Ground glass opacities Hilar/ mediastinal lymphnodes	BAL	
	Respiratory symptoms (cough, dyspnea)	Reticular, perilymphatic opacities		
	Autoimmune background (Sjogren..) as a predisponent condition	Opacities		
	Extrapulmonary involvement In a significant number of cases normal PFTs or restrictive impairment			
	Search for serum monoclonal component			
	Lymphocytes with small to medium-sized irregular nuclei, CD19+, (centrocytic-like or monocytoid appearance); plasmocytic differentiation. Lymphoepithelial lesions. Perilymphatic distribution of the neoplastic infiltrate light chain restriction			
T cell rich B cell	Respiratory symptoms (cough, dyspnea, chest pain, acute respiratory failure)	Multiple nodules	Surgical biopsy, CryoTBB	Chemotherapy
Lymphoma (LYG)		Diffuse reticulonodular infiltrates (rare)		Rituximab
	Systemic manifestations (fever, malaise, weight loss)	Cavitation (10–25%)		
	Extrapulmonary involvement (skin, CNS, kidney…)			
	Leukopenia or lymphopenia (CD4+ lymphopenia) in about 20–30% of cases; serologic evidence of prior EBV infection			
	Perivascular/vascular polymorphous Infiltrate, necrosis of coagulative type Scattered (or sheets of) large B cells expressing markers of EBV infection; cells relative to the reactive lymphocyte (CD3+, mainly) background is used to grade the lesions			
Large B Cell	Most usually affects adults in the sixth and seventh decades	Nodule or large masses	Surgical lung biopsy	Rituximab
Lymphoma	Symptoms include cough, hemoptysis, low grade fever and asthenia		CryoTBB	Chemotherapy
			Transthoracic biopsy	

Table 39.1 (continued)

Clinical entity	Clinico-pathologic key points	Main CT scan features	Main diagnostic step(s)	Therapeutic options
Intravascular B cell lymphoma	Occurs in older patients	Peripheral wedge	Surgical Biopsy	Chemotherapy
	Dyspnea; pulmonary hypertension; clinical onset mimicking pulmonary thromboembolism	Shaped lesions; pleural effusion (bilateral); mosaic oligoemia; normal CT aspects/diffuse pulmonary uptake on FDG-PET	cryoTBB biopsy	Rituximab
	Systemic symptoms (fever…)			
	Symptoms manifesting an extrapulmonary involvement (CNS, skin…). Important reduction of PAO_2 and $PaCO_2$ in spite of normal lung volumes			
	A significant increase of LDH; a variant associated with hemophagocytic syndrome has been reported mostly in Asian populations			
	Intravascular (small vessels, capillaries) neoplastic lymphoid cells (in the majority of cases expressing B markers); the pattern may be misinterpreted as "interstitial pneumonitis" or "minimal changes"			
Extra-nasal-type NK/T cell Lymphoma	Systemic symptoms (fever, malaise, weight loss)	Nodules or masses (possibly excavated)	Surgical biopsy	Chemotherapy
	Respiratory symptoms (dyspnea, cough, acute respiratory failure)		cryoTBB biopsy Transthoracic biopsy	
	Superimposed infections. Extrapulmonary involvement (skin,…)			
	Angiocentric infiltration of lung tissue by packed lymphoma cells (small, medium sized or angulated or serpentine nuclei)			
	Azurophilic cytoplasmic granules in Giemsa preps			
	Neoplastic cells are CD2+, CD56+, and cytotoxic molecules (granzyme and perforin) are positive			
	In situ hybridization for EBV encoded RNA (EBER) is positive			

Nodular Lymphoid Hyperplasia

Nodular lymphoid hyperplasia, also known as "pseudolymphoma," is a localized mass characterized by a lymphoid infiltrate with the lack of evidence of clonality despite immunohistochemical and genetic studies. The most common clinicoradiological feature is a localized and asymptomatic mass, only rarely presenting fever and/or elevated erythrocyte sedimentation rate (ESR). The lesion is usually curable by surgical excision. Finally, it is needed to evaluate the possibility of nodular lymphoid hyperplasia (pseudolymphoma) in the lung as a potential manifestation of immunoglobulin (Ig)G4-related disease [1].

Clinical Vignette

A 37-year-old Nigerian male was admitted to our hospital suffering with cough and fever with chills. The patient immigrated from Nigeria 1 year prior to presentation. He reported no exposure to tuberculosis (Figs. 39.1, 39.2 and 39.3).

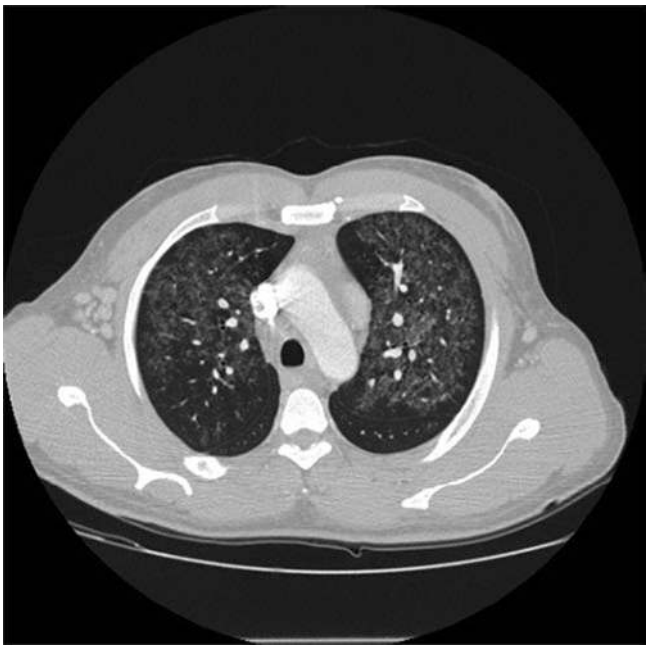

Fig. 39.1 Lung window of the contrast-enhanced CT scan of the chest. Multiple centrilobular ground glass opacities are present in both upper lobes. A relative subpleural sparing and mild septal thickening are also present

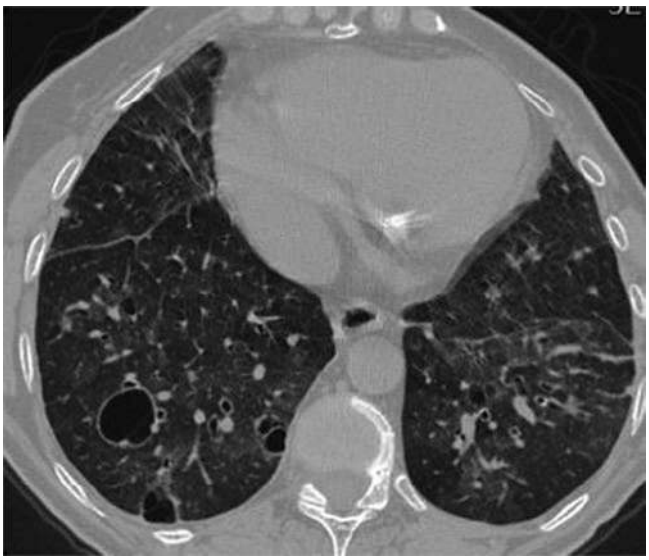

Fig. 39.3 CT scan shows bilateral areas of ground glass attenuation, with a patchy distribution. Some cyst, variable in size are present in both lower lobes, mainly on the right side. Mild interlobular septal thickening is also present. Findings are consistent with LIP

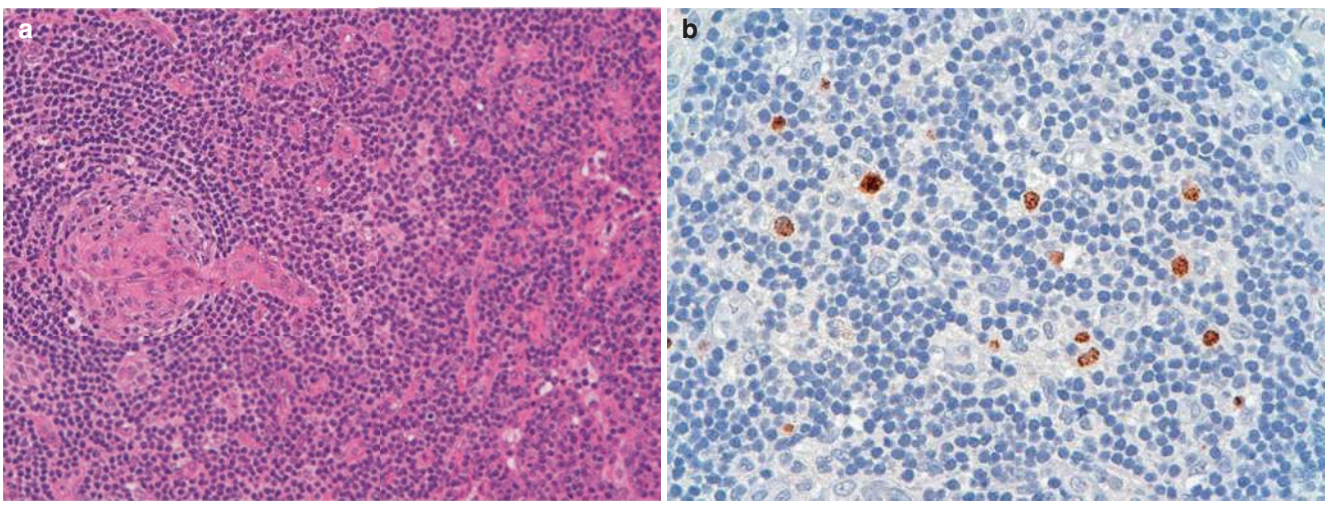

Fig. 39.2 (**a**, **b**) Histological finding of axillary nodes biopsy: (**a**) A burned out follicle with a prominent, hyalinized penetrating blood vessel (lollipop appearance); characteristic "onion skin" appearance due to the lamination of the mantle cell layers. (**b**) Focal immunoreactivity for HHV8. Interfollicular expansion composed predominantly of plasma cells and some degree of atypia associated with follicular hyperplasia

Lymphocytic Interstitial Pneumonia (LIP)

The rare Lymphocytic interstitial pneumonia (LIP) pattern is characterized by the presence of widespread aggregates of B and T reactive lymphocytes within the lung interstitium [3]. LIP is associated with a large variety of conditions including serum protein abnormality (monoclonal gammopathy, polyclonal dysproteinemia, hypogammaglobulinemia), immunological and infectious diseases (Sjögren syndrome—25% of cases—primary biliary cirrhosis, myasthenia gravis, Hashimoto thyroiditis, pernicious anemia, agammaglobulinemia, autoimmune hemolytic anemia, systemic lupus erythematosus, celiac disease, HIV infection, EBV infection, chronic active hepatitis, *Pneumocystis* infection, tuberculosis), drug-related lung injury, graft versus host disease (GVHD) due to allogeneic bone marrow transplantation, and hypersensitivity pneumonitis (extrinsic allergic alveolitis). LIP occurs more commonly in women and the mean age is around 55 years. Presenting symptoms are progressive cough and dyspnea, weight loss, fever, and arthralgias. Common physical findings are bibasilar crackles and finger clubbing (reported in about 50% of cases). Pulmonary function tests show reduction of lung volume, reduction of DLCO, hypoxemia and, usually, hypocapnia. The chest radiograph characteristically shows bibasilar reticulonodular infiltrates; a mixed alveolar-interstitial pattern can occur when infiltrates coalesce and cause compression of the alveoli. Typical HRCT abnormalities consist of areas of ground glass attenuation and poorly defined centrilobular nodules and subpleural small nodules, mostly bilateral (>90%) and with a diffuse distribution (>60%). Other common findings are thickening of bronchovascular bundles, interlobular septal thickening (82%), cystic lesions (68%) (Fig. 39.3) [4], and lymph node enlargement (68%). Less common findings include nodules 1–2 cm in diameter (41%), airspace consolidation (41%), emphysema (23%), bronchiectasis (18%), and pleural thickening (18%). Honeycombing and pulmonary hypertension appears in advanced disease. Pleural effusion is infrequent, except in HIV related LIP. Usually the presence of pleurisy, large nodules, and mediastinal adenopathy is suggestive for pulmonary lymphoma. Histologically, LIP is characterized by a heavy interstitial lymphoid infiltrate with minor peribronchiolar involvement. Granuloma formation is rare. Intra-alveolar accumulation of small lymphocytes, scanty granulation tissue tufts, and proteinaceous material along with type II cell hyperplasia are ancillary findings. Immunohistochemistry using CD20 shows that B cells are mainly represented in lymphoid follicles with germinal centers (CD10+, Bcl6+, Bcl2−), whereas interstitial, interalveolar, lymphocytes are prominently T cells. At molecular investigation, no rearrangements of immunoglobulin heavy chain genes and T cell receptor gene can be evidenced. Epstein–Barr virus (EBER test) can be identified in lung biopsy specimens from both HIV infected and non-infected patients [5, 6].

Clinical Vignette

A 75-year-old man with a history of progressive impairment of his general condition, intermittent fever, and weight loss was admitted. The peripheral blood picture was unremarkable. Right-sided pneumonia and bilateral pleural effusions were apparent on chest radiographs. Chest CT showed areas of alveolar consolidation with air bronchograms, ground glass attenuation, the presence of the "halo sign" and peribronchovascular nodules (Fig. 39.4a–c). The clinical and radiological picture worsened over 40 days and despite antibiotic treatment with macrolides. Transbronchial lung biopsies via rigid bronchoscopy were performed but the pathologic examination was inconclusive. Therefore, transthoracic fine needle aspiration/biopsy samples were obtained under CT guidance. The pathologic examination revealed histologic pattern compatible with nonspecific interstitial pneumonia (NSIP). However, this diagnosis was not felt to be compatible with the clinical and radiological presentation, which included a significant increase of the right pleural effusion and evidence of anemia (Hb—6.5 g/dL). We suspected a lymphoproliferative process and medical thoracoscopic lung biopsy was performed which revealed primary pulmonary MALT lymphoma by immunohistochemical analysis of pleural tissue specimens (Fig. 39.5a–c). Bone marrow examination was negative.

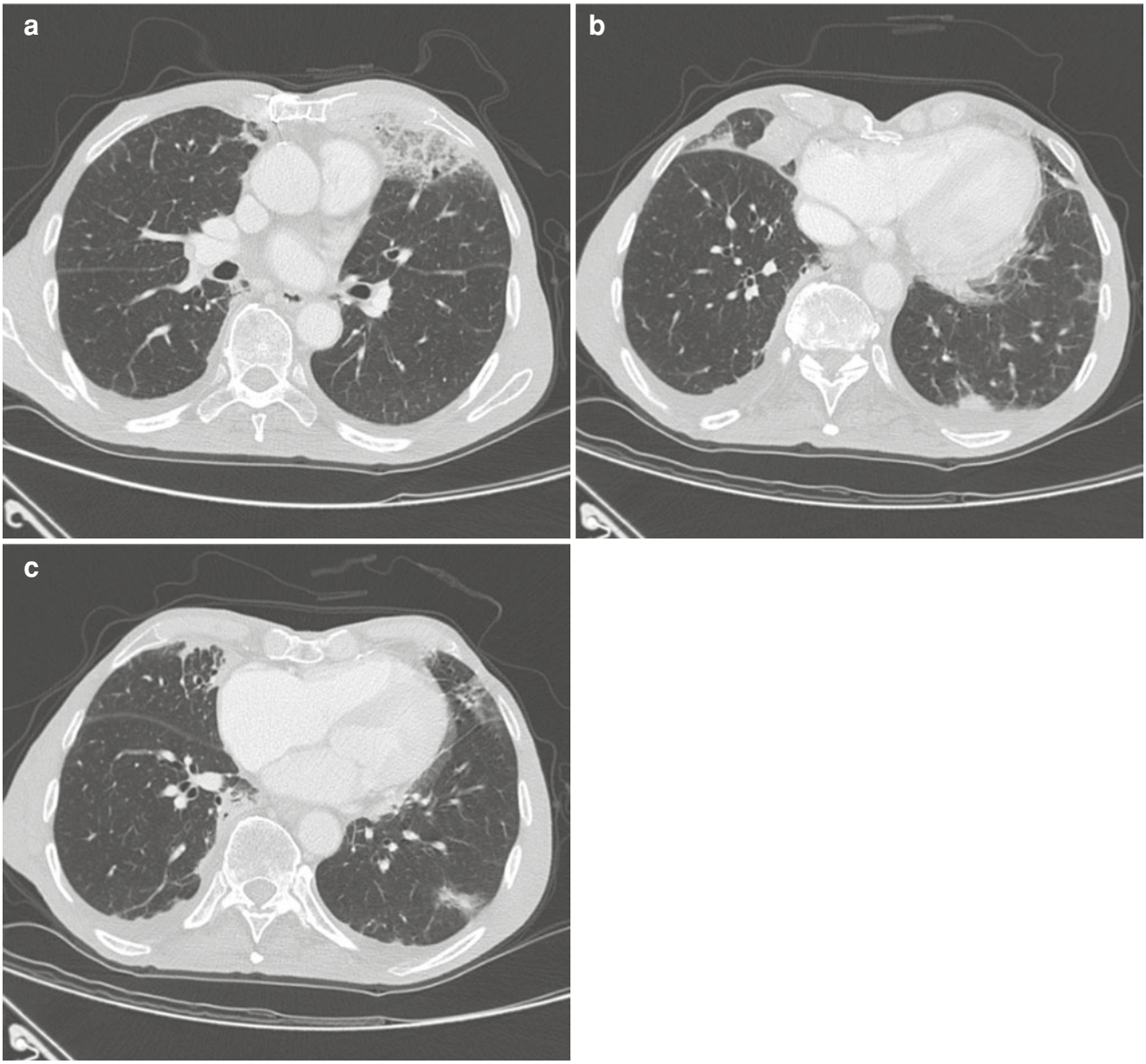

Fig. 39.4 CT scan shows bilateral consolidations, (**a**) particularly in the middle lobe (**b**) and in the posterior segment of left lower lobe (**b**). Moderate ground glass attenuation with interlobular septal thickening is present in the lingula and in the middle lobe. (**c**) Small bilateral pleural effusions are present

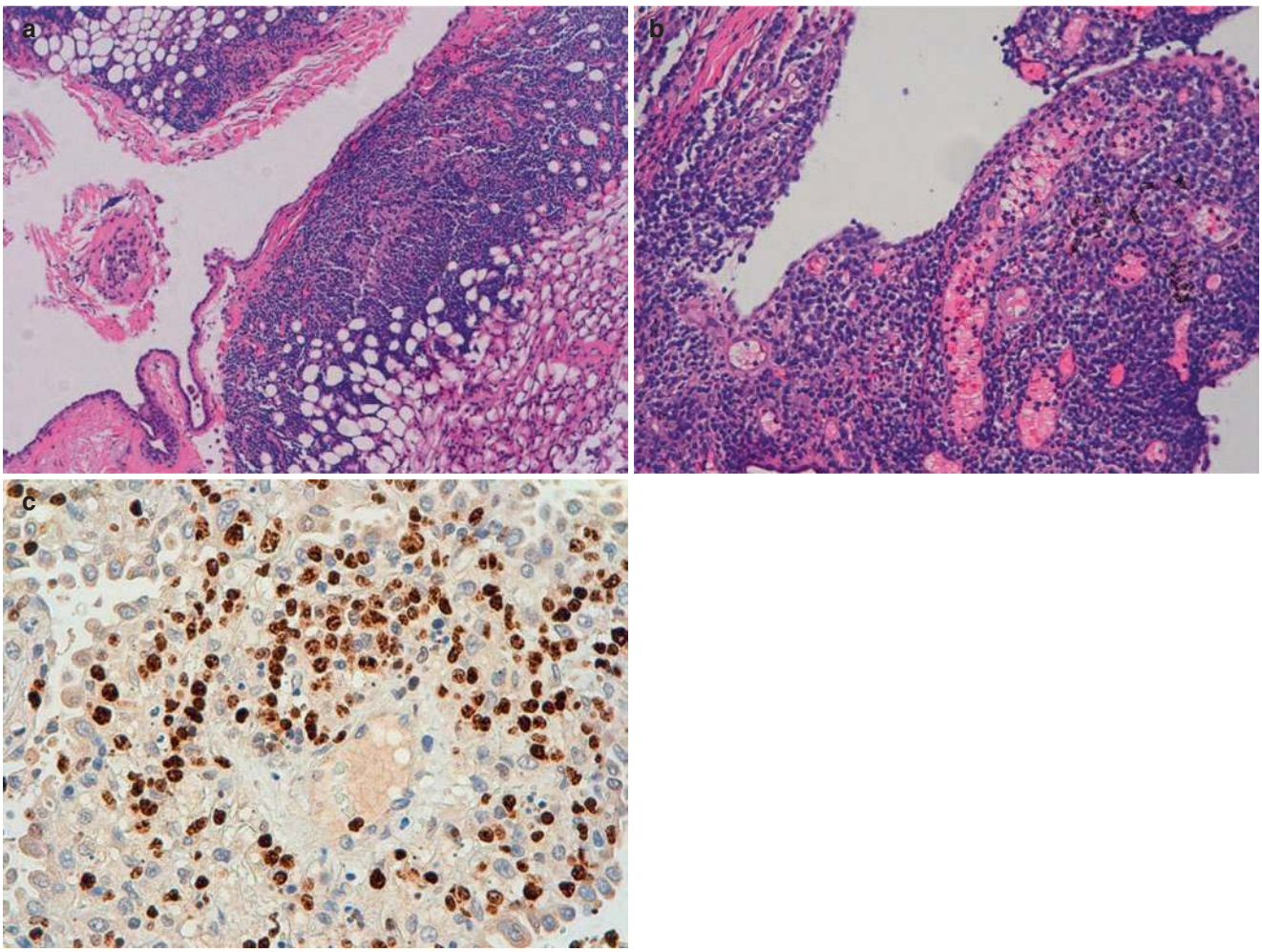

Fig. 39.5 Medical thoracoscopic lung biopsy; (**a**) In this low magnification view, the neoplastic cells extensively infiltrate the parietal pleura; (**b**) High magnification view of the pleural neoplastic infiltrate composed of small- to medium-sized B lymphocytes with relatively abundant, pale cytoplasm; occasional plasma cells are present. (**c**) Monotypic expression of K light chains

Treatment with corticosteroid and immunosuppressive drugs may lead to resolution. Median survival is 11.5 years. The outcome is unpredictable and may vary from resolution to death (caused in most fatal cases by progression to fibrosis, *cor pulmonale* and respiratory failure, superimposed infection, or to development of a complicating lymphoma).

Clinical Vignette

A 61-year-old woman with a history of worsening dyspnea and low grade fever lasting for at least 4 months. Upon presentation to the hospital, physical examination and radiological chest X-ray were unremarkable. Peripheral blood tests were normal except for a slight increase of LDH (340 U/L) (normal range 120–240 U/L) and mild thrombocytopenia. Soon after admission, however, he developed acute respiratory failure. A contrast enhanced CT ruled out acute pulmonary thromboembolism but documented a mild bilateral pleural effusion (Fig. 39.6a, b). He required intubation and mechanical ventilation. Pancytopenia and laboratory features consisting with a diagnosis of hemophagocytic syndrome appeared. A few days later the patient died in spite of supportive treatment. At autopsy a diagnosis of intravascular large B cell lymphoma involving the lung was made (Fig. 39.7a, b).

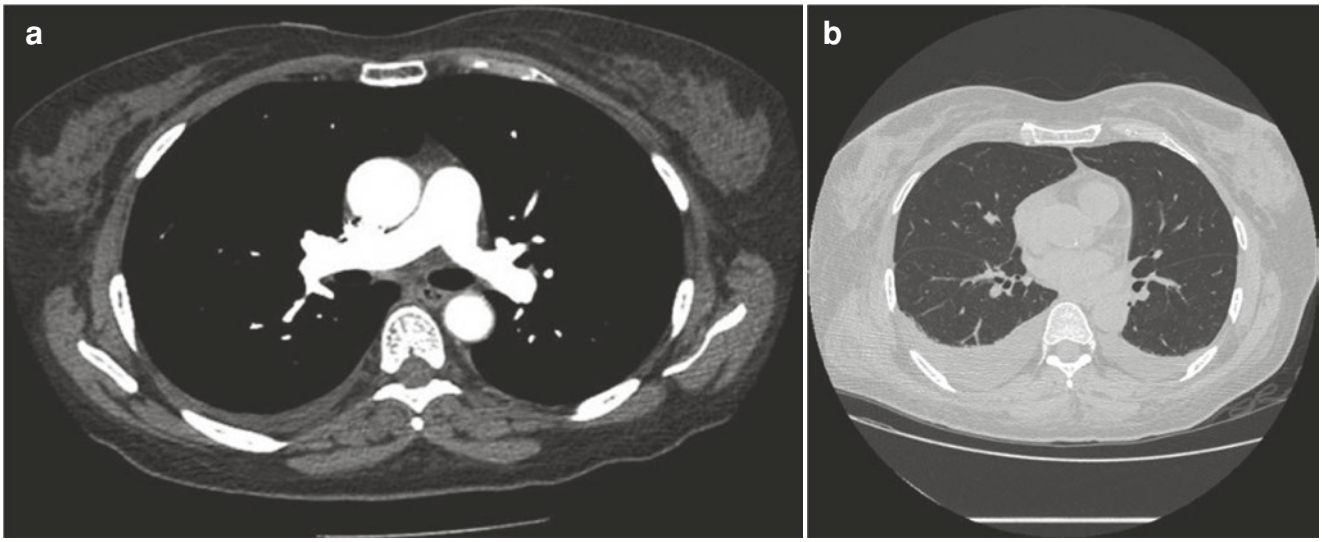

Fig. 39.6 (**a**, **b**) A contrast enhanced CT of the chest ruled out any proximal or sub-segmental pulmonary embolism but shown a mild bilateral pleural effusion and no parenchymal involvement

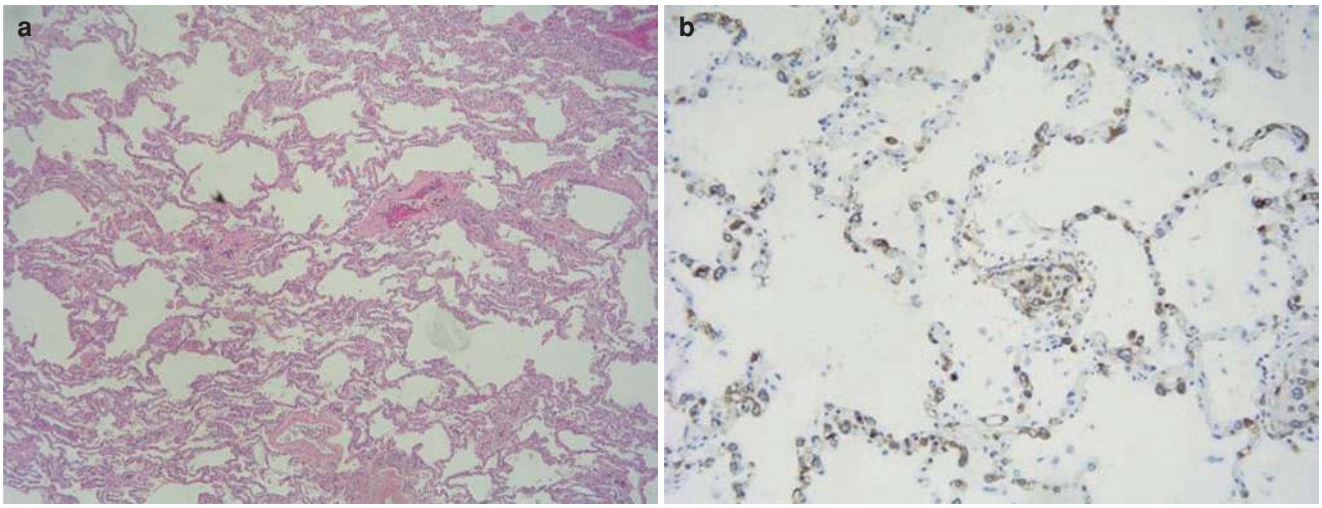

Fig. 39.7 Autopsy findings; (**a**) The neoplastic lymphoid cells are mainly lodged in the lumina of vessels in the lung tissue. The tumor cells are large with prominent nucleoli. (**b**) The tumor cells are highlighted by staining with CD20

Follicular Bronchitis/Bronchiolitis

Follicular bronchitis/bronchiolitis is a term introduced to describe the predominant peribronchial lymphocytic infiltrate with abundant germinal centers, often associated with various allergic diathesis, immunodeficiency disorders (*HIV infection*, common immunodeficiency syndromes), and collagen vascular diseases [7]. Patients usually present dyspnea, occasionally fever and cough, hypoxemia, hypocapnia; either obstructive or restrictive spirometric patterns have been reported. The chest radiograph shows bilateral reticular or nodular opacity. Common HRCT findings are centrilobular nodules, bronchiolar dilatation, *tree in bud* and mosaic perfusion patterns. Expiratory dynamic HRCT scans are important to assess air trapping. Flow cytometry of bronchoalveolar lavage (BAL) usually document a slight increase of polyclonal B lymphocytes. Surgical lung biopsy is often performed to obtain a definite histological diagnosis. Therapy with corticosteroids and also with macrolides at low dose may have some benefit.

Castleman Disease

Castleman disease is an uncommon clinicopathological entity first described in 1956 [8]. Nowadays Castleman disease is a term used to identify a heterogeneous group of hematological disorders that mainly affect the lymph nodes [9–12]. The spectrum of histopathology changes ranges from atrophic germinal centers with hypervascularization to hyperplastic germinal centers with polytypic plasmacytosis.

Unicentric Castleman disease involves a single region and generally has hyaline vascular/ hypervascular histopathological features. When the thorax is involved, unicentric Castleman disease appears with mediastinal or hilar giant lymph nodes; symptoms are usually absent or when present they are related to the mass effect of the lesion (superior vena cava syndrome, obstruction of large airways). Very rarely it manifests as a pulmonary mass. Surgical excision is curative in the large majority of cases.

Multicentric Castleman disease (MCD) involves different lymph node stations and manifests with laboratory markers of systemic inflammation. The histopathological background can be classified into three groups: plasmacytic, mixed, and hypervascular [38]. MCD is an aggressive disorder that potentially leads to fatal multiple organ dysfunction caused by a *cytokine storm*, often including IL-6. ~50% of MCD cases are related to an uncontrolled HHV-8 infection. In such cases, HIV infection or, more rarely, another cause of immune-suppression enables HHV-8 to escape host immune control and signal for excessive cytokine production and polyclonal lymphoproliferation. In half of the HIV- negative and HHV-8-negative MCD cases, the etiology is still unclear. In HHV-8- negative MCD cases, two clinical phenotypes have been identified. Patients present with either heterogenous clinical symptoms—which can include intense episodes of thrombocytopenia, anasarca, fever/elevated C-reactive protein, renal dysfunction/reticulin myelofibrosis, organomegaly, megakaryocytic hyperplasia, and normal gamma globulin level (MCD-TAFRO)—or a less intense inflammatory syndrome, normal/elevated platelet counts, and polyclonal hyper-gammaglobulinemia. Lung involvement in MCD is characterized by lymphoplasmacytic (with lymphoid follicles) and fibroinflammatory lesions with a lymphatic distribution (visceral pleura, interlobular septa, and bronchovascular bundles). Obstructive phlebitis and eosinophilic infiltration are typically absent. Plasma cells are usually clustered in sheets. In HHV-8-related MCD, interstitial lymphocyte infiltrates mimicking LIP are more frequently observed. Immunohistochemistry analysis documents the presence of HHV-8 [13]. HRCT scan features include areas of ground glass attenuation, peri-lymphatic nodules, reticular changes associated to enlarged mediastinal/hilar lymph nodes and very rarely cysts. The evolution towards HHV-8-positive large B cell lymphoma may be observed in HHV-8-related MCD. Patients often present with low-grade fever, cough and dyspnea. HRCT of the lung may show hilar and mediastinal lymphadenopathies, multiple nodules of different sizes, cysts, patches of ground glass opacities and LIP-like images. The main therapeutic options include corticosteroids, immunosuppressive therapy (cyclosporin A, cyclophosphamide, etc.), rituximab or rituximab-based therapy, and anti-IL-6 therapies (e.g. tocilizumab and siltuximab) [14, 15].

Primary Pulmonary Lymphomas

Primary Pulmonary Lymphomas (PPL) is defined as a clonal lymphoid proliferation affecting one or both lungs (parenchyma and/or bronchi) in a patient with no detectable extrapulmonary involvement at diagnosis or during the subsequent 3 months.

The World Health Organization Classification of tumors of lung (WHO 2017) [2] include three forms of PPL: B cell primary pulmonary NHL, Marginal zone B cell lymphoma of mucosa-associated lymphoid tissue (MALT) type, primary pulmonary diffuse large B cell lymphoma (DLBCL), and Lymphomatoid granulomatosis (LYG). Nevertheless, the lung may rarely be the primary site of presentation of most types of lymphomas such as Follicular lymphoma (FL), Mantle cell lymphoma (MCL), extraosseous plasmacytoma (EP), Large B cell lymphoma arising in HHV8-associated multicentric Castleman disease, plasmablastic lymphoma (PBL), different subtypes of T/NK lymphomas, Hodgkin Lymphoma, and others.

Primary pulmonary non-Hodgkin lymphoma (NHL) is very rare and accounts for 0.4% of all lymphomas and 3.6% of extranodal lymphomas. Mature B cell neoplasms are the prevalent phenotype.

Primary Pulmonary B Cell Non-Hodgkin Lymphomas (PPBL)

The most common histological type is mucosa-associated lymphoid tissue type (MALT) B cell lymphoma, which represents 70–90% of all primary pulmonary NHL [1, 2]. Diffuse large B cell lymphoma (DLBCL) occurs only in 10% of PPBL cases. In some cases, transformation from MALT lymphoma to DLBCL may occur. Clinically, PPBLs present with non-specific symptoms. Radiologically, they can present as consolidation, well-defined masses or nodules. Therefore, PPBLs can easily be radiologically confused with primary lung carcinoma or metastases when presenting as multiple masses or/and nodules but, obviously, they have different treatments and prognosis. The main diagnostic criterion for PPBL is the absence of extrapulmonary involvement.

Therefore, in patients with biopsy-proven lymphoma of the lung, PPBL is diagnosed if extrapulmonary involvement is ruled out. B cell primary pulmonary NHL are subdivided into low- grade B cell PPLs (58–87%) and high-grade B cell PPLs (11–19%). The high-grade B cell PPBLs spread rapidly into mediastinal and extra-thoracic locations. This may lead to underestimation of true incidence.

Primary Pulmonary MALT B Cell Lymphoma

Primary pulmonary MALT lymphoma is a rare extranodal lymphoma that is usually of the low-grade B cell type and is considered to arise from the mucosa-associated lymphoid tissue (MALT) of the bronchus (histologically distinct from true intrapulmonary lymph nodes). Low-grade B cell lymphomas represent 50–90% of all primary lung lymphomas. MALT-associated malignant lymphomas develop most frequently in the stomach and, more rarely, in the bowel, salivary glands, larynx, and thyroid gland [16]. Unlike the model of gastric MALT lymphoma and *Helicobacter pylori*, no triggering of antigens has been identified in the primary pulmonary MALT lymphoma. Nevertheless, recent studies have detected the microorganism *Achromobacter xylosoxidans* with significant frequency [17]. Among the non-gastrointestinal MALT lymphomas,the pulmonary lymphoma is the most frequent (up to 19% among MALT lymphomas).

Pulmonary MALT-lymphomas seem to arise on pre-existing inflammatory accumulations of organized lymphoid tissue (lymphoid follicles of the bronchus-associated lymphoid tissue – BALT). BALT is inconspicuous in adults, but it undergoes hyperplasia in patients with chronic immune-mediated diseases such as chronic infections, connective tissue diseases, rheumatoid arthritis, and Sjögren syndrome [18, 19]. These inflammatory processes are likely related to chronic antigen stimulation, as in other extranodal lymphomas, where this correlation (and especially that with infections) is now well established and also relevant for specific therapy. Accordingly, the occurrence of intra-clonal sequence variations (ongoing mutations) is a common finding in both gastric and pulmonary lymphomas, indicating the role of antigen stimulation in their pathogenesis [20, 21]. In a proportion of pulmonary lymphomas, correlations have been clearly established with conditions where the immune system is abnormally stimulated/ deregulated, such as in autoimmune diseases (Sjögren syndrome, Hashimoto thyroiditis, systemic lupus erythematosus-SLE, rheumatoid arthritis), or immunodeficiency (either primary or acquired). Very rarely, an association between yellow nail syndrome and MALT lymphoma in the lung has been observed.

About half of the patients with primary pulmonary MALT lymphoma are asymptomatic at presentation, and nearly half of these cases are identified on the basis of abnormal radiological findings [19, 22]. The pulmonary symptoms are non-specific like cough, dyspnea, chest pain, and occasional hemoptysis, but are more common than constitutional symptoms like body weight loss, fever, night sweats, or fatigue. These symptoms may present for several weeks to months before diagnosis. This indolent behavior explain why many cases of pulmonary MALT-lymphoma have been previously defined as "pseudo-lymphoma" [23]. Laboratory findings are non-specific and usually normal: only few patients have increased levels of lactate dehydrogenase (LDH) and/or Beta2-microglobulin in the serum and also less frequently a monoclonal band in serum immuno- electrophoresis is found. Radiologic feature of MALT lymphoma are solitary, well-delineated masses with air bronchogram. Although hilar and mediastinal lymphadenopathy is not a prominent radiologic finding, nodal involvement is documented at pathologic analysis in about 30% of cases. HRCT findings include: areas of alveolar consolidation more frequently centered on dilated bronchi, ground glass attenuation, the presence of "halo sign," peribronchovascular nodules, "tree in bud pattern," peribronchovascular thickening and septal lines [24]. The lesions are multiple in more than 70% of cases. The so-called angiogram sign previously considered typical of low-grade lymphoma in the lung has been observed in other numerous alveolar filling disorders. Radiographic findings may remain unvaried for several years. Cases of endo-tracheobronchial polypoid MALT lymphoma have been reported, often causing unilateral lung hyper-transparency. MALT lymphomas have generally been reported without increased fluorine 18-fluorodeoxyglucose (18-FDG) accumulation on positron emission tomography (PET). The outcome of MALT-type PPL is generally favorable. More than 80% of the cases have a 5-year survival rate, and the median survival is more than 10 years. The overall survival is better than other types of non-Hodgkin lymphoma [18, 19]. Clinical features associated with poor prognosis in a series of PPL included patients over 60 years of age, elevated serum lactate dehydrogenase and elevated serum beta2 microglobulin levels [19].

As with other types of extranodal MALT lymphomas, a variety of cytogenetic abnormalities have been demonstrated in P-MALTL, including translocations and/or trisomies, which can provide very useful diagnostic information [1, 2]. The most frequent cytogenetic abnormalities in P-MALTL are the t(11;18)[q21;q21], observed in ≤50% [3, 8]. In this translocation, the N-terminus of the API2 gene is fused with the C-terminus of the MALT lymphoma translocation gene 1 (MALT1), forming the protein API2-MALT1, an oncogenic fusion protein that is able to generate a stable, non-canonical nuclear factor-κB-activating fragment. API2-MALT1 translocation is specific to MALT lymphoma and frequently occurs in the absence of inflammation. t(14;18)(q32;q21) and t(1;14)(p22;q32) are observed in a proportion of

P-MALTL. These chromosomal abnormalities are able to bring either the BCL10 or the MALT1 gene to the IGH locus, thus deregulating their expression. Interestingly, as previously observed in gastric lymphomas where t(11;18) can serve as a molecular marker for cases not responding to *H. pylori* eradication, this translocation defines a distinctive clinicopathologic subtype of pulmonary MALT-lymphomas characterized by the absence of any underlying autoimmune disease and lack of plasmacytic differentiation [2].

At histological analysis the pulmonary structure is effaced by abnormal lymphocyte infiltration, predominantly localized along bronchovascular bundles, interlobular septa and visceral pleura, in a lymphangitic pattern [25]. As MALT lymphomas arising at other sites, pulmonary MALT- lymphoma is formed by the accumulation of clonal lymphoid cells characterized by the morphological and biological features of marginal-zone B cells. Marginal-zone cells, that are particularly abundant in the spleen, are post-germinal center lymphocytes with memory functions that migrate from lymphoid tissues to extranodal sites where they can rapidly become antibody producing plasma cells upon stimulation. Morphologically, lymphoma cells are similar to normal marginal-zone cells, exhibiting a spectrum of cytological features (small-round cells, centrocyte-like cells, monocytoid B cells), characterized by small and irregular nuclei, inconspicuous nucleoli, and abundant clear cytoplasm. Neoplastic lymphocytes typically accumulate around non-neoplastic lymphoid follicles, forming poorly defined sheets of cells at the periphery of the mantle zones, extending into the lung parenchyma. The presence of reactive follicles, that can be particularly abundant and are presumably pre-existing the lymphoma development, can pose diagnostic problems at morphological and also immunophenotypical analysis. The presence of lympho-epithelial lesions (neoplastic lymphoid cells infiltrating bronchiolar epithelium) is frequent and involve bronchiolar and bronchial epithelial structures. Histologically the differential diagnosis includes all pulmonary diseases characterized by accumulation of lymphoid follicles, and in particular the spectrum of follicular hyperplasia, follicular bronchiolitis, and LIP, as well as, more rarely, hypersensitivity pneumonitis, inflammatory pseudotumor, intraparenchymal thymoma, and Castleman disease. For these reasons, the use of immunophenotypical and molecular techniques is recommended to substantiate the histological diagnosis of pulmonary MALT lymphoma, especially when the tissue samples are scanty [26]. In a consistent proportion of cases it is possible to demonstrate lymphoplasmacytic differentiation, with a significant plasma cell component exhibiting immunoglobulin light chain restriction. It is possible that at least some cases of primary plasmacytoma of the lung (a rare low-grade tumor of unclear etiopathogenesis presenting as isolated nodules or diffuse) can in fact be included in the clinicopathologic spectrum of MALT lymphomas, together with localized pulmonary amyloidosis (another lesion that has been described in association with pulmonary marginal lymphoma).

Pulmonary Plasmacytoma

Pulmonary plasmacytoma is a plasma cell malignancy that most commonly occurs in the upper respiratory tract. Plasmacytoma located in the lung is an unusual finding, and in such cases the disease may be confined to the lung and regional lymph nodes or may be disseminated. The most common location for plasmacytoma is the submucosa of the upper airways [27, 28]. It is an extremely rare tumor, less than 50 cases are reported in literature and in fact represent only the 6% of all extraosseous plasmacytomas. About the 7% of patients affected by plasma cell myeloma have intrathoracic disease, and it is rarely confined into the lungs. When only located in the lower respiratory tract (primary pulmonary plasmacytoma), diagnosis can be particularly difficult. The less differentiated plasmablastic pulmonary plasmacytoma occurs mainly in patients with advanced HIV infection. Phenotypically similar to mature plasma cells, the malignant cells appear immature, most like plasmablasts. Prognosis in HIV+ patients is poor (5.5 months) even if recent small reports suggest it may have improved after highly active anti-retroviral therapy (HAART) advent. The relationship between plasma cell myeloma, solitary plasmacytoma of bone, and extraosseous plasmacytoma is not well understood. For some authors, these three entities represent different aspects of the same disease spectrum, whereas others regard solitary plasmacytoma of bone as a rare manifestation of plasma cell myeloma. Extraosseous plasmacytoma should, however, be regarded differently, and the diagnosis restricted to tumors that occur outside the bone marrow, may infiltrate nearby lymph nodes or cause distant metastasis. In immunocompetent patients pulmonary plasmacytoma is more frequently observed in the upper respiratory tract. Common clinical findings are cough, dyspnea, and hemoptysis. Laboratory features include paraproteinemia and urinary Bence Jones. When involving the lung, plasmacytomas might be considered within the spectrum of MALTL, as previously described. The most frequent radiologic finding is a pulmonary nodule or mass near the hilum. Lobar consolidation and bilateral diffuse infiltrates have also been described, but this manifestation is very rare [29].

Follicular Lymphoma

Follicular lymphoma is generally an indolent B cell lymphoproliferative disorder of transformed follicular center B cells. *Follicular lymphoma* is characterized by diffuse lymphade-

nopathy, bone marrow involvement, splenomegaly, and less commonly other extranodal sites of involvement such as gastrointestinal tract, lung, skin, and other sites [2]. It affects adults (median age 59 years) and it is more frequent in females (male/female ratio 1/1.7). In general, cytopenia can occur but constitutional symptoms of fever, night sweats, and weight loss are uncommon. Primary lung involvement is usually asymptomatic. HRTC scan shows ground glass opacities sometimes with a "crazy paving" pattern or nodules. Diagnosis is based on histology. Immunohistochemical staining is positive in virtually all cases for cell surface CD20, CD10, and nuclear Bcl6. Monoclonal light chain restriction can be demonstrated on cryostat sections (when available). Membrane expression of bcl-2 protein can be demonstrated in the majority of cases, corresponding to the characteristic translocation t(14;18)(q32;q21) involving the IgH/bcl-2 genes. The Follicular Lymphoma International Prognostic Index (FLIPI) prognostic model for FL uses five independent predictors of inferior survival: age > 60 years, hemoglobin <120 g/L, serum LDH > normal, Ann Arbor stage III/IV, number of involved nodal areas >4. The presence of 0–1, 2, and ≥3 adverse factors defines low, intermediate, and high-risk disease with median 10-year survivals in the pre-rituximab era of approximately 71, 51, and 36 months, respectively. Chemotherapy plus rituximab (anti-CD20), has improved response rates [30].

Diffuse Large B Cell Lymphoma

Diffuse large B Cell lymphoma (DLBCL) as a group is the second most common type of primary pulmonary lymphoma and most usually affects adults in the sixth and seventh decades [2, 31, 32] Morphological, biological and clinical studies have subdivided DLBCL into morphological variants, molecular subtypes and distinct disease entities [2]. The main morphological variants are centroblastic, immunoblastic, and anaplastic. The molecular subtypes are the germinal center B cell and the activated B cell. However, many cases remain that may be biologically heterogeneous, and have no clear and accepted criteria for subdivision. The centroblastic variant is characterized by cells with oval to round vesicular nuclei, multiple nuclear membrane-bound nucleoli, and scanty pale cytoplasm. The immunoblastic variant contains large lymphoid cells with round to oval vesicular nuclei and a single centrally located prominent nucleolus with scant to moderate basophilic cytoplasm. In some cases, plasmacytic differentiation may be seen, with eccentrically located nuclei. The anaplastic variant is characterized by large pleomorphic cells with bizarre irregular nuclei, often with multinucleated forms, and variable amounts of cytoplasm.

Lymphoma cells are positive for mature B cell related antigens (CD20, CD79a, PAX5), and variably express differentiation markers than can be used to further define the subtypes: CD10 (30–50%), BCL6 (60–90%), MUM1 (35–65%), BCL2 (47–84%), and CD5 (5–10%), etc. Some DLBCL cases, especially the anaplastic variant, are positive for CD30. Ki67 staining is usually >40%; in some cases, it may be >90. BCL6(3q27) rearrangement is seen in ≤30% of DLBCL. ~20–30% of DLBCL cases have t(14;18) involving the BCL2 gene. MYC (8q24) rearrangement occurs in ~8–14% of DLBCL cases. Cases with MYC and BCL2 and/or BCL6 rearrangement are called "double/triple-hit lymphomas" and are classified in a separate category of "High-grade B cell lymphoma with MYC and BCL2 and/ or BCL6 rearrangement" [3]. In a minority of cases, markers for Epstein–Barr virus (EBV) infection may be detected (EBV-positive diffuse large B cell lymphoma not otherwise specified).

Diffuse large B cell lymphomas often occur in patients with underlying immunological disorders such as immunosuppression in solid organ transplantation, HIV infection, and Sjögren syndrome [33]. Patients are usually symptomatic with respiratory symptoms (cough, dyspnea, hemoptysis), fever, and weight loss.

Common radiological and CT findings include single pulmonary mass, and atelectasis; pleural effusion may be present. In HIV patients or in other immunosuppressed hosts, multiple excavated opacities are more frequently found. Survival is poor in patients with underlying immunologic disorders such as AIDS and transplantation. R-CHOP (rituximab, cyclophosphamide, doxorubicine, vincristine, and steroids) is the treatment of choice; the 5-year progression-free and overall survival rates were found to be ~60% and ~65%, respectively [2].

Intravascular large B cell lymphoma is a rare subtype of large B cell lymphoma with an estimated frequency of <1% of all lymphomas. This rare entity is characterized by an intravascular proliferation of clonal B cells with little to no parenchymal involvement and usually without involvement of lymphoid tissues and occasionally peripheral blood [1, 2, 31]. Proliferation of CD20 positive neoplastic cells in blood vessels of parenchymal organs results in vessel obliteration and ischemia. The clinical presentation is highly variable, ranging from no or limited organ involvement to multiple organ failure. Two major patterns of clinical presentation have been recognized: the so-called classic form (mostly present in Western countries), which is characterized by symptoms related to the mainly involved organs (predominantly central nervous system, skin and lungs) and a hemophagocytic syndrome-associated form, originally documented as an Asian variant, in which patients present with multiorgan failure, hepatosplenomegaly and pancytopenia, B symptoms, particularly fever. The diagnosis of intravascular lymphoma is often difficult. Rare presentations with pulmonary arterial hypertension or respiratory insufficiency

with air trapping have been reported. LDH, soluble interleukin 2 receptor (sIL-2R), and ESR are usually elevated. Hypercalcemia may be observed, though rarely. Pulmonary function tests show a markedly decreased diffusing capacity. Chest X-ray may be normal or show reticulo-nodular infiltrates or pleural effusion. CT findings may include bilateral reticular shadow, ground glass opacity, wedge-shaped subpleural opacities, and pleural effusion. A random skin biopsy of normal-appearing skin or transbronchial (cryo)biopsies are often helpful in making the diagnosis in subjects presenting mainly with thoracic symptoms/signs [34]. Cytological analysis of pulmonary capillary blood cells has been reported as useful for the identification of the disorder. Intravascular lymphoma usually shows rapid progression and short survival, with at best transient remissions. Treatment is usually with the R-CHOP regimen. The poor prognosis in these patients reflects, at least in part, frequent delays in diagnosis and initiation of therapy.

Lymphomatoid Granulomatosis

Lymphomatoid granulomatosis (LYG) is an angiocentric and angio-destructive lymphoproliferative disease involving extranodal sites, composed of EBV-positive B cells admixed with reactive T cells, which usually predominate [2, 31]. The lesion has a spectrum of histological grade and clinical aggressiveness, which is related to the proportion of large B cells. Although it may affect virtually any organ, it is most frequently characterized by pulmonary, skin, and central nervous system involvement. This condition usually affects adults (average age 50) with a predilection for males (sex ratio male to female 2:1) and for patients with underlying immunodeficiency (HIV + patients, Wiskott-Aldrich syndrome). However, occurrence in childhood has been documented. Few subjects are asymptomatic. Nearly 90% of patients report chronic respiratory symptoms, mainly cough, chest pain, and dyspnea, accompanied by B symptoms such as fever, weight loss, and sweating. Hemoptysis or acute respiratory distress syndrome rarely occur. Laboratory findings are characterized by increased ESR and, in a minority of cases, lymphopenia, leukocytopenia, and low CD4+ lymphocyte count. Lung nodules are the most common feature in chest radiographs, occurring in perhaps 80% of cases, and cavitation may be noted in 20% of cases [35]. In about 30% of patients, pleural effusion is present at the beginning. Hilar lymphadenopathies are found in less than 25% of cases. Uncommon radiologic features reported in literature include: single nodules, alveolar opacities, small thin-walled cystic lesions, and reticulonodular diffuse lesions. Differential diagnosis in patients with LYG is a real challenge: granulomatosis with polyangiitis, other necrotizing vasculitides, necrotizing nodular sarcoidosis, infections, bronchogenic carcinoma and metastatic tumors, organizing pneumonia, and IgG4 related fibroinflammatory disease [1, 36]. The clinical course is highly variable [37]. Patients may show waxing and waning of their disease; in grade 1 forms and when the lesions are localized to the lungs, spontaneous resolving may be observed in up to 27% of cases [36, 38]. One-third of patients with grade 1 lesions progress to malignant lymphoma, whereas two-thirds of patients with grade 2 lesions develop lymphoma. The aggressive form of disease is lethal within 2 years, in spite of aggressive therapy. Death is often caused by a progressive pulmonary involvement. However, high-dose therapy (with or without stem cell transplantation) can be effective therapeutic options in some cases and should be considered in all patients with refractory and multiply relapsed LYG [39, 40]. From the pathologic point of view, the term LYG includes a group of related lesions characterized by the infiltration of pulmonary parenchyma by an heterogeneous cell population composed of a large number of reactive T-lymphocytes, a variable proportion of large EBV-infected B cells (as defined by co-expression of B cell related antigens and EBV markers [2, 36]. The lymphoid infiltrate often surrounds pulmonary arteries and veins and typically invades the walls of these vessels. Necrosis is a frequent feature of the disease. LYG lesions are heterogeneous, and have been graded depending on the proportion of neoplastic B cells and surrounding reactive T cells, the degree of lymphocytic atypia, and the heterogeneity of the infiltrate, distinguishing three grades. Grade 1 lesions contain few or no EBV-infected cells (less than 5 per high-power field), usually lack necrosis, and are polymorphous. Monoclonality is usually difficult to demonstrate. Grade 2 lesions have scattered EBV-infected cells (5–20 per high-power field) and foci of necrosis, but they remain polymorphous. The grade 3 forms can be considered as diffuse large B cell lymphomas; foci of necrosis are evident and sheets of markedly atypical cells (resembling immunoblasts or resembling Reed–Sternberg cells) infiltrate the lung parenchyma in an angiocentric fashion. The T cell component is non-neoplastic by definition, exhibits an activated cytotoxic phenotype, and can be considered as a reactive response to infected/neoplastic B cells. Chemokines such as IP-10 and Mig, elaborated as the result of the EBV infection may be responsible for vascular damage by promoting T cell adhesion to endothelial cells. LYG needs to be distinguished, histologically, from other diseases characterized by polymorphous lymphoid infiltration (angioimmunoblastic lymphadenopathy, infection due to Epstein–Barr virus, acute and fibrinous organizing pneumonia, inflammatory sarcomatoid carcinoma), IgG4 related fibroinflammatory disorder, and by lesions characterized by zonal coagulative necrosis and prominent angio-invasion, including extranodal NK/T (nasal-type) T cell lymphoma, and granulomatosis with polyangiitis (Fig. 39.8a, b).

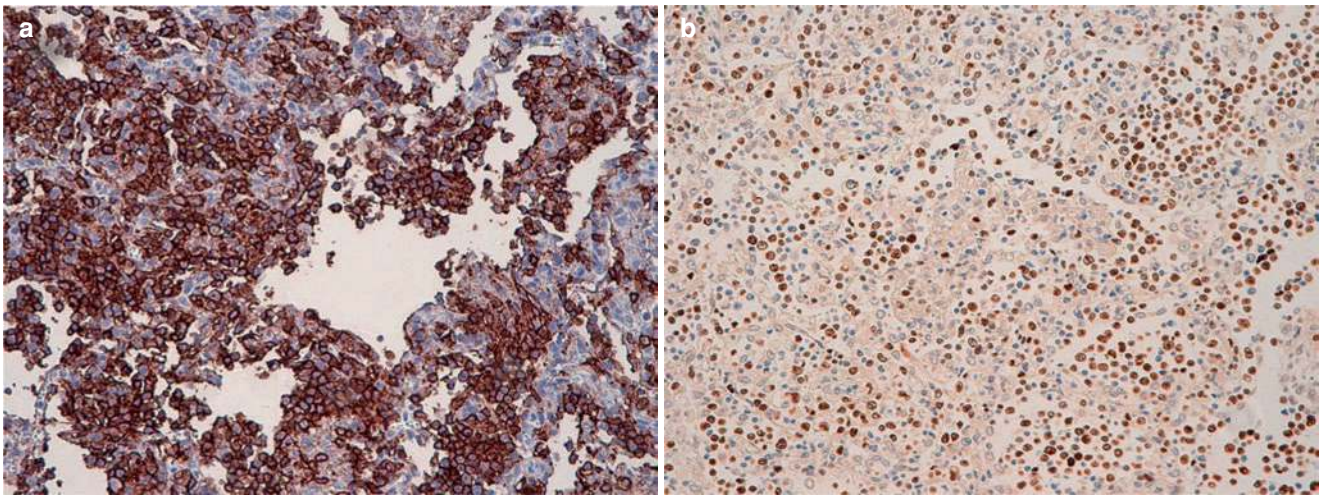

Fig. 39.8 (**a**) Lymphomatoid granulomatosis: the lymphomatous cells have B: CD20+ (10× IIC). (**b**) Lymphomatoid granulomatosis: positive signals of EBV in the nucleus of lymphomatous cells by in situ hybridization with EBER (Epstein–Barr virus encoded RNAs) probe (10×)

T/Natural Killer-Cell Primary Pulmonary Lymphomas (T/NK PPL)

Different types of extranodal T/NK cell lymphomas can occur primary in the lungs: nasal-type T/NK lymphoma, peripheral T cell lymphoma not otherwise specified, anaplastic large T cell lymphoma, mycosis fungoides [2, 41].

Extranodal NK/T cell lymphoma, nasal type is a predominantly extranodal lymphoma of NK cell or T cell lineage, characterized by vascular damage and destruction, prominent necrosis, cytotoxic phenotype, and association with EBV. It is defined as NK/T cell lymphoma because although most cases appear to be genuine NK cell neoplasms, some cases are of cytotoxic T cell lineage [2]. It is not exceptional in Western countries, but predominantly affects middle-aged men in Asia, Mexico, and South America. It presents as tumors or destructive lesions in the nasal cavity, maxillary sinuses, palate, and also the lung.

When occurring in the lung, it can present many clinical and radiological similarities with LYG (Fig. 39.9a–f). Clinically pulmonary (hemoptysis, chest pain) and systemic symptoms (fever, asthenia) are common. Laboratory tests may document an important CD4+ lymphocytopenia in peripheral blood and the disease may manifest with coexisting atypical pulmonary infections and with hemophagocytic syndrome [42]. CT scan documents nodules or masses with an important necrotic component. Diffuse ground glass attenuation is another rarer imaging profile. This lymphoma ranges from monomorphic small−/medium-sized to large cell lymphomas and is characterized by frequent features of angio-invasion/angiocentrism, and common necrosis accounting for frequent diagnostic difficulties on small biopsies. In cases where the neoplastic cells are admixed with an inflammatory component and/or in small biopsies, the lesions may be mistaken for a reactive process.

The neoplastic cells usually are CD3ε+, CD2+, CD5-, CD7+, CD16+/−, and CD56+/−, and have an activated cytotoxic profile. Most cases are derived from NK cells, but up to 38% of the cases are CD56-negative clonal T cells with a γδ or more rarely αβ TCR configuration at molecular analysis. By definition, all cases are associated with EBV, which is best demonstrated by in situ hybridization [2]. EBV infection is characterized by a type II latency program with expression of EBERs, LMP1, and EBNA2 [2]. The prognosis of nasal NK/T cell lymphoma is variable, with some patients responding well to chemotherapy and others dying of disseminated disease despite aggressive therapy. Historically, the survival rate has been poor (30—40%), with some improvements in recent years. Regimens incorporating asparaginase are currently the standard. For stage I/II disease, combined chemotherapy and radiotherapy is recommended. Recent studies have documented consistent PD-L1 expression by neoplastic cells in the vast majority of the cases, and recent reports indicate that antagonization of PD1-PD-L1 interactions might represent a therapeutic option for extranodal T/NK cells lymphomas refractory to standard lines of chemotherapy [43].

Peripheral T cell lymphoma not otherwise specified (NOS) is a heterogeneous category of nodal and extranodal mature T cell lymphomas that do not correspond to any of the specifically defined entities of mature T cell lymphoma in the current classification. The cytological spectrum is extremely broad, from polymorphous to monomorphic. Most cases consist of numerous medium-sized and/or large cells with irregular, pleomorphic, hyperchromatic, or vesicular nuclei, prominent nucleoli, and many mitotic figures. Clear cells and Reed–

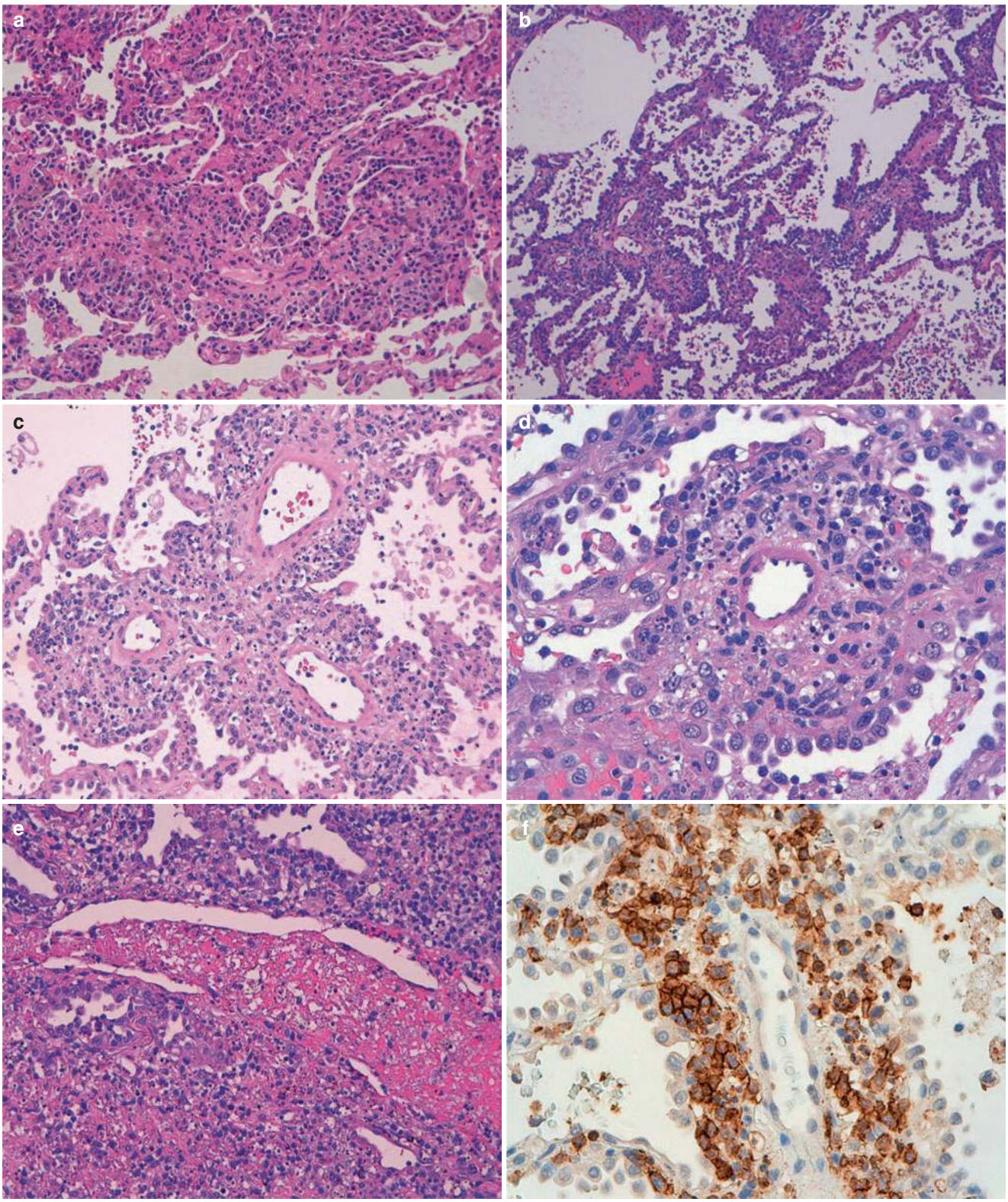

Fig. 39.9 (**a**) Extranodal NK/T lymphoma, nasal type: the lymphomatous infiltrate shows interstitial perivascular infiltration of small, medium-sized cells with irregular nuclei (2× EE); (**b**) Extranodal NK/T lymphoma, nasal type: the lymphomatous infiltrate shows interstitial perivascular infiltration of small-, medium-sized cells with irregular nuclei (4× EE); (**c**) Extranodal NK/T lymphoma, nasal type: the lymphomatous infiltrate shows interstitial perivascular infiltration of small-, medium-sized cells with irregular nuclei (10× EE); (**d**) Extranodal NK/T lymphoma, nasal type: the lymphomatous infiltrate of small-, medium-sized cells with irregular nuclei and apoptotic bodies shows perivascular infiltration of a small artery (20× EE); (**e**) Extranodal NK/T lymphoma, nasal type: the lymphomatous infiltrate has an angiocentric angiodestructive pattern associated with coagulative necrosis and apoptotic bodies (20× EE); (**f**) Extranodal NK/T lymphoma, nasal type: the lymphomatous cells have T immunophenotype: CD3+ (20× IIC)

Sternberg-like cells can also be seen. Fever, asthenia, and respiratory failure are the main symptoms at onset. Laboratory tests may document lymphopenia and eosinophilia. Serum autoantibodies may be documented. Hemophagocytic syndrome is a rare and ominous complication. CT scan findings are alveolar consolidations, nodules, ground glass attenuation; part of these features) may be explained by organizing pneumonia around the lymphoid neoplastic infiltrates.

Anaplastic large cell lymphoma was previously recognized as Ki-1 lymphoma for the strong expression of the activation antigen CD30/Ki-1 by neoplastic cells. It has rarely been described as primary pulmonary presentation; masses or single nodules are the features observed at CT. The patients present with B symptoms [1, 2].

Mycosis fungoides in its rare granulomatous variant may involve primary the lungs. Patients present with fever, lymphopenia, eosinophilia, and increased ESR and LDH. CT features include nodules with halo-signs, peripheral consolidation, and a crazy paving pattern [44]. Due to its rarity and lack of clinicoradiological specificity, the diagnosis is always difficult and requires expert histopathological analysis.

Primary Pulmonary Hodgkin Lymphoma (PPHL)

PPHL is a very rare entity and has to be distinguished from the more common intrathoracic nodal Hodgkin disease secondarily involving the lung [45, 46]. Due to its rarity, epidemiological data are scarce. In a review of 60 cases recorded in the world literature, PPHL is more common than men, shows bimodal age distribution (<35 years and >60 years), without a significant correlation with cigarette smoke [47]. Dry hacking cough is the most common presenting symptom. Radiologically, it appears as a solitary mass or multinodular disease. Inhomogeneity or cavitation of these lesions is common [47]. Rarely, it manifests as a diffuse infiltrate along the lymphatic routes. Cases of primary diffuse infiltrative lung disease due to an Epstein Barr virus associated lymphoproliferative disorder with features simulating Hodgkin lymphoma superimposed on a honeycomb lung background have been reported in patients receiving long-term low-dose methotrexate therapy for rheumatoid arthritis [37]. The differential diagnosis includes tuberculous, fungal infections, metastatic carcinomas, non-Hodgkin lymphomas, granulomatosis with polyangiitis, and Langerhans cell histiocytosis.

Post-Transplantation Lymphoproliferative Disorders

Post-transplant lymphoproliferative disorders (PTLDs) are lymphoid or plasmacytic proliferations that develop as a consequence of immunosuppression in a recipient of a solid organ or stem cell allografts. They constitute a spectrum ranging from usually EBV-driven polyclonal proliferations to EBV-positive or EBV-negative proliferations indistinguishable from a subset of B cell or (less often) T/NK cell lymphomas that occur in immunocompetent individuals [2]. The monomorphic and classic Hodgkin lymphoma types of PTLD are further categorized as in non-immunosuppressed patients, according to the lymphoma they resemble. With the rare exception of EBV-positive MALT lymphomas, indolent B cell lymphomas (e.g., follicular lymphoma and EBV-negative MALT lymphomas in allograft recipients) are designated as they are in the immunocompetent host and not considered a type of PTLD [2]. The clinicopathological features comprehend "Benign plasmacytic hyperplasia and infectious-mononucleosis-like PTLD" which arise in oropharynx or lymph nodes and are polyclonal proliferations with evidence of multiple EBV infectious events but no evidence of oncogene or tumor-suppressor gene alterations; "polymorphic lymphoproliferative disorder" that may be nodal or extranodal and is usually monoclonal; "monomorphic PTL classified according to lymphoma classification (predominantly B cell neoplasms or less often T cell neoplasms) widely disseminated and monoclonal; *Hodgkin lymphoma* and *Hodgkin-like PTLD* (Table 39.2). Incidence varies depending on organ recipient (<1% renal recipients; hepatic and cardiac allografts 1–2%; heart-lung or liver- bowel allografts 5%). Marrow allograft recipients in general have a low risk of PTLD (1%). Risk factors for this disorder include HLA-mismatched donor, T cell depletion of the

Table 39.2 Post-transplant lymphoproliferative disorders. WHO classification [2]

Categories of post-transplant lymphoproliferative disorder (PTLD)
Non-destructive PTLDs
Plasmacytic hyperplasia
Infectious mononucleosis
Florid follicular hyperplasia
Polymorphic PTLD
Monomorphic PTLDs (classify according to lymphoma they resemble)
B-cell neoplasms
Diffuse large B-cell lymphoma
Burkitt lymphoma
Plasma cell myeloma
Plasmacytoma
Other[a]
T-cell neoplasms
Peripheral T-cell lymphoma, NOS
Hepatosplenic T-cell lymphoma
Other
Classic Hodgkin lymphoma PTLD

[a]Indolent small B-cell lymphomas arising in transplant recipients are not included among the PTLDs, with the exception of EBV-positive marginal zone lymphomas

graft, anti–T cell agents, older age of donor, splenectomy, and mismatch in CMV or EBV status between recipient and donor. PTLD frequently present in the first year after transplantation, especially in EBV-seronegative recipients who acquire early post-transplant EBV infection, often from the donor. This pattern of presentation is particularly common in children. However, the median time to PTLD in some studies, especially those of adult populations, is several years, and as many as 15—25% of cases occur >10 years after the transplant. PTLD had an earlier onset in allo-human stem cell transplants than in solid organ recipients (4 vs. 64 months), and appears to be EBV-positive in almost allo-transplants, in contrast to solid organ transplants [48]. Lung involvement is seen in 20% of patients. The majority of PTLD are associated with Epstein–Barr virus infection. The majority of patients have a negative serology for Epstein–Barr virus and Cytomegalovirus before transplantation. The clinical manifestations of PTLD commonly include mononucleosis-type syndrome (fever, fatigue, sore throat), regional lymphoid enlargement, and a disseminated disease [48]. It is very difficult to diagnose without a history of post-transplantation and histology confirmation. Because the symptoms of PTLD are often similar to those of other complications of transplantation, particularly infection and organ rejection, a high index of PTLD suspicion is crucial to preventing a delay in diagnosis. Imaging thorax features are characterized by mediastinal/hilar lymph nodes enlargement, parenchymal consolidative masses (with or without necrotic lower attenuation), ill-defined nodules or nodular consolidations. Pleural effusion is not infrequently detected [49]. These lesions are PET positive.

Diagnosis and Staging

Different invasive procedures are used to obtain diagnostic tissue. Endoscopic bronchial or trans-bronchial biopsy is the most frequently used. When the lesion appears in the central airways, a large biopsy obtained by rigid bronchoscopy is rarely required for obtaining tissue samples for a precise diagnosis [50]. Open-lung biopsy or video-assisted thoracoscopic surgery can be chosen if tissue from endoscopy biopsy is not sufficient. BAL does not allow a complete analysis for an accurate diagnosis, but can be highly improved when molecular and immunophenotypic studies are available [50]. The diagnostic yield of *transbronchial biopsy* is higher when a bronchus sign is present in CT scan or when a transbronchial cryobiopsy is utilized [51]. CT imaging plays an important role in directing to the appropriate biopsy site. Fiberoptic bronchoscope is usually wedged into the most extensively involved pulmonary segments to perform BAL and transbronchial biopsy. Fluoroscopy and *endobronchial radial ultrasonography (EBUS)* are also valuable tools to detect pulmonary masses or consolidation, thus increasing the diagnostic yield of transbronchial biopsy [52]. However, the absence of specific signs in a large quote of those samples necessitates further diagnostic investigations. Almost all patients with suspicious of pulmonary lymphomas undergo a bronchoscopy and transbronchial biopsies, but only in less than half cases (30–50%) it is possible to reach a histological diagnosis without a surgical lung biopsy. *BAL* is an essential tool for the differential diagnosis of sub-acute or chronic alveolar opacities, and seems to be valuable for the positive diagnosis of PPL. Differential diagnosis of PPL includes viral, bacterial or opportunistic pneumonia, radio-induced and drug induced pneumonitis, tuberculosis, sarcoidosis, cryptogenic organizing pneumonia, alveolar proteinosis, exogenous lipoid pneumonia, alveolar hemorrhage, bronchioloalveolar cell cancer, hypersensitivity pneumonitis, eosinophilic pneumonia, vasculitis, and primary or metastatic lung tumors. Differential diagnosis is primary based on clinicoradiological and histological findings, however, BAL is particularly valuable to exclude an alternative diagnosis. In about two-third of patients affected by MALT lymphoma, and in particular in those cases in which the CT scan shows alveolar and/or ground glass opacities, BAL shows lymphocytic alveolitis (lymphocytes >20% total cells), a high percentage of cells expressing a B phenotype and in some cases cytological features consistent with low-grade malignant lymphoma (medium sized lymphoid cells with lymphoplasmocytoid differentiation and irregular nuclear borders). Flow cytometry and immunocytochemical analysis of BAL fluid represent mandatory procedures to document a monotypic expression of surface light chains (indicating a clonal B cell proliferation) [53]. Recent studies report that genotyping investigation on BAL fluid can contribute to the diagnosis of MALT lymphoma with a sensitivity and sensibility higher than flow cytometry or immunocytochemical investigations. In particular immunoglobulin heavy chain gene rearrangement analysis by PCR of alveolar lymphocytes is highly sensitive and specific (97% specificity, 95% negative predictive value) to detect clonal alveolar lymphocytes population in patients with B cell pulmonary NHL. Therefore when a dominant B cell clone is not documented on BAL fluid more invasive investigation could be dismissed [54]. In other lymphomas BAL is less sensitive and specific. Rarely Reed-Sternberg/Hodgkin's cells may ~~also~~ be detected. Morphologic and flow cytometry analysis of *trans-parietal fine needle aspiration/biopsy* samples obtained under fluoroscopic, CT scan or echographic guide, may be diagnostic in a minority of cases but this procedure is of value in the diagnosis of post-transplant lymphoproliferative disorders.

When a pleural effusion is present *medical thoracoscopy* may be also diagnostic. When these less invasive procedures fail the definitive diagnosis rely on histological examination

of surgical samples (*video-assisted thoracoscopy or open lung thoracotomy).*

Immunohistochemical analysis is mandatory in diagnosing all types of pulmonary lymphomas. The neoplastic lymphocytes are characterized in fact by distinct molecular profiles that can be easily demonstrated on routine paraffin sections, and can be utilized to distinguish pulmonary MALT lymphoma from reactive processes and also other lymphomas. The analysis of immunoglobulin light chains (kappa and lambda) can occasionally provide evidence of clonal expansion, especially in cases with increased secretory differentiation. Neoplastic marginal-zone cells can be characterized by either positive markers (e.g., the abnormally expressed CD43 antigen) or by the absence of a variety of relevant markers, including those expressed by follicular lymphoma (CD10+, Bcl6+), mantle cell lymphoma (cyclin D1 nuclear expression), chronic lymphocytic leukemia (CD5+, CD23+) [2].

Flow cytometry can provide relevant information by revealing the presence of clonal B cell populations characterized by immunoglobulin light chain restriction, as well as illustrating an antigenic profile compatible with the diagnosis.

PCR molecular genetic analysis can provide information regarding the presence of clonal lymphocyte population by investigating rearrangements of either immunoglobulin or T cell receptor genes. This analysis can be performed, due to its extraordinary sensitivity, on very small amount of tissue, but the possible occurrence of false-negative and false-positive results must be taken into account.

Staging procedures to evaluate the extension of the disease will include a complete physical examination of the patient, laboratory tests such as beta2 microglobulinemia, LDH, lymphocytic total count, lymphocyte subsets analysis, serology for HIV, Cytomegalovirus, and Epstein–Barr viruses infection, thoracic, abdominal and pelvic CT scan, bone marrow biopsy. CT-PET provides morphologic and metabolic information increasing the diagnostic accuracy in the initial staging, and in the subsequent follow-up of lymphomas, although in low-grade lymphomas PET might result negative or vice versa it could be positive in lung inflammatory lesions (drug related lung injury, infections, etc.). Different studies have documented that an extensive staging in patients with non-gastrointestinal MALT lymphoma might be useful as a multi-organ involvement occurs at the beginning in 30% of patients [55] with dissemination to lymph nodes (18%) bone marrow (7%) and for lung a simultaneous specific gastric localization o gastric relapse in 14% of patients [56].

Treatment

The knowledge of biology and pathogenetic mechanisms leading to lymphoid neoplastic proliferation is greatly expanded in recent years [57]. This improvement of comprehension has been mirrored in a more detailed classification [2] and in more effective treatments. For localized indolent low-grade lymphomas (MALT lymphoma) a conservative approach, mainly in elderly, is advised. Surgery or radiotherapy may be indicated when only a nodule is detected. Treatment with chemotherapy and rituximab is however indicated in the large majority of cases [58]. Traditional chemotherapic regimens are reported in Table 39.3. New drugs or the different use of already known drugs [immune check point inhibitors such as pembrolizumab and nivolumab, tiroxine kinase inhibitors such as ibrutinib and acalabrutinib, the antibody-drug conjugates polatuzumab vedotin and pinatuzumab vedotin, duvelisib, a first-in-class oral dual inhibitor of phosphoinositide 3-kinase-δ,-γ, PI3K-inhibitors such as copanlisib, brentuximab vedotin, and bendamustine], radioimmunotherapy and more experience in allogeneic stem cells transplant represent consolidated treatment approaches in more aggressive tumors [59]. In PTLD the modulation of immunosuppression is also an important therapeutic step.

Table 39.3 Chemotherapeutic regimens and doses

Regimen	Dose	Frequency
R-CHOP		Every 21 days
Cyclophosphamide	750 mg/m^2 IV	
Doxorubicin	50 mg/m^2 IV	
Vincristine	1.4 mg/m^2 IV	
Prednisone, fixed dose	100 mg daily PO	
Rituximab	375 mg/m^2 IV	
(Rituximab, Etoposide phosphate, Prednisone, Vincristine sulphate, Cyclophosphamide, and Doxorubicin hydrochloride) R-EPOCH[a]		Every 21 days
Etoposide	50 mg/m^2/d IV	
Doxorubicin	10 mg/m^2/d IV	
Vincristine	0.4 mg/m^2/d IV	
Cyclophosphamide	750 mg/m^2 IV	
Prednisone	60 mg/m^2 bid PO	
Rituximab	375 mg/m^2 IV	
R-CVP		Every 21 days
Cyclophosphamide	1000 mg/m^2 IV	
Vincristine	1.4 mg/m^2 IV	
Prednisone, fixed dose	100 mg daily PO	
Rituximab	375 mg/m^2 IV	
FCR		Every 28 days
Fludarabine	25 mg/m^2/d IV	
Cyclophosphamide	250 mg/m^2/d IV	
Rituximab	375 mg/m^2	
B-R		Every 28 days
Bendamustine	90 mg/m^2/d IV	
Rituximab	375 mg/m^2 IV	

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[a]R-EPOCH (Rituximab, Etoposide phosphate, Prednisone, Vincristine sulphate,Cyclophosphamide, and Doxorubicin hydrochloride)

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Pulmonary Manifestations of Hematological Malignancies

40

Focus on Pulmonary Chronic Graft-Versus-Host Disease

Laïla Samy, Louise Bondeelle, and Anne Bergeron

Introduction

Hematological malignancies, such as lymphoma or leukemia, can lead to various pulmonary complications related to the disease itself or its treatment. Although there has been significant advancement in the management of these patients over the past two decades, more than half will develop pulmonary complications. Among those cases, one-quarter will be of noninfectious etiology [1]. Hematopoietic stem cell transplantation (HSCT) has become a mainstay of treatment in various hematological diseases, including aplastic anemia, high-risk acute leukemia, myelodysplastic syndrome, and myelofibrosis. Despite major advances in HSCT, patients must often manage multiple infectious and noninfectious complications, such as graft-versus-host disease (GVHD), which can involve the lungs in a variety of ways. Thus, pulmonologists should be aware of the potential pulmonary complications that can occur and their treatment. In this chapter, we briefly review nontransplant- and transplant-related noninfectious pulmonary complications of hematological malignancies with a particular focus on late noninfectious pulmonary complications occurring after allogeneic HSCT, including bronchiolitis obliterans syndrome.

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Noninfectious Pulmonary Complications of Hematological Malignancies: Non-HSCT Related

When evaluating a patient with a hematological malignancy, pulmonary involvement can be approached according to its pathophysiological process as follows: direct invasion from the malignancy and indirect reactions that can be immunological or treatment related (Table 40.1). First, direct invasion will depend on the underlying malignancy. Lymphoma, for example, can arise in the lung parenchyma. When presenting as a mediastinal mass, compression of airways or neurovascular structures, such as the vena cava, can occur and should be promptly recognized [2]. Chronic lymphocytic leukemia typically infiltrates the lung parenchyma and airways in 26–41% of cases and can be identified via monoclonal proliferation in lymphocytic bronchoalveolar lavage fluid or lung or endobronchial biopsy [3–5]. Plasmacytoma in multiple myeloma can manifest as a lung mass and be mistaken for primary lung cancer [6]. Second, there can be a variety of malignancy-related indirect manifestations [7, 8]. For example, acquired pulmonary alveolar proteinosis, characterized by a crazy paving pattern on chest CT and positive PAS staining on bronchoalveolar lavage, has been associated with various hematological malignancies, especially myeloid disorders [8–10]. Third, treatment-related pulmonary complications can occur from direct parenchymal toxicity via drugs or radiation or indirectly from cardiogenic or noncardiogenic pulmonary edema. Many drugs used to treat hematological diseases can cause lung damage. Certain drugs have been associated with different lung involvement, such as pulmonary fibrosis or diffuse alveolar hemorrhage. *Pneumotox.com* is a useful French website that collects data on drug-induced lung diseases. Bleomycin, commonly used in Hodgkin's lymphoma, is a classic example of a drug that can induce lung toxicity. It can induce severe interstitial lung disease that can manifest in various manners from diffuse alveolar damage to interstitial fibrosis [11–13]. The most frequent drugs associated with lung toxicity are listed in

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Table 40.1 Nonspecific noninfectious pulmonary complications reported in hematological malignancies

Hematological malignancies	Pulmonary complications
Acute leukemia	Organizing pneumonia Sweet syndrome Alveolar proteinosis
Lymphoma/chronic lymphocytic leukemia	Sarcoid-like granulomatosis Langerhans histiocytosis Lung cancer
Myeloma	Amyloidosis Venous thromboembolism
Waldenstöm macroglobulinemia	Intra-alveolar hemorrhage Pulmonary edema Amyloidosis Lung cancer
Myelodysplastic/ myeloproliferative disorders	Extramedullary hematopoiesis Sweet syndrome Diffuse infiltrative lung disease in the context of autoimmune disorders Eosinophilic pneumonia Alveolar proteinosis Organizing pneumonia Pulmonary hypertension

Table 40.2 Main drugs used for the management of patients with hematological malignancies known to induce lung toxicities

Antibiotic chemotherapeutic agents	Bleomycin, Mitomycin C
Alkylating agents	Busulfan, cyclophosphamide, chlorambucil, melphalan, ifosfamide, procarbazine
Antimetabolites	Methotrexate, 6-mercaptopurine, cytosine arabinoside, fludarabine
Nitrosamines	Bischloroethyl nitrosourea (BCNU), chloroethyl cyclohexyl nitrosourea (CCNU), methyl-CCNU
Tubulin-acting agents	Vinblastine, etoposide
Other chemotherapeutic agents	All-trans retinoic-acid (ATRA), Imatinib mesylate, dasatinib, bortezomib
Immune checkpoint inhibitors	Ipilimumab, nivolumab, pembrolizumab, atezolizumab
Molecular targeted agents	Ibrutinib, idelalisib, ruxolitinib, venetoclax
Immunomodulatory agents	Interferons, anti-interleukin-2, TNF alpha inhibitors
mTOR inhibitors	Sirolimus, temsirolimus, everolimus
Monoclonal antibodies	Brentuximab, rituximab, gemtuzumab ozogamicin, alemtuzumab
Miscellaneous	Blood transfusion, GM-CSF, G-CSF

Table 40.2. Pulmonary cardiogenic or noncardiogenic edema is frequent and can be due to hyperhydration required before chemotherapy, cardiotoxicity secondary to the use of anthracyclines or increased capillary permeability from drugs, such as all-trans-retinoid acid, cytosine arabinoside, imatinib or dasatinib [14]. Hence, once an infectious process has been excluded, the clinical presentation, CT scan imaging, and very often bronchoscopic examination (BAL +/− biopsies) are all crucial elements in identifying the correct diagnosis.

HSCT-Related Noninfectious Pulmonary Complications

Hematopoietic stem cell transplantation (HSCT) has evolved significantly over the past two decades, now becoming a mainstay of treatment in many malignant and benign hematological disorders and in various congenital diseases, such as congenital dyskeratosis. It is now even being explored in autoimmune diseases, such as systemic sclerosis. There have been major advances in HSCT with regard to donor selection, conditioning and immunosuppressive regimens, and infectious prophylaxis. These factors have contributed to increased survival following HSCT and, by doing so, uncovered various pulmonary complications [15]. The goal of HSCT is to replace the patient's bone marrow with healthy stem cells. First, the patient receives a conditioning regimen that can be myeloablative or nonmyeloablative. This aggressive chemotherapy induces moderate cytopenia to complete aplasia by destroying the patient's stem cell production to the default of being unable to target diseased cells. Subsequently, donor stem cells are transplanted. They contain both immature CD34+ cells, which engraft in the receiver's bone marrow and resume hematopoiesis, and donor T cells, which attack residual leukemic cells located in the patient's tissues. This concept is called the "graft vs. leukemia/lymphoma" effect (GVL) and occurs at the expense of "graft vs host disease" (GVHD). Hence, depending on the reason for HSCT, the hematologist will juggle the immunosuppressive regimen to balance the GVL effect with GVHD. The most common and fatal complications of HSCT are infectious, but here, we focus on noninfectious pulmonary complications, which can be divided between early and late complications. A cutoff of 100 days post-HSCT is used to differentiate both. Currently, clinical presentation takes precedence to the timing of onset since acute and chronic GVHD manifestations, especially skin and gastrointestinal manifestations, have been found to occur at any time following transplantation. However, this finding is less true for pulmonary complications, for which a time-based approach remains accurate [16].

Early Onset Pulmonary Complications Following HSCT

Idiopathic pneumonia syndrome (IPS) is used as an umbrella term to group some of the early complications of HSCT. It is comprised of a very heterogeneous group of

diseases that primarily involve the pulmonary parenchyma, such as organizing pneumonia (OP), acute interstitial pneumonitis (AIP), and acute respiratory distress syndrome (ARDS), or the vascular endothelium, including peri-engraftment respiratory distress syndrome (PERDS), noncardiogenic capillary leak syndrome, and diffuse alveolar hemorrhage (DAH) [17–19]. Other early complications of HSCT include secondary pulmonary alveolar proteinosis (PAP) and drug toxicity [10].

IPS is defined as widespread alveolar injury as evidenced by multilobar airspace disease, without evidence of lower respiratory tract infection, cardiac dysfunction, acute renal failure or iatrogenic fluid overload despite thorough evaluation. The reported incidence rate of IPS ranges from 5% to 10% depending on the type of transplant (autologous or allogeneic) and the conditioning regimen used [17, 20, 21]. Retrospective data have identified various risk factors for IPS, including a myeloablative conditioning regimen, especially if total body irradiation is performed, high-grade acute GVHD, older recipient age, and acute leukemia or myelodysplastic syndrome, as reasons for HSCT [22]. IPS occurs at a median of 21 days, usually within the first 3–7 weeks post-HSCT. An overall mortality rate from IPS as high as 60% has been reported and rises to 100% when mechanical ventilation must be initiated [17, 21]. Currently, the mainstay of treatment remains high-dose systemic corticosteroids, along with usual supportive care [19]. Several drugs have been studied over the years in animal models, but none have found their way into clinical practice at this time. TNF-alpha inhibitors have yielded encouraging results when added to corticosteroids in small retrospective and prospective trials [23–25]. Unfortunately, the first randomized trial of etanercept combined with corticosteroids versus placebo ended prematurely due to slow accrual [26]. Among the 34 randomized patients, there were no differences in treatment response at 28 days. Other agents currently investigated include keratinocyte growth factor, defibrotide, macrolides, N-acetylcysteine, and Th17-suppressing molecules. In light of the heterogeneous nature of IPS, the better characterization of lung involvement post-HSCT will allow for more disease-specific treatment research.

PERDS is a well-known early HSCT complication that typically occurs within 5 days of engraftment. PERDS occurs due to massive proinflammatory cytokine release following engraftment, resulting in noncardiogenic pulmonary edema from capillary leakage, fever, and rash. PERDS can also involve the liver, kidneys, skin, or gut [19]. Early recognition of PERDS is essential since a good prognosis can be achieved with glucocorticoids. Although PERDS has a favorable initial response to steroids, it has recently been associated with lower overall 2-year survival post-HSCT [27].

Late-Onset Pulmonary Complications

Late-onset noninfectious pulmonary complications (LONIPCs) represent a heterogeneous group of conditions comprising bronchiolitis obliterans syndrome (BOS); interstitial lung diseases (ILDs), including organizing pneumonia, lymphoid interstitial pneumonia, eosinophilic pneumonia, diffuse alveolar damage, acute fibrinous organizing pneumonia, nonspecific interstitial pneumonia and pleuroparenchymal fibroelastosis; vascular diseases (microangiopathy, thromboembolic disease, pulmonary hypertension); and pleural effusion [15]. Many of these diseases have similar presentations to their idiopathic forms [28]. Hence, when evaluating a patient with LONIPC, using a systematic approach similar to that used in any patient with interstitial lung disease (ILD) can be useful. According to a recent prospective observational single-center study called ALLOPULM, which studied more than 200 patients who underwent allogeneic HSCT, LONIPC has a cumulative incidence of 19.8% at 36 months following transplantation [29]. In the same study, the risk factors identified included history of chest irradiation prior to HSCT, lower respiratory tract infection within the first 100 days following HSCT, and low mean forced expiratory flow (MFEF25–75%). The occurrence of LONIPC was associated with a doubled risk of death post-HSCT, underscoring the importance of prompt diagnosis and treatment. The most frequent LONIPC diagnosed was BOS, followed by ILD.

Bronchiolitis Obliterans (BO)

BO is the only condition that has been clearly associated with chronic GVHD. It is also the main LONIPC diagnosed following HSCT [29]. BO usually occurs from 6 months to 2 years post-HSCT but can seldom occur earlier or later [30]. The reported incidence of BO is difficult to assess due to disparities in the diagnostic criteria used among studies. According to several retrospective data, it ranged from 2% to 26% [20, 30–32]. The incidence increases to 14% in the subpopulation of patients who develop extrathoracic chronic GVHD [33]. More recently, ALLOPULM reported a cumulative incidence of BOS at 36 months of 10.7% [29].

Pathophysiology

The pathophysiology of BO is still not fully understood. Given its correlation with chronic GVHD, it is believed to be related to immune-mediated attack of airway epithelial cells by donor T lymphocytes, as well as B cell stimulation, autoantibody synthesis, and systemic fibrosis [18]. When examining lung biopsies from patients diagnosed with BO, two different patterns have been observed: lymphocytic and constrictive bronchiolitis obliterans. Lymphocytic infiltration is

located in the bronchiolar wall with a variable degree of inflammation and damage, whereas the constrictive pattern involves fibrous tissue deposition within the submucosa of the bronchium with or without minimal chronic inflammation [34]. It is thought that the lymphocytic infiltrate represents the earlier stage of BO, leading to definitive cicatricial obliteration of the airway lumen. However, the clinical presentation appears to be similar in both histologic subtypes, although the lymphocytic pattern tends to be more treatment responsive. A recent study examining 61 lung biopsies in patients with LONIPC showed a variety of histological patterns that have not been previously described, such as narrow fibrous and cellular bronchiolitis or bronchiolectasis [35]. Although some patients had a diagnosis of BO, the authors did not correlate the histopathology findings with the clinical diagnosis. However, this study suggested that BO might be associated with patterns other than the two histologic subtypes described above.

Diagnosis

A definite diagnosis of BO is made when there is histological evidence of bronchiolar wall thickening, inflammatory fibrosis and narrowing of the airway lumen [36] (Fig. 40.1b). That said, obtaining a lung biopsy in HSCT patients is challenging given their overall frailty [37]. Hence, in 2014, the NIH updated the previously established diagnostic criteria based on pulmonary function testing to facilitate diagnosis (Table 40.3) [38]. Based on these criteria, the term "bronchiolitis obliterans syndrome" (BOS) appeared to dissociate it from biopsy-proven BO. In the context of extrathoracic chronic GVHD in one separate organ system, a diagnosis of BOS can be made if there is evidence of airway obstruction (FEV1/FVC <0.7 or < fifth percentile), FEV1 < 75% of predicted with ≥10% decline over less than 2 years not correcting greater than 75% predicted with albuterol, absence of documented infection and one of the two typical changes on CT scan (air trapping, airway thickening or bronchiectasis) or evidence of air trapping on PFT (RV > 120% or predicted and elevated RV/TLC). That said, it is well known that sig-

Table 40.3 BOS diagnosis criteria NIH 2014

In the presence of a distinctive manifestation of chronic GVHD, the clinical diagnosis of BOS is sufficient to establish the diagnosis of chronic GVHD when all of the following criteria are met:
1 FEV1/vital capacity <0.7 or < the fifth percentile of predicted
(a) Vital capacity includes forced vital capacity or slow vital capacity, whichever is greater
(b) The fifth percentile of predicted is the lower limit of the 90% confidence interval
(c) For pediatric or elderly patients, use the lower limits of normal, defined according to National Health and nutrition examination survey III calculations
2 FEV1 < 75% of predicted with ≥10% decline over less than 2 years. FEV1 should not correct to >75% of predicted with albuterol, and the absolute decline for the corrected values should still remain at ≥10% over 2 years
3 Absence of infection in the respiratory tract, documented with investigations directed by clinical symptoms, such as chest radiographs, computed tomographic (CT) scans, or microbiologic cultures (sinus aspiration, upper respiratory tract viral screen, sputum culture, and bronchoalveolar lavage)
4 One of the two supporting features of BOS:
(a) Evidence of air trapping by expiratory CT or small airway thickening or bronchiectasis by high-resolution chest CT or
(b) Evidence of air trapping by PFTs: Residual volume > 120% of predicted or residual volume/total lung capacity elevated outside the 90% confidence interval

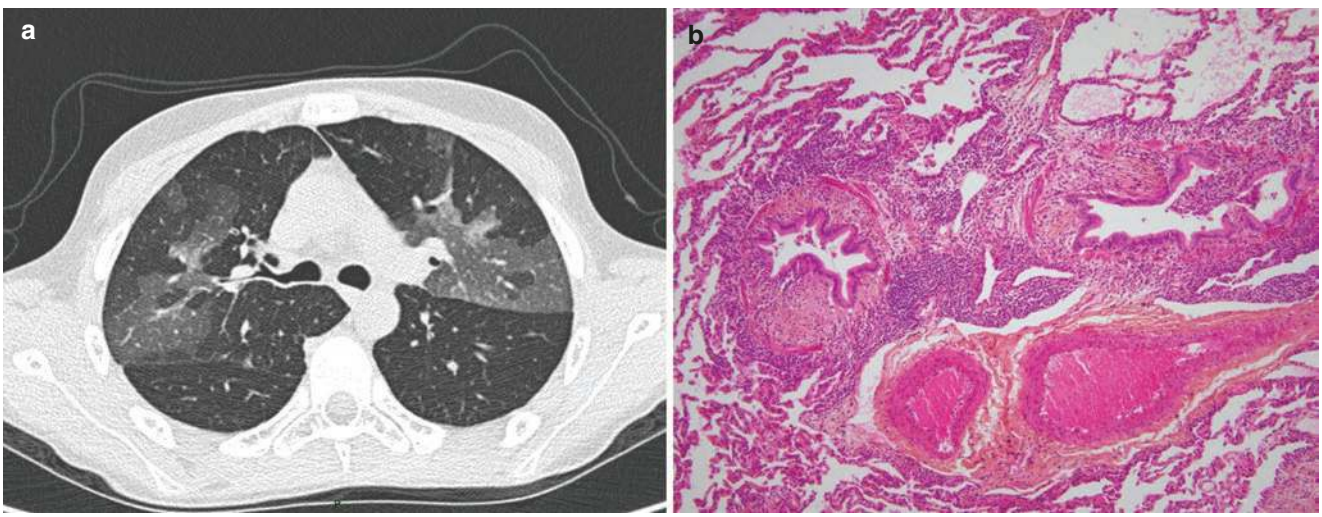

Fig. 40.1 Lung computed tomography (CT) scan (**a**) and lung biopsy (**b**) from a patient who was diagnosed with bronchiolitis obliterans 12 months after an allogeneic hematopoietic stem cell transplantation. The CT scan shows a mosaic pattern (**a**). The histological analysis shows a bronchiolar wall thickened by inflammatory fibrosis located between the epithelium and the smooth muscle. The airway lumen is narrowed (HES ×100) (**b**)

nificant air trapping can lead to a relative decrease in FVC, which can translate into a normal FEV1/FVC ratio despite significant airflow obstruction [39, 40]. Given the predominance of small airway involvement in BO, patients develop gas trapping early in the disease process with similar reductions in FEV1 and FVC on initial spirometry, leading to a normal FEV1/FVC ratio. In fact, in the ALLOPULM cohort described above, the patients had variable lung function. Among the 22 patients diagnosed with BOS, 64% had a normal FEV1/FVC ratio at diagnosis, but 91% developed a low FEV1/FVC ratio, indicating airflow obstruction at least once over the 36-month follow-up [29]. Consequently, the NIH criteria, which mandate a ratio of FEV1/FVC <0.7 and at the same time recognize air trapping as a diagnostic criterion, seem inappropriate. In the setting of diagnosed chronic GVHD in one other organ, the presence of lung GVHD can be confirmed solely on the basis of pulmonary function test criteria. However, if there is no other systemic manifestation of chronic GVHD, a lung biopsy is required to ascertain the diagnosis of BO according to the NIH criteria, although it is very rarely performed in clinical practice. Clinically, patients with BOS can present with nonspecific symptoms, such as progressive dyspnea on exertion, dry cough or wheezing, but they can also be asymptomatic. Computed tomography (CT) of the chest often illustrates hyperinflation with or without mosaic attenuation, bronchiectasis, bronchial thickening, and centrilobular nodules (Fig. 40.1a). Risk factors for BOS that have been identified in several retrospective studies include older age of recipient, acute GVHD, busulfan-based conditioning regimen, stem cell source, degree of HLA incompatibility, presence of gastroesophageal reflux, gammaglobulin levels, type of GVHD prophylaxis, underlying blood disorder, and tobacco use [15, 30, 32]. In ALLOPULM, early specific factors were identified as predictive of BOS. The most significant ones were the use of peripheral blood stem cells; bronchial abnormalities on computed tomography (CT) at 100 days post-HSCT, such as bronchial thickening and centrilobular nodules; the occurrence of lower respiratory tract infection within the first 100 days following HSCT; and a decrease of ≥10% in FEV1 between pretransplant and day 100 posttransplant pulmonary function testing [29]. The natural history of BOS is unclear. Some studies have suggested that there is a relative stabilization in FEV1 following the initial decline [41]. Additionally, the occurrence of viral lower respiratory tract infections (LRTIs) has been identified as a trigger that leads to an abrupt decline in lung function [42]. A recent randomized trial of patients with BOS found an improvement in FEV1 of 200 mL and 12% in 25% of patients in the placebo group [43]. This spontaneous improvement could be related to the natural history of BOS or expected recovery following an LRTI. BOS has been associated with a 1.6-fold increase in mortality after diagnosis [30, 44, 45]. This rate worsens if BOS occurs within the first year post-HSCT [32, 44]. Thus, performing systematic PFT following HSCT can help to identify those at increased risk of BOS and allow for early treatment initiation. Similarly, using a handheld spirometer at home was attempted for early recognition of FEV1 decline. Although the measurements were reliable, the poor compliance of patients remained a major obstacle [46].

Management of BOS

Several treatments for BOS have been investigated, but data interpretation of these studies is challenging given their retrospective nature and the poor measurement of treatment response [47]. In fact, some studies have measured general GVHD as an endpoint or considered a stable FEV1 as a good response, although this choice probably reflects the natural history of BOS. Given that BOS often occurs with concomitant extrathoracic chronic GVHD, the first step in management should be to optimize the immunosuppressive regimen, especially if respiratory decline occurs during tapering of these drugs. Systemic steroids can be tried, but their efficacy in BO has not been clearly established at the expense of increased mortality from infectious complications [48]. Azithromycin alone was one of the first therapeutic agents studied in a randomized fashion for the treatment of BOS. Unfortunately, it did not show any significant difference in absolute FEV1 at 4 months and even a tendency toward a decreased percentage of predicted FEV1 [49]. However, combining fluticasone, azithromycin, and montelukast (FAM) appeared more promising. In fact, a prospective, nonrandomized, open-label trial demonstrated a steroid-sparing effect with stabilization of FEV1 [50]. Although this approach has not been very successful in improving lung function, it is currently recommended by experts in North America despite the more significant benefit observed by combining inhaled budesonide/formoterol [48]. Indeed, a randomized, controlled trial of 32 highly selected patients with BOS following HSCT showed a significant improvement in FEV1 of 260 mL after 1 month of inhaled budesonide/formoterol, compared with 5 mL in the placebo group [43]. In an attempt to decrease BOS onset, azithromycin alone, initiated at the time of transplant, was studied in a randomized fashion. Surprisingly, the study ended prematurely due to an increased disease relapse rate in the treatment group [51]. Following this outcome, concerns arose regarding whether azithromycin initiated at the time of BOS diagnosis had similar adverse effects. Consequently, a recent large, retrospective trial showed an increased risk of solid malignancy but not hematological relapse in patients with BOS receiving azithromycin [52]. In our center, we have been more reluctant to initiate azithromycin in this patient population given the minimal benefit and potentially serious adverse events. In practice, we initiated budesonide formoterol at doses of 800 mcg and 24 mcg twice per day, based

on a previously discussed randomized trial [43]. Once there has been improvement or stabilization of the disease, the dose can be slowly decreased to a maintenance dose of 400 mcg of budesonide twice per day. Lung transplantation should be considered in some cases in which the severity of airflow obstruction is debilitating and treatment refractory. For instance, a pan-European series of lung transplant recipients following HSCT showed comparable outcomes to patients with other end-stage diseases [53–55].

Post-HSCT Organizing Pneumonia

Organizing pneumonia (OP) is characterized by intra-alveolar connective tissue plugs of granulation tissue consisting of intermixed myofibroblasts and connective tissue that fill the lumen of the distal airways and extend into the alveolar ducts in association with chronic interstitial inflammation [56] (Fig. 40.2b). OP can be idiopathic (cryptogenic organizing pneumonia) or secondary to various diseases, including postinfection diseases related to connective tissue disease, drug- or radiation-induced diseases, hematological malignancies, lung transplantation or allogeneic HSCT. OP is a well-recognized entity following HSCT. In fact, a strong association has been described between the occurrence of OP and previous signs of acute or chronic GVHD [57]. In 2003, Freudenberger et al. identified a median time of 108 days post-HSCT of OP onset [57]. However, there seemed to be two peaks of OP onset: one within the first 100 days post-HSCT and another 2–3 years afterwards. In the earlier form, constituting 22% of cases, the respiratory symptoms followed immunosuppressive treatment tapering [57]. The clinical presentation is similar to COP, mimicking nonresolving pneumonia with fever, cough, and dyspnea. Radiologically, OP can present in a similar way to COP with dense alveolar infiltrates. However, when related to HSCT, OP tends to present with an interstitial bronchovascular pattern that does not wax and wane, like COP typically does [57–60] (Fig. 40.2a). On PFT, a restrictive pattern can be found in 43% of patients, but an obstructive defect is seldom observed. The treatment of OP includes early initiation of high-dose corticosteroids, with a generally good response with resolution or stabilization. However, steroids should be tapered very slowly to decrease relapse risk [57, 61, 62].

Other Late-Onset NonInfectious Pulmonary Complications (LONIPCs)

As mentioned earlier, the approach to ILD should be the same as for a non-HSCT recipient. Indeed, all idiopathic interstitial pneumonia (IIP) patterns described in the international multidisciplinary classification have been observed following HSCT apart from usual interstitial pneumonia [28, 61]. These ILDs can be drug induced but can also occur solely from HSCT itself or present in the setting of an autoimmune disorder [7]. Recently, a retrospective study from a single center reported 15 cases of pleuroparenchymal fibroelastosis, of which 7 had histological confirmation [63]. The heterogeneity and rarity of ILD in the setting of HSCT explain the paucity of evidence. In a retrospective study combining all cases of ILD (including organizing pneumonia), diagnosis occurred at a median time of 11.3 months following allogeneic HSCT [61]. Symptoms are nonspecific, including cough, dyspnea, and fever. A thorough examination should be performed seeking signs of connective tissue disease. Bronchoalveolar lavage is warranted to exclude an infectious process. Alveolar lymphocytosis (≥15%) has been observed in 67% of cases but could be missing. Pulmonary function tests are more often restrictive, but concomitant

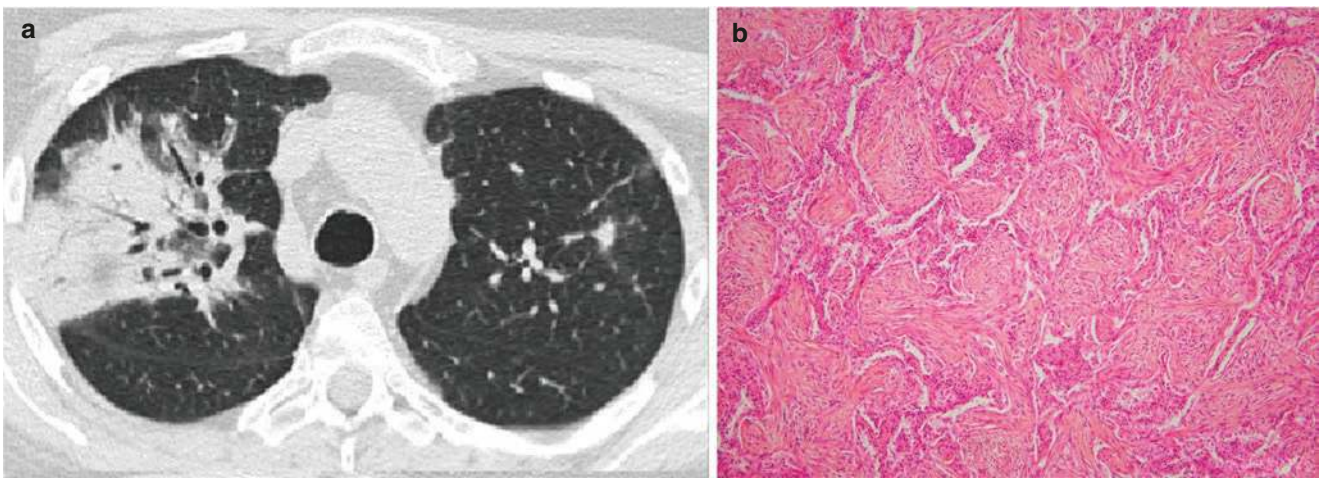

Fig. 40.2 Lung computed tomography (CT) scan (**a**) and lung biopsy (**b**) from a patient who was diagnosed with organizing pneumonia 8 months after an allogeneic hematopoietic stem cell transplantation. The CT scan shows an alveolar condensation (**a**). On lung biopsy, all the alveolar spaces are filled by fibroblast plugs (HES ×100) (**b**)

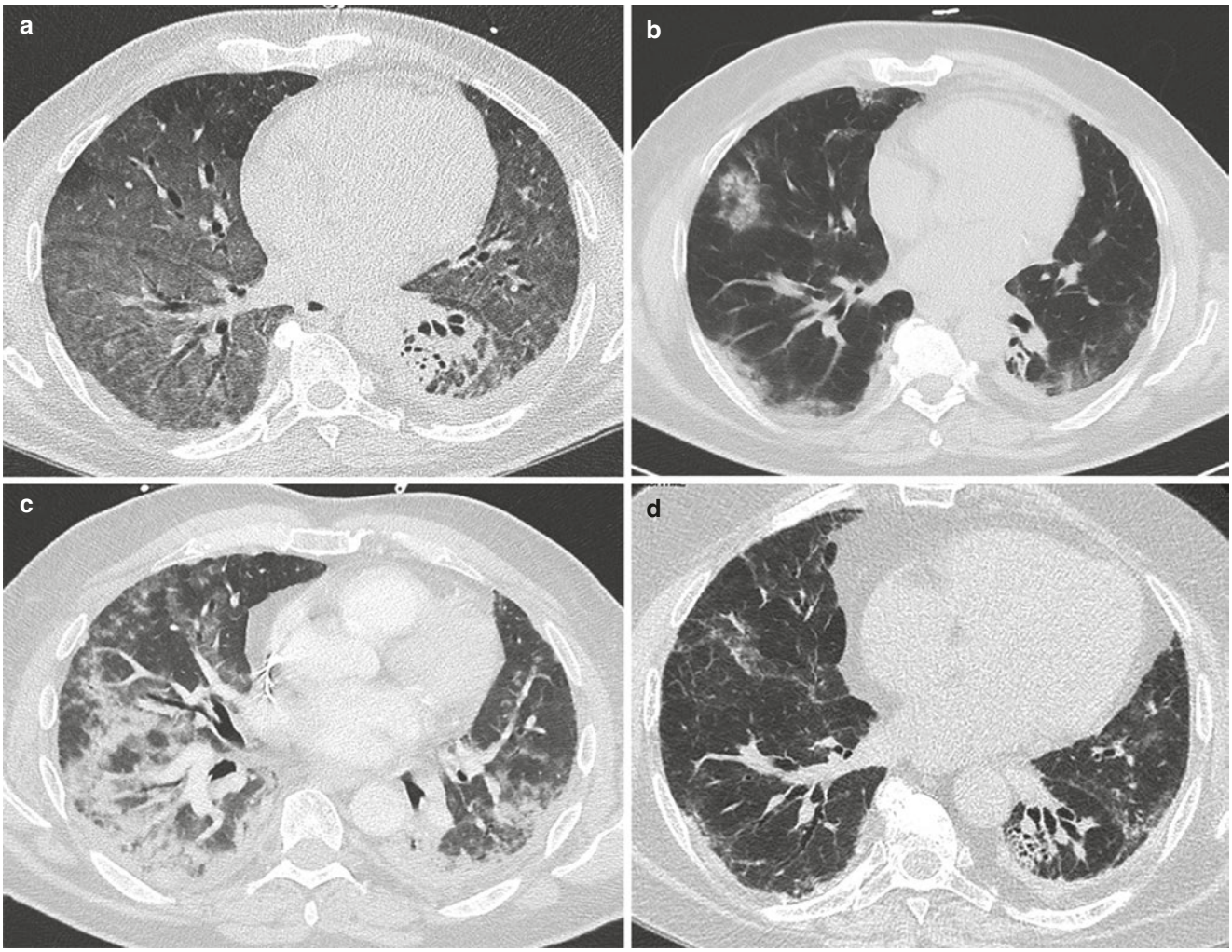

Fig. 40.3 Lung computed tomography (CT) scans from a patient who was diagnosed with an interstitial lung disease (ILD) 12 months after an allogeneic hematopoietic stem cell transplantation. At this time, he had no active signs of chronic graft-versus-host disease (GVHD) and was receiving 10 mg prednisone and mycophenolate mofetil for GVHD prophylaxis. The CT scan initially showed diffuse ground glass opacities (**a**). Bronchoalveolar lavage found a lymphocytic alveolitis and no pathogens. Doses of prednisone were increased and the patient improved. However, over a 2-year period, the ILD relapsed when prednisone was stopped despite sirolimus as a sparing agent, requiring reintroduction of prednisone (**b**, **c**). At the last follow-up, while taking 10 mg prednisone, the CT scan was improved but showed signs of pulmonary fibrosis with traction bronchiectasis and distorted fissures (**d**). Pulmonary function testing showed restrictive ventilatory defect

obstruction can be seen. The treatment approach should depend on the ILD pattern, knowing that fibrosis tends to be less steroid responsive. The prognosis is usually poor and worsens with the extent of the fibrosis. For instance, PPFE has a reported mortality rate of 47% with poor outcomes following lung transplant [63]. Diagnosis should be made promptly and suspected when facing a case of atypical, subacute or unresolving pneumonia (Fig. 40.3).

Conclusion

There can be various pulmonary complications related to hematologic diseases. It is important to have a systematic approach and entertain each diagnostic hypothesis thoroughly when faced with these patients. Chronic GVHD in the setting of HSCT has been associated with bronchiolitis obliterans syndrome, but other pulmonary compli-

cations following HSCT can arise, such as organizing pneumonia, idiopathic pneumonia syndrome, and other interstitial lung diseases.

Clinical Vignette

A 22-year-old woman underwent geno-identical peripheral stem cell transplantation in June 2018 after nonmyeloablative conditioning for refractory Hodgkin's lymphoma. She had previously received multiple lines of chemotherapy and autologous hematopoietic stem cell transplantation, as well as mediastinal and left supraclavicular irradiation. In February 2019, she was hospitalized with influenza A, which was treated with oseltamivir. In March 2019, she developed neuromuscular graft-versus-host disease, for which corticosteroid therapy at 1 mg/kg/day prednisone combined with cyclosporine was started. Cyclosporine was replaced by mycophenolate mofetil in December 2019 due to a lack of significant improvement in neuromuscular GVHD. In September 2019, she presented with a new episode of parainfluenza 3 respiratory infection. GVHD initially limited the patient's activities, and she started to feel short of breath in July 2019. While lung function was normal in March 2019 with an FEV1 of 101% of the predicted value, the May 2019 and September 2019 PFTs showed a major FEV1 decline with a new-onset severe obstructive ventilatory defect (Fig. 40.4a). A thorough infectious workup did not identify a respiratory pathogen. While the pretransplant thoracic CT scan was normal (Fig. 40.4b), the CT scan showed a mosaic pattern (Fig. 40.4c). The diagnosis of bronchiolitis obliterans syndrome was made. At this time, she was receiving prednisone 15 mg/day and mycophenolate mofetil, which were then replaced by ruxolitinib and formoterol/budesonide. Extrathoracic cGVHD was under control. In July 2020, noninvasive ventilation and long-term oxygen therapy were introduced. She is currently awaiting a lung transplant.

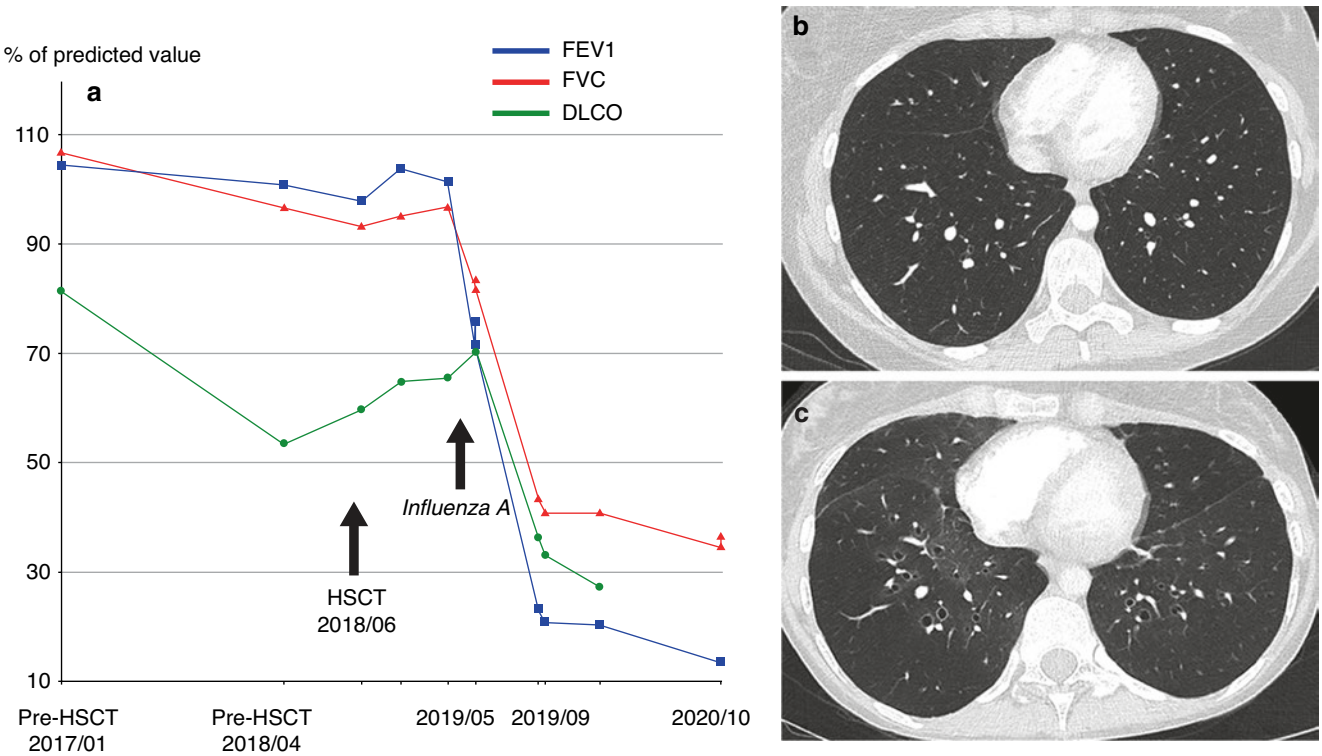

Fig. 40.4. Lung function trajectory during the follow-up (**a**). The pretransplant chest CT scan was normal (**b**, **c**), while the CT scan at the bronchiolitis obliterans syndrome diagnosis showed a mosaic pattern

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Pulmonary Hypertension in Orphan Lung Diseases

41

David Montani, Pierre Thoré, Étienne-Marie Jutant, and Marc Humbert

Introduction

In the ERS/ESC guidelines for the diagnosis and the treatment of pulmonary hypertension, pulmonary hypertension (PH) has been defined as an increase in mean pulmonary arterial pressure (mPAP) >20 mmHg at rest as assessed by right heart catheterization (RHC) [1]. This new hemodynamic definition was proposed during the 6th world symposium on pulmonary hypertension (WSPH), bringing back the threshold to consider mPAP as pathologic from ≥25 mmHg (historical hemodynamic definition of PH) to >20 mmHg, corresponding to the mean of mPAP in the general population (14 mmHg) plus two standard deviations (3.3 mmHg) as the upper limit of normal [2]. Precapillary PH, defined by normal pulmonary arterial wedge pressure (PAWP) and increased pulmonary vascular resistances (PVR) ≥2 Wood Units (WU), includes different subgroups of PH, including pulmonary arterial hypertension (PAH) (which itself has orphan disease status), PH due to chronic lung diseases, chronic thromboembolic pulmonary hypertension and PH with unclear and/or multifactorial mechanisms (Table 41.1). PH associated with parenchymal lung diseases is characterized in the vast majority of cases by a modest increase of pulmonary arterial pressure, resulting from pulmonary vasoconstriction and mild vascular remodeling due to chronic hypoxemia [3]. However, the increase in pulmonary arterial pressure may seldomly be out-of-proportion to the severity of the underlying lung disease, reflecting a specific pulmonary vascular involvement. Unfortunately, there is no consensus on the hemodynamic or functional definition of the "out-of-proportion PH" occurring in the context of chronic lung diseases.

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Table 41.1 Updated clinical classification of pulmonary hypertension (adapted from [1])

1. Pulmonary Arterial Hypertension (PAH)
1.1. Idiopathic
1.1.1. Non-responders at vasoreactivity testing
1.1.2. Acute responders at vasoreactivity testing
1.2. Heritable
1.3. Associated with drugs and toxins
1.4. Associated with:
1.4.1. Connective tissue disease
1.4.2. HIV infection
1.4.3. Portal hypertension
1.4.4. Congenital heart diseases
1.4.5. Schistosomiasis
1.5. PAH with features of venous/capillaries (PVOD/PCH) involvement
1.6. Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension associated with left heart disease
2.1. Heart failure:
2.1.1. with preserved ejection fraction
2.1.2. with reduced or mildly reduced ejection fraction
2.2. Valvular heart disease
2.3. Congenital/acquired cardiovascular conditions leading to post-capillary pulmonary hypertension
3. Pulmonary hypertension associated with lung diseases and/or hypoxia
3.1. Obstructive lung disease or emphysema
3.2. Restrictive lung disease
3.3. Lung disease with mixed restrictive/obstructive pattern
3.4. Hypoventilation syndromes
3.5. Hypoxia without lung disease
3.6. Developmental lung disorders
4. PH associated with pulmonary artery obstructions
4.1. Chronic thromboembolic pulmonary hypertension
4.2. Other pulmonary artery obstructions
5. PH with unclear and/or multifactorial mechanisms
5.1. Hematologic disorders
5.2. Systemic disorders
5.3 Metabolic disorders
5.4. Chronic renal failure with or without hemodialysis
5.5. Pulmonary tumour thrombotic microangiopathy
5.6. Fibrosing mediastinitis

PAH pulmonary arterial hypertension, *PCH* pulmonary capillary hemangiomatosis, *PVOD* pulmonary veno-occlusive disease

Classification of Pulmonary Hypertension

The current classification of PH revised during the 2022 ESC/ERS Guidelines on pulmonary hypertension is presented in Table 41.1 [1]. The group 1 corresponds to all forms of PAH, including idiopathic PAH, heritable PAH, drugs and toxins induced PAH, and PAH associated with different conditions (connective tissue disease, HIV infection, portal hypertension, congenital heart disease, schistosomiasis or chronic hemolytic anemia). A subgroup 1.5 includes a rare entity characterized by a predominant pulmonary venous or capillary involvement: pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH). Pathologic and genetic studies have demonstrated that PVOD and PCH represents distinct naming of the same entity [4–8]. Group 2 includes post-capillary PH associated with left heart diseases, defined by an increased PAWP (above or equal to 15 mmHg, or above) and normal PVR [9]. Group 3 was defined as "PH associated with lung diseases and/or hypoxia." In this group, the predominant cause of PH is hypoxemia as a result of either chronic lung disease, impaired control of breathing, or residence at high altitude; however, the precise prevalence of PH in all these conditions remains unknown [10]. In this group, combined pulmonary fibrosis and emphysema represents a category of lung disease characterized by a mixed obstructive and restrictive pattern frequently associated with severe PH [11, 12]. Group 4 defined chronic thromboembolic pulmonary hypertension (CTEPH) [13]. Group 5 corresponds to heterogeneous conditions with unclear or multifactorial etiologies. This group includes hematological disorders (5.1), systemic disorders (5.2), metabolic disorders (5.3), chronic renal failure (5.4) or fibrosing mediastinitis (5.6).

In the evaluation of PH occurring in the context of orphan lung diseases, physicians should rule out other types of PH (in particular post-capillary PH and CTEPH) and screen for other risk factors of PAH (connective tissue disease, portal hypertension, HIV infection). Of note, precapillary PH associated with orphan lung diseases may be observed in different subgroups of this classification: in group 1 (1.2: small patella syndrome and hereditary hemorrhagic telangiectasia, 1.6: PVOD/PCH), group 3 (syndrome of combined pulmonary fibrosis/emphysema, lymphangioleiomyomatosis), and group 5 (sarcoidosis, pulmonary Langerhans cell histiocytosis, neurofibromatosis).

Pulmonary Hypertension Associated with Sarcoidosis (Group 5.2)

Sarcoidosis is a multisystem disease characterized by granulomatous inflammation of unknown cause, with pulmonary involvement being one of the commonest disease manifestations [14–16].

PH may complicate sarcoidosis with an estimated prevalence of 2.5–15% in unselected patients [17–21] but this prevalence can vary largely according to the population studied. PH has been estimated to be between 47% and 53.8% in patients with persistent dyspnea [22–24] and as high as 74% in patients with advanced parenchymal lung disease on transplantation waiting list [25, 26]. In addition, PH emerge more commonly in radiologic stage 4 pulmonary sarcoidosis, accounting for up to 66–74% of all sarcoidosis-associated PH (SaPH) [17, 27–29]. Nevertheless, interpretation of the true prevalence of PH in sarcoidosis is limited because right heart catheterization was not performed

in many studies, despite the low accuracy of echocardiography to detect PH and confirm its mechanism [19, 22, 30].

Pathological processes underlying SaPH are complex and multiple, and may fall under different groups according to the current clinical classification of PH [1]. Parenchymal lung disease related to sarcoidosis can result in extensive interstitial fibrosis with destruction of the pulmonary vascular bed, and together with alveolar hypoxia, may promote the development of mild or moderate precapillary PH [16, 20, 31, 32]. Although PH is frequently associated with advanced fibrotic lung disease in sarcoidosis [22, 32, 33], there is occasionally a significant discrepancy between the severity of lung disease with the severity of PH. This suggests that alternate mechanisms, other than direct obliteration of the vascular bed by the fibrotic process, may participate to the development of PH [20, 34]. In the absence of parenchymal involvement, a true vascular involvement should be suspected [16, 34–37]. In fact, distal arterial or venous infiltration by granulomas may occur. Notably, pulmonary venular lesions have been frequently reported, mimicking PVOD (Fig. 41.1) [32, 34, 35, 38]. A post-capillary component may induce SaPH mainly through direct myocardial involvement by cardiac sarcoidosis causing heart failure with preserved left ventricular ejection fraction, or through ischemic or hypertensive heart disease secondary to cortico-induced arterial hypertension or diabetes mellitus [22, 31, 39]. Furthermore, hepatic involvement may exceptionally result in porto-pulmonary hypertension [40]. Finally, enlargement of intrathoracic lymph nodes or fibrosing mediastinitis can lead to extrinsic compression of the proximal pulmonary vasculature [27, 34, 41–43]. In summary, the often multifactorial nature of SaPH is best considered under a specific subgroup in the classification of PH: "unclear and/or multifactorial mechanisms" [1] (Table 41.1).

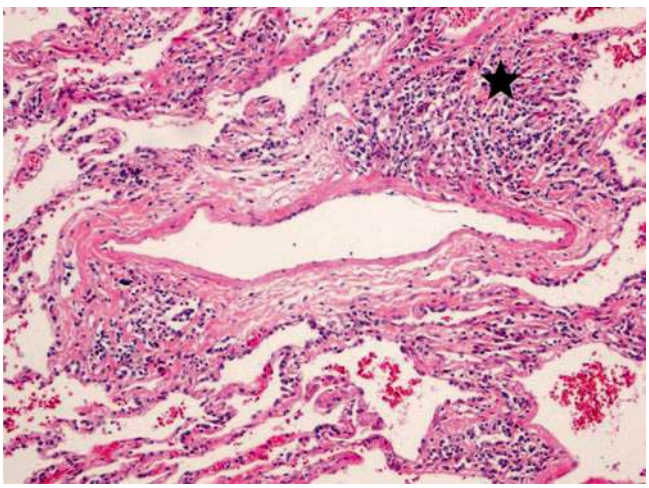

Fig. 41.1 Pathologic assessment of a patient with pulmonary hypertension associated with sarcoidosis. Pulmonary venous involvement is frequently observed in pulmonary hypertension associated with sarcoidosis. Epitheloid giant-cell granulomas (*) can be observed in the vicinity of veins, and may lead to their obstruction. Magnification 100, hematoxylin-eosin staining

Several studies have demonstrated a correlation between severity of the disease and PH occurrence, in particular for mild or moderate PH [20, 22, 25, 33]. Moreover, PH in sarcoidosis has been associated with oxygen desaturation during 6 min walking test and low DLCO [28, 29, 31, 33]. Interestingly, others biomarkers of PH such as NT-proBNP have failed to predict PH occurrence in sarcoidosis, although it has been demonstrated to be increased in cardiac involvement [44]. However, PH may be present in all stages of sarcoidosis [20, 34] and referral for formal RHC is mandatory if PH is suspected [31].

It is recognized that patients with SaPH have a worse prognosis compared to those without precapillary PH [22, 45, 46]. Five-year survival in SaPH has been estimated to be 55% [27]. Risk factors associated with mortality include high level of mPAP, African American ethnicity and chronic respiratory failure requiring oxygen therapy [45].

Oxygen therapy should be prescribed if chronic hypoxemia is present to prevent hypoxic vasoconstriction. The efficacy of immunosuppressive therapy on pulmonary vascular disease in sarcoidosis is not clear because these treatments have not demonstrated consistent benefits [16, 23, 47]. However, immunosuppressant use could benefit to a specific SaPH subpopulation: indeed, a significant effect has been described in a specific population where PH was related to extrinsic compression pulmonary vessels by mediastinal metabolically active lymph nodes [27].

The use of PAH specific therapy in SaPH is currently not recommended, but in clinical practice, patients with severe precapillary PH are often treated with one or a combination of these off-label drugs [48]. Such treatments have predominantly been assessed in open-label observational studies [23, 24, 27, 28, 49–54]. However, a multicenter, double-blind, randomized trial comparing bosentan versus placebo in 35 patients with sarcoidosis and concomitant precapillary PH showed improvements in hemodynamics (mPAP and PVR), but no effect on exercise capacity (6-min walking distance (6MWD) or functional class) in patients treated with bosentan [55]. A meta-analysis of available studies on specific therapies in SaPH, a recent retrospective study of SaPH patients registered within the French Pulmonary Hypertension Registry between 2004 and 2015 and a large retrospective cohort study confirmed these data showing that hemodynamic improvement under PAH specific therapy regimen often does not result in an improvement in NYHA functional class, exercise capacity of quality of life [27, 28, 56]. However, a randomized placebo-controlled trial evaluating the efficacy of oral prostacyclin analogue selexipag in SaPH is running [57].

Gas exchange deterioration may also occur following vasodilator therapy via uncoupling of hypoxic pulmonary

vasoconstriction, resulting in worsening of ventilation/perfusion mismatch [58]. Furthermore, potential risk of pulmonary edema can occur in cases with predominant venular involvement in a manner similar to PVOD [24, 59]. Thus, current guidelines do not support the use of PAH specific therapy in SaPH and off-label use of these therapies should only be considered in experienced PH centers.

Finally, because of the poor prognosis of SaPH and the lack of efficacy of specific PAH therapy, lung transplantation should be considered early in the course of the disease, despite the fact that the presence of PH prior to lung transplantation represents a risk factor of peri-transplant mortality [45] and primary graft dysfunction [60].

PH Associated with Pulmonary Langerhans Cell Histiocytosis (Group 5.2)

Langerhans cell histiocytosis is an inflammatory myeloid neoplasia characterized by clonal expansion of myeloid precursors infiltrating organs and differentiating into Langerhans cells [61]. Pulmonary involvement usually occurs as a single-system disease but can, in scarce cases, be associated with extrapulmonary manifestations [62]. Pulmonary Langerhans cell histiocytosis (PLCH) predominantly affect young smoker adults and constitutes a rare cause of diffuse parenchymal lung disease [62]. PH can complicate the course of PLCH and severe PH is frequently reported in advanced disease [62–65]. Prevalence of severe PH (formerly defined by mPAP ≥35 mmHg) in PLCH patients referred for lung transplantation assessment has been reported to range from 44% to 100% [63, 64] significantly higher than other chronic lung diseases such as COPD or IPF [63].

In contrast with PH related with classic interstitial lung diseases, despite lung parenchymal impairment, PLCH related PH is not classified in group 3 PH but in group 5 "unclear and/or multifactorial mechanisms" [1]. Indeed, discrepancy between hemodynamic severity and lung parenchymal involvement is frequently observed in PLCH related PH. In fact, hemodynamic parameters and pulmonary function tests are not correlated, suggesting that a specific pulmonary vascular involvement occurs independently of parenchymal lesions [63, 64].

Histopathological studies have shown a specific and diffuse pulmonary vasculopathy which is usually characterized by a proliferative vasculopathy with intimal fibrosis and medial hypertrophy involving the small to medium-sized pulmonary arteries and septal veins. This vascular involvement predominantly affects the pulmonary veins and, to a lesser extent, the muscular pulmonary arteries (Fig. 41.2) [63, 66, 67]. Notably, a significant venous involvement with a "veno-occlusive pattern" is present in up to one third of patients [63, 68]. Uncommonly, vascular lesions are due to direct infiltration by Langerhans cells [63, 67]. Finally, vascular lesions may be observed in areas free from parenchymal lesions [63, 67] and, interestingly, vascular lesions adjacent to areas of parenchymal involvement appeared less severe [67].

Exercise limitation in PLCH patients looks multifactorial (i.e., ventilatory and cardiocirculatory) [69, 70] although hemodynamic impairment appears to be the main source in PLCH related PH [71].

There are few data about the use of PAH specific therapies in PLCH related PH. Some case reports describe improvement in functional class, hemodynamic and 6MWD, without deterioration of gas exchange or occurrence of pulmonary edema under endothelin receptor antagonists (ERA), phosphodiesterase type 5 inhibitors (PDE5i) or prostaglandins

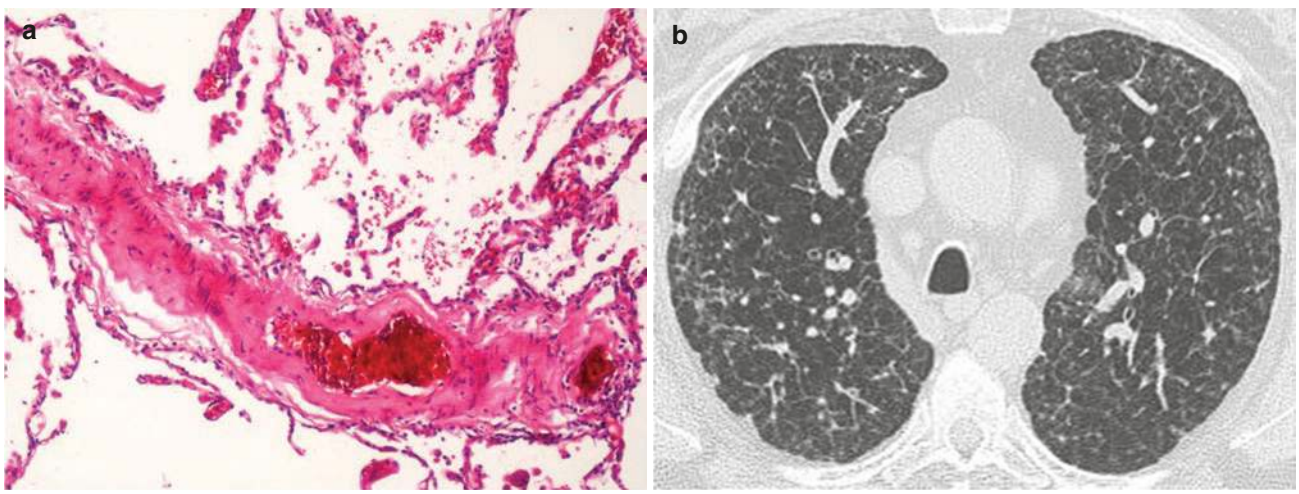

Fig. 41.2 Pathologic assessment and high-resolution CT of the chest of a patient with pulmonary hypertension associated with pulmonary Langerhans cell histiocytosis. (**a**) Diffuse pulmonary vasculopathy which predominantly involves the pulmonary veins and, to a lesser extent, the muscular pulmonary arteries. See intimal fibrosis of a septal vein with partial obliteration. Magnification 100, hematoxylin-eosin staining. (**b**) High-resolution CT of the chest showing multiple small cysts and nodules

(PGI), mainly used in monotherapy regimen [72–79]. However, there have not been yet prospective randomized controlled trials to assess the effectiveness and safety of PAH specific therapies in PLCH related PH.

In a retrospective study of 29 patients with PLCH related PH, Le Pavec et al. demonstrated severe hemodynamic impairment with 66% of subjects displaying a mPAP ≥40 mmHg [80]. In 23 of the 29 patients from this cohort, PH was diagnosed with a mean delay of 11 years after the initial diagnosis of PLCH. In this retrospective study, PAH specific therapies improved hemodynamics (mPAP and pulmonary vascular resistance) associated with an improvement in functional class in 2/3 of the patients and an increase of 6MWD >10% in 45% of patients. Functional class was the only predictor of death and the use of PAH specific therapy was not associated with improvement in survival [80].

PAH specific therapies appeared to be relatively safe in this context, nor significant worsening of gas exchange nor pulmonary edema related to potential venular involvement were reported in PLCH related PH. However, severe acute pulmonary edema has been reported by other authors during initiation of intravenous epoprostenol therapy [63, 67, 68].

Effects of cladribine, a cytotoxic agent used in progressive PLCH, on PLCH related PH are not known. Nevertheless, it was reported to improve hemodynamic in one patient previously treated with bosentan, in parallel to improvement in clinical status, lung function, 6MWD and lung parenchymal impairment on high-resolution computed tomography (HRCT) [81].

Recently, mutations in the mitogen-activated protein kinase (MAPK) pathway including the well-known of dermatologic-oncologists *BRAF*^{V600E} mutation, have been highlighted in up to 50% of LCH [82–84]. This important step forward opens the door to new treatment possibilities with targeted therapies directed against MAPK pathway. To date, there are no data concerning the use of such therapies in PLCH and their potential impact on pulmonary vascular involvement.

Lungs or heart-lung transplantation remains the treatment of choice for end-stage PLCH and/or for severe PLCH related PH [64]. Of note, recurrence of PLCH in lung allografts has been reported and risk of recurrence was associated with the presence of extrapulmonary disease prior to transplantation [64, 85, 86].

PH in Combined Pulmonary Fibrosis and Emphysema (Group 3.3)

Combined pulmonary fibrosis and emphysema (CPFE) was first described as a distinct entity characterized by diffuse destruction of the lung parenchyma in 2005 [11]. This syndrome, typically occurring in male smokers, results from the combined effects of centrilobular or paraseptal emphysema in the upper lobes and lung fibrosis in the lower lobes [11, 87–90]. Despite extensive parenchymal involvement, pulmonary function tests are often well preserved in this condition, but associated with marked reduction in the DLCO and severe hypoxemia [11, 90, 91]. Precapillary PH frequently complicates the course of CPFE with a prevalence ranging from 47% to 90%, depending on the method of detection (i.e., echocardiography or RHC), which is more frequent than in COPD or IPF alone [11, 12, 92]. Hemodynamic impairment develops early after the diagnosis of CPFE, is usually severe, and appears correlated with the degree of emphysema on HRCT [12, 91, 92].

CPFE related PH is classified in subgroup 3.3 "*Lung disease with mixed restrictive/obstructive pattern*" (Table 41.1) [1]. The main assumption regarding the mechanism of PH in this context, is the association of alveolar destruction from emphysema and alveolar membrane thickening from fibrosis, leading to reduced lung perfusion and obliteration of the pulmonary vascular bed [10, 93]. However, a true pulmonary vasculopathy, in some extent similar to what is classically observed in PAH, was described in histologic studies of CPFE related PH patients. Vascular remodeling usually associates intimal fibrosis, medial hypertrophy of small pulmonary arteries, and in situ thrombosis, but without plexiform lesions [94–96]. In addition, a certain degree of venular involvement can sometimes be observed, but without major capillary impairment [95]. Interestingly, some vascular lesions can develop in areas of normal lung [94].

A retrospective study reported the hemodynamic, functional, and survival characteristics of 40 patients displaying PH associated with CPFE [92]. At the time of diagnosis, RHC revealed moderate to severe PH (mPAP of 40 ± 9 mmHg, PVR of 6.5 ± 2.6 WU, and cardiac index of 2.5 ± 0.7 L/min/m^2). Furthermore, 85% of the patients were in either functional class III or IV, with a mean 6MWD of only 244 ± 126 m. Moreover, univariate analysis found that DLCO <22%, PVR > 6.1 WU, and cardiac index <2.4 L/min/m^2 were predictive factors of death [92].

Prognosis of CPFE is highly affected from the development of PH with a 1-year survival of CPFE related PH patients estimated at 60 ± 10% [92].

Interestingly, CPFE could also be present in connective tissue diseases, with a similar prevalence of PH [97].

Although some published case reports suggest an improvement in hemodynamics of CPFE related PH under PAH specific therapy [92, 98–100], PAH specific therapies are not recommended due to the lack of published evidence and the potential risk of aggravating hypoxemia by worsening ventilation/perfusion mismatch [10, 58]. Finally, lung transplantation should be considered in selected patients and

supportive care for chronic respiratory failure, especially oxygen therapy, is required.

PH Associated with Neurofibromatosis Type 1 (Group 5.2)

Neurofibromatosis type 1 (NF1), also known as von Recklinghausen disease, is one of the most common genetic diseases with a prevalence of 1/3000 to 1/6000, an incidence of 1/2000 to 1/3000 and almost complete penetrance before the age of 5 [101]. This disease is caused by mutations in the neurofibromin 1 (NF1) gene, which codes for a cytoplasmic protein involved in tumor suppression called neurofibromin. Neurofibromin is a guanosine triphosphatase (GTPase)-activating protein (GAP) that acts as a negative regulator of signal transmitted by Ras [102]. Its loss is associated with constitutive activation of transcription pathways: the mitogen-activated protein (MAP) kinase pathway ending by ERK activation and the mammalian target of rapamycin (mTOR) pathway, mediated by activation of the PI3kinase-AKT pathway and by the TSC1-TSC2 complex. The diagnosis of NF1 is clinical, based on the presence of at least two out of seven clinical criteria (café au lait spots, cutaneous or subcutaneous neurofibromas plexiform neurofibromas, axillary or groin freckles, glioma of the optic pathways, Lisch nodules on the iris, bone dysplasia, first-degree family history) [103]. The characteristics of the disease vary widely from patient to patient, and some may develop respiratory complications such as airway plexiform neurofibromas, intrathoracic meningoceles, cysts, bullae, or interstitial infiltrates that can go up to pulmonary fibrosis and also PH [101]. Initially PH has been described as a consequence to an advanced parenchymal disease, but then several case reports and a series of eight cases of PH associated with NF1 (PH-NF1) published by our team showed that patients with mild or absent lung parenchymal abnormalities can develop PH (Fig. 41.3) [104]. Using data from the French Pulmonary Hypertension Network, our team then reported in 2020 the clinical, functional, hemodynamic, and radiographic characteristics as well as the responses to specific treatments for PAH in 49 patients with a combination of PH and NF1 [105]. Thus, it has been shown that PH-NF1 mainly affects women (female/male sex ratio of 3.9) whereas, due to its autosomal dominant transmission with full penetrance, NF1 is equally distributed between men and women. The onset of PH was late in history with a median age at diagnosis of 62 years (min-max 18–82). At diagnosis, PH was hemodynamically severe (mPAP of 45 mmHg and PVR of 10.7 WU) and was accompanied by major dyspnea with >90% of patients in NYHA functional class III or IV. The pulmonary function tests showed the existence of a major diffusion impairment (median DLCO: 30% of theoretical) associated with severe hypoxemia (median PaO_2 in ambient air: 56 mmHg). Systematic analysis of chest scans showed associated pulmonary parenchymal lesions in most patients (cysts, ground glass opacities, emphysema and reticulations) most often moderate, not explaining the severity of PH. Histological data available in some of these patients revealed non-specific interstitial pneumonia (NSIP) and intense pulmonary vascular remodeling. The response to specific treatments for PAH is generally disappointing and the prognosis poor, with a 5-year transplant-free survival of 42%. Transplantation is an option to be evaluated early, despite the risks of complications under immunosuppressants in these patients at risk of cancer. Thus, four patients were transplanted, 3 of whom

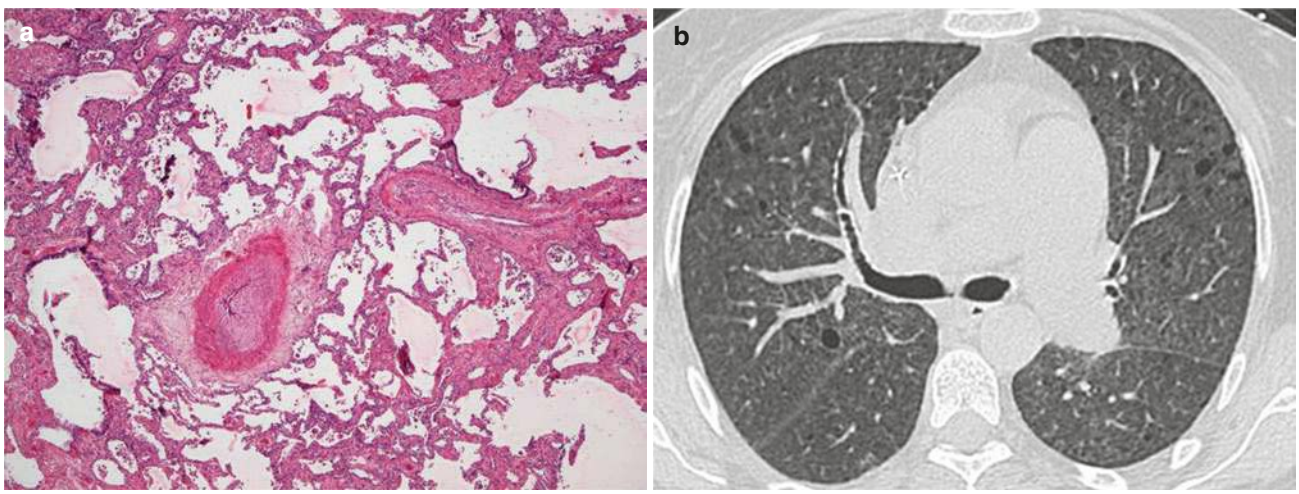

Fig. 41.3 Pathologic assessment and high-resolution CT of a patient with NF1-associated pulmonary hypertension. (**a**) Interstitial fibrosis with partial loss of parenchymal architecture associated with pronounced arterial remodeling complete occlusion by intimal fibrosis. Magnification 40, hematoxylin-eosin staining. (**b**) High-resolution CT of the chest showing diffuse small rounded lung cysts

were still alive at the time of the study. The severity of PH "disproportionate" to the radiological abnormalities, the predominance of women and the observed pulmonary vascular remodeling, suggest the existence of a pulmonary microvascular disease associated with NF1. Research is needed to elucidate how the mutation of NF1 and its action on the Ras and mTOR signaling pathway may participate in the development of vascular remodeling and PH.

As a consequence, NF1 related PH was classified in group 5 in the updated clinical classification of pulmonary hypertension, among other forms of PH with unclear/multifactorial mechanisms [1]. PH represents a rare but severe complication of NF1 that is characterized by a late onset, with female predominance, severe functional and hemodynamic impairment, and poor outcome. Specific PAH therapy seems to have only modest effect in these patients and these patients should be referred for lung transplantation if eligible.

PH Associated with Lymphangioleiomyomatosis (Group 3)

Lymphangioleiomyomatosis (LAM) is a rare multisystem metastasizing neoplasm predominantly affecting women in their reproductive years, with an estimated prevalence of 1–9/1,000,000 people [106–108]. It may occur sporadically or, in about 30% of patients, in the setting of tuberous sclerosis complex (TSC) with mutations in the *TSC1* and *TSC2* genes, coding for hamartin and tuberin respectively [109–111]. The current accepted model for LAM is consistent with Knudson's "two-hit" hypothesis of tumor development: an initial mutation in either *TSC1* or *TSC2* is followed by a second hit represented by loss of heterozygosity, causing the loss of function of either *TSC1* or *TSC2* gene products [112]. A major role of the complex hamartin-tuberin is to inhibit the mammalian target of rapamycin (mTOR) pathway. Thus, LAM is the consequence of a dysregulation of the mTOR pathway, leading to an abnormal proliferation of smooth muscle like cells (also called LAM cells) along lymphatics in the lungs and abdomen that leads to diffuse cystic lung disease, recurrent pneumothoraces, benign renal tumors, pleural and peritoneal chylous effusions, and abdominal lymphangioleiomyomas [111, 113]. At the pulmonary level, metalloprotease secretion by the LAM cells leads to the formation and progression of thin wall cysts, which in turn are responsible for airflow obstruction, low DLCO, and chronic respiratory insufficiency [114–116]. In addition, serum levels of vascular endothelial growth factor-D (VEGF-D), which promotes the lymphatic vessels expansion, have been shown to be higher in LAM patients than in healthy controls and than in patients with other cystic lung diseases [117]. Sirolimus, an mTOR inhibitor has been shown to slow the rate of lung function decline, to decrease VEGF-D serum levels, to be effective on extra-thoracic lesions of LAM and to improve quality of life [118, 119]. However, lung transplantation remains the only option for patients with advanced respiratory disease [120–126].

It was shown that the emergence of PH can complicate the evolution of LAM in about 7% and 45% of patients with LAM, whatever the stage of the disease, and at time of lung transplantation, respectively [116, 124, 127, 128]. Thereby, the European Respiratory Society guidelines for the diagnosis and management of LAM has underlined that PH has not been reported frequently in LAM patients and that screening for PH is not recommended in patients with non-severe LAM [120]. However, it was suggested that estimation of PAP should be performed in patients considered for lung transplantation [122]. In the updated classification of PH, PH associated with LAM has been switched from group 5 to group 3 [1, 2]. Indeed, it was shown that PH is usually mild in LAM, and is associated with severely altered pulmonary function [127, 129, 130]. There are two major hypotheses that can explain PH in LAM patients. The first is the classic hypoxic vasoconstriction mechanism which occurs in the context of severe parenchymal distortions caused by cysts [116, 128]. This is supported by several studies reporting a significant correlation between hemodynamic severity in one hand, lung function and PaO_2 level in the other hand [127–130]. In addition, it was shown that sirolimus is effective in improving pulmonary hemodynamics, in parallel with significant improvements of FVC, FEV1, and PaO_2 [128, 130]. The second is related to an up regulated mTOR secretion by the LAM cells, activation of mTOR complexes 1 and 2 in the context of hypoxia which in the end lead to vascular smooth cell proliferation and PH [129, 131, 132].

In a retrospective multicenter study, Cottin et al. reported 20 patients with LAM and precapillary PH confirmed by right heart catheterization [129]. The mean age at diagnosis of PH was 49 years with a mean time interval between LAM and PH diagnosis of 9.2 years. Hemodynamics showed moderate PH with a mPAP of 32 ± 6 mmHg, a cardiac index of 3.5 ± 1.1 L/min/m^2, and PVR of 4.7 ± 2.3 WU, with only four patients (20%) having a mPAP >35 mmHg. These hemodynamic results suggested that in the majority of cases, PH was mild or moderate and related to the severity of pulmonary involvement [129]. Pulmonary function tests showed a decreased FEV1 at 42 ± 25% and DLCO at 29 ± 13% with blood gases showing mild hypoxemia (PaO_2 of 55.5 ± 9.8 mmHg in room air) [129]. Only six patients received oral PAH specific therapy and showed a decrease in mPAP and PVR from baseline. The authors showed that the overall probability of survival at 2 years was 94% [129].

In conclusion, mild to moderate PH is relatively a common finding in LAM patients with severe lung involvement. Chronic hypoxemia and pulmonary capillary destruction

caused by cystic lung lesions may represent the predominant mechanism of PH in this setting. Sirolimus, by improving lung function and hypoxemia, might improve pulmonary hemodynamics in these patients. Nevertheless, some patients may have specific pulmonary vascular involvement, and one potential mechanism may be the activation of mTOR, as proposed in patients with NF1-associated PH. These patients may be candidates for specific PAH therapies, but further studies are needed in order to assess this possibility.

Hereditary Hemorrhagic Telangiectasia (Group 1.2)

Hereditary hemorrhagic telangiectasia (HHT), also called Rendu–Osler–Weber syndrome, is a vascular disorder with an estimated prevalence of 1/6000 people. It is characterized by mucocutaneous telangiectasias, recurrent epistaxis, macroscopic arteriovenous malformations (particularly in the pulmonary, hepatic, and cerebral circulations), and more rarely PH [133, 134]. Diagnosis of HHT is clinical and considered definite in the presence of at least 3 of the 4 Curaçao criteria, including (1) spontaneous and recurrent epistaxis, (2) multiple mucocutaneous telangiectasia at characteristics sites, (3) visceral involvement with pulmonary, liver, cerebral, spinal or gastrointestinal arteriovenous malformations (AVMs), and (4) a family history [135]. HHT is inherited in an autosomal dominant fashion with late-onset penetrance and nearly complete penetrance (97%) at the age of 60 years. Several genes have been implicated in the pathogenesis of HHT, including *endoglin* (*ENG*) on chromosome 9, encoding endoglin (HHT type 1) activin receptor-like kinase-1 (*ACVRL1*) located on chromosome 12, encoding ALK-1 (HHT type 2), and, far less frequently, *mother against decapentaplegic homolog 4* (*MADH4*) on chromosome 18, encoding SMAD4 (combined syndrome of HHT and juvenile polyposis) [136–138]. These genes are involved in the transforming growth factor-β (TGF-β) signaling pathway: homo and/or heterodimers of BMP9 and BMP10 are high infinity ligands of a receptor complex formed by the association of ALK-1, endoglin and bone morphogenetic protein-receptor type II (BMPRII), which, once activated, induces the phosphorylation and thus the activation of the SMAD proteins (including SMAD4), transcription factors implicated in the growth and the proliferation of endothelial cells [139–143]. Thereby, HHT causing genes are involved in the same signaling pathway than the *BMPR2* gene, the main predisposing gene of heritable PAH.

Main pulmonary vascular involvement in HHT is characterized by the development of AVMs which may responsible of the creation of clinically significant right-to-left shunts, causing hypoxemia, paradoxical embolism, stroke, and cerebral abscesses [144]. In addition, PH can complicate the course of about 8% of HHT patients and several mechanisms may be involved in the genesis of high pulmonary pressures [145].

Most commonly, the presence of systemic shunts through AVMs, mostly located in the liver, creates a high pulmonary flow and increased cardiac output, resulting in hyperkinetic pulmonary hypertension, hemodynamically characterized by elevated mPAP, high cardiac output and low to normal PVR. Recently, antiangiogenic therapy with bevacizumab (anti-VEGF antibodies) showed promising results in reducing the size of hepatic AVMs and thus decreasing cardiac output and pulmonary pressures [146, 147]. However, the potential deleterious impact of VEGF pathway inhibition on pulmonary vasculature remains a matter of debate [148]. Other drugs such anti-angiopoietin antibodies, or immunosuppressive drugs (i.e., tacrolimus and sirolimus) have been investigated during the last years, mostly in preclinical models and induced significant effects in reducing systemic AVMs. However, their effects on pulmonary pressure and high cardiac output were not assessed [149–152]. Interventional strategies, including ligation, banding or embolization of the hepatic arteries are not recommended anymore, because of the important morbidity and mortality associated with these procedures in this population [153]. Finally, liver transplantation is being considered in patients with refractory high outflow heart failure despite optimal medical management and induces in the majority of cases a dramatic improvement in pulmonary hemodynamics [154–156].

However, HHT is also associated, in a restricted population, with PAH characterized by remodeling of small pulmonary arteries, with broadly similar histologic lesions than observed in idiopathic PAH [157–159]. The prevalence of PAH (in the absence of liver AVMs) is currently estimated to be lower than 5% in HHT patients [160]. Many case series have reported the association of *ACVRL1* mutations and PAH in HHT patients without any other cause of PH [157–159, 161–163]. At the opposite, only few cases of PAH in *endoglin* mutants have been reported, although *endoglin* and *ACVRL1* mutations are present in a comparable proportion in the population, suggesting a less potent association between *endoglin* and PAH [158, 162, 164]. We previously demonstrated that PAH patients carriers of an *ACVRL1* mutation are significantly younger (21.8 ± 16.7 years) at PAH diagnosis, as compared to *BMPR2* mutation carriers (35.7 ± 14.9 years) and non-carriers (47.6 ± 16.3 years) with a more rapid disease evolution [161]. Interestingly, *ACVRL1* mutation carriers may develop severe PAH without any clinical evidence of HHT because of the early development of PAH in these patients and the late-onset penetrance of *ACVRL1* mutations for HHT manifestations [161]. PAH specific therapies are currently approved in these patients, by analogy with idiopathic PAH and other heritable PAH in view of the patho-

physiologic clinical and hemodynamic similarities of these conditions. However, special attention should be taken in these patients presenting with AVMs. Indeed, PAH specific medications, because of their vasodilator properties can major the risk of systemic bleeding (systemic AVMs), hypoxemia worsening, by increasing the intrapulmonary shunt through pulmonary AVMs, or acute right afterload increase and thus right heart failure.

In conclusion, the absence of HHT clinical manifestation in PAH patients should not exclude the diagnosis of PAH associated with *ACVRL1* or *endoglin* mutation and a detailed familial history and a careful examination of PAH patients and first-degree relatives for signs of HHT may help detect these patients.

Pulmonary Veno-Occlusive Disease (Group 1.5)

Pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH) are uncommon forms of PH whose diagnosis, as difficult it is to differentiate from that of PAH, is of paramount importance for an appropriate management of these patients [165, 166]. In view of the difficulty to accurately diagnose PVOD, these true prevalence and incidence appreciations are arduous. However, it has been suggested that PVOD represents 3–12% of histological forms of cases initially considered as idiopathic PAH [167, 168]. Whereas idiopathic PAH shows a distinct female preponderance, PVOD is characterized by a male/female ratio around 1 [5, 169]. Although initially considered to be two different conditions, it is now well-admitted that PVOD and PCH are two presentations of the same disease, with respect to numerous common traits and overlapping features [166]. Indeed, histological examination of lung samples shows extensive and diffuse occlusion of pulmonary veins by fibrous tissue and intimal thickening involving preferentially venules and small veins in lobular septa in PVOD (Fig. 41.4), and localized capillary proliferations which could obstruct veins and venular walls in PCH [4, 8, 167, 170]. Indeed, a clinicopathologic study analyzing specimens from 35 patients diagnosed as having either PVOD or PCH concluded that lesions of capillaries were present in 3/4 of cases diagnosed as PVOD and that significant venous involvement was present in 4/5 cases initially diagnosed as PCH [8]. It has been hypothesized that capillary hemangiomatosis may result from an angioproliferative process associated with venous obstruction, as observed in PVOD. Furthermore, the discovery of a common genetic background in PVOD or PCH families confirmed that the terms "PVOD" and "PCH" described the same entity [7, 171]. According to these observations PVOD/PCH was grouped in a subgroup of group 1, entitled "group 1.5: PAH with features of venous/capillaries (PVOD/PCH) involvement" in the current classification of PH (Table 41.1) [1].

In 2014, biallelic mutations of the *eukaryotic translation initiation factor 2 alpha kinase 4* (*EIF2AK4*) gene were identified in 100% of familial form of PVOD/PCH and 25% of sporadic PVOD/PCH [7, 171, 172]. Thereby, *EIF2AK4* is now recognized as the major genetic risk factor for PVOD/PCH. Heritable PVOD/PCH is an autosomal recessive disease, characterized by a male/female ratio of 1:1, and by a lower age at PVOD/PCH diagnosis compared to non-heritable PVOD/PCH patients [7]. In sporadic, non-genetic forms of PVOD/PCH, some risk factors and associated conditions have been highlighted. Indeed, cases of PVOD/PCH are diagnosed in the context of treatment with a number of chemotherapeutic regimens, notably alkylating agents such as cyclophosphamide and mitomycin [173–175]. PVOD/PCH has also been reported as a complication of hematologic or solid organ malignancies, peripheral blood stem cell transplantation, bone marrow transplantation, and radiotherapy. Of note, occupational exposure to solvent with trichloroethylene is also frequently described [176]. Moreover, a higher tobacco exposure and an increased proportion of smokers in PVOD/PCH as compared to PAH were reported [5]. This difference was not explained by the difference in the male/female ratio, since the increased tobacco exposure was observed in both genders. This relationship is also supported by the described association between PVOD/PCH and pulmonary Langerhans cell histiocytosis, a pulmonary disease occurring almost exclusively in smokers. Finally, it is increasingly described that a certain number of disease-associated PH exhibit significant degree of venular involvement. It is mainly shown in connective tissue diseases, especially, systemic sclerosis [177, 178], inflammatory diseases such sarcoidosis [179], or Langerhans cell histiocytosis [68]. However, the relative infrequency of these different associations highlights the difficulty in establishing whether it is the disease or its associated treatment that is responsible for the onset of PVOD/PCH.

PVOD/PCH is associated with a poor prognosis and require specific management, justifying the diagnosis of the subgroup of PVOD/PCH patients among PAH patients early in the course of the disease. A definitive diagnosis of PVOD/PCH requires histological examination of lung samples or identification of bi-allelic mutations in *EIF2AK4* gene, in particular in familial form of PVOD/PCH. However, lung biopsies are associated with a significant mortality risk in patients with established pulmonary vasculopathy and thus is contraindicated. Thereby, pathological confirmation is usually obtained from autopsy or lung explants, and treatment decisions are usually based on clinic-radiological grounds. Distinguishing PVOD/PCH from PAH on clinical grounds alone is difficult since physical findings are often identical.

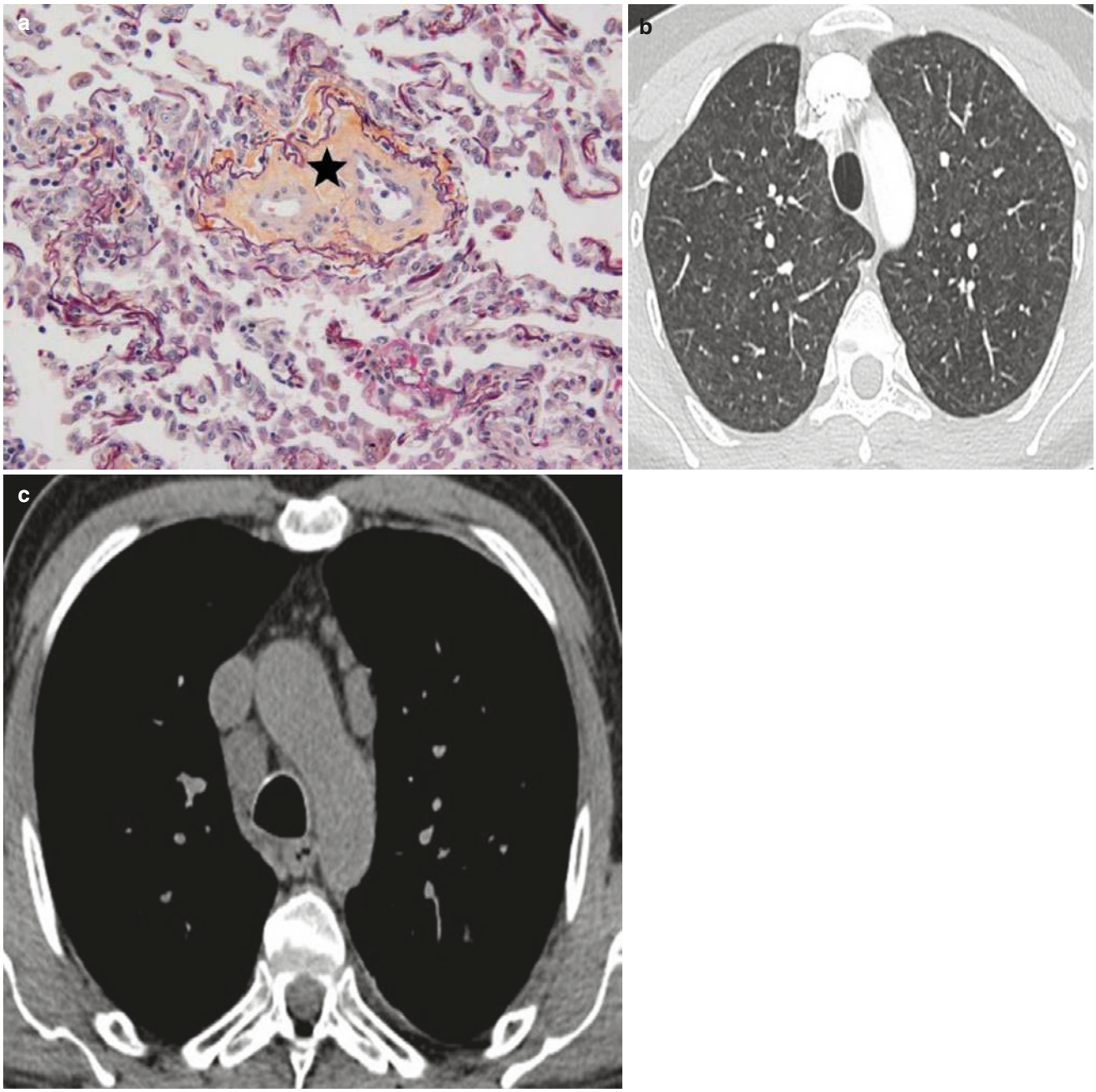

Fig. 41.4 Pathologic assessment and high-resolution CT of a patient with pulmonary veno-occlusive disease. (**a**) Fibrous obstruction of a septal vein (*) associated with capillary proliferation. Magnification 400, hematoxylin-eosin staining. (**b**) High-resolution CT of the chest showing diffuse poorly-defined centrilobular nodular opacities with associated septal line thickening. (**c**) High-resolution CT of the chest showing mediastinal lymph node enlargement

As in PAH, the installation of symptoms is usually insidious, marked by progressive dyspnea, asthenia and symptoms related to right heart failure in more advanced disease. Because of the non-specific aspect of this symptomatology, PVOD/PCH diagnosis is frequently made later in the course of the disease, when symptoms are already well established. Digital clubbing and Raynaud phenomenon have been associated with PVOD/PCH but are observed no more frequently than in idiopathic PAH [5]. Auscultatory crackles and pleural effusions may be indicative of acute pulmonary edema, occurring particularly after initiation of PAH specific therapy. In PVOD/PCH, measured values of the pulmonary artery wedge pressure (PAWP), formerly called pulmonary capillary wedge pressure (PCWP), a misleading term, are

characteristically in the normal range despite the involvement of pulmonary venules. In fact, in the context of PVOD/PCH, pressure measurements that are recorded when a catheter is wedged in a branch of the pulmonary artery reflect pressures in the larger veins which are typically unaffected by the disease process. Thus, pulmonary artery wedge pressure measured in PVOD/PCH do not reflect the true capillary pressure, making obsolete the term of PCWP [5, 180]. Obviously, due to the site of vascular involvement in PVOD/PCH, the true pulmonary capillary pressure is increased, explaining the frequent occurrence of pulmonary edema especially when vasodilator drugs are applied on the pulmonary circulation. As a result, PVOD/PCH is characterized by a pattern of precapillary PH on RHC even though the anatomic obstruction is predominantly post-capillary. Interestingly, PVOD/PCH is associated with a similar proportion (12%) of acute vasodilator responders as idiopathic PAH. In contrast to idiopathic PAH, however, an acute response in PVOD/PCH is not associated with a better prognosis and a long-term response to calcium channel blockers has never been observed [181].

A non-invasive approach has been proposed to screen PH patients with a high clinical suspicion of PVOD/PCH [165, 180, 182]. These include high-resolution computed tomography of the chest, arterial blood gases, DLCO, and more rarely bronchoalveolar lavage. On HRCT of the chest, the triad of diffuse ground glass opacification in a centrilobular distribution, septal thickening, and mediastinal lymph node enlargement is common and highly suggestive of PVOD/PCH in patients with precapillary PH [183, 184] (Fig. 41.4). Indeed, PVOD/PCH patients are characterized by significantly lower resting partial pressure of arterial oxygen and DLCO compared to those with idiopathic PAH [169, 180]. Finally, PVOD/PCH patients have significantly increased numbers of hemosiderin-laden macrophages and relatively high average Golde score (yet usually <100) on bronchoalveolar lavage [185].

The response to medical therapy and prognosis of PVOD/PCH are poor. An important clinical hallmark of PVOD/PCH is that about 50% of the patients may experience potentially life-threatening deterioration due to severe pulmonary edema after initiation of specific PAH therapy [5, 180], which is the result of an increased pulmonary blood flow against a post-capillary fixed obstruction. Although pulmonary edema has been reported with all specific PAH therapies [5], it has been reported clinical, functional, and hemodynamic improvements in PVOD patients with cautious use of intravenous epoprostenol used as a bridge therapy to lung transplantation in selected patients [180]. Furthermore, some very moderate clinical and hemodynamic improvement have been reported in some isolated cases or small case series [186–191]. In addition, the existence of an inflammatory background in PVOD/PCH patients could prompt some physicians to introduce immunosuppressive agents in these patients. Nonetheless, data relative to this subject in the literature are scarce and such therapies are currently not recommended by the last international guidelines [1]. Recently, a series of three cases of idiopathic or heritable PVOD with features of undetermined immune diseases who experienced clinical and hemodynamic stabilization or improvement under immunosuppressive therapies including glucocorticoids and mycophenolate mofetil was reported [192]. However, because of the dysregulated immunity presented by these patients, it is not clear whether and how frequently immunosuppressants could improve this condition even in the absence of immune dysregulation.

Nevertheless, because of the overall poor response to specific PAH therapy and poor outcomes, lung transplantation remains the treatment of choice of PVOD/PCH.

Small Patella Syndrome (Group 1.2)

TBX4 syndrome is an autosomal dominant syndrome affecting at diverse degrees and depending on the patients, the lower limbs, the pulmonary parenchyma, and the pulmonary vasculature. The *TBX4* gene is a member of the T-box gene family, transcription factors playing dominant roles in the development of numerous organs [193–195].

Historically, *TBX4* syndrome has been described as a dysplasia of the lower limbs, characterized by hypoplasia or aplasia of the patella, ossification defects of the ischia, and inferior pubic rami and anomalies of the feet dominated by the existence of a large gap between the first and the second toes and flat feet, explaining why this syndrome was classically named small patella syndrome (SPS) or coxo-podo-patellar syndrome [196]. It was not until 2013 that the involvement of mutations in the *TBX4* gene in the development of a pulmonary vasculopathy has been highlighted [197]. Indeed, *TBX4* plays a major role in the development and branching of the lungs, and its mutations may result in bronchial, parenchymal, and pulmonary vascular abnormalities such as tracheal and bronchial diverticula, thickened and irregular bronchial walls, peri-bronchial cysts or emphysematous-like lesions (Fig. 41.5) [198, 199].

TBX4 mutations can sometimes result in the development of PAH, classified in the group 1.2: "heritable PAH" of the updated classification of PH (Table 41.1) [1]. Its clinical presentation is close to that seen in idiopathic PAH and the classical female predominance is also a constant [199]. PAH in these patients occurs with a bimodal distribution mode with a first peak during early childhood [197–200] and a second peak in late adulthood [199]. To date, *TBX4* mutations are considered to represent about 6% of pediatric PAH and 3% of adult-onset PAH [199, 201]. However, with respect to its implication in the growth of the lungs and the lower limbs, *TBX4*-related PAH patients can also present anomalies typical of small patella syndrome and/or parenchymal abnormali-

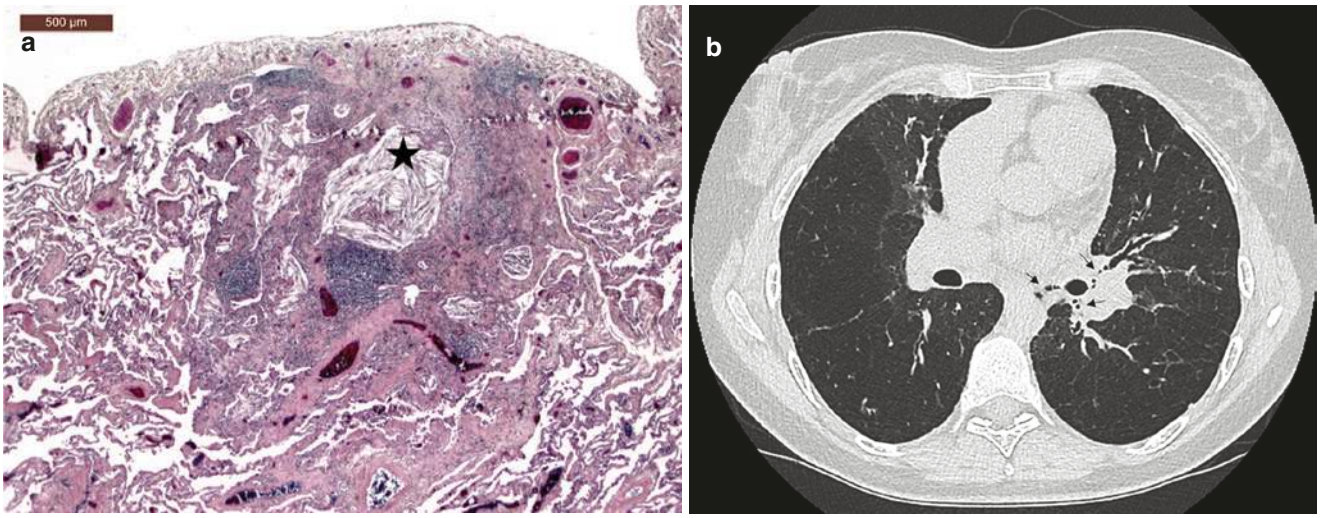

Fig. 41.5 Pathologic assessment and high-resolution CT of a patient with *TBX4*-related PAH with lung parenchymal involvement. (**a**) Interstitial fibrosis with remodeled vessels and cholesterol cleft deposits (*). (**b**) 3-mm thick transverse CT section of the upper lobes. Presence of multiple tracheal and bronchial diverticula (arrow), associated with the presence of emphysema in both lungs

ties [198, 199, 202]. At diagnosis, PH is classically precapillary with severe hemodynamic involvement. Features of SPS are found in most of cases but can frequently be missed if the examination of the lower limbs is not rigorous, and HRCT of the chest, whose examination must be meticulous, reveals bronchial lesions and parenchymal lesions in about 60% and 90% of cases, respectively [199]. However, penetrance of SPS, lung anomalies, and PAH is incomplete, and a same mutation in subjects, from a same family or not, can result in different phenotypes of expression, from a totally asymptomatic clinical picture, to a subject combining PAH, SPS, and lung parenchymal anomalies [199, 203, 204].

Pathological assessment of the lungs of *TBX4*-related PAH patients confirms the existence of a typical vasculopathy, and reveals distal lung development abnormalities associated with the presence of cholesterol cleft inclusions located in the perivascular connective tissue, the pathophysiological significance of which is currently unknown (Fig. 41.5) [198, 199].

As classically observed in other heritable PAH, initiation of PAH specific therapies allows clinical and, to a lesser extent, hemodynamic improvement. The prognosis remains severe and lung transplantation remains, to date, the only curative option [199].

Conclusion

In conclusion, PH can occur in several orphan lung diseases, including sarcoidosis, Langerhans cells histiocytosis, neurofibromatosis, lymphangioleiomyomatosis, and combined pulmonary fibrosis and emphysema. As classically observed in end-stage chronic lung diseases, PH may be a consequence of hypoxic vasoconstriction and vascular bed restriction, and thus appears proportionate with the severity of the parenchymal involvement. However, a specific pulmonary vascular involvement (in particular in sarcoidosis, neurofibromatosis, and pulmonary Langerhans cell histiocytosis) may also develop, associated with severe "out-of-proportion" precapillary PH, usually associated with a poor prognosis. During the last 20 years, mutations in *ACVRL1* or *TBX4*, 2 genes well-known to be responsible for the HHT syndrome and the SPS, respectively, were identified as genes of interest in heritable PAH. In these patients, PAH is usually (but not always) accompanied by characteristic phenotypic traits related to these syndromes. PVOD represents a rare pulmonary vascular disease, with a clinical presentation close to idiopathic PAH, but with important differences in diagnosis, management, and outcome (Box 41.1).

Clinical Vignette

A 71-year-old man was referred for progressive exertional dyspnea. The patient had a history of atrial fibrillation with pacemaker implantation few years ago, obstructive apnea syndrome treated with continuous positive pressure, abdominal aortic aneurysm, and he was a former smoker (50 pack-year). He presented a combined pulmonary fibrosis and emphysema syndrome with typical HRCT of the chest features (Fig. 41.6). PFTs revealed an obstructive pattern on spirometry, a nearly normal plethysmography measurement and a markedly reduced DLCO (Table 41.2). During the 6 months period preceding his admission, he presented a respiratory worsening with an increased

dyspnea (NYHA functional class IV), and severe hypoxemia (PaO_2 at 32 mmHg at ambient air), that couldn't be fully explained by lung involvement. Echocardiography revealed elevated pulmonary pressures associated with dilated right heart chambers and a flattening of the interventricular septum. Brain natriuretic peptide was mildly elevated at 162 pg/mL (normal <80), and 6MWD was reduced to 396 m with desaturation from 82% to 72%. RHC was performed and revealed severe precapillary PH with mPAP, PAWP, CI, and PVR at 49 mmHg, 11 mmHg, 1.5 L/min/m^2, and 13.6 WU, respectively (Table 41.2). Specific PAH therapies are classically not recommended apart from group 1 PH. However, it can be considered in experts centers, in case of severe PH [1]. Thereby, specific combination PAH therapy associating an endothelin receptor antagonist and a phosphodiesterase type 5 inhibitor was sequentially and carefully introduced. Six months later, despite specific PAH therapy, reassessment showed no clinical improvement (NYHA functional class III and decrease in 6MWD to 260 m), despite a mild hemodynamic improvement (mPAP 41 mmHg, CI 1.7 L/min/m^2 and PVR 8.1 WU). To date, the benefit/risk ratio of PAH specific therapies in this indication remains to be determined.

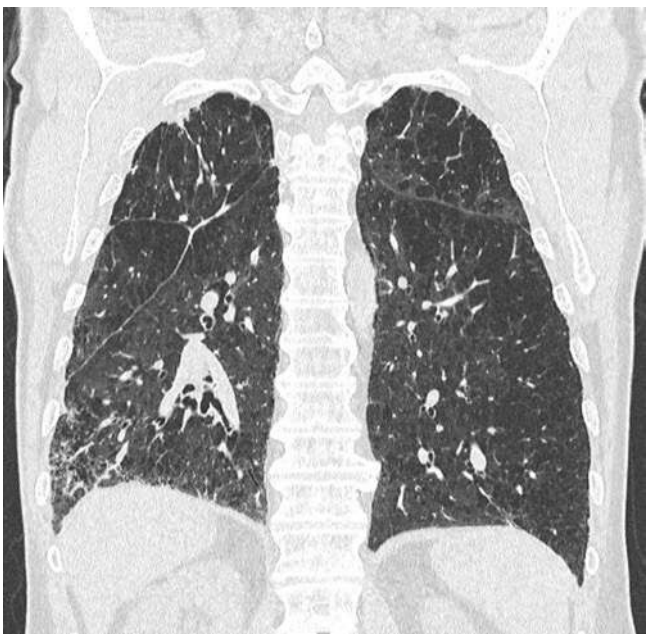

Fig. 41.6 HRCT of the chest showing a typical combined pulmonary fibrosis and emphysema syndrome. 1-mm-thick frontal CT section depicting the presence of diffuse emphysema, associated with the presence of reticulation pattern, cystic lesions, and traction bronchiectasis with a predominance in the lower lobes and in the right lung

Table 41.2 Pulmonary function tests and hemodynamic assessment at time of PH diagnosis

Pulmonary function tests		Right heart catheterization	
FVC [L (% pred.)]	4.4 [122]	RAP (mmHg)	9
FEV_1 [L (% pred.)]	2.23 [80]	mPAP (mmHg)	49
FEV_1/FVC ratio	0.5	PAWP (mmHg)	11
TLC [L (% pred)]	6.4 [98]	CI (L/min/m^2)	1.5
DLCO [% pred]	31	PVR (WU)	13.6

CI cardiac index, *DLCO* diffusing capacity for carbon monoxide corrected for hemoglobin, *FEV_1* forced expiratory volume in 1 s, *FVC* forced vital capacity, *mPAP* mean pulmonary arterial pressure, *PAWP* pulmonary arterial wedge pressure, *PVR* pulmonary vascular resistance, *RAP* right atrial pressure, *TLC* total lung capacity, *WU* wood units

Box 41.1 Diagnostic Criteria for Severe PH

The diagnosis of PH is confirmed by right heart catheterization.

According to the 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension [1], precapillary PH is defined by:
mPAP >20 mmHg
PAWP ≤ 15 mmHg
PVR ≥ 2 WU
In orphan lung diseases, "severe PH":
Was historically defined by: mPAP >35 mmHg, and/or CI <2.5 L/min^1/m^2
Is currently defined by: PVR >5 WU

CI cardiac index, *mPAP* mean pulmonary arterial pressure, *PAWP* pulmonary arterial wedge pressure, *PH* pulmonary hypertension, *PVR* pulmonary vascular resistances, *WU* wood units

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42 Drug-Induced/Iatrogenic Respiratory Disease: With Emphasis on Unusual, Rare, and Emergent Drug-Induced Reactions

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Introduction

Drugs have been known to cause adverse respiratory reactions since at least 1880, when Sir William Osler published an autopsy report of a fatal case of opioid-related alveolar edema [1, 2]. Since then, the literature on iatrogenic and drug-induced respiratory disease has expanded to over 30,700 Medline searchable articles. Therapeutic drugs, substances of abuse, contrast media, chemicals (solid, liquid, or gases), solvents, household compounds, waterproofing agents, air conditioner fluid, glue, irradiation, and medical, imaging or surgical procedures can all cause respiratory injury (Tables 42.1 and 42.2). To date, 1650 drugs, chemicals, agents, and procedures (up from 920 listed in the last edition of this chapter) can cause injury in the form of any of the 784 clinical, imaging, bronchoalveolar, and histopathologic patterns of involvement identified so far. Since 1997, drugs, patterns of injury, and the specific literature are indexed in Pneumotox, a set of daily updated web service and Apps [3, 4] (Table 42.3, Figs. 42.1, 42.2, 42.3, 42.4, 42.5, and 42.6).

Adverse iatrogenic and drug reactions can target any anatomical site of the respiratory system, including the lung parenchyma, central, large or small airways, serosal surfaces, pulmonary circulation, cardiovascular system, respiratory muscles and/or nerves, central nervous system, chest wall or blood (i.e., hemoglobin) alone or in combination. Drugs may also elicit such systemic conditions as lupus, vasculitis or sarcoid-like reactions with involvement of the lung, pleura, heart, or pulmonary circulation. Drugs can cause acute reactions which may be life-threatening within minutes. Large effusions of blood, fluid, chyle, or air/gas in the pleural, pericardial, mediastinal or the retropharyngeal space can cause life-threatening or fatal vessel, airway or organ compression in addition to the consequences of blood or body fluid losses. Pneumotox was developed as a resource for practicing clinicians, to provide freely available and immediate access to iteratively refined and updated information on drugs and the adverse event patterns that they produce [3, 4].

Drug-induced respiratory disorders (DIRDs) have become a common diagnostic consideration in adults and children with new respiratory symptoms and exposure to a compatible drug. Distinguishing DIRDs from idiopathic conditions can be difficult, since drug-induced respiratory reactions often mimic idiopathic conditions (Table 42.4). Early consideration of DIRD is important, however, since delaying the detection, diagnosis, management, and drug removal can be detrimental, exposing patients to superfluous investigation, off-target therapies, and progressive lung injury.

The time from starting treatment with a drug to onset of the reaction varies widely, from a few seconds or minutes with drug-induced bronchospasm, anaphylaxis, pulmonary edema, or angioedema, to days, months or years for pulmonary fibrosis, pulmonary hypertension or pleural effusion. Occasionally, DIRD will manifest months or years *after* cessation of exposure to the drug, creating significant challenges for establishment of a causal link. Diagnostic criteria (Table 42.3) and grading systems for DIRD have been published [5–7] and are available on the frontpages of Pneumotox. An accurate diagnosis rests on a meticulous drug history, identification of the causal drug, evaluation of drug timing, matching drug or drugs and pattern or patterns of involvement, exclusion of other causes and improvement or resolution with drug withdrawal.

Interstitial/infiltrative lung disease (ILD) is the main pattern of drug-induced (DI) lung injury, accounting for two-thirds of the cases of parenchymal lung involvement due to drugs. DI interstitial lung disease (DILD) can be subsumed into the majority of patterns of ILD, including (1) interstitial pneumonias (cellular or fibrotic), including nonspecific

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Table 42.1 Patterns of involvement from drugs—classic purveyor drugs—incidence

	Typical manifestation/pattern	Incidence/Relative risk (RR)	Risk factors	Clinical presentation	Time to onset	Management	Comments—remarks
ACEI (ARB)	Cough	RR 2.5	Varies with the ACEI	Dry chronic cough	w-y	DW	Resolves in all patients
ACEI (ARB)	Angioedema	0.1–0.4%—RR = 7.7	Dark-skinned people	Acute UAO—Asphyxia	w-y	DW, FFP, ecallantide	Emergency management +++. Fatal in 5%
Amiodarone	ILD, ARDS, AH	1–4%	Dosage, time on the drug, O_2	Dyspnea, cough	d-y	DW—CST	Residual fibrosis not unusual
Antibiotics	PIE—Anaphylaxis	–	Atopy	Dyspnea—Anaphylaxis: life-threatening	w-min	DW, CST, resuscitation	Beware of other PIE etiologies Be prepared to manage anaphylaxis appropriately (MC ± ECMO)
Anticoagulants (oral)	DAH. Hematoma around the Aw	Unusual—Can be life-threatening	Parallels the INR	Dyspnea, anemia, stridor	w-y	DW vitamin-K FFP, transfusion	BAL diagnostic on gross examination
Anticonvulsants	DRES syndrome	Up to 1/1000	Familial incidence	Skin, internal organ involvement	mo-y	DW—supportive case	Mortality about 5%
Aspirin—salicylate	Subacute pulmonary edema	45% of those poisoned/intoxicated	The elderly	NCPE, metabolic acidosis	h–mo	DW, alcalinization, dialysis	Common—Mortality up to 15%
ATRA/As_2O_3	Pulmonary edema, DAH	6–27%. Less if pretreatment with CS	Leukocytosis	Pulmonary edema ARDS DAH	d	Supportive Rx + CST	Mortality up to 13%
Beta-blockers	Acute severe bronchospasm	Classical. Uncommon with novel B-	Preexisting atopy—asthma	Acute severe bronchospasm/asthma	min	Supportive + DW	Fatal in up 5%
Bleomycin	Pulmonary infiltrates—ARDS	10–22%	Retreatment, ageing, being a smoker, dose, i.v., infusion, O_2	Basilar—diffuse infiltrates—consolidation	w-mo	Supportive + DW + CS + MV ECMO	Up to 24%—Beware of excessive O_2 in air
Chemo agents	Pulmonary infiltrates—ARDS	Usually about 5%	Dose, O_2, CSF	Basilar/diffuse infiltrates	w-y	DW + CS	Fatality if DAD present
Cyclophosphamide	Pulmonary infiltrates—ARDS—Pulmonary fibrosis	Up to 12%	Dose, O_2	Basilar/diffuse infiltrates	w-y	DW + CS	Up to 40% mortality
Drugs of abuse	Acute pulmonary edema—Pulmonary infiltrates—ARDS—EoP—PHTn—bronchosmasm—pneumoconiosis	Common in those exposed	Depends on compound—Dose—Self-injection of crushed tablets	Acute pulmonary edema—Pulmonary Infiltrates—Pneumothorax—Burns—PHTn	min-y y	DW (corticosteroids)—MV Treat PHT, consider Tx	Panoply of Aes UDS indicated as early as possible
Ergolines	Pleural effusion—Pleural thickening	Unknown	None identified	Chest pain—Restrictive lung dysfunction	y	DW CST rarely indicated	No fatalities. Permanent restriction
Gemcitabile	Pulmonary infiltrates—ARDS—NCPE—HUS	0.03–2% 2.2%	Concomitant bleomycin or irradiation	NCPE, ARDS, DAH, acute renal failure	within 2 mo	DW CST	Mortality: 20%
Gold (rare nowadays)	Acute NSIP	Unknown	None identified	Diffuse pulmonary infiltrates	w-y	DW + CST	Drug fallen out of favor

ICI	Many patterns of involvement—cardiotoxicity common	Common: 2–25%	Preexisting ILD—Combo ICI therapy	Pulmonary infiltrates, lymphadenopathy, pleura	w-mo	DW	CST
Lipids (p.o.)	Exogenous lipoid pneumonia	15% in institutionalized patients	Age—Chronic aspiration	Basilar infiltrates	mo-y	DW. CST?	A disease of the elderly or with achalasia
Methotrexate	Acute NSIP	0.9–3%	? Preexisting ILD	Diffuse pulmonary infiltrates	w-y	DW. CST	
Minocycline	Eosinophilic pneumonia—Acute pulmonary eosinophilia	Unknown	? Atopy	Apical peripheral or diffuse infiltrates	w-mo	DW. CST	Distinctive pattern
	Autoimmune ANA/ANCA disease	Unknown		Pleuropulmonary reaction		DW. CST. IS. Plasma exchange	When assayed ANA in 45%; ANCA in 7%
							Patients may develop PAN
m-TOR inhibitors	Pulmonary infiltrates	Up to 35%	To some extent, dose-related	Basilar pulmonary infiltrates—DAH	w-mo	Dose reduction. DW. CST	Fatal cases among DAH patients
							ILD may equate efficacy in RCC
							Diagnostic challenge in lung Tx recipient
Nitrofurantoin	Acute pleuropulmonary reaction	1/5000	None identified	Acute dyspnea + chest pain	d-w	DW. CST	
	Chronic ILD or fibrosis	1/15,000–45,000	Time on the medication	Chronic dyspnea	mo-y	DW. CST	ANA in some patients
NSAIDs	Asthma, anaphylaxis	Clinical: 3%	Atopy	Acute bronchospasm	min	O_2, CST, MV	Cross reaction among COX1 inhibitors
	Eosinophilic pneumonia	Higher during airway challenge	None identified	Bilateral infiltrates	mo	DW. Corticosteroids	Induction of tolerance possible
Nitrosoureas	Acute lung injury—ARDS	3–5% overall	Dose, time on the medication, young age	Basilar or diffuse infiltrates	w-mo	DW. Corticosteroids	A fraction will respond to CST
	Pulmonary fibrosis			Basilar or diffuse infiltrates	mo	DW. Corticosteroids	Can be devastating
Phenytoin	DRES syndrome	1/1000–1/10,000	Family history	Multiorgan involvement	w	DW. Corticosteroids	Patients may cross-react with other anticonvulsants
Radiocontrast media	Anaphylaxis	02/100,000 PY—1.2/million doses	Atopy	CV collapse, CP arrest, angioedema, shock	min	Withdrawal	Supportive case, resuscitation
Sulfasalazine	Eosinophilic pneumonia		? Inflammatory Bowel Disease	Basilar or diffuse infiltrates and eosinophilia	mo	DW. Corticosteroids	Needs be separated from effect of IBD on lung
	Organizing pneumonia						
TKI	ILD—DAD—ARDS	1–5% in Japan. Much less in the West	Prior ILD	Basilar or diffuse infiltrates	d-w	DW. Corticosteroids	Fatality rate up to 40%

ATRA: tretinoin—all trans retinoic acid—As_2O_3: arsenic trioxide, C = condition, CSF: colony-stimulating factors, DRESS: the syndrome of drug rash, eosinophilia and systemic symptoms, DW: drug therapy withdrawal ("dechallenge test"). To be done with caution as regards the underlying condition, that may flare up, ECMO extracorporeal membrane oxygenation, FFP: fresh frozen plasma, HUS: hemolytic and uremic syndrome, ICI: immune checkpoint inhibitors, LVDF left ventricular dysfunction or failure, PAN: *polyarteritis nodosa*, PIE: pulmonary infiltrates and eosinophilia, RCC: renal cell carcinoma, RR: risk ratio of developing the condition vs. untreated subjects (when data available), TKI: tyrosine kinase inhibitors
w: weeks, y: years, min: minutes, d: days, mo: months

Table 42.2 Main drug families capable of causing respiratory damage

Drug or family		Incidence	Involvement	Comment
Abused drugs/ substances	Heroin, cocaine, crack, cannabis	*****	Thermal airway injury	Crack cocaine
			Catastrophic bronchospasm	Snorted/insufflated heroin
			Pulmonary edema	Heroin overdose
			DAH	Cocaine or levamisole toxicity
			Pneumothorax/ pyopneumothorax	Injection of drug in subclavian/ jugular vein by mate
			Cutaneous necrotic plaques	Cocaine-levamisole toxicity
			Endocarditis	Intravenous drug use
ACE inhibitors	Captopri, enalapril, ramipril …	*****	Cough	Chronic. Abates with drug avoidance
		****	**Angioedema**	Underdiagnosed. Ay lead to asphyxia. Relapses upon rechallenge
				Sartans not entirely safe
		*	PIE	Rare
Aphetamine-like anorexigens	Aminorex, fenfluramine, benfluorex	***	PHT/Valvular heart disease	Drugs were discontinued
Antibiotics	Minocycline, sulfasalazine, penicillin	****	**Anaphylaxis**	Can cause ARF, shock, and death
	Daptomycin		**AEP**	Can cause ARF. Good prognosis
Anticonvulsants	Carbamazepine, phenytoin, lamotrigine	****	**DRESS**	Rash, end-organ involvement, PIE in about 10%
Anticoagulants (oral)	Coumadin, warfarin, superwarfarin	***	**Bland DAH**	Risk parallels the INR
	New direct anticoagulants (DOA)	**	**Laryngeal or tongue hematoma**	May cause acute UAO
Anticoagulants—Thrombolytic agents	Heparin, SK, UK, alteplase, superwarfarin	**	**Bland DAH**	May be confused with pulmonary edema
		**	**Hemothorax**	May cause tamponade and CV collapse
Antidepressants	Sertraline, venlafaxine	**	**AEP**	
			DRESS	
Antithyroid drugs	Propylthiouracil, benzylthiouracil	***	**Capillaritis, DAH**, systemic vasculitis	p- or c- or both c- and p-ANCA present, often anti-HNE at high titers
				Renal involvement common
Angiotensin receptor blockers	Sartans	**	**Angioedema**	Risk 1/10 to 1/20 compared to the risk of ACEIs
Beta agonists (parenteral tocolyticcs)	Salbutamol, terbutaline, isoxuprine	***	**NCPE**	Mostly in parturients. Fatal in 5%
Beta-blockers	Most β-blocking drugs	***	**Catastrophic bronchospasm**	Can be fatal
		**	*Lupus* syndrome	Pleural/pleuropericardial effusion and a positive ANA titers
		*	ILD/OP	Low evidence for causality
Biologics	Anti-TNF agents rituximab omalizumab	**	**Hypersensitivity**, **anaphylaxis**	
		**	**Acute ILD**	More common with rituximab or infliximab
		**	Pulmonary granulomatosis	More common with etanercept
		**	*Lupus* syndrome	Serositis and high ANA and at times anti-ds-DNA

Table 42.2 (continued)

Drug or family		Incidence	Involvement	Comment
Blood, blood products	Blood, blood components, FFP	****	TRALI/TACO	Onset in 6–8 h of transfusion
Curares (NMBA)	Pancuronium, tubocurarine	***	**Severe bronchospasm**	
		**	**Anaphylaxis**	
Cytotoxic agents	Bleomycin, busulfan, cyclophosphamide	***	Transient pulmonary infiltrates	Caution as rechallenge may cause full-blown NCPE/ARDS
	Gemcitabine, nitrosoureas, taxanes	****	**NCPE, DAH, ARDS**	May relapse on rechallenge
			Pulmonary fibrosis	Some will benefit corticosteroid therapy
	Oxaliplatin	**	**Anaphylaxis**	Can be fatal
DMARDs	NSAIDs	****	**Acute asthma**. PIE	Class effect
	Methotrexate	****	**Acute cellular NSIP-like**	Needs be separated from an infection and *Pneumocystis* pneumonia
	Leflunomide	**	Cellular NSIP-like	Described mostly in Japanese RA patients. May be an artifact
	Tacrolimus	*	"ILD"	Described almost exclusively in Japanese RA patients
	Biologics	****	ILD/SLE/DAH	See under TNF-alpha inhibitors
Ergots	Bromocriptine, cabergoline	****	Pleural effusion	Anorexigens produced similar effects
	Ergotamine, DHE, methysergide		Pleural thickening	
	Nicergoline, pergolide	***	Acquired valvular heart disease	
ICI	Nivolumab; pembrolizumab	ILD, OP, ARDS, lymhadenopathy	Differential with underlying neoplastic condition essential	
	Atezolizumab (see Pneumotox)	*****	Pleural effusion	
Interferon alfa/beta		**	Cellular NSIP-like ILD	New drugs to treat viral hepatitis C infection may decrease the incidence
			OP	
			Sarcoid-like reaction	
Leukotriene receptor antagonists	Montelukast, pranlukast, zafirlukast	**	Eosinophilic granulomatosis polyangiitis	Causal relationship need be examined in each case
Lipids (aspirated/ inhaled) hydrocarbon	Paraffin, naphtha, kerosene	*****	Exogenous lipoid pneumonia, HCP	Free lipids in sputum, BAL or tissue
Lipids (infused)	Parenteral nutrition, excipients	**	Fat embolism	
m-TOR inhibitors	Everolimus, sirolimus, temsirolimus	****	Cellular NSIP-like, OP, **DAH**	Dose-related. Abates dose reduction or discontinuance
			Rare PAP pattern	
NSAIDs, aspirin	ASA, ibuprofen, indomethacin, …	****	**Severe bronchospasm**	Relapses on rechallenge
	Naproxen, piroxicam	**	PIE	Relapses on rechallenge
	Aspirin	***	**NCPE**	Anion gap, metabolic acidosis, high salicylate levels in blood
Platelet GPIIb/IIIA inhibitors	Abciximab, clopidogrel, eptifibatide, ticlodipine, tirofiban	***	**DAH**	

(continued)

Table 42.2 (continued)

Drug or family		Incidence	Involvement	Comment
Radiation therapy	Lung	****	**Radiation-induced lung injury**	Localizes along radiation beam
	Lung	***	Stereotactic radiation therapy	nodule/Mass. Whorled appearance. Can be tracer-avid on PET scan
	Mediatinum	**	**Mediastinal fibrosis**	Compression of pulmonary vein
	Trachea	**	Stenosis	
	Endobronchial	**	**Dehiscence**	Fatal hemoptysis
	Breast	***	OP	Corticosteroid may be indicated
	Liver	**	**ARDS**	^{131}I (radioiodine)
Statins	Fluvastatin, pravastatin, simvastatin	***	Cellular NSIP-like	Ground-glass on HRCT
			OP	Fixed or migrating alveolar opacities
			ARDS	Statin myopathy can be present in association
TKI inhibitors	Erlotinib, gefitinib	***	**DAD/ARDS**	Difficult to separate from underlying disease or from an infection
				Baseline ILD may increase risk of developing the condition
	Imatinib	**	Cellular NSIP-like	Class effect of these medications
	Dasatinib	**	Pleural exudate, chylous effusion	
TNF alpha-antibody therapy	Etanercept, infliximab, adalimumab	***	**Accelerated ILD**	May mimic an infection or exacerbation of underlying rheumatoid lung
			Pulmonary granulomatosis	May mimic sarcoidosis
			Opportunistic infections incl. TB	Pretherapy evaluation as regards latent TB indicated using TST and IGRA

Boldface: potentially life-threatening conditions
* Rare
***** Very frequent
ACEI: angiotensin converting enzyme inhibitors, AEP: acute eosinophilic pneumonia, ANA: antinuclear antibody, Ds-ANA: anti double strand antibody, ANCA: antineutrophil cytoplasmic antibody antibodies, ARDS: adult respiratory distress syndrome, ARF: acute respiratory failure, ASA: acetylsalicylate, CV: cardiovascular, DAD: diffuse alveolar damage, DAH: diffuse alveolar hemorrhage, DHE: dihydroergotamine, DRESS: drug rash with eosinophilia and systemic symptoms, HCP: hydrocarbon pneumonitis, ICI: immune checkpoint inhibitors, ILD: interstitial lung disease, INR: international normalized ratio, NMBA: neuromuscular blocking agents, NCPE: noncardiac pulmonary edema, NSIP: nonspecific interstitial pneumonia, OP: organizing pneumonia, PAP: pulmonary alveolar proteinosis, PHT: pulmonary hypertension, PIE: pulmonary infiltrates and eosinophilia, RA: rheumatoid arthritis, SLE: systemic *lupus erythematosus*, TB: tuberculosis, UAO: upper airway obstruction

interstitial pneumonia (NSIP), organizing-pneumonia, acute or chronic eosinophilic-pneumonia, desquamative interstitial-pneumonia (DIP), lymphocytic interstitial pneumonia (LIP), giant cell interstitial pneumonia (GIP), and usual interstitial pneumonia or fibrotic nonspecific interstitial pneumonia; (2) alveolar filling disorders (phospholipidosis or alveolar proteinosis (PAP)), exogenous lipoid pneumonia, amiodarone pulmonary toxicity, pulmonary edema, alveolar hemorrhage. The list of histopathological patterns is available under heading "XVI" in Pneumotox [3, 4]. Other mechanisms and patterns of injury include airway-, pleural-, mediastinal-, and neuromuscular involvement, drug-induced vasculopathies, systemic reactions induced by drugs, and a *potpourri* of variegated and unusual patterns of drug-induced injury [3, 4]. Drugs can also cause cardiac injury in the form of valvular heart disease, cardiomyopathy, myocarditis, pericarditis, pericardial effusion, arrhythmias, coronary heart disease, coronary spasm, or heart block. Consequent drug-induced left ventricular dysfunction may cause cardiogenic pulmonary edema [3, 4]. Pneumotox lists >70 patterns of drug-induced cardiac involvement, and 50 drugs capable of causing cardiogenic pulmonary edema. The App Cardiotox is free and available for download [8].

DIRD as a whole are rare. Relatively common causative drugs include (Table 42.4) angiotensin-converting enzyme inhibitors (ACEI), amiodarone, anticoagulants, beta-blockers, chemo agents (bleomycin, busulfan, cyclophosphamide, and nitrosoureas, among many others), antibiotics (daptomycin, minocycline, penicillin, trimethoprim-sulfamethoxazole [9]), methotrexate (although the incidence of pulmonary compli-

Table 42.3 Check list for diagnosing drug-induced/iatrogenic respiratory disease or reactions

Absence of pulmonary disease prior to therapy with the suspected drug
Respiratory event is unlikely to develop in the course of the underlying disease
Confirmed exposure to the drug
Eligible drug (Drug singularity?)
Absence of prodromal signs and symptoms prior to exposure to the drug
Appropriate timing (latency time, time to onset) relative to taking the medication
Pattern appropriate for the drug under scrutiny
Confirmatory data in the literature (qualitative = consistency. Quantitative = magnitude)
Suggestive/Supportive symptoms, imaging (CXR, HRCT, nuclear medicine), laboratory data, BAL, pathology
Laboratory evidence including plasm levels, UDS
Reasonable exclusion of other causes including an infection and the adverse effect of comedications
Improvement, abatement or resolution with discontinuation of the drug, preferably without recourse to corticosteroids
Lack of recurrence of signs and symptoms is patient not rechallenged with the drug[a]
Relapse following rechallenge with the drug[b]

[a] Drug-induced organizing pneumonia may show replicas despite drug discontinuation

[b] Rechallenge can be hazardous or lethal

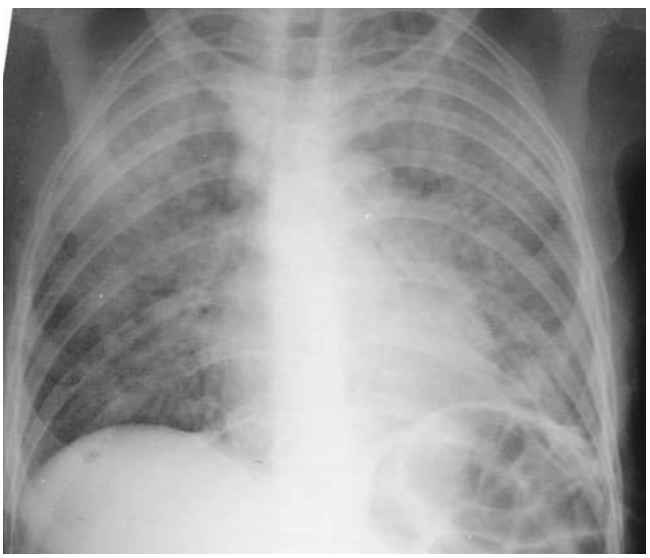

Fig. 42.1 Acute severe cellular ILD and pulmonary edema with acute respiratory failure (confirmed by open lung biopsy). Young lady. Methotrexate lung (note chest tube on left side post-lung biopsy). It is generally impossible to anticipate the exact histopathologic pattern of involvement from data on chest imaging. The disease resolved in a few weeks following drug withdrawal and corticosteroid therapy (i.v. then p.o.)

cations of that drug are not as high as in the past), nitrofurantoin, anticonvulsants, statins, nonsteroidal anti-inflammatory drugs (NSAIDs), and salicylate [3, 4]. The current literature does not always reflect this, because well-known drug reactions tend to be published less frequently. Emerging drugs and inhaled agents are increasingly implicated in DIRD, including immune checkpoint inhibitors (anti-PD1, -PDL1, -CTLA4) [10], monoclonal antibodies (TNF-alpha-, CD20-(rituximab)) [11], e-cigarette liquids or vapor [12], tyrosine- or protein kinase inhibitors (e.g., BCR-ABL, mTOR), anticoagulants (platelet glycoprotein IIB/IIIA receptor-, antithrombin-), antiviral drugs (reverse transcriptase inhibitors), substances of abuse (cannabinoids, levamisole), and cosmetic agents (silicone, hyaluronate or autologous fat). Drugs, corresponding patterns of involvement, and literature (minimized for space constraints here) can be easily accessed in Pneumotox [3, 4]. A further difficulty is that treatments with TNF-alpha inhibitors or other targeted agents including immune checkpoint inhibitors can be complicated by opportunistic or non-opportunistic bacterial, mycobacterial (including de novo or reactivation pulmonary or extrapulmonary tuberculosis), viral or fungal infections [13].

Warning symptoms are occasionally present before full-blown adverse drug reactions become manifest. However, most drug-induced respiratory reactions occur unexpectedly in patients receiving therapeutic doses of the drug. Overdose of drugs including opioids [14] and drug poisoning [15] is generally considered outside the province of adverse reactions to drugs. However, this will be touched upon when appropriate, as drug overdose can manifest with pulmonary edema, alveolar hemorrhage, ARDS, metabolic acidosis, airway bleeding, acute ventilatory depression, and/or aspiration pneumonia.

Drug overdose can occur with minute amounts of novel hyperpotent drugs of abuse (e.g., carfentanyl, synthetic cannabinoids) or toxic chemicals (e.g., the weaponized "Novichoks" "Новичок" organophosphates). These can cause acute respiratory failure and death. The corresponding toxidromes [16–18] must be available or known, because medical personnel must be protected, and antidotes are available to counter the pharmacological action of opiates, anticoagulants, methemoglobinemia-inducers, and organophosphates. Care must be taken to have antidotes readily available at all hospitals [19].

Some adverse drug-induced respiratory reactions may result from sequential, downstream or domino adverse effects. Examples include (1) Amiodarone-induced thyrotoxicosis followed by arrhythmias, heart failure, and/or pulmonary edema [20], (2) amiodarone-induced hypothyroidism,

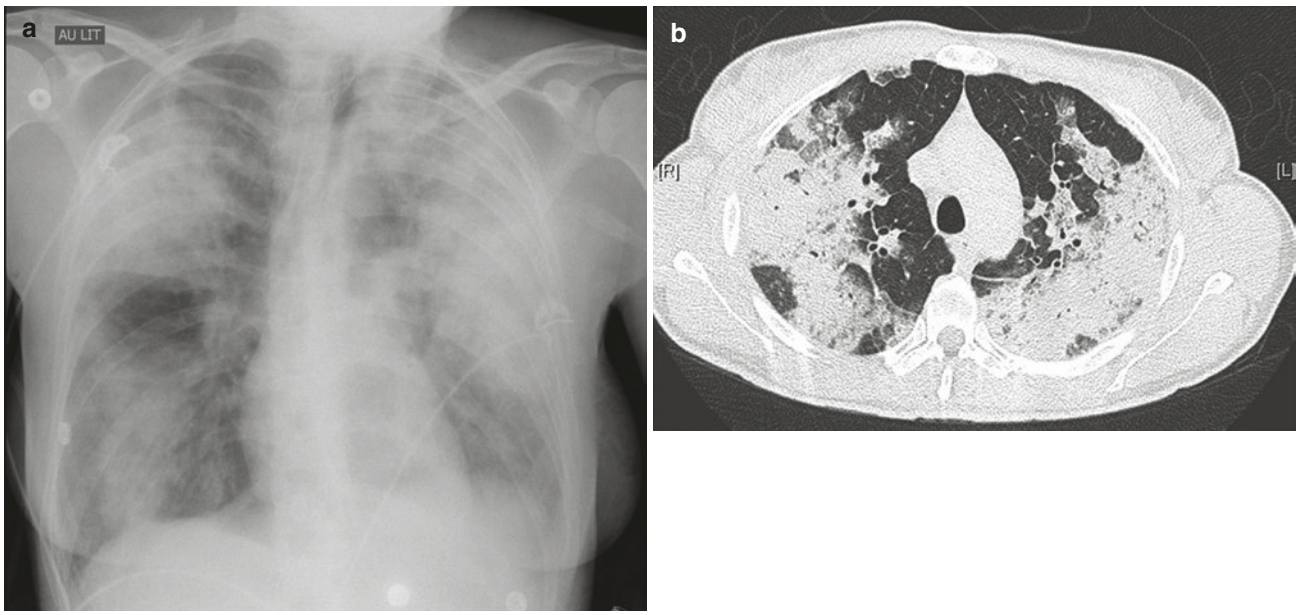

Fig. 42.2 (**a**, **b**) Acute eosinophilic pneumonia and acute respiratory failure presumably due to a LTRA. The matching CT scan is shown on (**b**). Eosinophilic pneumonia often has a predilection for the bilateral subpleural and apical areas of the lung

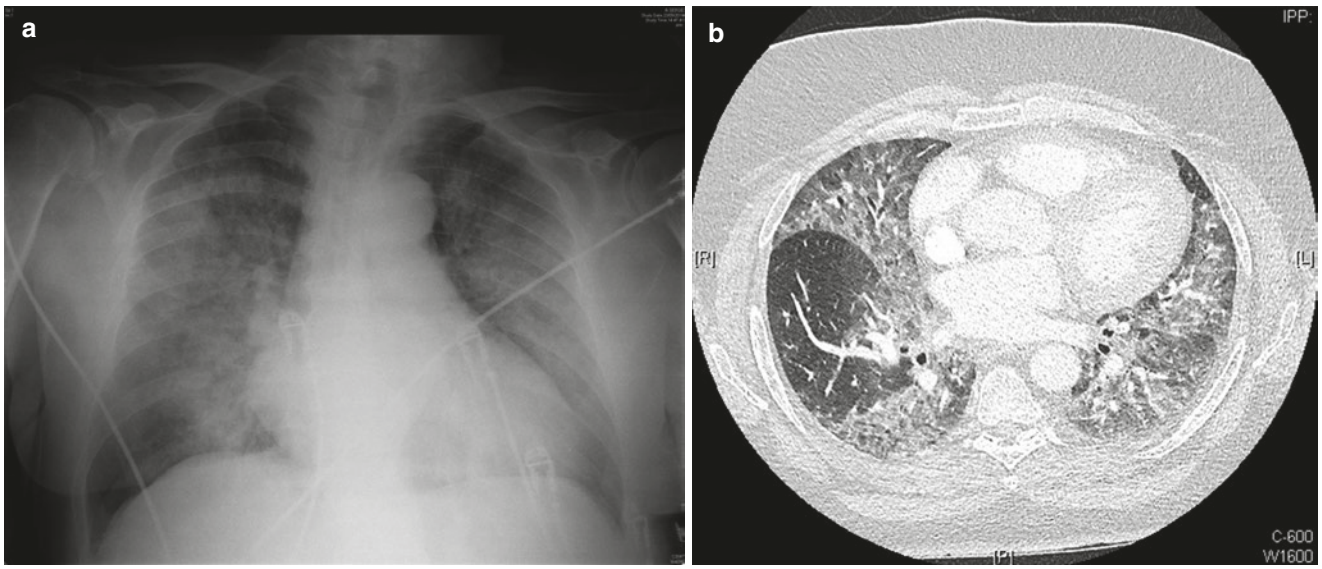

Fig. 42.3 (**a**, **b**) Acute amiodarone-induced pulmonary toxicity/Amiodarone lung. (**b**) CT. This complication often occurs following thoracic or cardiovascular surgery, even after only a few days on the medication, causing diagnostic difficulties. The trauma or surgery and liberal oxygen therapy may trigger the onset of this complication

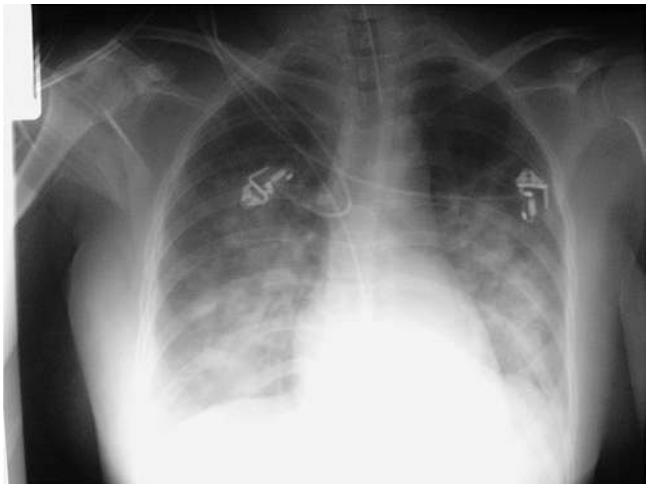

Fig. 42.4 Acute drug-(tocolytic agent in this case) induced pulmonary edema. In each patient, it is necessary to separate cardiogenic or overload pulmonary edema from noncardiogenic pulmonary edema using imaging (particularly vascular pedicle size, presence of pleural effusion or effusions, and heart size), cardiac ultrasound, cardiac biomarkers, measurement of filling pressure. Diuretic therapy is reserved for cardiogenic/overload pulmonary edema

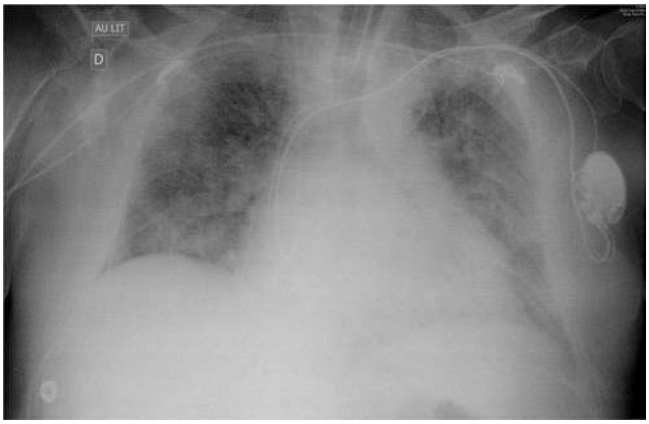

Fig. 42.5 Drug-induced alveolar hemorrhage. All anticoagulants can produce alveolar hemorrhage. Brodifacoum (superwarfarins) can also produce this complication. Superwarfarin must be searched actively in plasma. Superwarfarins are now present as an adulterant in many cannabinoid samples

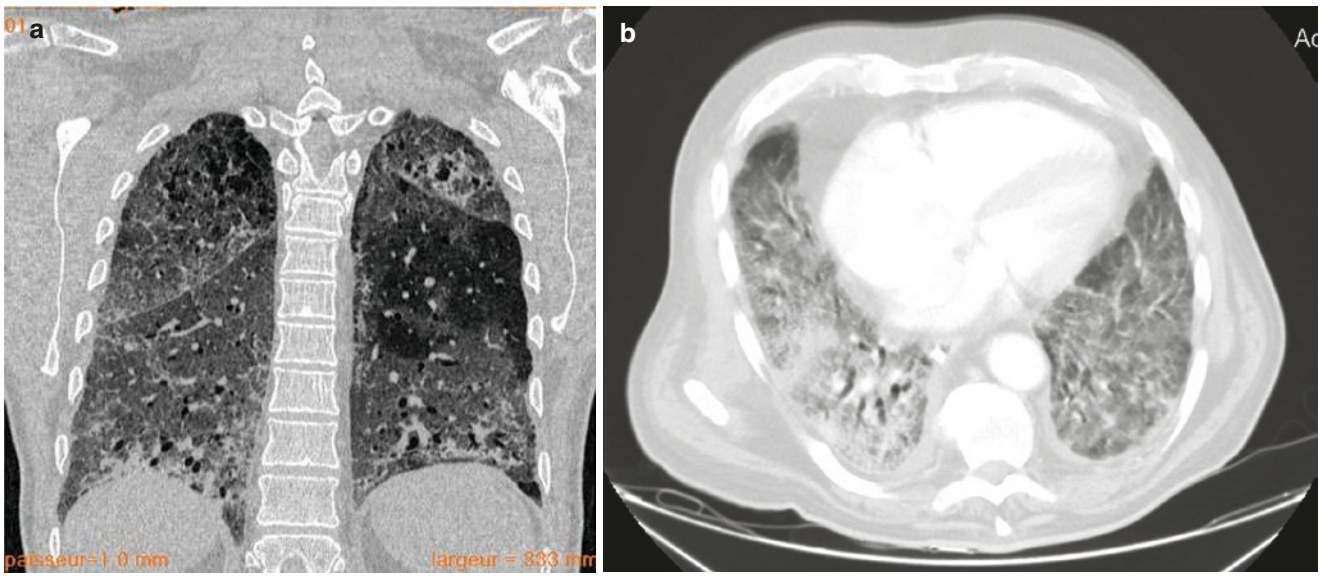

Fig. 42.6 (**a**, **b**) Bleomycin-induced ARDS (severe bleomycin pulmonary toxicity). Full list of drugs causing acute ILD, eosinophilic pneumonia, organizing pneumonia, pulmonary edema, alveolar hemorrhage or ARDS is available on Pneumotox. Drug-induced allergic or hypersensitivity-related emergencies including anaphylaxis, and methemoglobinemia, though life-threatening, may not express themselves on plain imaging. Drug-induced upper airway obstruction can be visualized on CT or MRI, although emergent cases require immediate endoscopy and securing the airway. Detailed list of imaging patterns (n = 75) of drug-induced/iatrogenic respiratory disease or reactions available on section XVI in pneumotox website and XVII on the App

pericardial effusion, and tamponade [21], (3) epinephrine (adrenaline)- (used to treat drug-induced angioedema) or licorice-induced hypertension, heart failure, and pulmonary edema [22], (4) self-i.v. administration of drugs of abuse causing right-sided endocarditis followed my metastatic pulmonary embolism and multiple lung abscesses [23] and opioid-induced ventilatory depression [14] and antidote (naloxone)-induced pulmonary edema [24].

Table 42.4 Lung diseases commonly considered as idiopathic that can be induced by drugs

Pattern	% Drug-induced	Established or suspected causal drugs or agents (see Pneumotox for full list)
NSIP-cellular	3–5%	Nitrofurantoin, immune checkpoint inhibitors (ICI)
Eosinophilic pneumonia	12–17%	Antibiotics, NSAIDs
ILD with a granulomatous component	–	Interferon, BCG-therapy, anti-TNF antibody therapy, ICI
Organizing pneumonia	20–30%	Nitrofurantoin, amiodarone, statins, interferons, ICI
Pulmonary fibrosis	–	Amiodarone, chemotherapy, nitrofurantoin, radiation therapy, ICI
Exacerbated pulmonary fibrosis	–	Amiodarone, chemotherapy, TKI, TNF antagonists, ICI
Accelerated pulmonary fibrosis (AIP)	–	Amiodarone, anti-TNF agents, nitrofurantoin
Sarcoidosis-like reaction	–	Interferons, ICI
Hilar or mediastinal lymphadenopathy	–	Interferons, BCG therapy, ICI
Pulmonary alveolar proteinosis	–	Busulfan, imatinib, sirolimus
Pulmonary edema	–	Tocolytic agents, heroin, opiates, salicylate, hydrochlorothiazide, chemo agents, naloxone
ALI/ARDS	9.5%	Amiodarone, chemotherapy agents, ICI, radiation therapy
Diffuse alveolar hemorrhage	11–18%	Anticoagulants, platelet aggregation inhibitors, propylthiouracil, cocaine-levamisole, superwarfarins (brodifacoum)
Angioedema	70%	ACEI, ARB
Deterioration of asthma	8%	Beta-blockers (oral/topical), NSAIDs
Chronic cough	–	ACEI (ARB)
Pleural effusion incl. chylothorax	–	Amiodarone, dantrolene, dasatinib, ergots, imatinib, statins, irradiation
Pulmonary embolism	–	Lenalidomide, neuroleptic agents, thalidomide
Disordered breathing during sleep	–	ACEI, opiates
Lone dyspnea	–	Ticagrelor
Hiccup	–	Chemotherapy drugs
Lupus and serositis	10%	Anticonvulsants, beta-blockers, anti TNF-antibody therapy
DRES syndrome	100% (by definition)	Anticonvulsants, minocycline
ANCA-related DAH and/or vasculitis	High if dual ANCA or polyspecific ANCA present	Cocaine-levamisole, hydralazine, propylthiouracil
Eosinophilic granulomatosis with polyangiitis	–	LTRA, omalizumab
Polymyositis	–	Statins, ICI
Pulmonary aspergillosis	–	Chemotherapy, marijuana, ICI
Cardiomyopathy	–	Methamphetamine, chemo agents, anticancer drugs, cocaine, ICI, imatinib

In such patients, an accurate drug history taking is needed in all cases
Full list of causal drugs per syndrome available in Pneumotox and Pneumotox App. See text and references
Drug therapy withdrawal indicated whenever possible (underlying disease permitting)
Follow-up may show improvement following drug discontinuation in drug-induced cases
Blank: no reliable data available
ICI: immune checkpoint inhibitors, LTRA: leukotriene receptor antagonists

Epidemiology

The incidence of pulmonary toxicity due to most drugs is low-to-very low. Given that DIRDs generally have a prevalence of under 1/2000 (and many much lower), a large number of these conditions qualify as orphan diseases. Among the 1650 current drugs and agents known to cause respiratory injury, 1011 do so rarely with fewer than ten reports in the world literature [3, 4]. The rigor of published reports varies widely [25] and some date back many years. Guidelines and good publication practice for classifying and characterizing adverse drug reactions are not always followed. In addition, patients may have received corticosteroid or other disease-modifying therapy, making it difficult to evaluate the

effect of drug withdrawal and to assign causality; an assessment which (unfortunately) is often inadequately performed [5, 6, 26].

Relatively "common" pulmonary toxins such as nitrofurantoin or amiodarone have a DIRD incidence rate of 0%, 2%, and 1.9%, respectively. Incidence is possibly higher in Japanese compared to caucasians patients. Chemotherapeutic agents with relatively well characterized incidence rates of DIRD including chemo agents: 1–3%, crizotinib: 1.8%, brigatinib: 7%, ceritinib: 1.1%, alectinib 2.6%, and lorlatinib: 1.8%. Even higher incidence rates (3.5–20%) can be observed with the use the novel immune checkpoint inhibitors (ICI) [27], or when more than one ICI is given concomitantly. DIRD due to tyrosine kinase inhibitors is also relatively common (1–5% depending on severity grade). These estimates should be viewed with caution, as both the definition of DILD and diagnostic criteria are variable between studies and countries. Reported DIRD incidences as high as 50% in early phase 1 or 2 combination chemotherapy trials with bleomycin, CCNU, gemcitabine, or dasatinib and irradiation may have hampered the development of these agents if methods of assessment had not advanced. Recently, histopathology descriptors have been used to name roentgenographic patterns of involvement [28–30]. The accuracy, reliability, and reproducibility of these methods are unknown. Studies blindly comparing imaging and pathology have shown suboptimal agreement [31, 32]. The Fleischner Society glossary of terms remains an important reference which can be used to describe and classify imaging characteristics [33], and as was employed to construct the imaging section in Pneumotox [3, 4]. Estimates of the fraction of ILD due to drugs in ILD populations ranged between 3% and 5% [34], 9.5% in ARDS [35], 11–18% in alveolar hemorrhage [36], 12–17% in eosinophilic pneumonia [37], 3% for organizing pneumonia due to amiodarone [38], or drugs 28% [39], and 1–3% for breast radiation-induced organizing pneumonia or cryptogenic organizing pneumonia (COP) [40].

Overall, it is estimated that 8% of DIRD are preventable if risk factors, adjusted drug dosage and guidelines are implemented and followed [41, 42]. Approximately 4% of all DIRDs are lethal, partly because patients are deliberately or inadvertently rechallenged with the culprit drug [43]. Atopy and asthma are considered risk factors for allergic reactions and anaphylaxis. Pre-existing ILD may predispose to the risk of developing drug- or radiation-induced pneumonitis [44, 45].

Timing, Chronology, Delay Time

About a fifth of all DIRDs exhibit a rapid or precipitous onset immediately after the first administration of the drug or agent. Such reactions include drug-induced flash pulmonary edema [46], catastrophic bronchospasm [47], hypersensitivity, anaphylaxis [48], acute ventilatory depression and respiratory failure [49, 50], coronary vasospasm [51], suffocation:asphyxia from inhaled substances, gases or chemicals [52, 53]. However, the majority of drug-induced or iatrogenic pulmonary, pleural, vascular, mediastinal, cardiovascular or lymphatic reactions develop more slowly months or years into treatment. Rarely, the adverse reaction develops after termination of treatment with the drug, typically a chemo agent such as nitrosoureas or amiodarone, or chest radiation therapy.

Route of Administration

Drugs can cause respiratory disease regardless of the route of administration, although the oral and parenteral routes are more commonly implicated. Drugs that are inhaled, given topically in the form of application or instillations into the pleural space, epidural or intrathecal space, vertebral body, eyes, urinary bladder, female genital tract, or delivered subcutaneously or transdermally, can all cause respiratory injury.

Patterns of Involvement [3, 4]

DIRD may manifest in the form of parenchymal lung disease, pulmonary infiltrates, pulmonary hemorrhage, storage lung diseases, or involvement of the central, large or distal airways, pleural and/or pericardial surface, heart, pulmonary circulation, coronary arteries, mediastinum, respiratory muscles, central nervous system, nerve and nerve endings, or hemoglobin [3, 4]. Drugs or families [e.g., beta-blockers, nonsteroidal anti-inflammatory drugs (NSAIDs)] or salicylate may cause a stereotypical pattern of injury [e.g., acute bronchospasm, angioedema, pulmonary edema, or ILD] [3, 4] (Table 42.2). In general, drugs produce more than one pattern of respiratory involvement, as exemplified by amiodarone and immune checkpoint inhibitors (ICI) which outnumber almost any other drugs in terms of patterns of injury (with 83 and 90 patterns, respectively). It is equally important to be vigilant for adverse effects (sometimes severe) of drugs in extrapulmonary organs or organ systems, especially during treatments with amiodarone, TKI or ICI.

Illicit/abused drugs and agents including ethanol can cause severe respiratory issues and are therefore also harbored in Pneumotox. In the past 40 years, the death toll from opioids due either to ventilatory depression, falls or aspiration increased several-fold in the US [54], now as high as 3.3% of the exposed population. Subversion of drug use, cinnamon, pepper, herbal therapy, dietary supplements, energy drinks, "incense" and concoctions purchased via the Internet

[55] emerged as a novel cause of life-threatening injury, burns, fainting, choking, bronchospasm, or acute respiratory failure or ARDS [56]. Room air in "Meth-Labs" can harbor toxic chemicals capable of causing life-threatening or fatal injury to the owner, manufacturer, family, kids, law enforcement officers, coroner, firefighters, forensic personnel and/or healthcare workers [57, 58]. Other presentations of DIRD include drug-induced occupational asthma in the pharmaceutical industry [59], and lung injury in pets or other animals that can be similar to those in humans [3, 4].

Diagnosing Drug-Induced Respiratory Disease (DIRD)

Early consideration that a drug or a combination of drugs, abused substances, electronic cigarettes (-e-cigarettes), electronic nicotine delivery systems (ENDS), chemicals, household chemicals, or radiation therapy may be the cause for a respiratory problem is important for optimal patient care, because: (1) Further damage can be avoided by withdrawing the drug or exposure early, (2) Invasive procedures such as lung biopsy and/or empiric corticosteroid therapy can be avoided pending the outcome of drug holiday or exposure withdrawal (which can be diagnostic if followed by resolution of all presenting signs and symptoms), (3) Inadvertent re-administration of the causal drug can be fatal. A high index of suspicion is needed at all times in adults, children, and in the newborn, where vertical transmission of drug-induced respiratory adverse effects from the mother to the infant is possible. Classic papers on causality assessment and scoring remain valuable resources [6].

A few drugs are reserved for treatments in females or males, and DIRD occur preferentially or exclusively in one gender (e.g., nilutamide is a therapy used to treat prostate carcinoma, and i.v. tocolytics can produce pulmonary edema in women). Altered sensorium and inability to communicate with the patient in the emergency setting may complicate history taking at the bedside, leading to reliance on information from relatives, friends, family physician or pharmacists. Urine drug screens and measurements of blood levels of drugs (e.g., salicylate), illicit drugs, chemicals (e.g., paraquat, brodifacoum, organophosphates) in blood are helpful but not all results are immediately available. It is important to obtain samples early in the course of events, before the drug or metabolites are cleared from the blood or urine. Drugs differ widely in terms of time to onset, symptoms, clinical radiographic, laboratory, bronchoalveolar lavage, and pathological pattern and outcome (see Pneumotox and [3, 4]). Determination of latency period and time course of symptoms vs. exposure and matching the suspected drug with the observed pattern of involvement is key to establishing the correct diagnosis. Diligent consideration of other plausible causes and etiologies of the presenting illness is required, as drug-induced pneumonitis is a diagnosis of exclusion and infectious lung diseases and pulmonary involvement from systemic diseases may present similarly. The expansive differential diagnosis depends on drug, underlying background, comorbidities, clinical and epidemiologic context, presentation, pattern of involvement and whether the patient was being exposed to one or more than one drug, immunosuppressive agents, dietary supplements and/or drug of abuse. Clinical improvement or resolution of symptoms following drug discontinuance favors a drug etiology. However, acute severe drug-induced lung disease, including pulmonary edema, alveolar hemorrhage, ARDS or systemic reactions may not improve in an immediate and linear fashion upon simple drug discontinuance. In such situations, corticosteroid therapy or immunosuppressants may be indicated. Lack of recurrence within an appropriate observational period off the drug also supports the drug etiology, while relapse after rechallenge with the drug, be it inadvertent or deliberate, is indisputable evidence for causality of the drug or its excipients. Of course, rechallenging patients with the putative offending drug can be hazardous and sometimes fatal, so appropriate consideration for that approach is imperative. Criteria for rechallenging patients include: (1) the drug is vital, (2) there is no adequate substitute, (3) rechallenge is not always followed by relapse (based on literature), (4) a protocol for induction of tolerance with or without corticosteroid therapy is available, (5) rechallenge is validated by a multidisciplinary discussion, (6) rechallenge can be conducted in a safe environment (i.e., in a setting with adequate resuscitative equipment), (7) detailed informed consent is obtained. Overall, 1.4% of all DIRD cases are rechallenged, leading to death in as many as 7% of those so tested (extracted from references in [3, 4]). Immediately negative rechallenge does not exclude the diagnosis of DIRD.

A lung biopsy is obtained in approximately 6.2% of all DILD cases reported in the literature. Except in rare circumstances (e.g., with amiodarone pulmonary toxicity or when distinctive foreign drug material is present in lung tissue), changes are at most "compatible" or "consistent" with, and less often, "suggestive" of the drug etiology [60, 61]. This limits the potential contribution of lung tissue sampling, inasmuch as complications may occur following lung biopsy be it open-, transbronchial-, or cryo-. Still, lung biopsy may prove useful to rule out a non-iatrogenic etiology. Table 42.5 lists the pathology patterns of iatrogenic lung disease and whether the bronchoalveolar lavage can be used as a surrogate test [62]. Diagnostic criteria are summarized in Table 42.3 and on the Pneumotox frontpage. Though in a number of cases respiratory reactions were definitely ascribed to a drug, more often the drug etiology is represented as likely, probable or possible, with all the uncertainty

Table 42.5 Drug-induced/Iatrogenic respiratory disease: Pathology

Histopathologic pattern	Typical drug or drugs causing the pattern	Frequency	BAL surrogate?	Consistent with	Suggestive	Specific
Cellular ILD, NSIP-cellular-like	ICI, ethotrexate, nitrofurantoin, sirolimus	Common	Y if lymphocytic	X		
Eosinophilic pneumonia	Minocycline, NSAIDs, drugs of abuse	Common	Y		X	
Organizing pneumonia (OP pattern)	Amiodarone, interferon, statins, ICI	Common	N	X		
Acute Fibrinous Organizing Pneumonia (AFOP)	Amiodarone, ICI, statins	Uncommon	N	X	X	
ILD with a granulomatous component	BCG, ICI, interferon, methotrexate	Common	Y?	X	X	
ILD with a necrotizing granulomatous component	BCG, marijuana, methotrexate	Uncommon	Y?	X		
Diffuse alveolar damage DAD	Amiodarone, chemotherapy, ICI, irradiation	Common		X	X	
A reactive epithelium, pneumocyte atypia	Alkylating chemotherapy, irradiation	Common	Y	X	X	
Diffuse alveolar hemorrhage DAH	Anticoagulants, platelet aggregation inhibitors, superwarfarins	Quite common	Y	X		
Pulmonary fibrosis, NSIP-fibrotic	Chemotherapeutic drug, amiodarone, ICI	Common	N	X		
Pleuroparenchymal fibroelastosis	Cyclophosphamide, status post-transplantation	Rare	N	X		
UIP pattern	Chemotherapeutic drugs, bleomycin	Common	Y?	X		
DIP pattern	Amiodarone, nitrofurantoin, sirolimus	Unusual	N	X		
GIP pattern	Nitrofurantoin	Rare	Sometimes	X		
LIP pattern. Lymphoid hyperplasia	Amiodarone, anticonvulsants	Unusual	Sometimes	X		
PAP pattern—secondary PAP	Busulfan, dasatinib, sirolimus	Rare	Y	X	X	
Endogenous lipoid pneumonia—phospholipidosis	Amiodarone	Very common	Y		X	X
Exogenous lipoid pneumonia	Paraffin, mineral oil, excipients	Common	Y			X Lipid staining diagnostic
Interstitial foreign body granuloma	Abused drugs, excipients, talc, silica, from aspirated or self-injected tablets	Uncommon	Y			X
Smudged parenchymal necrosis	Amiodarone	Uncommon	N		X	X
Pneumoconiosis, talcosis	Abused drugs, talc	Uncommon	Y			X
Amyloid deposits	Insulin	Rare	N			X
Crystal storage disease	Clofazimine	Rare	N			
Diffuse pulmonary calcification	Calcium replacement	Rare	N	X		
Bland pulmonary edema	Chemotherapy, salicylate, heroin	Common	N	X		
Subacute/acute cellular bronchiolitis	Aspirated food, e-cigarette, vedolizumab, tobacco smoke, talc	Uncommon	N		X	X (if demonstrable food particulate matters in tissue)

(continued)

Table 42.5 (continued)

Histopathologic pattern	Typical drug or drugs causing the pattern	Frequency	BAL surrogate?	Consistent with	Suggestive	Specific
RB-ILD	Tobacco smoke	Common	Sometimes		X (if pigmented macrophages present)	
Constrictive obliterative bronchitis	? Penicillamine ? Gold. *Sauropus androgynus*	Rare	ND	X		
Foreign body bronchiolitis	Talc	Uncommon	Y			X
Pulmonary capillaritis	ATRA, PTU	Rare	N	X		
Pulmonary vasculitis other than capillaritis	Hydralazine, L-tryptophan	Rare	N	X		
Eosinophilic vasculitis	L-tryptophan	Uncommon	Y		X	
Fat/marrow embolism	Parenteral nutrition, propofol, vertebroplasty	Uncommon	Y		X	
Silicone embolism	Fluid silicone	Uncommon	Y			X
Foreign body vasculopathy	Talc, excipients from i.v. injected tablets	Uncommon	N			X
Elemental mercury embolism	Liquid mercury	Rare	N			X
Cement embolism	Acrylate cement	Uncommon	N			X
Crystal pulmonary embolism	i.v. lipids	Rare	N		X	
Venoocclusive disease	Antineoplastic chemotherapy	Uncommon	N	X		
Pulmonary hypertension	Anorexigens	Quite common[a]	N	X		
Pleuritis	Radiation therapy, drug lupus	Common	N	X		
Eosinophilic pleuritis	Propylthiouracil PTU	Uncommon	N	X		
Pleural fibrosis	Amiodarone, ergots, drug-induced lupus	Common	N		X	
Fire eater's lung	Kerdane, petrolatum	Uncommon	?		X	
Kayexalate lung	Kayexalate	Uncommon	Y			X
Carbonaceous deposits	Crack cocaine	Uncommon	Y			X

See section XVI in Pneumotox and in the Pneumotox App
Consistent with = pathology shows nonspecific findings and cannot supports the diagnosis
Suggestive = pathology findings are distinctive enough to support the diagnosis
Specific = changes (almost) pathognomonic
Where BAL can reasonably be used as a surrogate, consider deferring the lung biopsy, pending the results of BAL and drug withdrawal or dechallenge test
The results of the transbronchial lung biopsy may not match those of the open lung biopsy
Progress of cryo lung biopsy continues
Blank/void cell indicates absence of data
ICI: immune checkpoint inhibitor(s)
[a] Drug has been recalled

that such wording may carry, and nuances that are dependent on who is formulating the opinion and the language of reporting person [63, 64]. In the transportation accident reporting world, virtually certain or almost certain corresponds to >99% probability of occurrence, very or highly likely to >90%, likely or probable to >66%, about as likely as not or more or less likely to 33–66%, unlikely or improbable to <33%, very or highly unlikely to <10% and exceptionally unlikely to <1% probability [65].

Uncommon and Rare Drug-Induced/Iatrogenic Respiratory Disease

It is beyond the reasonable scope of this chapter to cover all drugs known to cause respiratory problems. A comprehensive list is available since 1997 in Pneumotox along with references, the reader is referred to [3, 4]. We shall concentrate here on severe, rare, poorly known, problematic and preventable DIRDs.

Drugs and Agents Fallen Out of Favor

Prescription hexamethonium, mecamylamine, aminorex, L-tryptophan, fenfluramine, dexfenfluramine, phentermine, and benfluorex caused interstitial lung disease, ARDS, eosinophilic tissue damage, or pulmonary hypertension. These drugs are not available anymore. They are still indexed in Pneumotox, because any recalled drug may be obtained from a shelf somewhere, be synthetized in the home, be used experimentally, regain popularity in light of new indications (e.g., thalidomide), or because drug congeners may produce the same or similar adverse reactions (e.g., benfluorex *v*. fenfluramine). Mitomycin-C is far less used now that it was in the past and mitomycin pulmonary toxicity has become a rare occurrence, though rare cases emerge following instillation of the drug in the urinary bladder to treat bladder carcinoma [66]. The same concerns apply to mitomycin-induced hemolytic and uremic syndrome.

The antirheumatics, gold and penicillamine, have fallen into disuse since the advent of methotrexate, leflunomide, and the newer TNF-alfa and JAK antagonists. Gold-induced pneumonitis and penicillamine-associated obliterative bronchiolitis are for now diseases of the past. Penicillamine was not cited in a recent paper on airway disease in rheumatoid arthritis (RA) [67].

Amphetamine-like anorectics (aminorex in the 1960s, fenfluramine-dexfenfluramine in the 1990s, benfluorex in the 2000s) were recalled due to an epidemiologically significant surge of acquired pulmonary hypertension (PHT) and valvular heart disease. In the 1970s, aminorex was shown to cause pulmonary hypertension and plexiform pulmonary arterial changes in young women who used the drug as a weight reducing agent. Death occurred after an average 3.5 years on the drug from right ventricular failure. An epidemic of PHTn and valvular heart disease was also reported with the use of the then newer anorexigens fenfluramine and dextro-isomer dexfenfluramine in the 1980s and 1990s [68]; this resolved with recall of the drugs. Household manufacture of aminorex was responsible for sporadic PHT. Aminorex is a metabolite of levamisole, a veterinary antihelminthic agent widely present as an adulterant added by purveyors in cocaine. Only one case of pulmonary hypertension has been reported following exposure to cocaine-levamisole. Benfluorex, which was marketed as an antidiabetic drug is in fact closely related to fenfluramine. An epidemic of valvular heart disease and PHT developed (mostly in France) following long-term exposure to the drug [69], prior to its recall in 2009.

Several members of the thiazolidinedione (glitazones) family were discontinued in some countries owing to their propensity to cause capillary leak, pleural effusions, and irreversible heart failure.

L-tryptophan once was a popular nutraceutical. The compound produced an epidemic of "eosinophilia-myalgia syndrome," with an increase in blood eosinophils. About half of affected patients presented with small irregular or dense radiographic opacities in the lung and with pleural effusion. An ARDS picture was noted in a few. Minute amounts of contaminants formed during the synthesis of tryptophan at the Showa Denko plant in Japan were blamed as the cause for the syndrome. Incident cases diminished sharply after L-tryptophan was recalled. Only sporadic cases are now being reported.

Dronedarone was designed to supplant amiodarone. Unfortunately, severe liver injury and sporadic ILD cases have prevented this drug from being released [3, 4].

Flavocoxid, a dietary supplement/medical food marketed under the tradename Limbrel® was recalled by the company in 2017–2018 under FDA action following reports of severe ILD.

A thorough history for DIRD must include use of herbal therapies, as many plants have been reported to cause pulmonary infiltrates, ARDS, bronchiolitis obliterans or arrhythmia.

Potentially Life-Threatening Drug-Induced/Iatrogenic Emergencies (Table 42.6)

Pulmonologists, internal medicine specialists, oncologists, radiologists, anesthesiologists, surgeons, emergency physicians, intensive care and ENT specialists, nurses, dental surgeons may be confronted with unexpected acute life-threatening drug-induced respiratory and/or systemic emergencies. Acute reactions may affect the lung, upper airway, small airways, pulmonary circulation, pleura, pericardium or they can be systemic with associated pulmonary involvement. Clinical presentations include diffuse pulmonary infiltrates, acute airway obstruction, pleural or pericardial effusion, acute pulmonary hypertension. Causality can be straightforward when a reaction occurs during or immediately following administration of the drug. Onset can be within seconds. Some reactions develop electively during the intra- or perioperative period, leading to difficult diagnostic and management challenges. Consideration of drug-induced etiologies is paramount as drug withdrawal can be life-saving.

Acute Drug-Induced/Iatrogenic Emergencies with Diffuse Pulmonary Infiltrates and ARDS (Table 42.7)

The Adult Respiratory Distress Syndrome (ARDS) is defined by the triad of pulmonary infiltrates in the absence of cardiac failure, and a ratio of partial pressure of oxygen in arterial blood to FiO_2 of less than 200. Different underlying pulmonary processes can lead to an ARDS picture including pulmonary edema, diffuse alveolar damage, severe infiltrative

Table 42.6 Life-threatening drug-induced/iatrogenic respiratory reactions

Pattern of DI involvement	Typical timing to onset	Develops in	Typical drugs or compounds[a]	Main complications
Angioedema and UAO	Immediate-to-late	min-h	ACEI, ARB	UAO, throat closure, locked airway, asphyxia
Anaphylaxis	Immediate	min	Drugs, biologics, RCM, latex	Bronchoconstriction, shock, pulmonary edema
Laryngospasm	Immediate	sec		Asphyxia, NPPE
Sudden catastrophic bronchospasm	Immediate	min	β-blockers, NSAID, aspirin, muscle relaxants, abused drugs	Locked airway, ARF, hypoxia, brain death
Acute intraoperative DI respiratory problem	Intraoperative, immediate	sec-min	See specific table	Anaphylaxis, acute bronchospasm, death
Flash pulmonary edema	min	min	Adrenaline, abused drugs, chemo, RCM	Hypoxemia, ARDS
Noncardiac pulmonary edema	min-h (months with oral drugs)	min-h	Chemo, hydrochlorothiazide, salicylate (dose-related)	Hypoxemia, ARDS
ARDS-DAD	d-y	h-d	Amiodarone, bleomycin, blood, chemo agents, paraquat	Hypoxemic ARF
			TKI, oxygen, radiation therapy	May evolve to pulmonary fibrosis
Alveolar hemorrhage	d-mo	h-d	All anticoagulants, platelets inhibitors, cocaine, PTU	ARDS, clotting in central airway
Dense acute interstitial lung disease	w-y	h-d	Methotrexate	Hypoxemic ARF/ARDS
Acute amiodarone pulmonary toxicity	d-y	h-d	Amiodarone	Hypoxemic ARF/ARDS. Late pulmonary fibrosis
Acute eosinophilic pneumonia	d-mo	h-d	Minocycline, cocaine, venlafaxine, tobacco/marijuana smoke	Hypoxemic ARF/ARDS
Acute radiation-induced lung injury	w	d-w	Radiation therapy to the chest	Hypoxemic ARF/ARDS
Catastrophic pulmonary hypertension	Intraoperative, immediate	min	Protamine	Acute RVF, hypoxemia
Acute foreign body embolism	h-d	h-d	Lipids, silicone, hyaluronate, acrylate cement	Acute RVF
Opportunistic infection	w-y	d	Corticosteroids, immunosuppressants, anti-TNF	ARF/ARDS (undistinguishable from DIRD)
Massive pleural/pericardial effusion/bleeding	w-y	h-d	Dantrolene, *lupus*-inducing drugs, all anticoagulants	Compression/tamponade
Acute methemoglobinemia	h-d	min-h	Benzocaine, dapsone, nitrites, oxidizing/occupational agents	Tissue hypoxia, pulmonary edema, brain damage
Ventilatory arrest	Immediate	sec	Opiates, colimycin	Tissue hypoxia
Neuromuscular failure	h-d	min-h	Aminosides, curares, dantrolene, narcotics	Hypoxemic ARF
Acute left ventricular failure	h-d	h-d	Doxorubicin, fluorouracil	Pulmonary edema
Multiple Organ Dysfunction Syndrome	w-mo	d	Drugs that induce DRESS	Multi-organ dysfunction/failure

See Pneumotox

Abbreviations: ACEI: ACE inhibitors ARDS: adult respiratory distress syndrome; ARF: acute respiratory failure; DAD: diffuse alveolar damage; DAH: diffuse alveolar hemorrhage; DI: drug-induced; DIRD: drug-induced respiratory disease; DRESS: drug rash eosinophilia and systemic symptoms; NCPE noncardiac pulmonary edema; NPPE: negative pressure pulmonary edema; NSAID: nonsteroidal anti-inflammatory drug; NSIP: nonspecific interstitial pneumonia; PTU: propylthiouracil; RCM: radiocontrast media; RILI: radiation-induced lung injury; RVF: right ventricular failure; TKI: tyrosine kinase inhibitor; UAO: acute airway obstruction

h: hours, d: days, w: weeks, mo: months, sec: seconds

[a] Complete list of offenders see pneumotox.com

lung disease including cellular NSIP, organizing pneumonia, eosinophilic pneumonia, or alveolar hemorrhage. In practice, lung tissue is rarely available for review. However, certain clinical and gas exchange features are suggestive of particular histopathological pattern-based classifications used by pathologists, which has practical implications as regards recognition and management, assessment of drug causality, and treatment. For instance, the majority of ARDS cases defined clinically show features of diffuse alveolar damage (DAD) on pathological examination [60, 70, 71]. In

Table 42.7 Drug-induced/Iatrogenic ARDS

	Clinical pathological diagnosis	Subpattern	Pathology	Typical drugs/agents	Time to onset	Tempo	BAL	Imaging (may predominate in LL)	Diagnosis
1.	Pulmonary edema								
	Noncardiogenic (NCPE)	Pulmonary edema	NCPE—Alveolar flooding	Chemo, ARA-C, HCT, tocolytic β2 agonists, heroin,	Short	Acute	?	GGO + pleural effusion	Normal heart, short tempo
		Flash PE	NCPE	Adrenaline, RCM	Ultrashort <5 min	Hyperacute	?	Haze, GGO, lobular thickening	Tempo, foam at mouth
		Transient pulmonary infiltrates	Mild NCPE, DAD, vasculitis	Paclitaxel, ATG	Short	Acute		Slight haze, GGO, lobular thickening	Short-lived; relapse on rechallenge
		Pulmonary edema and shock	NCPE	Hydrochlorothiazide	Short	Acute Hyperacute	?	Alveolar shad ± pleural eff.	Tempo, shock, relapse on rechallenge
		Salicylate pulmonary edema	NCPE, DAD	Salicylate	Variable	Subacute	?	Alveolar shadowing ± pleural eff.	Salicylamide, metabolic acidosis, anion gap
		Imaging-related NCPE	NCPE	Radiocontrast media	Very short	Acute, hyperacute	?		
		Drug addict	NCPE	Heroin, methadone					
		TRALI	Pulmonary edema, DAD, DAH	Hemotherapy, IVIG	Within 8 h	Acute	?	Bilateral infiltrates or whiteout	Tempo—Relevant antibody in donor
		NPPE	Negative pressure pulmonary edema	Inspiration against a restricted or closed airway	Short	Subacute-Acute			Obstructed airway
	Cardiogenic PE								Echocardiography (US)
	Fluid overload								
		TACO	PE	Hemotherapy	Short				
		Infusional	PE	Overzealous fluids	Short				
		Cardiotoxicity related	PE	Cardiotoxic drugs, ICI	Progressive				
		Drug-induced CAD	PE	Coronarotoxic drugs 5 FU	Short				

(continued)

Table 42.7 (continued)

	Clinical pathological diagnosis	Subpattern	Pathology	Typical drugs/agents	Time to onset	Tempo	BAL	Imaging (may predominate in LL)	Diagnosis
2.	Acute ILD								
		Chemotherapy lung	Pulmonary edema, NSIP, DAD, reactive pneumocytes	Chemo agents, ICI	Days-Weeks	Acute/ Subacute	N + reactive cells	Haze, GGO, consolidation, whiteout	
		Acute ILD	Dense NSIP w/wo pulmonary edema or DAD	Methotrexate, nitrofurantoin, mTOR inhibitors	Variable	cute	L/N	Bilateral infiltrates	Exclusion/BAL: Pathology in selected cases
		Acute granulomatous ILD	Acute granulomatous ILD	BCG, fludarabine, IFN, MTX	Variable	Acute	L	Bilateral infiltrates	Pathology
		Acute foreign body reaction	Foreign body granuloma	Talc, crospovidone, excipients, food	Subacute	Subacute	-	Bilateral infiltrates	BAL, pathology
		Acute eosinophilic pneumonia	AEP	Minocycline, daptomycin	Weeks	Acute	E	Bilateral infiltrates	Eos blood/BAL
		Acute OP/AFOP	OP/AFOP w/wo foam cells	Amiodarone, statins, ICI	Variable	Acute	M	Bilateral infiltrates	Pathology
		Accelerated pulmonary fibrosis	Dense interstitial fibrosis	Bleomycin, nitrosoureas, anti-TNF agents, paraquat	Days to weeks	Subacute	N	Bilateral infiltrates	Pathology
		Acute amiodarone lung	NSIP w/wo a DIP and/ or endogenous lipoid pneumonia pattern	Amiodarone	Weeks-months	Acute	M	Bilateral infiltrates	BAL/Pathology
		Acute postoperative APT	DAD + foam cells	Amiodarone	Acute	Acute	M	Bilateral infiltrates	BAL/Pathology
3.	DAH								
		Bland DAH	DAH	All anticoagulants, antiplatelet	Variable	Acute	RBC	Bilateral infiltrates	BAL
		ANA-related DAH	DAH	Hydralazine, PTU, anti-TNF	Variable	Acute	RBC	Bilateral infiltrates	BAL + Ab
		ANCA-related	DAH w/wo capillaritis	PTU, cocaine levamisole	Variable	Acute	RBC	Bilateral infiltrates	BAL + Ab
		Secondary DAH	DAH and silicone or hyaluronate	Silicone, hyaluronate	Short	Subacute	RBC	Bilateral infiltrates	BAL, silicone, hyaluronate
4.	Exacerbation of preexisting IPF								
		Subacute	NSIP/OP + fibrosis	Any drug causing ILD, COVID19 vaccine	Variable	Acute	L/E/N	Aggravated bilateral infiltrates	? BAL
		Precipitous	DAD + PF	Amiodarone, anti TNF, chemo, COVID19 vaccine	Variable	Acute	N	Bilateral infiltrates	–
5.	Acute vasculopathy								
		Fat embolism syndrome	Fat embolism	Amphotericin, propofol	Short	Acute	AM[a]	Bilateral infiltrates	BAL
		Silicone embolism sd	Silicone embolism	Subcutaneous fluid silicone injections	hours-days	Subacute/ Acute	AM[a]	Bilateral infiltrates	BAL/Pathology
6.	RILI	Outside the radiation field	DAD	Irradiation (chemo aggravate)	Weeks	Subacute	L	Haze, GGO	BAL, imaging

Abbreviations, see text

[a] AM: macrophages containing foreign body inclusions

a smaller proportion of patients, the histological pattern corresponds to pulmonary edema, acute-NSIP, or pneumonitis with granulomatous, eosinophilic, organizing, fibrinous organizing, storage-disease-like ILD features, or alveolar hemorrhage. Although distinctive, pathology patterns are rarely specific for the drug etiology [60], except in the case of amiodarone, which may show evidence for pulmonary storage disease and the presence of foam cells [72] (Table 42.5). When drugs are suspected as the cause of ARDS, examination of the literature, characteristic findings on imaging (see the eye catcher section in Pneumotox and below) [3, 4], careful medical history and drug history, bronchoalveolar lavage, early urine drug screen for the timely detection of substances of abuse, meticulous exclusion of other causes particularly an infection, response to drug therapy withdrawal, a trial of i.v. corticosteroid therapy and timely discussion of ECMO are indicated. Pneumothorax and/or pneumomediastinum may develop as a consequence of mechanical ventilation [3, 4, 73]. Data in Tables 42.5 and 42.7 provide information about causes of drug-induced or iatrogenic ARDS/DAD and may help deduce appropriate management strategies.

Drug-Induced Noncardiac Pulmonary Edema

Most often, drug-induced pulmonary edema is of the noncardiac type (NCPE) with normal left ventricular function and filling pressure, normal ejection fraction, brain natriuretic peptide (BNP) levels, and pulmonary capillary wedge pressure, when measured. Drug-induced NCPE may escape recognition and diagnosis. The time from the first exposure to the drug and full-blown pulmonary edema can be very rapid or delayed. For instance, pulmonary edema in the form of lobular shadowing and septal lines on CT images occurred in 25 s after administration of radiocontrast material in one case [46] or minutes in the case of flash pulmonary edema [e.g., from radiocontrast media, epinephrine (adrenaline) or intravenous heroin], often within hours days or more with salicylate or hydrochlorothiazide. Noncardiogenic pulmonary edema may evolve into acute respiratory failure and a fully developed ARDS picture. Cardiac ultrasound, urine drug screen (depending on context and extrapulmonary signs and symptoms), and naloxone reversal test are indicated. Acute drug-induced noncardiogenic pulmonary edema can develop following deliberate (suicidal) or inadvertent overdose of such drugs as salicylate, adrenaline, tricyclic antidepressants, calcium channel blocking drugs (amlodipine, chlordiazepoxide, nicardipine, nifedipine, verapamil), carbamates, carbamazepine, colchicine, dibenzazepine, haloperidol, insulin, naloxone, phenothiazines, propoxyphene, salicylate, zolpidem or drugs of abuse (heroin, amphetamines, cocaine, codeine, fentanyl). Drug-induced NCPE can develop following oral, parenteral or topical administration of drugs including epinephrine (adrenaline), ATRA, arsenic trioxide (As_2O_3), CSFs, hydrochlorothiazide, lidocaine, naphazoline, opiates, propofol; tocolytic agents, chemo drugs (gemcitabine, methotrexate, mitomycin C, taxanes), and radiocontrast agents, among 219 causal drugs or agents (up from 171 in the earlier edition of this chapter) [3, 4]. DI-NCPE can develop following even one tablet of the offending drug. Pulmonary edema can also be a manifestation of drug-induced (DI) anaphylaxis. The diagnosis is sometimes raised by patient or family who astutely observe the temporal relationship between exposure and onset of symptoms with rechallenge at home. Abrupt onset in seconds, minutes or in a few hours with resolution in hours or days upon drug stoppage are suggestive of DI pulmonary edema. There may be a stepwise increase in edema severity concomitant with each inadvertent readministration of the causal drug [74]. Severe pulmonary edema in drug abusers may be heralded by a plume of pink protein-rich (plasma to edema fluid protein ratio >0.7) and frothy sputum at the mouth [75]. Fever, hypotension, shock, and hemoconcentration concomitant with pulmonary infiltrates characterize those cases with hydrochlorothiazide pulmonary edema. Transient pulmonary infiltrates waning in a few hours have been noted after exposure to crack cocaine, hydrochlorothiazide, nitrofurantoin, and anti-thymocyte globulin [3, 4]. Drug-induced pulmonary infiltrates may be indicative of fleeting pulmonary edema or DAD, and a few case reports support that contention [76]. Imaging findings can also include diffuse haze, ground-glass shadows, septal line thickening (consistent with excess fluid in lung), and sometimes pleural fluid is present as an associated feature. There is typically little or no enlargement of the cardiac silhouette or vascular pedicle on chest imaging [77] in NCPE, since alveolar flooding is caused by increased vascular permeability. Unless overzealous resuscitation with fluids leads to volume overload pulmonary edema [78]. On pathological examination, interstitial congestion and alveolar filling with acellular proteinaceous fluid are noted in NCPE [61]. Hyaline membranes, alveolar fibrin, and resolving DAD are found in cases with overlapping features of DAD or acute fibrinous organizing pneumonia (AFOP) [60, 61]. Some DI-NCPE cases present with DAH [79]. Diuretics are generally considered of uncertain benefit in DI-NCPE, as intravascular volume may be on the low side due to fluid extravasation to the lung and other tissues. Care should be taken to avoid drug re-exposure in cases of DI-NCPE, as severe relapses may follow [80]. Mortality in DI-NCPE can be as high as 5–20% (extracted from reference in [3, 4]).

The respiratory manifestations of salicylate poisoning are worthy of special mention because of the prevalence of aspirin overdoses. Salicylate-induced pulmonary edema can occur in both acute and chronic users, with a predilection for the aged and patients with renal dysfunction [81]. Patients may present with fever, systemic, and neurologic symptoms including obtundation and anion-gap metabolic acidosis. A

serum salicylate level of 30 mg/dL or greater is the threshold above which pulmonary and systemic toxicity is more likely to develop. Blood levels of drug(s) should be measured in the acidotic patient, since dialysis can be life-saving in severe salicylate poisoning. Values above 100 mg/dL are associated with poor outcomes. Management of salicylate NCPE includes serum and urine alkalinization, with hemodialysis being reserved for cases with pulmonary edema, distant organ damage *and* blood levels >100 mg/dL [81].

Drug-Induced Cardiogenic Pulmonary Edema

Drug-induced and iatrogenic cardiac and/or overload pulmonary edema can complicate chemotherapy [82], treatments with drugs, and/or overzealous administration of fluids [3, 4, 8]. Cardiogenic pulmonary edema may occur early or late [83] as a complication of drugs or radiation therapy causing acute, chronic or delayed left- or bi-ventricular dysfunction. Drugs and abused substances can also cause myocarditis and consequent heart failure [84]. Causal drugs include epinephrine/adrenaline, anthracyclines, chemo agents, fluoropyrimidines, immune checkpoint inhibitors, sunitinib, and drugs of abuse. Acute left ventricular dysfunction may also result from drug-induced coronary vasospasm or myocardial infarction, as seen with amphetamine, cocaine, fluoropyrimidines, or oxaliplatin-based chemo regimens [3, 4, 8]. Cardiac biomarkers can aid in establishing the diagnosis. Drug therapy withdrawal is necessary, underlying disease permitting. Appropriate vigilance is important, because cardiotoxicity impacts the lung in multiple ways [8]. Cardio-oncology is a rapidly emerging field [85].

The "Chemotherapy Lung"

This complication may occur during or following treatments with many antineoplastic drugs of multiagent chemotherapy regimens, with an average incidence of 1–5% [3, 4]. High drug dosages, rapid as opposed to slow infusion of intravenous drugs, coadministration of bleomycin, gemcitabine, inhaled oxygen, rituximab, radiation therapy, or CSF can be triggering or potentiating. Causal drugs include antibiotics (bleomycin, mitomycin C), alkylating agents (busulfan, chlorambucil, cyclophosphamide, melphalan), antimetabolites (azathioprine, cytosine arabinoside, gemcitabine, fludarabine, 6-mercaptopurine, methotrexate), etoposide, nitrosoureas, oxaliplatin, and oxaliplatin-based regimens, and taxanes. Recent additions to the list include tyrosine kinase inhibitors (TKI) (erlotinib, gefitinib), cetuximab, irinotecan, and pemetrexed. The condition manifests with dyspnea, cough, hypoxemia, diffuse haze or ground-glass that may progress to dense bilateral opacities and volume loss. HRCT discloses inter- and/or intralobular septal thickening, ground-glass attenuation and in some patients, moderate unilateral or bilateral pleural effusion are also present [86]. Early pulmonary involvement in patients on bleomycin or chemo agents [87] should be monitored as patients may develop further restrictive lung function, deterioration of diffusing capacity for carbon monoxide, denser pulmonary opacities or full-blown ARDS if the drug is continued. Caution is advised in the asymptomatic patient on bleomycin when the diffusing capacity for CO drops by more than 40% from baseline on serial measurements. Unfortunately, despite awareness of the risks, bleomycin pulmonary toxicity continues to escape early detection of and fatal bleomycin lung still occurs [88]. The potential merit of systematic follow-up of pulmonary physiology in those exposed to other chemo agent remains unclear at the present time. BAL is generally performed in symptomatic patients to exclude Pneumocystis or viral pathogens including COVID19, which drug-induced lung injury may resemble. An increase in BAL neutrophils and hemosiderin-laden alveolar macrophages has been found in BAL. Bizarre type II pneumocytes reflecting alkylating agent-induced cellular atypia may be identified, particularly in patients exposed to busulfan. Lung biopsy is infrequently performed, because of the risks entailed and its modest diagnostic contributions, as drug-induced changes are largely nonspecific [60]. Pathology may disclose interstitial edema, alveolar fibrin, hyaline membranes, resolving or organizing alveolar damage, atypical alveolar lining cells, and/or fibrosis [60, 61, 71]. The histopathological changes of DAD which are typical in ARDS, can also be observed in the context of an infection, hematopoietic stem cell or solid organ transplantation, or concomitant with an exacerbation of pre-existing idiopathic pulmonary fibrosis of unknown cause. No inciting factor is found in about 20% of DAD cases. For practical reasons, drug-induced ARDS is considered plausible if the workup for an infection or other etiologies is negative and there is a compatible drug history. Antibiotics, corticosteroids, cyclophosphamide, imatinib, or IVIG have been tested in an attempt to improve the chemotherapy lung. Results of these rescue treatments are unpredictable and can be detrimental. About 40% of early chemotherapy lung cases will respond to corticosteroid therapy. More advanced cases may evolve to recalcitrant and progressive ARDS, or transition to irreversible pulmonary fibrosis. Mortality of drug-induced chemotherapy lung can be as high as 45%.

Drug-Induced/Iatrogenic Alveolar Hemorrhage

Drugs

Diffuse alveolar hemorrhage (AH/DAH) occurs when blood enters the alveolar spaces through capillaries rendered permeable by inflammation or injury. Bleeding and alveolar filling in the deep lung causes shortness of breath, hypoxemia, anemia, and diffuse haze or ground-glass, mottled opacities, or consolidation. Even though DAH may be suspected on the basis of batwing or diffuse fluffy opacities on imaging, the diagnosis may prove elusive until BAL is performed showing progressively bloodier return on sequential fluid aliquots.

Hemoptysis and an increase in the diffusing capacity for carbon monoxide are inconstant features. A significant, abrupt drop in hemoglobin is indicative of severe blood loss. Additional severity may stem from clotting in the distal lung and/or major airways, which may lead to airway obstruction and worsening hypoxia. Prolonged retention of anticoagulants (e.g., the rodenticide brodifacoum) can cause DAH for extended periods of time. Drug-induced alveolar hemorrhage can be isolated (denoted bland DI-DAH), or it can occur in conjunction with such extrapulmonary features as skin necrosis, microscopic hematuria, renal failure, heart, and/or other organ involvement and/or positive serologies for anti-neutrophil cytoplasmic antibodies (ANCAs) of various specificity, or anti-nuclear antibodies (ANAs) [89]. This may have mechanistic relevance. DI-DAH may mimic the clinical manifestations and the laboratory features of systemic ANCA-related vasculitis, *lupus*, or Goodpasture's syndrome. Even if the lung biopsy reveals pulmonary capillarities in addition to DAH, whether this finding informs the diagnosis and management of DI-DAH as compared to a more conservative approach is unclear.

History taking in patients with DAH should include exposure to hydrocarbons, crack cocaine, marijuana or tobacco smoke or fumes of snorted crack cocaine or heroin, pesticides, anticoagulants, the rodenticide brodifacoum, paraquat, hyaluronate, and fluid silicone [3, 4]. Early urine drug screen for abused drugs (recognizing that fluid resuscitation can dilute the sample and influence results), and evaluation of brodifacoum or paraquat in plasma are indicated. Therapy with 152 different drugs can cause AH (up from 103 listed in 2017) [3, 4]. These include compounds which interfere with the coagulation cascade or with platelets such as glycoprotein IIB/IIIA inhibitors of the chemical (clopidogrel, eptifibatide, ticlopidine, tirofiban) or biologic type (abciximab), vitamin-K antagonists, heparin, thrombolytic agents, direct (new) oral anticoagulants and superwarfarins, amiodarone, antithyroid drugs (carbimazole, methimazole, propylthiouracil), m-TOR inhibitors (everolimus, sirolimus), cocaine, the adulterant levamisole, all-transretinoic acid (ATRA), arsenic trioxide (As_2O_3), dextran-70, and penicillamine. Seven drugs have been associated with ANCA-related DAH and ten with Goodpasture-like syndrome [3, 4]. Agranulocytosis and an infection may accompany AH cases resulting from exposure to propylthiouracil or cocaine-levamisole. DAH can occur following percutaneous coronary intervention and is easily mistaken for pulmonary edema unless the BAL is performed. Inhalation of e-cigarette vapor and cryoballoon ablation for atrial fibrillation have also been associated with the development of AH. Mortality in DI-AH can be as high as 30–50%.

Superwarfarin Rodenticides

4-hydroxycoumarin (a.k.a. brodifacoum) is a rodenticide capable of causing devastating hemorrhage in adults, children, and animals including pets and prey birds. Brodifacoum is a vasculotoxic superwarfarin which blocks the actions of vitamin K1. Rodents fed pellets containing the compound die from internal bleeding. Accidental brodifacoum poisoning has been described in nontarget populations (companion animals, humans, and birds) and the clinical characteristics are similar across all species. Brodifacoum poisoning in humans occurs by a number of mechanisms including accidents in factory workers or in children, deliberate ingestions (suicidal, Munchausen syndrome), ingestions by proxy or with criminal intent, by inhalation of laced crack cocaine, marijuana or cannabinoids, inadvertent exposures, and intake that is "impossible-to-track." The diagnosis of brodifacoum poisoning should be raised in any severe unexplained bleeding (AH, airway, internal bleeding) with persistent and profoundly altered coagulation studies. Pink excreta have been described [90]. Brodifacoum can be detected qualitatively and quantitively in plasma and followed serially. Brodifacoum's extended biological half-life (1–2 months) accounts for persistent coagulopathy, which requires prolonged (up to 1 year) vitamin-K replacement therapy. Clinical presentation of brodifacoum poisoning can be with epistaxis, hematemesis, AH or neurologic symptoms depending on the predominant site of bleeding. A pink coloration of body fluids from the dye contained in pellets have been reported. Laboratory studies (to be performed before administering Vit-K) reveal prolonged prothrombin and activated thromboplastin times with diminished activity of the vitamin K-dependent coagulation factors II, VII, IX, and X. Patients may improve initially with the administration of fresh frozen plasma (FFP) and vitamin-K [91]. Relapse of bleeding and AH can occur due to the very slow elimination kinetics of brodifacoum requiring prolongation of vitamin K replacement therapy until coagulation returns to normal. A series described three cases intoxicated with inhaled "spice" or "K2" cannabinoid mixed with superwarfarins. All three developed coagulopathy and bleeding. Synthetic opioids and marijuana appear to be now laced with brodifacoum [3, 4]. Inhalation of brodifacoum can cause particularly severe bleeding due to bypass of the enterohepatic circulation and first pass liver metabolism. Although the majority of brodifacoum poisoning in humans are non-fatal, forensic pathologists, coroners, and veterinarians may be confronted with brodifacoum-related deaths from AH and internal hemorrhage and should be familiar with the clinical presentation.

Fluid silicone injections into the gluteal region or in the buttocks by cosmetic surgeons or by unqualified illicit "lay" operators during clandestine surgery sessions for the purpose of cosmetic mammaplasty or body augmentation, sometimes in the context of transsexualism, can cause very severe pulmonary and neurologic complications [92]. The "silicone embolism syndrome" (SES) occurs when a fraction of administered silicone gains access to the pulmonary circula-

tion, resulting in acute lung injury, ARDS, and/or AH. Some dermal fillers (hyaluronate, polyalkylimide) have also been implicated. The SES shares several clinical and imaging features with the fat embolism syndrome, including petechiae. Right to left shunting enables access of fluid silicone to the systemic circulation, causing brain damage, life-threatening neurological impairment, and/or distant organ failure. The SES may develop within minutes-to-a few hours of the cosmetic procedure. Shorter delay times portend greater severity. Clinical presentation may include any combination of fever, dyspnea, nonproductive cough, chest pain, hypoxemia, hemoptysis, petechiae, and obtundation. Imaging studies may disclose bibasilar or diffuse infiltrates on chest radiography and subpleural basilar or diffuse areas of alveolar shadowing or consolidation on NRCT. Silicone injection in the breast and mammaplasty produce distinctive soft tissue changes on imaging. BAL in SES may reveal silicone vacuoles in macrophages or multinucleated giant cells in the form of large, pleomorphic, cytoplasmic vacuoles, and inclusions on a background of abundant neutrophils and red cells. Pulmonary pathology discloses nonstainable (except with prolonged oil red-0 staining for 72 h) interstitial vacuoles with a peripheral, refractile meniscus of silicone on dark field microscopy [93]. Silicone droplets may conform to the shape of pulmonary capillaries. Energy dispersive X-ray analysis can confirm the chemical composition of silicone. Outcome of the SES depends on the volume of fluid silicone injected and whether silicone escapes the pulmonary circulation. Early onset of symptoms and neurologic presentations are associated with very high mortality [92].

Inhalation or rarely injection of straight cocaine may be followed in a few hours by an acute episode of DAH. Cocaine may account for up to 12% of DAH cases admitted to the hospital. The true prevalence is likely even higher, as patients may be reluctant to give an accurate drug history. AH is common at autopsy in drug addicts, present in 58% of cases in one study. AH caused by cocaine has a wide spectrum of severity. Indeed, while most crack cocaine users exhibit at least subclinical AH in the form of hemosiderin-laden macrophages in the BAL, both cocaine and crack cocaine can cause clinically-manifest and sometimes massive AH limited to the lung. The etiology and clinical presentation of cocaine-associated AH has changed in the recent past, as most cocaine samples seized in the USA and in Europe are now laced with levamisole, an immunomodulator drug that was once used to treat rheumatoid arthritis in humans and is now only available as a veterinary deworming agent. Pharmaceutical grade levamisole purportedly enhances the euphorisant effects of cocaine, but the compound mainly poses a risk of neutropenia, agranulocytosis, skin vasculitis and extensive necrosis, and end organ involvement. Although this had been described in the 1970s, there is a resurgence of similar such cases recently in levamisole-laced cocaine users. Cocaine-levamisole toxicity manifests more often with heated (crack) cocaine inhalation than with cocaine snorting, in the form of malaise, arthralgias involving the larger joints and cutaneous manifestations including a retiform purpura or large painful hemorrhagic bullae or necrosis involving typically, but not invariably, the face, earlobes or other areas of the body, notably the skin of the limbs. This corresponds to focal thrombotic vasculopathy with intravascular fibrin formation leading to occlusion and ischemic skin necrosis, and less often to true vasculitis with IgM, IgA, IgG, and C3 deposits. Skin involvement may be extensive, requiring reconstructive surgery. Notable laboratory features include neutropenia (<3000) or agranulocytosis, which constitutes a relevant risk factor for superimposed infections, and auto-antibodies (speckled antinuclear antibodies, anti-cardiolipin antibodies, ANCA). Interestingly, ANCA often occur at a high titer, with a perinuclear (anti-PR3) and/or cytoplasmic (anti-myeloperoxidase (MPO)) staining pattern or reacting with multiple components of neutrophil granules including, characteristically, human neutrophil elastase (HNE), lactoferrin, cathepsin G in addition to proteinase 3 and MPO. Concomitant dual positivity to both MPO and PR3 targets (100% and 50% in one series, respectively) is suggestive. Rarely, anti-double strand DNA antibodies are found. The panoply of pleiomorphic antibody positivities at high titers should draw attention to drug etiologies. AH develops in a fraction of cocaine-levamisole poisoned patients, noted in one study of 3 of 30 such cases [3, 4]. Other organ damage can be present in the form of ENT involvement including sinusitis (possibly due also to cocaine snorting) in 44%, kidney injury in eight (severe in two, with evidence of pauci-immune glomerulonephritis in one), and vasculitis in three [3, 4]. Clinicians may arrive at the correct diagnosis of cocaine-levamisole toxicity in the presence of characteristic skin changes, neutropenia, and ANCA antibodies that are now part of the evaluation in the patient with exposure. An algorithm has recently been proposed for patients with cutaneous involvement that would also apply to any AH case in a patient suspect of being a cocaine-user, starting with cocaine urine screen which, if negative, this is followed by GC/MS measurement for levamisole in urine if the clinical suspicion of levamisole toxicity is strong. The next step is measurement of ANCAs which, if positive, will confirm the diagnostic suspicion of cocaine-levamisole toxicity. Work-up for end-organ dysfunction (lung, kidney, liver) is indicated. A toxicology study on urine in addition to paraphernalia in the patient's residence in legal cases may also suggest the presence of cocaine and levamisole.

Pneumotox lists 38 drugs that have been associated with the development of ANCA-positive vasculitis [3, 4]. The antithyroid drugs propylthiouracil (PTU), benzylthiouracil, and methimazole can also produce a form of vasculopathy that resembles that induced by levamisole. Patients who are

on PTU for at least a few weeks can present with any combination of neutropenia or agranulocytosis, necrotic skin changes or gangrene, and pathologically-demonstrable eosinophilic or neutrophilic vasculitis. Similar to levamisole, patients present with violaceous skin changes, vasculitis in the skin, pinna or limbs, and DAH in a subset. Patients typically have elevated ANCA titers. Importantly, ANCA are rarely elevated in untreated Grave's disease, and these antibodies are strongly associated with therapy with antithyroid drugs of any significant duration. Moderately elevated titers of both perinuclear and, less often, cytoplasmic, ANCA develop in 33–50% of patients chronically treated with propylthiouracil or benzylthiouracil. However, the majority of such patients have no symptoms and do not develop clinically evident disease. Propylthiouracil need not be discontinued in such cases, but ANCA titers should be monitored and the patient warned of the possible development of suggestive symptoms and signs, as acute AH or other forms of pulmonary, pleural, pericardial or extrathoracic manifestations of systemic vasculitis may develop after several months of treatment in up to 2.5% of them. ANCA with specificity to more than one lysosomal antigen constitute a distinctive serological profile for drug-related ANCAs. The p-ANCA exhibit MPO or dual MPO- and PR3 staining and antilactoferrin—neutrophil elastase—cathepsin and/or azurocidin specificity. Titers are also found to be much higher in *drug-induced* as opposed to *naturally-occurring* ANCA-related disease. Among 250 ANCA-positive cases, 30 (12%) had very high (>12-fold above the median) anti-MPO titers and all of these 30 had clinical features of vasculitis. Ten of these 30 had been exposed to hydralazine, three to propylthiouracil and five to penicillamine, allopurinol, or sulfasalazine [94]. There was a strong association between the presence of anti-neutrophil elastase and/or antilactoferrin antibodies and exposure to one candidate toxic drug [95]. Therapy with antithyroid drugs, or hydralazine should be sought in cases of vasculitis coexisting with high ANCA titers [96]. From 25% to 60% of patients on chronic propylthiouracil therapy who happen to develop overt ANCA-related disease or vasculitis have pulmonary involvement, typically in the form of AH with or without histologically demonstrable capillaritis. Tissue granulomatous and necrotizing inflammation has been reported. Although some form of renal involvement ranging from microscopic hematuria to necrotizing and/or crescentic glomerulonephritis is present in up to 75% of the patients, renal outcomes are better and mortality is lower in propylthiouracil-related as opposed to idiopathic ANCA-related renal disease. Terminal renal failure is noted in about 5%. Overall mortality is approximately 15%, with a few patients dying from uncontrollable DAH [3, 4]. Patients with the most severe involvement will necessitate induction therapy with corticosteroids, cyclophosphamide, and plasma exchange in a manner similar to idiopathic vasculitis. Cases with ANCA- or mixed ANCA and ANA-related autoimmune disease have occurred with the use of penicillamine, minocycline, or hydralazine. ANCA titers will fall in most patients upon drug discontinuance, but in a fraction, elevated levels will remain for years without necessarily evidence for disease.

Contrasting with idiopathic *lupus*, DAH is very unusual in drug-induced *lupus* (if it truly exists at all).

Anti-basement membrane-related AH (Goodpasture's like) was considered an idiopathic condition. However, a study of 28 carefully-documented Goodpasture cases showed that 89% of the patients were either smokers, or gave a history of exposure to inhaled cocaine (in 36%), cannabis or heroin [97], raising the possibility that Goodpasture may be triggered by drugs or chemicals.

Such drugs as TNF antagonists, procainamide, levamisole, and interferon have been associated with circulating antiphospholipid/antisynthetase-antibodies or syndromes [3, 4].

Transfusion Reactions: TACO–TRALI

Acute noninfectious respiratory reactions following blood transfusion include anaphylaxis, transfusion-associated circulatory overload (TACO), and transfusion-related acute lung injury (TRALI). These entities carry a significant risk of respiratory failure.

TACO (see also under iatrogenic cardiac pulmonary edema) has an incidence of 1–8% and develops when the recipient's circulatory system is overwhelmed by the volume transfused or by the rate at which it is infused to the patient. Poor left ventricular reserve associated with underlying heart failure, aging or diabetes mellitus are risk factors for TACO to develop. TACO manifests with hydrostatic pulmonary edema and is often difficult to separate from TRALI on clinical and/or imaging. In a recent survey among oncology patients [78], the incidence of TACO was 0.84 per 1000 transfusions, representing 6.6% of all transfusion reactions. This was higher compared with 1–6% in nononcology populations. Among notable risk factors for TACO, hematologic malignancies, receipt of cardiotoxic chemotherapy, preexisting oxygen use, hypertension, renal insufficiency, daily use of corticosteroids, diuretics, beta-blockers, and elevated NT-proBNP were found. Elevated NT-pro-BNP may help differentiate TACO from TRALI.

TRALI (the term was coined in 1985 [82]) is a form of post-transfusion ARDS that ranks as the leading cause of death from hemotherapy in the US. In the majority of TRALI cases, a demonstrable immune-mediated syndrome is evident. TRALI may occur following transfusion of blood or components including platelets, solvent-detergent plasma, i.v. immunoglobulins (IVIG) or fresh frozen plasma (FFP). Among transfused compounds, platelets demonstrate higher risk. The clinical presentation includes pulmonary infiltrates, hypoxemia, and ARDS (or deterioration of preexisting

ARDS) [98] within 6–8 h of transfusion without evidence for heart failure or TACO [98]. Mechanical ventilation may be required for 12–96 h. Patient-related risk factors for TRALI include an older age, smoking, chronic alcohol abuse, an underlying inflammatory condition and elevated IL8 levels, sepsis, mechanical ventilation and with potentially barotraumatic insufflation pressures, recent surgery or trauma or a positive fluid balance. Blood- and transfusion-related factors include the presence in the donor pool of at least one (generally multiparous) female donor, bearing a pathogenic antibody. There is an average fivefold increased risk of TRALI if one donor has detectable anti-HLA I or II or anti-HNA3 antibodies at a high titer and with a high affinity for cognate antigens in the recipient. Other factors for TRALI include "shelf age" of the transfused blood, and maternal-to-child transfusion. Although TRALI occurs in 1/5000–7000 transfusions, in ICU, trauma or surgical care settings the incidence is up to 1–5% of those transfused. TRALI mitigation strategies have reduced the incidence in the recent years [82]. Signs and symptoms include dyspnea, hypoxemia, hypotension, fever, transient leukopenia due to granulocyte sequestration in the pulmonary circulation and moderate eosinophilia. A generally-held hypothesis is that TRALI occurs in the context of a "two-hit" process. Sepsis, inflammation, mechanical ventilation or surgery causing pretransfusional pulmonary leukocyte sequestration is the predisposition, and transfusion of blood components containing an anti-HLA or HNA antibody is the trigger for full-blown TRALI. Accordingly, TRALI is more common in patients with sepsis or following surgery or gastrointestinal bleeding, where incidence can be as high as 15%. Transfer of complement-activating HLA class I or II, granulocyte-specific or lymphocytotoxic antibodies from one or more donors presumably activates neutrophils causing leukosequestration and this is followed by precipitation of sharp-edged cholesterol crystals which mechanically injure the pulmonary venules, causing endothelial fenestration, fluid leakage, and pulmonary edema resulting in ARDS [99]. An antibody directed against a cognate antigen of the recipient is identified in the donor in about 75% (50–85%) of TRALI cases, which are then designated as immune TRALI. The remainder of cases are labeled nonimmune TRALI, with mechanisms that are less clearly defined. Redox active lipids formed during blood storage may play a role, explaining why blood with longer shelf life has a propensity to cause TRALI more often than freshly-prepared samples. While the majority of TRALI patients recover in a few days, death from respiratory failure or multiple organ dysfunction occurs in 10–18%. Although recognition of TRALI can clearly guide safer donor selection, prevention has been suboptimal due to poor awareness of the syndrome outside the blood transfusion medicine community until recently. Examination of donor products must be carried out expeditiously, aiming at the expeditious detection of an antibody, followed by removal of the implicated donor from the pool. In a retrospective study [100], out of five patients who received multiple transfusions from the same donor, four suffered relapse and only two of eight severe reactions were reported to the blood safety authority. Risk reduction strategies include avoidance of unnecessary transfusions, transfusion of washed components, screening potential donors for antibodies, choosing products from male donors or of female donors without a history of pregnancy and testing negative for antibodies, more proximate donor selection, and increasing the number of donors per sample to dilute any possible antibody [101].

Acute Cellular Interstitial/Infiltrative Lung Diseases

Many drugs can cause acute forms of interstitial lung disease with gas exchange characteristics of ARDS (Table 42.6).

Acute Cellular Nonspecific Interstitial Pneumonia Pattern

Causal drugs include amiodarone, BCG therapy, bleomycin, crizotinib, m-TOR inhibitors (sirolimus, everolimus, and temsirolimus), fludarabine, gols, imatinib, immune checkpoint inhibitors, interferons, leflunomide, methotrexate, nitrosoureas, nitrofurantoin, and pemetrexed among 177 candidate drugs, of which 55 can cause a definite pattern of cellular nonspecific interstitial pneumonia on pathology [3, 4]. Recent evidence implicates new oral anticoagulants [102] and SARS COVID 19 vaccination [103, 104] as novel causes. Clinical presentation is with cough, fever, rapidly-progressive diffuse pulmonary infiltrates with a predilection for denser images in the dependent regions of the lung, i.e., the bases or posterior areas in the erect or supine patient, respectively. Patients can show a prodromal phase of mild ILD where HRCT may disclose discreet haze, early ground glass or a mosaic pattern of attenuation which resembles that of hypersensitivity pneumonitis. The disease can then accelerate with little notice if the drug is continued and sometimes, even following withdrawal, cause respiratory failure requiring ventilatory support and/or ECMO. Imaging discloses a mixture of inter- and/or intra-lobular septal thickening, crazy-paving, consolidation and air bronchograms, volume loss, and associated pleural effusion. BAL typically shows increased lymphocyte counts, with a CD8+ or, less often, CD4+-dominant subtype pattern. A neutrophil- or eosinophil-dominant BAL has also been reported [3, 4]. The BAL profile is influenced by timing of the test into the course of the disease, and whether patients have received corticosteroid therapy [105]. The BAL is useful to exclude coincidental or drug-associated bacterial, viral, fungal, or parasitic infection. It may be difficult to separate acute drug-induced-pulmonary infiltrates from *Pneumocystis jiroveci* pneumonia. It may be especially difficult to separate true pneumocystis pneumonia from acute drug-induced ILD with pneumocystis colonization when a rt-PCR signal for Pneumocystis is detected and in the

absence of positive stains for organism. Pathology discloses interstitial inflammation with dense interstitial mononuclear infiltrate and some degree of interstitial edema [106]. A risk/benefit analysis for lung biopsy or cryobiopsy is not available, and most physicians will use the BAL data as a surrogate marker and proceed with empiric drug withdrawal with or without corticosteroid- and anti-pneumocystis therapy (the latter for those patients who have risk factors: underlying malignancy, connective tissue disease, corticosteroid therapy, recent irradiation, low circulating CD4+ lymphocytes or an rt-PCR signal). Outcome of this form of drug-induced condition is good, typically with resolution of all signs and symptoms following drug discontinuance and corticosteroid therapy. Corticosteroid dosage is adjusted to response with tapering over a few weeks or months. High-dose methylprednisolone i.v. boluses have become popular in a certain literature from Asia to treat acute drug-induced ILD, but the merit of this form of therapy vs. a more conventional i.v. or oral dosage is not established. Rechallenging the patient with the culprit drug may lead to ILD relapse, but this is not seen in every patient, and is not advisable, as death may follow rechallenge with the drug. Pulmonary fibrosis following resolution of acute ILD is quite unusual, except in those patients with preexisting rheumatoid lung or idiopathic pulmonary fibrosis, who may suffer a permanent decrement in lung function after transient drug-induced deterioration and drug withdrawal.

Acute Eosinophilic Pneumonia

Acute eosinophilic pneumonia (AEP) has been reported with exposure to 62 drugs or agents, mainly antibiotics (minocycline, daptomycin), chloroquine, antidepressants, infliximab, mesalazine, NSAIDs, sertraline, cannabis, cocaine, e-cigarette vapor, heroin, drug excipients, tobacco smoke, incense and radiation therapy [3, 4]. Drugs causing AEP overlap with the 206 drugs capable of causing the more classic and less severe eosinophilic pneumonia. However, the boundary between the two conditions can be blurred clinically. AEP and eosinophilic pneumonia may be the same disease running a different clinical course, with AEP representing the upper end of the severity spectrum. AEP is an acute febrile illness that culminates with hypoxemic respiratory failure, diffuse white-out, pleural effusion, and ARDS. Mechanical ventilation is required in the majority of affected patients, and a few require ECMO. BAL eosinophils above 25% are typical and figures above 50% are common. Blood eosinophilia can be in the normal range in patients who have progressed rapidly or who have received a course of corticosteroids prior to admission. Massive BAL eosinophilia obviates the need for a confirmatory lung biopsy. For the diagnosis to be considered, parasitic or other infections, notably with *Strongyloides stercoralis* must be ruled out, also because corticosteroid therapy in this context can be extremely hazardous [107]. Blood/BAL eosinophils in the absence of an infection portend potentially reversible disease. Histopathologic analysis reveals tissue eosinophils on a background of rich mononuclear cell infiltrate and acute and/or organizing diffuse alveolar damage. Hyaline membranes are unusual [61, 108, 109]. Discontinuation of the drug or of exposure to cigarettes, marijuana or e-cigarette smoke/vapor are the mainstays of management. Corticosteroid therapy is used in the majority or patients. Outcome is generally good and fatalities are the exception.

Eosinophilic granulomatous with polyangiitis (EGPA; a.k.a. Churg-Strauss') may develop during treatments with 1 of 20 separate drugs [3, 4], notably leukotriene receptor antagonists (LTRA) or omalizumab. To get a full understanding of causation, one has to take into account the increased background rate of EGPA in the asthmatic patient, whether corticosteroid therapy has been tapered or withheld in those who are started on LTRA. There are indisputable cases of LTRA and drug-induced EGPA [110, 111], and withdrawal of LTRA or omalizumab should be considered in the patient who presents with EGPA of new onset.

Acute Granulomatous Interstitial Lung Disease

Forty drugs and families of drugs, including topical BCG therapy in the urinary bladder, interferon, methotrexate, TNF antagonists, ICI, and illicit drugs can cause ILD with a granulomatous component [112]. Although generally mild, this pattern can cause acute respiratory failure or ARDS [3, 4]. On imaging, granulomatous ILD has an established reputation for causing a miliary pattern or haze. In severe cases, micro-nodules tend to form a rapidly-progressive coalescent white-out pattern. Other identifiable causes for granulomatosis should be carefully excluded [113, 114], and the BAL fluid and lung tissue should be examined for bacterial, mycobacterial, fungal, and parasitic infection. The quest for diagnosis is both patient- and country-dependent as certain microorganisms (e.g., *Mycobacteria*, *Histoplasma*, *Cryptococcus*, *Blastomyces*, and *Coccidioidomycosis*) have a predilection for specific geographical areas or are more common in patients with a given underlying condition (e.g., *Pneumocystis* and CTD on immunosuppressive drugs, radiation therapy, long-term corticosteroid therapy). Noninfectious causes of pulmonary granulomas include environmental agents (bird droppings, beryllium, hot-tub), aspiration of food particulates, sarcoidosis, ANCA-related GPA, and rheumatoid arthritis. Central necrosis of the granulomas makes infection a more likely but not an absolute diagnostic consideration [114, 115]. This is seldom is seen in methotrexate lung [116].

A fraction of patients on long-term methotrexate (incidence estimates have dropped from 3% to 0.5% nowadays, down to a point where undisputable cases have become rare) will develop an acute pulmonary reaction without

any convincing features for an infection [117]. Lymphocytes are increased in the BAL in some but not all patients. A confirmatory lung biopsy is now rarely performed. Ruling out pneumocystis pneumonia by immunofluorescence and molecular techniques is vital as pneumocystis pneumonia may assume a non-necrotizing granulomatous pulmonary reaction. A review of the pathologic features of methotrexate pneumonitis revealed granuloma formation in 35%, giant cells in 26.5%, tissue eosinophils in 18%, or diffuse alveolar damage in 8% [116]. An ARDS picture in methotrexate lung can be caused by dense underlying interstitial lung disease with or without granuloma formation and superimposed DAD, pulmonary edema or AH [3, 4, 116].

Management of acute drug-induced granulomatous lung disease is similar to other forms of DIRD and consists of drug withdrawal, exclusion of an infection (particularly in patients exposed to corticosteroids, TNF-alpha antagonists, biologicals or BCG therapy), corticosteroid therapy and supportive care including mechanical ventilation. Mortality can be as high as 16% overall. Relapse occurs in 25–50% of patients, and death may follow in as many as half of patients who relapse after rechallenge with methotrexate [118].

Treatments of bladder carcinoma with topical BCG can lead to an acute pulmonary granulomatous reaction in about 3% of those so treated. In most patients, the disease is self-limited but fever and acute respiratory failure can develop in some patients. When tissue hypersensitivity is present, corticosteroid therapy is indicated. In a few patients, pulmonary granulomas correspond to infection with *M. bovis* BCG and molecular imprints can be found in lung or in other tissues. In such patients, additional chemotherapy against *M. bovis* is indicated, in addition to corticosteroid therapy [119].

Treatments with TNF antagonists can produce a systemic granulomatous reaction mimicking sarcoidosis, with an indolent course in most patients [3, 4]. Corticosteroid therapy may be indicated. Review of prior interferon gamma release assay is indicated to exclude antecedent infecting exposure to *M tuberculosis*. A granulomatous pulmonary reaction during treatments with biological therapy should prompt the diagnostic consideration of tuberculosis, miliary tuberculosis or any granulomatous pulmonary infection; all conditions to which TNF antagonists (particularly infliximab), or other biologicals including ICI predispose (Full list in Pneumotox [3, 4]). Tuberculosis can develop despite a negative pretherapy IGRA or preemptive chemoprophylaxis for LTBI, suggesting that treatment with these agents expose not only to reinfection but also to new infection [120].

A few drugs and substances of abuse can cause a foreign body pulmonary reaction that can be detected on pathology [121].

Acute Organizing Pneumonia (OP), Bronchiolitis Obliterans Organizing Pneumonia (BOOP), or Acute Fibrinous Organizing Pneumonia (AFOP) Patterns

Many agents and exposures, including 116 drugs, radiation therapy, excipients, and abused substances can cause organizing pneumonia [3, 4]. Collectively, drugs account for up to a third of biopsy-proven BOOP cases [39]. Approximately 9% of drug-induced/iatrogenic OP cases are lethal from uncontrollable respiratory failure. This is similar to what happens in cryptogenic OP (COP). The quality of evidence for drug causality in OP in the literature is inconsistent and often limited. Authors may attribute the term organizing pneumonia to a certain imaging pattern, with insufficient evidence. Interobserver reproducibility of imaging patterns is suboptimal [122]. The merit of using pathology descriptors to categorize imaging patterns [29, 30, 123] is unclear [86], inasmuch as radiographic patterns may change with time in a given patient, or may overlap [86], and roentgenographic appearances correlate poorly with pathology [31]. The former Fleischner Society terms [33] stay valid, and the imaging section in Pneumotox [3, 4] offers a classification derived from the latter [33].

Ascertaining drug causality is problematic because OP can be idiopathic, occur as a manifestation of a recent infection, upstream bronchial obstruction, or autoimmune disorders including connective tissue disease, inflammatory bowel disease, or inflammatory myopathies. In hematologic malignancies, OP can occur following stem-cell transplantation. The diagnosis of therapy-related OP should be entertained in the patient with migratory pulmonary opacities or diffuse infiltrates on sequential imaging, in some, a confirmatory histopathologic diagnosis, with exposure to a compatible drug and abatement of signs and symptoms following drug discontinuance be it with or without corticosteroid therapy, and absence of relapse over a prolonged follow-up period.

Acute fibrinous organizing pneumonia or AFOP is a pathologic pattern that has been reported in association with 19 distinct drugs [3, 4]. This severe OP variant is characterized by a dominant pattern of intra-alveolar fibrin and fibrin balls on a background of organizing pneumonia [124]. Organizing pneumonia and AFOP cases may represent the resolving phase of drug-induced acute lung injury/DAD. Compared to OP, AFOP carries a worse prognosis. Firm evidence that drugs cause AFOP is often elusive. One out of 17 patients described by Beasley was being treated with amiodarone. Two AFOP cases occurred in patients treated with a statin drug. Other causal drugs include bleomycin, mTOR inhibitors, ICI, and trimethoprim-sulfamethoxazole [3, 4]. Readministration of any suspect medication after recovery from an AFOP episode should be carefully discussed, lest fatal relapse may supervene.

Acute Amiodarone-Induced Pulmonary Toxicity (AIPT)

- Amiodarone-induced ARDS [3, 4].
  Although classic AIPT typically develops insidiously, some patients present acutely in the form of diffuse symmetrical or asymmetrical pulmonary infiltrates and respiratory failure requiring titrated oxygen therapy or mechanical ventilation. The interval between the earliest signs and symptoms of AIPT and development ARDS is unknown, and it is possible that ARDS represents an acute exacerbation of previously undiagnosed or subclinical AIPT. In one study in 514 ARDS cases, 49 (9.5%) were thought to be related to exposure to drugs. Fourteen of these 49 (28.5%), representing 2.7% of the whole ARDS population, were associated with exposure to amiodarone [35]. In another study, amiodarone was shown to increase the risk of developing ARDS approximately 3.8-fold [125].
- Postoperative Amiodarone-associated/induced ARDS [3, 4]
  This presentation can develop within days following cardiac, coronary bypass graft or surgical pulmonary resection. Features include onset within a few hours or days of surgery in patients who have been either chronically treated with amiodarone or in those who received the drug postoperatively. The complication can occur after a total amount of as little as 1100 mg of amiodarone. In one study, prophylactic amiodarone was given to combat supraventricular fibrillation post-resectional lung surgery [126]. This led to a sixfold increase in the incidence of ARDS compared to controls, with a 66% mortality. However, not all studies confirmed that finding since then. Pathological examination of lung tissue from amiodarone-associated ARDS patients reveals DAD on a background of pulmonary phospholipidosis [61]. It may take as little as 2 days on the drug to develop foam cells and endogenous lipoid pneumonia that are suggestive of AIPT. Foam cells can also be retrieved in the BAL of such patients. Intraoperative factors, such as high oxygen tensions, are thought to trigger postoperative occurrence of amiodarone-associated ARDS. Intraoperative single lung ventilation with 100% oxygen led to selective damage of the ventilated lung, while the "resting" lung was spared [127]. An intriguing feature of those who survive an episode of amiodarone-associated ARDS is that they can sometimes be restarted on amiodarone after surgery without recurrence. This is consistent with the view that amiodarone-associated ARDS may arise due to a two-hit interaction that includes exposure to amiodarone and peri- or intraoperative factors such as elevated high oxygen tension in the inhaled air, barotrauma, cytokine release, impaired thoracic lymphatic damage from surgery, or any combination thereof. The practical conclusion in terms of prevention is that liberal or prophylactic use of amiodarone and above-needed inspired oxygen tensions pre- and post-operatively should be avoided. Perioperative amiodarone is best reserved for symptomatic arrhythmia cases.
  Although the response of amiodarone-associated ARDS to corticosteroid therapy is unpredictable, many consider an early modest or moderate dosage of corticosteroids as good practice, provided other causes for ARDS are excluded. Clinical experience confirms that.
- Acute amiodarone-associated cellular NSIP [3, 4].
  Rarely, acute AIPT is in the form of dense cellular NSIP [3, 4]. This presentation occurs after relatively short periods on the medication, as opposed to the usual slowly-progressive AIPT. NSIP-like AIPT presents with diffuse haze or ground-glass, elevated lymphocytes in the BAL and a demonstrable response to corticosteroid therapy.
- AFOP and AEP [3, 4] are rare but possible patterns of AIPT on pathological evaluation [128]. Corticosteroid therapy is indicated (see paragraphs above).

Accelerated Pulmonary Fibrosis

- Chemo agents (including bleomycin, mitomycin C, nitrosoureas, and oxaliplatin-based chemo regimens), adalimumab, paraquat, and pemetrexed may cause rapidly progressive ILD and/or pulmonary fibrosis [3, 4]. On statistical grounds, the contribution of methotrexate to this syndrome is more uncertain now [129], even in the presence of a background of underlying rheumatoid pulmonary fibrosis [130, 131]. Drug-induced accelerated pulmonary fibrosis can occur following an episode of acute chemotherapy lung or, less often cellular ILD, or it develops insidiously months or years after completion of chemotherapy, amiodarone, or radiation therapy to the chest. In some cases, oxygen therapy may accelerate chemotherapy or amiodarone-induced fibrosis.
- Anti-TNF agents have been implicated in rapidly-progressive pulmonary fibrosis in rheumatoid arthritis (RA) and, rarely in inflammatory bowel disease [132]. A study examined 42 rheumatoid arthritis cases with acute progressive ILD while being treated with an anti-TNF agent (infliximab in 24, etanercept in 15, adalimumab in 3) [133]. Etanercept cases presented with granulomatous intrathoracic reaction and fared better than infliximab cases, which demonstrated a UIP pattern and had worse outcome. Currently, the causality of anti-TNF agents in terms of accelerated pulmonary fibrosis is debated [134–138].

Acute Exacerbation of Previously Known (Idiopathic) Pulmonary Fibrosis

Patients with pulmonary fibrosis (idiopathic and/or systemic disease-related) may unexpectedly deteriorate with rapid or precipitous decline in pulmonary function, new or accentuated pulmonary infiltrates, progressive respiratory failure, and the gasometric characteristics of ARDS. Although the

formal definition of an acute exacerbation of ILD (AEILD) cites no specific, identifiable precipitating factor, infection, inhalational injury and drugs can certainly trigger acute deteriorations. Drugs implicated in AEILD include antimetabolites, chemo agents, TKI, ICI, TNF alpha antagonists, amiodarone, and influenza vaccination [3, 4]. In 58 pathologically-confirmed DAD cases (15 with underlying pulmonary fibrosis), the drugs bleomycin, aracytine, gemcitabine, cocaine, and amiodarone were thought to have precipitated the acute deterioration in six and radiation therapy in one [139]. In 42 rheumatoid arthritis patients, TNF-alpha inhibitors were thought have caused the exacerbation [133]. While rheumatoid arthritis-associated ILD was once considered a relevant risk factor for the development of acute methotrexate pneumonitis [140], this view has changed lately [130, 131, 141] and methotrexate no longer appears nowadays contraindicated in patients with a background of rheumatoid pulmonary fibrosis.

- Fatal deterioration of previously diagnosed indolent pulmonary fibrosis has been reported in lung cancer patients treated with chemotherapy drugs, TKI, and/or ICI [3, 4]. In addition, drugs known to cause pulmonary toxicity in patients without pretherapy pulmonary abnormalities (e.g., amiodarone, statins) are often given to patients with smoking-related or idiopathic pulmonary fibrosis owing to age-related comorbidities. Out of an abundance of caution, we recommend withdrawal of any nonessential pneumotoxic drug in patients with pulmonary fibrosis who presents with acute exacerbation of the underlying disease.
- Recent case reports implicated SARS CoV2 vaccination as a cause for severe ILD [3, 4] [142] and exacerbation of pulmonary fibrosis [103]. In a recent letter, out of 26 patients presenting with an acute exacerbation of pulmonary fibrosis, there was none of the classic precipitating causes in ten individuals. Four of these ten gave a history of recent SARS-COVID19 vaccination as the sole potential explanation [104]. Adequate cohort studies in pulmonary fibrosis are needed to shed light to these preliminary observations about COVID-19 or influenza vaccination.

Anaphylaxis

Anaphylaxis is an explosive, potentially life-threatening allergic reaction that is primarily induced by food and drugs. Medications account for 25–36% of the cases [3, 4]. Insect stings and exercise are other significant eliciting factors. As of now, 222 drugs including antibiotics, NSAIDs, muscle relaxants, immunotherapy, oxaliplatin, biologicals (monoclonal antibodies used to treat rheumatoid arthritis (infliximab, etanercept)), and treatments for hematologic and solid malignancies including ICI, cetuximab, omalizumab, radiocontrast media, herbals, amino acids, and food supplements [3, 4] have been identified as a cause for anaphylaxis. Incidence, time to onset, populations at risk, and the adverse effects of rechallenging the patient are not equal between drugs and monoclonal antibodies. Atopy and parenteral administration of drugs exposes to a greater risk, as compared to oral administration. A multicenter study of anaphylaxis due to drugs given during a hospital stay identified 184 cases for review [143]. Incidence of anaphylaxis was 5–15 cases per 100,000 exposed patients for orally- or parenterally-administered analgesics and antibiotics and 32 per 100,000 for parenteral penicillin. Incidence for blood, dextran, pentoxifylline, and both ionic and nonionic contrast media ranged from 35 to 95 per 100,000. The rates for streptokinase and plasma were highest at 378 and 284 per 100,000, respectively. Cetuximab poses interesting though potentially severe risks in residents of the southeastern United States, where tick bites predispose to the risk of cetuximab hypersensitivity and anaphylaxis via antigenic cross reaction. Signs and symptoms of anaphylaxis include the rapid onset (within seconds or minutes; with drugs demonstrating the shortest time to onset of all triggers) of malaise, impending doom, fainting, wheezing, bronchospasm, upper airway obstruction and laryngeal edema, and/or lower airway edema and obstruction, cardiovascular collapse or shock, cramping, loss of consciousness, seizures, and pulmonary edema. Drugs (mainly antibiotics, radiocontrast media, and NSAIDs) and foods account for the bulk of causes of *fatal* anaphylaxis. Time to potentially fatal cardiac or respiratory arrest is within 5–7 min of drug administration giving little time for the unprepared healthcare team to act [144]. Death (3.6%) or irreversible hypoxic brain damage can occur [144]. Epinephrine (adrenaline) is the life-saving drug of choice that should be administered or auto-administered in a timely fashion (0.01 mg/kg intramuscularly to be repeated every 1–5 min in most symptomatic patients, along with large amounts of fluids) [145]. Epinephrine is often not given early enough [146] or it is given with inappropriate dosage or insufficient amounts before cardiopulmonary arrest develops [146, 147]. Epinephrine has its own risks, including acute systemic hypertension, pulmonary edema, and/or myocardial infarction [3, 4, 8]. Epinephrine autoinjection, supportive measures (fluids, oxygen, mechanical ventilation), avoidance of the sitting posture, elevation of the legs to help restore effective blood volume are paramount. All physicians and healthcare workers should be prepared to recognize, diagnose, and manage drug-induced anaphylaxis. Preemptive simulation practice is recommended [148] and can improve management skills [149]. Anaphylaxis is a common cause of litigation for malpractice [144].

Acute Vasculopathy

Acute vasculopathy with or without the development of ARDS may result from intravenous infusion of drugs or for-

eign material followed by embolization into the terminal pulmonary circulation [3, 4, 8]. Examples include fluid silicone, bone marrow, blood and components, autologous fat, calcium replacement therapy, liquid or elemental mercury, "inert" drug excipients or solvents, colony stimulating factors, aprotinin, protamine, gas from hemodialysis machine or from the ECMO setup, fat or lipid excipients (as in propofol, parenteral nutrition or mineral lipids). A comprehensive list is available in Pneumotox [3, 4, 8]. The mechanical consequences of i.v. injection of certain drugs or foreign material include obstruction of the pulmonary circulation to blood flow, traumatic vascular injury from sharp-edged embolized material or crystals, activation of the coagulation cascade, intravascular coagulation, and fluid leakage. Chronic consequences can include severe pulmonary hypertension, interstitial lung disease, and pneumoconiosis. A history of recent injection or infusion of drugs (including drugs of abuse), surgical procedure, liposuction or cosmetic surgery can aid in diagnosing the condition. Telltale signs of surreptitious drug use include venous access ("tracks") on the forearms or groin, foreign material deposits on fundoscopy, and paraphernalia in their home.

Methylmethacrylate cement embolism is a distinctive complication of vertebroplasty sessions [3, 4]. During kyphoplasty, acrylate cement is injected in the vertebral body [150]. Leakage of cement and bone marrow may occur in up to a quarter of patients so treated and is symptomatic in about 5%. Methylmethacrylate embolism is of interest to the interventional and diagnostic radiologist, orthopedic surgeon, pulmonologist, and cardiologist. On imaging, embolizing or embolized cement is in the form of dense tubular, branching, punctuate or wormlike shadows in paravertebral veins, heart, or pulmonary circulation [151]. This is best viewed on plain chest radiograph and *un*enhanced CT. High volume acrylate polymerization during transit through the heart or main pulmonary arteries can cause complete hindrance to blood flow and this can be fatal.

Transhepatic chemoembolization sessions may be complicated by vascular dissemination of doxorubicin and/or cyanoacrylate with or without iodized oil (Lipiodol) or radioactive material, causing pulmonary embolism, pleural effusion, acute pulmonary edema, and/or ARDS within hours of the procedure [3, 4].

Acute radiation induced lung injury resulting ARDS has become very unusual following radiation therapy to the chest, particularly since the advent of novel stereotactic techniques and establishment of safer radiation thresholds. The complication is almost exclusively reported in patients who receive concomitant irradiation and chemotherapy or total body irradiation. A single series reported on 15 patients with ARDS developing after administration of the radiochemical ^{131}I for the treatment of hepatocellular carcinoma. The ARDS was lethal in 12 patients (80%) [152].

Drug-Induced/Iatrogenic Airway Emergencies

Airway Obstruction as a Manifestation of Anaphylaxis

Central airway obstruction is common in (drug-induced) anaphylaxis, due to upper airway and laryngeal edema, as found at autopsy [153].

Drug-Induced Angioedema

About 70% of angioedema involving the upper air passages occur as a complication of therapy with drugs (124 are known to cause this condition), with ACEI accounting for 52% of angioedema cases [3, 4, 154]. Angioedema can cause severe upper airway obstruction [3, 4]. Angioedema can also affect the intestine causing relapsing abdominal pain and bowel obstruction. Angioedema typically occurs in isolation in the first few weeks or later and up to a few years into treatment with the culprit medication, with no clue to predict the development of the condition. Angioedema may develop concomitant with drug-induced anaphylaxis. Drug-induced angioedema can cause rapidly progressive upper airway obstruction and fatal asphyxia [155]. Epidemiological studies disclose an increasing incidence of this complication. Drug-induced upper airway obstruction occurs more often as a complication of chronic treatments with renin-angiotensin system inhibitors including ACEI and angiotensin receptor blockers (ARB) than with any other class of medications [154]. Incidence is less than that of ACEI-induced cough (about 1/30th), and there is no known mechanistic overlap between the two. Among ACEI, incidence is greater with enalapril and lisinopril as compared to captopril. Incidence of ARB-associated UAO is about 1/10th–1/20th compared to ACEI. Mild grades of airway or intestinal angioedema are notoriously underrecognized, and prolonged delays in diagnosis result in continuing exposure to the drug despite repeated episodes of mild lip, tongue, mouth, mouth floor or throat edema puts patients at risk of developing a major or fatal episode of central airway blockage and asphyxia [156]. Risk factors for angioedema include a disproportionate fourfold greater incidence in people of color (african-americans or afro-caribbeans) compared with caucasians. This accounts for a greater incidence of this complication in the US. Airway manipulation and the trauma of intubation are risk factors for acute angioedema. However, UAO can develop unexpectedly with no identifiable triggering factor. About 25% of patients give a history of previous spontaneously resolving episodes of mild perioral, oral or palpebral edema that failed to be identified and recognized as drug-related by healthcare professionals. Warning symptoms of impending angioedema include sore throat, drooling, dysphagia, pruritus, and the rapid development of edema of the lips, floor of the mouth, tongue and/or larynx. Type 1 angioedema is limited to the face, type 2, to the mouth floor, base of tongue and uvula,

and type 3 to the oropharyngeal, supraglottic and glottic region (though rarely involving the thoracic trachea). The risk of asphyxia is greater in patients with the type 2 or 3 angioedema. These patients are more liable to experience breathing difficulties and require admission to the ICU. It is important to identify and secure the airway early using the fiberoptic bronchoscope and endotracheal tube, since if the edema progresses, complete airway obliteration may occur. Identification of the airway lumen can be problematic and emergent cricothyrotomy or tracheostomy can be perilous in the context of asphyxia and anoxia. Irreversible hypoxic brain damage and death can result [156]. A few angioedema cases were complicated by laryngospasm with consequent negative pressure pulmonary edema or hemorrhage as a "domino" complication. About 40% of patients with drug-induced angioedema require admission to the ICU. And 10% of those require mechanical ventilation. Patients need to be monitored for an average of 2 days since rebound angioedema can occur despite drug discontinuation and appropriate management. Corticosteroids and antihistamines have unproven efficacy. The bradykinin-B2 receptor inhibitor icatibant has met with success in reducing the time to recovery from 33 to 4.4 h [157]. Other therapeutic drugs of interest include ecallantide, fresh frozen plasma, C1-inhibitor, and II-VII-IX-X factor concentrate [158]. Education of patients started on ACEI and ARB is critical, as is regular history taking for the occurrence of mild angioedema episodes anytime a new ACEI prescription is written. Rechallenge with the drug is hazardous, as severe or fatal UAO can recur after variable time on the medication [159]. A few cross-reactions to both ACEI *and* ARB have been reported in the same individual.

Hematoma Around the Upper Airway

Treatments with vitamin K antagonists, new oral anticoagulants, and exposure to or poisoning with superwarfarins (e.g., brodifacoum) can cause alveolar hemorrhage, hemothorax, hemopericardium, hemomediastinum, hemoptysis or epistaxis [3, 4]. Hematoma can develop in the esophageal wall or around the central airway, which can cause severe upper airway narrowing and obstruction that can be difficult to diagnose. The hematoma may localize in the neck, tongue, pharyngolarynx, retropharyngeal space or mediastinum in humans as well as in poisoned animals [3, 4]. Hematomas can cause lumenal narrowing and life-threatening airway obstruction. Being deep-seated, hematomas may not cause measurable blood loss and can escape recognition on endoscopy. Anticoagulant-induced esophageal hematomas may compress the tracheal wall [3, 4].

Blood originating from the lung may clot in the large airways and/or the central airway, causing life-threatening or fatal airway obstruction [160].

The "Pill Aspiration Syndrome"

Aspirated drug tablets (e.g., iron sulfate or alendronate pills to name a few) can lodge in the larynx [161], or damage the trachea, and/or large airway walls [162–164], causing unusual but suggestive endoscopic appearances and/or airway obstruction or ulceration that are sometimes mistaken for malignancy [3, 4]. Diagnostic error may occur because the pill or pills may not be longer visible, after being absorbed through the airway mucosa in the interval between aspiration and the time of clinical presentation.

Catastrophic Drug-Induced Bronchospasm

Severe sudden asthma can develop following oral or parenteral exposure to one of the 55 drugs capable of causing the syndrome, including drugs of abuse (cocaine, crack cocaine heroin), adenosine, analgesics, antibiotics, aspirin (salicylate), beta-blocking agents, e-cigarette vapor, lidocaine, and NSAIDs [3, 4]. Most of these drugs are either contraindicated or should be used very cautiously in patients with a history of asthma, particularly if severe or unstable at baseline. These contraindications may be overlooked, causing severe or fatal reactions upon exposure. Drugs cause more severe asthma attacks compared to other triggers. In one study, 8% of acute severe asthma attacks requiring mechanical ventilation in the ICU were triggered by an NSAID [165]. A history of severe, unstable difficult-to-control, corticosteroid-dependent asthma, atopy, nasal polyps, drug allergy or prior reaction with the same or drugs or congeners of the same family or class are risk factors. Though catastrophic bronchospasm may develop in a subject with no prior history of asthma (for instance, with nonselective β-blockers) [166], the complication generally occurs in patients with previously diagnosed asthma. Contrasting with drugs to which patients become sensitized upon repeated exposure (for instance, oxaliplatin, neuromuscular blocking agents), aspirin, and NSAID sensitivity/intolerance does not result from acquired sensitization but is rather inherent and constitutional to the patient. Patients may present with the Widal or Samter triad of recalcitrant sinusitis-nasal polyps, intermittent watery nasal discharge, difficult-to-treat asthma, and intolerance to NSAID of the COX-1 inhibitor family and to aspirin. Exposure to those drugs is followed within minutes to a few hours by an increase in nasal symptoms over baseline, and bronchospasm which can be severe. Avoidance of any COX1 NSAID including aspirin in such patients is essential. Desensitization or a state of tolerance using incremental dosages of the causal drug may be achieved if patients need to be treated again or to use these medications chronically. Importantly, continuous (e.g., daily or thrice weekly) exposure to the drug is necessary for maintenance of the desensitized state, otherwise intolerance returns in a few days and along with it comes the risk of relapse of a severe

asthma attack. The vast majority of patients with aspirin/NSAID-exacerbated sensitivity are able to tolerate selective COX-2 inhibitors, though caution is recommended in those susceptible to severe asthma attacks. Beta-blocker-induced bronchospasm can be abrupt and rapidly fatal [3, 4, 166–168]. This form of catastrophic asthma can be difficult to treat, as ongoing β-blockade may blunt the response to β2-agonist therapy. In 1996, the UK Medicines Control Agency had been notified 51 reports of bronchospasm that occurred as an adverse reactions to propranolol; 13 of the cases were fatal [166]. The bronchospasm was fatal in five of the six patients who gave a history of preexisting asthma [166]. Novel selective β-blockers may not induce measurable bronchospasm and may even confer a survival advantage to chronic obstructive pulmonary disease patients [169]. However, it is good practice to exercise due caution with this class of medications in asthmatics.

Inhaled/insufflated heroin, cocaine, and crack cocaine has coincided with a sizable increase in the rate of severe asthma attacks, admissions in emergency departments or death [3, 4]. In one study of 152 acute asthma cases, there were 42 cocaine and 47 heroin users [170]. Intubation rate was higher in cocaine or heroin users (21.4% and 17.0%, respectively) compared to nonusers, in whom the rate was 2.3%. Likewise, the prevalence of heroin insufflation was found to be 56% in a sequential ICU admission study in 23 patients [171]. In appropriate settings, a urine drug screen is indicated in the patient with acute asthma attack [171].

A popular test in young people is the "Dry Cinnamon Inhalation Challenge" whereby the adolescent subject attempts to inhale a large spoonful of the compound [172]. As not enough saliva is available to humidify and swallow the amount of fine cinnamon powder, inhalation, aspiration, and acute bronchospasm may follow. Foreign body bronchiolitis and ILD may also develop in the aftermath. The challenge seems less popular nowadays, and no further report has emerged since 2013 [172].

Peri-operative Emergencies (Table 42.8)

Few situations cause more distress and carry more risk than acute intraoperative catastrophic respiratory events, as the time allotted to understand and solve the issues is typically short or extremely short. Respiratory emergencies can be the direct consequence of drugs taken preoperatively at baseline or of anesthetic or nonanesthetic compounds given during the surgical or endoscopy procedure. Anaphylaxis (due to anesthetic agents, neuromuscular blocking agents, contrast media, latex or antibiotics), angioedema from angiotensin-converting enzyme inhibitors (see Table 42.6), explosive coughing from fentanyl, acute severe bronchospasm from anesthetic agents or muscle relaxants, pulmonary edema or ARDS as a complication of narcotics, dextran or transfusion of blood, plasma or proteins, nonthrombotic pulmonary embolism from aprotinin or methacrylate, protamine-induced acute pulmonary vascoconstriction, embolism of lipids or fat from propofol or from drug fillers, or drug-induced methemoglobinemia [3, 4]. The intraoperative occurrence elevates the severity of the event, in that diagnosis must be both rapid and accurate, and the course of the surgical procedure can be interrupted, delayed or compromised. Examples of scenarios that require emergent recognition and expeditious management include patients on preoperative ACEI who develop pre-, intra-, or postoperative acute angioedema and upper airway obstruction following the trauma of airway intubation [173] and intraoperative bronchospasm that can occur in patients who use beta-blockers and/or muscle relaxing agents.

Preoperative chloroquine, dapsone, metoclopramide, sulfonamide or recreational inhalants (amyl- or isobutyl-nitrite), intraoperative benzocaine, lidocaine, nitroglycerine, nitro compounds or nitric oxide (among 82 drugs or chemicals known to cause methemoglobinemia [3, 4]) may lead to methemoglobin formation, a condition where one and up to four of the four ferrous (Fe^{2+}) iron ions linked to each heme in the hemoglobin molecule become oxidized into the ferric state (Fe^{3+}) [174]. Fully oxidized Fe^{3+} is largely unable to bind and carry dioxygen (O_2). The condition manifests with the progressive or rapid onset of slate-grey cyanosis resistant to high-flow dioxygen, a chocolate-brown hue of blood that does not turn red when exposed to room air or when bubbled with oxygen [175]. Significant levels of methemoglobin (25–40% of total hemoglobin while normal is below 3%) are associated with low or erratic pulsed saturation (SpO_2) readings (60–70% range) despite normal or above normal *measured* (dissolved) partial pressure of dioxygen, depending on the FiO_2 the patients is exposed to. True hemoglobin saturation and the varied Hb species need be measured (not calculated or assumed from PaO_2 measurement), otherwise the diagnosis can be missed. A significant saturation gap (calculated *minus* measured SaO_2) is suggestive of methemoglobinemia [3, 4]. Multi (four) wavelength sensors are appropriate for measuring methemoglobin and carboxyhemoglobin in addition to oxy- and deoxyhemoglobin or SaO_2 can be measured spectrophotometrically in vitro. Methemoglobinemia in excess of 50–60% can induce arrhythmia, central nervous system symptoms, seizures, and coma. Metabolic acidosis can develop with MetHb levels in excess of 70%, that are potentially fatal. Treatment is with high flow inhaled oxygen and the reducing agent methylene blue administered at a rate of 1.5 mg/kg in 5 min, after which disappearance of discoloration, normalization of SpO_2, and a drop in methemoglobin should be observed within 1 h [176]. Careful monitoring of methemoglobin levels is required, as methemoglobin may reform. Readministration of methylene blue can be needed, but high dosages may cause paradoxical methemoglobin reformation. Failure to obtain response may

Table 42.8 Potentially catastrophic intra- and peri-operative drug-induced and iatrogenic emergencies

Step	Occurrence	Typical causal drugs	Risk factor	Management/prevention	Major complications
Intubation				Stoppage indicated as the first measure in all cases	
	Anaphylaxis	Muscle relaxants, crystalloids	Atopy?	Fluid resuscitation, CS, antihistamines, supportive	CV collapse
	Angioedema	ACEI/ARB	ACEI, ARB	O_2, identify airway passage via endoscopy, CST, antihistamines	Asphyxia
				Consider icatibant	Brain death
				If all fail: emergent tracheostomy	
	Airway tear or rupture	–	–	Secure airway, consider repair	Pneumomediastinum
					Mediastinitis
Induction					
	Apnea	Opiates, narcotics, colimycin		O_2, MV, naloxone	Hypoxia
	Explosive coughing	Fentanyl	Smoking	Dezocine, pentazocine, propofol	Wound dehiscence
Intraoperative					
	Angioedema	ACEI/ARB	ACEI, ARB	See above	Asphyxia
					Brain death
	Airway fire	Lime + sevoflurane interaction. Laser, cautery	Flamable mixtures	Switch off O_2, heat source and eliminate any fuel in the airway	Airway burns
					ARDS
	Anaphylaxis	Antibiotics, dextan, gelatin, heparin, latex, RCM	Atopy	Fluid resuscitation, CS, antihistamines, supportive	Death
	Catastrophic asthma	Adenosine, fentanyl, NSAIDs, propofol	Atopy, previously diagnosed asthma	Test dose? Preinterventional skin testing	Brain death
	TRALI	Blood and components	Antibodies in donor. Intervention can be the second hit required for TRALI to fully develop	Stringent transfusion policy. Autotransfusion. Male or nulliparous female donors only. Reduce blood storage time	ARDS
	Pulmonary edema	Alemtuzumab, fentanyl, ophtalmic phenylephrine, naphazoline	ND	Drug stoppage. Supportive care	ARDS
	ARDS	Dextran		Drug stoppage. Supportive care	ARDS
	Fat embolism	Propofol		Drug stoppage. Supportive care	ARDS
	Acute pulmonary embolism	TACE using doxorubicin		Drug stoppage. Supportive care	ARDS
	Acute pulmonary vasoconstriction	Reversal of heparin with protamine		Nitric oxide	CV collapse
				Drug stoppage. Supportive care	Death
	Cement embolism	Acrylate	Leakage from vertebral body	Drug stoppage. Supportive care	CV collapse, death
	Oxygen toxicity	Dioxygen (O_2)	Prior exposure to chemo agents	Monitor for lowest possible FiO_2	ARDS
	Methemoglobinemia	Benzocaine, dapsone, and other		O_2. Consider methylene blue. Ensure methylene blue availability	Pulmonary edema
					Hypoxic brain death

Postoperative, early					
	NPPE	–	Central airway or ET tube obstruction	Monitor ET tube or laryngeal tube patency	DAH, ARDS
	Pulmonary microthrombi	Aprotinin	(Drug was recalled in most countries)	Drug stoppage. Supportive care	CV collapse
	ILD exacerbation	Bleomycin, amiodarone	Dioxygen (O_2)	Monitor for the lowest possible FiO_2	ARDS
Postoperative, late					
	ILD/IPF exacerbation	Amiodarone, bleomycin, ICI, surgery	High intraoperative FiO_2	Monitor for lowest possible intraoperative FiO_2	ARDS
	Worse outcome	Blood		Restrictive transfusion policy	

result from ongoing exposure to the culprit drug or chemical or to a background of constitutional NADPH deficiency, especially in the newborn and in infants. Exchange transfusion and ECMO can be required. Ready availability of methylene blue should be monitored in all appropriate care settings, as immediate administration of the drug may be life-saving.

An important and often overlooked area is the pulmonary toxicity of molecular oxygen. In particular, elevated and FiO_2 on a previously drug- or radiation-exposed lung for even a short period of surgery may be damaging. Undeniable acute postoperative ILD and ARDS has been reported in patients previously exposed to amiodarone, bleomycin, chemotherapeutic drugs or radiation with no preoperative evidence for ILD [177]. "Whitening" of the single lung that had been ventilated using 100% oxygen during the surgical procedure in an amiodarone-exposed patient is consistent with this view [127]. Maintaining the intraoperative FiO_2 at the lowest level required to ensure an adequate SaO_2 is indicated in any patient who has a history of exposure to pneumotoxic drugs, particularly amiodarone, bleomycin, nitrosoureas, chemotherapeutic agents, or radiation.

Cases of negative pressure pulmonary edema (NPPE) have increased since the 1980s [178]. This form of pulmonary edema appears to be related to the barotrauma of forceful inspirations against a closed extrathoracic airway. Markedly negative swings of intrathoracic pressure can cause exudation of fluid or blood [178] from damaged or stress-fractured capillaries toward the interstitium and alveolar spaces [179]. Causes of airway closure have included biting or obstruction of the endotracheal or laryngeal tube, goiter, trauma, amygdalitis, oropharyngeal surgery, tonsillectomy, vocal cord adduction, peri-anesthetic laryngospasm, laryngeal edema, septoplasty, foreign body (including throat packs) inhalation or aspiration and any type of rapid-onset upper-airway obstruction including rheumatoid arthritis-associated airway closure, or ACEI-induced upper airway obstruction [180]. The diagnosis is suggested with the sudden onset of dyspnea and hypoxemia in the appropriate, often postoperative clinical setting, accompanied by bilateral batwing pulmonary shadowing. Severe cases can be complicated by full-blown pulmonary edema, froth at the mouth, and/or alveolar hemorrhage. Although pneumomediastinum and hemoptysis can be part of the clinical manifestations of NPPE, these manifestations require examination of the upper airway and/or esophagus for possible laceration. The treatment of NPPE is mainly supportive and directed at reversing hypoxemia and restoring airway patency. Diuretic administration can result in hypovolemic shock requiring fluid resuscitation. NPPE is best prevented if maintenance of a patent airway is ensured in the perioperative setting at all times.

Other Rare Presentations

Pulmonary Nodules and Masses

Pulmonary reactions to 18 discreet drugs or radiation can be in the form of a pulmonary a nodule, nodules or a mass [3, 4]. The reverse halo sign has also been described [3, 4]. Amiodarone, bleomycin, and ICI toxicity have all been reported to present as pulmonary nodules or masses [3, 4]. The main differential in these cases such as these is typically malignancy or an infection. Nodules with ill-defined borders are a classic complication of chest radiation therapy, particularly with the novel stereotactic body radiation therapy techniques [3, 4] in which the gantry rotates around the patient's body. Areas of radiation-induced lung injury may assume a whorled or convoluted appearance and are densest in the areas that have received the greatest doses of radiation. Uptake values on PET scan tend to decrease with time, as opposed to recurrence of the underlying malignancy in which SUV tends to increase with time on serial PET scan examination.

Although a bilateral diffuse pattern of involvement is more common, a solitary lung nodule or a mass also is a classic manifestation of mineral oil aspiration, and the name paraffinoma is appropriate [3, 4] [181]. Paraffinoma may be tracer-avid on PET scan and mimic pulmonary malignancy [3, 4].

Multiple nodules can develop in children or in adults during or following therapy with carbamazepine, minocycline, hydralazine, and antineoplastic agents including bleomycin and ICI [3, 4]. The main issue is ruling out progression in those patients with an underlying malignant condition. Review of pretherapy chest imaging, response of the underlying disease to treatment, 18F-PET imaging, watchful follow-up or a lung biopsy can be indicated. Nonneoplastic nodules, when examined on pathology, may correspond to areas of organizing or eosinophilic pneumonia [3, 4].

Disease-modifying antirheumatic drugs (DMARDs) including methotrexate, leflunomide, and anti-TNF agents have been temporally associated with the development or progression of pulmonary rheumatoid nodules. This is known as pulmonary nodulosis and occurs mainly in patients with rheumatoid arthritis but not exclusively so [3, 4]. Nodules are moderately tracer-avid on 18F-PET-scan examination. The main issues are eliminating an infection (e.g., tuberculosis or histoplasmosis), particularly in patients exposed to TNF antagonists, and malignancy as rheumatoid arthritis is more prevalent in smokers or former smokers. Drug discontinuation, maintenance of therapy with DMARDs, or rituximab have met with some success. The mechanism(s) of nodule formation induced by these drugs is unclear.

Amiodarone pulmonary toxicity may manifest as a mass or multiple round-shaped opacities or masses in about 10%

of the cases. Large masses are coined amiodaronoma [3, 4]. The nodules and masses in amiodarone pulmonary toxicity tend to exhibit indistinct, ill-defined borders and can be surrounded by a halo of decreasing attenuation peripherally [182]. Nodules can be deep-seated in the lung, or they are noted peripherally abutting the pleura, causing localized pleural thickening and/or pleuritic chest pain. Nodules may be discovered incidentally on CT and may exhibit high attenuation on CT due to the bi-iodinated chemical structure of amiodarone [3, 4]. On pathology, nodular APT shows the classic features of APT including chronic interstitial inflammation, infiltration by myofibroblasts, and the presence of organizing pneumonia and foam cells, which are most intense in the center of the lesion and decrease peripherally. Other patients present which one or more rounded or indented masses up to several centimeters in their largest dimension [3, 4, 183]. There may be decreased attenuation in the center of the mass consistent with aseptic necrosis. Ruangchira-Urai et al. described the pathologic features of four such nodular APT cases [183]. Three had received a high maintenance dose of 800 mg amiodarone daily for 7 months or more. None of the four patients had a preoperative diagnosis of APT and the indication for excision was the suspicion of malignancy. The 18F-PET-scan was positive in the single patient so tested [183]. Histopathology in all four patients showed "*vacuolated histiocytes massed within alveoli to form macroscopic nodules with tissue breakdown*," smudged geographic necrosis and purulent abscesses. On electron microscopy, the characteristic cytoplasmic inclusions were present in histiocytes and macrophages. Awareness of these types of unusual, yet distinctive APT presentations may obviate the need for resectional lung biopsy in some cases. Also, the drug history should be given to the pathologist, it is notable that this information was unavailable to the pathologist at the time of examination in the four cases above [183].

Pleuroparenchymal Fibroelastosis

This distinctive syndrome has been better delineated and named [184–186] in the past few years [3, 4]. Clinical presentation is with shortness of breath exaggerated on exercise, tachypnea, chest pain on inspiration, restrictive physiology, biapical pleural thickening on imaging [186], and a downhill disease course that is often complicated by spontaneous difficult-to-treat pneumothorax or pneumomediastinum. The pathologic features include dense subpleural fibrosis with a prominent mesh of elastin fibers and intervening collagen [184, 185], and there is abrupt transition to a normal architecture in the deeper lung underneath the pleura [186]. Although most such cases are deemed to be idiopathic, a few were followed exposure to chemotherapeutic agents [187] (notably cyclophosphamide [188]) or occurred in recipients of stem cell or lung transplant [186].

Late Radiation-Induced Injury

Beside classic radiation-induced pneumonitis, a subset of atypical distressing, sometimes devastating radiation-induced injuries to the chest, heart, mediastinum, neck or esophagus may occur. Clinical presentations include painful myositis of intercostal muscles, constrictive pericarditis, coronary- or valvular heart disease, fibrosing mediastinitis, phenic nerve injury, chronic compressive pleuropericardial effusion or thickening, neck musculature problems and the "dropped-head syndrome," or swallowing disorders causing aspiration and chronic aspiration pneumonia and lung destruction.

Chest Pain

Drug-induced acute transfixing chest pain can be a cause for presentation for emergency care [3, 4]. The condition can result from drug-induced pleuritis, or subpleural drug-induced pulmonary involvement, acute coronary artery disease or spasm, pulmonary vasoconstriction, pericarditis or without association to clinically demonstrable disease [3, 4]. Drug-induced acute chest pain has been reported with the use of nitrofurantoin, low- and high-dose methotrexate, statins, lupus-inducing drugs including beta-blockers, interferons, carbamazepine, hydralazine, sulfasalazine, mesalazine, bleomycin, 5-fluorouracil, vindesine, adenosine 5′-triphosphate, triptans, cocaine, crack cocaine, and blood transfusion [3, 4]. Failure to identify the drug etiology exposes the subject to the risk of future distressing relapses and readmissions. Acute transient chest pain has also been reported following sclerotherapy of esophageal varices, arteriovenous closure of brain arteriovenous malformations, kyphoplasty, and cryoablation for atrial fibrillation or in the context of drug-induced esophageal erosion [3, 4].

Rebound Phenomenon

Rebound consists in a flare of the underlying disease that may occur upon withdrawal of a vital therapy drug and can be life-threatening. Examples include rebound pulmonary hypertension upon cessation of prostacyclin or nitric oxide, relapse of amiodarone pulmonary toxicity or DRESS or the development of acute radiation pneumonitis after tapering or abrupt removal of corticosteroid therapy, early relapse of ACEI-associated angioedema or of methemoglobinemia despite removal of specific therapy or antidote, recurrence of the clinical manifestations of opioid toxicity following too early termination of naloxone, and the ruxolitinib withdrawal syndrome [3, 4].

Recall Pneumonitis

Recall is the flare that follows the administration of small amounts of a drug or agent in a patient with a history of exposure to pneumotoxic drugs or radiation [3, 4]. Recall pneumonitis can develop in the previously irradiated area

following administration of chemotherapy or ICI. Other examples include ARDS triggered by oxygen in patients previously exposed to amiodarone [127].

Thoracic Bezoars: Gossipybomas

Bezoars and pharmacobezoars are aggregates of food or other foreign material or drugs. They may localize in the chest, obstructing the central airway or esophagus (sometimes rendering the esophagus spontaneously visible on a chest radiograph).

Pharmacobezoars including body packing may act as a slow release drug reservoir capable of releasing the drug and "mysteriously" perpetuating the adverse effects despite apparent withdrawal of the drug [189].

Postoperative leftovers (surgical sponge, throat packs, surgical fabric or catheters) may lead to a foreign body retention named gossypibomas or textilomas [3, 4]. These have distinctive HRCT features [190] and can simulate chest malignancy [191, 192].

Respiratory Diseases Considered Idiopathic That May Be Drug-Induced (Table 42.4)

A number of common diseases commonly named as "idiopathic" including such ILD as cellular NSIP, organizing pneumonia, pulmonary alveolar proteinosis, pulmonary fibrosis, exacerbated pulmonary fibrosis, sarcoidosis, ILD with a granulomatous component, hilar or mediastinal lymphadenopathy, pulmonary edema, ARDS, alveolar hemorrhage, angioedema, deterioration of asthma, chronic cough, pleural effusion including chylothorax, pulmonary embolism, emphysema, disordered breathing during sleep, hiccup, and such systemic syndromes as *lupus*, drug rash with eosinophilia and systemic symptoms, ANCA-related vasculitis, eosinophilic granulomatosis and polyangiitis, interstitial pneumonia with autoimmune features, myositis or polymyositis, the multiple organ dysfunction syndrome, or cardiomyopathy can all be triggered or caused by drugs [3, 4]. Consideration of the drug etiology can be rewarding in terms of reversal of all signs and symptoms with drug removal.

Eye Catchers

The reader is invited to visit the appropriate section of "eye-catching" images in pneumotox, where drug-induced and iatrogenic conditions may be so distinctive as to enable almost instant diagnosis [3, 4].

Conclusion

Drug-induced and iatrogenic respiratory problems are manifold and can be immediately life-threatening or fatal. Many are rare if not exceptional. Prevention rests on educating ourselves and our colleagues and pupils in all specialties about the respiratory reactions that may occur with the drugs they prescribe, identifying risk factors, a high index of suspicion, examining any sign or symptom or constellation thereof for possible drug-relatedness using pneumotox and the literature [3, 4], avoidance of hazardous combination treatments, prompt identification of the causal agent and its removal, reliable measures to avoid inadvertent rechallenge with the culprit drug, and publication of cases. It is worth mentioning that household substances and chemicals can also cause eminently preventable acute lung or respiratory injury [3, 4]. For all causes and patterns of injury, Pneumotox can be accessed at any time through the appropriate website or App.

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Malignant Mimics of Orphan Lung Diseases

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Nicolas Girard

A variety of rare malignant and benign tumors that develop in the lung, the pleura, and the mediastinum, may have a propensity to mimic orphan lung diseases at some level of examination, as they may share with these clinical, imaging, pathological, and even molecular and genomic features. Lung cancer is by far the most frequent intrathoracic malignancy, and it is then the first diagnosis to consider when facing a rapidly growing lesion involving the lung, the pleura, and/or the mediastinum, especially in smokers [1, 2]. However, physicians may be aware of uncommon and rare neoplastic and non-neoplastic disorders, that have a propensity to mimic other pulmonary diseases at some level of examination, especially rare, orphan entities that are less frequent for physicians who may not be aware of differential diagnoses [3–5]. Several frequent and rare intrathoracic tumors are associated with a peculiar phenotype, as such entities may share some of the clinical, radiological, pathological, and even molecular and genomic features of non-neoplastic orphan lung diseases. Numerous disorders may be considered, but the challenges in the differential diagnosis are well illustrated through the examples of bronchioloalveolar carcinoma, as well as primary pulmonary lymphomas and vascular sarcomas. All of these entities are rare, which may hamper rapid and accurate diagnosis.

Pseudotumors have further been described in the thorax, historically also referred to as pseudoneoplasms, but currently restricted to a specific heterogeneous group of diseases characterized by a circumscribed fibrous tissue associated with inflammatory and myofibroblastic cells, which may be observed in multiple diseases [6]. Among those, neoplastic/non-neoplastic borderline disorders have been identified, such as inflammatory myofibroblastic tumor with clonal proliferation, thus nowadays considered as a true malignancy with treatment opportunities that include standard anticancer therapies [6]. Molecular, oncogenic alterations that are observed in pulmonary carcinomas may be shared by borderline orphan lung diseases. Other rare pulmonary disorders are emerging as borderline neoplastic-non-neoplastic entities, which require multidisciplinary expertise both in the field of orphan pulmonary diseases and in thoracic oncology, including, for example, amyloidosis or Langerhans cell histiocytosis. Some of these entities are discussed elsewhere in this book.

Here, our objective is to provide the reader with a practical overview of these disorders. Key points for clinical practice are the identification of possible suggestive clinical and radiological features, a cautious interpretation of radiological or metabolic imaging, recommendations for specific pathological and molecular analyses on often small-size biopsies, and ultimately dedicated multidisciplinary expert discussion and networking to ensure expertise for the clinical decision-making.

Cancer Mimicking Orphan Lung Disease at Imaging

Malignant disorders may mimic some of landmark orphan lung diseases, as these may present radiologically as organizing pneumonia, interstitial lung disease, or even multiple cysts. Awareness of clinicians is key, as well as strict pretreatment workup, that may include molecular and genomic analyses.

Cancer Mimics of Organizing Pneumonia

Organizing pneumonia presents a classical diagnostic pitfall for lung cancer evaluation, as it may occasionally present as a solitary mass-like lesion, leading to unnecessary diagnostic procedures and even surgical resection, especially in heavy smokers who harbor a chronic lesion [7]. The landmark fea-

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ture of this condition consists of intra-alveolar fibroblast and myofibroblast, connective matrix organization that fills the alveolar spaces, the alveolar ducts, and the respiratory bronchioles. In patients treated for malignancies, cytotoxic drugs may induce organizing pneumonia. Although usually not presenting as a focal lesion, organizing pneumonia may mimic multiple pulmonary metastases as well. This has especially been reported historically with bleomycin treatment for germ-cell testicular cancer, embryonal tumors, and Hodgkin lymphoma, but is nowadays far more frequent with the use of immunotherapy with immune checkpoints inhibitors [8, 9]. Even in patients with a history of cancer, differential diagnosis is a clinical challenge, and may require multidisciplinary expert discussion to distinguish organizing pneumonia and recurrent cancer.

Conversely, the organizing pneumonia imaging pattern is shared with some primary lung malignancies, including bronchioloalveolar carcinoma and primary pulmonary lymphoma, that are characterized by tumor cell spread in the alveolar spaces, leading to a common radiological pattern of alveolar opacities with air bronchograms [7].

Lung Adenocarcinoma/Bronchioloalveolar Carcinoma

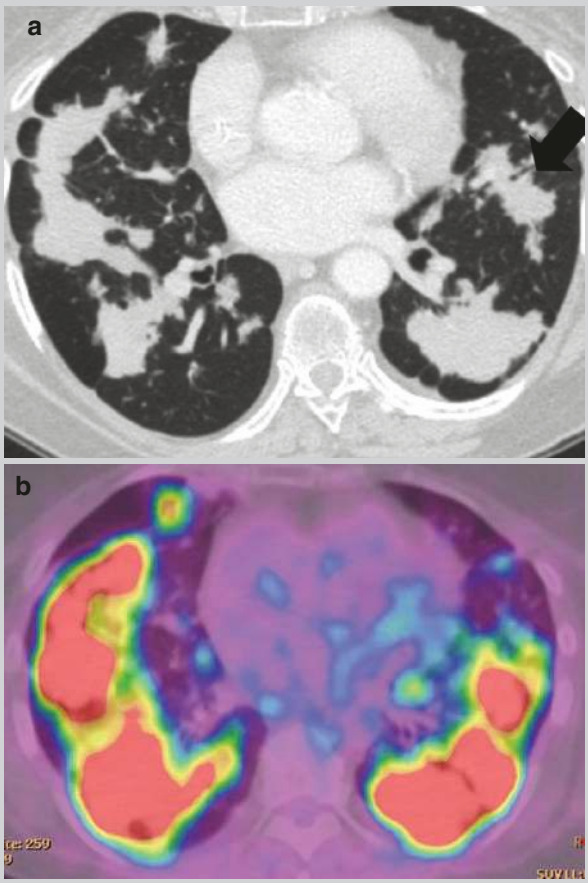
Bronchioloalveolar carcinoma has extensively been described elsewhere [10, 11]. It has actually been a term referring to several clinical-radiological-pathological entities of lung adenocarcinoma, which to varying degrees share a non-invasive lepidic cell growth pattern—a proliferation of tumor cells that progressively develops within the alveolar walls, filling the alveolar spaces without disturbing the normal lung architecture, with no pleural, stromal, or vascular invasion. These include: (1) mixed-type invasive adenocarcinoma with predominant lepidic growth, which has a very similar clinical and radiological presentation to other non-small cell lung carcinomas, (2) adenocarcinoma in situ—a pure lepidic growth proliferation, and (3) pneumonic-type lung adenocarcinoma, that is a distinct clinical-radiological-pathological entity. As stated above, the filling of alveolar spaces is a landmark feature of typical organizing pneumonia. The 2015 World Health Organization classification of lung adenocarcinoma deleted the term "bronchioloalveolar carcinoma" from the nomenclature to avoid historical misunderstanding [11].

Adenocarcinoma in situ, formerly known as pure bronchioloalveolar carcinoma, usually presents as a localized coin-like lesion, 3 cm or less in size, showing a predominant ground-glass pattern usually surrounding a solid lesion, possibly with air bronchograms, and located at the periphery of the lung parenchyma [11].

Molecularly, these tumors frequently harbor epidermal growth factor receptor (EGFR) mutations; *KRAS* mutations are frequently found in cases of mucin producing tumors [11]. These tumors may preferentially develop in non-smokers. Patients are usually asymptomatic. The lesion may show normal metabolic activity at 18-fluoro-2-desoxy-D-glucose Positron Emission Tomography (18-FDG PET) [12]. Given the localized nature of adenocarcinoma in situ, treatment usually consists of upfront surgery, producing a 95–100% disease-free survival rate. Metastatic progression is not observed, however, patients may present with multiple independent synchronous and metachronous tumors.

Pneumonic-type lung adenocarcinoma (PTLA) is a clinical-radiological-pathological entity that is not strictly defined in the histopathologic adenocarcinoma classification [13]. Histologically, PTLA is a heterogeneous disease, usually corresponding to mixed-type lung adenocarcinoma with predominant lepidic growth pattern, combined with papillary and acinar features, a desmoplastic fibrotic stromal reaction, and nodal, pleural, and vascular invasion. The clinical criteria to make a diagnosis of PTLA were the following: (1) evidence of a pneumonia-like consolidation, defined as a homogenous opacity in the lung characterized by little or no loss of volume, disappearance of blood vessel shadows and, sometimes, and the presence of an air bronchogram (Clinical Vignette) and (2) no concomitant bacterial pneumonia or obstructive pneumonia due to an exophytic lesion occluding the lumen of the main or lobar bronchi. The tumor is usually multifocal (65% of cases), slow growing with rare metastatic disease (5% of cases). It is associated with highly productive cough and progressive restrictive respiratory failure [13]. The epidemiology of PTLA differs from that of other non-small cell lung cancers, with less important epidemiologic links with tobacco smoking, an increased frequency in women and younger patients, and a better outcome (with a 5-year survival of 60%). Current treatment is based on recommendations established for other lung non-small cell carcinomas, including surgery for localized lesions and chemotherapy for disseminated tumors; the role for limited surgical resection is debated. Chemosensitivity is actually limited given the slow-growing pattern [14]. Molecular alterations are observed in about half of the patients [15], that may include *EGFR, KRAS* mutations, as well as *ROS1, RET, NTRK* gene fusions: these alterations predict the efficacy of targeted agents that are marketed or under investigation [15].

Clinical Vignette



A 66-year-old former smoker woman presented with progressive cough, and dyspnea. Chest radiography showed bilateral alveolar opacities, leading to prescribe antibiotics. Given the absence of symptom improvement, CT-scan imaging was done, and showed multiple bilateral alveolar condensation-like masses with irregular margins, some of which containing air bronchograms (a). Two subsequent lines of antibiotics were delivered, in the hypothesis of pulmonary infection. Ultimately, the patient presented with weight loss, and worsening of dyspnea. 18-fluoro-2-desoxy-D-glucose positron emission tomography scan showed hypermetabolism of all the lesions (b). Transparietal biopsy was performed, and pathological analysis showed adenocarcinoma cells with lepidic growth pattern and papillary architecture. No *EGFR* mutation was detected, nor other oncogene alteration at next-generation sequencing on DNA. The patient received platinum-based chemotherapy, leading to stable disease. Progression-free survival was 18 months. The patient subsequently received three lines of systemic therapies, including immune checkpoint inhibitors and antiangiogenic agents. Rebiopsy was then performed, leading to finally identify *RET* fusion. The patient currently receives RET inhibitor, leading to partial response. The patient is currently alive, 5 years after initial diagnosis

Primary Pulmonary Lymphoma

Pulmonary mucosa-associated lymphoid tissue (MALT) lymphoma is referred to as nodal marginal zone B cell lymphoma, with similar cytopathologic features to other MALT lymphomas, especially gastric lymphoma [16]. These low-grade lymphomas account for 70% to 90% of primary pulmonary lymphomas. At pathologic examination, MALT lymphoma appears as a diffuse infiltrate of small monomorphic lymphoid cells, with a typical lymphangitic growth pattern spreading along the bronchovascular bundles and interlobular septa, and forming solid nodules that fill the alveolar spaces and obliterate the normal lung architecture. Immunohistochemistry forms the basis of the subtype classification, with the expression of the pan-B-markers CD20 and CD79 and the absence of staining for CD5 and CD10 [16]. The proliferation is monotypic, with surface and/or cytoplasmic expression of immunoglobulin (Ig) M and, less frequently, IgG and IgA. Light chain restriction can be detected in the plasmacytic component using flow cytometry. MALT lymphomas are associated with unique chromosomal translocations, such as the t(11;18)(q21,q21) resulting in a fusion of the *API2* and *MALT1* genes, the t(1;14) (p22;q32) involving the *BCL10* and IgH genes— which is overall much less frequent, more specific to lung locations, and never found in high-grade lymphoma—and the t(14;18)(q32;q21) involving the IgH and *MALT1* genes [17]. In cases with the t(1;14) (BCL10/IgH) translocation, immunohistochemistry on paraffin-embedded tissues can detect the strong nuclear overexpression of BCL10. Amplification of the IgH gene from paraffin-embedded or cytologic samples with polymerase chain reaction (PCR)-based assays was demonstrated to be a reliable method to detect monoclonality in more than 60% of MALT lymphomas. Contrary to extrapulmonary MALT lymphomas, for which a strong relationship has been established with chronic bacterial inflammation related to *Helicobacter pylori* in the stomach and to *Chlamydia psittaci* in the ocular adnexa, no chronic infectious condition has been associated with pulmonary MALT lymphoma. MALT is absent in the normal bronchial tree and is thought to develop only after long-term inflammation secondary to smoking or to an autoimmune condition.

Clinically, MALT lymphoma has mainly been observed in patients older than 45 years, with a slight male predomi-

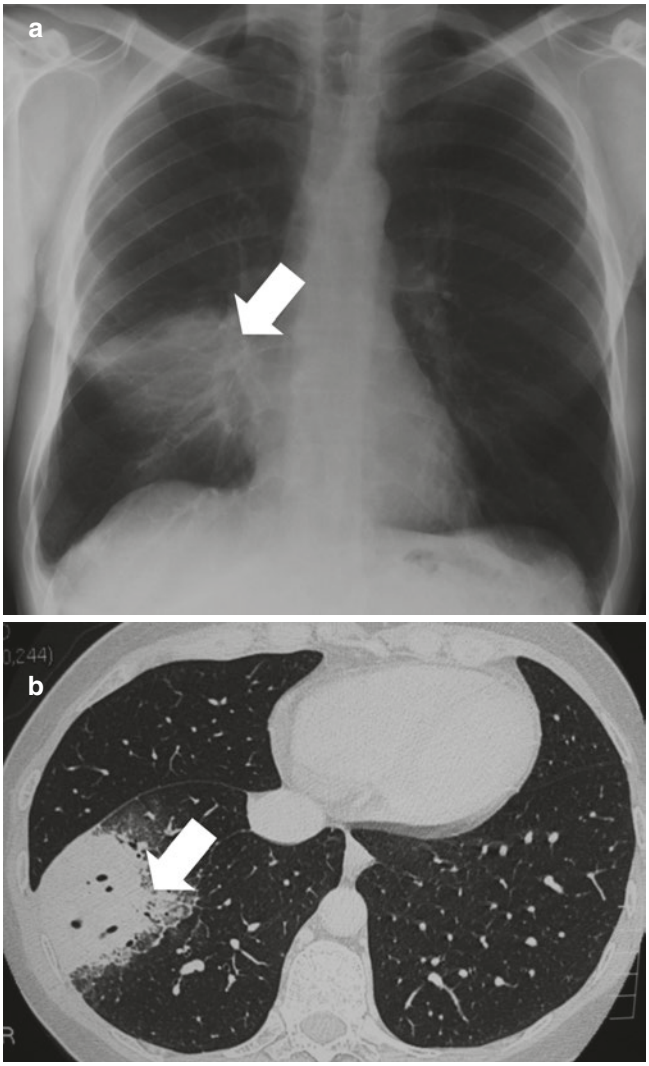


Fig. 43.1 Pulmonary primary MALT lymphoma in a 56-year-old man. (**a**, **b**) Chest radiography and computed tomography scan show persistent alveolar opacities in the right lower lobe, despite prolonged antibiotic therapy. Pathological examination of surgical biopsy showed lymphoplasmacytic-like cells of the marginal zone lymphoma associated with amyloid deposits. The patient received treatment with chlorambucil, which led to complete regression of the lesion

nance, but it may also arise in younger patients with underlying immunosuppression, especially related to human immunodeficiency virus (HIV) infection, or with inflammatory conditions such as Sjögren disease or rheumatoid arthritis, or in association with Epstein–Barr virus (EBV) infection [18, 19] (Fig. 43.1). Less than 50% of patients are symptomatic, with nonspecific symptoms including cough, dyspnea, and chest pain. Unlike the situation with other lymphomas, systemic signs such as fever, swelling, and weight loss are uncommon. Association with IgM or IgG blood monoclonal gammopathy is observed in 30% of cases.

Radiologically, MALT lymphoma exhibits three imaging patterns on chest radiography and computed tomography (CT), which are challenging for differential diagnosis: (1) the most frequent and suggestive is the "pneumonia-like" alveolar consolidation with air bronchograms typically localized in the middle lobe; (2) a "tumor-like" appearance with a solitary circumscribed nodular opacity (30% of cases) and possible central air bronchogram; and (3) the "infiltrative" pattern with diffuse poorly defined ground-glass opacities, assumed to represent early-stage disease before tumor cells invade alveolar spaces [20]. The combination of a nodular opacity with peripheral peri-bronchovascular ground-glass attenuation halo is common. Pleural effusion is unusual. Multiple cystic lesions may be observed, which may be associated with light chain deposition disease. Hence, differential diagnosis may be challenging with infection, cancer or interstitial diseases leading to frequent misdiagnosis if a complete workup is not conducted.

About a third of MALT lymphomas are multifocal at the time of diagnosis, a presentation that may hamper the determination of the primary pulmonary origin of the disease [18–20]. Pulmonary MALT lymphomas are associated with tumor locations in the gastric mucosa in 10% to 20% of patients and in the bone marrow in 15% to 20% of patients. Gastroscopy and bone marrow biopsy are then recommended; 18-FDG PET imaging may not be sensitive enough to exclude extrathoracic disease. The Ann Arbor staging system, although not designed for extranodal lymphoma, may be applied in pulmonary MALT lymphoma, which would be staged as IE (one site, extranodal) in case of lung unilateral or bilateral involvement, IIE (two sites, both above the diaphragm, extranodal) in case of hilar or mediastinal lymph nodes, or IV in case of multiple sites.

Pathological diagnosis actually requires a large, possibly surgical lung biopsy, because cytologic examination of bronchoalveolar lavage or fine-needle biopsy may show the CD20-positive B-cell infiltration but fail to exclude differential diagnoses, such as reactional lymphoid proliferation, follicular bronchiolitis, or lymphoid interstitial pneumonia. *MALT1* gene rearrangements may be identified on bronchoalveolar lavage [17].

Therapeutic options are based on the degree of tumor extension. Surgical resection ensures both the diagnosis and the treatment of nodular lesions, but MALT-type histology is usually unexpected when approaching a lesion thought to be NSCLC. In asymptomatic patients, a watch-and-wait attitude may be preferred to aggressive treatment. In the majority of patients MALT lymphoma requires more aggressive management, and standard-of-care is the combination of rituximab, an anti-CD20 antibody, with chlorambucil [21]. Several alternative options have been described, from single-agent therapy with chlorambucil, fludarabine, or rituximab to combined cytotoxic agents used for diffuse large-B cell lymphomas. Whether genomic profiles should drive the chemotherapy regimen is unclear, even if rituximab alone may be effective in case of *t*(11;18) translocation [21].

Prognosis of MALT lymphomas is usually excellent, with an indolent and localized prolonged course, and response to chemotherapy. Historical series reported 5-year survival rates

higher than 80%, and the more recent availability of rituximab may improve these results. Still patients may present with recurrences leading to sequential treatment; parenchymal or bronchial sequelae may ensue, leading to chronic obstructive disease or pulmonary fibrosis. Local and systemic recurrences develop in about 50% of cases, but are usually controllable with chemotherapy. Evolution to high-grade B-cell lymphoma is seen in less than 5% of cases. Young age at diagnosis is the most significant favorable prognostic factor.

Cancer Mimics of Interstitial Lung Diseases

Besides lymphangitis carcinomatosis, several rare intrathoracic tumors may present with an interstitial and/or a micronodular pattern, such as epithelioid hemangioendothelioma and lymphomatoid granulomatosis.

Lymphangitic Carcinomatosis

Pulmonary lymphangitic carcinomaosis is a metastatic lung disease characterized by the diffuse infiltration and obstruction of the pulmonary parenchymal system by tumor cells [22, 23]. Pulmonary lymphangitic carcinomatosis accounts for up to 10% of all thoracic metastases. Patients are usually diagnosed in their fifth decade. Dyspnea is usually the chief symptom [22, 23]. Weight loss is also frequent, as well as cough. Hypoxemia is observed in 70% of patients.

Even if histologically confirmed, chest radiography may be normal in up to 30–40% of cases. High-resolution computed tomography (CT)-scan may show (1) uneven thickening of bronchovascular bundles, from the hilum to periphery, that resembles Kerley B lines, (2) a more limited or diffuse peripheral interlobular septal thickening producing polygonal arcades, and/or (3) a radiographic pattern referred to as "beaded chain" or "string of pearls" thickening of interlobular septa [22]. These features may be diffuse or localized, uni- or bilateral, and symmetric or not. Micronodules may be observed within the thickened septa. Rapidly progressive asymmetric lymph node involvement is found in 30% of patients. 18-FDG-PET scan shows diffuse parenchymal hypermetabolism in diffuse lymphangitic carcinomatosis, or a more linear or hazy area of FDG uptake.

Diagnosis is usually obtained through bronchial, transbronchial or open lung biopsy; percutaneous biopsy may also provide lung tissue materials allowing the diagnosis to be made. Pathological examination shows multiple tumor thrombi within the lymphatic vessels, associated with a desmoplastic reaction caused by tumor proliferation and lymphatic dilatation around the interlobular septa and peribronchovascular bundles. Tumor cells of adenocarcinoma type are the most likely to produce lymphangitic carcinomatosis, originating from the following primary anatomic locations: breast (33%), stomach (29%), lung (15%), pancreas (4%), and prostate (3%) [22]. Survival is usually poor, ranging from 3 to 6 months [21, 22].

Differential diagnosis includes other infiltrative lung diseases, sarcoidosis, as well as bacterial or fungal infections, such as pneumocystis jirovecii pneumonia (PJP), especially when immunosuppressive cytotoxic agents are employed for treatment of the primary cancer. Bronchoalveolar lavage is the key to making the diagnosis of PJP. Lymphangitic carcinomatosis may also be confused with drug-induced interstitial lung disease especially in patients receiving chemotherapy or targeted agents or immunotherapy, immune checkpoint inhibitors or antibodies (drug-conjugated or not). Imaging patterns are nonspecific and may include ground-glass opacities and interlobular septal thickening. Multiple forms of interstitial lung disease may occur within individual cancer patients.

Epithelioid Hemangio-Endothelioma

Epithelioid hemangio-endothelioma (EHE) is a low- to intermediate-grade mixed epithelioid, endothelial, and vascular tumor [24, 25]. Lung is the most frequent extrahepatic location (10% of cases); EHE can also arise from the liver (63% of cases), the bone (8% of cases), and the skin (6% of cases) [24, 25]. EHE is characterized by polypoid nodules, with a central sclerotic paucicellular zone, growing into the alveolar spaces with an angiocentric distribution. Lymphangitic spread may mimic metastatic carcinoma. Around 90% of EHEs are caused by the fusion of transcriptional co-activator with a PDZ-motif (*TAZ*) with calmodulin binding transcription activator 1 (*CAMTA1*), a central nervous system-specific transcription activator; the 10% of EHEs that lack the *TAZ-CAMTA1* fusion instead have a fusion of yes-associated protein (*YAP*) and transcription factor E3 (*TFE3*) genes (*YAP-TFE3*) [26]. EBV RNA sequences are detected in 90% of cases. Overlapping entities with IgG4-related disease have been described. Clinically, 80% of cases of EHE are diagnosed in white females [24–26]. The tumor is asymptomatic in 50% of cases; when present, symptoms are nonspecific and include pleuritic chest pain, nonproductive cough, dyspnea, and rarely hemoptysis. By CT imaging, EHE presents either with bilateral slow-growing perivascular multiple nodules, usually located adjacent to small vessels or bronchi, or with predominant infiltrative ground-glass opacities with a micronodular pattern, mimicking lymphangitic carcinomatous. EHE nodules usually range from 3 to 50 mm, and their numbers vary from 10 to 20 lesions. Nodules in patients with EHE may show increased uptake on 18-FDG PET scan. Although there are a few reports of spontaneous remission, the complete resection of all pulmonary nodules is the only curative treatment for EHE. Surgery remains effective even in cases of localized recurrence. In contrast, EHE is generally insensitive to chemotherapy (cisplatin-based) or radiotherapy. Treatment with rituximab or antiangiogenic kinase inhibitors, such as

sorafenib or bevacizumab, have been reported to be effective in isolated case reports [27]. In most cases, EHE is a slow-growing tumor that rarely metastasizes and is associated with a median survival of 5–6 years. Endobronchial spread, pleural effusion, and extended endovascular disease have been identified as unfavorable prognostic factors.

Angiosarcoma is a high-grade primary pulmonary vascular sarcoma that is considered to be a counterpart of EHE, although no direct transformation from EHE to angiosarcoma has been reported. Clinical features of angiosarcoma are similar to EHE, but massive hemoptysis is more frequent. Radiologic features of angiosarcoma include multiple nodules with a typical surrounding halo of ground-glass attenuation, and a characteristic "cauliflower-like" appearance on T2-weighted MRI [28]. This aspect may be shared by other disorders, including malignancies (e.g., adenocarcinoma with lepidic pattern (e.g., bronchioloalveolar carcinoma), metastatic sarcomas, choriocarcinoma, melanoma, lymphoma), infectious diseases (e.g., mycobacteriosis, aspergillosis, cytomegalovirus infection), granulomatosis with polyangiitis, and eosinophilic conditions. Distinguishing primary pulmonary angiosarcoma from extrathoracic angiosarcoma metastatic to the lung can be challenging. Management of angiosarcoma is not established: surgical resection is rarely possible owing to local and regional invasion and radiotherapy and chemotherapy are typically ineffective as seen in other locations of angiosarcoma. In immunocompromised patients, reduction of immunosuppressive agents may lead to reduce the burden of the disease.

Lymphomatoid Granulomatosis

Lymphomatoid granulomatosis (LG), previously called "angiocentric lymphoma," is a malignant B cell angiocentric and angiodestructive lymphoproliferative disorder [28–30]. For a long time, LG was considered an inflammatory granulomatous disease owing to a presentation similar to other granulomatosis, such as granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis. Now, LG is recognized as a true EBV-related lymphoid malignancy. Differential diagnosis also includes allergic bronchopulmonary aspergillosis. The lung is the most frequent location, but the disease may also involve the brain, the skin, and the liver [28–30].

Pathologically, LG forms multiple and confluent nodules composed of an atypical, angiocentric, and polymorphous lymphoid infiltration involving the vascular walls, from the subendothelium to the adventitial zones, with focal lumen obliteration. By immunohistochemistry, these lymphoid cells are characterized mostly as CD4+ T-lymphocytes, with scattered atypical B cells. Large B cells are infected with EBV in 65% of cases, and EBV status correlates with the grade of the lesion. Pulmonary biopsy is required in most cases to exclude other granulomatoses.

LG arises in middle-aged patients between 40 and 50 years old, with a male predominance. Nearly all patients present with respiratory and systemic symptoms, consisting of cough, dyspnea, hemoptysis, chest pain, fever, and weight loss. Peripheral and mediastinal lymphadenopathy is absent. Prolonged immunosuppression is a frequent underlying condition. Hypereosinophilia may be observed in the blood and/or in the bronchioalveolar lavage. The typical radiologic presentation consists of multiple smooth bilateral nodules ranging from 2 to 10 cm mainly localized in the lower lobes, exhibiting a peribronchovascular pattern and mimicking multiple metastases. As in other granulomatoses, convergent nodules may migrate and form cavitated pseudotumoral masses.

LG is considered a low-grade or early-stage lymphoma, and a histopathologic grading system has been developed based on the degree of cellular atypia and necrosis to predict the risk of evolution to high-grade lymphoma and to select patients for early aggressive treatment [30]. Chemotherapy based on the use of cyclophosphamide with high-dose steroids is the most frequently reported treatment. The additional use of rituximab has been reported [30]. The overall prognosis is grim, with a 5-year survival of 30% to 40%, owing to progression to nodal diffuse aggressive lymphoma in 20% to 50% of patients.

Cancer Mimics of Multiple Cystic/Cavitary Lung Disorders

Cystic Tumors

Multiple cystic lung disease (MCLD) is defined by the presence of multiple rounded well-defined lucencies of low-attenuating area in the lung parenchyma that have a wall thickness lower than 2 mm [31]. MCLD may lead to the development of spontaneous recurrent pneumothorax. As discussed elsewhere in this book, MCLD may be caused, among various disorders, by lymphangioleiomyomatosis, Langerhans cell histiocytosis, Sjögren disease or Birt-Hogg-Dubé syndrome.

Metastatic cancers of extrapulmonary origin may mimic MCLD when metastasizing to the lung, especially soft tissue sarcomas including angiosarcomas [32, 33], leiomyosarcomas, osteosarcomas, and synovial sarcoma. Primary tumor locations include soft tissues, bones, the scalp or the uterine endometrium. The occurrence of spontaneous pneumothoraces, which may be bilateral and recur in more than 40% of cases, is more frequent in angiosarcoma, and is associated with worse outcomes. Metastatic cysts may be associated with small-size nodules. In cases for which the information is available, pathological examinations have shown tumor cells in the wall of the cysts. Several case reports describe patients for whom metastatic sarcoma was ultimately diag-

nosed on lung biopsies, or even explanted lungs, after an initial diagnosis of lymphangioleiomyomatosis or pulmonary Langerhans cells histiocytosis [33].

In addition to sarcomas, MCLD-like metastases have been reported in bronchioloalveolar carcinoma, metastatic or primary germ-cell tumors, colorectal and pancreatic cancer.

Cavitating Tumors

The radiological features of cavities overlap with those of cysts. A cavity is a gas-filled space, seen as a lucency or low-attenuation area within a parenchymal nodule, focus of consolidation or mass [34]. Cavitation is a classical feature of pulmonary involvement by granulomatosis with polyangiitis, in combination with multiple bilateral pulmonary nodules. Cavitation is also a common feature of bronchogenic carcinoma, especially of squamous cell histology, and typically is not associated with extrapulmonary manifestations in the head and neck area, the skin, the joints or the kidney [34]. Serum proteinase 3-specific, cytoplasmic antineutrophil cytoplasmic antibodies (C-ANCA) are not elevated in patients with cancer. Granulomatosis with polyangiitis rarely presents with a solitary lung lesion; most solitary necrotising granulomas are actually of infectious nature and require histology in addition to typical clinical findings to support the diagnosis.

Cancer Mimics of Pulmonary Hypertension: Pulmonary Artery Sarcoma

Pulmonary artery sarcoma presents as an endoluminal polypoid or nodular mass, which spreads along the intima of the pulmonary artery. Histologic features consist of an undifferentiated spindle cell proliferation, with marked cellular pleomorphism and high mitotic index Leiomyosarcoma is the most frequent subtype (60% of cases) [35]. Pulmonary artery sarcomas mainly develop in patients in their fifth to sixth decade [35]. Symptoms may mimic pulmonary embolism, with dyspnea, chest pain, cough, and hemoptysis. Failure of anticoagulants to resolve the vascular obstruction in this setting, as well as the presence of symptoms of weight loss and fever (arising in 40% of cases), may suggest the diagnosis. Imaging findings also help differentiate between pulmonary artery sarcoma and pulmonary embolism: CT scanning may show a polypoid filling defect in the pulmonary artery but, in contrast to thromboembolic disease, sarcoma forms a contiguously soft, smooth, tapering tissue mass, sometimes accompanied by extravascular nodular spread in the parenchyma (40% of cases) and localized

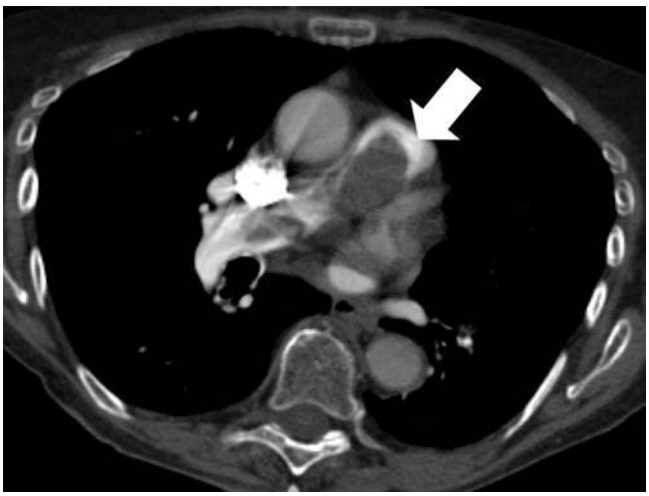


Fig. 43.2 Primary pulmonary artery sarcoma. Contrast enhanced computed tomography scan of a 79-year-old woman, which shows complete obstruction and enlargement of the pulmonary artery trunk. Hypermetabolism is detected at 18-fluoro-2-desoxy-D-glucose positron emission tomography scan. The patient underwent pulmonary endarteriectomy, complete resection of the tumor, and extensive left pneumonectomy. The patient died 25 months after surgery

ground-glass opacities (Fig. 43.2) [36]. Sarcoma also presents with a heterogeneous appearance including areas of necrosis and hemorrhage, and with intense hyperactivity on 18-FDG-PET scanning. Magnetic resonance imaging (MRI) shows intermediate to mildly increased signal on T1-weighted images, often with heterogenous enhancement. T2-weighted images may reveal intermediate to diminished signal intensity relative to skeletal muscle, but in some cases may show enhancement of the intravascular mass, a feature not typically encountered with uncomplicated thromboembolic disease. Surgery is the only potentially curative treatment and, even if performed emergently in the setting of acute right-sided heart failure, is amenable to attempted resection in only 60% to 75% of cases [35–37]. Alternatively, heart and lung transplantation may be an option for unresectable tumors, but has rarely been reported. A slight improvement of overall survival has also been reported following adjuvant chemotherapy and/or radiotherapy. Contrary to soft tissue sarcoma, prognosis is mainly related to tumor location, because half of the patients die as a result of the progressive obstruction of the pulmonary trunk [37]. In case of recurrence, reoperation is feasible in 30% of cases and radiation therapy and chemotherapy can be partially effective. However, in recent series, the overall median survival has remained low at 6–12 months.

Intrathoracic Pseudotumors

Pseudotumors represent a wide range of etiological, pathological, and clinical-radiological disorders, that all share some degree of reactive inflammation and may present with some cancer-related molecular hallmarks. Pseudotumors may mimic the clinical and radiological features of various intrathoracic diseases.

Inflammatory Myofibroblastic Tumor

Inflammatory myofibroblastic tumor (IMT) is the most representative of the pulmonary pseudotumors [6, 38] and encompasses a wide spectrum of lesions previously called "inflammatory pseudotumor," "fibroma," "fibroxanthoma," "fibrous histiocytoma," "plasma cell/mast-cell/solitary granuloma," "plasma cell histiocytoma complex," or "pseudosarcomatous tumor." IMT has a prevalence of 0.04% of resected pulmonary neoplasms in a surgical series of the Mayo Clinic.

IMT appears as an intraparenchymal, well-circumscribed mass of variable size (Fig. 43.3) [38, 39]. Histologically, the tumor is composed of an irregular proliferation of fibroblasts and myofibroblasts intermixed with an infiltrate of inflammatory cells, mainly lymphocytes and plasma cells. Three distinct histologic patterns are usually recognized:

1. Plasma cell variant, also called the "lymphoplasmacytic" variant, which is composed of inflammatory myxoid proliferation with fascicles of spindled fibroblasts or myofibroblasts, abundant lymphocytes and plasma cells, and minimal fibrous connective tissue.
2. Fibrohistiocytic type, which appears as a compact spindle cell pattern simulating fibrous histiocytoma that is characterized by a myxoid proliferation of fibroblasts and myofibroblasts associated with polyclonal plasma cells, xanthoma cells, and rare giant cells.
3. Organizing pneumonia-like type, which has a hypocellular pattern characterized by dense collagen with sparse spindle cells.

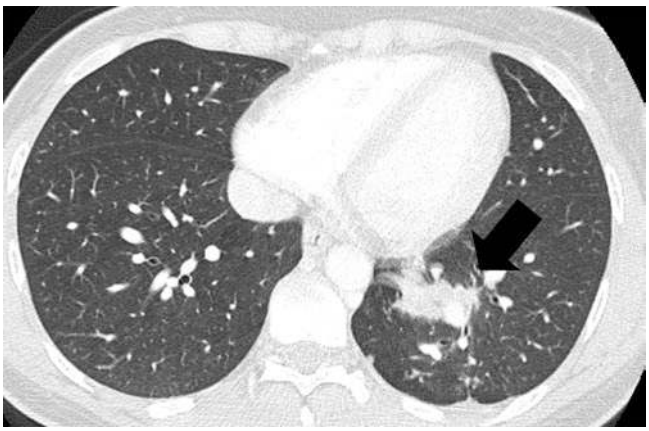


Fig. 43.3 Inflammatory myofibroblastic tumor. Computed tomography scan of a 31-year-old man who presented with persistent cough and hemoptysis following infectious pneumonia. A spiculated mass is located in the left lower lobe. Transparietal biopsy showed polymorphic inflammation without tumor cells. 18-fluoro-desoxy-glucose positron emission tomography showed focal hypermetabolism of the mass. Surgical resection was performed. The patient did not receive adjuvant treatment. No recurrence was observed after a 1-year follow-up

The proliferating myofibroblastic cells show no cellular atypia, no necrosis, and only rare mitotic figures. The myofibroblastic cells usually stain for vimentin and smooth muscle actin.

The concept of IMT as a proliferating neoplasm has been questioned [6]. More recently, clonal gene rearrangements have been observed [40–42], especially involving the *anaplastic lymphoma kinase* (*ALK*) gene. ALK overexpression is observed in 40% to 70% of IMTs at immunohistochemistry, but *ALK* rearrangement is identified in less than 30% of pulmonary IMT cases, and most frequently consists of t(1;2)(q21;p23) translocation implicating the *tropomyosin 3* gene [40–42]. Other translocations have been reported, including *ROS1* translocation [42]. Given the oncogenic nature of ALK activation, these data lead some authors to consider IMT as a true malignant neoplasm. Other elements further reinforce this concept, including the presence of vascular invasion, local recurrence rate as high as 25%, and the existence of multifocal lesions. IMT is also a consequence of immunologic disorders. IgG4 expression in polyclonal plasma cells extracted from intrathoracic IMTs has been associated sclerosing pancreatitis and retroperitoneal and mediastinal fibrosis, and IgG4-related disease. Overlap exists between IMT, IgG4-related disorders, and prototypic, high-grade inflammatory fibrosarcoma that exhibits prominent cellular atypia and necrosis. Finally, EBV and *human herpesvirus 8* infected myofibroblastic cells can be found in IMTs.

Pulmonary IMTs usually appear before the fourth decade, accounting for more than 50% of pulmonary tumors in children Contrary to its presentation at extrathoracic locations, the pulmonary IMT is usually solitary, and often forms a well-circumscribed peripheral mass, ranging from 2 to 15 cm in size. Calcifications are observed in 15% of cases. Stability in size over time is an important imaging feature that helps differentiation of IMT from more aggressive tumors. Mediastinal invasion is frequent but multifocal and bilateral IMTs are usually hypermetabolic on 18-FDG-PET scan.

Even if historically considered a benign lesion with possible spontaneous regression, IMT is usually treated by surgical resection due to its tendency to grow, to provoke local complications including hemoptysis and infection, and to relapse occasionally with lung/pleural and/or mediastinal

invasion (15–25% of cases and 3–5% of cases, respectively). The need for adjuvant treatment in case of incomplete resection has not been evaluated. In nonoperable patients, focal conformation radiotherapy or corticosteroids may represent an alternative. Corticosteroids are reported to induce objective responses in as many as 50% of cases, especially in predominantly plasma cell tumors and IgG4-positive tumors. In recurrent or multifocal lesions, chemotherapy may be based on regimens used for soft tissue sarcomas. ALK inhibitors are effective in case of *ALK*-rearranged IMT [42].

Sclerosing Mediastinitis and Hyalinising Granuloma

Similar to IMT, sclerosing mediastinitis and hyalinising granuloma both consist of tissue infiltration by dense collagen fibrosis forming lamellar bands, interspersed with lymphocytes and plasma cells [43–45]. These two entities differ by the primary anatomic location: sclerosing mediastinitis predominantly involves the mediastinum, with possible extension to the lung parenchyma; hyalinising granuloma occurs within the lung parenchyma without contiguous involvement of the mediastinum (Fig. 43.4). Overlap exists between these entities and other fibrosing disorders such as IMT, retroperitoneal fibrosis, and other IgG4-related disorders.

Borderline Neoplastic-Non Neoplastic Disorders

Excluded from this chapter are benign tumors and preneoplastic conditions of the lung, which have extensively been reviewed elsewhere [4]. Borderline neoplastic and non-neoplastic disorders include entities that are considered benign despite being associated with true neoplasms or presenting with some pathological or molecular characteristic of neoplasia, including clonal proliferation. These disorders may also present as pulmonary nodules or infiltrative disease, mimicking bronchogenic carcinoma or interstitial pneumonias, respectively.

Respiratory Papillomatosis

Some lesions thought to be benign may have a borderline presentation and outcome. One relevant example is recurrent respiratory papillomatosis. Papillomas usually present in the upper respiratory tract but may rarely spread to the lung parenchyma (less than 5% of cases) [46]. Histologically, squamous papillomas are usually exophytic with an epithelial layer covering a central fibrovascular core that forms a frondlike architecture protruding into the lumen of the airway. Papillomas may exhibit imaging features similar to those of lung cancer, including heterogeneous, cavitating, or poorly defined masses.

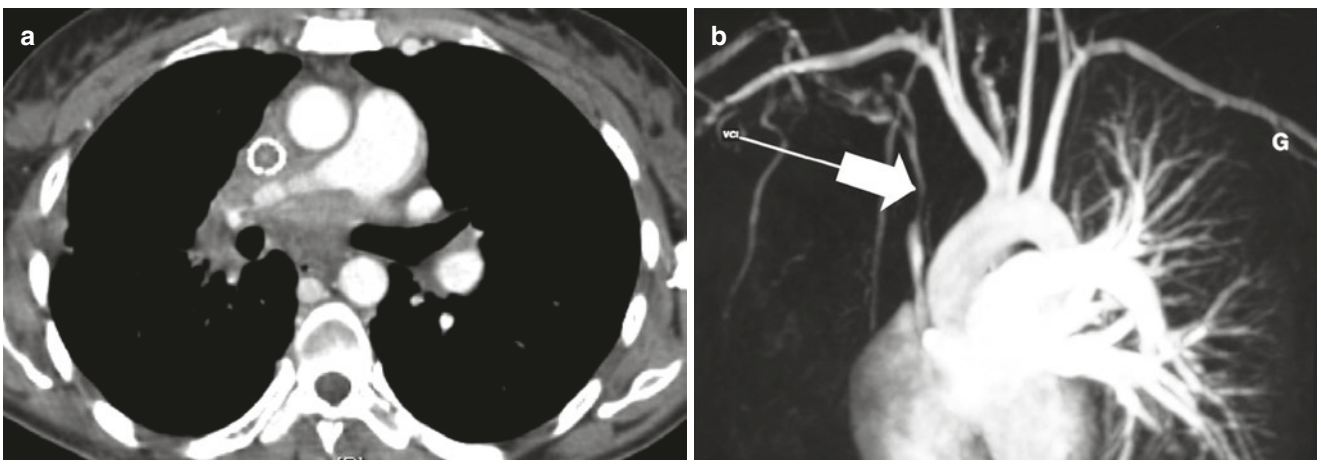


Fig. 43.4 Sclerosing mediastinitis. (**a**) Computed tomography scan of a 32-year-old woman who presented with progressive dyspnea and superior vena cava syndrome. Connective tissue proliferation infiltrates the entire mediastinum. Surgical biopsy was performed to make the diagnosis. (**b**) At magnetic resonance angiography, the caliber of the superior vena cava is reduced (arrow). An endoprosthetic tube was placed for palliation

Pulmonary papillomas may be solitary or multiple; if multiple, these are associated with multiple papillomas of the upper respiratory and aerodigestive tract. As in other locations, the pathogenesis of squamous papillomas is linked with human papillomavirus (HPV) infection, often acquired at birth [47]. Specifically, HPV type 11 infection has been reported to bear a high-risk of transformation of papilloma to squamous cell carcinoma. Molecularly, loss of the tumor suppressor genes *TP53*, *RB*, and *P21* has been reported in squamous cell carcinomas originating from papillomas. Mutation of HPV-11 with duplication of promoter and oncogene regions has been described in a case responding to vorinostat. 18-FDG-PET scanning may not be useful given the mild hypermetabolism of high-grade papillomas. Given this uncertain malignant potential and the difficult differential diagnosis with lung cancer, complete resection of papillomas is recommended though not always possible in the setting of multiple and bilateral lesions. The role of vaccines, antiangiogenic agents, and antiviral treatment in preventing evolution of pulmonary papillomas is unclear.

Amyloid and Non-amyloid Immunoglobulin Deposition Disorders

Amyloidosis is characterized histopathologically by tissue infiltration with amorphous eosinophilic material consisting of fibrillar protein with a β-sheet structural conformation, specifically stained by Congo red with a yellow-green birefringence under polarized light [48]. Amyloidosis has a highly variable clinical-radiological presentation. The lung parenchyma is involved in 30–80% of cases. Pulmonary amyloidosis may be localized or associated with systemic amyloidosis.

Pulmonary amyloidosis may present either as tumor-like lesions consisting of amyloid deposits, generally associated with peripheral lymphoplasmacytic infiltrate and multinucleated giant cells, or as an infiltrative parenchymal disease. Pulmonary amyloid nodules usually consist of AL ("amyloid light chain") amyloid, which is the most common subtype of amyloidosis deposits, consisting of lambda light chains. AL amyloidosis is primary in more than 80% of cases and associated with inflammatory or lymphoproliferative disease in 20% of cases. Serum and/or urinary monoclonal gammopathy is frequent.

Nodular amyloidosis is observed in patients in their seventh decade, without gender predominance [48–51]. Patients are usually asymptomatic. The lesion is solitary in about 30% of cases, corresponding to the so-called amyloidoma. When multiple nodules are present, symptoms may include cough, hemoptysis, or pleuritic chest pain due to pleural effusion. Radiologically, pulmonary nodules are rounded and sharply delimited usually mimicking neoplastic growth. Most nodules are peripheral and located in the lower lobes. The nodules may range from 5 mm to more than 15 cm, and are calcified in 20–50% of cases. The radiological differential diagnosis includes primary and secondary neoplasia, and granulomatous disease. Nodules have shown moderately increased activity at FDG-PET scan. Fine-needle biopsy may provide pathologic diagnosis. Pulmonary amyloid nodules may remain stable for years. Surgical resection is usually performed to obtain a definite diagnosis, but recurrence is frequent.

Besides nodular amyloidosis, diffuse parenchymal amyloidosis typically manifests as interstitial linear or nodular subpleural opacities. In the context of systemic amyloidosis, lymphadenopathy can be widespread and can affect hilar and mediastinal lymph nodes in the thorax. The enlarged lymph nodes may exhibit punctiform calcification. Dyspnea and cough are the most common symptoms. The prognosis of diffuse parenchymal amyloidosis presenting with clinical symptoms is poor. In one series, the median survival of patients with primary systemic amyloidosis affecting the lung was 16 months [49]. Most patients show progression to respiratory failure within 2 years, irrespective of whether the disease is limited to the lungs or affects additional organs. However, many patients also present with concomitant cardiac amyloidosis, which can be associated with rapid heart failure and death. Treatment of any underlying hematologic disease usually leads to regression of the monoclonal peak but has little effect on existing deposits.

Like amyloidosis, nonamyloidotic monoclonal immunoglobulin deposition disease (NAMIDD) initially described in the kidney where it is referred to as Randall disease, was recently reported to occur in the lung [51]. NAMIDD (also known as Light Chain Deposition Disease) presents with deposits that are not stained by Congo red dye and do not demonstrate birefringence under polarized light. These deposits most usually consist of light chains, frequently of kappa isotype, or more rarely of single heavy chains or of mixed light and heavy chains. Pulmonary NAMIDD most frequently presents as multiple parenchymal nodules or as a unique mass without functional consequences; deposition is usually limited to the lung without systemic involvement. NAMIDD may also present as multiple cysts or diffuse bronchiectasis with functional impairment, which may be severe [51]. Approximately half of the cases are associated with hematologic malignancies, mostly of lymphoplasmacytic nature [51]. Pulmonary NAMIDD may benefit from lung transplantation in cases of severe respiratory failure and in the absence of an underlying hematologic disorder [51].

Pulmonary Langerhans Cell Histiocytosis

Pulmonary Langerhans cell histiocytosis (PLCH) is a heterogeneous disease defined by the proliferation of Langerhans cells, corresponding to CD1a-positive histiocytes exhibiting Birbeck granules on electron microscopy [52]. These cells of dendritic lineage derive from CD34-positive bone marrow stem cells. If the lung is the sole location of the disease, it is called "pulmonary LCH." In less than 15% of cases, LCH in adults is associated with multisystem disease, corresponding to "acute disseminated LCH" involving the lung as well as the bone, the skin, and the pituitary gland. The pathogenic concepts about LCH mostly involve an uncontrolled immune response to a yet undetermined stimulus, leading to the recruitment of Langerhans cells in the lung parenchyma. Smoking exposure is found in the majority of patients developing pulmonary LCH which is thought to stimulate this process effects on the bronchiolar epithelium [52]. The true nature of LCH remains elusive. Strongly favoring the hypothesis of a neoplastic disorder is the observation that Langerhans cells, isolated from patients with either pulmonary or disseminated LCH, are clonal [53], and may harbor activating *BRAF* mutations, as well as mutations of the MAP2K1 pathway [53, 54]. However, the limited proliferation of Langerhans cells, the absence of cellular atypia, the low number of Langerhans cells in high-stage lesions, and the possibility of spontaneous regression argue against a truly cancerous nature of LCH.

Pathologically, LCH lesions are made of Langerhans cells that proliferate and aggregate to form stellate nodules in the interstitium, with a bronchiolocentric pattern and linear distal and proximal spread. High-stage lesions are characterized by disappearance of Langerhans cells, increased amounts of fibrosis, and cavitation of the nodules leading to cyst formation [52].

Clinically, pulmonary LCH develops in young smokers who present with nonspecific respiratory symptoms, including dyspnea, cough, and chest pain. Pneumothorax may herald the disease in 15% of patients; 10–25% of patients are asymptomatic. The most typical imaging feature is the combination of pulmonary multiple cysts and micronodules sparing the lower zones of the lung. Nodules, ranging from 5 mm to 2 cm in size, are centrilobular and may be solid or cavitated with smooth or irregular margins. LCH is an active process, with predominant nodular presentation at early stages of the disease, evolving to cavitated nodules, cysts of variable wall thickness, and confluent cystic lesions over time. Lesions of different ages are usually observed within the same subject. Rarely, pulmonary LCH presents as a single nodule, localized consolidation, or mediastinal disease. Increased uptake on 18-FDG-PET scanning is frequent.

Smoking cessation may lead to regression in as many as 25% of patients. No other treatment has been confirmed to be useful in pulmonary LCH, which may also regress spontaneously. Patients with progressive or multiorgan disease may benefit from chemotherapy with cladribine, which produced a 75% objective response rate in a landmark study of 13 patients [55]; cladribine may also reduce the growth and development of cystic lesions. *BRAF* mutations are associated with resistance to chemotherapy, but may predict the efficacy of RAF/MEK inhibitors [56]. Supporting the neoplastic hypothesis, pulmonary LCH can recur following lung transplantation.

Lessons Learned: Rare Tumors Vs. Orphan Lung Diseases

When facing a pulmonary tumor-like lesion, the primary hypothesis for clinicians should remain that the lesion represents lung cancer, the main differential diagnosis of rare pulmonary malignancies. The absence of a tobacco smoking history, especially in men, is more frequently seen for rare lung tumors and pseudotumors than for bronchogenic carcinoma (60% vs. 15%, respectively). Young age at diagnosis is another characteristic to consider, because more than 50% of rare tumors present before the fourth decade. Given the frequent initial suspicion of lung cancer, most patients undergo complete oncologic workup. 18-FDG-PET scan is usually not helpful for differential diagnosis. Preoperative biopsies and intraoperative frozen sections may not be sufficiently representative of the tumor to ensure accurate histopathologic diagnosis, especially in biphasic or composite tumors, for which small-size samples may identify only one cellular component. Frozen specimen collection and storage is mandatory to preserve the tumor for additional analyses.

Sophisticated molecular studies, including flow cytometry and genomic and cytogenetic analyses, play an increasingly important role in the accurate diagnosis of rare pulmonary tumors vs. orphan lung diseases, as morphology may not be sufficient for classification and evaluation of tumor grade. This is especially mandatory for lymphoma, IMT, or sarcomas. Systematic high-throughput genomic analyses, including DNA/RNA sequencing—possibly whole exome sequencing, is used to identify deregulated molecular pathways, which is not possible based on targeted, panel-based analyses designed for frequent tumors. These data may facilitate decisions regarding potential treatment strategies based on targeted agents. Family history is of interest to understand possible predispositions, and occupational/professional questionnaires may identify potential carcinogens;

although only limited environmental data are available for rare pulmonary tumors.

In many cases with a localized lesion in the lung parenchyma, initial surgical resection provides both the correct diagnosis and the first therapeutic step. However, preoperative diagnosis remains important for specific subtypes, such as lymphoma, for which extensive resection is not warranted, and for sarcoma, which usually does not spread to the mediastinal lymph nodes and thus would not require nodal resection. Surgical biopsy may be required to obtain sufficient tissue material for extensive pathologic and molecular diagnoses, especially when clinical-radiologic presentation is not typical of neoplastic or non-neoplastic disease.

In the absence of evidence-based recommendations, expert consensus is mandatory for selection of a specific therapeutic strategy, possibly based on strategies developed for lesions of similar histology arising in another anatomic location. As discussed, molecularly-tailored treatment may be useful, and systematic high-throughput genomic analyses, DNA/RNA sequencing, are then recommended. Also, these approaches highlight the need for multicenter collaboration to generate cohorts and to launch observational studies and clinical trials of rare lung tumors.

Ultimately, the management of patients requires continuous multidisciplinary expertise at each step of the disease. There has been a dramatic improvement in our knowledge in the last few years, through the development of large databases, translational research programs, and clinical trials. Access to innovative strategies represents a major challenge, because there is a lack of funding for clinical research in rare cancers as well as in orphan lung diseases and their rarity precludes the design of robust clinical trials that could lead to specific approval of drugs. In this context, patient-centered initiatives, such as the establishment of dedicated networks, are warranted. International societies, as well as patient advocacy groups provide infrastructure for global collaboration, and there are many advantages to having strong regional groups working on the same issue. There may be regional differences in risk factors, susceptibility, management and outcomes. The ability to address questions both regionally as well as globally is ideal to develop a full understanding of rare pulmonary tumors.

For rare thoracic tumors, the recent establishment of the European Reference Network EURACAN provides an infrastructure of more than 70 healthcare providers with high level of multidisciplinary expertise for the diagnosis, the management and follow-up of patients with rare cancers, including rare thoracic tumors [57]. The objectives of EURACAN include the updating and the assessment of current guidelines, the development of educational programs, dissemination and communication with patients groups, and the establishment of research projects, from the diagnostic workup of the disease to therapeutic strategies. A multidisciplinary tumor board is hosted by a pan-European online platform called the Clinical Patient Management System. The European network also provides an infrastructure for collaboration with diagnosis and pharmaceutical companies. One example may be the opening of dedicated cohorts in basket trials, in which patients with different tumors but the same mutation or biomarker receive the same treatment. By using molecular characterization for assessing new drugs, the network allows a better identification of patients and facilitates the recruitment in the trials. Integration with European Reference Network-Lung dedicated to rare pulmonary disease is key to address the challenges of differential diagnoses. Achieving the highest quality of patient care is the main objective of EURACAN.

Ultimately, as in cancer management, multidisciplinary expertise and discussion is warranted for the management of orphan lung diseases, from diagnosis, to definition of pretreatment workup, to therapeutic approach. Implementing multidisciplinary expert and reference networks is ongoing to ensure high level of quality and equality of care of patients.

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